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Correspondence

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Correction

Correction
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European Perspectives

European Perspectives
PREVALENCE AND PROGNOSTIC SIGNIFICANCE OF WALL-MOTION ABNORMALITIES IN ADULTS WITHOUT CLINICALLY RECOGNIZED CARDIOVASCULAR DISEASE: THE STRONG HEART STUDY, by Cicala et al.

Although it has been established that asymptomatic left ventricular systolic dysfunction predicts worse prognosis, the prognosis of regional-wall motion abnormalities in individuals without known cardiovascular disease has been uncertain. Cicala and colleagues examined the Strong Heart Study, an American Indian population-based cohort, to address the outcome of echocardiographic wall-motion abnormalities in previously undiagnosed cardiovascular disease. They observed that 5% of individuals had segmental and 1.5% had global wall-motion abnormalities by echocardiography. Not surprisingly, participants with segmental wall-motion abnormalities had a higher prevalence of cardiovascular disease risk factors, including diabetes and higher blood pressure, C-reactive protein, creatinine, and albuminuria. In 8 years of follow-up, those with either regional or global wall-motion abnormalities had an adjusted 2- to 3-fold increased risk of cardiovascular events and death. The present study is consistent with many previous studies suggesting that indicators of subclinical disease are associated with worse prognosis. The optimal management of indicators of silent ischemia is controversial and is not addressed by the present study. However, in the absence of data specifically addressing clinically unrecognized cardiovascular disease, strict adherence to guideline-based preventive therapy is indicated with evidence of subclinical disease. See p 143 (editorial p 126).

FAVORABLE LONG-TERM OUTCOME AFTER DRUG-ELUTING STENT IMPLANTATION IN NONBIFURCATION LESIONS THAT INVOLVE UNPROTECTED LEFT MAIN CORONARY ARTERY: A MULTICENTER REGISTRY, by Chieffo et al.

Surgery is the treatment of choice for unprotected left main coronary artery disease, but percutaneous intervention using drug-eluting stents is increasingly being used. Stenting of the ostium or body of the left main coronary artery is technically easier and usually only requires 1 stent; however, the short- and long-term outcome of these patients is not known. The study by Chieffo and colleagues evaluated 147 consecutive patients from 5 centers with stenosis in the ostium and/or the body of the left main coronary artery not involving the bifurcation. Technical success occurred in 99% of the patients, and there was only 1 death in the first 30 days. At long-term clinical follow-up (886±308 days), 5 patients died and 7 required target vessel revascularization. The present study demonstrates that drug-eluting stent implantation in patients with unprotected nonbifurcation left main coronary artery disease is safe and has a favorable long-term outcome. The study supports the need for a randomized clinical trial in order to compare outcomes of coronary intervention with drug-eluting stents versus coronary artery bypass surgery. See p 158.

OXIDANT STRESS IMPAIRS IN VIVO REENDOTHELIALIZATION CAPACITY OF ENDOTHELIAL PROGENITOR CELLS FROM PATIENTS WITH TYPE 2 DIABETES MELLITUS: RESTORATION BY THE PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR-γ AGONIST ROSIGLITAZONE, by Sorrentino et al.

Diabetes mellitus is often complicated by peripheral arterial disease, resulting in significant morbidity because of an increased need for revascularization procedures or limb amputation. In diabetes, advanced peripheral arterial disease results from accelerated atherosclerosis as well as impaired vascular repair processes. Endothelial progenitor cells (EPCs), resident in the bone marrow and released in response to vascular injury or tissue ischemia, have been shown to effect vascular repair. Although insufficient numbers of circulating EPCs have been associated with vascular dysfunction and adverse clinical outcomes, EPC function has also been shown to play a significant role in vascular repair. In diabetes mellitus, EPCs are dysfunctional and exhibit aberrant migration and tube formation capacity; however, the mechanism underlying this dysfunctional state remains largely unknown. In this issue of Circulation, Sorrentino et al examine EPC function in cells isolated from patients randomized to rosiglitazone or placebo and provide mechanistic insight into EPC dysfunction associated with diabetes mellitus. See p 163.
Recognizing Unrecognized Risk
The Evolving Role of Ventricular Functional Assessment in Population-Based Studies

David S. Owens, MD; Jonathan F. Plehn, MD

The rapid evolution of advanced cardiac imaging technologies has resulted in enhanced detection of subclinical disease with the potential for early implementation of therapeutic strategies and reduction in subsequent morbidity and mortality. Noninvasive assessment of ventricular function can provide evidence of prevalent coronary artery disease and cardiomyopathy and could supplant electrocardiography (ECG), the traditional marker of unrecognized myocardial infarction (UMI), in population screening. An appreciation of past efforts in this field is useful in understanding the potential future trajectories of these technologies.

Unrecognized Myocardial Infarction

Ever since Herrick’s initial description of classic angina in 1912, it has been known that incident myocardial infarction (MI) will go unrecognized in a substantial portion of the population. Patients with UMI either recall symptoms that are atypical of MI or have no recollection of any event at all. Initially, autopsy findings and, later, ECG evidence indicated that “silent” MIs were frequent in hospitalized populations. These observations were later extended to a free-living cohort with the first epidemiological data reported from the Framingham Heart Study in 1959 by Stokes and Dawber. These investigators noted that 21% of subjects with new ECG-documented MI on biennial serial examinations had either atypical symptoms that were not clearly related to MI or no apparent ischemia-related complaints. Kannel and Abbott later observed that new Q-wave infarctions detected on biennial Framingham examinations over a 30-year follow-up period were unknown to 28% of the men and 35% of the women who experienced them, with approximately half of these MIs unaccompanied by discernible symptoms on further investigation. More impressive still was the fact that after MI diagnosis, the 10-year death rate was at least as great in subjects with UMI as in those with recognized infarction (45% versus 39%). As shown in the Table, these results have been confirmed by reports from other investigators in locations ranging from Honolulu and Reykjavik to Israel and the Bronx, with UMI prevalence rates largely related to age and ranging from approximately 4% to 44% of all infarctions. Remarkably, with the exception of the Israeli Ischemic Heart Disease Study, all-cause death rates were similar in recognized MI and UMI in all of these reports.

Because of practical considerations, epidemiological investigations have relied on the relatively inaccurate measures of patient testimony, medical history, and ECG for the diagnosis of prevalent or incident MI. Although ECG is an inexpensive, safe, and expedient medium, the test characteristics of ECG are problematic because of limitations in sensitivity and, to a lesser degree, specificity. When the diagnostic criteria are based on Q waves, sensitivity is limited as these are detected in only half of all infarctions documented by delayed gadolinium-enhanced magnetic resonance imaging (Gd-MRI), the current imaging “gold standard” for MI diagnosis. The presence of a Q wave correlates best with overall size rather than with the transmural characteristics of the infarct, which leads to underdiagnosis of smaller infarcts. In addition, Cox demonstrated ECG reversion to normal of 5.6% of Q-wave infarctions over a 4-year period, which can further hamper sensitivity. Finally, most population-based studies fail to account for posterior infarcts in their diagnostic criteria by ignoring the development of right precordial R waves. Although less of an issue, the specificity of ECG MI diagnosis can be reduced by “pseudo-infarct patterns” found in conditions such as hypertrophic cardiomyopathy, emphysema, right ventricular hypertrophy, and infiltrative cardiomyopathy. The inclusion of repolarization abnormalities in diagnostic criteria will also serve to impair specificity. Despite these diagnostic vagaries, the ECG diagnosis of UMI will remain a part of the standard screening procedure simply because of its low cost and ease of use. However, imaging techniques that directly address cardiac pathology may be more predictive of outcome than ECG because they improve sensitivity without reducing specificity.

Unrecognized Left Ventricular Dysfunction

For more than 2 decades, echocardiography has been incorporated into prospective epidemiological assessment of cardiovascular risk in the United States and Europe, and a substantial body of literature has accrued describing the prevalence and prognosis of depressed systolic function in subjects who may or may not have knowledge of associated functional limitations. As in the case of UMI, congestive...
heart failure (CHF) symptoms may exist in but may not be recognized by individuals displaying depressed contractile patterns on imaging studies. Thus, it may be preferable to similarly label this scenario “unrecognized left ventricular dysfunction” (ULVD) instead of the commonly applied term “asymptomatic left ventricular dysfunction.” ULVD diagnosis was originally based on M-mode echocardiography–determined left ventricular (LV) fractional shortening or derived LV ejection fraction (EF) with the use of the Teicholz cubed formula. M-mode echocardiography, which images only a thin slice of the anteroseptal and posterolateral basal LV walls, can provide accurate assessment of global function when ventricular wall motion abnormalities are diffuse and equivalent but can be extremely inaccurate when segmental wall motion abnormalities (SMAs) are limited to areas beyond those interrogated by the narrow beam of ultrasound or affect only the basal segments. Despite this major limitation, early reports indicated that M-mode echocardiography could detect ULVD and predict development of CHF. Vasan and colleagues at Framingham observed that increments in both LV diastolic and systolic height-indexed chamber dimensions predicted incident CHF over an 11-year follow-up period (adjusted hazard ratio [HR] 1.47 for diastolic dimension) in a middle-aged cohort free from known heart failure or coronary disease. Although global systolic function determined by LV fractional shortening did not predict CHF in Framingham subjects, investigators from the Cardiovascular Health Study who had no history of coronary artery disease (CAD), were also excluded if there was evidence of Q-wave MI at baseline, which further limited the possibility of UMI in this overweight, diabetes-prone population. Nevertheless, 5% of subjects still displayed echocardiographic evidence of regional myocardial dysfunction in a coronary distribution consistent with UMI. After significant major CAD risk factors and M-mode echocardiography–determined EF were

<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>Age, y</th>
<th>Cohort Description</th>
<th>ECG Method</th>
<th>Incidence*</th>
<th>Prevalence, %</th>
<th>UMI, %</th>
<th>UMI, %/y</th>
<th>UMI vs RMI</th>
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</thead>
<tbody>
<tr>
<td>Western Collaborative Study Group</td>
<td>3049</td>
<td>39–59</td>
<td>Company employees</td>
<td>Manual</td>
<td>2.2</td>
<td>1.1</td>
<td>23</td>
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<td>Israeli Ischemic Heart Disease Study</td>
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<td>40–69</td>
<td>Civil servants</td>
<td>Computer/manual</td>
<td>3.6</td>
<td>Excluded</td>
<td>40</td>
<td>1.7</td>
<td>RMI higher</td>
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<td>MR FIT Study</td>
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<td>35–57</td>
<td>Intermediate risk for CAD</td>
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<td>Excluded</td>
<td>25</td>
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<td>Honolulu Heart Study</td>
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<td>45–68</td>
<td>Japanese-American men</td>
<td>Manual</td>
<td>0.7</td>
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<td>4–5</td>
<td>No difference</td>
</tr>
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<td>Framingham Study</td>
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<td>30–62</td>
<td>CAD excluded</td>
<td>Manual</td>
<td>2.2</td>
<td>Excluded</td>
<td>25</td>
<td>4–5</td>
<td>No difference</td>
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<tr>
<td>Bronx Aging Study</td>
<td>390</td>
<td>75–85</td>
<td>Elderly Bronx residents</td>
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<td>Reykjavik Study (males)</td>
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<td>33–79</td>
<td>Icelandic men</td>
<td>Minn code/manual</td>
<td>0.5–3.2</td>
<td>0.5–2.8</td>
<td>32</td>
<td>3–5</td>
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<tr>
<td>Reykjavik Study (females)</td>
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<td>33–79</td>
<td>Icelandic women</td>
<td>Minn code/manual</td>
<td>0.4–2.2</td>
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<td>33</td>
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<td>Suburban residents</td>
<td>MEANS/manual</td>
<td>3.8</td>
<td>N/A</td>
<td>43</td>
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</tbody>
</table>

MR FIT indicates Multiple Risk Factor Intervention Trial; HERS, Heart and Estrogen/progestin Replacement Study; ARIC, Atherosclerosis Risk In Communities; RMI, recognized myocardial infarction; Minn, Minnesota; NA, not applicable, and MEANS, Modular ECG Analysis System.

*Incidence per 1000 patient-years.

The Strong Heart Study

Until now, epidemiological imaging studies have failed to address the prognostic potential of regional wall motion abnormalities and have instead focused on analogues of EF that provided a more generalized assessment of ventricular function. In this issue of Circulation, Cicalet and associates examine the prevalence and prognostic significance of echocardiographic segmental and global wall motion abnormalities in American Indian subjects enrolled in the Strong Heart Study who had no history of coronary artery disease (CAD), stroke, or CHF. Subjects, who were 45 to 74 years of age, were also excluded if there was evidence of Q-wave MI at baseline, which further limited the possibility of UMI in this overweight, diabetes-prone population. Nevertheless, 5% of subjects still displayed echocardiographic evidence of regional myocardial dysfunction in a coronary distribution consistent with UMI. After significant major CAD risk factors and M-mode echocardiography–determined EF were respec-
controlled for, SMAs still conferred a 2.5-fold risk for any cardiovascular event (MI, stroke, incident CAD, or CHF) and a 2.6-fold greater risk for cardiovascular death. SMAs were predictive of each of the separate cardiovascular events except for stroke, and the latter may have been due to the low number of incident events over the 7-year follow-up period. When compared with subjects with known CAD and those without CAD who had normal wall motion, patients with SMAs displayed an intermediate risk for one of the outcomes within the predefined cardiovascular event cluster. In the smaller group of subjects with global wall motion abnormalities, a similar risk for cardiovascular events (adjusted HR 2.4) was found, although this was powered entirely by the high rate of incident CHF in this group. Though not significantly different, risk for cardiovascular death tended to be even higher in subjects with global dysfunction than in those with SMAs. It is disappointing that the qualitative stratification strategy for classifying SMA severity, as outlined in Cicala and colleagues’ Methods,15 is never pursued and that the authors fail to indicate whether there is a relationship between SMA severity/distribution and clinical outcome. In addition, the criteria for assigning subjects into the category of “global dysfunction” are a bit nebulous.

The report by Cicala et al15 is noteworthy for several reasons. First, to our knowledge it is the first population-based study in which SMAs and global hypokinesis have been analyzed separately and apart from measures of overall systolic function. The result is that SMAs, and not global dysfunction, appear to predict incident vascular disease. Perhaps even more interesting is the notion that SMAs in a coronary distribution, presumably a result of CAD in most cases, do not appear to carry the same predictive power for cardiovascular morbidity as does a history of CAD. As discussed above, multiple studies have indicated that recognized and unrecognized Q-wave MIs carry similar prognoses in terms of risk for death. Thus it might also be expected that echocardiographic UMI might have the same ability to predict cardiovascular events as a history of CAD, but this was not the case in this investigation.

Probably the best explanation for the apparent limitation in predictive value displayed by echocardiography is that it is a more sensitive test for prevalent CAD than is ECG. As discussed above, Q-wave infarctions, which are the major predictive marker in most ECG studies, are known to represent larger infarcts, which in turn may be indicative of more severe coronary and other forms of vascular disease. Because subjects with Q-wave MIs at baseline were excluded from analysis, those with larger infarcts, presumably carrying a more ominous prognosis, may have been filtered out, thereby leaving a select population with only echocardiographic abnormalities resulting in a lower risk for cardiovascular events.

Management of ULVD

The predictive value of ventricular functional imaging reported by the Strong Heart investigators suggests an increasingly important role for 2-dimensional echocardiography or allied technologies in population screening. In addition, this report serves to underline the importance of aggressive investigation of unsuspected ULVD detected in the clinical laboratory. This is where a line of caution must be drawn, however, because the discovery of ULVD will inevitably lead to further cardiac evaluation, which may be expensive, time consuming, uncomfortable, or even dangerous for the patient. Therefore, early ascertainment of ULVD should be a major requirement before more aggressive diagnostic procedures involving radiation exposure risks or invasive investigation are undertaken.

ULVD Ascertainment

Wall motion assessment is one of the most challenging aspects of echocardiography. This fact is supported by the wide variation in normal EFs reported in patients without known cardiac disease. For example, whereas McDonagh et al16 reported a mean EF of 47% in a healthy, middle-aged Scottish population, Redfield et al17 noted an EF of 64% in a population of similar age without known cardiac disease. Limitation in accurate endocardial edge identification, particularly in apically acquired windows, has plagued epidemiologists for decades and is one reason that the antiquated, though often more reliable, M-mode technology continues to be used in population studies. The relatively recent advent of harmonic imaging, continued overall improvement in instrument quality, and the use of contrast media when endocardial definition requires enhancement will help to improve study accuracy in this area. With these advances, all of which are currently available in clinical labs, accurate 2-dimensional quantification of EF and improved identification of SMAs are possible on a routine basis and may be feasible on an epidemiological basis. In any event, qualitative assessment of reduced EF, especially in “borderline” cases, ideally should be accompanied by quantification, preferably by using a biplane method with carefully drawn endocardial borders. Failure to visualize such borders should trigger the implementation of contrast imaging for enhanced accuracy or implementation of an alternative imaging modality.

The discovery of definite ULVD, whether regional or global, should trigger an etiologic search, initially in the realm of CAD. In the case of asymptomatic SMAs, the presence of wall thinning, absence of systolic wall thickening, and enhanced reflectivity in a typical coronary distribution provide adequate evidence for prior infarction. If only regional hypokinesis is apparent, the presence of confounding conditions such as conduction defects, right ventricular volume overload, and postoperative changes should be excluded. Performance of one of the newer quantitative echocardiographic methods designed to assess strain, such as tissue Doppler strain rate imaging or myocardial speckle tracking,18 may also be of value. The ability of strain rate imaging to distinguish nontransmural from transmural MI and normal myocardium has been documented in both animal and clinical studies,19,20 and threshold values with excellent test characteristics have been documented by Zhang and colleagues.20

If echocardiographic studies are less than definitive or the technology is unavailable, confirmation of infarction may be obtained with delayed-enhancement Gd-MRI or possibly contrast-enhanced multislice computed tomography.21 Gd-MRI can accurately document transmural or even subendo-
cardiac infarction. In the case of global ventricular dysfunction, a cardiomyopathy workup should also include an initial investigation of possible CAD. Gd-MRI assessment may again prove useful, as there is evidence that in up to 87% of cases the technique can distinguish ischemic from nonischemic pathologies. Another reasonable approach would be to pursue conventional or computed tomographic angiography to search for triple-vessel or left main CAD. In the interest of avoiding radiation exposure, our preference is to pursue MRI first and to proceed with computed tomographic angiography only if there is evidence of infarction or if the results are not definitive.

Therapeutic Approaches

If evidence of UMI is observed in a single-vessel distribution and no additional wall motion abnormalities are detected, then there is no clear indication for further investigation and aggressive medical intervention with statins, antiplatelet agents, and probably β-blockade should be pursued. It might be argued that imaging-based stress testing should be included in this algorithm, but until there is evidence that treatment of what would be considered “silent myocardial ischemia” has an outcome benefit, this is not presently indicated.

In the case of unrecognized global LV dysfunction, if CAD is discovered, then invasive evaluation and possibly revascularization may be indicated on the basis of appropriate anatomy and evidence of myocardial viability. In any case, the initiation of angiotensin-converting enzyme inhibition or receptor blockade is supported by the results from the Studies of Left Ventricular Dysfunction (SOLVD) Prevention Trial, in which subjects without symptoms of heart failure and EFs <35% took almost 3 times as long to develop CHF symptoms when treated with enalapril compared with placebo-assigned controls (8.3 versus 22.3 months). It should be noted that subjects in the Prevention arm of SOLVD were known to have existing cardiac disease, although they were not currently being treated with heart failure medications. Furthermore, there was an EF-dependent treatment effect, and treatment-assigned subjects with EFs in the 33% to 35% range received a benefit of only borderline significance. Thus, it is not certain that similar treatment of asymptomatic subjects screened for ULVD with mild or moderate EF reduction would result in outcome benefits equivalent to those seen in SOLVD.

Epidemiological Applications

Finally, it is unknown whether advanced imaging technologies that pose no radiation risk should play a major role in selective population risk screening. Enhanced detection of CAD with the use of tissue Doppler strain rate imaging or myocardial speckle tracking has yet to be reported in an epidemiological setting. Early strides are, however, being made in the epidemiological application of MRI. A recent report by Kwong and coworkers indicated that Gd-MRI evidence of even small amounts of myocardial necrosis conferred increased risks for major adverse cardiac events and cardiovascular death (HR 8.3 and 10.9) when compared with the presence of SMAs (HR 4.8 and 6.2) in subjects with suspected but undocumented CAD. The ongoing Multi-Ethnic Study of Atherosclerosis (MESA) has already documented subtle abnormalities of ventricular function related to carotid intimal thickness that may represent subclinical evidence of CAD. Finally, Gd-MRI is being used to assess prevalence and prognosis of UMI in a subgroup of the Aging Gene/Environment Susceptibility (AGES)–Reykjavik Study. Although the accuracy of technology such as this in detecting ULVD and UMI could lead to a quantum leap in cardiovascular risk assessment, only trials targeted at the treatment of high-risk subjects with ULVD can truly determine whether the benefits of advanced imaging implementation in population screening will justify the significant costs.

Disclosures

None.

References


Key Words: Editorials - coronary diseases - echocardiography - epidemiology - imaging - risk factors
A Replacement for Warfarin
The Search Continues
John W. Eikelboom, MD; Jeffrey I. Weitz, MD

Vitamin K antagonists (VKAs) such as warfarin are the only oral anticoagulants currently available for clinical use. Warfarin has numerous limitations, including slow onset and offset of action, a narrow therapeutic window, and a metabolism that is affected by diet, drugs, and genetic polymorphisms. Because of its unpredictable dose response, warfarin requires careful coagulation monitoring to ensure that a therapeutic anticoagulant effect is achieved. Variable dose requirements, concern about the risk of bleeding, and the need for frequent coagulation monitoring have prompted the development of new oral anticoagulants to replace warfarin. With a predictable anticoagulant response and little potential for food or drug interactions, these new agents have been designed to be administered in fixed doses without coagulation monitoring. Consequently, these drugs have the potential to simplify long-term anticoagulant therapy.

The clinical development of rivaroxaban is more advanced than that of apixaban. Favorable early results with rivaroxaban for the prevention of venous thromboembolism (VTE) in patients undergoing major orthopedic surgery prompted its recent evaluation in phase II clinical trials for the treatment of patients with acute symptomatic VTE. In the present issue of Circulation, Agnelli and colleagues report the results of the Oral Direct Factor Xa Inhibitor BAY 59-7939 in Patients With Acute Symptomatic Deep-Vein Thrombosis (ODIXa-DVT) study, a phase II randomized trial of rivaroxaban for the treatment of DVT. In that trial, 613 patients with symptomatic proximal DVT who did not have pulmonary embolism were randomized to receive fixed-dose oral rivaroxaban (at doses of 10, 20, or 30 mg twice daily or 40 mg once daily) or subcutaneous enoxaparin (at a dose of 1 mg/kg twice daily), followed by a VKA. Allocation to rivaroxaban or enoxaparin/VKA treatment was open label, but patients and investigators were blinded to the dose of rivaroxaban, and all outcomes were adjudicated centrally without knowledge of treatment allocation. The primary efficacy outcome was improvement in thrombotic burden (assessed by repeating the compression ultrasound and comparing the test results with those done at baseline) without recurrent symptomatic VTE or VTE-related death. The primary efficacy outcome occurred in 44% to 59% of patients receiving rivaroxaban and in 46% of those randomized to enoxaparin/VKA. There was no indication of a dose–efficacy relationship with rivaroxaban, but the incidence of bleeding (major plus minor) was higher with increasing doses of rivaroxaban, ranging from 5.0% to 11.6%, compared with a rate of 6.3% in patients treated with enoxaparin/VKA. Symptomatic VTE or death occurred in 2.1% of patients treated with rivaroxaban and in 0.9% of those given enoxaparin/VKA.

The ODIXa-DVT study is one of a pair of phase II trials evaluating the efficacy and safety of rivaroxaban for the treatment of DVT. Its companion study, the as-yet unpublished EINSTEIN-DVT trial, was of similar design but compared once-daily rivaroxaban (in doses of 20, 30, or 40 mg) with a heparin (either unfractionated heparin or low-molecular-weight heparin), followed by a VKA, in 543 patients with symptomatic DVT without associated symptomatic pulmonary embolism.

Therefore, apixaban is less likely to accumulate in patients with renal insufficiency than is rivaroxaban.

As direct inhibitors of factor Xa, rivaroxaban and apixaban inactivate free factor Xa and factor Xa incorporated within the prothrombinase complex equally well. In contrast, indirect factor Xa inhibitors such as fondaparinux have reduced capacity to inhibit factor Xa when it is incorporated within the prothrombinase complex. Whether inhibition of platelet-bound factor Xa endows direct factor Xa inhibitors with an advantage over indirect inhibitors remains to be established.

The features of the new oral anticoagulants in the most advanced stages of clinical development are listed in the Table and are compared with those of warfarin. Unlike warfarin, which reduces the functional levels of factors II (prothrombin), VII, IX, and X, these novel agents are directed against the active site of factor Xa or thrombin, the enzymes responsible for thrombin generation and fibrin formation, respectively (see the Figure). Rivaroxaban and apixaban target factor Xa, whereas dabigatran etexilate inhibits thrombin.

Rivaroxaban is a small molecule directed against the active site of factor Xa. After oral administration, it is absorbed in the stomach and small intestine with a bioavailability of 60% to 80%. Peak plasma levels are achieved in 3 hours, and the drug circulates with a half-life of 9 hours. Rivaroxaban is cleared via 2 pathways: ~65% is excreted unchanged in the urine, and the remainder is eliminated through the biliary/fecal route. Because of the predominance of the renal pathway of excretion, the half-life of rivaroxaban is prolonged in the elderly and in patients with renal impairment. Apixaban has properties similar to those of rivaroxaban except that the clearance of apixaban is mainly via the biliary/fecal route.

The ODIXa-DVT study is one of a pair of phase II trials evaluating the efficacy and safety of rivaroxaban for the treatment of DVT. Its companion study, the as-yet unpublished EINSTEIN-DVT trial, was of similar design but compared once-daily rivaroxaban (in doses of 20, 30, or 40 mg) with a heparin (either unfractionated heparin or low-molecular-weight heparin), followed by a VKA, in 543 patients with symptomatic DVT without associated symptomatic pulmonary embolism.
The primary efficacy outcome was deterioration in thrombotic burden (assessed by repeating the compression ultrasound and perfusion lung scan at 12 weeks and comparing the results with those obtained at baseline) or symptomatic recurrent VTE. This outcome occurred in 5.4% to 6.6% of patients randomized to rivaroxaban and in 9.9% of those given heparin/VKA. Again, there was no evidence of a dose–efficacy relationship with rivaroxaban, but in contrast to the results of the ODIXa-DVT trial, there was no dose response for bleeding. Clinically relevant bleeding occurred in 2.9% to 7.5% of patients randomized to rivaroxaban and in 8.8% of those treated with heparin/VKA.

The lack of a dose–efficacy response for rivaroxaban in the ODIXa-DVT trial, which evaluated total daily rivaroxaban doses ranging from 20 to 60 mg, and in the EINSTEIN-DVT trial, which examined daily doses ranging from 20 to 40 mg, suggests that there is a plateau for efficacy in this dose range. However, this low-dose fondaparinux regimen was as effective as conventional treatment doses of enoxaparin at preventing recurrent ischemia in patients with non–ST-elevation acute coronary syndromes. However, this low-dose fondaparinux regimen was associated with a 50% reduction in the risk of major and minor bleeding.

The significant dose relationship for bleeding with twice-daily administration, but not with once-daily dosing, raises the possibility that dose frequency might influence bleeding risk independently of dose intensity. This could occur if the sustained drug levels achieved with twice-daily dosing confer a greater bleeding risk than the high peak levels obtained with once-daily drug administration. However, comparison across these trials is potentially confounded by differences in the comparators, cointerventions, and outcome definitions. In the ODIXa-DVT trial, the major bleeding rates with 40 mg rivaroxaban once daily or 20 mg twice daily were both 1.7%, whereas the minor bleeding rates were 9.9% and 7.7% with once-daily and twice-daily dosing, respectively. These findings suggest that if dose frequency does influence the bleeding risk, its effect is likely to be minor.

The results of the ODIXa-DVT and EINSTEIN-DVT trials provide proof of principle for the efficacy and safety of rivaroxaban for the treatment of DVT. On the basis of these trials, the 20-mg once-daily dose of rivaroxaban has been chosen for evaluation in phase III randomized trials of rivaroxaban for the treatment of VTE and for the prevention of stroke in atrial fibrillation. However, has the optimal dose been identified in these phase II trials? The lack of a dose–efficacy response with daily rivaroxaban doses ranging from 20 to 60 mg suggests that lower doses also may be effective. For example, it is possible that the 10-mg once-daily dose that is currently being evaluated in phase III studies for the prevention of VTE in major orthopedic surgery would maintain efficacy for treatment of VTE while reducing the risk of bleeding. Support for the concept that lower anticoagulant doses may reduce bleeding without compromising antithrombotic efficacy is provided by the results of the Organization to Assess Strategies for Ischemic Syndromes 5 (OASIS-5) trial. In this study, the dose of fondaparinux used for VTE prophylaxis was as effective as conventional treatment doses of enoxaparin at preventing recurrent ischemia in patients with non–ST-elevation acute coronary syndromes. However, this low-dose fondaparinux regimen was associated with a 50% reduction in the risk of major and minor bleeding.

### Comparison of Warfarin to New Oral Anticoagulants in Advanced Stages of Clinical Development

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Dosing</th>
<th>Coagulation Monitoring</th>
<th>Half-Life, h</th>
<th>Renal Clearance, %</th>
<th>Interactions</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>Factor Xa</td>
<td>Fixed, once daily</td>
<td>No</td>
<td>9</td>
<td>65</td>
<td>Potent CYP3A4 inhibitors*</td>
<td>VTE prevention and treatment, stroke prevention in AF, acute coronary syndromes</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Factor Xa</td>
<td>Fixed, twice daily</td>
<td>No</td>
<td>9–14</td>
<td>25</td>
<td>Potent CYP3A4 inhibitors*</td>
<td>VTE prevention and treatment, stroke prevention in AF, acute coronary syndromes</td>
</tr>
<tr>
<td>Dabigatran etexilate</td>
<td>Factor IIa (thrombin)</td>
<td>Fixed, twice daily</td>
<td>No</td>
<td>14–17</td>
<td>100</td>
<td>Proton pump inhibitors†</td>
<td>VTE prevention and treatment, stroke prevention in AF, acute coronary syndromes</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Vitamin K epoxide reductase</td>
<td>Variable, once daily</td>
<td>Yes</td>
<td>40</td>
<td>0</td>
<td>Multiple drugs, dietary vitamin K</td>
<td>VTE prevention and treatment, stroke prevention in AF, secondary prevention after myocardial infarction, mechanical heart valves</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation.

*Includes ketoconazole, macrolides (eg, clarithromycin), and protease inhibitors (eg, atazanavir).

†Moderately reduces absorption.
These observations raise the possibility that more work should be done to determine the optimal dose of rivaroxaban to carry forward into the phase III program.

The composite primary efficacy outcomes in the ODIXa-DVT and EINSTEIN-DVT trials were driven primarily by changes in thrombotic burden as assessed by repeated compression ultrasonography and perfusion lung scanning. Previous studies have shown that venographic assessment of thrombus burden using the Marder score is a valid surrogate for recurrent DVT.12 Compression ultrasonography has largely replaced venography because compression ultrasonography is noninvasive and obviates the need for injection of contrast dye. In the ODIXa-DVT trial, changes in compression ultrasound findings were quantified with an adapted Marder score. Although this is a logical approach, such an ultrasound scoring system has never been directly compared with its venographic counterpart. Nonetheless, assessment of thrombus burden with repeated compression ultrasound examinations has been used successfully in phase II dose-finding studies with other anticoagulants.13,14

Unexpected hepatotoxicity during recent randomized evaluation of ximelagatran, the first oral direct thrombin inhibitor, has prompted intense scrutiny of the potential hepatic side effects of new oral anticoagulants, including rivaroxaban. During the first 3 weeks of treatment in the ODIXa-DVT trial, the incidence of alanine aminotransferase elevations >3 times the upper limit of normal was significantly lower in patients treated with rivaroxaban than it was in those given enoxaparin/VKA. This is not surprising because enoxaparin is known to transiently increase the levels of transaminases. After 3 weeks, the incidences of alanine aminotransferase elevations were low with both treatments. No patients in the enoxaparin/VKA group stopped treatment because of elevated liver enzymes, whereas 3 patients stopped treatment early in the rivaroxaban group, 2 of whom died soon thereafter of unrelated hepatic causes (metastatic malignancy and acute hepatitis B, respectively). There has been no suggestion of adverse hepatic effects with rivaroxaban in phase II trials for VTE prevention,5,7 but more long-term data are needed.

While the studies with rivaroxaban are well underway, apixaban and dabigatran etexilate are being evaluated in parallel development programs. Building on data from phase II trials for the prevention and treatment of VTE, apixaban has entered phase III evaluation for the prevention of VTE after major orthopedic surgery, for VTE prevention in medical patients, and for stroke prevention in atrial fibrillation. In contrast to rivaroxaban, a twice-daily regimen is being evaluated for these indications.

Of the new oral anticoagulants, dabigatran etexilate is the drug in the most advanced stages of development. An oral direct thrombin inhibitor, dabigatran etexilate is a double prodrug that undergoes esterase-mediated conversion to dabigatran, a small molecule that targets the active site of thrombin. A phase III trial comparing 2 different doses of once-daily oral dabigatran etexilate with subcutaneous dalteparin for VTE prophylaxis after knee replacement surgery revealed similar efficacy and safety.15 Other phase III orthopedic trials have been completed, and phase III studies evaluating dabigatran etexilate for VTE treatment and for stroke prevention in atrial fibrillation are ongoing.

Which is the better target, factor Xa or thrombin? Head-to-head trials of oral direct factor Xa and thrombin inhibitors are needed to address this question. Nonetheless, with the results of these clinical trials beginning to unfold, we are coming closer to finding a safer and more convenient replacement for warfarin.

Disclosures
Dr Weitz is a consultant for Bayer and served as a member of the independent central adjudication committee for ODIXa-DVT. Dr Eikelboom has received consulting fees and/or research funding from companies that are developing new anticoagulants (Bristol-Myers Squibb, Boehringer Ingelheim, Johnson & Johnson, Pfizer, and Sanofi-Aventis).

References

Key Words: Editorials ■ anticoagulants ■ thrombosis
SCN4B-Encoded Sodium Channel β4 Subunit in Congenital Long-QT Syndrome

Argelia Medeiros-Domingo, MD; Toshihiko Kaku, MD, PhD; David J. Tester, BS; Pedro Iturralde-Torres, MD; Ajit Itty, MD; Bin Ye, PhD; Carmen Valdivia, MD; Kazuo Ueda, MD, PhD; Samuel Canizales-Quinters, PhD; Maria Teresa Tusié-Luna, MD, PhD; Jonathan C. Makielski, MD; Michael J. Ackerman, MD, PhD

Background—Congenital long-QT syndrome (LQTS) is potentially lethal secondary to malignant ventricular arrhythmias and is caused predominantly by mutations in genes that encode cardiac ion channels. Nearly 25% of patients remain without a genetic diagnosis, and genes that encode cardiac channel regulatory proteins represent attractive candidates. Voltage-gated sodium channels have a pore-forming α-subunit associated with 1 or more auxiliary β-subunits. Four different β-subunits have been described. All are detectable in cardiac tissue, but none have yet been linked to any heritable arrhythmia syndrome.

Methods and Results—We present a case of a 21-month-old Mexican-mestizo female with intermittent 2:1 atrioventricular block and a corrected QT interval of 712 ms. Comprehensive open reading frame/splice mutational analysis of the 9 established LQTS-susceptibility genes proved negative, and complete mutational analysis of the 4 Na\textsubscript{v}\textsubscript{1.5}-subunits revealed a L179F (C535T) missense mutation in SCN4B that cosegregated properly throughout a 3-generation pedigree and was absent in 800 reference alleles. After this discovery, SCN4B was analyzed in 262 genotype-negative LQTS patients (96% white), but no further mutations were found. L179F was engineered by site-directed mutagenesis and heterologously expressed in HEK293 cells that contained the stably expressed SCN5A-encoded sodium channel α-subunit (hNa\textsubscript{v}1.5). Compared with the wild-type, L179F-β4 caused an 8-fold (compared with SCN5A alone) and 3-fold (compared with SCN5A + WT-β4) increase in late sodium current consistent with the molecular/electrophysiological phenotype previously shown for LQTS-associated mutations.

Conclusions—We provide the seminal report of SCN4B-encoded Na\textsubscript{v}\textsubscript{1.5} as a novel LQT3-susceptibility gene. (Circulation. 2007;116:134-142.)

Key Words: genetics □ ion channels □ long-QT syndrome

Long-QT syndrome (LQTS) represents the prototypic cardiac channelopathy that affects 1 in 3000 individuals and is characterized by QT prolongation, abnormal ventricular repolarization, and increased propensity for sudden cardiac death as a result of its trademark dysrhythmia of torsade de pointes. Since the first discovery in 1995 that pathogenic mutations in cardiac channels cause LQTS, 12 hundreds of mutations distributed among 9 genes comprise 75% of LQTS. Five genes encode critical, pore-forming, ion channel α subunits (SCNQ1, SCNQ2, SCNQ5, SCNQ2, and CACNA1C) and 4 encode ion-channel regulatory proteins (KCNE1, KCNE2, ANKB, and CAV3). However, 25% of patients with LQTS remain genotype-negative after evaluation of all known LQTS-susceptibility genes.3,4

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Because genes that encode cardiac channel interacting or auxiliary proteins can affect channel function, they are attractive candidates for the cause of LQTS. One set of auxiliary proteins belongs to the sodium channel β subunit (Na\textsubscript{v}\textsubscript{1.5}) gene family, where these Na\textsubscript{v}\textsubscript{1.5} subunits play a critical role in cell adhesion, signal transduction, channel expression at the plasma membrane, and voltage dependence of channel gating.6–9 Presently, 4 different Na\textsubscript{v}\textsubscript{1.5} subunits have been described (SCN1B, SCN2B, SCN3B, and SCN4B).10–14 All are detectable in cardiac tissue,15 but none have been linked to any heritable arrhythmia syndrome.
Case Report

The index case was a 21-month-old Mexican-mestizo girl, referred for evaluation of asymptomatic bradycardia with rates <60 bpm. Her 12-lead ECG revealed profound QT prolongation with a heart rate–corrected QT interval (QTc) of 712 ms and intermittent 2:1 atrioventricular (AV) block (Figure 1A). During 1:1 conduction, macroscopic T-wave alternans were observed (Figure 1B). Her past medical history included fetal bradycardia noted at 24 weeks of gestation and small ventricular septal defect that spontaneously closed by 6 months of age. Despite the severe electrocardiographic phenotype, the patient has remained asymptomatic during her first 5 years of life after placement of an epicardial pacemaker. On further inquiry, a family history of premature, unexpected, and unexplained sudden cardiac deaths that involved 2 paternal great aunts was elucidated (sudden cardiac death at 35 years after delivery of twins and sudden cardiac death at 8 years during exercise) (Figure 1C).

On the basis of the ECG findings, the patient’s ECG phenotype was found to be consistent with SCN5A-mediated LQT3, which shows a long isoelectric ST segment with late-onset T wave, and 2:1 AV block, which was shown previously to be associated with defective LQTS-susceptibility genes, in particular the cardiac sodium channel.16-18

Methods

Subjects

The study was performed according to the terms required by the Research Ethics Committee of the National Institute of Cardiology.
Through polymerase chain reaction, denaturing high-performance liquid chromatography, and direct DNA sequencing, we performed comprehensive open reading frame/splice site mutational analysis of all known LQTS-susceptibility genes (KCNQ1, KCNH2, SCN5A, ANKR, KCNE1, KCNE2, KCNJ2, CACNA1C, and CAV3) using previously published primers, followed by mutational analysis of the 4 Na<sub>\(\alpha\)β subunits encoded by SCN1B, SCN2B, SCN3B, and SCN4B. The flanking primers used in polymerase chain reaction amplification of the β subunits were designed with Oligo software (Molecular Biology Insights, Inc., Cascade, Colo.); primers, polymerase chain reaction, and denaturing high-performance liquid chromatography conditions are shown in Table 1.

**TABLE 1. Oligonucleotide Primers, Polymerase Chain Reaction, and Denaturing High-Performance Liquid Chromatography Conditions for Mutational Analysis of Na<sub>\(\alpha\)β Subunits**

<table>
<thead>
<tr>
<th>Gene-Exon</th>
<th>Forward Primer (5’ to 3’)</th>
<th>Reverse Primer (5’ to 3’)</th>
<th>Size, Base Pairs</th>
<th>MgCl&lt;sub&gt;2&lt;/sub&gt;, mmol/L</th>
<th>Thermal Cycling Method&lt;sup&gt;†&lt;/sup&gt;</th>
<th>Gradient 1, %B; Temp °C&lt;sup&gt;‡&lt;/sup&gt;</th>
<th>Gradient 2, %B; Temp °C&lt;sup&gt;‡&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCN1B-1</td>
<td>CTC CTC TGG CCC GCG TAT TA</td>
<td>CTC CCG CCG CCC CAG TGG</td>
<td>164</td>
<td>1&lt;sup&gt;*&lt;/sup&gt;</td>
<td>2</td>
<td>50.5 to 51.5; 67</td>
<td>48 to 58; 72</td>
</tr>
<tr>
<td>SCN1B-2</td>
<td>CCT GAC CTG AGG CTG CTG TC</td>
<td>TGC CCT CCC ATG CTC TCC C</td>
<td>227</td>
<td>1&lt;sup&gt;*&lt;/sup&gt;</td>
<td>2</td>
<td>56.6 to 66.6; 65</td>
<td></td>
</tr>
<tr>
<td>SCN1B-3</td>
<td>CTC TCC CCT CCC TGA CCA</td>
<td>GGC AGG CAG CAC CAG ACT CA</td>
<td>287</td>
<td>1&lt;sup&gt;*&lt;/sup&gt;</td>
<td>2</td>
<td>56.3 to 66.3; 63</td>
<td>52.6 to 62.6; 65</td>
</tr>
<tr>
<td>SCN1B-4</td>
<td>CAG CCT GGT CTA CCC CCT TA</td>
<td>CCC TGG GTG TCC TAC CAC CT</td>
<td>220</td>
<td>1&lt;sup&gt;*&lt;/sup&gt;</td>
<td>2</td>
<td>53.7 to 63.7; 62.5</td>
<td></td>
</tr>
<tr>
<td>SCN1B-5</td>
<td>CCG TCT GAT GGG GTC AC</td>
<td>TTA CGG CTG CCT CTT CCT TG</td>
<td>243</td>
<td>1&lt;sup&gt;*&lt;/sup&gt;</td>
<td>2</td>
<td>54.8 to 64.8; 63</td>
<td></td>
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<tr>
<td>SCN2B-1</td>
<td>CCA TTC CCT CCT TGT AGT TCT</td>
<td>CCC CAT CCT CCT CAC ATT GC</td>
<td>216</td>
<td>2</td>
<td>1</td>
<td>53.6 to 63.6; 61.5</td>
<td></td>
</tr>
<tr>
<td>SCN2B-2</td>
<td>CCA ACA TTC CCA AGC ACA</td>
<td>GAC CAG GGG CTT CAT GCA A</td>
<td>316</td>
<td>2</td>
<td>1</td>
<td>57.2 to 67.2; 62</td>
<td>57.2 to 67.2; 63.5</td>
</tr>
<tr>
<td>SCN2B-3</td>
<td>GCC ATC GTC CTC CAT GGT TGT</td>
<td>AGG TGG GTG GGA AGA GTC A</td>
<td>329</td>
<td>2</td>
<td>1</td>
<td>57.5 to 67.5; 63</td>
<td>57.5 to 67.5; 64</td>
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<tr>
<td>SCN2B-4</td>
<td>GCC TAG TGG GTG GAT GAG</td>
<td>CGA GCA GGC AGG GTC ACT G</td>
<td>346</td>
<td>2</td>
<td>1</td>
<td>57.9 to 67.9; 63.5</td>
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<tr>
<td>SCN3B-2</td>
<td>GCA GTC GCT GAC CCA GGA A</td>
<td>AGA GCC AAG CCA GCC AGA G</td>
<td>223</td>
<td>2</td>
<td>1</td>
<td>53.9 to 63.9; 59.5</td>
<td>53.9 to 63.9; 61.5</td>
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<tr>
<td>SCN3B-3</td>
<td>CTA CCC GGC CAT CTC TCC AA</td>
<td>CAG GAG CCA GGC TGG GAA C</td>
<td>316</td>
<td>2</td>
<td>1</td>
<td>57.2 to 67.2; 62.5</td>
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<tr>
<td>SCN3B-4</td>
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<td>TCT CCT GTC CAC AGA GAC C</td>
<td>358</td>
<td>2</td>
<td>1</td>
<td>57.2 to 67.2; 63.5</td>
<td></td>
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<tr>
<td>SCN3B-5</td>
<td>CTC AAT GAC GGC TCT AGG T</td>
<td>GCA GCA GCA TTA TGA AGG</td>
<td>258</td>
<td>2</td>
<td>1</td>
<td>55.3 to 65.3; 59.5</td>
<td></td>
</tr>
<tr>
<td>SCN3B-6</td>
<td>CTC TCT CCC CCT CTC GCT CTT</td>
<td>ACA ACC TGC CAT CCA CAT TC</td>
<td>219</td>
<td>2</td>
<td>1</td>
<td>53.7 to 63.7; 61.5</td>
<td></td>
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<tr>
<td>SCN4B-1</td>
<td>GCT GTG CCC AGT ATC CCA C</td>
<td>CCA CCA TCA TCA CTC GT G</td>
<td>241</td>
<td>2&lt;sup&gt;*&lt;/sup&gt;</td>
<td>1</td>
<td>47.2 to 57.2; 64</td>
<td>54.7 to 64.7; 67</td>
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<tr>
<td>SCN4B-2</td>
<td>CCC GAG GTG GCC AGT GAG C</td>
<td>GGA CCA CAG GGT AGG AGC C</td>
<td>373</td>
<td>2&lt;sup&gt;*&lt;/sup&gt;</td>
<td>1</td>
<td>58.5 to 68.5; 62</td>
<td></td>
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<tr>
<td>SCN4B-3</td>
<td>TCT GGG CTA CTT TCT CCC C</td>
<td>CTC CCA AGG TCA TCA CCA C</td>
<td>320</td>
<td>2</td>
<td>2</td>
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<td>SCN4B-4</td>
<td>GCT CCA GTG TGA CTC TGT GT</td>
<td>GCT GGC AGG AGG AGA GCA G</td>
<td>326</td>
<td>2</td>
<td>2</td>
<td>57.4 to 67.4; 61.5</td>
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<tr>
<td>SCN4B-5</td>
<td>TCC CCC TAC TCT TGC TCC</td>
<td>GGA CTC TGG TTA CTT GTC C</td>
<td>294</td>
<td>2</td>
<td>2</td>
<td>56.5 to 66.5; 63</td>
<td></td>
</tr>
</tbody>
</table>

Polymere chain reaction and other reactions were performed in 20-μl volumes with 50 ng of DNA, 16 pmol of each primer, 200 μM of each dNTP, 50 mmol/l KCl, 10 mmol/l Tris-HCl (pH 8.3), and 1.0 U of AmpliTaq Gold (Applied Biosystems, Branchburg, NJ). PCR indicates polymerase chain reaction; DHPLC, denaturing high-performance liquid chromatography.

<sup>*</sup>8% dimethyl sulfoxide was added to the reaction mixture. Polymerase chain reaction amplification was performed with a DNA Engine Tetrad thermal cycler.

†Thermal cycling method 1: 94°C for 5 minutes, followed by 5 cycles of 94°C for 20 s, 64°C for 20 s, and 72°C for 30 s; additional 35 cycles of 94°C for 20 s, 62°C for 20 s, 72°C for 30 s, and a final extension of 72°C for 10 minutes. Thermal cycling method 2: 94°C for 15 minutes, followed by 35 cycles of 94°C for 30 s, 58°C for 30 s, 72°C for 30 s, and a final extension of 72°C for 10 minutes.

‡DHPLC was performed with a 5% buffer B/minute gradient. The start and stop % buffer B followed by the temperature at which the gradient was performed is indicated in the table.

“Ignacio Chávez,” Mexico City, and the Mayo Foundation Institutional Review Board; written informed consent was obtained from all participants. Genomic DNA from the index case and all consenting family members was extracted from peripheral blood lymphocytes by use of standard techniques. Control DNA from 200 healthy Mexican-mestizo subjects was obtained from Unidad de Biología Molecular y Medicina Genómica, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City. Mexican-mestizo ethnicity resulted from admixture of racial ancestry that included European (Spanish) and indigenous descent, with smaller contribution from Asian and African groups. Two hundred additional control DNA samples (100 from white donors and 100 from black), obtained from Coriell Cell Repositories (Camden, NJ), were also examined.

In addition, 262 genotype-negative patients (180 females; 96% white; age at diagnosis, 25±16 years; mean QTc, 470±60 ms) with a suspected clinical diagnosis of congenital LQTS were referred previously for genetic testing to the Mayo Clinic Windland Smith Rice Sudden Death Genomics Laboratory, were included.

**Functional Assay**

Cloning, mutagenesis, and voltage-clamp techniques were performed as previously described.18 Briefly, the WT-β4 was cloned from human heart cDNA with reverse transcriptase–polymerase chain reaction and 2 primers: 5’-AGAGAACAGGACTATGGCCG-3’ and 5’-TTTCTATCATCAGAAGGGG-3’. The WT-β4 was subcloned into pcDNA3 and confirmed by DNA sequencing analysis. L179F-β4 was engineered by site-directed mutagenesis with the following primers: Na<sub>\(\alpha\)4 L179F sense 5’-ATGGGGCTCTTCTACTTCACTCCGGTACGAAGAGTGGC-3’ and Na<sub>\(\alpha\)4 L179F antisense 5’-CTTGGATCAGGAGGTAAGGATGAGGGAGCGGCG-3’. The WT-β4 or L179F-β4 was subcloned into pIrrGF1 vector, a mammalian expression vector (kindly provided by Dr David Johns from the Johns Hopkins University, Baltimore, Md), which contains IRES and GFP. These WT-β4 and L179F-β4 constructs were expressed heterologously in HEK 293 cells that contain stably expressed SCN5A-encoded sodium channel α subunits (hNa<sub>\(\alpha\), 1.5; hH<sub>\(\alpha\), GeneBank accession #AY148488). Macroscopic sodium current was measured by standard
precipitated with 1 M glycerol and coexpressed in HEK cells. The preparation was immuno-precipitated with mouse anti-HA monoclonal antibody (Zymed Laboratories, South San Francisco, Calif) and then electrophoretically separated by 12% SDS-PAGE. After immunoblotting with 0.5 g/mL rabbit anti-Myc polyclonal antibody (Sigma-Aldrich, St Louis, Mo.), immune complexes were developed with the ECL-plus kit (Amersham Biosciences, Piscataway, NJ).

whole-cell-patch-clamp method with use of an Axopatch 200B amplifier and pClamp8.0 software (Axon Instruments, Foster City, Calif). “Steady-state” activation, inactivation, and recovery from inactivation were performed and analyzed as previously described.19,30 The conditioning step for inactivation and recovery was 1 s, and holding potential and recovery potential was −140 mV. Activation and inactivation were fitted to standard Boltzmann function. Recovery time course and the time course of current decay were fitted with a biexponential function. Summary data are shown as the mean±SEM with statistical significance determined by the Student t test.

Biochemical Analysis

Coimmunoprecipitation between SCN5A and β4 subunit was performed with a SCN5A-labeled with HA and β4 subunit labeled with Myc and coexpressed in HEK cells. The preparation was immunoprecipitated with 1 μg of mouse anti-HA monoclonal antibody (Zymed Laboratories, South San Francisco, Calif) and then electrophoretically separated by 12% SDS-PAGE. After immunoblotting with 0.5 μg/mL rabbit anti-Myc polyclonal antibody (Sigma-Aldrich, St Louis, Mo.), immune complexes were developed with the ECL-plus kit (Amersham Biosciences, Piscataway, NJ).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscrip as written.

Results

After a negative mutational analysis of the 9 known LQTS-susceptibility genes, we identified a C to T base mutation at position 535, which yielded a novel L179F-SCN4B missense mutation (leucine [L] to phenylalanine [F] at position 179, when the full-length gene product is considered) by denaturing high-performance liquid chromatography and DNA sequencing (Figure 1D). This mutation was absent in 800 reference alleles, which included 400 ethnicity-matched, Mexico-mestizo alleles. SCN4B mutational analysis of 262 genotype-negative LQTS patients (predominantly white) was negative.

L179 localizes to the transmembrane spanning region (Figure 2A), is relatively conserved across species (Figure 2B), and a substitution with phenylalanine is predicted to alter secondary structure (data not shown). L179F cosegregated properly through a 3-generational pedigree with incomplete penetrance. QTc values and ages are shown in Figure 1C. Although other family members displayed QTc values above normal average, the index case exhibited the only severe ECG phenotype detected on this pedigree, and despite the severe ECG anomalies, the index case has never experienced syncope or torsade de pointes. However, no premortem ECGs were available for either of the sudden-death victims and 1 of the decedents was proven to have been an obligate mutation carrier.

When the wild-type (WT) SCN4B and the L179F mutant SCN4B were transfected transiently into an HEK cell line that stably expressed the most common SCN5A transcript in humans (H558/Q1077del),20 robust sodium current traces were recorded and no significant differences in current amplitude and time course were noted in comparison to SCN5A alone (Figure 3A and Table 2). The steady-state voltage dependence of activation and inactivation of the sodium channel were analyzed with standard protocols and fitted with the use of a Boltzmann function. Voltage dependence of inactivation but not activation was modified by L179F mutant (Figure 3, B and C). This small but significant 3.42-mV positive shift in inactivation (WT-β4, −82.52±0.74 (n=9), to L179F-β4, −79.10±0.59 (n=9); P<0.05) increases the window current and could be arrhythmogenic. More importantly, this voltage shift in inactivation indicates a consistent effect and an interaction of the α subunit with β4 in the heterologus system.

Compared with SCN5A alone, L179F-β4 caused a dramatic 8-fold increase in late sodium current at −60 mV, which is consistent with an effect on terminal repolarization to prolong the QT interval as previously shown for LQT3-associated mutations in SCN5A. In fact, the increase in late sodium current exceeded that of the classic mutation that causes LQT3 (ΔKPQ) in the pore-forming, SCN5A-encoded α subunit (Figure 4).21 Table 2 presents a summary of current density and the remaining gating param-
Statistically significant changes in recovery kinetics, particularly a significant increase in the slow Tau of recovery, were noted. Coimmunoprecipitation experiments (Figure 5) showed that both WT-β4 and L179F-β4 were present when SCN5A was specifically immunoprecipitated by a labeled tag.

**Discussion**

We provide the first report to detail SCN4B as a novel LQTS-susceptibility gene on the basis of identification of a novel missense mutation (L179F) that cosegregated properly, was absent in 800 reference alleles, and produced a “gain-of-function” Na+,1.5 current in a family with no other identifiable LQTS-associated mutations.

L179F cosegregated properly with incomplete penetrance, which is typical for heritable arrhythmia syndromes like LQTS. Genetic testing in LQTS has demonstrated that 40% of carriers of LQTS-related mutations had a QTc within normal limits.4,22 Penetrance, expressivity, and phenotype do not depend solely on the primary LQTS-associated mutation, as these can be influenced by modifier genes.19 Thus far, no modifiers have been identified to account for the extreme QT prolongation and intermittent 2:1 AV block in the index case or the sudden death in the obligate carrier compared with the milder ECG phenotype seen in other genotype-positive living family members. Intermittell functional 2:1 AV block in the setting of LQTS has an incidence of 4% to 5% in pediatric series,23 is usually an isolated disorder, and is associated with a high mortality rate of >50% regardless of treatment.24,25 Symptoms could appear at a very young age; neonatal paroxysmal bradycardia and/or hydrops fetalis are common findings. The phenomenon occurs in the setting of a very long, rate-dependent, effective refractory period.26 QRS complex is usually narrow; however, in spite of this, infrahisian block locations have been documented,26–28 although suprahisian block is not ruled out and the level of the block could depend on the genotype. Until now 3 genes have been associated with 2:1 AV block: SCN5A, KCNH2, and CACNA1.17,27–38 Our data suggest that perturbations in the SCN4B-encoded β4 subunit constitute another pathogenic mechanism for 2:1 AV block in patients with LQTS.

According to the proband’s family history, the 2 sudden deaths occurred during exercise or after delivery; these triggers have been previously associated with the KCNQ1 and KCNH2 genes, respectively; nevertheless, no mutations in these genes were found in our patient. Although exertional syncope more likely suggests LQT1, and the presence of cardiac events during the postpartum period more likely suggests LQT2, 44% of patients referred for LQTS genetic testing because of exertional syncope and 25% with family history of an event that occurred postpartum did not have LQT1 to LQT6.39 Importantly, the genotype-phenotype relationships for the rare subtypes of LQTS, mainly those that involve ion channel interacting proteins, have not been determined.

Ion channels exist as macromolecular complexes with several auxiliary proteins known as channel interacting proteins that localize to or are involved in the plasma membrane, extracellular matrix, intracellular proteins, cytoskeleton anchoring, and signal transduction.9 In principle, perturbations in any component of this complex may affect the proper function of the pore-forming channel subunit itself. Voltage-gated sodium channels have a pore-forming α subunit and 1
similar in sequence and associate noncovalently with channel Nav1.5 plus sodium channel in ventricular myocytes is composed of studies in mouse hearts indicate that the primary cardiac subunits. Na_v1.1 to Na_v1.9 41 and 4 different Na_v subunits (Nav1.1, Na_v1.3, and Nav1.6, are also expressed in heart plus subunits 13,14 Immunocytochemical studies in in LQT3 and Brugada syndrome. However, among all the β subunits, only β1 has been associated with human disease, namely febrile seizures. 42

Na_β subunits are proteins with type I topology characterized by an extracellular N-terminal cleaved region, a transmembrane segment, and a cytoplasmic domain with a C-terminal tail. Na_β subunits contain an extracellular Ig-like fold, often found in cell adhesion molecules 43 that target ion channels to the plasma membrane and mediate interactions with signaling molecules. Na_β1 and Na_β3 are similar in sequence and associate noncovalently with α subunits. Na_β2 and Na_β4 are related proteins that are disulfide-linked to α subunits. 15,14 Immunocytochemical studies in mouse hearts indicate that the primary cardiac sodium channel in ventricular myocytes is composed of Na_1.5 plus β2 and/or β4 subunits in intercalated disks, whereas other isoforms, such as Na_1.1, Na_1.3, and Na_1.6, are also expressed in heart plus β1 or β3 in the transverse tubules. 15 Knockout mice that lack the sodium channel β1-subunit display spontaneous generalized seizures and ataxia, 44 whereas mice that lack the β2-subunit have increased susceptibility to seizures. 45

The β4 subunit is distinguished by a cytoplasmic tail insert (KKLITFILKKTREK) from amino acid 184 to 197 when the full gene product is considered, or amino acid 154 to 167 when the mature protein after cleavage is considered, as shown in Figure 2A. This cluster of lysine and hydrophobic residues has been implicated recently with a transient and resurgent sodium conduction contributing to the short refractory period seen in the SCN8A-encoded sodium channel of cerebellar Purkinje cells 46 and may serve as an endogenous open-channel blocker. 13

Enzymatic removal of this endogenous blocker generated a

<table>
<thead>
<tr>
<th>TABLE 2. Summary of Current Density and Gating Parameters</th>
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</tr>
<tr>
<td>h_m density</td>
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<tr>
<td>Activation</td>
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<td>Recovery from inactivation</td>
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<tr>
<td>Decay, -20 mV</td>
</tr>
<tr>
<td>τ Fast, ms</td>
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<td>τ Slow, ms</td>
</tr>
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All data are represented as mean±SD. h_m indicates robust sodium current.

*P<0.05 vs SCN5A.
†P<0.05 vs WT-β4.

![Figure 4](https://example.com/figure4.png)

**Figure 4.** Effect of coexpression of L179F-β4 mutant on late sodium current. A, Representative sodium current traces in response to a step to -60 mV for 700 ms from a holding potential of -140 mV (protocol inset) are shown. Leak-subtracted currents were normalized to peak current and are shown on a scale such that peak current is off-scale to emphasize the small late component. B, Summary data showed that L179F-β4 mutant increased late sodium current during the window of terminal repolarization as much as the α subunit sodium channel mutation (ΔKPQ) that causes LQT3. 21
delay in channel recovery. This resurgent current, induced by the β4 cytoplasmic tail, has been demonstrated also in the cardiac isoform in vitro and a putative S6-binding site within the inner cavity of hNav1.5 has been suggested.47 This mechanism is analogous to that seen in patients with SCN5A-mediated LQT3 and raises the possibility that L179F-β4 represents a primary loss-of-function mutation in SCN4B that secondarily precipitates a gain-of-function on Na1.5. In fact, the accentuation in late sodium current rendered by L179F-β4 is greater than many primary mutations in the SCN5A-encoded α subunit itself. Unlike SCN5A mutations, however, the gain-of-function mechanism in these experiments for L179F-β4 is confined to the window current and would primarily affect and slow terminal repolarization rather than the classic accentuation of late sodium current at more depolarized membrane potentials that would prolong the action potential plateau.

Experiments were performed in heterologous mammalian expression systems, a standard technique for characterization of LQTS mutations. These systems, however, lack the native environment of the cardiac cell and did not include β1, β2, or β3 subunits, or other components of the Na channel macromolecular complex such as caveolin-3. As such, the effects may differ and be more severe in a more complete and native environment. However, direct concordance between the degree of channel dysfunction and the manifest clinical severity is not necessarily present. Nonetheless, the molecular phenotype was consistent with LQT3, and in combination with the clinical data and genetic cosegregation supports the L179F mutation in the sodium channel β4 subunit as disease associated.

In the present report we have provided proof of principle that mutations in SCN4B may contribute to the pathogenic substrate for some cases of LQTS by alteration of the cardiac sodium channel current (Na1.5). Our study provides the first human disease associated with perturbations in the sodium channel β4 subunit. Notably, mutations in CAV3-encoded caveolin-3 were demonstrated recently as a novel LQTS-susceptibility gene (LQT9).48 In coexpression studies that involved heterologous expression of only the α subunit and mutant caveolin-3, marked accentuation of the late sodium current was observed, similar to that seen here with L179F-β4. Thus, SCN4B (LQT10) joins CAV3 (LQT9) as rare LQTS-susceptibility genes that encode cardiac sodium encode cardiac channel interacting proteins that, when disrupted, yield a LQT3-like molecular/electrophysiological phenotype.

Acknowledgments
We are grateful to Salvador Ramirez-Jimenez for technical assistance. We are particularly indebted to the index case and family members for their participation in this study.

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Disclosures
None.

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**CLINICAL PERSPECTIVE**

Long-QT syndrome (LQTS) is a potentially lethal heritable arrhythmia syndrome that affects an estimated 1 in 3000 persons. Since the sentinel discovery of cardiac channel mutations as its pathogenic basis in 1995, LQTS has been viewed as a “cardiac channelopathy.” To date, 9 LQTS-susceptibility genes have been discovered, and 5 of these genes encode the critical ion channel pore-forming \(\alpha\) subunit whereas the other 4 genes encode cardiac channel interacting proteins. Presently, \(\approx 20\%\) of LQTS remains genetically elusive, and cardiac channel interacting protein–encoding genes represent the latest targets of investigation. Sodium channel \(\beta\) subunits are crucial regulatory proteins. Four different \(\beta\) subunits (\(\beta1\) to \(\beta4\)), encoded by *SCN1B* through *SCN4B*, respectively, have been described. All are detectable in cardiac tissue but none have been related to any arrhythmogenic disease. In the present study, we discovered that *SCN4B* is a novel albeit rare LQTS-susceptibility gene (LQT10). Consistent with the Towbin Final Common Pathway Hypothesis, a single missense mutation (L179F) in the 228-amino acid that contains \(\beta4\) subunit conferred a secondary gain-of-function clinical and biophysical phenotype to the sodium channel macromolecular complex. The mutation converted the \(\alpha\) subunit of the otherwise intact Na\(_1\) 1.5 into a channel with accentuated late sodium current that essentially mimicked mutations that cause LQTC.
Prevalence and Prognostic Significance of Wall-Motion Abnormalities in Adults Without Clinically Recognized Cardiovascular Disease

The Strong Heart Study

Silvana Cicala, MD, PhD; Giovanni de Simone, MD; Mary J. Roman, MD; Lyle G. Best, MD; Elisa T. Lee, PhD; Wenyu Wang, PhD; Thomas K. Welty, MD; James M. Galloway, MD; Barbara V. Howard, PhD; Richard B. Devereux, MD

Background—Left ventricular wall motion (WM) abnormalities have recognized prognostic significance in patients with coronary or other heart diseases; however, whether abnormal WM predicts adverse events in adults without overt cardiovascular disease has not been assessed. Our objective was to determine whether echocardiographic WM abnormalities predict subsequent cardiovascular events in a population-based sample.

Methods and Results—Participants (n=2864, mean age 60.8 years, 64% women) without clinically evident cardiovascular disease in the second Strong Heart Study examination who had complete echocardiographic WM assessment were studied. Echocardiographic assessment revealed that 5% of participants (n=140) had focal hypokinesia, and 1.5% (n=42) had WM abnormalities. Relationships between WM abnormalities and fatal and nonfatal cardiovascular events (including myocardial infarction, stroke, coronary artery disease, and heart failure; n=554) and cardiovascular death (n=182) during 8.2 years follow-up were examined. In Cox regression, after adjustment for age, gender, waist/hip ratio, systolic blood pressure, and diabetes mellitus, segmental WM abnormalities were associated with a 2.5-fold higher risk of cardiovascular events and a 2.6-fold higher risk of cardiovascular death (both P<0.0001). In similar multivariable models, global WM abnormalities were associated with a 2.4-fold higher risk of cardiovascular events (P=0.001) and a 3.4-fold higher risk of cardiovascular death (P=0.003).

Conclusions—Echocardiographic left ventricular WM abnormalities in adults without overt cardiovascular disease are associated with 2.4- to 3.4-fold higher risks of cardiovascular morbidity and mortality, independent of established risk factors. (Circulation. 2007;116:143-150.)

Key Words: echocardiography ■ follow-up studies ■ prognosis ■ mortality

Echocardiographic evaluation of wall motion (WM) is a simple, well-validated method to assess segmental left ventricular (LV) function. The presence of qualitative WM abnormalities has been demonstrated to be an independent predictor of cardiovascular events in groups of patients with myocardial infarction (MI), unstable angina, typical chest pain, and congestive heart failure (CHF); however, regional WM abnormalities may also occur without history or clinical and ECG signs of coronary artery disease. No information exists on the association of echocardiographic WM abnormalities with subsequent cardiovascular morbidity and mortality in unselected adults without overt cardiovascular disease (CVD). Accordingly, we examined whether echocardiographic LV WM abnormalities predict cardiovascular outcomes in a population-based sample of adults without overt CVD, independently of established cardiovascular risk factors.
LV dimensions were used to calculate LV mass with a necropsy-lateral, and inferior walls.23 Segments were scored as having normal inferior walls) and into 4 segments at the apex (septum, anterior, muscles (anterior and posterior septum and anterior, lateral, and

Assessed by a visual, semiquantitative method in parasternal long-axis and short-axis views. According to the Mayo Clinic criteria, the LV was divided into 5 segments at the base and at the papillary muscles (anterior and posterior septum and anterior, lateral, and inferior walls) and into 4 segments at the apex (septum, anterior, lateral, and inferior walls).33 Segments were scored as having normal systolic wall thickening (≥30%), or as having mild (systolic wall thickening 20% to 29%), moderate (systolic wall thickening 10% to 19%), or severe (systolic wall thickening ≤10%) hypokinesia, or as being akinetic or dyskinetic.24 Segmental WM abnormalities were considered present for the analyses discussed here if present in 2 contiguous segments in a coronary territory. Hypokinesia was classified as global when it symmetrically involved all segments or segmental if it was predominantly localized to specific segments. Reliability and intraobserver and interobserver variability of WM assessment in the reading center have been reported previously from a separate series of 111 hypertensive patients with echocardiograms repeated 1 to 4 weeks apart (intraclass correlation coefficient for single segment measurements: absolute agreement = 0.69, 95% confidence interval [CI] 0.69 to 0.84; reliability coefficient $\kappa = 0.87$, $P<0.001$; $\kappa$ for normal/abnormal WM = 0.60, $P<0.001$).25 Otherwise-eligible participants without complete assessment of WM (n=90) were also excluded from analysis.

Clinical End Points

Observation for end points extended from the date of echocardiography to the end of 2003. Fatal and nonfatal cardiovascular events, including MI, stroke, coronary heart disease, and heart failure, were identified from sources in each community and through annual follow-up of participants and verified through death certificates and review of medical records, as described previously.4,15 An independent review panel of physicians who were blinded to echocardiographic data adjudicated deaths as cardiovascular if caused by MI, stroke, sudden death due to definite coronary heart disease,11,15,16 or CHF.17 Similarly, medical records were reviewed by an expert physician panel to identify nonfatal cardiovascular events that occurred after the second SHS examination. In patients experiencing more than 1 adverse event, only the first event was considered in analyses of the combined end point of fatal and nonfatal cardiovascular events. Follow-up for nonfatal events and mortality was 99% and 99.8% complete, respectively. Echocardiogram reports were returned to participants’ healthcare providers, but few if any evaluations for coronary artery disease were provoked in 1993 to 1995 by these reports.

Statistical Analysis

Descriptive statistics for the various covariates are shown as either percentages or means with SDs. In the presence of skewed distributions, the median was calculated and the interquartile range (between the 25th and 75th percentiles) given. $\chi^2$ Statistics were used to identify categorical variable differences, whereas 1-factor ANOVA was used to identify continuous variable differences among groups without or with segmental or global WM abnormalities, with multiple comparisons by the REGW-F post hoc test (Ryan, Einot, Gabriel, & Welsch F test) when needed. The Kruskal-Wallis test was used to identify differences of C-reactive protein among groups because of skewed distribution.

Event rates were displayed by Kaplan-Meier plots. Log cumulative hazard functions were computed by Cox proportional hazards analysis with forced entry of covariates. Age, gender, waist-hip ratio, systolic blood pressure, and diabetes mellitus were considered together with WM abnormalities in all models. Other models were performed that additionally considered established clinical predictors of cardiovascular events (current smoking, total/HDL cholesterol, and serum creatinine), these plus markers of preclinical CVD (microalbuminuria and LV mass index), and, finally, all of the above plus markers of inflammation (C-reactive protein and fibrinogen). Hazard ratios (HRs) with 95% CIs for all first cardiovascular events and for cardiovascular death were examined. For each baseline characteristic, a univariable proportional hazards regression model was used to estimate the HR and its 95% CI. Finally, likelihood functions from the Cox models with or without WM abnormalities (both adjusted for standard cardiovascular risk factors) were compared. The difference between 2 likelihood functions has an 1-degree-of-freedom $\chi^2$ distribution.26

To assess the ability of Cox models with or without segmental WM abnormalities to discriminate participants who experienced cardiovascular events from those who did not, we used a version of the $c$ statistic, which was calculated on the basis of all possible pairs of participants, at least 1 of whom had CVD.27 Analogous to the area under the receiver operating characteristic curve, $c$ represents an estimate of the probability that the Cox model assigns a higher risk to participants who develop a cardiovascular event early in the follow-up period than to those who develop cardiovascular events late or never develop the disease in the follow-up period. A $c$ value of ≥0.7 indicates good discrimination ability, and the closer the $c$ value is to 1.0, the better is the discrimination ability. Interaction between WM abnormalities and gender, diabetes mellitus, or hypertension was tested by adding cross-product terms of WM abnormalities and these variables into the models. To place the results of the present analyses in context, univariable Kaplan-Meier curves were constructed for SHS participants excluded from the present analyses because of clinically recognized CVD versus the groups with or without segmental WM abnormalities in the present report and compared by the log-rank method. The null hypothesis was rejected at 2-tailed $P<0.05$. Analyses were performed with SPSS 12.0.

The authors had full access to and take full responsibility for the integrity of the data and performed all reported analyses. All authors have read and agree to the manuscript as written.
Results

Characteristics of Study Population in Relation to WM Abnormalities

A total of 2864 eligible participants (mean age 60±8 years; 1839 women [64%]) with complete baseline WM assessment and without prevalent CVD at the time of echocardiographic examination were included in the present analysis. At echocardiographic evaluation, 140 participants (5%) had segmental WM abnormalities and 42 (1.5%) had global WM abnormalities. Among participants with segmental WM abnormalities, 105 (75%) had mild hypokinesia in at least 2 contiguous segments in a coronary territory, 23 (17%) had moderate hypokinesia, and 12 (8%) had severe hypokinesia, akinesia, or dyskinesia. Similarly, among participants with global WM abnormality, hypokinesia was classified as mild in 34 participants (82%), moderate in 4 (10%), and severe in 4 (8%).

Clinical characteristics of the study population are reported in Table 1. Participants with WM abnormalities were more likely to be male; had higher mean C-reactive protein, fibrinogen, and creatinine; and were more likely to have microalbuminuria or macroalbuminuria than participants with normal WM. Progressively higher mean LV mass and lower LV ejection fraction were observed in participants with segmental and global WM abnormalities than in those with normal WM. Body mass index was lower in participants with segmental WM abnormalities than in those with normal or global WM abnormality. Participants with segmental WM abnormalities had higher systolic, diastolic, and pulse pressures and higher prevalence of diabetes mellitus than participants with normal WM. The average time from the echocardiographic examination to the first cardiovascular event or to the end of follow-up in the present study cohort was 8.2±2.2 years.

Prognostic Impact of Segmental WM Abnormalities

The cumulative incidences of combined fatal and nonfatal cardiovascular events and of cardiovascular mortality were

<table>
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<th>Variable</th>
<th>Normal WM (n=2684)</th>
<th>Segmental WM Abnormalities (n=140)</th>
<th>Global WM Abnormalities (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, %</td>
<td>35</td>
<td>50§</td>
<td>63§</td>
</tr>
<tr>
<td>Age, y</td>
<td>59±8</td>
<td>61±8</td>
<td>58±8</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>31.3±6.2</td>
<td>29.0±5.9§</td>
<td>32.4±8.7</td>
</tr>
<tr>
<td>Waist/hip ratio, %</td>
<td>96±6</td>
<td>95±6</td>
<td>96±5</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>129±19</td>
<td>135±27†</td>
<td>129±20</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>75±10</td>
<td>78±10*</td>
<td>78±11</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>54±16</td>
<td>58±22*</td>
<td>52±17</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>45</td>
<td>56*</td>
<td>45</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>31</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>190±39</td>
<td>185±41</td>
<td>181±44</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>119±34</td>
<td>114±34</td>
<td>115±34</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>42±13</td>
<td>41±15</td>
<td>40±13</td>
</tr>
<tr>
<td>C-reactive protein, mg/dL</td>
<td>3.8 (2.0–7.0)</td>
<td>4.4 (2.0–8.1)*</td>
<td>5.5 (2.7–11.2)§</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>358±80</td>
<td>379±105*</td>
<td>392±81†</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.9±0.7</td>
<td>1.6±2.1§</td>
<td>1.4±1.6§</td>
</tr>
<tr>
<td>Microalbuminuria, %</td>
<td>21</td>
<td>29*</td>
<td>15</td>
</tr>
<tr>
<td>Macroalbuminuria, %</td>
<td>10</td>
<td>26§</td>
<td>28§</td>
</tr>
<tr>
<td>LV mass, g/m².⁷</td>
<td>40.4±9.4</td>
<td>47.7±16.2§</td>
<td>50.7±13.8§</td>
</tr>
<tr>
<td>Ejection fraction, % (by Teichholz formula)</td>
<td>64.8±6.4</td>
<td>50.9±11.7§</td>
<td>45.3±7.5§</td>
</tr>
<tr>
<td>0.45–0.54, n (%)</td>
<td>30 (1)</td>
<td>41 (25)</td>
<td>36 (60)</td>
</tr>
<tr>
<td>0.35–0.44, n (%)</td>
<td>5 (0.1)</td>
<td>21 (13)</td>
<td>6 (10)</td>
</tr>
<tr>
<td>≥0.34, n (%)</td>
<td>0 (0)</td>
<td>8 (5)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Cardiac medications, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>17</td>
<td>20</td>
<td>29§</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>19</td>
<td>19</td>
<td>23</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>5</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Diuretic</td>
<td>12</td>
<td>15</td>
<td>25§</td>
</tr>
<tr>
<td>Calcium blocker</td>
<td>10</td>
<td>16</td>
<td>14</td>
</tr>
</tbody>
</table>

Data are mean±SD, percentage, or median (interquartile range).

*P<0.05, †P<0.001, ‡P<0.005, §P<0.0001 vs group with normal WM.

P<0.05, #P<0.0001 vs group with global WM abnormalities.
2.5- to 3-fold higher in participants with segmental WM abnormalities than in those with normal WM (both $P<0.0001$; Table 2). Participants with segmental WM abnormalities also had higher cumulative incidences of each of the component end points.

In univariable Cox models, segmental WM abnormalities (Table 2; Figures 1 and 2) were associated with more frequent occurrence over time of both first cardiovascular events and cardiovascular death. These associations were confirmed after adjustment for age, gender, waist-hip ratio, systolic blood pressure, and diabetes mellitus (Table 2). Of note, tests of interaction were not significant between segmental WM abnormalities and gender ($P=0.30$ and 0.06), diabetes mellitus ($P=0.87$ and 0.09), or hypertension ($P=0.99$ and 0.36) for cardiovascular events and cardiovascular mortality.

Additional analyses were performed with inclusion of additional markers of risk for CVD (current cigarette smoking, total/high-density lipoprotein cholesterol, and serum creatinine). In these models, segmental WM abnormalities remained a significant predictor of first cardiovascular event (HR 1.9, 95% CI 1.3 to 2.7, $P=0.001$) but not of cardiovascular mortality (HR 1.5, 95% CI 0.8 to 2.7, $P>0.20$). The c statistic was 0.70 for the Cox model for first cardiovascular events with segmental WM, which indicates good discrimination ability and was modestly higher than the c statistic of 0.69 for the model without WM abnormalities. Additionally, comparison between $-2 \log$ likelihood values demonstrated that the likelihood of cardiovascular events was significantly higher in the model including than in the model excluding WM abnormalities ($P<0.0001$). In a further model that added microalbuminuria and LV mass index (as markers of preclinical CVD) to the previous covariates, the association of WM abnormalities with total cardiovascular events was not altered substantially (HR 2.0, 95% CI 1.4 to 2.9, $P<0.0001$). Finally, the further addition of C-reactive protein and fibrinogen (previously found to be associated with cardiovascular outcomes in this population-based cohort$^{28–30}$ to the model did not significantly change the association between segmental WM abnormalities and cardiovascular events (HR 2.0, 95% CI 1.4 to 2.9, $P<0.001$).

LV ejection fraction was also entered into the regression model that accounted for gender, age, waist-hip ratio, systolic

---

**TABLE 2. Cumulative Incidence and HRs of All Cardiovascular Events and Cardiovascular Death in Participants With or Without Segmental WM Abnormalities**

<table>
<thead>
<tr>
<th>End Point</th>
<th>Normal WM, Cumulative Incidence</th>
<th>Segmental WM Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate* No. (%)</td>
<td>Rate* No. (%)</td>
</tr>
<tr>
<td>Cardiovascular events</td>
<td>27.4 (18.0)</td>
<td>91.0 (42.1)</td>
</tr>
<tr>
<td>Single components</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>7.1 (5.4)</td>
<td>16.1 (11.4)</td>
</tr>
<tr>
<td>Stroke</td>
<td>3.1 (2.4)</td>
<td>5.5 (4.3)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>12.1 (8.8)</td>
<td>28.5 (18.6)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>5.2 (4.0)</td>
<td>16.1 (11.4)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>7.5 (5.6)</td>
<td>28.5 (18.6)</td>
</tr>
</tbody>
</table>

*Per 1000 patient-years of follow-up.†Models adjusted for age, gender, waist-hip ratio, systolic blood pressure, diabetes mellitus, and global dysfunction.

---

**Figure 1.** Kaplan-Meier plot of cumulative cardiovascular events according to presence or absence of segmental LV WM abnormalities.

**Figure 2.** Kaplan-Meier plot of cumulative cardiovascular mortality according to presence or absence of segmental LV WM abnormalities.
blood pressure, diabetes mellitus, and segmental WM abnormalities. In this model, segmental WM abnormality was still associated with a 1.9-fold increased risk of first cardiovascular events (95% CI 1.3 to 2.8, \(P=0.001\)), independently of low ejection fraction (HR = 1.5 for ejection fraction < 0.55 versus normal values, 95% CI 1.1 to 2.0, \(P=0.006\)).

In a separate analysis, the outcomes of the studied subgroups with or without WM abnormalities were compared with participants with prevalent CVD who were excluded from the primary analyses of the present study. Compared with subjects without prevalent CVD who had normal WM, the risks of cardiovascular events or cardiovascular death were > 3-fold higher in participants without prevalent CVD who had WM abnormalities (\(P<0.0001\)) and > 5-fold higher in participants with prevalent CVD (\(P<0.0001\); Figures 3 and 4).

**Prognostic Impact of Global WM Abnormalities.** Similar to segmental WM abnormalities, first cardiovascular events and cardiovascular death were 2.2-fold and 2.7-fold more frequent in participants with global WM abnormalities than in those with normal WM (both \(P<0.005\); Table 3). These associations were confirmed after adjustment for age, gender, waist/hip ratio, systolic blood pressure, and diabetes mellitus (Table 3). When ejection fraction was entered into the previous regression models, the risks of first cardiovascular event and cardiovascular mortality associated with global WM abnormalities did not retain statistical significance (both \(P=NS\)), whereas low ejection fraction did (HR 3.1, 95% CI 2.4 to 3.9 and HR 3.6, 95% CI 2.4 to 5.4, respectively; both \(P<0.0001\)).

**Discussion**
The present study demonstrates for the first time that echocardiographic detection of LV WM abnormalities in unscreened adults without clinically recognized CVD identifies a subgroup at intermediate risk of subsequent cardiovascular events and cardiovascular death between participants with prevalent CVD and those with neither recognized CVD nor abnormal WM. This finding is made more striking by the fact that it was obtained in a population-based cohort rather than in a group of clinical patients in whom echocardiographic evaluation could have been prompted by nonspecific symptoms.

**Prevalence and Correlates of WM Abnormalities**
The present study detected segmental and global WM abnormalities in 5% and 2%, respectively, of adults without known CVD. Gardin et al identified\(^{31}\) segmental WM abnormalities in 5.5% of a population of predominantly white adults aged 65 to 69 years and in 1.9% of a subset of participants with...
neither ischemic heart disease nor hypertension in the Cardiovascular Health Study. The present study included hypertensive individuals but identified segmental or global WM abnormalities in 3.6% and 1.4% of normotensive participants, respectively. Consistent with the present findings, Gardin et al. found WM abnormalities to be more common in men and in hypertensive participants. In the present study, segmental WM abnormalities were associated with the presence of diabetes mellitus. These results are consistent with previous observations from the SHS of an association of abnormal global LV function with diabetes mellitus. Adults with segmental LV dysfunction had lower body mass index than participants with normal or globally abnormal LV function. This association persisted after adjustment for difficulty of echocardiographic imaging, which is consistent with the previously reported association between LV systolic dysfunction and reduction of body mass index in participants with LV dysfunction.22

The present study also documented associations of both segmental and global WM abnormalities with measures of preclinical CVD, including elevated LV mass index and albuminuria. Moreover, levels of fibrinogen and C-reactive protein, markers of inflammation that predict incident cardiovascular events and death in population-based cohorts, were higher in participants with WM abnormalities, but this did not affect the increased likelihood of cardiovascular events associated with WM abnormalities.

### WM Abnormalities and Prediction of Cardiovascular Outcome

The relation of segmental WM abnormalities to cardiovascular events has been demonstrated previously in acute ischemic heart disease3–6 and CHF.7 Moller et al. recently confirmed that regional WM abnormalities assessed immediately after an acute MI independently predict death and hospitalization for CHF. The present study extends these observations by demonstrating that WM abnormalities also predict subsequent clinical cardiovascular events in an elected population of adults without recognized CVD. Of note, the rates of cardiovascular events and cardiovascular death in participants with WM abnormalities but without clinically recognized CVD were closer to the rates in individuals excluded from the present study because of prevalent CVD than to the rates detected in participants without overt CVD who had normal LV WM.

In the relatively normal clinical conditions found in the present study population, incidentally detected WM abnormalities can be related to transient ischemic dysfunction, myocardial scar, stunning/hibernation, cardiomyopathy, or different combinations of these conditions. In particular, epidemiological studies have established that a number of MIs (from 5% to as many as 20% in reports from Framingham) go undetected at the time of occurrence.36–38 In a previous report, indirect ECG evidence of clinically unrecognized MI predicted subsequent cardiovascular events, but assessment of LV WM was unavailable in that study.36 In addition, previous studies suggest that the long-term cardiovascular prognosis of individuals with silent MI may be similar to that of subjects with recognized MI.39–43 Individuals with ECG Q waves, the most commonly used method to detect unrecognized MIs, have been excluded from the present analysis, but this would not rule out all silent MIs, because imaging studies have greater sensitivity for detecting transmural or partial-thickness scar than do ECG Q waves.44,45

Detection of segmental LV WM abnormality improved risk stratification even after adjustment for the effect of low LV ejection fraction in the present analyses. Consistent with the present observation, regional WM abnormality was found to be more important than global LV systolic function for predicting adverse cardiovascular events in patients receiving thrombolytic therapy for ST-elevation MI.4,35,47 In the present study, segmental WM abnormality predicted cardiovascular outcome independent of level of ejection fraction, consistent with the presence of normal global LV ejection fraction in nearly 60% of SHS participants with segmental WM abnor-

### TABLE 3. Cumulative Incidence and HRs of All Cardiovascular Events and Cardiovascular Death in Participants With Global WM Abnormalities

<table>
<thead>
<tr>
<th>End Points</th>
<th>Rate*</th>
<th>No. (%)</th>
<th>Unadjusted HR (95% CI)</th>
<th>P</th>
<th>Adjusted HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular events</td>
<td>60.2</td>
<td>13 (32.5)</td>
<td>2.2 (1.3–3.8)</td>
<td>0.003</td>
<td>2.4 (1.4–4.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Single components</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>6.6</td>
<td>2 (5.0)</td>
<td>1.1 (0.4–3.5)</td>
<td>0.87</td>
<td>1.0 (0.3–3.2)</td>
<td>0.97</td>
</tr>
<tr>
<td>Stroke</td>
<td>3.2</td>
<td>1 (2.5)</td>
<td>3.1 (1.0–10.0)</td>
<td>0.06</td>
<td>3.1 (1.0–9.8)</td>
<td>0.06</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>22.1</td>
<td>6 (15.0)</td>
<td>2.1 (1.1–4.2)</td>
<td>0.04</td>
<td>1.9 (0.9–3.9)</td>
<td>0.07</td>
</tr>
<tr>
<td>Heart failure</td>
<td>10.1</td>
<td>3 (7.5)</td>
<td>2.9 (1.4–6.3)</td>
<td>0.006</td>
<td>3.1 (1.5–6.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>17.9</td>
<td>5 (12.5)</td>
<td>2.7 (1.2–6.1)</td>
<td>0.017</td>
<td>3.4 (1.5–7.7)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*Per 1000 patient-years of follow-up.
†Models adjusted for age, gender, waist-hip ratio, systolic blood pressure, diabetes mellitus, and segmental WM abnormalities.
‡Compared with participants with normal WM (data in Table 2).
Wall-Motion Abnormalities and Prognosis

42. Kwong RY, Chan AK, Brown KA, Chan CW, Reynolds HG, Tsang S, Davis RB. Impact of unrecognized myocardial scar detected by cardiac magnetic resonance imaging on event-free survival in patients presenting with signs or symptoms of coronary artery disease. Circulation. 2006;113:2733–2743.

**CLINICAL PERSPECTIVE**

In the Strong Heart Study, a large, population-based study, the prognostic value of echocardiographic left ventricular wall motion (WM) abnormalities was evaluated in 2864 participants without clinically recognizable cardiovascular disease. Relationships between WM abnormalities and fatal and nonfatal cardiovascular events (including myocardial infarction, stroke, coronary artery disease, and heart failure; n=554) and cardiovascular death (n=182) during 8±2 years follow-up were examined. In Cox regression, after adjustment for age, gender, waist/hip ratio, systolic blood pressure, and diabetes mellitus, segmental WM abnormalities were associated with a 2.5-fold higher risk of cardiovascular events and a 2.6-fold higher risk of cardiovascular death (both P<0.0001). In similar multivariable models, global WM abnormalities were associated with a 2.4-fold higher risk of cardiovascular events (P=0.001) and a 3.4-fold higher risk of cardiovascular death (P=0.003). These results demonstrate that echocardiographic left ventricular WM abnormalities in adults without overt cardiovascular disease predict 2- to 3.5-fold higher risks of cardiovascular morbidity and mortality, independent of established risk factors. Thus, detection of regional left ventricular dysfunction by echocardiography, and probably by other techniques, strongly predicts cardiovascular events and death. Given the adverse prognostic of echocardiographic evidence of regional left ventricular dysfunction in adults without established cardiovascular disease, it may be prudent to treat established cardiovascular risk factors in these individuals more intensively. Whether individuals with regional left ventricular dysfunction would benefit from additional evaluation to identify asymptomatic coronary artery disease or early cardiomyopathy requires further study.
Risk of Cardiovascular and All-Cause Mortality in Individuals With Diabetes Mellitus, Impaired Fasting Glucose, and Impaired Glucose Tolerance

The Australian Diabetes, Obesity, and Lifestyle Study (AusDiab)

Elizabeth L.M. Barr, MPH; Paul Z. Zimmet, PhD; Timothy A. Welborn, PhD; Damien Jolley, MSc; Dianna J. Magliano, PhD; David W. Dunstan, PhD; Adrian J. Cameron, MPH; Terry Dwyer, MD; Hugh R. Taylor, MD; Andrew M. Tonkin, MD; Tien Y. Wong, PhD; John McNeil, PhD; Jonathan E. Shaw, MD

Background—Diabetes mellitus increases the risk of cardiovascular disease (CVD) and all-cause mortality. The relationship between milder elevations of blood glucose and mortality is less clear. This study investigated whether impaired fasting glucose and impaired glucose tolerance, as well as diabetes mellitus, increase the risk of all-cause and CVD mortality.

Methods and Results—In 1999 to 2000, glucose tolerance status was determined in 10 428 participants of the Australian Diabetes, Obesity, and Lifestyle Study (AusDiab). After a median follow-up of 5.2 years, 298 deaths occurred (88 CVD deaths). Compared with those with normal glucose tolerance, the adjusted all-cause mortality hazard ratios (HRs) and 95% confidence intervals (CIs) for known diabetes mellitus and newly diagnosed diabetes mellitus were 2.3 (1.6 to 3.2) and 1.3 (0.9 to 2.0), respectively. The risk of death was also increased in those with impaired fasting glucose (HR 1.6, 95% CI 1.0 to 2.4) and impaired glucose tolerance (HR 1.5, 95% CI 1.1 to 2.0). Sixty-five percent of all those who died of CVD had known diabetes mellitus, newly diagnosed diabetes mellitus, impaired fasting glucose, or impaired glucose tolerance at baseline. Known diabetes mellitus (HR 2.6, 95% CI 1.4 to 4.7) and impaired fasting glucose (HR 2.5, 95% CI 1.2 to 5.1) were independent predictors for CVD mortality after adjustment for age, sex, and other traditional CVD risk factors, but impaired glucose tolerance was not (HR 1.2, 95% CI 0.7 to 2.2).

Conclusions—This study emphasizes the strong association between abnormal glucose metabolism and mortality, and it suggests that this condition contributes to a large number of CVD deaths in the general population. CVD prevention may be warranted in people with all categories of abnormal glucose metabolism. (Circulation. 2007;116:151-157.)

Key Words: epidemiology ■ diabetes mellitus ■ mortality ■ risk factors ■ cardiovascular diseases ■ risk factors

It is well established that diabetes mellitus increases the risk of all-cause and cardiovascular disease (CVD) mortality1–7 and that this relationship is independent of traditional cardiovascular risk factors.8–10 Recognition is now growing that even nondiabetic levels of hyperglycemia, as observed in impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), may also be associated with an elevated risk of CVD and premature mortality.11,12

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Evidence for the relationships between IFG, IGT, and all-cause and CVD mortality is primarily derived from a series of large meta-analyses9,10,13; however, several reasons exist to be cautious about interpreting these findings. First, the component studies used different blood sample types (eg, whole blood and plasma) and different glucose assays.9,10,13 Second, some studies did not fully adjust for concomitant CVD risk factors.13 Third, these analyses may have limited relevance to contemporary populations, because baseline data were collected up to 20 years ago.9,10,13 The Australian Diabetes, Obesity, and Lifestyle Study (AusDiab) is a recently conducted national, population-based study of 11 247 adults that provides an opportunity to investigate the contribution of different categories of abnormal glucose metabolism to the risk of all-cause and CVD mortality.

Methods

Baseline measurements for the AusDiab survey were collected in 1999 to 2000 on 11 247 noninstitutionalized people aged ≥25 years.

Continuing medical education (CME) credit is available for this article. Go to http://cme.ahajournals.org to take the quiz.

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From the International Diabetes Institute (E.L.M.B., P.Z.Z., D.J.M., D.W.D., A.J.C., J.E.S.), Caulfield, Victoria, Australia; Department of Medicine (T.A.W.), University of Western Australia, Nedlands, Western Australia; Monash Institute of Health Services Research (D.J.), Clayton, Victoria, Australia; Murdoch Children’s Research Institute (T.D.), Royal Children’s Hospital, Prahran, Victoria, Australia; Centre for Eye Research Australia (H.R.T., T.Y.W.), University of Melbourne, East Melbourne, Victoria, Australia; and Department of Epidemiology and Preventive Medicine (A.M.T., J.M.), Monash University, Prahran, Victoria, Australia.

Correspondence to Elizabeth L.M. Barr, International Diabetes Institute, 250 Kooyong Rd, Caulfield, Victoria, 3162, Australia. E-mail lbarr@idi.org.au

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Methods and response rates have been described previously.14 Briefly, people were recruited from 42 randomly selected urban and nonurban Census Collector Districts, 6 in each of the states and the Northern Territory of Australia. Of the 20,347 eligible people who completed a household interview, 11,247 (55.3%) attended a biomedical examination. Compared with nonresponders, responders to the biomedical examination were equally likely to report “ever being told they had diabetes” (6.2% [95% confidence interval [CI] 5.2% to 7.1%] versus 6.4% [95% CI 5.7% to 7.1%]) but were more likely to have “suspected they had diabetes” (0.5% [95% CI 0.4% to 0.7%] versus 1.5% [95% CI 1.3% to 1.7%]). Data on age, sex, use of antihypertensive and lipid-lowering medications, previous CVD (angina, coronary heart disease, or stroke), and smoking were collected by interviewer-administered questionnaires. Measurements included blood pressure,15 anthropometrics,16 and a fasting (≥9 hours) blood sample. All participants, except for pregnant women and people taking hypoglycemic medication, underwent a 75-g oral glucose tolerance test. Fasting plasma glucose (FPG), 2-hour plasma glucose (2-hour PG), fasting serum total cholesterol, triglycerides, and high-density lipoprotein cholesterol were measured with an Olympus AU600 analyzer (Olympus Optical, Tokyo, Japan). All specimens were analyzed at a central laboratory.

Categories of abnormal glucose metabolism were determined according to the 1999 World Health Organization criteria.17 Participants were classified as having known diabetes mellitus (KDM) if they reported having physician-diagnosed diabetes mellitus and were either taking hypoglycemic medication or had FPG ≥7.0 mmol/L or 2-hour PG ≥11.1 mmol/L. Participants were classified as having newly diagnosed diabetes mellitus but who had FPG ≥7.0 mmol/L or 2-hour PG ≥11.1 mmol/L were classified as having newly diagnosed diabetes mellitus (NDM). Of those classified as having KDM at baseline, 92% had type 2 diabetes mellitus. The results for participants with type 1 and type 2 diabetes mellitus were pooled for the present analysis. Participants determined not to have diabetes mellitus were classified as having either IFG (FPG ≥6.1 and <7.0 mmol/L with 2-hour PG <7.8 mmol/L), IGT (2-hour PG ≥7.8 and <11.1 mmol/L, or normal glucose tolerance (NGT; FPG <6.1 mmol/L and 2-hour PG <7.8 mmol/L).

Mortality status and underlying and contributory causes of death were determined by linking the AusDiab cohort to the Australian National Death Index (NDI). Name, sex, date of birth, state, date of last contact, and date of death (if available) were used to match participants to the NDI. The accuracy of the NDI for ascertainment of CVD deaths and vital status has been established previously.18 Only high-level matches were accepted as confirmed deaths, and wherever possible, deaths were confirmed by direct communication with the decedent’s family. People who were not matched to the NDI were assumed to be alive. Deaths were attributed to CVD if the underlying cause of death was coded I10-I25, I46.1, I48, I50-I99, or R96 according to the 2006 International Classification of Diseases 10th revision (ICD-10). In addition, participants with uncomplicated diabetes mellitus (ICD-10 codes E109, E119, or E149) or unspecified hyperlipidemia (ICD-10 code E785) as an underlying cause of death on the death certificate were assumed to be alive. Deaths were attributed to CVD if the smaller number of CVD deaths. Deaths due to non-CVD causes are a competing risk for CVD mortality, and therefore we also investigated the risk (HR and 95% CI) of non-CVD mortality for the groups with different abnormalities of glucose tolerance compared with NGT. Variables significant in univariate analysis at the 25% level were entered into the multivariate model. In addition, other variables known to be confounders were included in the model. Multicollinearity between covariates was examined by calculating the mean and individual covariate variance inflation factors. None of the individual covariate variance inflation factors were greater than 2, and the mean variance inflation factors for all covariates included in the all-cause and CVD mortality models were 1.25 and 1.22, respectively. For all-cause mortality, we controlled for age, sex, previous CVD (angina, coronary heart disease, or stroke), smoking (including current or ex-smokers), hypertension (blood pressure ≥140/90 mm Hg or antihypertensive medication use), waist circumference, lipid-lowering medication use, and total cholesterol-high density lipoprotein cholesterol ratio. For CVD mortality, we controlled for the same covariates, except diastolic blood pressure was included rather than hypertension because it showed a stronger relationship with CVD mortality. For non-CVD mortality, we controlled for age, sex, smoking, waist:hip ratio, and previous CVD. The contribution of each covariate to the model was tested by χ² log-likelihood analysis. The assumptions required for proportional hazards were met, and these were assessed with graphs of log-log plots of the relative hazards by time and scaled Schoenfeld residuals. Analyses were conducted with SPSS version 14.0 (SPSS, Chicago, Ill) and Stata Statistical Software version 9.2 (StataCorp, College Station, Tex).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Baseline Characteristics According to Categories of Abnormal Glucose Metabolism

The AusDiab study comprises 11,247 participants. These analyses are based on 10,428 participants (93%) who had complete data for the variables under investigation. Table 1 shows that compared to those with NGT, the other categories of abnormal glucose metabolism (ie, IFG, IGT, NDM, and KDM) generally had worse risk factor profiles.

All-Cause and CVD Mortality

Over a median follow-up of 5.2 years, 298 deaths occurred (180 in males), which represents an all-cause mortality rate of 5.5 per 1000 person-years. Of those who had KDM, 11.8% had died within the follow-up period. By comparison, 6.2% who had NDM, 5.2% who had IGT, 3.9% who had IFG, and 1.7% who had NGT at baseline had died. For women, the proportions of those deceased were 9.8%, 5.6%, 4.2%, 3.2%, and 1.1%, and for men, the proportions were 13.4%, 6.9%, 6.6%, 4.3%, and 2.5% for KDM, NDM, IGT, IFG, and NGT, respectively. Figure 1 shows the unadjusted all-cause mortality HR (95% CI) for IFG, IGT, NDM, and KDM compared with NGT according to baseline age. In those aged 25 to 44 years, no deaths occurred among those with NDM or KDM, and although the risk of death was elevated in IFG and IGT,
the CIs were wide owing to the small number of deaths in this age group. In those aged 45 to 65 years, the risk of all-cause mortality increased steadily across the glucose tolerance categories. In people aged ≥65 years, the pattern was less consistent, but the risk of death was highest in those with KDM (HR 2.6, 95% CI 1.8 to 3.7). Similar patterns remained consistent, but the risk of death was highest in those with KDM and IFG, but not IGT, compared with NGT.

The risk of CVD mortality was also significantly greater for those with IGT and IFG had a 50% to 60% greater mortality risk. Persons with KDM had a mortality risk that was more than 2 times greater than those with NGT, and those with IGT and IFG had a 50% to 60% greater mortality risk. The risk of CVD mortality was also significantly greater for those with KDM and IFG, but not IGT, compared with NGT.

Finally, the importance of abnormal glucose metabolism to the risk of CVD mortality is supported by the present finding that 65% of all CVD deaths occurred in people with abnormal glucose metabolism at baseline.

The unadjusted cumulative incidence of all-cause mortality (Figure 2A) and CVD mortality (Figure 2B) for NGT, IFG, IGT, NDM, and KDM is outlined in Figure 2. Table 2 shows the adjusted HR (95% CI) for IFG, IGT, NDM, and KDM compared with NGT. The risk of total and CVD mortality was increased for all categories of abnormal glucose metabolism, although this was not significant for NDM for all-cause and CVD mortality or for IGT for CVD mortality.

When stratified by sex, the risk of all-cause mortality for IFG, IGT, NDM, and KDM compared with NGT was similar for men and women (data not shown). However, because stratification by sex decreased the statistical power for the analyses, for women, only IGT (HR = 1.7, 95% CI 1.1 to 2.8) and KDM (HR = 2.5, 95% CI 1.4 to 4.3) and for men, only KDM (HR = 2.1, 95% CI 1.3 to 3.2) remained significant predictors of all-cause mortality after controlling for other covariates.

**Noncardiovascular Mortality**

Of the 260 participants for whom cause-specific mortality data were available, 172 (66.2%) were classified as non-CVD deaths, of which 102 (59.3%) were attributed to malignant neoplasm (ICD-10 codes C00–C97). Compared with NGT, the HRs (95% CIs) for non-CVD mortality were 2.3 (1.5 to 3.6) for KDM, 1.0 (0.5 to 1.9) for NDM, 1.6 (1.1 to 2.3) for IGT, and 1.3 (0.7 to 2.3) for IFG, after adjustment for age and sex. These associations remained unchanged after the inclusion of smoking, waist:hip ratio, and previous CVD in the model.

**Discussion**

The primary findings from this large, national, population-based cohort study indicate that after adjustment for the traditional CVD risk factors, the 5-year mortality from all causes was significantly greater for KDM, IFG, and IGT than for NGT. Persons with KDM had a mortality risk that was more than 2 times greater than those with NGT, and those with IGT and IFG had a 50% to 60% greater mortality risk. The risk of CVD mortality was also significantly greater for those with KDM and IFG, but not IGT, compared with NGT.

Finally, the importance of abnormal glucose metabolism to the risk of CVD mortality is supported by the present finding that 65% of all CVD deaths occurred in people with KDM, NDM, IFG, or IGT at baseline.

Experimental studies have long indicated that abnormal glucose metabolism increases the likelihood of macrovascular disease because it disrupts normal endothelial function, accelerates atherosclerotic plaque formation, and contributes to plaque rupture and subsequent thrombosis.19 In addition, the risk attributed to other CVD risk factors such as hypertension and dyslipidemia may be compounded by the presence of abnormal glucose metabolism.19

There have been many studies that have demonstrated that diabetes mellitus is an important risk factor for both all-cause and CVD mortality.1–7 The present finding of a strong

**TABLE 1. Baseline Characteristics According to Categories of Abnormal Glucose Metabolism: the AusDiab Study**

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>NGT</th>
<th>IFG</th>
<th>IGT</th>
<th>NDM</th>
<th>KDM</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>10 428</td>
<td>7662</td>
<td>610</td>
<td>1298</td>
<td>433</td>
<td>425</td>
</tr>
<tr>
<td>Age, y</td>
<td>51.4 (14.2)</td>
<td>48.8 (13.6)</td>
<td>53.9 (12.6)</td>
<td>58.5 (13.8)</td>
<td>61.5 (13.0)</td>
<td>63.6 (11.8)</td>
</tr>
<tr>
<td>Male</td>
<td>4711 (45.2)</td>
<td>3310 (43.2)</td>
<td>423 (69.3)</td>
<td>528 (40.7)</td>
<td>219 (50.6)</td>
<td>231 (54.4)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.0 (5.0)</td>
<td>26.2 (4.5)</td>
<td>28.7 (4.7)</td>
<td>28.7 (5.5)</td>
<td>30.0 (6.0)</td>
<td>30.0 (6.2)</td>
</tr>
<tr>
<td>Waist:hip ratio</td>
<td>0.87 (0.09)</td>
<td>0.85 (0.09)</td>
<td>0.92 (0.08)</td>
<td>0.89 (0.09)</td>
<td>0.92 (0.09)</td>
<td>0.93 (0.08)</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>90.9 (13.9)</td>
<td>88.4 (13.0)</td>
<td>98.3 (12.3)</td>
<td>95.5 (13.7)</td>
<td>100.7 (14.7)</td>
<td>101.7 (14.6)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>129.4 (18.7)</td>
<td>126.1 (17.3)</td>
<td>134.0 (17.1)</td>
<td>137.5 (19.3)</td>
<td>144.3 (19.3)</td>
<td>143.6 (20.8)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>70.2 (11.8)</td>
<td>69.0 (11.4)</td>
<td>74.1 (11.3)</td>
<td>72.3 (12.1)</td>
<td>75.5 (12.7)</td>
<td>73.5 (12.0)</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>3388 (32.5)</td>
<td>1844 (24.1)</td>
<td>262 (43.0)</td>
<td>687 (52.9)</td>
<td>297 (68.6)</td>
<td>298 (70.1)</td>
</tr>
<tr>
<td>TC, mmol/L</td>
<td>5.66 (1.07)</td>
<td>5.60 (1.05)</td>
<td>5.90 (1.09)</td>
<td>5.87 (1.08)</td>
<td>5.94 (1.11)</td>
<td>5.41 (0.96)</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.42 (0.38)</td>
<td>1.45 (0.38)</td>
<td>1.31 (0.35)</td>
<td>1.40 (0.39)</td>
<td>1.30 (0.39)</td>
<td>1.26 (0.36)</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.28 (0.89, 1.90)</td>
<td>1.17 (0.81, 1.70)</td>
<td>1.55 (1.05, 2.24)</td>
<td>1.60 (1.10, 2.28)</td>
<td>1.90 (1.30, 2.90)</td>
<td>1.77 (1.20, 2.54)</td>
</tr>
<tr>
<td>Lipid-lowering medication use</td>
<td>902 (8.6)</td>
<td>440 (5.7)</td>
<td>80 (13.1)</td>
<td>159 (12.2)</td>
<td>71 (16.4)</td>
<td>152 (35.8)</td>
</tr>
<tr>
<td>Previously reported CVD†</td>
<td>845 (8.1)</td>
<td>443 (5.8)</td>
<td>67 (11.0)</td>
<td>143 (11.0)</td>
<td>70 (16.2)</td>
<td>122 (28.7)</td>
</tr>
<tr>
<td>Smoker‡</td>
<td>4706 (45.1)</td>
<td>3356 (43.8)</td>
<td>327 (53.6)</td>
<td>577 (44.5)</td>
<td>206 (47.6)</td>
<td>240 (56.5)</td>
</tr>
</tbody>
</table>

Data are mean (SD), n (%), or median (25th, 75th percentile). Significant differences (P < 0.001) between categories of abnormal glucose metabolism were observed for all baseline characteristics. TC indicates total cholesterol.

*Hypertension defined as blood pressure ≥140/90 mm Hg or use of antihypertensive medication.
†CVD defined as previously reported angina, coronary heart disease, or stroke.
‡Smoker defined as either current or ex-smoker.
association between KDM and mortality is consistent with these data. However, we did not find a significant association between NDM and all-cause or CVD mortality, although after adjustment for known risk factors, NDM was associated with a 30% increased risk (HR 1.3, 95% CI 0.9 to 2.0) for all-cause mortality, and an 80% increased risk (HR 1.8, 95% CI 0.9 to 3.6) for CVD mortality. This may have been due to the relatively small number of deaths among those in the NDM group (n = 27) over the 5-year follow-up period. Even though risk is greater in those who have been diagnosed with diabetes mellitus for a longer period of time, other longer-term studies have reported that people identified with NDM are also at significantly greater risk for both all-cause and CVD mortality.8,9,20 Fewer studies have investigated the impact of IGT and IFG on all-cause and CVD mortality,2,8,20–23 with most of the evidence derived from large meta-analyses that combined results from a number of diverse populations (occupation- and population-based samples).9,10,13 The DECODE (Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe) and DECODA (Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Asia) meta-analyses reported that IGT, not IFG, was a strong predictor of all-cause mortality and CVD mortality. The differences between the present study data and the DECODE and DECODA analyses could reflect different study methods. The DECODE and DECODA meta-analyses compared the IFG group with people without IFG, whereas the comparison group in the present study consisted of people who had both “normal” FPG (<6.1 mmol/L) and 2-hour PG (<7.8 mmol/L) values, which allowed better discrimination of mortality risk between those with IFG and NGT. Furthermore, these meta-analyses relied on different blood glucose samples (eg, whole blood and plasma) and analyzed the glucose measurements with different assays. This meant that glucose values obtained from whole blood had to be manipulated statistically before the results were pooled with the plasma glucose results. Consequently, this could have influenced the precision of the results reported in the studies. The AusDiab study used a single assay to analyze all plasma glucose samples, and analyses were performed in a central laboratory according to standardized criteria.

In contrast with the findings from DECODE,9 DECODA,10 and Coutinho et al11 that showed a significant positive
relationship between IGT and CVD mortality, we found that IGT was only a significant predictor for all-cause mortality, not for CVD mortality. This may be largely explained by our observation that IGT was significantly associated with non-CVD mortality. Although our ability to investigate the specific non-CVD causes of death was limited by inadequate sample size, it is possible to infer that in the present study cohort, IGT may increase the risk of cancer mortality, because the underlying cause for the majority (59.3%) of non-CVD deaths was attributable to malignant neoplasm. This concurs with the findings reported by other studies.21,24,25 Other explanations include the possibility that the effects of IGT on CVD mortality may be mediated by the clustering of hypertension, dyslipidemia, and hyperglycemia rather than by hyperglycemia per se, although the age- and sex-adjusted CVD mortality rates also were not higher in participants with IGT. Misclassification of IGT status due to single oral glucose tolerance test to determine the participants’ glucose metabolism status, and therefore, misclassification may have occurred. The use of self-reported CVD as a covariate may also represent some measurement error; however, studies conducted in community-based populations have found self-reported myocardial infarction,32–34 stroke,32–35 and ischemic heart disease33 to be moderately to highly accurate in determining disease status. Furthermore, to account for CVD event measurement error, other covariates associated with CVD, such as age, sex, hypertension, lipids, lipid-lowering medication use, and waist circumference, were also included in the multivariante models. Misclassification of death status and cause of death was also possible, because these outcomes were determined through matching the cohort to the NDI, which is derived from death certificate data. However, a previous study has shown that the ascertainment of vital status and CVD deaths through the NDI is robust, with sensitivity and specificity for the identification of deaths being 93.7% and 100%, respectively, and sensitivity and specificity for CVD deaths being 92.5% and 89.6%, respectively.18 Inadequate statistical power as a result of the shorter follow-up period has also limited our ability to conduct further stratified analyses at this time, although it is planned that this will be explored after a longer follow-up period.

In summary, this large, contemporary, population-based cohort study provides further data on the relationship between abnormal glucose metabolism and CVD and all-cause mortality. These findings suggest that strategies to prevent premature mortality, particularly CVD death, need to be

### TABLE 2. HRs (95% CIs) for All-Cause and CVD Mortality According to Categories of Abnormal Glucose Metabolism: the AusDiab Study

<table>
<thead>
<tr>
<th>Category</th>
<th>Deaths, n (%)</th>
<th>Mortality Risk, HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Age and Sex Adjusted</td>
<td>Multivariate Adjusted*</td>
</tr>
<tr>
<td>NGT</td>
<td>130 (1.7)</td>
<td>1.0</td>
</tr>
<tr>
<td>IFG</td>
<td>24 (3.9)</td>
<td>1.6 (1.0–2.5)</td>
</tr>
<tr>
<td>IGT</td>
<td>67 (5.2)</td>
<td>1.4 (1.1–2.0)</td>
</tr>
<tr>
<td>NDM</td>
<td>27 (6.2)</td>
<td>1.4 (0.9–2.1)</td>
</tr>
<tr>
<td>KDM</td>
<td>50 (11.8)</td>
<td>2.5 (1.8–3.5)</td>
</tr>
<tr>
<td>CVD mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NGT</td>
<td>31 (0.4)</td>
<td>1.0</td>
</tr>
<tr>
<td>IFG</td>
<td>10 (1.6)</td>
<td>2.9 (1.4–5.9)</td>
</tr>
<tr>
<td>IGT</td>
<td>16 (1.2)</td>
<td>1.3 (0.7–2.3)</td>
</tr>
<tr>
<td>NDM</td>
<td>12 (2.8)</td>
<td>2.2 (1.1–4.4)</td>
</tr>
<tr>
<td>KDM</td>
<td>19 (4.5)</td>
<td>3.4 (1.9–6.0)</td>
</tr>
</tbody>
</table>

*For all-cause mortality, adjusted for age, sex, previously reported CVD, smoking (current or ex-smoker), hypertension (blood pressure ≥140/90 mm Hg or use of antihypertensive medication), waist circumference (cm), lipid-lowering medication use, and total cholesterol:high-density lipoprotein cholesterol ratio. For CVD mortality, adjusted for age, sex, previously reported CVD, smoking (current or ex-smoker), diastolic blood pressure (mm Hg), waist circumference (cm), lipid-lowering medication use, and total cholesterol:high-density lipoprotein cholesterol ratio.

IFG and IGT are genuine risk factors for mortality and not just precursors of diabetes mellitus. These findings are consistent with the presence of a continuous relationship between increasing blood glucose and increased risk of CVD and all-cause mortality.13,26,27 Several studies have shown that abnormal glucose metabolism is present in approximately two thirds of patients with acute myocardial infarction or coronary artery disease.28–30 However, it is difficult to generalize some of these results to the wider community because they are derived from clinic- and hospital-based populations and are subject to survivor bias. Furthermore, the cross-sectional nature of the studies limits conclusions about causality. The present study extends this previous work, because our longitudinal, population-based data showed that 65% of all CVD deaths occurred in those with diabetes mellitus, IFG, or IGT at baseline. This figure of 65% is far higher than the prevalence observed in the general population aged ≥25 years (reported to be 24%) and is also higher than the prevalence of abnormal glucose metabolism (reported to be 53%) seen in Australian adults aged ≥75 years.31 This suggests that the public health benefits of targeting CVD prevention toward those with “prediabetes” and diabetes mellitus would be significant.

The findings of the present study need to be considered within the context of its limitations. The differences between responders and nonresponders indicate that the cohort may not have been fully representative of Australian adults; however, these differences are unlikely to affect the strength of the relationships between glucose tolerance categories and mortality. The present study has relied on the results of a single oral glucose tolerance test to determine the participants’ glucose metabolism status, and therefore, misclassification may have occurred. The use of self-reported CVD as a covariate may also represent some measurement error; however, studies conducted in community-based populations have found self-reported myocardial infarction,32–34 stroke,32–35 and ischemic heart disease33 to be moderately to highly accurate in determining disease status. Furthermore, to account for CVD event measurement error, other covariates associated with CVD, such as age, sex, hypertension, lipids, lipid-lowering medication use, and waist circumference, were also included in the multivariante models. Misclassification of death status and cause of death was also possible, because these outcomes were determined through matching the cohort to the NDI, which is derived from death certificate data. However, a previous study has shown that the ascertainment of vital status and CVD deaths through the NDI is robust, with sensitivity and specificity for the identification of deaths being 93.7% and 100%, respectively, and sensitivity and specificity for CVD deaths being 92.5% and 89.6%, respectively.18 Inadequate statistical power as a result of the shorter follow-up period has also limited our ability to conduct further stratified analyses at this time, although it is planned that this will be explored after a longer follow-up period.

In summary, this large, contemporary, population-based cohort study provides further data on the relationship between abnormal glucose metabolism and CVD and all-cause mortality. These findings suggest that strategies to prevent premature mortality, particularly CVD death, need to be
targeted not only to people with diabetes mellitus but also toward people with milder forms of abnormal glucose metabolism.

Acknowledgments
We are most grateful to Shirley Murray (AusDiab project manager) and Sue Fourmel (administration) for their invaluable contribution to the study. We would also like to thank Marita Dalton (AusDiab field coordinator 1999–2000), Theresa Whalen, Annaliese Bonney (AusDiab field coordinators 2004–2005), all the AusDiab support staff, and especially the participants for volunteering their time to be involved in the study.

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Disclosures
Dr Welborn is the primary investigator on several obesity studies funded by the National Heart Foundation Australia, is a collaborator on the Asia-Pacific Collaboration on Coronary Heart Disease, has received speaker payments from Novo Nordisk Pharmaceuticals, Eli Lilly and Company, Sanofi-Synthelabo, Aventis Pharma, and Servier, and is an honoree consultant and advisor to the boards of Abbott Australasia, Roche Diagnostics Australia, Sanofi-Synthelabo, and Aventis Pharma. The remaining authors report no conflicts.

References
The findings from this large, national, population-based cohort study indicate that 5-year mortality from all causes is significantly greater for people with previously known diabetes mellitus, impaired fasting glucose, and impaired glucose tolerance than for those with normal glucose tolerance. Persons with known diabetes mellitus had a mortality risk that was more than 2 times greater than for those with normal glucose tolerance, and those with impaired glucose tolerance and impaired fasting glucose had a 50% to 60% greater mortality risk, even after adjustment for age, sex, and other traditional cardiovascular disease risk factors, such as hypertension and hyperlipidemia. The risk of cardiovascular disease mortality was also significantly greater for those with known diabetes mellitus or impaired fasting glucose, but not for those with impaired glucose tolerance, compared to those with normal glucose tolerance. Furthermore, 65% of all cardiovascular disease deaths in the entire population occurred in people who had known diabetes mellitus, newly diagnosed diabetes mellitus, impaired fasting glucose, or impaired glucose tolerance at baseline. These findings suggest that a large number of cardiovascular disease deaths occur in people with abnormal glucose metabolism and that strategies to prevent premature mortality and particularly cardiovascular disease death need to be targeted not only to people with diabetes but also to people with milder forms of abnormal glucose metabolism.

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Favorable Long-Term Outcome After Drug-Eluting Stent Implantation in Nonbifurcation Lesions That Involve Unprotected Left Main Coronary Artery
A Multicenter Registry

Alaide Chieffo, MD; Seung J. Park, MD, PhD; Marco Valgimigli, MD; Young H. Kim, MD, PhD; Joost Daemen, MD; Imad Sheiban, MD; Alessandra Truffa, MD; Matteo Montorfano, MD; Flavio Airoldi, MD; Giuseppe Sangiorgi, MD; Mauro Carlino, MD; Iassen Michev, MD; Cheol W. Lee, MD, PhD; Myeong K. Hong, MD, PhD; Seong W. Park, MD, PhD; Claudio Moretti, MD; Erminio Bonizzoni, PhD; Renata Rogacka, MD; Patrick W. Serruys, MD, PhD; Antonio Colombo, MD

Background—The presence of a lumen narrowing at the ostium and the body of an unprotected left main coronary artery but does not require bifurcation treatment is a class I indication of surgical revascularization.

Methods and Results—A total of 147 consecutive patients who had a stenosis in the ostium and/or the midshaft of an unprotected left main coronary artery (treatment of the bifurcation not required) and were electively treated with percutaneous coronary intervention and sirolimus-eluting stents (n=107) or paclitaxel-eluting stents (n=40) in 5 centres were included in this registry. In 72 patients (almost 50%), intravascular ultrasound guidance was performed. Procedural success was achieved in 99% of the patients; in 1 patient with stenosis in the left main coronary artery ostium, a >30% residual stenosis persisted at the end of the procedure, and the patient was referred for coronary artery bypass graft surgery. During hospitalization, no patients experienced a Q-wave myocardial infarction or died. One patient died 19 days after the procedure because of pulmonary infection. At long-term clinical follow-up (886±308 days), 5 patients had died; 7 patients had target vessel revascularization (5 repeat percutaneous coronary interventions and 2 coronary artery bypass graft surgeries), and of these only 1 patient had a target lesion revascularization. Angiographic follow-up was performed in 106 patients (72%) with a late loss of 0.01 mm. Restenosis in the left main trunk occurred only in 1 patient (0.9%).

Conclusions—Percutaneous coronary intervention with sirolimus-eluting stents or paclitaxel-eluting stents implantation in nonbifurcation left main coronary artery lesions appears safe with a long-term major adverse clinical event rate of 7.4% and a restenosis rate of 0.9%. (Circulation. 2007;116:158-162.)

Key Words: coronary arteries ■ coronary stenosis ■ revascularization ■ stents
The decision to perform PCI instead of surgery was considered when 1 of these 2 conditions was present: (1) suitable anatomy for stenting and preference by patient and by referent physician for a percutaneous approach or (2) suitable anatomy for stenting and disincentive for surgery defined as a EuroSCORE (European system for cardiac operative risk evaluation) ≥6 and/or Parsonnet score ≥13 and/or prior bypass surgery with failure of all conduits (n=2).

Coronary angioplasty and DES implantation were performed according to the practice of complete coverage of the diseased segment.12-15 Our stenting technique in ostium and/or shaft unprotected LMCA has been previously described.16 At the start of the procedure, a bolus of unfractionated heparin (100 IU/kg) was administered to achieve an activated clotting time ≥250 seconds. Glycoprotein IIb/IIIa inhibitors were administered at the discretion of the operator. Clinical follow-up was scheduled for all patients at 1, 6, 12, and 24 months by office visit or direct telephone call to the patients. Patients eligible for longer clinical follow-up were contacted at 36 and 48 months.

Dual antiplatelet therapy (aspirin 100 mg/d and 75 mg/d clopidogrel or 250 mg ticlopidine twice daily) was administered according to local practice (for at least 6 months after the procedure in Rotterdam and Turin and 12 months in Milan and Seoul). All patients were advised to maintain lifelong use of aspirin (100 mg/d).

Angiographic follow-up was scheduled between 4 and 9 months or earlier if noninvasive evaluation or clinical presentation suggested the presence of ischemia.

Definitions

The events analyzed during hospital stay and at long-term clinical follow were death, coronary artery bypass grafting (CABG), myocardial infarction (MI), restenosis, target lesion revascularization (TLR), and target vessel revascularization (TVR). Procedural success was defined as revascularization in the target lesion with <20% residual stenosis according to angiography and with the patient released from the hospital free of any of these events: death, MI, or CABG.

Deaths were classified as either cardiac or noncardiac. Death of unknown cause was adjudicated as cardiac. Non-Q-wave MI was defined as elevation of serum creatine kinase MB isoenzyme that was 3 times the upper limit of normal in the absence of pathological Q waves.

Restenosis was defined as >50% luminal narrowing at the segment site (stent and 5 mm proximal and distal) demonstrated at the follow-up angiographies, regardless of clinical symptoms of the patient. TLR was defined as any revascularization performed on the treated segment; TVR was defined as any reintervention performed on the treated vessel and also included treatment of any segment in left anterior descending and circumflex artery.

Major adverse cardiac events (MACE) were defined as a composite of cardiac death, MI, and TVR.

The Parsonnet score and EuroSCORE were used to stratify the risk of death at 30 days.17,18 The patients were stratified as high risk in the presence of a EuroSCORE ≥6 and/or Parsonnet score ≥13 and/or prior bypass surgery with failure of all conduits.

Statistical Analysis

Continuous data were reported as means or median and interquartile range as appropriate. Event-free survival during follow-up on long-term clinical follow-up (886±308 days) was evaluated according to the Kaplan-Meier method. SAS version 8.2 (SAS Institute, Cary, NC) was used for the analysis.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Baseline clinical, lesion, and procedural characteristics are summarized respectively in Tables 1 and 2. Quantitative coronary angiography measurements are reported in Table 3.

From a total population of 790 patients with unprotected LMCA electively treated in our centers with PCI and DES, 147 patients (18.6%) had ostial and/or shaft left main disease. Twenty-nine patients (19.7%) had diabetes and 64 patients (43.5%) had unstable angina. Mean age was 62.6±12.3 years and left ventricular ejection fraction 55.2±11.3%. Median and interquartile ranges of EuroSCORE and Parsonnet scores were respectively 4 (1 to 7) and 5 (2 to 11.5). Sixty patients (40.8%) were treated because of a EuroSCORE ≥6 and/or Parsonnet score ≥13 (n=58) and/or prior bypass surgery with failure of all conduits (n=2); 87 patients (59.2%) because of patients and referring physician’s preference. In 77 patients the stenosis was located at the ostium, in 41 patients the stenosis was located in the mid-shaft, and in 29 patients the stenosis was located both at the ostium and in the mid-shaft of the LMCA. Fifty-one patients (34.7%) had right coronary artery disease; 22 patients had concomitant right coronary artery treatment. The number of

| TABLE 1. Clinical Characteristics of the Study Population (n=147 Patients) |
|-----------------------------|------------------|
| Age, y                      | 62.6±12.3        |
| Female gender, n (%)        | 56 (38.1)        |
| Hypertension, n (%)         | 84 (57.1)        |
| Hypercholesterolemia, n (%) | 74 (50.3)        |
| Smoking, n (%)              | 45 (30.6)        |
| Diabetes mellitus, n (%)    | 29 (19.7)        |
| Unstable angina, n (%)      | 64 (43.5)        |
| LVEF, %                     | 55.2±11.3        |
| EuroSCORE                   | 4 (1 to 7)       |
| Parsonnet score             | 5 (2 to 11.5)    |
| EuroSCORE ≥6 and/or Parsonnet ≥13, n (%) | 58 (39.4) |
| RCA disease, n (%)          | 51 (34.7)        |
| RCA concomitant treatment, n | 22               |

Continuous data were reported as mean±SD or as median and interquartile range as appropriate. LVEF indicates left ventricular ejection fraction; RCA disease, presence of angiographically critical stenosis in right coronary artery; and RCA concomitant treatment, treatment of right coronary artery stenosis during the index procedure.

| TABLE 2. Lesion and Procedural Characteristics of the Study Population (n=147 Patients) |
|---------------------------------|---------|
| Ostial, n (%)                   | 77 (52) |
| Shaft, n (%)                    | 41 (28) |
| No. of lesions treated          | 1.53±0.7 |
| No. of lesions treated          | 1.86±1.5 |
| IABP, n (%)                     | 3 (2.0) |
| Use of GP IIb/IIIa inhibitors, n (%) | 18 (12.2) |
| IVUS guidance, n (%)            | 72 (48.9) |
| Predilation, n (%)              | 57 (38.7) |
| Cypher stent implantation, n (%) | 107 (72.8) |
| Taxus stent implantation, n (%)  | 40 (27.2) |
| Stent length, mm                | 14.5±7.5 |
| Maximum balloon diameter, mm    | 3.7±0.9  |
| Maximum pressure inflation, atm  | 17.0±4.9 |

Data are presented as percentages, mean±SD, or mm as appropriate. IABP indicates intraaortic balloon pump implantation; GP, glycoprotein.
treated vessels was 1.53±0.7 and the number of lesions 1.86±1.5; in 39 patients (26%) of the patients left anterior descending or circumflex arteries were also treated during the index procedure. An intraaortic balloon pump was used in 3 patients; 18 patients (12.2%) had elective administration of glycoprotein IIb/IIIa inhibitors. In 72 patients (49%) intravascular ultrasonic (IVUS) guidance was performed. Reference vessel diameter of the LMCA was 3.66±0.5 mm. Predilation was performed in 57 patients (38.7%); cutting balloon was used in 11 of these patients. One hundred and seven patients were treated with sirolimus-eluting stents, and 40 patients were treated in 11 of these patients. One hundred and seven patients were treated with paclitaxel-eluting stents. Maximum balloon diameter was performed in 57 patients (38.7%); cutting balloon was used in-stent. MLD indicates minimal lumen diameter.

In-Hospital and Long-Term MACE
In-hospital and long-term clinical outcome are illustrated in Table 4. During hospitalization no patient experienced a Q-wave MI or died. Five patients (3.4%) had a non–Q-wave MI. One patient required elective CABG as a result of an unsuccessful procedure (residual stenosis >20% after stenting). One patient died 19 days after the procedure because of a pulmonary infection. At 886±308 days, 1 patient died of brain tumor, and 4 patients (2.7%) died of unknown causes at 208, 606, 1149, and 1360 days. No cases of angiographically proven stent thrombosis were observed but stent thrombosis could not be excluded in the 4 patients who died of unknown causes. The clinical characteristics of the 4 patients who died of unknown causes are illustrated in Table 5. Seven patients (4.7%) underwent a TVR: 5 repeat PCIs and 2 CABG. In 6 of these 7 patients the intervention was performed on lesions in other coronary segments (left anterior descending and/or circumflex artery). One patient had a TLR because of the occurrence of a restenosis in the shaft of the LMCA. MACE at follow-up occurred in 11 patients (7.4%) (Figure). Angiographic follow-up was performed in 106 patients (73%) with a late loss of −0.01 mm. Restenosis in left main trunk occurred only in 1 patient (0.9%).

Discussion
The main findings of the present study are: (1) DES implantation for ostial and mid-shaft LMCA stenosis that did not require bifurcation treatment appeared to be safe and effective; (2) the MACE rate at 886±308 days was 7.4%; and (3) the restenosis rate in this anatomic subset of patients was 0.9% with a late loss of −0.01 mm.

Current European Society of Cardiology and American Heart Association/American College of Cardiology guidelines consider the presence of a stenosis in the LMCA (if CABG is not eligible) a class IIb or IIa indication of PCI, respectively.2,3 According to these guidelines,3 in cases where CABG is eligible, PCI has a class III indication irrespective of the lesion location. Some retrospective studies that evaluate surgical treatment for this disease reported an in-hospital mortality that varied from 1.7% to 7.0% and a 1-year mortality of 6% to 14%.19–22 Recently, encouraging results have been reported with elective

### TABLE 3. Quantitative Coronary Angiography Measurements

<table>
<thead>
<tr>
<th></th>
<th>Total Population (n=147)</th>
<th>Patients With Angiographic Follow-Up (n=106)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference diameter, mm</td>
<td>3.49±0.5</td>
<td>3.50±0.5</td>
</tr>
<tr>
<td>MLD, mm</td>
<td>1.43±0.5</td>
<td>1.50±0.5</td>
</tr>
<tr>
<td>Stenosis, %</td>
<td>58.6±13</td>
<td>57.2±12</td>
</tr>
<tr>
<td>Lesion length, mm</td>
<td>7.3±4.5</td>
<td>6.9±4.4</td>
</tr>
<tr>
<td><strong>Postprocedure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final reference diameter, mm</td>
<td>3.66±0.5</td>
<td>3.69±0.5</td>
</tr>
<tr>
<td>Final MLD, mm</td>
<td>3.27±0.8</td>
<td>3.29±0.9</td>
</tr>
<tr>
<td><strong>Angiographic follow-up</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference at follow-up, mm</td>
<td>3.60±0.6</td>
<td></td>
</tr>
<tr>
<td>MLD at follow-up, mm</td>
<td>3.34±0.6</td>
<td></td>
</tr>
<tr>
<td>Late loss, mm</td>
<td>−0.01±0.08</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean±SD. All measurements and results are in-stent. MLD indicates minimal lumen diameter.

### TABLE 4. MACE at Hospitalization and at Long-Term Clinical Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>In Hospital</th>
<th>Follow-Up (886±308 Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac death, n (%)</td>
<td>0</td>
<td>4 (2.7)</td>
</tr>
<tr>
<td>Cardiac death in 60 high-risk patients, n (%)</td>
<td>0</td>
<td>4 (6.6)</td>
</tr>
<tr>
<td>Cardiac death in 87 low-risk patients, n (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total death, n (%)</td>
<td>1 (0.7)</td>
<td>5 (3.4)</td>
</tr>
<tr>
<td>Q-wave MI, n (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Non-Q-wave MI, n (%)</td>
<td>5 (3.4)</td>
<td>0</td>
</tr>
<tr>
<td>TLR, n (%)</td>
<td>1 (0.7)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>TVR, n (%)</td>
<td>1 (0.7)</td>
<td>7 (4.7)</td>
</tr>
<tr>
<td>MACE, n (%)</td>
<td>6 (4.0)</td>
<td>11 (7.4)</td>
</tr>
</tbody>
</table>

Data are presented as percentages. The follow-up time is presented as mean±SD. High-risk patients were defined as EuroSCORE ≥6 and/or Parsonnet ≥13 and/or prior bypass surgery with failure of all conduits.

### TABLE 5. Clinical Characteristics of the 4 Patients Who Died of Unknown Causes

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td>76</td>
<td>41</td>
<td>75</td>
<td>84</td>
</tr>
<tr>
<td>Gender</td>
<td>female</td>
<td>male</td>
<td>male</td>
<td>female</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>30</td>
<td>25</td>
<td>40</td>
<td>35</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>EuroSCORE</td>
<td>16</td>
<td>6</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Parsonnet score</td>
<td>34</td>
<td>19</td>
<td>18</td>
<td>26</td>
</tr>
<tr>
<td>Stent type</td>
<td>Taxus</td>
<td>Taxus</td>
<td>Cypher</td>
<td>Cypher</td>
</tr>
<tr>
<td>Angiographic follow-up</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Prescribed duration of dual antiplatelet therapy, mo</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Time of death after procedure, d</td>
<td>208</td>
<td>606</td>
<td>1149</td>
<td>1360</td>
</tr>
</tbody>
</table>
DES implantation in LMCA with a 1-year mortality of 0% to 5%. In these registries, the need for TLR varied from 0% to 14%. Most of the patients included in these series had distal LMCA stenoses that required bifurcation treatment: the frequency of LMCA stenosis at the ostium and/or the shaft that did not involve the distal segment was 6% to 34%. The presence of ostial and mid-shaft lesions in the LMCA was associated with a more favorable outcome and a low restenosis rate, which was significantly higher (8% to 17%) for distal left main lesions, especially with the 2-stent techniques.

No study has been undertaken so far specifically to evaluate PCI with DES in this particular anatomic subset of patients, primarily because of the low frequency of this disease subset. Few data are available on long-term clinical follow-up of patients with unprotected LMCA lesions treated with DES.

Despite the clinical characteristics of the patients (43.5% had unstable angina and almost 40% had a EuroSCORE ≥6 and/or a Parsonnet score ≥13), the occurrence of in-hospital MACE, which included non–Q-wave MI (defined as an elevation of serum creatine kinase MB isoenzyme that was 3 times the upper limit of normal), was low (6.0%). These initially favorable outcomes were maintained at a median of 886 days with a MACE rate of 7.4%. No cases of angiographically proven stent thrombosis were observed, but stent thrombosis could not be excluded in the 4 patients (2.7%) who died of unknown causes (all of them had a left ventricular ejection fraction <40%, a EuroSCORE ≥6, and/or a Parsonnet score ≥13). Therefore, in the worst possible scenario we could assume a cumulative thrombosis rate at a mean of 886 days of 2.7% (95% confidence interval [CI], 1 to 7).

Seven patients had a TVR (5 were treated with PCIs; 2 were treated with CABG). Of these, only 1 patient required TLR because of in-Taxus restenosis in the LMCA shaft. Furthermore, the restenosis rate in our multicenter experience was only 0.9% with a late loss of −0.01 mm. This finding is mostly explained by the favorable anatomic location. Nevertheless, an important factor could have been that in almost 50% of our patients IVUS guidance was performed. IVUS guidance in the DES era is still controversial, especially in this particular subset of lesions. Agostoni et al reported in a small series that IVUS guidance, used in 41% of the total 58 patients who underwent the procedures, was not associated with additional clinical benefit with respect to angiographically assisted stent deployment in patients with LMCA stenosis.

Study Limitations

This is a retrospective multicenter registry. No a priori sample size has been calculated. In addition, no centralized core quantitative coronary angiography laboratory was established. Moreover, the number of patients analyzed is small, primarily because of the low occurrence of this anatomic subset of lesions in the general population. Another limitation is the length of clinical follow-up. No specific attempt was made to extend dual antiplatelet therapy beyond 6 to 12 months, and no detailed information was available on antiplatelet therapy in the patients who had died at follow-up. Furthermore, silent restenosis could not be completely excluded because of the low rate of angiographic follow-up (73%).
Conclusions
In this multicenter registry, the use of DES in nonbifurcation unprotected LMCA stenosis appeared to be safe and effective. Six-month angiographic follow-up showed a restenosis rate of 0.9% with a cumulative cardiac mortality of 2.7% at a median follow-up of 886 days.

Disclosures
None.

References
Oxidant Stress Impairs In Vivo Reendothelialization Capacity of Endothelial Progenitor Cells From Patients With Type 2 Diabetes Mellitus

Restoration by the Peroxisome Proliferator-Activated Receptor-γ Agonist Rosiglitazone

Sajoscha A. Sorrentino, MD*; Ferdinand H. Bahlmann, MD, PhD*; Christian Besler, BS; Maja Müller, BS; Svenja Schulz, BS; Nina Kirchhoff, BS; Carola Doerries, MD; Tibor Horváth, BS; Anne Limbourg, MD; Florian Limbourg, MD; Danilo Fliser, MD; Hermann Haller, MD; Helmut Drexler, MD; Ulf Landmesser, MD

Background—Endothelial progenitor cells (EPCs) are thought to contribute to endothelial recovery after arterial injury. We therefore compared in vivo reendothelialization capacity of EPCs derived from patients with diabetes mellitus and healthy subjects. Moreover, we examined the effect of treatment with the peroxisome proliferator-activated receptor-γ agonist rosiglitazone on oxidant stress, nitric oxide (NO) bioavailability, and the in vivo reendothelialization capacity of EPCs from diabetic individuals.

Methods and Results—In vivo reendothelialization capacity of EPCs from diabetic patients (n=30) and healthy subjects (n=10) was examined in a nude mouse carotid injury model. Superoxide and NO production of EPCs was determined by electron spin resonance spectroscopy. Thirty patients with diabetes mellitus were randomized to 2 weeks of rosiglitazone (4 mg BID PO) or placebo treatment. In vivo reendothelialization capacity of EPCs derived from diabetic subjects was severely reduced compared with EPCs from healthy subjects (reendothelialized area: 8±3% versus 37±10%; P<0.001). EPCs from diabetic individuals had a substantially increased superoxide production and impaired NO bioavailability. Small-interfering RNA silencing of NAD(P)H oxidase subunit p47phox reduced superoxide production and restored NO bioavailability and in vivo reendothelialization capacity of EPCs from diabetic patients. Importantly, rosiglitazone therapy normalized NAD(P)H oxidase activity, restored NO bioavailability, and improved in vivo reendothelialization capacity of EPCs from diabetic patients (reendothelialized area: placebo versus rosiglitazone, 8±1% versus 38±5%; P<0.001).

Conclusions—In vivo reendothelialization capacity of EPCs derived from individuals with diabetes mellitus is severely impaired at least partially as a result of increased NAD(P)H oxidase–dependent superoxide production and subsequently reduced NO bioavailability. Rosiglitazone therapy reduces NAD(P)H oxidase activity and improves reendothelialization capacity of EPCs from diabetic individuals, representing a potential novel mechanism whereby peroxisome proliferator-activated receptor-γ agonism promotes vascular repair. (Circulation. 2007;116:163-173.)

Key Words: endothelium ■ nitric oxide synthase ■ oxidative stress ■ PPAR gamma ■ progenitor cells

Accelerated vascular disease is the principal cause of death and disability in patients with diabetes mellitus. Endothelial injury is thought to represent a crucial step in initiation and progression of atherosclerotic vascular disease.1,2 This concept has recently been supported by the close association of endothelial dysfunction, as observed in diabetic individuals,3 with cardiovascular events.2 Furthermore, insufficient numbers of endothelial progenitor cells (EPCs) have been related to endothelial dysfunction4 and an adverse clinical outcome,5 further suggesting that endothelial injury in the absence of sufficient circulating progenitor cells promotes progression of vascular disease. Moreover, 2 recent studies have observed an
association of reduced EPC numbers with peripheral artery disease and its severity in diabetic patients.\textsuperscript{6,7} Experimental studies have demonstrated that EPCs promote endothelial repair after injury.\textsuperscript{8–10} In diabetic patients, however, an impaired migration capacity and tube formation of EPCs have been observed in vitro,\textsuperscript{11,12} and a diabetes-induced delay in reendothelialization by EPCs has been described for diabetic mice,\textsuperscript{13} raising the question of whether the in vivo reendothelialization capacity of human EPCs from patients with diabetes mellitus is altered. Moreover, mechanisms underlying EPC dysfunction in diabetic individuals remain largely unknown. In the present study, we therefore compared the in vivo reendothelialization capacity of EPCs derived from diabetic and healthy subjects and analyzed mechanisms of EPC dysfunction.

Increased oxidant stress has been proposed as a molecular mechanism for vascular complications in diabetes mellitus, in part by reducing nitric oxide (NO) availability.\textsuperscript{14} In this respect, we and others have observed a role of endothelial NO synthase (eNOS) for EPC mobilization and function in studies using eNOS-deficient mice.\textsuperscript{15–17} We therefore examined the role of oxidant stress and NO bioavailability for the in vivo reendothelialization capacity of EPCs.

Notably, peroxisome proliferator-activated receptor (PPAR)-\textgamma stimulation, a promising treatment for diabetes mellitus, has recently been shown to stimulate NO production in mature endothelial cells in vitro.\textsuperscript{18} Moreover, experimental studies have suggested that PPAR-\textgamma stimulation may exert antioxidant effects.\textsuperscript{19} In a small, uncontrolled clinical study, it has been proposed that rosiglitazone improves EPC in vitro function (ie, migratory activity).\textsuperscript{20} In the present study, diabetic individuals were therefore randomized to 2-week treatment with the PPAR-\textgamma agonist rosiglitazone or placebo, and effects on superoxide and NO production and the in vivo reendothelialization capacity of EPCs were analyzed.

Methods

Patient Characteristics and Study Protocol

Written informed consent was obtained from all participants, and the study protocol was approved by the local ethics committee. Patients were included into the study between March 2004 and August 2005. Peripheral venous blood samples (60 mL) were obtained for EPC isolation from individuals with type 2 diabetes mellitus (n = 30) and healthy subjects (n = 10). Those with diabetes were randomized (3:2) to 2-week rosiglitazone (4 mg BID PO) or placebo therapy. Patient characteristics are shown in Tables 1, 2, and 3.

Isolation and Cultivation of EPCs

EPCs were isolated and cultured as described in detail previously.\textsuperscript{17,21,22} In brief, peripheral blood mononuclear cells were isolated by density gradient centrifugation with Biocoll (Biochrom, Berlin, Germany), and 10\textsuperscript{5} cells were cultured on fibronectin-coated 6-well plates in endothelial cell basal medium-2 (containing 5 mmol/L glucose) supplemented with endothelial growth medium–SingleQuots exactly as indicated by the manufacturer except for hydrocortisone (Clonetics, Inc). After 4-day culture, nonadherent cells were removed by washing plates with PBS. Remaining cells were trypsinized and used for in vitro and in vivo functional analysis.

### TABLE 1. Characteristics of Healthy and Diabetic Subjects

<table>
<thead>
<tr>
<th></th>
<th>Healthy (n=10)</th>
<th>Diabetic (n=30)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>65±3</td>
<td>65±2</td>
<td>NS</td>
</tr>
<tr>
<td>Gender, M/F</td>
<td>7/3</td>
<td>28/2</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index, kg/m(^2)</td>
<td>27±1</td>
<td>30±1</td>
<td>NS</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>99±5</td>
<td>110±2</td>
<td>NS</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>5.4±0.1</td>
<td>6.6±0.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>92±4</td>
<td>142±6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>131±12</td>
<td>120±8</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>50±4</td>
<td>43±4</td>
<td>NS</td>
</tr>
<tr>
<td>C-reactive protein, mg/dL</td>
<td>1.37±0.5</td>
<td>1.41±0.43</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine, ( \mu )mol/L</td>
<td>82±4</td>
<td>80±2</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean±SEM. HbA1c indicates glycohemoglobin; LDL, low-density lipoprotein; and HDL, high-density lipoprotein.

EPC Characterization

Adherent EPCs were characterized by dual staining for acetylated low-density lipoprotein and lectin as described previously and by flow cytometry analysis for expression of endothelial marker proteins (CD31, von Willebrand factor [vWF], and kinase-insert domain receptor [KDR]) and the monocytic lineage marker CD14 (see the online-only Data Supplement for more details). The vast majority of cells cultured for 4 or 7 days from healthy subjects and diabetic subjects were double positive for acetylated low-density lipoprotein–lectin staining and expressed both endothelial marker proteins and the monocytic marker CD14 at comparable levels (online-only Data Supplement Figure 1). EPC quantification and acetylated low-density lipoprotein–lectin staining were performed as described previously and in the online-only Data Supplement.

### TABLE 2. Characteristics of Diabetic Subjects Receiving Placebo or Rosiglitazone Treatment

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=12)</th>
<th>Rosiglitazone (n=18)</th>
<th>( P ) (Between Groups After Treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>64±2</td>
<td>65±2</td>
<td>&gt;0.9*</td>
</tr>
<tr>
<td>Gender, M/F</td>
<td>11/1</td>
<td>17/1</td>
<td>0.65†</td>
</tr>
<tr>
<td>Body mass index, kg/m(^2)</td>
<td>30±1</td>
<td>30±1</td>
<td>&gt;0.9*</td>
</tr>
<tr>
<td>Medication, n/N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE/ARB</td>
<td>10/12</td>
<td>14/18</td>
<td>0.88†</td>
</tr>
<tr>
<td>ASA</td>
<td>6/12</td>
<td>11/18</td>
<td>0.99†</td>
</tr>
<tr>
<td>Diuretic</td>
<td>4/12</td>
<td>11/18</td>
<td>0.58†</td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>5/12</td>
<td>11/18</td>
<td>0.79†</td>
</tr>
<tr>
<td>Nitrates</td>
<td>2/12</td>
<td>5/18</td>
<td>0.90†</td>
</tr>
<tr>
<td>( \beta )-Blocker</td>
<td>4/12</td>
<td>9/18</td>
<td>0.82†</td>
</tr>
<tr>
<td>Statin</td>
<td>5/12</td>
<td>11/18</td>
<td>0.79†</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SEM where appropriate. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; and ASA, acetylsalicylic acid.

*Bonferroni corrected.
†\( \chi^2 \) Analysis.
Animals and In Vivo Reendothelialization Assay

Male NRM1nu/nu athymic nude mice, aged 7 to 10 weeks, were used to allow injection of human EPCs. Animals were anesthetized with ketamine (100 mg/kg IP) and xylazine (5 mg/kg IP). Carotid artery electric injury was performed as described previously. In brief, the left common carotid artery was injured with a bipolar microregulator (ICCS50, ERBE-Elektromedizin GmbH, Tueningen, Germany). An electric current of 2 W was applied for 2 seconds to each millimeter of carotid artery over a total length of exactly 4 mm with the use of a size marker parallel to the carotid artery.

EPCs (5 x 10⁵ cells) were resuspended in 100 µL of prewarmed PBS (37°C) and transplanted 3 hours after carotid injury via tail vein injection with a 27-gauge needle. The same volume of PBS was injected into placebo mice. Three days after carotid injury, endothelial regeneration was evaluated by staining denuded areas with 50 µL of solution containing 5% Evans blue dye via tail vein injection as described previously. The reendothelialized area was calculated as difference between the blue-stained area and the injured area by computer-assisted morphometric analysis.

EPC Superoxide Production and NAD(P)H and Xanthine Oxidase Activity

EPC superoxide (O₂⁻) production and NAD(P)H and xanthine oxidase activity were determined by electron spin resonance (ESR) spectroscopy analysis with the use of the spin-trap 1-hydroxy-3-carboxy-pyrrolidine (CPH; Alexis Corporation) in 250,000 resuspended or homogenized EPCs as described previously and in the online-only Data Supplement.

EPC Adhesion to Endothelial Cells In Vitro

A monolayer of human umbilical vein endothelial cells (Cambrex, Taufkirchen, Germany) was prepared 48 hours before the assay by plating 2 x 10⁵ cells (passage 1 to 5) in each well of a 4-well plate. Human umbilical vein endothelial cells were pretreated with tumor necrosis factor-α (BD Biosciences; 1 ng/mL; 12 hours) or media. Then 1 x 10⁵ diI-labeled EPCs were added to each well and incubated for 3 hours at 37°C. Nonattached cells were gently removed with PBS, and adherent EPCs were fixed with 4% paraformaldehyde and counted in 4 random fields.

EPC Migration In Vitro

EPC migration was evaluated with the use of a modified Boyden’s chamber assay as described previously. Briefly, cell suspensions (1 x 10⁵ cells per well) were placed in the upper chamber, and the lower chamber was filled with medium containing human recombinant vascular endothelial growth factor (50 ng/mL; R&D Systems). The chamber was incubated for 16 hours (37°C). Migration activity was evaluated as mean number of migrated cells in 3 high-power fields per chamber.

Small-Interfering RNA Transfection

NAD(P)H oxidase subunit p47phox, cNOS, and PPAR-γ expression were silenced with the use of Validated Stealth RNAi (Invitrogen, Carlsbad, Calif), adapting the manufacturer’s protocol after determining optimal transfection conditions (data not shown). The small-interfering RNA (siRNA) sequences (sense strands) used for targeting human p47phox, cNOS, and PPAR-γ were 5’-CCGAGAGCGCAGUAUACCACCUU-3’, 5’-UGUUGUACUGGACUCUCUCUUCU-3’, (Invitrogen primer number: 1043808E5), 5’-UGUUGUACUGGACUCUCUCUUCU-3’ (Invitrogen primer number: 95777G10), and 5’-UCAGGCCCGGAGAUCCUCGCCUAU-3’ (Invitrogen primer number: 11155H08). A Stealth RNAi Negative Control Duplex (Invitrogen) was used as a negative control. In preliminary experiments, transfection efficiency was >90% of EPCs as determined by transfection with fluorescence-labeled siRNA. All siRNA transfections were performed for 24 hours preceding subsequent EPC measurements.

Western Blot Analysis

Protein extracts were subjected to SDS-PAGE, transferred to polyvinylidene fluoride membranes, and probed with anti-human antibodies for NAD(P)H oxidase subunits p22phox, p47phox, p67phox, or eNOS (Santa Cruz Biotechnology, Santa Cruz, Calif), followed by enhanced chemiluminescence detection.

Statistical Analysis

Data in the text and figures are expressed as mean±SD. Differences between means of groups were compared with the use of Wilks λ 1-way MANOVA testing, followed by Student or Welch t test. Comparisons between frequencies were performed by χ² analysis. To account for inflation of experiment type-1 error due to multiple testing, Bonferroni correction was used for multiple comparisons of results presented in Tables 2 and 3 and the figures. The rationale of the Bonferroni adjustments for the results presented in Tables 2 and 3 and the figures was as follows: A primary and secondary weighting of hypotheses (primary: placebo versus rosiglitazone; secondary: in vitro experiments) was performed, and Bonferroni corrections were applied separately to each hypothesis. A Bonferroni-corrected probability value of <0.05 was considered statistically significant. A nonparametric analysis using the Wilcoxon rank sum test was performed when appropriate. All statistical analyses used SPSS statistical software (SPSS version 14).

The primary end point of the present study was the in vivo reendothelialization capacity of EPCs, which was therefore used to determine the study size. For the randomized substudy (effect of rosiglitazone versus placebo therapy in diabetic patients), the relation between the treatment groups. With the assumption of a common SD of 15%, a sample size of 30 patients randomized 2:1 was needed to have a power of 90% to reject the null hypothesis in favor of the alternative hypothesis with a 0.025 type I error.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

In Vivo Reendothelialization Capacity of EPCs From Diabetic Subjects Is Severely Reduced

Transplantation of EPCs from healthy subjects (n=10) markedly accelerated reendothelialization of denuded carotid arteries in nude mice (Figure 1A and 1B). Confocal laser scanning microscopy analysis of a subgroup of nude mice (n=5) revealed that transplanted EPCs were attached at the site of vascular injury (Figure 1C). Notably, in vivo reendothelialization capacity of EPCs derived from diabetic subjects (n=30) was markedly reduced (Figure 1A and 1B). To further determine whether EPCs from diabetic subjects had a delayed or diminished response, reendothelialization was examined later (ie, 7 days after EPC transplantation in a subgroup of healthy and diabetic subjects [n=5]). Seven days after transplantation of EPCs from healthy subjects, the endothelial layer was almost completely restored, whereas...
EPCs from diabetic individuals had no significant effect on reendothelialization (Figure IIA and IIB in the online-only Data Supplement). To evaluate whether a potential contamination of EPCs with endothelial cells may have contributed to reendothelialization, human endothelial cells (5×10⁵ cells) were transplanted into 5 nude mice but had no effect on reendothelialization (Figure IIC and IID in the online-only Data Supplement).

Fluorescence-activated cell-sorting analyses revealed a similar endothelial marker protein (vWF, CD31, and KDR) and monocytic lineage marker (CD14) expression on EPCs from healthy and diabetic subjects, suggesting that EPCs

### TABLE 3. Characteristics of Diabetic Subjects Before and After Placebo or Rosiglitazone Treatment

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=12)</th>
<th>Rosiglitazone (n=18)</th>
<th>p* (Between Groups After Treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>112±3</td>
<td>109±2</td>
<td>&gt;0.9</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>6.9±0.4</td>
<td>6.9±0.4</td>
<td>&gt;0.9</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>149±12</td>
<td>144±10</td>
<td>&gt;0.9</td>
</tr>
<tr>
<td>Insulin levels, μU/mL</td>
<td>18.3±2.9</td>
<td>25.3±9.0</td>
<td>&gt;0.9</td>
</tr>
<tr>
<td>HOMA index</td>
<td>6.8±1.6</td>
<td>9.1±1.2</td>
<td>&gt;0.9</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>137±9</td>
<td>123±9</td>
<td>&gt;0.9</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>47±5</td>
<td>46±4</td>
<td>&gt;0.9</td>
</tr>
<tr>
<td>Free fatty acids, mg/dL</td>
<td>11.6±1.33</td>
<td>11.9±1.7</td>
<td>&gt;0.9</td>
</tr>
<tr>
<td>C-reactive protein, mg/dL</td>
<td>1.0±0.3</td>
<td>0.6±0.3</td>
<td>&gt;0.9</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>77±2</td>
<td>80±3</td>
<td>&gt;0.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosiglitazone (n=18)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>110±3</td>
<td>103±4</td>
<td>0.340</td>
</tr>
<tr>
<td>After</td>
<td>135±6</td>
<td>124±5</td>
<td>0.250</td>
</tr>
<tr>
<td>p*</td>
<td>35.7±5.3</td>
<td>38.5±6.7</td>
<td>&gt;0.9</td>
</tr>
<tr>
<td></td>
<td>11.9±1.3</td>
<td>11.8±1.7</td>
<td>&gt;0.9</td>
</tr>
<tr>
<td></td>
<td>108±7</td>
<td>112±7</td>
<td>&gt;0.9</td>
</tr>
<tr>
<td></td>
<td>40±2</td>
<td>41±2</td>
<td>&gt;0.9</td>
</tr>
<tr>
<td></td>
<td>11.8±1.6</td>
<td>8.4±1.2</td>
<td>&gt;0.9</td>
</tr>
<tr>
<td></td>
<td>1.5±0.8</td>
<td>0.70±0.2</td>
<td>0.690</td>
</tr>
<tr>
<td></td>
<td>83±4</td>
<td>82±4</td>
<td>0.640</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SEM where appropriate. Hba1c indicates glycohemoglobin; HOMA, Homeostasis Model Assessment; LDL, low-density lipoprotein; and HDL, high-density lipoprotein.

*pBonferroni-corrected.

Figure 1. A, Reendothelialized area at day 3 after carotid injury in nude mice with placebo injection (n=15), transplantation of EPCs from healthy subjects (n=10), or diabetic subjects (n=30; each 5×10⁵ EPCs). B, Representative photographs. EPCs from each patient or healthy subject were injected into 2 nude mice; mean values of reendothelialized area are shown. C, Confocal laser scanning microscopy (magnification ×80): top, carotid artery 3 days after injury showing PKH26-labeled EPCs (red) attached to isolecitin-B4–stained endothelium (green); bottom, contralateral uninjured carotid artery (nuclei stained blue; TO-Pro3). Data are representative of 5 separate experiments. D through F, ESR spectroscopy analyses of superoxide production (D) and NAD(P)H oxidase activity (F) of EPCs from diabetic subjects (n=30) and healthy subjects (n=10) are shown, as well as representative ESR spectra of superoxide production (E).
from diabetic subjects did not lose endothelial marker proteins (Figure I in the online-only Data Supplement).

**Superoxide Production and NAD(P)H Oxidase Activity Are Increased in EPCs From Diabetic Subjects**

EPCs from diabetic subjects had a markedly increased superoxide production compared with EPCs from healthy subjects (Figure 1D and 1E). Notably, activity of NAD(P)H oxidase, a major oxidant enzyme, was substantially increased in EPCs from those with diabetes mellitus (Figure 1F).

Of note, xanthine oxidase (XO) activation dependent on NAD(P)H oxidase has been observed in endothelial cells.30 In EPCs from diabetic subjects, XO activity was increased compared with EPCs from healthy subjects (1.52±0.14 versus 0.83±0.04 pmol O₂⁻/250 000 EPCs per minute; P<0.05; n=6 to 12). XO activity in diabetic EPCs was normalized after NAD(P)H oxidase inhibition by apocynin (data not shown), suggesting NAD(P)H oxidase–dependent XO activation.

**NAD(P)H Oxidase Inhibition Restores In Vivo Reendothelialization Capacity of EPCs From Diabetic Subjects**

Both siRNA silencing of NAD(P)H oxidase subunit p47⁷⁷ox⁰⁰ and NADPH oxidase inhibition by apocynin (100 μmol/L; 24 hours; data not shown) resulted in a markedly reduced NAD(P)H oxidase activity and superoxide production of EPCs from diabetic individuals (Figure 2A to 2C). Importantly, p47⁷⁷ox⁰⁰ siRNA silencing (n=6) restored in vivo reendothelialization capacity of diabetic EPCs (Figure 2D and 2E), suggesting a critical role of NAD(P)H oxidase activation for impaired reendothelialization capacity.

A potential mechanism whereby NAD(P)H oxidase activation may impair EPC in vivo reendothelialization capacity relates to a subsequently reduced NO bioavailability. Notably, EPCs from diabetic subjects had a markedly reduced NO bioavailability (Figure 3A and 3B).

**EPC NO Bioavailability Is Critical for In Vivo Reendothelialization Capacity**

eNOS-specific siRNA silencing substantially reduced eNOS protein expression (Figure 3C; n=8) and NO production of EPCs from healthy subjects (data not shown). Importantly, eNOS-specific siRNA silencing markedly impaired in vivo reendothelialization capacity of EPCs from healthy subjects (Figure 3D and 3E; n=8), suggesting a crucial role of EPC NO bioavailability for in vivo reendothelialization capacity. In contrast, eNOS-specific siRNA transfection of diabetic EPCs did not reduce in vivo reendothelialization capacity (n=8; data not shown).

Importantly, siRNA silencing of p47⁷⁷ox⁰⁰ restored NO bioavailability of EPCs from diabetic subjects (Figure 3F), whereas no effect was observed in EPCs from healthy subjects (data not shown).

**EPC Protein Expression of NAD(P)H Oxidase Subunits and eNOS**

Avogaro et al recently observed increased expression of NAD(P)H oxidase subunit p22⁷⁷ox⁰⁰ in monocytes from individu-
als with diabetes mellitus. In the present study, protein levels of NAD(P)H oxidase subunits p22phox, p67phox, and p47phox in EPCs from diabetic subjects compared with healthy subjects were as follows: p22phox: 260±11006126%; P=NS; p67phox: 86±5%; P=NS; p47phox: 159±49%; P=NS; n=5). eNOS protein levels were not significantly different in EPCs from diabetic subjects compared with healthy subjects (data not shown).

Effects of PPAR-γ Agonist Rosiglitazone on EPCs From Diabetic Subjects In Vitro
Treatment of diabetic EPCs with rosiglitazone in vitro reduced superoxide production and NAD(P)H oxidase activity and increased NO bioavailability, which was prevented by PPAR-γ-specific siRNA transfection (Figure 4A to 4D). Furthermore, rosiglitazone treatment prevented XO activation in diabetic EPCs (data not shown). Moreover, 24-hour in vitro treatment of diabetic EPCs with rosiglitazone improved their in vivo reendothelialization capacity (n=6; data not shown).

Endothelial Adhesion and Migration Capacity of EPCs
EPCs from diabetic subjects had a markedly reduced capacity to adhere to tumor necrosis factor-α–activated endothelial cells and an impaired migratory response to vascular endothelial growth factor compared with EPCs from healthy subjects (Figure 5A to 5C). Importantly, p47phox siRNA silencing and treatment with polyethylene glycol–superoxide dismutase (50 U) restored both adhesion capacity to activated endothelial cells and migratory response of EPCs from diabetics (Figure 5A to 5C). Furthermore, both the NO donor 2,2′-(hydroxynitrosohydradino)bis-ethanamine (DETA-NO; 500 μmol/L) and rosiglitazone (10 μmol/L) restored adhesion and migration capacity of EPCs from diabetic subjects, whereas no significant effect was observed in EPCs from healthy subjects (Figure 5A to 5C).

Effects of Oral Treatment With the PPAR-γ Agonist Rosiglitazone on EPCs From Diabetic Subjects: A Randomized, Placebo-Controlled Clinical Study
Rosiglitazone, but not placebo therapy, substantially reduced superoxide production and NAD(P)H oxidase activity in EPCs from diabetic subjects (Figure 6A and 6B). Moreover, rosiglitazone therapy increased NO bioavailability (Figure 6C) and, importantly, restored in vivo reendothelialization capacity of EPCs from diabetic subjects (Figure 6D and 6E).
EPC numbers were reduced in diabetic subjects compared with healthy subjects (175±81 versus 299.5±162 EPCs per high-power field; P<0.05). Two-week rosiglitazone but not placebo therapy increased EPC numbers in diabetic subjects as assessed by acetylated low-density lipoprotein–lectin staining (Figure IIIA and IIIB in the online-only Data Supplement). No significant changes of metabolic parameters were observed after 2-week rosiglitazone therapy (Tables 2 and 3). No significant differences existed with respect to the patient characteristics shown in Table 1 between patients randomized to rosiglitazone or placebo therapy at baseline (ie, before therapy).

**Discussion**

The present study demonstrates a severe impairment of in vivo reendothelialization capacity of EPCs derived from diabetic subjects compared with healthy subjects. Furthermore, our findings suggest that increased oxidant stress, in particular NAD(P)H oxidase activation, and a subsequently reduced NO bioavailability of diabetic EPCs represent major mechanisms leading to impaired in vivo reendothelialization capacity and in vitro function. siRNA silencing of p47phox, a critical NAD(P)H oxidase subunit, normalized superoxide production and restored NO bioavailability and in vivo reendothelialization capacity of EPCs from diabetic subjects.

Notably, both in vitro and 2-week oral therapy with the PPAR-γ agonist rosiglitazone inhibited NAD(P)H oxidase, reduced superoxide production, and restored NO availability and in vivo reendothelialization capacity of EPCs derived from diabetic subjects.

EPCs have been shown to promote endothelial repair after injury in recent experimental studies.8–10 The present study, however, demonstrates that in vivo reendothelialization capacity is largely lost in EPCs from diabetic subjects, suggesting a profound alteration of the endogenous endothelial repair system mediated by EPCs. EPCs from diabetic and healthy subjects had a similar expression of CD31, vWF, and KDR, suggesting that impaired reendothelialization capacity was not associated with loss of endothelial marker proteins. A substantial portion of EPCs expressed the monocytic marker CD14, as has been observed previously.32,33 Notably, it has been shown recently that transfusion of CD14+/KDR+ but not CD14+/KDR− cells accelerated reendothelialization in nude mice, suggesting that only monocytic cells with endothelial markers promote reendothelialization.34 Furthermore, Romagnani et al35 have suggested that blood-derived EPCs are to a significant extent derived from CD14+/CD34low cells. Production of growth factors has been suggested to contribute to EPC function but is likely not sufficient to promote reendothelialization. Whereas monocytes and macrophages are known to produce growth factors,36 they have not been shown to stimulate reendothelialization.34 Two recent studies have suggested that despite a phenotypic overlap of EPCs with macrophages and dendritic cells, EPCs display unique eNOS expression that likely is a reliable marker of endothelial phenotype.37,38 Impor-
tantly, in the present study EPC-mediated reendothelialization was eNOS dependent (ie, was abolished after eNOS siRNA silencing), strongly suggesting that the observed reendothelialization response depends on eNOS-containing EPCs.

In previous studies, we and others have observed a role of eNOS for mobilization and EPC function by using eNOS-deficient mice. Furthermore, Ii et al have suggested that EPCs represent repositories of eNOS activity in experiments using bone marrow cells from eNOS-deficient mice. In eNOS-deficient mice, however, impaired maturation of EPCs in the bone marrow may contribute to impaired EPC function. The present study provides direct evidence that NO bioavailability in EPCs is critical for in vivo reendothelialization capacity.

Importantly, NO bioavailability was restored in EPCs from diabetic subjects after NAD(P)H oxidase inhibition, associated with a restored reendothelialization response, suggesting that increased NAD(P)H oxidase activity impairs reendothelialization capacity of diabetic EPCs by reducing NO availability. The concept that increased superoxide production from NAD(P)H oxidase is critical for impaired EPC functionality is further supported by our observation that both NAD(P)H oxidase inhibition and superoxide dismutase treatment improved endothelial adhesion and migratory capacity of EPCs from diabetic subjects.

Of note, 2 previous studies have suggested that EPCs from healthy subjects have a reduced superoxide production compared with mature endothelial cells, suggesting that well-controlled superoxide production is important for EPC functionality. Furthermore, EPCs isolated from glutathione peroxidase-1–deficient mice have an impaired ability to promote angiogenesis, suggesting that reduced antioxidant capacity impairs EPC in vivo function. The present study suggests that EPC function may be highly dependent on a well-controlled oxidant stress because EPC NO availability (which is highly sensitive to oxidant stress) is critical for their in vivo function.

In addition, increased p38 mitogen-activated protein kinase phosphorylation has been reported in EPCs from patients with coronary disease and in mononuclear cells from diabetic mice. Because NAD(P)H oxidase activation promotes p38 mitogen-activated protein kinase phosphorylation, it is tempting to speculate that increased p38 mitogen-
activated protein kinase phosphorylation may represent an additional potential pathway whereby NAD(P)H oxidase may alter EPC function in diabetics.

Furthermore, in EPCs from diabetic mice, an increased expression of thrombospondin-1 has recently been shown, which may further contribute to impaired EPC adhesion and migration activity and a reduced reendothelialization response in diabetes mellitus.13

Short-term in vitro rosiglitazone treatment of EPCs from diabetic subjects reduced NAD(P)H oxidase activity and restored NO availability in the present study. PPAR-γ siRNA silencing prevented these effects of rosiglitazone, suggesting that PPAR-γ agonism exerts a direct effect on NAD(P)H oxidase in diabetic EPCs. Of note, in vitro treatment with the PPAR-γ agonist pioglitazone prevented oxidant stress–induced apoptosis in human EPCs, further supporting a role of PPAR-γ for EPC function.44

Importantly, 2-week oral rosiglitazone therapy restored in vivo reendothelialization capacity of EPCs from diabetic subjects in the present study. PPAR-γ agonism had no significant effect on glucose or insulin levels, insulin resistance (as indicated by the Homeostasis Model Assessment index), or nonesterified fatty acids within this time, suggesting that effects on EPC functionality were likely independent of metabolic changes. This concept is further supported by the observation that short-term in vitro rosiglitazone treatment of EPCs from diabetics improved both in vitro and in vivo functionality. Interestingly, a previous study has suggested that nonesterified fatty acids stimulate NAD(P)H oxidase in endothelial cells45; however, high concentrations of nonesterified fatty acids were necessary to stimulate the enzyme, suggesting that minor changes of plasma nonesterified fatty acid levels are unlikely to change EPC NAD(P)H oxidase activity. In agreement with this consideration, we did not observe a correlation between changes in nonesterified fatty acid levels and EPC NAD(P)H oxidase activity, suggesting that this may not be a major mechanism whereby rosiglitazone therapy exerts an effect on EPCs, at least after short-term treatment.

Of note, a reduced capacity for endothelial repair is thought to contribute to impaired long-term outcome after coronary intervention in diabetics.46 Beneficial effects of PPAR-γ agonism on EPC reendothelialization capacity provide a potential explanation for antirestenotic effects observed after PPAR-γ agonist treatment after coronary intervention.47 No-
tably, a recent experimental study has suggested that rosiglitazone treatment in mice promoted angiogenic progenitor cell differentiation toward the endothelial lineage associated with attenuated restenosis after angioplasty.48 Moreover, the present findings may have implications for treatment strategies using autologous cell transplantation. Given the severe impairment of in vivo reendothelialization potential of EPCs from diabetics, pretreatment of these cells with rosiglitazone represents a promising strategy to improve their regenerative potential.

In the present study, a currently widely applied protocol to obtain blood-derived EPCs was used. Further standardization of EPC definitions and nomenclature will be important for future studies, in particular to be able to better compare results between different groups.

In summary, the present study demonstrates that in vivo reendothelialization capacity of EPCs derived from diabetics is severely impaired, at least in part, as a result of increased NAD(P)H oxidase–dependent superoxide production and subsequently reduced NO bioavailability. Treatment with the PPAR-γ agonist rosiglitazone reduced NAD(P)H oxidase activity, increased NO availability, and restored in vivo reendothelialization capacity of EPCs from diabetics. Improved EPC reendothelialization capacity may represent a novel mechanism contributing to vasculoprotective effects of PPAR-γ agonism likely independent of glycemic control.

Acknowledgments
We thank Eva Niemczyk and Barbara Hertel for excellent technical assistance and Dr Cornelia Froemke and Dr Jana Prokein for help with statistical analyses.

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Disclosures
None.

References
Accelerated vascular disease is a principal cause of increased mortality and morbidity in patients with diabetes mellitus. Importantly, endothelial injury is thought to represent a major mechanism whereby diabetes promotes initiation and progression of atherosclerosis and restenosis after vascular intervention. Notably, recent experimental studies have suggested that circulating endothelial progenitor cells contribute to endogenous endothelial repair mechanisms after vascular injury. The present study demonstrates a severe impairment of the in vivo reendothelialization capacity of endothelial progenitor cells derived from subjects with type 2 diabetes mellitus compared with healthy subjects that may contribute to an impaired endogenous endothelial repair capacity and a delayed healing after vascular injury in patients with diabetes mellitus. Furthermore, our findings suggest that increased oxidant stress, in particular NAD(P)H oxidase-derived overproduction of reactive oxygen species impairs postischemic neovascularization in mice with type 1 diabetes. Am J Pathol. 2006;169:719–728.

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CLINICAL PERSPECTIVE

Accelerated vascular disease is a principal cause of increased mortality and morbidity in patients with diabetes mellitus. Importantly, endothelial injury is thought to represent a major mechanism whereby diabetes promotes initiation and progression of atherosclerosis and restenosis after vascular intervention. Notably, recent experimental studies have suggested that circulating endothelial progenitor cells contribute to endogenous endothelial repair mechanisms after vascular injury. The present study demonstrates a severe impairment of the in vivo reendothelialization capacity of endothelial progenitor cells derived from subjects with type 2 diabetes mellitus compared with healthy subjects that may contribute to an impaired endogenous endothelial repair capacity and a delayed healing after vascular injury in patients with diabetes mellitus. Furthermore, our findings suggest that increased oxidant stress, in particular NAD(P)H oxidase activation and a subsequently reduced nitric oxide bioavailability, represents important mechanisms underlying impaired in vivo reendothelialization capacity of endothelial progenitor cells from diabetic patients. Of note, both in vitro and 2-week oral therapy with the peroxisome proliferator-activated receptor-γ agonist rosiglitazone restored the in vivo reendothelialization capacity of endothelial progenitor cells derived from diabetic individuals, likely at least in part by inhibiting NAD(P)H oxidase activity and increasing nitric oxide availability. Improved reendothelialization capacity of endothelial progenitor cells may therefore represent a novel mechanism contributing to vasculoprotective effects of peroxisome proliferator-activated receptor-γ agonism likely independent of glycemic control.
Coronary Artery Involvement in Children With Kawasaki Disease
Risk Factors From Analysis of Serial Normalized Measurements

Brian W. McCrindle, MD, MPH; Jennifer S. Li, MD; L. LuAnn Minich, MD; Steven D. Colan, MD; Andrew M. Atz, MD; Masato Takahashi, MD; Victoria L. Vetter, MD; Welton M. Gersony, MD; Paul D. Mitchell, MSc; Jane W. Newburger, MD, MPH; for the Pediatric Heart Network Investigators

Background—Most studies of coronary artery involvement and associated risk factors in Kawasaki disease have used the Japanese Ministry of Health dichotomous criteria. Analysis of serial normalized artery measurements may reveal a broader continuous spectrum of involvement and different risk factors.

Methods and Results—Clinical, laboratory, and echocardiographic measurements obtained at baseline and 1 week and 5 weeks after presentation were examined in 190 Kawasaki disease patients as part of a clinical trial of primary therapy with pulse steroids in addition to standard intravenous immunoglobulin. Maximum coronary artery z score normalized to body surface area was significantly greater than normal at all time points, decreasing significantly over time from baseline. A maximal \( z \) score \( \geq 2.5 \) at any time was noted in 26% of patients. Japanese Ministry of Health dimensional criteria were met by 23% of patients. Significant independent factors associated with greater \( z \) score at any time included younger patient age, longer interval from disease onset to treatment with intravenous immunoglobulin, lower serum IgM level at baseline, and lower minimum serum albumin level. \( z \) Scores of the proximal right coronary artery were higher than those in the left anterior descending branch.

Conclusions—Analyses of serial normalized coronary artery measurements in optimally treated Kawasaki disease patients demonstrated that for most patients, measurements are greatest at baseline and subsequently diminish; baseline measurements appear to be good predictors of involvement during early follow-up. When a more precise assessment is used, risk factors for coronary artery involvement are similar to those defined with arbitrary dichotomous criteria. (Circulation. 2007;116:174-179.)

Key Words: Kawasaki disease ■ coronary disease ■ echocardiography ■ Pediatrics ■ risk factors

Coronary artery involvement remains the most important complication after Kawasaki disease (KD) and involves a continuous spectrum ranging from no apparent involvement in the majority of patients to the presence of multiple giant aneurysms. Involvement is assessed serially with echocardiography primarily by quantifying internal coronary artery diameters, although subtle qualitative features have been described. Commonly used definitions of coronary artery involvement have relied on the Japanese Ministry of Health criteria, which dichotomously define abnormalities as a maximum absolute internal diameter \( > 3 \) mm in children \( < 5 \) years of age or \( > 4 \) mm in children 5 years and older, or a segment 1.5 times greater than an adjacent segment, or the presence of luminal irregularity. This definition contains subjective elements, incompletely accounts for patient size, and ignores any continuum or time course. More recently, regression equations based on measurements from nonfebrile normal children have been used to calculate \( z \) scores based on body surface area. These allow a continuous measurement and assessment of the time course of involvement.

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Studies of risk factors associated with coronary artery involvement have also used a dichotomous definition usually

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From the University of Toronto (B.W.M.), The Hospital for Sick Children, Toronto, Canada; Duke University Medical Center (J.S.L.), Durham, NC; University of Utah (L.L.M.), Salt Lake City, Utah; New England Research Institutes (S.D.C., P.D.M.), Watertown, Mass; Medical University of South Carolina (A.M.A.), Charleston, SC; Children’s Hospital of Los Angeles (M.T.), Los Angeles, Calif; Children’s Hospital of Philadelphia (V.L.V.), Philadelphia, Pa; Columbia University Medical Center (W.M.G.), New York, NY; and Children’s Hospital Boston (J.W.N.), Boston, Mass.
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Correspondence to Dr Brian McCrindle, The Hospital for Sick Children, 555 University Ave, Toronto, Ontario, Canada M5G 1X8. E-mail brian mccrindle@sickkids.ca

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consistent with the Japanese Ministry of Health criteria. No study has used serial measurements of z scores to study the spectrum of involvement, time course of change, and associated risk factors. In addition, identified risk factors, such as younger patient age and male gender, laboratory abnormalities (such as higher white cell or neutrophil count, lower platelet count, higher C-reactive protein, higher erythrocyte sedimentation rate, lower serum albumin, and lower hemoglobin or hematocrit), treatment delay, and persistent or prolonged fever, have been inconsistent in their association with coronary artery abnormalities. Therefore, we sought to use serial assessments of normalized coronary artery dimensions to determine the spectrum and early time course of coronary artery involvement and, using these data, to define associated clinical and laboratory factors. This work represents a secondary analysis of data from the Pediatric Heart Network’s Randomized Trial of Pulse Steroid Therapy in Kawasaki Disease.

Methods
The study design consisted of a randomized, double-blind, placebo-controlled multicenter trial, with randomization stratified by young age (<1 or ≥1 year of age) and gender, balanced within center, with equal numbers assigned to each treatment arm. Inclusion criteria for enrollment in the trial included diagnosis of typical KD by meeting modified criteria from recent American Heart Association guidelines, presentation within 10 days of illness onset, and informed consent. Exclusion criteria for trial enrollment included prior treatment with intravenous immunoglobulin (IVIG) or systemic steroids, presence of another disease known to mimic KD, previous diagnosis of KD, and the presence of contraindications to steroid and aspirin use. Trial patients were randomized to receive either a single dose of intravenous methylprednisolone or an identical placebo before receiving conventional-dose IVIG and aspirin. For patients with persistent or recurrent fever, an additional dose of IVIG was given. Patients had standardized echocardiograms performed within 48 hours of enrollment (initial) and at 1 and 5 weeks after randomization. Echocardiograms were adjudicated in a core laboratory. To ensure a homogeneous study population, we excluded 9 of the 199 patients enrolled in the trial from the present analysis because they did not receive the assigned study drug (n=2), were subsequently not to meet entry criteria (n=6), or did not have any study echocardiograms (n=1). Some patients were included in the analysis with initial echocardiograms performed after having received IVIG (34 at 1 day, 3 at 2 days, and 1 patient at 8 days after IVIG).

Statistical Analysis
Coronary artery dimensions were normalized for body surface area as z scores (SDs from a predicted normal mean) based on nonlinear regression equations derived from a normal nonfebrile population. The normal group comprised 221 healthy children aged 0 to 18 years seen in the noninvasive laboratory at Boston Children’s Hospital for echocardiographic evaluation during the years 1987 to 2000 who had no evidence of structural or functional heart disease. Acquired or congenital heart disease and other systemic disorders were excluded by review of the medical history, ECG, chest radiograph, and echocardiogram. Specific exclusion criteria included acute or chronic systemic disorder, hypertension, a family history of hypertrophic or dilated cardiomyopathy, and height, weight, or height for weight percentile outside the range of normal. The age distribution was 37% aged 0 to 1 year, 17% aged 1 to 5 years, 17% aged 5 to 10 years, 14% aged 10 to 15 years, and 6% aged 15 to 18 years. Nonlinear regression equations based on body surface area were derived. The predicted value for a patient of a given body surface area can be obtained by solving the first exponential regression equation, and the associated SD of that predicted value can be obtained by solving the second linear regression equation. The z score is obtained by dividing the difference between the actual measurement and the predicted measurement by the SD:

\[ z = \frac{\text{measurement} - \text{predicted measurement}}{\text{SD}} \]

For the purposes of analysis, only serial measures of the z scores of the pLAD and pRCA branches were used. Normal values do not currently exist for distal segments or the circumflex branch. Although normal values exist for the left main coronary artery, we chose to exclude this measurement from analysis because normal anatomic variations make its interpretation less reliable, and it is exceedingly rare to have enlargement of the left main coronary artery in KD without accompanying dilation of the pLAD. The same limitation relative to reliability applies to assessment of the circumflex branch and more distal segments, with regard to standardization of location of assessment and consistency of adequate visualization. Mixed linear regression analysis for repeated measures was used for the analysis. This technique is robust in that it makes use of both arterial branch measurements at all time points (rather than a maximal measurement from a single time point), uses the z score as a continuous rather than a dichotomous outcome measure, allows determination of trends over time from fever onset, and allows the identification of independent factors that are associated with higher z scores at any time or that may influence the time course of change. Variables that were tested are shown in the table in the online-only Data Supplement. Mean imputation was used to replace missing values for independent variables only. Of note, models created without imputation of missing values were very similar to those with imputation. Statistical analyses were performed with SAS statistical software version 9 (SAS Institute, Inc, Cary, NC).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Patient Characteristics
Of the 190 patients included in this analysis, 62% were males, with a mean age of 3.3 years (range 2 months to 12.3 years) and a mean duration of illness of 6.6±1.4 days at the time of enrollment. Race or ethnic group was white for 58%, black for 18%, Asian for 14%, American Indian or Alaskan Native for 2%, Native Hawaiian or other Pacific islander for <1%, more than 1 race or ethnic group for 7%, unknown for <1%, and Hispanic for 17% of subjects. Half (51%) were randomized to and received intravenous methylprednisolone.

Figure 1 shows the distributions of the maximum z score of the greater of the pRCA and pLAD over time. At initial assessment, the majority of patients had z scores well above a normal population predicted value of zero, with a median of 1.43 for the patients. Some decrease was noted at 1 and 5 weeks, although z scores remained elevated. At least 1 pRCA or pLAD z score ≥2.5 noted on at least 1 echocardiogram over the 5-week period was found for 26% of patients included in the analysis, and 5% had at least 1 z score ≥5.

By Japanese Ministry of Health criteria, 44 patients (23%) met dimensional criteria for involvement. This included 41 patients <5 years of age who had at least 1 dimension of a coronary artery segment >3 mm over the 5-week period.
patients at subsequent echocardiograms. If the maximum
gram, they did not increase above 2.5 for 94% of such
score was
the pRCA and pLAD were
independent factors independently associated with a greater
manner with increasing age category at enrollment. Addi-
onset to treatment with IVIG, a lower IgM level measured at
any time included greater number of days from disease
remained increased
78% of subjects.

Of the 6 patients with any dimension >4 mm, 2 had
dimensions >4 mm in either the pRCA or pLAD, 2 in the left
main coronary artery only, and 1 in the distal left anterior
descending coronary artery only. The remaining patient had
dimensions >4 mm in nearly all branches, with increases in
size noted from the initial to the 5-week assessment. One
additional patient had an isolated aneurysm that measured
4 mm noted in the mid right coronary artery with no proximal
aneurysm. No patient had a giant aneurysm, ie, with maximal
internal lumen diameter ≥8 mm. Abnormal vessel tapering or
luminal irregularities were not assessed.

Time Trends From Initial Assessment
Trends over time were explored. If the maximum z scores of
the pRCA and pLAD were <2.5 at the initial echocardi-
ogram, they did not increase above 2.5 for 94% of such
patients at subsequent echocardiograms. If the maximum z
score was ≥2.5 at the initial echocardiogram, the z score
remained increased ≥2.5 over the 5 weeks of follow-up for
78% of subjects.

Independent Factors
Mixed linear regression analysis of repeated measures of z
scores of the pRCA and pLAD demonstrated 6 independent
risk factors associated with a greater magnitude of z score. A
linear decrease in z score occurred from initial assessment
over the 5 weeks of follow-up (Table). z Scores of the pRCA
were significantly greater than those of the pLAD at all time
points. Younger patient age at enrollment was independently
associated with a greater z score at all time points. Figure 2A
shows the independent relationship of age at enrollment with
z scores. Least squares mean z scores decreased in a linear
manner with increasing age category at enrollment. Additional
factors independently associated with a greater z score at
any time included greater number of days from disease
onset to treatment with IVIG, a lower IgM level measured at
initial assessment, and a lower minimum albumin level noted
over the 5-week period. A similar analysis to that of age was
performed with categories and quintiles and showed a linear
relationship with no clear cut point that indicated increased
risk for these variables (Figure 2B, 2C, and 2D). Likewise,
various transformations of independent variables did not
improve the fit of the model. No factor significantly influ-
enced the noted time trend toward reduction in z score. Of
note, the main clinical trial did not show a significant impact
of the addition of pulse steroid therapy to IVIG on coronary
artery outcomes, although a trend in favor of benefit was
noted for those patients resistant to IVIG.

Discussion
Definitions of Coronary Artery Involvement
We have defined a more precise spectrum of coronary artery
involvement using serial normalized coronary artery dimen-
sions and determined associated risk factors. In 1984, the
Japanese Ministry of Health established the first definitions
of coronary artery involvement in KD patients. These criteria
have been widely adopted in reporting the prevalence of
coronary artery abnormalities, associated factors, and the
effects of interventions. However, it is recognized that these
definitions are arbitrary, fail to account for patient size, and
reflect only the time point of maximal dimension. De Zorzi et
al explored the distribution of coronary artery dimensions,
adjusted for body surface area as z scores using linear
regression equations derived from a normal afebrile control
population, in patients with KD whose arteries were classified
as “normal” by Japanese Ministry of Health criteria. They
noted that 27% of patients having no coronary artery involve-
ment by Japanese Ministry of Health criteria had a least 1
coronary artery z score >2, or 2 SDs from normal based on
body surface area. Involvement was maximal in the first 10
days of illness, similar to the present findings and other
reports.

As reported in the present study, attention to the continuous
and varying nature of coronary artery dimensions may reveal

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**Figure 1.** Maximum z score of either the pLAD or pRCA branch diameters according to time from randomization. Box encloses the 25th to 75th percentile, line represents the median, and tails represent the 5th and 95th percentiles. Cross represents the mean value. Outliers are not depicted, with minimum and maximum values as follows: initial assessment, −1.76, 9.73; 1 week, −1.07, 15.3; 5 weeks, −1.33, 15.3.

**Table 1.** Independent Factors Associated With Higher z Score of the Diameter of the pLAD and pRCA Branches (n=190 Patients)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate (SE)*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>4.08 (0.69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>pRCA (vs pLAD)</td>
<td>0.17 (0.06)</td>
<td>0.009</td>
</tr>
<tr>
<td>Shorter time from enrollment to echocardiogram (d)</td>
<td>0.010 (0.002)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Younger age at enrollment (y)</td>
<td>0.14 (0.04)</td>
<td>0.001</td>
</tr>
<tr>
<td>Lower minimum albumin level (g/dL)</td>
<td>0.83 (0.17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Greater time from fever onset to treatment with IVIG (d)</td>
<td>−0.14 (0.06)</td>
<td>0.03</td>
</tr>
<tr>
<td>Lower serum IgM level at initial assessment (mg/dL)</td>
<td>0.005 (0.002)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

*From mixed linear regression analysis of repeated measures. No significant interactions existed between factors or between factors and time course. Mean imputation was used to replace missing values for independent variables. The intercept refers to the intercept of the multivariable regression equation with the y-axis and represents the modeled baseline value of z score, which is then influenced by the presence or absence of the value of the listed factors weighted by their respective parameter estimate.
a broader spectrum of involvement. Furthermore, long-term studies have suggested that coronary arteries that would be defined as having had no involvement based on Japanese Ministry of Health criteria may demonstrate functional abnormalities. Thus, it is possible that these criteria are insensitive for identifying patients with more subtle involvement who may still be at increased risk for accelerated atherosclerosis and thus warrant ongoing assessment and counseling. In the future, more precise methods to detect mild degrees of coronary artery involvement may better define KD patients who should be monitored more closely for premature atherosclerotic cardiovascular disease.

Risk Factors for Coronary Artery Involvement

Using serial assessments of dimensions, we defined 6 risk factors independently associated with a continuous normalized measure of coronary artery involvement. Although our assessment is more precise, the risk factors determined are similar to those previously reported with dichotomous definitions, particularly the Japanese Ministry of Health criteria applied at the time of maximal luminal dimension. Several studies have further focused on risk factors for aneurysms, particularly giant coronary artery aneurysms (≥8 mm in diameter). In examining serial z scores of coronary artery dimensions measured over the first 5 weeks after presentation, we defined the early time course of change and identified younger patient age, longer time to treatment, lower initial IgM level, and lower minimum albumin level to be significantly and independently associated with a higher z score at any time. These risk factors confirm the findings of previous studies that used Japanese Ministry of Health criteria.

Demographic, clinical, and management factors have been previously noted to be associated with coronary artery involvement. Demographic risk factors reported have included male gender, race, and younger patient age, particularly less than 1 year of age. Older patient age has been less consistently reported and may be more related to delays in diagnosis and treatment. The absence or presence of particular clinical criteria has not been reported to be a risk factor, nor has the presence of concomitant infections or arthritis. Prolonged or persistent fever has been consistently reported as a risk factor, as has recurrence of KD. Management factors have been prominent, particularly delays in diagnosis and treatment. Anderson et al noted that delayed diagnosis was not significantly related to healthcare system factors but was related to dispersion over time in the development of clinical features. Early treatment has been debated as a risk factor, although it may be a risk factor for unresponsiveness to IVIG. Egami et al studied risk factors for unresponsiveness to IVIG and noted many of the same risk factors as for coronary artery involvement.

There has been a great deal of focus on laboratory factors, and threshold values are suggested for clinical decision making in algorithms with regard to diagnosis and treatment. Hematologic factors have included lower hemoglobin or hematocrit, lower platelet count, and higher white cell count, often with higher neutrophil or band components. Burns et al reported that higher β-thromboglobulin was significantly associated with aneurysm formation. Lower serum albumin has been a prominent risk factor, and lower serum sodium and potassium and higher alanine aminotransferase have been reported. Inflammatory markers have been interesting, with higher C-reactive protein being an inconsistent risk factor. There has been some interest in serum cytokines, with elevations in interleukin-6 and interleukin-8 reported as risk factors. We noted that a lower IgM level at initial assessment was significantly associated with higher coronary artery z scores. Previous studies have reported that lower initial IgG level, adjusted for age, was a risk factor. Later in the course of KD, higher IgG and lower IgA have been
reported to be significantly associated with coronary artery involvement.14–48

**Study Limitations**

The findings of the present study must be viewed in light of some potential limitations. The present study population did not include patients with incomplete presentations, those presenting beyond 10 days from fever onset, and those not treated with IVIG or other dosing regimens of IVIG. Thus, our study findings may not be completely generalizable to the total population of patients being identified with potential KD in clinical practice. Normalization as z scores was based on regression equations derived from observations in nonfebrile normal children. Normative data are not available for distal coronary artery segments. Thus, our analyses focused on normalized measurements of the pLAD and pRCA rather than reported from semiquantitative assessment, and distal arterial segments are rarely aneurysmal without at least some proximal dilation. Patients were not followed up beyond 5 weeks after presentation, and therefore, longer-term changes were not studied. The prevalence of severe coronary artery involvement was lower compared with other studies addressing associated factors, which either included more patients with aneurysms or focused on them specifically.

**Summary**

On the basis of the present results, we noted that for patients with typical KD treated in accordance with current guidelines within the first 10 days of illness, coronary artery dimensions are significantly increased in the first 5 weeks after presentation, although the prevalence of aneurysms is low. With serial normalized measurements, initial measurements appear to be good predictors of involvement during early follow-up, with patients whose initial z score is <2.5 maintaining that score during early follow-up. We defined 6 independent risk factors associated with our more precise analysis of a continuous spectrum of coronary artery involvement. The risk factors we noted are similar to those reported from studies using arbitrary dichotomous definitions of coronary artery involvement. Understanding the risk factors for coronary artery involvement in KD patients may facilitate the identification of low-risk children in whom extensive and frequent testing may be unnecessary, as well as high-risk children who may require closer monitoring and may be candidates for additional therapies.

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**Disclosures**

None.

**References**

Kawasaki disease is an acute, self-limited vasculitis of unknown cause associated with the development of coronary artery aneurysms in infants and children. Studies of risk factors for coronary artery involvement usually define involvement dichotomously as either present or absent based on measurement of maximal arterial diameters. The present study analyzed serial normalized measurements and noted that dimensions were maximal at baseline assessment at presentation and diminished thereafter but remained above normal in the majority over the 5-week period of observation. Associated risk factors were identified and were similar to those defined with arbitrary dichotomous criteria. The definition of coronary artery involvement has important implications for follow-up, and the identification of risk factors may distinguish those high-risk patients who might require increased surveillance or more aggressive treatment.
Treatment of Proximal Deep-Vein Thrombosis With the Oral Direct Factor Xa Inhibitor Rivaroxaban (BAY 59-7939)
The ODIXa-DVT (Oral Direct Factor Xa Inhibitor BAY 59-7939 in Patients With Acute Symptomatic Deep-Vein Thrombosis) Study

Giancarlo Agnelli, MD; Alexander Gallus, MB, FRACP; Samuel Z. Goldhaber, MD; Sylvia Haas, MD; Menno V. Huisman, MD, PhD; Russel D. Hull, MBBS, MSc; Ajay K. Kakkar, MD, PhD; Frank Misselwitz, MD, PhD; Sebastian Schellong, MD; for the ODIXa-DVT Study Investigators

Background—An effective and safe oral anticoagulant that needs no monitoring for dose adjustment is urgently needed for the treatment of diseases that require long-term anticoagulation. Rivaroxaban (BAY 59-7939) is an oral direct factor Xa inhibitor currently under clinical development.

Methods and Results—This randomized, parallel-group phase II trial in patients with proximal deep-vein thrombosis explored the efficacy and safety of rivaroxaban 10, 20, or 30 mg BID or 40 mg once daily compared with enoxaparin 1 mg/kg BID followed by vitamin K antagonist. Each treatment was administered for 12 weeks. The primary efficacy end point was an improvement in thrombotic burden at day 21 (assessed by quantitative compression ultrasonography; ≥4-point improvement in thrombus score) without recurrent symptomatic venous thromboembolism or venous thromboembolism–related death. The primary safety end point was major bleeding during 12 weeks of treatment. Outcomes were adjudicated centrally without knowledge of treatment allocation. The primary efficacy end point was achieved in 53 (53.0%) of 100, 58 (59.2%) of 98, 62 (56.9%) of 109, and 49 (43.8%) of 112 patients receiving rivaroxaban 10, 20, or 30 mg BID or 40 mg once daily, respectively, compared with 50 (45.9%) of 109 patients treated with enoxaparin/vitamin K antagonist. There was no significant trend in the dose–response relationship between rivaroxaban BID and the primary efficacy end point (P=0.67). Major bleeding was observed in 1.7%, 1.7%, 3.3%, and 1.7% of patients receiving rivaroxaban 10, 20, or 30 mg BID or 40 mg once daily, respectively. There were no major bleeding events with enoxaparin/vitamin K antagonist.

Conclusions—Results of this proof-of-concept and dose-finding study support phase III evaluation of the orally active direct factor Xa inhibitor rivaroxaban, because efficacy and safety were apparent in the treatment of proximal deep-vein thrombosis across a 3-fold range of fixed daily dosing. (Circulation. 2007;116:180-187.)

Key Words: thrombosis ■ thromboembolism ■ deep-vein thrombosis ■ factor Xa ■ anticoagulants

Currently available anticoagulants have well-known limitations.1 Low–molecular-weight heparins require subcutaneous administration. Vitamin K antagonists (VKAs) are orally active but require laboratory monitoring for dose initiation and adjustment, have a narrow therapeutic window, and are subject to drug and food interactions. An orally active, safe, and effective anticoagulant that requires no monitoring for dose adjustment would have the potential to radically simplify the management of thromboembolic disorders.

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From the Division of Internal and Cardiovascular Medicine–Stroke Unit, University of Perugia, Perugia, Italy (G.A.); Flinders Medical Centre and Flinders University, Adelaide, Australia (A.G.); Brigham and Women’s Hospital, Harvard Medical School, Boston, Mass (S.Z.G.); Institute for Experimental Oncology and Therapy Research, Munich, Germany (S.H.); Leiden University Medical Center, Leiden, the Netherlands (M.V.H.); Foothills Hospital, Calgary, Alberta, Canada (R.D.H.); Thrombosis Research Institute and Barts and the London School of Medicine, London, United Kingdom (A.K.K.); Bayer HealthCare AG, Wuppertal, Germany (F.M.); and University Hospital Carl Gustav Carus, Dresden, Germany (S.S.).
Guest Editor for this article was Alan T. Hirsch, MD.
The online-only Data Supplement, consisting of an Appendix that lists the ODIXa-DVT Study Investigators, is available with this article at http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.106.668020/DC1.
Correspondence to Giancarlo Agnelli, MD, Division of Internal and Cardiovascular Medicine, University of Perugia, Ospedale S. Maria della Misericordia, Perugia, Italy. E-mail agnellig@unipg.it
© 2007 American Heart Association, Inc.
Circulation is available at http://www.circulationaha.org DOI: 10.1161/CIRCULATIONAHA.106.668020
fold selectivity than for other related serine proteases, and also inhibits prothrombinase activity and clot-associated FXa activity.\textsuperscript{5,6} Rivaroxaban has predictable pharmacokinetics and pharmacodynamics in healthy subjects and those undergoing orthopedic surgery.\textsuperscript{7,8} The relative bioavailability of rivaroxaban is high (\textasciitilde80\%); it has a dual mode of excretion, primarily via the renal route (66\%) and also by the fecal/biliary route; and it is excreted primarily as unchanged drug.\textsuperscript{10} Maximum plasma concentrations are reached in 2 to 4 hours in healthy subjects, and it has a half-life of \textasciitilde9 hours in young healthy subjects and 12 hours in healthy elderly subjects (aged \textasciitilde75 years).\textsuperscript{7,11} Rivaroxaban should not require routine laboratory monitoring and can be given as a fixed dose.

The aim of this phase II dose-finding study was to explore the efficacy and safety of rivaroxaban, relative to standard therapy, for the treatment of acute proximal deep-vein thrombosis (DVT). This proof-of-concept study was planned to assess the ability of rivaroxaban to treat existing clots, because previous studies have shown that short-term anticoagulation with rivaroxaban, for up to 10 days, can prevent VTE after major orthopedic surgery.\textsuperscript{12-14} This is the first study to evaluate an orally active FXa inhibitor for the treatment of a disease that requires long-term anticoagulation.

Methods

Study Patients

Patients with symptomatic acute thrombosis of the popliteal or more proximal veins, confirmed by complete compression ultrasound (CCUS) were considered for enrollment in the present study if they were aged 18 years or over, had no symptoms of pulmonary embolism (PE), had not received a VKA, and had received no more than 36 hours of treatment with unfractionated heparin or a low–molecular-weight heparin (3 doses 12 hours apart or 2 doses 24 hours apart).

The main exclusion criteria were related to bleeding risk: cerebral ischemia; intracerebral bleeding or gastrointestinal bleeding within the past 6 months; neurosurgery within the past 4 weeks or other surgery within the past 10 days; an active peptic ulcer; a known liver function (transaminases >2\times ULN); impaired liver function (transaminases >2\times ULN); a likelihood of reduced oral drug absorption (severe inflammatory bowel disease, short gut syndrome); and child-bearing potential without effective contraception. Patients were also excluded if they required thrombolytic therapy or treatment with antiplatelet agents, nonsteroidal anti-inflammatory drugs with a half-life \textasciitilde17 hours, or potent CYP3A4 inhibitors, such as ketoconazole. Short-term analgesia with acetylsalicylic acid, 500 mg/d, was permitted before and during the study.

Study Design

The ODIXa-DVT (Oral Direct Factor Xa Inhibitor BAY 59-7939 in Patients With Acute Symptomatic Deep-Vein Thrombosis) study was a multinational, multicenter, partially blinded, parallel-group study in which patients were randomized by central computer, within 36 hours of confirmed diagnosis of symptomatic proximal DVT, to receive 1 of 4 double-blinded dose regimens of rivaroxaban or open-label standard anticoagulant therapy for 12 weeks (Figure 1). Patients in the oral rivaroxaban treatment groups received double-blinded doses of 10, 20, or 30 mg twice daily (BID) or 40 mg once daily, with food, for 12 weeks. Pharmacokinetic and pharmacodynamic data and phase II DVT prevention trials\textsuperscript{12-14} suggested these doses were likely to be effective and safe. Patients in the open-label, standard-anticoagulant group received enoxaparin 1 mg/kg BID by subcutaneous injection and a VKA (warfarin, phenprocoumon, or acenocoumarol, as agreed in participating countries). Enoxaparin was given for at least 5 days and until the INR had reached 2 to 3 for 2 consecutive days; the VKA was continued for 12 weeks. Clinical follow-up continued until 30 days after the last dose of study medication. Anticoagulant therapy after 12 weeks was at the investigators’ discretion.

The study complied with the Declaration of Helsinki and Good Clinical Practice guidelines, was approved by local Institutional Review Boards, and required written and informed consent before patients were enrolled. Study results were reviewed regularly by an expert Independent Data Safety Monitoring Board.

Study Procedures

Proximal DVT at baseline was confirmed by CCUS examination. A baseline perfusion lung scan was undertaken within 72 hours of the CCUS and within 36 hours of starting study drug. The CCUS examination and perfusion lung scan were repeated on mean day 21 (range, 18 to 26); an additional CCUS examination was performed on day 84±14 days.

To ensure a high quality of standardized CCUS, all sonographers received CCUS training, and study centers were certified by the Central Adjudicating Laboratory before subjects were recruited. In addition, investigators were advised that asymptomatic perfusion defects are frequent findings when patients with proximal DVT have routine lung scans and should not alter clinical management.\textsuperscript{15} The protocol required patients to continue with study medications after mean day 21 (range, 18 to 26) if local review of the CCUS and lung scan results found no deterioration. However, continued study treatment was subject to the investigator’s clinical judgment if local adjudication suggested asymptomatic deterioration.
Efficacy and Safety Outcomes
The primary efficacy outcome was an improvement in thrombotic burden at mean day 21 (range, 18 to 26; defined as a ≥4-point reduction in the thrombus score as measured by CCUS examination) without confirmed symptomatic extension or recurrence of DVT, confirmed symptomatic PE, or VTE-related death. Secondary efficacy outcomes included an improvement in thrombus score of ≥4 points as measured by CCUS examination and/or an improved perfusion lung scan on day 21, without deterioration in the other and/or without symptomatic recurrence of VTE; an improvement in CCUS examination score at 3 months (84±14 days); the incidence of symptomatic and confirmed PE or VTE (recurrence or extension) during the 3 months of study therapy.

Clinically suspected extension or recurrence of DVT was investigated by CCUS examination, and suspected PE by lung scanning and/or spiral computerized tomography and/or angiography. If investigations were negative, study treatment was continued and the planned CCUS and lung scan examinations were undertaken. Study treatment was stopped upon confirmation of VTE or significant bleeding, which was managed according to usual clinical practice.

The primary safety outcome was the incidence of major bleeding with onset no later than 2 days after the last dose of study drug. Secondary safety outcomes included the incidence of minor bleeding events. Bleeding was considered major if it was fatal, affected a critical organ (retropitoneal, intracranial, intraocular, or intra-articular), or was clinically overt and led to treatment cessation, a fall in blood hemoglobin ≥2 g/dL, or transfusion of 2 or more units of packed red blood cells or whole blood; all other overt bleeding events were considered minor.16

All clinically suspected VTE, bleeding events, deaths, and paired perfusion lung scans (see below) were adjudicated, without knowledge of the treatment group, by an independent central adjudication committee at the Henderson Research Centre, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada.

Scoring of CCUS and Perfusion Lung Scan Examinations
Video recordings of CCUS examinations and copies of perfusion lung scans were adjudicated centrally without the knowledge of the treatment group (CCUS Adjudication Committee, University Hospital Carl Gustav Carus, Dresden, Germany). A score reflecting the burden of leg vein thrombus was defined a priori and was analogous to the venography score described by Marder et al.17 It included all affected proximal and distal vein segments and took into account the thrombus diameter. It was derived from central adjudication of video documents taken at the standardized CCUS examination (Figure 2). In a previous study, high interobserver agreement existed in identifying affected proximal and distal venous segments in symptomatic patients (κ=1.0 and κ=0.90, respectively) with this CCUS protocol.18 The score for each affected venous segment (except for the deep femoral) was adjusted for thrombus diameter (assessed under full compression and compared with the diameter of the corresponding artery). The segment score was increased 1.5-fold if its compressed diameter was ≥1.5 times the arterial diameter and reduced 0.5-fold if this was ≥0.5 times the arterial diameter. The minimum qualifying score was 1 (isolated thrombosis of a popliteal vein with a diameter ≤0.5 times that of the popliteal artery), and the maximum possible score was 64 (thrombosis in all named venous segments of the leg, each with a diameter ≥1.5 times that of the corresponding artery). CCUS videos were assessed centrally by 2 independent readers, with discrepancies in thrombus scoring resolved by consensus. The ultrasound scoring system used in the present study was shown to have very low interobserver variability. For the purposes of the present study, an improvement in thrombotic burden between paired examinations was defined as a ≥4-point reduction in the CCUS score. Standard 6-view perfusion lung scans were obtained after intravenous injection of 99mTc-labeled macroaggregated albumin and adjudicated centrally as improved, unchanged, or showing new defect(s) in lung perfusion between paired examinations.

Laboratory Assessments
Blood samples were collected for central laboratory analysis of clinical chemistry, blood cell counts, and blood coagulation before randomization and on treatment days 1, 7±2, 21±2, 56±4, 84±4, and 114±4 (clinical chemistry only). Blood coagulation results were withheld from investigators, who managed VKA by monitoring INR locally. Electrocardiography was performed on days 1, 21±2, and 84±4.

In patients whose liver function tests became abnormal, the decision to stop blinded rivaroxaban therapy or continue under close laboratory supervision was based on a predetermined algorithm. Treatment was discontinued if the derived creatinine clearance fell below 30 mL/min (confirmed by 2 consecutive readings).

Statistical Analyses
The projected sample of 120 patients per twice-daily rivaroxaban treatment group was derived with nQuery Advisor, version 4, module PGT 1-1 (Statistical Solutions Ltd, Cork, Ireland), with the assumptions of a linear dose effect, a positive outcome relative to the primary efficacy end point in 32%, 43%, and 54% of patients receiving 10, 20, and 30 mg BID, respectively, and that 75% of patients would be available for efficacy analysis. This sample size would yield a 2-sided type I error rate of 0.05 for the trend test and a type II error rate of 0.15, corresponding to a power of 85%. It was planned that a similar number of patients would be given rivaroxaban 40 mg once daily and the active comparator, so that a total of 600 patients would be randomized.

The primary efficacy analysis (to determine the dose-response relationship between twice-daily rivaroxaban and the primary effi-
The baseline characteristics of the 604 randomized patients who received study treatment (safety population) are shown in Table 1. The treatment groups were similar. Seventy-six patients were not eligible for efficacy analysis at day 21 for the following reasons: baseline or day 21 CCUS not evaluable (n=50); insufficient compliance (n=12); CCUS examination fell outside the prespecified time window (n=10); study medication ceased too early relative to CCUS (n=3); and DVT not detected at baseline (n=1). Thus, 528 patients were included in the per-protocol analysis of the primary efficacy end point. A total of 530 patients (87.7%) continued treatment until 84 days.

Of all patients randomized to receive rivaroxaban, 73 discontinued treatment for the following reasons: adverse event (n=41), consent withdrawn (n=10), death (n=2), insufficient therapeutic effect (n=1), noncompliance with study drug (n=2), protocol violation (n=16), and lost to follow-up (n=1). Ten patients in the enoxaparin/VKA group discontinued study drug for the following reasons: adverse event (n=1), consent withdrawn (n=7), death (n=1), and protocol violation (n=1). In patients treated with a VKA, the average proportion of time within the target INR range of 2.0 to 3.0 was ≈60.0%.

**Efficacy Outcomes**

The proportion of patients who met primary outcome criteria for efficacy was similar among all 4 rivaroxaban dose groups and the enoxaparin/VKA group. The primary efficacy end point (improvement of ≥4 points in thrombus score in the absence of recurrent VTE and VTE-related death) was observed in 53 (53.0%) of 100, 58 (59.2%) of 98, 62 (56.9%) of 109, and 49 (43.8%) of 112 patients receiving rivaroxaban 10, 20, or 30 mg BID or 40 mg once daily, respectively, compared with 50 (45.9%) of 109 of those treated with enoxaparin/VKA (Table 2). No significant trend was observed in the dose-response relationship between twice-daily rivaroxaban and the primary efficacy end point (P=0.67).

During the initial 21-day treatment period, 2 symptomatic, confirmed, recurrent VTE events occurred in patients receiving rivaroxaban (1 proximal DVT in each of the 10- and 20-mg BID groups [per-protocol population]). A nonfatal PE occurred in the rivaroxaban 30-mg BID group in the intention-to-treat population.

At 3 months, the efficacy end point was observed in 71 (71.0%) of 100, 70 (71.4% of 98), 80 (73.4%) of 109, and 77 (68.8%) of 112 of patients receiving rivaroxaban 10, 20, or 30 mg BID.

**Results**

Between March 2004 and June 2005, 636 patients were enrolled in the study, and 613 were randomized; 23 were not randomized because of protocol violation (n=21) or adverse events (n=2; Figure 3). An additional 9 patients, all randomized to rivaroxaban, did not receive study medication because of protocol violation (n=6) or withdrawn consent (n=3).

**TABLE 1. Baseline Characteristics According to Treatment Groups: Safety Population (n=604)**

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>Enoxaparin/VKA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 mg BID (n=119)</td>
<td>20 mg BID (n=117)</td>
</tr>
<tr>
<td>Sex, % male</td>
<td>58.8</td>
<td>57.3</td>
</tr>
<tr>
<td>Age, y</td>
<td>58.5±15.3</td>
<td>57.5±15.9</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>81.9±17.6</td>
<td>79.7±17.3</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.1±5.1</td>
<td>27.3±5.2</td>
</tr>
<tr>
<td>Height, cm</td>
<td>170.2±9.6</td>
<td>170.7±11.7</td>
</tr>
</tbody>
</table>

OD indicates once daily; BMI, body mass index. Values are mean±SD.
mg BID or 40 mg once daily, respectively, compared with 78 (71.6%) of 109 of those treated with enoxaparin/VKA. Values are given for those patients with valid measurements at 3 months.

During the extended treatment period (between days 21 and 84), an additional 7 VTE-related events occurred in the per-protocol population: 2 fatal PEs (1 in the rivaroxaban 10-mg BID group and 1 in the rivaroxaban 40-mg once-daily group); 2 nonfatal PEs (1 in the rivaroxaban 20-mg BID group and 1 in the rivaroxaban 40-mg once-daily group); and 3 proximal DVTs (1 in the rivaroxaban 30-mg BID group, 1 in the 40-mg once-daily group, and 1 in the enoxaparin/VKA group). The same events were observed in the intention-to-treat population, and an additional proximal DVT was observed in the safety population in a patient receiving enoxaparin/VKA, as well as 3 deaths not related to VTE (1 in the rivaroxaban 10-mg group and 2 in the rivaroxaban 20-mg group). Table 3 summarizes the incidence of symptomatic recurrent VTE events throughout the entire treatment period.

Safety Outcomes
Major bleeding was observed in 1.7%, 1.7%, 3.3%, and 1.7% of patients receiving rivaroxaban 10, 20, or 30 mg BID or 40 mg once daily, respectively (Table 4). Two events occurred in each of the 10- and 20-mg BID and 40-mg once-daily groups, and 4 events occurred in the 30-mg BID group. No major bleeding events occurred in the enoxaparin/VKA group. No significant trend was observed in the dose-response relationship for rivaroxaban BID and major bleeding (P=0.39). The incidence of minor bleeding events is shown in Table 4.

Fourteen patients died: 13 (2.7%) of 478 given rivaroxaban and 1 (0.8%) of 126 in the enoxaparin/VKA group (relative risk 3.4, 95% confidence interval [CI] 0.56 to 33.07). No deaths reported during the study were considered drug related. Two deaths in the rivaroxaban groups were attributed to PE (see above). One rivaroxaban patient died of liver failure (see below).

Most of the remaining deaths were attributed to malignancies, including metastatic cancer and lung cancer. Other causes of death included septicemia, disseminated intravascular coagulation, and pneumonia.

Other Observations
The incidence of treatment-emergent alanine aminotransferase (ALT) elevations >3×ULN in the rivaroxaban groups ranged from 1.9% to 4.3% compared with 21.6% in the enoxaparin/VKA-treated group, and this was not dose dependent. Approximately half of the ALT elevations in the rivaroxaban-treated patients occurred during the first 3 weeks of treatment (Table 5). In the enoxaparin/VKA-treated patients, the majority of ALT elevations occurred during the first 2 weeks of treatment (Table 5). Beyond 21 days, the proportions of rivaroxaban- or VKA-treated patients with ALT elevations >3×ULN were similar (1.9% versus 0.9%) with similar 95% CIs (Table 5). The overall median time to elevation of ALT >3×ULN was 10.5 days in the 4 rivaroxaban treatment groups and 7 days in the enoxaparin/VKA group. One patient had ALT >3×ULN in combination with bilirubin ≥2×ULN; this patient died of acute liver failure (details below).

Rivaroxaban was stopped prematurely in 3 patients because of elevated liver enzyme levels. Two had early elevations of liver aminotransferases. In 1, ALT and aspartate aminotransferase began to increase on the day after the initiation of treatment, which was stopped after 5 days; ALT and aspartate aminotransferase levels returned to below the ULN. In the other, ALT and aspartate aminotransferase were elevated on the day of study drug initiation before first intake of study drug, when treatment was stopped immediately. This patient died 2.5 weeks later of carcinoma with liver metastases.

In the third patient, rivaroxaban 40 mg once daily was stopped after 23 days owing to a diagnosis of hepatitis B with raised liver aminotransferases; viral serology showed acute

### Table 2. Incidence of Primary Efficacy End Point (Thrombus Regression at Day 21 [Days 18–26]) Without Recurrent Symptomatic VTE or VTE-Related Death: Per-Protocol Population (n=528)

<table>
<thead>
<tr>
<th>Rivaroxaban</th>
<th>10 mg BID (n=100)</th>
<th>20 mg BID (n=98)</th>
<th>30 mg BID (n=109)</th>
<th>40 mg OD (n=112)</th>
<th>Enoxaparin/VKA (n=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved, n (%)</td>
<td>53 (53.0)</td>
<td>58 (59.2)</td>
<td>62 (56.9)</td>
<td>49 (43.8)</td>
<td>50 (45.9)</td>
</tr>
<tr>
<td>95% CI, %</td>
<td>42.8–63.1</td>
<td>48.8–69.0</td>
<td>47.0–66.3</td>
<td>34.4–53.4</td>
<td>36.3–55.7</td>
</tr>
<tr>
<td>Deteriorated, n (%)</td>
<td>1 (1.0)</td>
<td>1 (1.0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

OD indicates once daily.

### Table 3. Incidence of Recurrent DVT, PE, or VTE-Related Death up to Day 84 (+14): Intention-to-Treat Population (n=543)

<table>
<thead>
<tr>
<th>Rivaroxaban</th>
<th>10 mg BID (n=106)</th>
<th>20 mg BID (n=100)</th>
<th>30 mg BID (n=111)</th>
<th>40 mg OD (n=114)</th>
<th>Enoxaparin/VKA (n=112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>2 (1.9)</td>
<td>2 (2.0)</td>
<td>2 (1.8)</td>
<td>3 (2.6)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Death (VTE-related)</td>
<td>1 (0.9)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.9)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>PE, nonfatal</td>
<td>0 (0.0)</td>
<td>1 (1.0)</td>
<td>1 (0.9)</td>
<td>1 (0.9)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Recurrent DVT</td>
<td>1 (0.9)</td>
<td>1 (1.0)</td>
<td>1 (0.9)</td>
<td>1 (0.9)</td>
<td>1 (0.9)</td>
</tr>
</tbody>
</table>

OD indicates once daily. Values are n (%).
hepatitis B with seroconversion during the study period, and the patient died of acute liver failure 48 days after starting treatment. One month before inclusion in the study, this patient received 2 transfusions because of anemia during palliative chemotherapy for metastatic uterine sarcoma. Liver histology, taken at autopsy, showed postnecrotic fibrosis with compensatory hyperplasia without acute inflammatory changes. The most likely cause of liver failure was fatal hepatitis B infection; however, a contribution from rivaroxaban or 1 of the concomitant medications the patient had received cannot be excluded. One patient stopped rivaroxaban because of an increased creatinine level on the day of study drug initiation, seen before the first intake of study drug (167 μmol/L; ULN 106 μmol/L).

**Discussion**

In this dose-finding study, 4 fixed-dose regimens of rivaroxaban spanning a 3-fold daily dosing range were evaluated for the treatment of proximal DVT. Thrombus burden after 3 and 12 weeks of treatment was consistently reduced with each rivaroxaban dose, to a similar extent as with enoxaparin/VKA. Therefore, the present study does not indicate whether once- or twice-daily dosing of rivaroxaban is optimal. Nevertheless, when the present results are considered together with those from another recently concluded dose-ranging study that explored daily rivaroxaban doses of 20 to 40 mg, it appears the lowest (20 mg/d) dose shows the most promise for further clinical development.

The present study, like other recent phase II dose-ranging treatment trials in DVT,19,20 used change in thrombus burden combined with perfusion lung scanning as a surrogate measure of efficacy. Change in thrombus burden as a surrogate outcome measurement has been validated by consistent findings demonstrating that changes in thrombus burden, as assessed by venography, are related to recurrent VTE events during therapy.22–24 However, venography is uncomfortable for patients and exposes them to radiation and the risk of contrast media–related adverse events. Furthermore, a significant proportion of patients are likely to refuse the second

**TABLE 5. Incidence of Treatment-Emergent ALT Elevations >3×ULN**

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Rivaroxaban* (All Doses)</th>
<th>Enoxaparin/VKA</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;14 d</td>
<td>6/446 (1.3)</td>
<td>22/116 (19)</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.5–2.9</td>
<td>12.3–27.3</td>
</tr>
<tr>
<td>14–21 d</td>
<td>2/286 (0.7)</td>
<td>2/70 (2.9)</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.1–2.5</td>
<td>0.4–9.9</td>
</tr>
<tr>
<td>&gt;21 d</td>
<td>8/429 (1.9)</td>
<td>1/115 (0.9)</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.8–3.6</td>
<td>0.0–4.8</td>
</tr>
</tbody>
</table>

Values collected before or on the same day that study medication was initiated were considered baseline.

*No dose-response relationship was shown; therefore, dosing groups were pooled.
examination, thereby increasing the likelihood of incomplete evaluations. CCUS is accurate in patients with symptomatic DVT. Thus, for the purposes of the present study, we converted the validated venographic surrogate measure to ultrasound using a standardized examination protocol (CCUS) that was validated internally and externally in previous studies. We also designed a scoring system that closely resembled the venographic Marder score. The blinded central adjudication process, with 2 independent adjudicators and consensus reading in cases of discrepancy, provided a high standard of procedural quality. The reliability of the 3-week-outcome measurement is supported by a previous study, in which pairs of venograms were obtained 3 weeks apart to assess treatment efficacy. In that study, the proportion of patients with treatment response after 3 weeks in the standard treatment arm was consistent with the results of the present study.

Concern about the possible hepatotoxicity of orally absorbed, direct-acting, clotting factor–specific anticoagulants was raised by the recent experience with ximelagatran, an orally absorbed prodrug for the direct thrombin inhibitor melagatran. Rivaroxaban, unlike melagatran, is an FXa inhibitor, but it is essential to seek evidence of possible effects on liver function. Enoxaparin is known to raise ALT levels, and the incidence of treatment-emergent ALT elevations during the first 3 weeks of drug exposure was substantially lower in the rivaroxaban groups. Beyond 21 days, the pooled point estimates of 1.9% for ALT >3×ULN with rivaroxaban and 0.9% in the VKA group had similar 95% CIs. Liver failure in the patient who died was attributed to acute hepatitis B infection; however, a contribution from rivaroxaban or I of the other concomitant medications the patient received cannot be excluded. The case emphasizes the need for continuing surveillance for liver toxicity in large-scale phase III studies. Although more deaths occurred in the rivaroxaban group, most were attributed to malignancies, including metastatic cancer and lung cancer, and none were considered drug related.

The strengths of the present study include its double-blind, parallel-group comparison among rivaroxaban dosing regimens, central randomization, and central adjudication of all outcomes by expert committees blinded to treatment allocation. Furthermore, a large proportion of patients met the criteria for the primary efficacy analysis. In this phase II study, patient safety was reinforced by reevaluation of the thrombosis burden after 3 weeks, to minimize the chance of exposing patients to an ineffective dose and to allow investigators to react if patients showed a significant but asymptomatic increase in thrombus burden, as interpreted locally at the time of repeat testing.

One limitation of the present trial is that compared with phase III evaluations, study patients were younger, and few had active cancer (<3%), which may have reduced the likelihood of thrombus extension or bleeding events. Another limitation is that as in most phase II VTE treatment studies, efficacy was evaluated with a surrogate end point (the change in thrombus burden, derived by scoring the extent of thrombosis observed on repeated extended CCUS examinations).

In conclusion, this proof-of-concept and dose-finding study suggests that rivaroxaban, an orally active, direct FXa inhibitor, may have efficacy and safety in the treatment of proximal DVT across a 3-fold daily dosing range. Large phase III trials comparing clinical outcomes with rivaroxaban or low–molecular-weight heparin/VKA across a wide spectrum of patients are needed to confirm these observations.

Acknowledgments

We would like to thank Dr E. Muehlhofer and A. Kunde for their valuable contributions to this study.

Source of Funding

This study was supported by Bayer HealthCare AG.

Disclosures

Drs Agnelli, Gallus, Goldhaber, Haas, Huisman, Hull, and Kakkar received reimbursement as members of the ODIXa-DVT steering committee. Dr Gallus received a research grant for the ASPIRE trial investigating aspirin for the secondary prevention of venous thromboembolism and received honoraria as a consultant to Bayer HealthCare, GlaxoSmithKline, sanofi-aventis, AstraZeneca, Astellas, and Progen. Dr Haas received a research grant from Lilly for a phase IIa study with a factor Xa inhibitor, received honoraria from AstraZeneca, and is a member of a speakers’ bureau for sanofi-aventis and GlaxoSmithKline; she also has participated as an expert witness for German medicolegal cases. Dr Kakkar has received research grants from AstraZeneca to support the PERCIEVE registry and from sanofi-aventis for basic research on a low–molecular-weight heparin; he is a consultant to Bayer, sanofi-aventis, and Emisphere, for which he has received honoraria, and has also received honoraria from Pfizer, Merck, and BoehringerIngelheim. Dr Schellong was reimbursed as a member of the ODIX-a-DVT adjudication committee and was a consultant on the study; he also received a research grant to undertake a substudy of phase II prevention of venous thromboembolism trials with rivaroxaban to validate an ultrasound method. Dr Misselwitz is an employee of Bayer HealthCare AG and owns stock in the company.

References

Rivaroxaban for Proximal Vein Thrombosis

Agnelli et al

Currently available anticoagulants are effective but are administered parenterally (eg, low–molecular-weight heparins) or are difficult to manage because they require laboratory monitoring to adjust the dose (eg, vitamin K antagonists). Rivaroxaban is an oral direct factor Xa inhibitor in advanced clinical development. Rivaroxaban has been shown to be safe and effective as enoxaparin for prophylaxis of venous thromboembolism after major orthopedic surgery. This randomized, parallel-group phase II trial in patients with proximal deep-vein thrombosis explored the efficacy and safety of rivaroxaban 10, 20, or 30 mg twice daily or 40 mg once daily compared with enoxaparin 1 mg/kg BID followed by a vitamin K antagonist. Thrombus burden after 3 and 12 weeks of treatment was uncommon in all treatment groups. The predictable pharmacological profile of rivaroxaban, which does not include the need for coagulation monitoring, makes it an attractive proposition for both short- and long-term anticoagulation. Confirmation of this potential therapeutic benefit for any clinical thromboembolic indication would require completion of multiple investigations to verify the observed benefit and risk. In addition, the long-term safety of this potential new therapeutic molecule will require careful evaluation in a larger population of individuals who would be anticipated to receive such treatment.
L-Arginine Supplementation in Peripheral Arterial Disease
No Benefit and Possible Harm
Andrew M. Wilson, MBBS, PhD; Randall Harada, MD; Nandini Nair, MD, PhD; Naras Balasubramanian, PhD; John P. Cooke, MD, PhD

Background—L-Arginine is the precursor of endothelium-derived nitric oxide, an endogenous vasodilator. L-Arginine supplementation improves vascular reactivity and functional capacity in peripheral arterial disease (PAD) in small, short-term studies. We aimed to determine the effects of long-term administration of L-arginine on vascular reactivity and functional capacity in patients with PAD.

Methods and Results—The Nitric Oxide in Peripheral Arterial Insufficiency (NO-PAIN) study was a randomized clinical trial of oral L-arginine (3 g/d) versus placebo for 6 months in 133 subjects with intermittent claudication due to PAD in a single-center setting. The primary end point was the change at 6 months in the absolute claudication distance as assessed by the Skinner-Gardner treadmill protocol. L-Arginine supplementation significantly increased plasma L-arginine levels. However, measures of nitric oxide availability (including flow-mediated vasodilation, vascular compliance, plasma and urinary nitrogen oxides, and plasma citrulline formation) were reduced or not improved compared with placebo. Although absolute claudication distance improved in both L-arginine– and placebo-treated patients, the improvement in the L-arginine–treated group was significantly less than that in the placebo group (28.3% versus 11.5%; \( P = 0.024 \)).

Conclusions—In patients with PAD, long-term administration of L-arginine does not increase nitric oxide synthesis or improve vascular reactivity. Furthermore, the expected placebo effect observed in studies of functional capacity was attenuated in the L-arginine–treated group. As opposed to its short-term administration, long-term administration of L-arginine is not useful in patients with intermittent claudication and PAD. (Circulation. 2007;116:188-195.)

Key Words: amino acids ■ atherosclerosis ■ endothelium ■ nitric oxide ■ peripheral vascular disease

Endothelium-derived nitric oxide (NO) is a potent endogenous vasodilator with vasoprotective properties. In patients with cardiovascular risk factors or disease, inactivation or reduced synthesis of NO impairs endothelium-dependent vasodilation. Furthermore, the vasoprotective actions of NO are attenuated by cardiovascular risk factors.

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L-Arginine is the precursor of NO. In animal models of cardiovascular disease, supplementation with L-arginine improves vasodilation and increases vascular NO synthesis. In preclinical studies, long-term administration of L-arginine inhibits atherosclerosis and myointimal hyperplasia and enhances angiogenesis. More importantly, short-term studies in patients with cardiovascular risk factors or disease indicated that L-arginine supplementation may increase NO synthesis and improve vasoreactivity. In patients with severe peripheral arterial disease (PAD), intravenous infusion of L-arginine (30 g over 30 minutes) increases limb blood flow 2-fold and to the same extent as prostaglandin E\(_2\). The increase in limb blood flow is associated with parallel increases in urinary nitrogen oxides, as well as plasma and urinary cGMP, consistent with increased NO synthesis.

There are limited options for medical management of intermittent claudication. A nutritional adjunct to PAD therapy seems low risk, and the scientific rationale for L-arginine supplementation seems sound. Accordingly, we initiated a randomized clinical trial of L-arginine supplementation with the aim of improving vascular reactivity and functional capacity in patients with PAD.

Methods
The Nitric Oxide in Peripheral Arterial Insufficiency (NO-PAIN) trial was a prospective, single-center, randomized, double-blind, placebo-controlled National Heart, Lung, and Blood Institute–funded study of the efficacy and safety of oral L-arginine supplementation in patients with intermittent claudication. The trial was
approved by the institutional review board at Stanford University; registered at www.clinicaltrials.gov (No. NCT00284076); and monitored by an external Data and Safety Monitoring Board and a National Heart, Lung, and Blood Institute program officer. Written informed consent was obtained from each patient.

Patients
Inclusion criteria were age of at least 45 years, unilateral or bilateral PAD confirmed by a resting ankle-brachial index (ABI) <0.9, stable intermittent claudication for the previous 3 months, and the ability to walk 1 to 12 minutes on a treadmill. Variability of maximum walking distances between 2 consecutive screening treadmill tests was <25%. Exclusion criteria included ischemic rest pain, ulceration or gangrene, history in the previous 3 months of acute coronary syndrome or revascularization involving the peripheral or coronary arteries, major amputation, malignancy within the previous 5 years (except for treated nonmelanoma skin cancer), proliferative retinopathy, uncontrolled hypertension, or active inflammatory, infectious, or autoimmune diseases. A 1-month washout period was also required before enrollment for patients taking pentoxifylline, cilostazol, prostanooids, l-carnitine, or l-arginine. Patients were advised to maintain their current lifestyle habits related to diet, tobacco, and exercise during study participation.

Eligible patients were randomly assigned to either l-arginine (1 g TID with meals) or placebo. l-Arginine was manufactured by Ajinomoto Inc and encapsulated by Cosmo-Pharm Inc. Bioavailability studies before study initiation confirmed that active study drug increased plasma arginine levels. Amino acid analysis (Beckman 6300 analyzer; Beckman) at the Stanford Clinical Laboratory after the completion of the study showed 95.8% and 97.9% recovery of l-arginine in randomly selected capsules from the remaining lot of l-arginine and 0% recovery of l-arginine from randomly selected capsules from placebo.

Study Procedures
Assessment of Functional Capacity
Graded treadmill tests were performed at 3 and 6 months after randomization, according to the Skinner-Gardner protocol. Initial claudication distance (ICD) and absolute claudication distance (ACD) were recorded. Two consecutive treadmill tests were performed within 1 week at baseline (before administration of study drug); 1 test was performed at 3 months; and 2 treadmill tests were performed after 6 months on study drug. Functional status was also assessed by the Walking Impairment Questionnaire and the Health Status Survey SF-36 questionnaire (SF-36).

Vascular Studies
ABI was measured after 10 minutes of supine rest with a hand-held Doppler. Systolic pressures were measured at the dorsalis pedis, posterior tibial, and brachial arteries bilaterally. The right and left ABI values were calculated by taking the higher pressure of the 2 brachial arterial systolic pressures. The index ABI was defined as the ABI of the extremity with the lowest value.

Flow-mediated vasodilation of the brachial artery was measured with the use of an Acuson Sequoia C256 high-resolution ultrasound unit with a 14-mHz probe (Siemens Inc). Vascular studies were performed in a quiet, darkened room with the patient in a fasting state. After measurement of the brachial artery diameter, a blood pressure cuff on the forearm was inflated to a pressure of 50 mm Hg above systolic pressure for 5 minutes. After deflation, measurements of the brachial artery diameter were performed at 30, 45, and 60 seconds during reactive hyperemia. Electronic calipers were used for the measurement of artery diameter. Flow-mediated vasodilation was expressed as the maximal percent change in diameter from the resting condition during the period of reactive hyperemia.

Vascular compliance was measured with the use of a CVProfilor DO 2020 (Hypertension Diagnostics Inc). A tonometer was positioned over the radial artery to obtain a stable waveform. The measurement of oscillatory compliance has been shown to be at least partially dependent on NO availability and it correlates with measures of flow-mediated vasodilation in the same subjects. Coefficients of variation for these tests performed in our laboratory have been published previously.

Patients ingested a low-nitrate diet for 24 hours before testing, fasted overnight, and were given low-nitrate water to consume for 12 hours before blood samples and urine were collected for safety laboratory studies; urinary and plasma nitrogen oxides; amino acid analysis; and plasma asymmetrical dimethylarginine (ADMA) levels. Venous blood was collected into EDTA-coated tubes on ice and plasma stored at −80°C. Nitrogen oxide measurements were performed by Greiss reaction with a colorimetric assay; plasma arginine, ornithine, and citrulline were measured with an amino acid analyzer; and plasma ADMA was measured by immunoassay.

A questionnaire to elicit adverse events, a pill count to assess compliance, and a treadmill test were conducted at 3- and 6-month follow-up. Secondary measures such as ABI, flow-mediated vasodilation, vascular compliance, and basic clinical laboratories were repeated at 6 months.

Statistical Analysis
The change in ACD was prespecified as the primary end point. ACD values were log transformed. Secondary efficacy end points included changes in ICD, SF-36 and Walking Impairment Questionnaire measures, ABI, flow-mediated vasodilation, vascular compliance, urinary and plasma nitrogen oxides, and plasma amino acid levels. Sample size calculation for the primary end point was based on the results of a pilot, dose-ranging study. These calculations indicated that 120 patients randomized into 2 treatment groups would provide 90% power at a 1-sided α level of 0.05 to reject the null hypothesis assuming a 20% increase in ACD over placebo in the l-arginine group.

Thus, we sought to enroll at least 132 patients to allow for an anticipated dropout of 10%.

Baseline characteristics in the 2 groups were compared by Student t test or Mann-Whitney test. The primary efficacy analysis, based on a modified intention-to-treat principle, included all patients who received at least 1 dose of blinded study treatment and had at least 1 valid postrandomization treadmill test. A last observation carried forward method was applied to missing 6-month data. Comparisons of 6-month changes from baseline in efficacy and laboratory values between the 2 groups were conducted with an ANCOVA model with terms for treatment and baseline values. All statistical comparisons between mean treatment-related changes from baseline were performed with the model-adjusted (least-squares) mean values rather than unadjusted raw means. Nonparametric tests were used to analyze nonnormally distributed data when appropriate. In all cases, P<0.05 was used to indicate statistical significance. All analyses were performed with SPSS software, version 12.0.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
A total of 2365 people presented for the study. After initial telephone screening, 687 provided consent and underwent further onsite screening. Most exclusions from those providing consent were due to normal ABI. Thus, 133 patients were randomized (67 subjects randomized to placebo and 66 to l-arginine). The numbers of discontinuations were similar between the groups, resulting in 61 patients in the placebo group and 58 patients in the l-arginine group. Baseline characteristics of the 2 treatment groups were not different (Tables 1 and 2).

Laboratory Measures
Plasma arginine increased in the group receiving the active study drug, as did plasma ornithine (Figure 1) and blood urea nitrogen (from 20.3±6.8 to 22.9±9.8 mg/dL at 6 months;
Surprisingly, plasma citrulline levels did not increase in the arginine group (Figure 1). In the placebo group, no changes occurred in plasma levels of arginine, ornithine, or urea.

Plasma and urinary nitrogen oxides rose slightly in the placebo group but not with L-arginine treatment (Figure 2 and Table 3). Plasma ADMA levels were high in both groups at baseline (Table 3) but did not change significantly over 6 months, nor were there any significant changes in clinical chemistry, hematology, lipid measures, glucose, or insulin in either group (data not shown).

Vascular Studies
No group differences existed for ABI or vascular compliance measurements (Table 4). ABI increased slightly in both groups (Table 4). No correlation existed between change in ABI and ACD ($r = -0.116$, $P = 0.23$). Surprisingly, mean flow-mediated vasodilation in the L-arginine group decreased after 6 months, whereas flow-mediated vasodilation in the placebo group increased. This resulted in a significant difference in the mean change of flow-mediated vasodilation between the 2 groups (Figure 2), although the changes within the groups did not reach statistical significance (Figure 2).

Functional Capacity
Walking distances (ICD and ACD) increased in both groups from baseline to last observation carried forward through 6 months (Table 5). In the placebo group, ACD increased significantly from baseline to 3 months and baseline to 6 months, whereas no significant change

### Table 1. Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=67)</th>
<th>L-Arginine (n=66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD, y</td>
<td>72±7</td>
<td>73±9</td>
</tr>
<tr>
<td>Women</td>
<td>18 (27)</td>
<td>14 (21)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>52 (78)</td>
<td>52 (79)</td>
</tr>
<tr>
<td>Black</td>
<td>5 (7)</td>
<td>6 (9)</td>
</tr>
<tr>
<td>Asian/Pacific Islands</td>
<td>5 (7)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Mixed or other</td>
<td>4 (6)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>20 (30)</td>
<td>20 (30)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>60 (90)</td>
<td>62 (94)</td>
</tr>
<tr>
<td>Statins</td>
<td>42 (63)</td>
<td>44 (67)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>19 (28)</td>
<td>21 (32)</td>
</tr>
<tr>
<td>ACEI and/or ARB</td>
<td>37 (55)</td>
<td>36 (55)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>30 (45)</td>
<td>28 (42)</td>
</tr>
<tr>
<td>Long-acting nitrates</td>
<td>9 (13)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>12 (18)</td>
<td>6 (9)</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>2 (3)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>12 (18)</td>
<td>8 (12)</td>
</tr>
<tr>
<td>Index leg ABI, mean±SD</td>
<td>0.56±0.18</td>
<td>0.59±0.17</td>
</tr>
<tr>
<td>Median ACD, m (IQ range)</td>
<td>292 (185–438)</td>
<td>258 (173–350)</td>
</tr>
<tr>
<td>Median ICD, m (IQ range)</td>
<td>94 (62–152)</td>
<td>75 (57–111)</td>
</tr>
</tbody>
</table>

Data are n (%) unless otherwise indicated. Statins indicates 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; and IQ, interquartile. No significant differences were seen between variables.

### Table 2. Baseline Clinical Laboratory Measures

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=67)</th>
<th>L-Arginine (n=66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>184±139.7</td>
<td>180.5±47.9</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>49.7±16.8</td>
<td>49.8±15.3</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>103.7±32.5</td>
<td>99.1±38.1</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>158.1±113.1</td>
<td>163.6±143.1</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>41.8±4.1</td>
<td>40.2±4.6</td>
</tr>
<tr>
<td>Platelets, $\times 10^{12}/\mu$L</td>
<td>232.8±60.7</td>
<td>225.5±51.0</td>
</tr>
<tr>
<td>BUN, mg/dL</td>
<td>20.5±8.4</td>
<td>21.1±7.7</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.2±0.4</td>
<td>1.2±0.4</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>113.2±33.7</td>
<td>116±50.1</td>
</tr>
</tbody>
</table>

Data are mean±SD unless otherwise indicated. HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; and BUN, blood urea nitrogen. No significant differences were seen between variables.
occurred in the L-arginine group between baseline and 3 months (Figure 3). The change in baseline to 6 months reached significance (P=0.04). No significant intragroup differences existed between 3- and 6-month time points. Subjects receiving L-arginine manifested significantly less improvement in ACD (mean improvement of 11.5% in the L-arginine group versus 28.3% in the placebo group) (Figure 4). The change in ICD in the L-arginine group tended to be less than in the placebo group (39.6% versus 47.1%; P=0.06). Quantitative composite measures of quality of life with the use of the Walking Impairment Questionnaire or SF-36 were similar between the treatment groups (data not shown).

**Adverse Events**

The adverse event profile for the safety population is summarized in Table 6. Of these, 9 in each group were considered serious events. No group differences existed in serious or total adverse events.

**Discussion**

The major observation of the present study is that long-term administration of L-arginine does not improve walking distance in patients with PAD. Furthermore, the data indicate that long-term administration of L-arginine may even impair functional capacity, perhaps through an adverse effect on vascular reactivity. Specifically, significant group differences were observed in flow-mediated vasodilation and in plasma and urinary nitrogen oxide elaboration.

**Rationale for L-Arginine Supplementation**

These findings were unexpected. In previous studies, we and others have shown that short-term administration of L-arginine (the NO precursor) improves endothelial vasodilator function of coronary or peripheral arteries in patients

![Figure 3](image-url)
with cardiovascular disease. The improvement in vascular reactivity is likely due to the metabolism of L-arginine to NO because it is associated with increases in urinary or plasma nitrogen oxides and cGMP.

We hypothesized that administration of L-arginine would enhance NO synthesis and, by so doing, improve calf blood flow and functional capacity in patients with PAD. This hypothesis was based on the observation that patients with PAD have elevated plasma levels of ADMA. ADMA is a methylated arginine analogue and an endogenous competitive inhibitor of NO synthase. ADMA is metabolized by the enzyme dimethylarginine dimethylaminohydrolase (DDAH). In conditions in which DDAH is impaired or deficient, ADMA accumulates. Vascular DDAH is impaired by the oxidative stress associated with elevated levels of cholesterol, blood glucose, triglycerides, or homocysteine. Preclinical and human studies indicate that ADMA adversely affects angiogenesis and vascular regeneration and accelerates vascular disease. Infusion of ADMA increases systemic resistance, reduces cardiac output and vascular compliance, and lessens cerebral blood flow in humans.

**Other Studies of L-Arginine Supplementation and Functional Capacity**

This is the largest randomized clinical trial, of the longest duration, to assess the effect of L-arginine on functional capacity. Several small studies of relatively brief duration have shown a beneficial effect of L-arginine on functional capacity. In patients with PAD (n=39), Boger and colleagues showed that intravenous administration of L-arginine (8 g BID) for 2 weeks improved femoral endothelium-dependent vasodilation, increased urinary nitrogen oxides and cGMP, and increased walking distance compared with placebo. Maxwell and colleagues reported that oral L-arginine supplementation (3 g BID, as part of a nutraceutical supplement) for 2 weeks improved ACD in patients with PAD (n=41). Previously, we performed a pilot study to establish the lowest effective oral dose of L-arginine to improve walking distance. Patients with PAD and intermittent claudication (n=80) were randomly assigned to oral doses of 0, 3, 6, or 9 g of L-arginine daily in 3 divided doses for 12 weeks. We observed a trend for a greater increase in walking distance in the group treated with 3 g L-arginine daily and a trend for an improvement in walking speed in patients treated with L-arginine. Similar observations related to the beneficial effects on functional capacity of L-arginine have been made in patients with coronary artery disease and in patients with congestive heart failure.

Although these studies were typically small and of short duration, they are consistent with mechanistic preclinical studies. In hypercholesterolemic mice, plasma ADMA levels are elevated, and endothelial vasodilator function is impaired. In these animals, L-arginine supplementation increases exercise capacity in association with an increase in limb blood flow and urinary nitrogen oxides. In addition to its action as a vasodilator, NO mediates angiogenesis. In the NO synthase–deficient mouse, angiogenesis in response to limb ischemia is impaired, as demonstrated by capillary densitometry. By contrast, in the DDAH transgenic mouse, plasma ADMA levels are

![Figure 4. Change in walking distances. Oral administration of L-arginine for 6 months was associated with significantly less improvement in ICD and ACD. Values are mean±SE percent change from baseline.](image-url)
low, NO synthesis is increased, and the angiogenic response to limb ischemia is augmented. In New Zealand White rabbits, L-arginine enhances the angiogenic response to surgically induced limb ischemia. Thus, by improving vascular reactivity and/or vascular regeneration, augmenting the synthesis of endothelial NO improves limb blood flow and exercise capacity.

**L-Arginine Tolerance?**

The discordance between the results of the present study and those of previous work might be explained by the fact that the present study was of longer duration. Perhaps counterregulatory mechanisms are activated in response to prolonged administration of the NO precursor. This is true of sustained administration of exogenous NO donors such as nitroglycerin, which causes nitrate tolerance. Multiple mechanisms may be involved in nitrate tolerance, including neurohumoral adjustments, oxidative stress, or inhibition of nitroglycerin bioactivation. Could similar mechanisms exist to counter an upregulated synthesis of endogenous NO? Of relevance to this question, Moncada and coworkers found that NO synthase inhibitors enhanced vascular responsiveness to exogenous nitrates. They suggested that removal of endogenous NO induced a supersensitivity to nitrovasodilators at the level of soluble guanylate cyclase.

Induction of arginase expression is a mechanism that could be involved in “arginine tolerance.” Arginase metabolizes L-arginine to ornithine and urea. Arginase in the intestine and liver is responsible for extensive first-pass metabolism of L-arginine. In our study, ornithine and urea levels were increased in the arginine-treated individuals, consistent with the action of arginase. However, we also observed a significant elevation of plasma arginine levels, and therefore arginase cannot be invoked as the sole cause of counterregulation.

We had anticipated that arginine administration would increase both NO and citrulline levels by the action of NO synthase. We observed no increase in either. Perhaps L-arginine administration triggers a mechanism to inhibit NO synthase. A transient increase in vascular NO levels could inhibit DDAH and cause ADMA to increase. However, we did not observe an increase in plasma ADMA levels in the arginine-treated patients. Alternatively, it is possible that a transient increase in NO levels could inhibit NO synthase activity by nitrosylation of NO synthase itself or the arginine transporter to counter any arginine-induced increase in NO production.

**Potential Adverse Effects of Long-Term L-Arginine Therapy**

In our study, the improvement in ACD in the placebo-treated patients was 28.3%, similar to the placebo effect in other studies. By contrast, long-term L-arginine therapy was associated with only an 11.5% increase in ACD. The improvement in ACD was significantly different between the 2 groups and might indicate an adverse effect of L-arginine on functional capacity. The reduced improvement might be due to an arginine-induced derangement of the NO synthase pathway, with a paradoxical reduction in NO production.

In a recent randomized clinical trial, long-term therapy with oral L-arginine supplementation in patients after myocardial infarction (6 g/d for 6 months; n = 150) did not improve ejection fraction or vascular compliance, and the study was terminated prematurely for safety concerns. By contrast, in a larger study of shorter duration (6 g/d for 30 days; n = 750), L-arginine tended to reduce major adverse cardiovascular events. Taken together, these studies are also consistent with a benefit of short-term administration, which is lost with long-term administration (ie, arginine tolerance).

The present study was based on the hypothesis that L-arginine would reverse the competitive inhibition of NO synthase by ADMA. Accumulating evidence indicates that ADMA contributes to endothelial dysfunction in cardiovascular disease and may be an independent predictor of cardiovascular events. In mice, overexpression of DDAH reduces plasma ADMA, increases NO synthesis, and reduces systemic vascular resistance. The reduction in ADMA is associated with vascular protection, as shown by a greater capacity for angiogenesis, and a resistance to vascular lesion formation. Agents that increase DDAH expression or activity may be useful in the treatment of cardiovascular disease. Indeed, there are currently several disease-modifying drugs that reduce ADMA, including metformin, rosiglitazone, converting enzyme inhibitors, and angiotensin receptor antagonists. Of course, each of these agents has other metabolic and hemodynamic effects that are antiatherogenic.

**Conclusion**

In a randomized, double-blind, placebo-controlled trial in patients with intermittent claudication, oral L-arginine supplementation (3 g/d for 6 months) was less effective than placebo in improving measures of endothelial function and treadmill exercise. L-Arginine is not a useful nutritional adjunct in patients with intermittent claudication and PAD.

**Acknowledgments**

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Disclosures
Dr Cooke is the inventor of patents owned by Stanford University for diagnostic and therapeutic applications of the NO synthesis pathway from which he receives royalties. Dr Cooke is a consultant to Ajinomoto and United Therapeutics. The other authors report no conflicts.

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**CLINICAL PERSPECTIVE**

L-Arginine is a semiessential amino acid and is the precursor for nitric oxide (NO). The vasodilator action of NO resembles that of nitroglycerin. Its vasodilator and vasoprotective effects are attenuated in patients with cardiovascular disease or risk factors. Previous studies in cardiovascular patients reveal that short-term administration of L-arginine restores endothelium-dependent, NO-mediated vasodilation. Small pilot studies of brief duration indicate that L-arginine supplementation improves vascular function as well as symptoms in patients with peripheral arterial disease. Accordingly, we performed a randomized clinical trial to determine whether long-term L-arginine supplementation (1 g TID for 6 months) is useful in patients with symptomatic peripheral arterial disease. The primary end point was walking distance by treadmill testing. Secondary end points included measures of vascular function, including flow-mediated vasodilation and vascular compliance, and biochemical measures of NO synthase activity. L-Arginine supplementation increased plasma L-arginine levels but did not increase metabolites of NO synthase (plasma citrulline and nitrogen oxides). Furthermore, L-arginine supplementation did not improve measures of vascular function. Surprisingly, the increment in walking distance in the placebo group was greater than that in the group treated with L-arginine. As opposed to its short-term use, long-term L-arginine supplementation does not improve vascular function or symptoms in patients with peripheral arterial disease. The absence of a long-term benefit might be explained by “arginine tolerance.”
Is septal ablation preferable to surgical myomectomy for obstructive hypertrophic cardiomyopathy?

Surgical Myectomy Remains the Primary Treatment Option for Severely Symptomatic Patients With Obstructive Hypertrophic Cardiomyopathy

Barry J. Maron, MD

The evolving alcohol septal ablation versus surgical myectomy controversy represents a crossroad in the management of obstructive hypertrophic cardiomyopathy (HCM). Indeed, in this now polarized debate within the cardiovascular community, between the traditional and established (ie, surgery) and the new and percutaneous (ie, ablation), much is at stake for the HCM patient population. Furthermore, this issue has become increasingly important given the visibility recently afforded the pathophysiological significance and frequency of left ventricular (LV) outflow gradients in this disease.1,2

Response by Fifer p 206

In the course of this discussion, I will vigorously defend surgery as the primary treatment of choice when outflow obstruction (gradient ≥50 mm Hg at rest or with physiological exercise) produces heart failure symptoms refractory to maximal medical management (New York Heart Association functional classes III and IV).3,4 To this purpose, I will rely on the 50-year experience and substantial body of evidence available in HCM, as well as my own personal extensive association with and work in this disease spanning >30 years and several hundred publications—neither as a surgeon or interventional cardiologist nor with any particular allegiance to either discipline. The message expressed herein is prosurgery, but it is by no means antiablation, for this treatment modality has proved useful (although with a selective role) in the management of HCM.

Surgical Septal Myectomy

Historical Context

When surgical septal myectomy (Table 1) was initially introduced in the early 1960s at several North American and European centers, it was regarded as revolutionary and has subsequently stood the test of time. The classic myectomy (Morrow operation)5 relieves obstruction by resection of a relatively small amount of muscle (2 to 5 g) from the proximal ventricular septum, thereby widening the outflow tract and abolishing flow drag (or Venturi) forces that promote systolic contact between mitral valve and hypertrophied septum, resulting in immediate gradient reduction6,7 (Figure 1). More recently, some surgeons have creatively modified the myectomy resection to be wider and to extend more distally, allowing more complete reconstruction of the LV outflow tract, which may be necessary in some patients.8–12

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.
From the Minneapolis Heart Institute Foundation, Minneapolis, Minn.
Correspondence to Barry J. Maron, MD, Minneapolis Heart Institute Foundation, 920 E 28th St, Ste 60, Minneapolis, MN 55407. E-mail hcm.maron@mhif.org
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Dr W.P. Cleland at Hammersmith Hospital (London) was the first surgeon to perform a myectomy, but the operation was soon abandoned in the United Kingdom for decades. Thereafter, Drs Andrew Morrow at the National Institutes of Health, John Kirklin at the Mayo Clinic, and Wilfred Bigelow and William Williams at Toronto General pioneered surgical intervention (first myotomy and then myectomy), permitting surgical myectomy to emerge as the primary treatment option for severely symptomatic drug-refractory patients with outflow obstruction in many centers throughout the world.

Operative Risk
In its early years, myectomy was accompanied by ≥5% procedural mortality. Although such operative risk is now clearly obsolete, surgery continues to be frequently misrepresented as an outdated and risk-prone option by its opponents.

Over the last 15 years, with the advantage of contemporary cardiac preservation techniques and intraoperative echocardiography, myectomy has been associated with remarkably low operative mortality approaching zero at major centers (Figure 2). In the combined and continuing experience of the Mayo Clinic, the Cleveland Clinic, and Toronto General Hospital over the last 10 to 12 years, >1500 consecutive isolated myectomy operations have been performed without a postoperative death. The Mayo Clinic also reports no operative deaths in young children over this period (n=56). It is essential that this very low operative mortality risk, rather than irrelevant data transposed from the very early surgical experience, be cited to current myectomy candidates.

In contrast, the procedure-related mortality for alcohol ablation is 1.5% (up to 5%). Therefore, paradoxically, the risk of myectomy is lower than that of ablation. These contemporary data dispel the misplaced notion that myectomy is a risky undertaking because it is surgery, and that alcohol ablation is safe solely because it is percutaneous.

Heart Failure Benefit
The vast amount of data assembled worldwide over 40 years clearly substantiates that myectomy results in immediate and permanent abolition of mechanical obstruction to LV outflow (and mitral regurgitation) with normalization of LV pressures. As a consequence, surgery achieves relief and often elimination of disabling heart failure symptoms and restores exercise capacity and quality of life. In the most recent long-term postoperative analysis, almost 85% of patients became asymptomatic or only mildly symptomatic (New York Heart Association class I or II) an average of 8 years (and up to 25 years) after myectomy. No evidence exists that myectomy itself increases arrhythmogenicity or predisposes to systolic dysfunction and the end stage. Furthermore, the preponderance of evidence from observational, comparative studies with alcohol septal ablation shows that myectomy affords more consistent and complete hemodynamic and symptomatic benefit and is associated with fewer procedural complications and reinterventions.

Survival Benefit
In addition to heart failure reversal, myectomy also promotes long-term survival. Operated patients experience enhanced longevity indistinguishable from that expected in the general population and superior to that of nonoperated patients with obstruction. After myectomy, survival free from all-cause mortality is 98%, 96%, and 83% at 1, 5, and 10 years, and survival free from HCM-related mortality (heart failure and sudden death) is 99%, 98%, and 95%, respectively. Therefore, surgical septal myectomy favorably alters the natural course of HCM, providing a reasonable expectation for normal or nearly normal life expectancy. These data

### TABLE 1. Advantages and Disadvantages of Surgical Septal Myectomy

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom relief known to persist long term</td>
<td>Requires thoracotomy/cardiopulmonary bypass, 5- to 7-day hospitalization, and recovery period</td>
</tr>
<tr>
<td>Immediate, permanent reduction/abolition of outflow gradient; reoperation not necessary</td>
<td>Requires cardiac surgeon experienced with myectomy (which may necessitate patient referral/travel)</td>
</tr>
<tr>
<td>Permits direct visualization of outflow tract anatomy by operating surgeon</td>
<td></td>
</tr>
<tr>
<td>Can identify/correct mitral apparatus abnormalities and tailor resection precisely to distribution of septal thickening</td>
<td></td>
</tr>
<tr>
<td>Permits repair of associated cardiac lesions if necessary*</td>
<td></td>
</tr>
<tr>
<td>With very rare exceptions, does not require permanent postoperative device therapy or reoperation</td>
<td></td>
</tr>
<tr>
<td>Changes disease course by affording long-term survival equivalent to general population</td>
<td></td>
</tr>
<tr>
<td>No postoperative intramyocardial scar</td>
<td></td>
</tr>
</tbody>
</table>

*For example, mitral and aortic valve disease, coronary artery disease, and membranous subaortic stenosis.
should not, however, be interpreted as a justification for intervention with either surgery or alcohol ablation at a much earlier time in the clinical course of HCM.

These substantial benefits of myectomy constitute compelling evidence supporting surgery as the gold standard treatment. In contrast is the unsettling and unsubstantiated claim by some in the interventional cardiology community that surgery should be marginalized or abandoned, has no significant role in the management of HCM, or in fact has already been usurped by alcohol ablation. Furthermore, given the available data, it seems somewhat less than respon-

Figure 1. Septal myectomy operation. Classic surgical strategy as originally depicted by Dr Andrew G. Morrow. Rectangular myectomy trough (length, ~3 to 4 cm) from just below aortic valve to beyond site of mitral–septal contact and intraventricular obstruction. Some myectomy surgeons now routinely extend this resection more distally. From Maron et al97 with permission from the publisher. Copyright © 1983, Oxford University Press.

Figure 2. Contemporary low operative risk. Consecutive number of isolated septal myectomies (without associated cardiac operations or prior alcohol ablation) successfully performed since the last operative death at the 3 most active North American surgical centers: Mayo Clinic (Joseph Dearani, Gordon Danielson, Hartzell Schaff); Cleveland Clinic (Bruce Lytle, Nicholas Smedira); and Toronto General Hospital (William G. Williams, Anthony Ralph-Edwards). Data to end of 2005. †Includes only adult patients. ‡Includes 2 relatively new myectomy programs: Roosevelt-St Luke’s Hospital Center (Daniel Swistel) and Tufts- New England Medical Center (Hassan Rastegar), each with no operative deaths (n=51 and n=38, respectively).

Figure 3. Survival benefit from surgical myectomy. Survival from all-cause mortality after isolated myectomy at the Mayo Clinic (gold) does not differ from matched general US population (white) (P=0.2) and is superior to nonoperated HCM patients with obstruction (green) (P<0.001). From Ommen et al,15 with permission from the publisher. Copyright © 2005, the American College of Cardiology Foundation.
sible to arbitrarily proclaim alcohol ablation to be the “new gold standard for the 21st century” or, remarkably, to argue that myectomy represents an impediment to the development of alcohol ablation.

### Technical Considerations

Unlike alcohol ablation, for which precise targeting of the septum may be constrained by the size and distribution of septal perforator coronary arteries, the flexibility afforded the surgeon by direct visual inspection permits recognition of all morphological abnormalities that contribute to mechanical LV outflow obstruction. These include inhomogeneous thickness of the septum (Figure 4) and papillary muscle anomalies such as direct insertion into anterior mitral leaflet (Figure 5). In addition, recognition that greatly elongated mitral valve leaflets can produce obstruction (even after adequate myectomy) has led to valve repair or plication in some cases. Myectomy avoids mitral valve replacement and can be regarded as a “pure” intervention, rarely leaving behind implanted devices (pacemakers and defibrillators) and never potentially arrhythmogenic myocardial scarring. The complexity and heterogeneity of outflow tract morphology (and necessity for the transaortic approach) have formulated the customary recommendation that septal myectomy be performed by surgeons having specific experience with this operation and HCM.

### Alcohol Septal Ablation

#### Historical Context

Despite the known benefits of myectomy, it has historically been an aspiration in HCM to develop alternative treatment strategies for operative candidates with obstacles to low-risk surgery (eg, obesity, important comorbidity, particularly advanced age, or insufficient motivation for surgery). In the early 1990s, dual-chamber pacing was promoted as an alternative (or replacement) for surgery but proved less effective than myectomy, and in randomized trials, perceived clinical benefit represented only a placebo effect.

In 1995, Dr Ulrich Sigwart applied percutaneous methodology to HCM in which 2 to 4 cm³ of 96% ethanol is introduced into a septal perforator branch of the left anterior descending coronary artery (often guided by myocardial contrast echocardiography) to intentionally produce an infarction in the ventricular septum. After a transient drop in gradient as a result of stunning, ultimate resolution of obstruction requires several months of septal remodeling, leading to outflow tract widening and reduced mitral valve systolic anterior motion (ie, in effect mimicking the pathophysiology of myectomy).

### Clinical Results

Results of alcohol ablation (Table 2) have now been documented in numerous short-term observational studies (average follow-up, ≈0.5 to 3 years). Ablation reduces LV outflow obstruction, although on average somewhat less than myectomy (residual rest gradient, 20 to 25 versus 0 to 10 mm Hg for surgery). Improvements in symptoms and exercise capacity may occur, according to
the principle that interventions that relieve outflow gradient in HCM will likely improve heart failure symptoms. However, treatment failures have been reported in a substantial minority of patients \(35,39,68-71\) (ie, up to 25%) \(69\) (Figure 6), particularly in those with large outflow gradients \(69\); induced complete heart block requiring permanent pacemaker dependency occurs in 5% to 33% of patients. \(35,36,39,59\)

**Emergence and Concerns**

Over the last 7 years, enthusiasm for alcohol septal ablation has accelerated exponentially, with this technology now considered part of routine interventional practice. Interest in ablation has seemed unbridled, instinctually driven by the erroneous assumption that contemporary and percutaneous (“nonsurgical”) strategies are always implicitly more benign and advantageous than traditional open heart surgery. \(33,41-45,74-76\) Indeed, there have been more alcohol septal ablation procedures (estimated \(>5000\)) performed in the last 5 to 7 years than myectomies in \(>45\) years \(51,74-76\); overall, most septal reduction interventions for obstructive HCM are now probably alcohol ablations.

But do these developments in management strategy really serve the best interests of the HCM patient population? First, the disproportionate number of percutaneous versus surgical procedures is a legitimate concern, given that the professed clinical threshold (ie, magnitude of symptoms and gradient) professed for both treatments is identical. \(3,4,11,74-76\) Consequently, it is an inescapable conclusion that less stringent patient selection criteria are used for alcohol ablation than for surgery, with many patients undergoing ablation prematurely (often with only mild symptoms after less than maximal medical management). Of note, over the past 14 years, only \(\approx 5\%\) of my large HCM cohort have required referral for either surgery or ablation.

Second, we have witnessed virtual elimination of myectomy in several European countries (eg, Germany, Switzerland) \(17,18\) and some respected centers in the United States (eg, Stanford) \(20\), all formerly strong proponents of surgical management. In such clinical settings, myectomy has been relegated to the challenging task of relieving obstruction after a failed ablation (and in the presence of large septal scars), a circumstance that also results in pacemaker dependency and may be associated with more complicated technical considerations and hospital course. \(10,77,78\) Certainly, the loss of myectomy expertise for a generation of cardiac surgeons cannot be viewed as advantageous for the future management of HCM. On the other hand, interventional alcohol ablation has been widely criticized for its failure to establish formal rigorous training and to define acceptable levels of expertise. \(11,26,35,41\)

Third, interest in alcohol ablation as a novel treatment strategy has created a virtual flood of observational studies (often published with priority) from a variety of clinical laboratories. This skewing of the recent literature has been so pervasive that it is likely that many newly trained cardiolo-
gists may not even be fully aware of the surgical option (Table 3). In addition, it is worth citing certain specific limitations of the available ablation literature, including incomplete patient follow-up in some reports, underreporting of complications and death rates in inexperienced interventional laboratories sporadically performing ablation, and the unfortunate forced retraction of a major ablation article from a highly respected medical journal.

**Clinical Implications of the Scar**

A major and largely unresolved issue connected to septal ablation relates to the potential long-term consequences of alcohol-induced necrosis and myocardial infarction as an arrhythmogenic substrate that predisposes susceptible patients to lethal reentrant ventricular tachyarrhythmias. This is not an idle consideration that can be easily dismissed, given that HCM is the most common cause of sudden death in young people.

Some observers have suggested that the alcohol-induced scar does not represent a true infarction because of its...

---

**TABLE 2. Advantages and Disadvantages of Alcohol Septal Ablation**

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percutaneous technique (does not require surgeon, cardiopulmonary bypass, or open heart operation)</td>
<td>Procedural mortality not insignificant</td>
</tr>
<tr>
<td>Short in-hospital stay</td>
<td>Produces large, transmural infarct with arrhythmogenic potential and possible increased sudden death risk</td>
</tr>
<tr>
<td>Inflexible; confined to anatomic distribution of septal perforator artery, cannot be tailored to complex LVOT anatomy</td>
<td>Inflexible; confined to anatomic distribution of septal perforator artery, cannot be tailored to complex LVOT anatomy</td>
</tr>
<tr>
<td>Not infrequently associated with CHB requiring permanent pacemaker</td>
<td>Not infrequently associated with CHB requiring permanent pacemaker</td>
</tr>
<tr>
<td>Defibrillator implantation not uncommon because of heightened sudden death risk</td>
<td>Defibrillator implantation not uncommon because of heightened sudden death risk</td>
</tr>
<tr>
<td>Not infrequently requires repeated interventions</td>
<td>Not infrequently requires repeated interventions</td>
</tr>
<tr>
<td>Relief of gradient not immediate, requiring several weeks to fully evolve</td>
<td>Relief of gradient not immediate, requiring several weeks to fully evolve</td>
</tr>
<tr>
<td>Often ineffective in patients with highest gradients</td>
<td>Often ineffective in patients with highest gradients</td>
</tr>
</tbody>
</table>

CHB indicates complete heart block; LVOT, LV outflow tract.

---

**TABLE 3. Popular Misconceptions, Myths, Rationalizations, and Excuses Used to Ignore Surgical Myectomy for Patients With Obstructive HCM**

<table>
<thead>
<tr>
<th>Misconceptions, Myths, Rationalizations, and Excuses Used to Ignore Surgical Myectomy for Patients With Obstructive HCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>I do not believe in surgery.</td>
</tr>
<tr>
<td>Surgical risk is too high.</td>
</tr>
<tr>
<td>Do they really do surgery for HCM anymore?</td>
</tr>
<tr>
<td>You do not hear much about surgery.</td>
</tr>
<tr>
<td>You hear a lot more about alcohol ablation now.</td>
</tr>
<tr>
<td>Our surgeons are afraid (or refuse) to do a myectomy.</td>
</tr>
<tr>
<td>Our surgeon has never done a myectomy.</td>
</tr>
<tr>
<td>We just cannot send all these patients out to Mayo for surgery.</td>
</tr>
<tr>
<td>We do alcohol ablation first and, if unsuccessful, then another ablation, and then maybe transplant. What else is there?</td>
</tr>
<tr>
<td>Myectomy causes dilated cardiomyopathy and leads to heart transplant.</td>
</tr>
<tr>
<td>Alcohol septal ablation is safe and benign, not like surgery.</td>
</tr>
<tr>
<td>Why would anyone have surgery if he or she had a choice?</td>
</tr>
<tr>
<td>Surgery also produces an infarct just like ablation.</td>
</tr>
<tr>
<td>Ablation must be better than surgery because it is newer.</td>
</tr>
</tbody>
</table>

As actually told to the author by cardiologists, 2004 to 2006.

---

**Figure 6.** Failed alcohol septal ablation. Because septal perforator distribution was inappropriate for the ventricular septal (VS) target area, thinning of the wall occurred distal to systolic anterior motion (single arrow), resulting in persistence of outflow obstruction as a result of mitral-septal contact (double arrows) and disabling heart failure symptoms. RV indicates right ventricle; LA, left atrium. From Kimmelstiel and Maron, copyright © 2004, with permission from the American Heart Association.
chemically (rather than ischemic) origin and controlled size. However, recent morphological and magnetic resonance studies unequivocally show the alcohol ablation infarct to be both transmural and extensive, encompassing 10% of the overall LV myocardial mass (30% of the septum) (Figure 7). Repeated alcohol ablations (occurring in 20% to 25% of patients) will result in even larger areas of necrosis and healed infarction caused by coronary occlusion. Contrary to a misconception that persists for some reason, surgical myectomy does not produce intramyocardial scarring, a likely explanation for the rarity of important arrhythmias long term postoperatively. Although mild endocardial thickening may develop at the site of surgical resection, it is neither a scar nor arrhythmogenic.

The precise long-term risk for life-threatening arrhythmias after alcohol ablation is unresolved and requires greatly extended follow-up studies. However, the fact that such ablation-related events do frequently occur is now well established, with 13 deaths reported in 1 study and with 13 deaths reported in 1 study and with a rate of 8% per year, and with 13 deaths reported in 1 study, and as evidenced by recent enthusiasm for prophylactic defibrillator implantation after ablation. Therefore, unlike myectomy, it is possible that alcohol-imposed infarcts could act as a new HCM risk factor, compounding the underlying myocardial electric instability already present in some patients, for whom unpredictable sudden death risk is known to extend over many decades. Consequently, for some patients, alcohol ablation could represent an unfavorable net tradeoff of gradient relief for increased arrhythmia risk.

Indeed, alcohol ablation is unique among cardiovascular treatment strategies by aspiring to hemodynamic benefit via destruction of myocardial tissue and, in the process, contradicting a major tenet of preventive cardiology, to minimize the likelihood of infarction and scarring. Recently introduced experimental septal reduction interventions, which circumvent surgery and ablation (eg, coil embolization, stenting, radiofrequency ablation), also impose sizable septal infarctions similar to those incurred with alcohol. Finally, early experience suggests that myectomy performed after failed alcohol septal ablation may be associated with more complicated technical considerations and hospital course.

Considerations for late postprocedural arrhythmias have led to the prudent recommendation that alcohol ablation should be confined largely to adults of relatively advanced age in whom the potential risk period is shortest. Although some practitioners have inadvisably lowered the age of acceptability for ablation well into childhood, it is the prevailing view of HCM experts that alcohol septal ablation should be strongly discouraged in children, adolescents, and young adults.

Another unfortunate byproduct of this controversy and the euphoria associated with relieving obstruction with alcohol ablation is the misconception that LV outflow gradients (traditionally, a highly visible feature of HCM) are always the predominant clinical facet of this complex disease. As a consequence, other important issues such as risk stratification for sudden death, family screening, and genetic counseling may not always receive the attention they deserve.

**Patient Autonomy and the “Gatekeeper” Effect**

The rapid penetration of alcohol ablation into cardiology practice has often been associated with preferential referral for this procedure without the explicit presentation of other available treatment options (ie, surgical myectomy). This strategy represents an ethical dilemma and, in effect, violates the important principle of patient autonomy (ie, that patients possess a fundamental right to full disclosure of all medical information that may potentially affect their health, safety, and risk for death or injury, as well as an opportunity to actively participate in treatment decisions that dictate their medical destiny) (Table 3). Similar considerations triggered the recent Guidant Affair, in which industry executives withheld from patients and their physicians crucial information about defective implantable defibrillators, known only by the corporation to be unreliable in preventing sudden death.

Cardiologists in the role of gatekeeper bear a similar responsibility with respect to ablation and myectomy: to fully inform patients on the advantages and disadvantages of both septal reduction treatments (Table 3). If patients are not fully apprised of all therapeutic options, they are, in effect, deprived of the opportunity to formulate truly informed decisions. Indeed, this is a fundamental premise of those specialty centers of excellence focused on the diagnosis and management of HCM (where both expert surgery and ablation are available). Finally, recognition that the patient autonomy principle applies to decisions about ablation or surgery requires a willingness to override the inherent resistance to...
referring patients out of institutions and networks that lack accomplished myectomy surgeons (to those that do) when this strategy represents a clear benefit to patients. Such recommendations for HCM are not unlike those made by an American College of Cardiology/American Heart Association consensus panel regarding preferential patient referral for mitral valve repair to centers experienced with that particular operation.\textsuperscript{95}

**Final Thoughts**

The central issue in the current myectomy versus ablation debate resides with proper patient selection. The American College of Cardiology/European Society of Cardiology expert panel recently commissioned to establish consensus guidelines for the management of HCM (including practitioners of surgery and ablation),\textsuperscript{3} and unfortunately largely ignored by the interventional community, formally advocated septal myectomy as the primary treatment option for disabling drug-refractory heart failure symptoms resulting from outflow obstruction. Alcohol septal ablation is regarded as an important but nevertheless alternative intervention for selected patients who are not optimal surgical candidates. Because a prospective randomized trial comparing alcohol ablation and myectomy is impractical and unlikely to occur to resolve this debate,\textsuperscript{96} there is little reason to look beyond the more-established surgical myectomy as the first option for most patients.

Alcohol ablation has been heavily promoted by interventional cardiology over the last several years,\textsuperscript{33,34,39,41–45,63} but now it is imperative that the pendulum swing back toward surgery.\textsuperscript{11,51} Indeed, there does not appear to be a compelling reason to aggressively advance a new invasive treatment option for obstructive HCM (ie, alcohol ablation) that may result in pacemaker and defibrillator dependency, increase the risk for late sudden death, incur potential complications from the implanted devices, and convey a not-inconsequential procedural mortality rate. This is particularly true when an established and time-honored intervention (surgical myectomy) is available that has already served this patient population exceptionally well for >45 years by virtue of extremely low operative risk, more consistent amelioration of symptoms resulting from permanent relief of mechanical impedance to LV outflow, and a documented survival benefit affording the opportunity to achieve normal life expectancy.

**Disclosures**

None.

**References**


Response to Maron

Michael A. Fifer, MD

I have the highest regard for Dr Maron’s unsurpassed experience and expertise in hypertrophic cardiomyopathy. I agree with him that the principle of patient autonomy requires that cardiologists fully inform patients about all treatment options, but I feel obliged to point out that we must compare apples to apples. It is not appropriate to compare the apples of idealized septal myectomy outcomes reported from a very few centers, beginning after the steep portions of practitioners’ learning curves and omitting patients undergoing concomitant cardiac surgery, to the oranges of actual septal ablation outcomes reported from the very early experience with the procedure. It would be misleading to equate the highly selected surgical mortality figures chosen by Dr Maron with those of patients in actual clinical practice. The mortality rate of septal myectomy is not zero! Furthermore, the need for postmyectomy permanent device therapy arises more than rarely, and we as well as others have performed septal ablation in patients who had undergone unsuccessful septal myectomy. The theoretical concern that septal ablation would increase the incidence of fatal arrhythmias has fortunately not been realized; indeed, the publication of Lawrenz et al cited by Dr Maron is actually entitled “Transcoronary Ablation of Septal Hypertrophy Does Not Alter ICD Intervention Rates in High-Risk Patients With Hypertrophic Obstructive Cardiomyopathy.” I agree with Dr Maron that patients should undergo septal reduction therapy only after truly optimal medical therapy has failed, following a balanced and dispassionate presentation of the treatment options and in the context of comprehensive management of their disease.
Hypertrophic cardiomyopathy (HCM) is a disease characterized by primary hypertrophy of the left (and sometimes right) ventricle. The clinical manifestations of the disease are dyspnea, angina, and a continuum encompassing lightheadedness, presyncope, syncope, and sudden death. Although HCM often is caused by an identifiable mutation in a gene coding for a sarcomeric protein and inherited in an autosomal-dominant pattern, many patients do not have any relatives in whom the disease is manifest. The prevalence of HCM is estimated to be 0.2%, with ~600,000 Americans affected.

Several anatomic variants of HCM exist. Of these, hypertrophic obstructive cardiomyopathy (HOCM) is the variant that has been the subject of the most intense investigation. HOCM was previously termed idiopathic hypertrophic subaortic stenosis and is characterized by 4 closely related pathoanatomic features (Figure 1). Obstruction to left ventricular (LV) outflow is caused by bulging of the thickened septum into the left ventricular outflow tract (LVOT) during systole, with apposition of the anterior (occasionally posterior) leaflet of the mitral valve, which demonstrates systolic anterior motion. Mitral regurgitation usually is present, although the degree varies greatly among patients with HOCM.

LVOT gradients may be present at rest or only during Valsalva maneuver or exercise (provocable obstruction). A recent report suggests that if patients with provokable gradients are included, most patients with HCM have the obstructive form of the disease.

Management of HCM
The management of HCM may be considered as consisting of 4 elements (Table 1). For patients at high risk of sudden death, implantation of a cardioverter–defibrillator is considered. In patients with HOCM, the first line of therapy for symptoms consists of medications with negative inotropic properties that diminish the extent of septal bulging into the LVOT; these are \(\beta\)-blockers, calcium channel blockers (of which there has been the largest experience with verapamil), and disopyramide. In most patients, symptoms can be adequately controlled with these medications used alone or in combination. In patients with HOCM and symptoms refractory to optimal medical therapy, mechanical measures aimed at relief of the outflow tract obstruction are considered.

Septal Myectomy
The original mechanical management of patients with HOCM and refractory symptoms consisted of septal myotomy, or...
simple incision of septal muscle, first performed in 1958.5,6 Myotomy was soon replaced by septal myectomy, or removal of septal muscle.7,8 In this approach, the surgeon visualizes the thickened septum through an incision in the aortic root and excises a rectangular segment from the basal septum toward the apex. In patients with septal thickness >15 to 18 mm, septal myectomy incurs a risk of causing a ventricular septal defect; in these cases, an alternative strategy is repair or replacement of the other structure implicated in LVOT obstruction, namely the mitral valve.

Pacing
Dual-chamber pacing with a short atrioventricular delay was suggested as early as 1968 as an innovative approach for the management of HOCM.9 Although marked beneficial effects of pacing were reported in uncontrolled series,10 these findings have not been reproduced in randomized controlled trials.11,12 although a suggestion exists that a small subset of patients benefits from pacing.12

TABLE 1. Elements of the Management of HCM

Screen first-degree relatives for HCM
Avoid strenuous exertion, especially burst activity and isometric exercise, and volume depletion
Control symptoms
Assess risk for and prevent sudden death

Adapted from Binder et al13 with permission of the publisher. Copyright © 2005, The Massachusetts Medical Society.

Septal Ablation
Transcatheter ablation of the septum with ethanol was first performed at the Royal Brompton Hospital in London in 1994.13,14 The first patient to undergo septal ablation had severe symptoms despite β-blockade and a resting gradient of 25 mm Hg that increased markedly during the Valsalva maneuver. Peak creatine kinase was 2500 U/L. She was discharged 3 days after septal ablation and was asymptomatic 10 months later. The results were similar for the other 2 patients in the initial report, both of whom also had LVOT gradients that were low at rest and higher in response to provocative maneuvers.

Because the proximal septal branches of the left anterior descending coronary artery supply the conduction system as well as the basal septum, atrioventricular block is a common complication of septal ablation. For this reason, a temporary pacemaker is placed before the procedure. With standard coronary angioplasty guiding catheters, guidewires, and balloon catheters, the most proximal septal branch that can be catheterized is entered, and the angioplasty balloon is inflated. X-ray contrast is injected through the balloon catheter to confirm filling of the septal branch and absence of backflow into the left anterior descending coronary artery itself. Correct catheter placement also is confirmed by myocardial contrast echocardiography (see below). Dehydrated ethanol, usually 1 mL at a time, is then injected slowly through the balloon catheter, causing a targeted myocardial infarction; the usual total dosage of ethanol is 1 to 3 mL. Patients receive narcotics and experience mild to moderate chest pain, usually burning in quality. The gradient can usually be reduced to <20 mm Hg (Figure 2). In some cases, ethanol is injected selectively into septal subbranches;15 in others, it is injected into 2 or 3 septal branches. After delivery of ethanol, distal flow in the affected septal branch is slow or absent (no-reflow phenomenon; see Figure 3).16

Myocardial contrast echocardiography was introduced into the procedure to localize the septal branch supplying the critical septal segment (ie, the point of mitral valve contact and maximal flow acceleration).17,18 Myocardial contrast may

Figure 1. Schematic depiction of 4 elements of the pathoanatomy of HOCM showing asymmetric septal hypertrophy (ASH), systolic anterior motion (SAM) of the anterior leaflet of the mitral valve, an LVOT gradient, and mitral regurgitation (MR). LA indicates left atrium. Reprinted from Fifer.1

Figure 2. Preablation (A) and immediately postablation (B) LV and femoral arterial pressures in the first patient to undergo septal ablation at Massachusetts General Hospital. Reprinted from Fifer.1
be achieved with agitated x-ray contrast or an echocardiographic contrast agent. Myocardial contrast echocardiography may identify inappropriate sites for injection of ethanol such as a septal branch supplying myocardium too close to the apex, papillary muscle, inferoposterior LV, or right ventricle. Incorporation of this technique reduces the number of septal branches into which ethanol is injected and may both improve success rate and lower marker release and the need for pacing.17,19

Peak creatine kinase is $\approx$500 U/L per 1 mL ethanol injected. In patients with failed septal ablation who subsequently undergo septal myectomy, we have found pathological evidence of necrosis of the vascular endothelium (Figure 4), suggesting that ethanol is toxic to both the coronary circulation and the myocardium.16

What Do We Know About the Efficacy and Safety of Septal Myectomy?

Septal myectomy performed by skilled surgeons at high-volume centers results in abolition of the LVOT gradient and relief of symptoms in the great majority of cases (Table 2).20–23 Results in patients with provokable obstruction are comparable to those in patients with resting obstruction.20 Early mortality, which was high in the early experience with this operation, has been reduced to $\leq$2\% in young or middle-aged otherwise healthy patients undergoing isolated septal myectomy. In older patients, those with comorbid conditions, and those requiring other concomitant cardiac surgery, mortality is considerably higher.22,24,25

Complications of septal myectomy include those peculiar to the operation (eg, ventricular septal defect [1\%])20,26 and complete heart block for which a permanent pacemaker is required [3\% to 10\%, lower in the absence of preexisting conduction system disease]).20–22,26 And those that pertain to any cardiac operation (eg, postoperative bleeding with tamponade, sepsis, and stroke).20–22 Postoperative left bundle-branch block occurs in 40\% to 56\% of patients.24,26,27 When septal myectomy is successful and uncomplicated, studies with a mean follow-up of 6 to 12 years indicate that the improvement is usually sustained.20–22,25,26 Successful septal myectomy results in a decrease in LV mass that is much greater than that attributable to the removal of the septal myocardium itself and that undoubtedly results from relief of pressure overload.28

What Do We Know About the Efficacy and Safety of Septal Ablation?

Septal ablation performed by skilled operators at high-volume centers results in a marked immediate decrease in LVOT gradient in the great majority of patients.17,29–32 In a sizable subset of patients, the gradient response is triphasic, with immediate reduction, early reappearance, and by 3 months after the procedure, sustained fall.33,34 This sequence suggests that myocardial stunning may be responsible in large part for the immediate reduction in gradient. After recovery from stunning, ultimate gradient reduction is associated with remodeling of the septum with an increase in LVOT area.35 Improvement in symptoms occurs over the same 3-month period. Symptom relief and gradient reduction are achieved in $>80\%$ of patients (Table 3).32,36,37 A clinical impression exists that patients with septal thickness approaching or exceeding 30 mm may not achieve full benefit from septal ablation.

In association with the amelioration of the LVOT gradient, the degree of mitral regurgitation decreases,17,29,38 as does the size of the left atrium.17,39 In response to a reduction in the systolic pressure load, systolic myocardial function improves
in the free wall and hypertrophy regresses throughout the LV (as after aortic valve replacement for aortic stenosis; Figure 5). Reduction in LVOT gradient and regression of LV hypertrophy are accompanied by improvement in diastolic LV function, which correlates with an increase in exercise capacity.

Two studies have demonstrated that, as with septal myectomy, the benefit of septal ablation in patients with provokable gradients is similar to that in patients with resting gradients. These studies provide retrospective support for Sigwart’s performance of septal ablation in his first 3 patients, all of whom had provokable obstruction. The standard provocation for deciding whether a patient is a candidate for septal ablation is exercise. Because exercise is not practical in an instrumented patient, patients triaged to ablation on the basis of exercise-induced gradients may receive dobutamine or isoproterenol during the procedure to provide a gradient suitably high to serve as a “target” for ablation.

Temporary complete atrioventricular block occurs during the procedure in approximately half of the patients. After the procedure, right bundle-branch block is present in approximately half of the patients. A corollary is that patients with preexisting left bundle-branch block usually require permanent pacing after ablation. Another corollary is that patients who undergo sequential septal ablation and septal myectomy (which frequently causes left bundle-branch block) also are likely to require permanent pacing. Although the rate of permanent pacemaker placement was as high as 38% early in the septal ablation experience, it has fallen with the introduction of myocardial contrast echocardiography and the use of lower dosages of ethanol, with 1 group reporting an incidence of <10%.

In-hospital mortality is 0% to 4%. Deaths have been due to coronary dissection, pulmonary embolism, refractory ventricular fibrillation, right ventricular perforation by the temporary pacemaker, pump failure, and heart block. In-hospital sustained ventricular tachyarrhythmias occur in 5% of cases. The theoretical concern that after septal ablation, arrhythmic sudden death resulting from superimposition of a myocardial infarction on a cardiomyopathic substrate would be common has fortunately not been realized in clinical practice. In patients with preexisting risk factors for sudden death, an implantable cardioverter–defibrillator may be placed before septal ablation.

Other complications of the procedure are remote myocardial infarction caused by aberrant ethanol injection or collateral circulation and ventricular septal rupture. Because of the latter potential complication, septal ablation should not be performed if septal thickness at the site of planned ethanol delivery is <15 mm.

### Comparison of Septal Ablation and Septal Myectomy

There have been no prospective randomized trials comparing septal ablation with septal myectomy. Investigators have compared the results of septal ablation with those of septal myectomy in several nonrandomized studies (Table 4). In none of these retrospective studies have patients been adequately matched for age, gender, and other clinical predictors of outcome in HOCM.

### TABLE 2. Results of Septal Myectomy

<table>
<thead>
<tr>
<th>Authors</th>
<th>Institution</th>
<th>No.</th>
<th>Early Mortality, %</th>
<th>PPM Rate, %</th>
<th>NYHA Class, %</th>
<th>Late Survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heric et al</td>
<td>Cleveland Clinic</td>
<td>178</td>
<td>6</td>
<td>4</td>
<td>10</td>
<td>71 23</td>
</tr>
<tr>
<td>Robbins and Stinson</td>
<td>Stanford</td>
<td>158</td>
<td>3</td>
<td>2</td>
<td>NA</td>
<td>NA 92</td>
</tr>
<tr>
<td>Wu et al</td>
<td>Toronto General Hospital</td>
<td>338</td>
<td>1.5</td>
<td>0.8</td>
<td>6</td>
<td>98 Combined</td>
</tr>
<tr>
<td>Ommen et al</td>
<td>Mayo Clinic</td>
<td>289*</td>
<td>NA</td>
<td>0.7</td>
<td>1.0</td>
<td>88 Combined</td>
</tr>
</tbody>
</table>

PPM indicates permanent pacemaker; NA, not applicable.

*Isolated myectomy only.

### TABLE 3. Results of Septal Ablation

<table>
<thead>
<tr>
<th>Authors</th>
<th>Institution</th>
<th>No.</th>
<th>Early Mortality, %</th>
<th>PPM Rate, %</th>
<th>Follow-Up, mo</th>
<th>NYHA Class, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gietzen et al</td>
<td>Bielefeld</td>
<td>157</td>
<td>2.5</td>
<td>25</td>
<td>10±8</td>
<td>55 40</td>
</tr>
<tr>
<td>Fernandes et al</td>
<td>Baylor</td>
<td>130</td>
<td>1.5</td>
<td>13</td>
<td>43±14</td>
<td>79 NA</td>
</tr>
<tr>
<td>Faber et al</td>
<td>German registry</td>
<td>242</td>
<td>1.2</td>
<td>9.6</td>
<td>5±2</td>
<td>47 41</td>
</tr>
</tbody>
</table>

PPM indicates permanent pacemaker; NA, not applicable.
In an institution at which both procedures were regularly performed, patients were triaged according to clinical factors, so the groups were not comparable. In particular, the 25 patients undergoing septal ablation were older and had a higher prevalence of comorbid conditions than did the 26 patients undergoing myectomy. At the 3-month follow-up, the gradient reduction was more complete in the surgical cohort, whereas the 2 groups had similar reductions in symptoms, septal thickness, and degree of mitral regurgitation. No deaths occurred in either group.

In the second study from 2 hospitals that each favored 1 of the procedures, patients were triaged according to institutional preference. In this study, it was possible to match patients for age and LVOT gradient. Forty-one patients were included in each group. At the 1-year follow-up, severity of symptoms, maximal oxygen uptake, LVOT gradient, septal thickness, and degree of mitral regurgitation were similar for the 2 therapies. There was 1 death during septal ablation as a result of coronary dissection.

A third study compared the effects of septal ablation in 20 patients with those of septal myectomy in 24 patients. Patients who underwent myectomy were younger than those who had ablation. There was 1 death in each group. Although improvements in LVOT gradient and New York Heart Association (NYHA) class were similar in the 2 groups, the increase in maximal oxygen uptake was higher in the patients who underwent surgery.

In a fourth study, patients were triaged to ablation or surgery on the basis of age and other clinical factors. The outcomes of 54 patients undergoing septal ablation were compared with those of 48 patients undergoing septal myectomy. Relief of symptoms was more complete in the surgical group. More late deaths occurred in the ablation group.

A comparison of echocardiographic indexes of diastolic function an average of 5 months after intervention demonstrated no difference between septal ablation and septal myectomy.

### Which Patients Are Candidates for Mechanical Therapy for HOCM?

Mechanical therapy is appropriate for patients with HOCM who have symptoms (exertional dyspnea, angina, and/or “hemodynamic” syncope) that interfere significantly with lifestyle and are refractory to optimal medical therapy. The clinical threshold for performing septal ablation should be identical to that for performing septal myectomy.

Optimal therapy consists of β-blockade titrated to symptom relief, heart rate, or an adverse reaction. In patients with substantial symptoms despite optimal β-blockade, disopyramide, starting as 150 mg BID in the controlled-release form, may be added. Although disopyramide administration is sometimes limited by QT prolongation, a retrospective mul-

### TABLE 4. Studies Comparing Septal Ablation With Septal Myectomy

<table>
<thead>
<tr>
<th>Authors</th>
<th>Institution(s)</th>
<th>Ablations, n</th>
<th>Myectomies, n</th>
<th>How Triaged</th>
<th>Efficacy</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nagueh et al⁵¹</td>
<td>Baylor (ablation), Mayo</td>
<td>41</td>
<td>41</td>
<td>Institutional preference</td>
<td>No difference in NYHA class, exercise capacity, or gradient</td>
<td>Death in 2% ablation vs 0% myectomy; PPM in 22% ablation vs 2% surgery</td>
</tr>
<tr>
<td>Qin et al⁵⁸</td>
<td>Cleveland Clinic</td>
<td>25</td>
<td>26</td>
<td>Age, comorbid conditions, need for concomitant surgery</td>
<td>No difference in NYHA class; &gt;50% gradient reduction in 76% ablation vs 100% myectomy</td>
<td>No deaths; PPM in 24% ablation vs 8% myectomy</td>
</tr>
<tr>
<td>Firoozi et al⁵⁵</td>
<td>St. George’s Hospital</td>
<td>20</td>
<td>24</td>
<td>Age, patient and physician choice</td>
<td>No difference in NYHA class or gradient; exercise capacity better after myectomy</td>
<td>Death in 5% ablation vs 4% myectomy; PPM in 15% ablation vs 4% myectomy</td>
</tr>
<tr>
<td>Ralph-Edwards et al⁵²</td>
<td>Toronto General Hospital</td>
<td>54</td>
<td>48</td>
<td>Age, patient and physician choice</td>
<td>NYHA class I or II in 41% ablation vs 72% myectomy</td>
<td>Late death in 11% ablation vs 0% myectomy</td>
</tr>
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PPM indicates permanent pacemaker.
ticenter study provides some evidence against a proarrhythmic effect of the drug in patients with HOCM. In patients with noncardiac side effects of β-blockade, verapamil usually is substituted.

In patients without resting LVOT gradients of at least 30 to 50 mm Hg, exercise may bring out a provokable gradient. Patients with obstruction at rest or during exercise are candidates for mechanical therapy if they have symptoms that interfere substantially with their lifestyles despite truly optimal medical therapy. Published guidelines suggest that patients undergoing mechanical therapy should be in NYHA class III or IV. Because patients in NYHA class II have, by definition, symptoms during ordinary physical activity, some of these patients also are appropriate candidates for either septal ablation or septal myectomy. Patients in class II are, in fact, often managed with either septal ablation or septal myectomy. On the other hand, some patients in NYHA class III choose to live with their symptoms rather than undergo interventional or surgical management.

Retrospective studies have suggested that prognosis in HCM is related to the presence of a resting LVOT gradient and that prognosis in HOCM is favorably affected by septal myectomy. In the absence of conclusive prospective data to indicate that reducing or abolishing the gradient improves prognosis, however, mechanical therapy should not be offered to patients, even those with large gradients, if they have no or mild symptoms.

In some cases, HOCM is associated with intrinsic abnormalities of the mitral valve. These and other patients who require concomitant valve surgery or coronary bypass grafting should undergo septal myectomy rather than septal ablation. Surgery also should be considered for patients with atrial fibrillation who might benefit from a concomitant maze procedure.

**Advantages of Septal Myectomy**

1. The success rate for septal myectomy is higher than that for septal ablation. This difference results in part from the dependence of the septal ablation procedure on the vagaries of septal anatomy.
2. Sustained relief of outflow obstruction occurs immediately after septal myectomy but may be delayed by up to 3 months after septal ablation.
3. Longer-term data are available for septal myectomy than for septal ablation, a consideration of particular relevance to the management of younger patients.
4. Although both septal myectomy after failed septal ablation and septal ablation after failed septal myectomy have been carried out successfully, the former is more common. Because septal ablation often causes right bundle-branch block and septal myectomy often causes left bundle-branch block, patients undergoing the 2 procedures in sequence incur a very high risk of complete heart block, necessitating permanent pacing. A younger patient may therefore be better served by the strategy of primary septal myectomy to avoid the prospect of decades of permanent pacing.

**Advantages of Septal Ablation**

1. Septal ablation has the potential for greater patient satisfaction because of absence of a surgical incision and need for general anesthesia, the lower amount of pain, and the much shorter recovery time.
2. The benefit of alcohol septal ablation in older patients is similar to that in younger patients. Because the risks of cardiac surgery, particularly stroke, increase with age, ablation may offer an advantage in older patients.
3. The cost of septal ablation is less than that of septal myectomy.

**What We Do Not Know**

1. No randomized trials have been conducted on septal ablation versus septal myectomy.
2. Conclusive data on the effect of either septal ablation or septal myectomy on life expectancy are not available.
3. Although it is clear that life-threatening ventricular tachyarrhythmias after septal ablation are rare, they have been reported in sporadic cases. In the absence of definitive data, a reasonable strategy is to consider septal ablation a potential risk factor for sudden death. A corollary is that patients with preexisting risk factors (recurrent syncope, family history of sudden death in association with HCM, ventricular tachycardia, severe hypertrophy, or abnormal blood pressure response to exercise) should be considered for implantation of a cardioverter–defibrillator before septal ablation.
4. The first septal ablation was performed in 1994; thus, long-term follow-up data in substantial numbers of patients are not available.
5. Studies comparing the cost-effectiveness of septal ablation and septal myectomy have not been done.
6. It is not known whether the outcomes of septal ablation and septal myectomy described at high-volume centers can be reproduced at other institutions.

Thus, although some have expressed strong, well-reasoned opinions in support of either septal ablation or septal myectomy as the procedure of choice, existing data are inconclusive, so the management decision in many cases depends critically on patient choice.

**Application to Patient Care**

Triage of patients to septal ablation or septal myectomy is illustrated by the following recent real-life cases from Massachusetts General Hospital.

Case 1: A 43-year-old man had exertional dyspnea and angina despite β-blockade. Septal thickness was 16 mm, and LVOT gradient 72 mm Hg. On the combination of a β-blocker and disopyramide, his symptoms remitted.
Case 2: A 61-year–old man had severe lightheadedness and exertional dyspnea despite optimal medical therapy in association with HOCM and pulmonary fibrosis. Septal thickness was 22 mm, and LVOT gradient 116 mm Hg. Because of his pulmonary disease, the patient underwent septal ablation.

Case 3: A 27-year–old man had presyncope and progressive exertional angina and dyspnea despite optimal medical therapy. Septal thickness was 26 mm, and LVOT gradient 184 mm Hg. His symptoms were refractory to medical therapy. Because of his young age and marked hypertrophy, the patient underwent septal myectomy.

Case 4: A 73-year–old woman had severe bisided heart failure in association with HOCM and chronic obstructive pulmonary disease. Septal thickness was 24 mm, and LVOT gradient 121 mm Hg. Diuresis was limited by hypotension and azotemia. Because she was in need of immediate relief of outflow obstruction and despite her concomitant pulmonary disease, the patient underwent septal myectomy.

Case 5: A 46-year–old woman had disabling angina, dyspnea, and lightheadedness despite optimal medical therapy. Septal thickness was 19 mm, and LVOT gradient 121 mm Hg. Both mechanical options—septal ablation and septal myectomy—were offered to the patient.

For patients like the last one, clinical decision making is not informed by clear-cut data demonstrating that either septal ablation or septal myectomy is superior. For such “gray-area” patients, the principle of patient autonomy dictates that it is appropriate for the properly informed patient to choose between the 2 procedures.

What to Tell Patients
Patients’ decisions depend critically on the information given to them by their physicians and the manner in which it is presented. To enable the patient to make what for him or her is the best decision, the physician must present a thorough and objective comparison of the 2 procedures. The physician must recognize that local outcomes for either septal ablation or septal myectomy may not match those from high-volume centers. For example, the incidence of heart block for which permanent pacing is indicated may be higher for both procedures than that reported from a few select centers. All percentage estimates should be modified accordingly. Representative considerations to communicate to patients are the following:

1. The medium-term success rate for septal myectomy (≈90% to 95%) is higher than that for septal ablation (≈80% to 90%).
2. Clinical benefit is realized immediately after recovery from septal myectomy but may be delayed for up to 3 months after septal ablation.
3. Neither the long-term success rate for septal ablation nor the long-term consequences of the septal ablation scar is known.
4. The mortality rates of the 2 procedures (in otherwise healthy patients) are comparable (≈1% to 2%).
5. The chance of needing a permanent pacemaker is much higher after septal ablation (≈10% to 15%) than after septal myectomy (≈5%).
6. Although it is possible to have septal myectomy after failed septal ablation, the likelihood of needing a permanent pacemaker is extremely high after that sequence.
7. In older patients, the chance of having a stroke is lower with septal ablation than with septal myectomy.
8. The recovery time after septal myectomy is much longer than that after septal ablation.

What Patients Will Choose
Cardiologists and their patients are confronted by the choice between percutaneous transcatheter and surgical therapies much more often in coronary artery disease than in HOCM. In the setting of coronary artery disease, most, but not all, patients for whom either procedure would be appropriate choose percutaneous coronary intervention over coronary artery bypass grafting. The choice appears to be motivated by substantial value placed by the patient in the avoidance of the incision, general anesthesia, pain, and/or long recovery associated with surgery. These factors also have engendered extension of nonsurgical interventional procedures to the management of congenital and valvular cardiac lesions.

Similarly, and for the same reasons, most gray-area patients with HOCM choose septal ablation over septal myectomy. Patients are of course influenced by the information presented to them by physicians. It is important to emphasize that not all patients fall into the gray area; as illustrated above by the case examples, many patients exist for whom the cardiologist should direct the management to either septal ablation or septal myectomy. It is also critical that gray-area patients be allowed to choose between the options in an unhurried, unpressured environment and to seek counsel from family, friends, other patients with HCM, and other physicians.

Conclusions
Longer-term follow-up will permit judgment on the durability of the medium-term amelioration of LVOT gradient and improvement in symptoms observed in most patients after septal ablation. No data exist to support extending the current indications for mechanical management of HOCM to patients with only mild symptoms. If cardiologists adhere to strict inclusion criteria for septal ablation and septal myectomy, with either procedure performed only in patients with symptoms that interfere substantially with their lifestyles and are refractory to truly optimal (usually
2-drug) medical therapy, few centers offering the procedures are likely to maintain reasonable minimum case volumes. Operators performing the procedures at lower rates may have lower success and higher complication rates. Accordingly, performance of both septal ablation and septal myectomy should be confined to regional referral centers. The mechanical procedures should be offered only in the context of a program that integrates expertise in all aspects of HCM, including genetic counseling and arrhythmia management.

Future comparisons of the results of septal ablation and septal myectomy would be aided by adoption of a standard definition of success of the procedures. One possible definition would be improvement by ≥1 NYHA or Canadian Cardiovascular Society class and gradient reduction by ≥50% at 3 months after the procedure. Clinical equipoise would allow performance of a multicenter randomized trial comparing septal ablation and septal myectomy. Because mortality is low after both procedures, selection of a primary end point such as exercise capacity is advisable.

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Disclosures
Dr Fifer has received honoraria for speaking on HCM in general and on septal ablation in particular.

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Response to Fifer
Barry J. Maron, MD

Dr Fifer has presented a reasonable portrayal of the surgery versus alcohol ablation controversy in obstructive hypertrophic cardiomyopathy (HCM), which at times has seemed much like a conflict between diametrically opposed forces of interventional cardiology and surgery. However, his title is revealing: “Most Fully Informed Patients Choose Septal Ablation Over Septal Myectomy.” Indeed, HCM experts believe patients often choose septal ablation because they are not fully informed as to these competing strategies. How else to reconcile Dr Fifer’s concession that myectomy is more successful than ablation and is associated with enhanced long-term survival equivalent to the general population? It is also gratifying that Dr Fifer recognizes ablation as a potential risk factor for sudden death due to the alcohol-induced transmural infarction. Nevertheless, a disappointing note is Dr Fifer’s perpetuation of the old unfortunate myth that procedural mortality is higher with myectomy than ablation, when he selectively cites outdated and 20-year–old surgical experiences irrelevant to current patients. Mortality is now lower with myectomy than ablation, even approaching zero at HCM centers. Similarly, Dr Fifer’s assertion that patients with only mild heart failure symptoms should be ablation candidates is unsettling. Here he appears to dispute and contradict the American College of Cardiology/European Society of Cardiology expert consensus recommendation that patients with severe unrelenting symptoms (class III) are most deserving of consideration for septal reduction, with myectomy usually the preferred option. We can all agree that fully informed patients and the principle of patient autonomy are critical. The anecdotal case reports from Dr Fifer’s institution seem very reasonable, but are they truly typical of the information provided most other HCM patients? The alcohol ablation euphoria argues that the myectomy option is not always presented accurately, a situation that has proved unfavorable to the best interests of HCM patients.
Development of Systems of Care for ST-Elevation Myocardial Infarction Patients

Executive Summary

Endorsed by Aetna, the American Ambulance Association, the American Association of Critical-Care Nurses, the American College of Emergency Physicians, the Emergency Nurses Association, the National Association of Emergency Medical Technicians, the National Association of EMS Physicians, the National Association of State EMS Officials, the National EMS Information System Project, the National Rural Health Association, the Society for Cardiovascular Angiography and Interventions, the Society of Chest Pain Centers, the Society of Thoracic Surgeons, and UnitedHealth Networks

Alice K. Jacobs, MD, FAHA, Chair; Elliott M. Antman, MD, FAHA; David P. Faxon, MD, FAHA; Tammy Gregory; Penelope Solis, JD

Although the mortality benefit of early reperfusion with either fibrinolytic therapy or primary percutaneous coronary intervention (PCI) for patients with ST-segment elevation myocardial infarction (STEMI) has been well established,1,2 in the United States, there is great variation in which type of reperfusion treatment is chosen and in which patient it is administered.3 In fact, approximately 30% of STEMI patients do not receive any reperfusion therapy despite its availability and the absence of contraindications to its use.4 Moreover, in those patients treated with reperfusion, fewer than 50% receive treatment with a door-to-needle time within 30 minutes, and only 40% are treated within a door-to-balloon time within 90 minutes as recommended by the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines.6 In addition, sex and racial disparities in the delivery of STEMI care persist.7

Furthermore, evidence from multiple randomized trials suggests that primary PCI is superior to fibrinolytic therapy in reducing the rates of death, reinfarction, intracranial bleeding, reocclusion of the infarct artery, and recurrent ischemia (even when interhospital transport to a PCI-capable center is required) when performed in a timely fashion by experienced centers2,8; however, fibrinolytic therapy is the mainstay of treatment in the United States and around the globe because it is more widely available.3 Of the nearly 5000 acute care hospitals in this country, approximately 2200 have catheterization laboratories and among those, only 1200 are capable of performing PCI9. Therefore, the delivery of timely primary PCI to the majority of STEMI patients is extremely challenging, particularly in rural areas. Most disturbing is the fact that up to 20% of patients with STEMI are not eligible for fibrinolytic therapy, and yet 70% of those patients do not receive primary PCI, although it is the only reperfusion option.4,10

It is these considerations that have fueled the concept of systems and centers of care for STEMI patients and the mounting enthusiasm for the potential benefits of regional STEMI networks.11,12 In this context, “system” is defined as an integrated group of separate entities within a region providing specific services for the system that could include emergency medical services (EMS) providers, a community hospital(s), a tertiary center(s), and others. “Center” is defined as an entity such as a community or tertiary hospital that provides patient care services for a specific specialty or service.13 It is hoped that highly coordinated systems and
centers across the continuum of care (from patient entry to discharge and encompassing EMS, emergency departments [EDs], community and tertiary hospitals, and payers) will improve both the quality of services and outcomes for STEMI patients. Of note, several pilot programs using different models of systems and centers, which will be detailed in subsequent sections, have met with early success.14–16

AHA Initiative

Given the concerns about the unmet need in the care of many of the nearly 400,000 patients with STEMI in the United States,17 the minority of STEMI patients treated with primary PCI despite its superiority if performed in a timely fashion, and the number of patients ineligible for fibrinolytic therapy, the AHA convened a multidisciplinary Acute Myocardial Infarction Advisory Working Group to develop recommendations for strategies to increase the number of STEMI patients with timely access to primary PCI. Although the focus was on primary PCI, it was noted that the strategies to be recommended must result in improved quality of care and outcomes for all STEMI patients and must ensure access and adherence to other important evidence-based therapies. To assist the group in developing the AHA’s position and role in defining the optimal care for patients treated with primary PCI, PricewaterhouseCoopers was selected to prepare a report on the desirability, feasibility, and potential effectiveness of establishing (regional) systems and/or centers of care. Their research approach was both qualitative and quantitative and determined that developing systems and/or centers of care for STEMI patients treated with primary PCI would have significant policy and financial implications.13 It was clear, however, that nearly all stakeholders interviewed or surveyed supported a primary PCI certification program and agreed that the AHA’s main focus should be on leveraging its relationships to ensure that the appropriate constituencies were involved.

On the basis of this report, the Advisory Working Group recommended that the next step after development of the initial consensus statement was to convene a conference for all stakeholders to begin to develop an implementation plan in concert with the recommendations that would emanate from the meeting. Because of the potential demographic, political, and financial impact of the development of strategies to increase the availability of timely primary PCI, the Advisory Working Group developed the following principles to guide this initiative:

1. Patient-centered care as the number 1 priority;
2. High-quality care that is safe, effective, and timely;
3. Stakeholder consensus on systems infrastructure;
4. Increased operational efficiencies;
5. Appropriate incentives for quality, such as “pay for performance,” “pay for value,” or “pay for quality”;
6. Measurable patient outcomes;
7. An evaluation mechanism to ensure that quality-of-care measures reflect changes in evidence-based research, including consensus-based treatment guidelines;
8. A role for local community hospitals so as to avoid a negative impact that could eliminate critical access to local health care; and
9. A reduction in disparities of healthcare delivery, such as those across economic, educational, racial/ethnic, or geographic boundaries.

AHA Conference: Development of Systems of Care for STEMI Patients

Conference Participants and Process

In late March 2006, the AHA convened a 3-day conference with multidisciplinary groups of physicians (noninvasive and interventional cardiologists, cardiac surgeons, emergency care and critical care practitioners, and internists), nurses, EMS personnel, community and tertiary hospital administrators (including representation from rural areas), payers, quality and outcomes experts, and government officials involved in the care of STEMI patients. These thought leaders were charged with reviewing the current state or system of care, developing the ideal implementation system, addressing the gaps and barriers between the current and ideal system, and formulating recommendations for research, programs, and policy from the perspective of the constituency they were to represent. Members of key organizations representing key constituents were in attendance:

- Patients: Centers for Disease Control and Prevention, Health Resources and Services Administration, and National Heart, Lung, and Blood Institute
- Physicians: AHA Councils on Cardiopulmonary, Perioperative, and Critical Care; Cardiovascular Surgery and Anesthesia; and Clinical Cardiology; ACC; American College of Emergency Physicians; American College of Physicians; National Association of EMS Physicians; The Society for Cardiovascular Angiography and Interventions; and The Society of Thoracic Surgeons
- Nurses: AHA Council on Cardiovascular Nursing, American Association of Critical-Care Nurses, and Emergency Nurses Association
- EMS: American Ambulance Association, Association of Air Medical Services, National Association of State EMS Directors, National EMS Management Association, National EMS Information Systems, and National Association of Emergency Medical Technicians
- Community hospital/regional center: American Hospital Association, National Rural Health Association, Society for Chest Pain Centers, and State Hospital Associations
- Payors: Aetna, Centers for Medicare and Medicaid Services, Blue Cross and Blue Shield Association, and UnitedHealth Networks
- Evaluation/outcomes: AHA Quality of Care and Outcomes Research Interdisciplinary Working Group, Agency for Healthcare Research and Quality, US Food and Drug Administration, Joint Commission on Accreditation of Healthcare Organizations, and National Quality Forum

The goals of the conference were as follows: (1) to achieve consensus on the guiding principles for the establishment of a system (urban/suburban and rural) of care for STEMI patients; (2) to develop the ideal implementation system from the perspective of each stakeholder (ie, patient, physician, EMS, ED, local hospital, tertiary center, and payer) in terms
of outcomes and quality of care; (3) to understand the barriers, gaps, and policy implications; and (4) to develop recommendations. Several provocative presentations, including “State of the Science,” “The Trauma Center Model,” and “The European Experience,” in addition to pilot programs of systems and centers of care in Minnesota, North Carolina, and Boston, Mass, served as a framework for this conference and stimulated extensive interchange of ideas between all participants. After the plenary sessions, each stakeholder working group reviewed the current literature, engaged in thorough and challenging discussion, and generated summary documents that can be found in the online version of this issue of Circulation.18–27 The purpose of this executive summary is to capture the salient issues involved in the care of STEMI patients from the perspective of each constituent, to propose an agenda to improve the quality of care and outcomes of patients with STEMI, and to begin to outline the AHA’s next steps in this ongoing initiative.

Conference Working Groups

Patient and Public Perspective

It is generally agreed that the care provided to patients with STEMI is unlike most other hospital care. It usually involves rapid and complex decisions and, often, quick transport to a PCI-capable hospital for a critically ill patient for whom family and friends may not be present. The relationship of this critical and time-sensitive situation to the patient’s wishes, fears, expectations, beliefs, and values should not be underestimated.

In addition, the role and responsibility of the patient at the onset of STEMI, before contact with the medical system, are of paramount importance. Currently, there is inadequate recognition by the patient and the lay community of the symptoms of STEMI and the urgency of activating EMS. The problem of delay after symptom onset, attributed to denial, preference for a “wait-and-see” approach, fear of a “false alarm,” reluctance to “bother” or burden the medical system, and existing stereotypes for risk, has been longstanding; however, given the known benefits of early reperfusion, efforts to decrease this delay have been given increased attention. Regrettably, public awareness campaigns and community-based interventions have not yet been effective in reducing the time from symptom onset to first medical contact or in increasing the number of patients who activate EMS.28 In fact, currently, ≈76% of STEMI patients arrive at the hospital via self-transport or transport by family and friends.29 Furthermore, there exist marked disparities in access to and quality of care delivered.

In the ideal system, patients and the public would recognize the symptoms of STEMI and the importance of time to treatment, be familiar with their community hospital’s role in the delivery of STEMI care, and understand the implications involved in interhospital (rapid) transfer for PCI. Moreover, the patient would not be “penalized” by the reimbursement system if their symptoms were found not to be due to STEMI after activation of EMS and arrival in the ED. The ideal system would promote culturally competent educational efforts with clear and consistent messages and would include patient representatives on community planning coalitions.

Patient care across the continuum of services, from entry into the system to discharge back to the community provider, would be highly coordinated and patient-centered.

To achieve the ideal system for patients and the public, the gaps and barriers imposed by literacy level, socioeconomic factors, insurance status, preapproval policies of insurance plans, and instructions to patients provided by physicians and health plans regarding an action plan at the onset of symptoms of STEMI will need to be overcome. It will also be necessary to gain an increased understanding of the components of effective communication and educational interventions.

Physician Perspective

Currently, primary care and specialist physicians tend to work in isolation rather than in integrated networks in caring for STEMI patients, particularly at entry into the medical system. This is especially true in rural areas, where physicians may lack easy access to educational opportunities and a large volume of STEMI patients. Many physicians have experienced decreasing reimbursement for services,30 and the potential financial impact of a loss of patients (and prestige) to PCI-capable centers is of concern. Furthermore, physician training in continuous quality improvement techniques has been lacking.

In the ideal system for physicians, multidisciplinary teams (including primary care, ED, and noninvasive and interventional cardiology physicians) would work together in a seamless fashion to ensure that evidence-based care is delivered to STEMI patients according to ACC/AHA guidelines at entry into the system, during the hospital stay, at discharge, and throughout long-term follow-up in the community setting. At every step, each physician would play an important and clearly defined role. Of utmost importance is the transitioning of care back to the community physician after the acute event.31

The ideal system would provide opportunities for all physicians to participate in community education for patients and for EMS providers. In addition, there would be opportunities for physicians to be leaders in continuous quality improvement initiatives for STEMI programs that include the acute and the follow-up phase of care. Physicians, nurses, EMS personnel, and other providers would work together to establish evidence-based protocols and demonstrate credible commitment to the goal of achieving timely infarct-artery patency for all STEMI patients.

To achieve the ideal system for physicians, the development of team-based methods for overcoming professional, financial, organizational, and regulatory gaps and barriers will be necessary. Furthermore, alignment of the goals and incentives for all physicians within all hospital settings will be required, with the realization that physicians drive both the quality and the cost of care.

EMS and ED Perspective

Currently, EMS regions are governed separately by state. There are more than 300 different regions in the United States, with nearly 1000 hospital-based EMS systems.32 Yet, hospital-based systems account for only 6% of the total, with fire-based services accounting for 45%, and other public third services and private operators making up the remaining 49%.13
EMS ambulances are staffed by various personnel and provide different levels of care (basic life support, advanced life support, and 12-lead ECG) and services, including mode of transport (ground versus air), in rural and urban areas. However, the AHA’s advanced cardiovascular life support chest pain algorithm importantly contributes to the prehospital assessment, triage, and treatment of patients with suspected STEMI in most EMS systems.33

Despite the fact that prehospital ECGs have been reported to decrease door-to-needle and door-to-balloon times,34,35 they are performed on fewer than 10% of STEMI patients,36 and there is a discrepancy between reported availability37 and documented use. Furthermore, there is little information on how these ECGs are integrated into the system of care for STEMI patients, and standardized training on the performance, interpretation, and transmission of ECGs is lacking.

Two current EMS policies have a negative impact on timely access to primary PCI for STEMI patients. First, the majority of community protocols traditionally have directed EMS teams to transport patients with chest pain to the nearest hospital, under the assumption that most hospitals could provide fibrinolytic therapy to STEMI patients. With the increasing use of primary PCI as the preferred reperfusion strategy, many communities are considering whether it is best to transport such patients to the nearest PCI-capable hospital instead.15 Second, transport between a non–PCI-capable hospital to one that provides the service is often the “next available” ambulance rather than a 9-1-1 system of activation.

As noted above, because a minority of STEMI patients use EMS for entry into the medical system,28 the majority have their first medical contact on entry into the ED. This poses a challenge to ED personnel, because EDs are often overcrowded, and patients arriving by ambulance typically receive attention and treatment faster than patients who transport themselves. Although the ACC/AHA guidelines recommend that the initial ECG be obtained within 10 minutes of arrival of a patient with chest pain, ED capacity and staffing may result in delay, and patients presenting with atypical symptoms may wait considerably longer. Depending on local practice patterns, multiple consultations with primary care physicians and cardiologists may be required before a reperfusion strategy is initiated.

In the ideal system for EMS and EDs, standardized point-of-entry protocols (created by state-based coalitions of EMS personnel, emergency physicians, and cardiologists and supported by payers and administrators) would dictate which patients are transported to the nearest facility and which patients are transported to the nearest PCI-capable facility, in part based on the acquisition, interpretation, and transmission of prehospital 12-lead ECGs. The catheterization laboratory team would be activated by EMS personnel in the field or by emergency physicians after receiving transmitted ECGs. Patients transported to a non–PCI-capable hospital by EMS would remain on the stretcher with EMS personnel in attendance until the decision about whether to transport to a PCI-capable hospital has been rendered. For patients who transport themselves to a non–PCI-capable hospital and require primary PCI, activation of EMS via a 9-1-1 system would occur. An ideal system would also foster a coordinated curriculum to teach EMS providers and ED staff to care for STEMI patients and provide feedback on performance or compliance with guidelines.

To achieve the ideal system for EMS, a complete understanding of the technological and financial barriers to acquiring prehospital ECGs will need to be obtained, because equipment costs and reliability of data transfer have been major barriers to widespread implementation. Protocols on how prehospital ECGs should be performed and interpreted (and by whom) will need to be established. Standardized point-of-entry protocols based on local geography and resources will need to be developed that integrate the prehospital, interhospital, and receiving-hospital care. For those patients transported directly to PCI-capable hospitals, it will be important to determine the safety of longer transport times and whether the added time to reperfusion will negate the benefit of primary PCI in specific patient subsets.

To achieve the ideal system for EDs, a thorough assessment of the staffing patterns, overcrowding issues, and ability to avoid time “on diversion” (periods during which the ED is not accepting new patients brought in by ambulance) will need to occur. Ongoing training of ED staff on STEMI care and ECG interpretation will be necessary. Reperfusion checklists, standard pharmacological regimens and order sets, clinical pathways, and single-call activation systems will require collaborative input from multidisciplinary teams.

Non–PCI-Capable (STEMI Referral) Hospital Perspective

Because the majority of STEMI patients present to hospitals that do not have the capability to perform primary PCI, it is these facilities that will play a pivotal role in increasing the number of patients with timely access to mechanical reperfusion. Currently, several states have allowed increasing numbers of hospitals without cardiac surgery on site to offer primary PCI to STEMI patients, even in catheterization laboratories that do not perform nonemergency (“elective”) PCI procedures. Alternatively, some STEMI patients are transported from non–PCI-capable to PCI-capable hospitals after evaluation and initial treatment despite the inherent delay to reperfusion and often without standardized protocols to guide rapid triage and transfer. In a few states, non–PCI-capable hospitals are “bypassed” by EMS, and patients presumed to have STEMI are transported directly to hospitals capable of performing primary PCI.

Although a few early observational studies from single institutions and 1 underpowered randomized trial demonstrated the potential efficacy and safety of performing primary PCI at hospitals without cardiac surgery on site,38,39 there is concern that the proliferation of primary PCI in this setting has the potential to result in the creation of low-volume institutions40 that would have difficulty sustaining a PCI program because of cost and lack of personnel to provide continuous coverage. In the ideal system, standardized point-of-entry protocols would dictate those STEMI patients to be transported directly to a PCI-capable facility based on specific criteria for risk, contraindications to fibrinolysis, and the proximity of the nearest PCI service. Those patients transported by EMS or who arrive via self-transport or via family or friends at a non–PCI-capable hospital would be treated...
according to standardized triage and (potential) transfer protocols. Incentives would be provided to rapidly treat STEMI patients in accordance with ACC/AHA guidelines and transfer them to the PCI-capable hospital for primary PCI by use of reperfusion checklists, standard pharmacological regimens and order sets, and clinical pathways, with attention to details such as eliminating continuous intravenous infusions and tubing. In addition, rapid and efficient data transfer to the PCI-capable hospital and data collection and feedback would be integrated into the system of care. Finally, after the patient’s discharge from the PCI-capable hospital, integrated plans for the return of the patient to the local community for follow-up care would be provided routinely.

To achieve the ideal system for non–PCI-capable hospitals, the integral role of these hospitals within the system must be recognized. Hence, the designation of “STEMI referral hospital” would promote these facilities as “haves” rather than as “have-nots” and minimize any potential halo effect on other services vital to the local community. This designation of “STEMI referral hospital,” based on specific criteria, would garner prestige. It will also be necessary to eliminate financial disincentives to transfer STEMI patients to “STEMI-receiving hospitals.” Finally, as discussed previously, the frequently unacceptably long interhospital transportation time must be reduced.

**PCI-Capable (STEMI-Receiving) Hospital Perspective**

A STEMI-receiving hospital is defined as any hospital that performs primary PCI and currently receives STEMI patients through 1 of 3 pathways: directly from home or community, via transport by EMS, or via transport from a STEMI referral hospital. Each presentation offers opportunities for improving time to treatment and access to primary PCI. At these STEMI-receiving hospitals, time to reperfusion is delayed by the decision-making process on arrival, particularly if both fibrinolytic therapy and primary PCI are routinely used, by overcrowding and shortage of staff in the ED, and by the time to activate and assemble the catheterization laboratory team, particularly during off-hours and on weekends. In fact, late presentation after symptom onset, comorbid conditions, and the absence of pain have been shown to be independent predictors of increased time to reperfusion. Furthermore, not all hospitals that perform PCI provide the service continuously. Finally, the lack of standardized treatment protocols and single-call catheterization laboratory activation systems contribute to the delay in achieving infarct-artery patency.

In the ideal system, prehospital ECG diagnosis of STEMI, ED notification, and catheterization laboratory activation would occur according to standard algorithms that would facilitate a short ED stay or transport directly from the field to the catheterization laboratory. Similarly, single-call systems from STEMI referral hospitals with universal patient acceptance by STEMI-receiving hospitals would result in immediate activation of the catheterization laboratory team without the need for additional review or determination of bed availability. Primary PCI would be provided as routine treatment for appropriate STEMI patients 24 hours per day and 7 days per week. Each STEMI-receiving hospital would have a written commitment from the hospital’s administration to support the program. A multidisciplinary group with representation from the ED, EMS, the cardiac catheterization laboratory, the quality improvement team, and the coronary care unit that includes both physicians and nurses would meet regularly to identify problems and implement solutions. A formal continuing education program that includes practical implementation training for staff would be designed and instituted. A mechanism for monitoring program performance, process measures, and patient outcomes would be established.

To achieve the ideal system for STEMI-receiving hospitals, a better understanding is required of the extent of a shift in STEMI patients cared for by STEMI-receiving hospitals and the impact of reallocation of resources and capacity. Criteria for STEMI-receiving hospital certification would be developed that would include hospital and physician volume, continuous primary PCI service, and door-to-balloon time goals, and the designation would preclude time “on diversion.”

**Payer Perspective**

Increasing the number of STEMI patients with access to primary PCI will likely require rethinking and restructuring by purchasers (organizations, such as employers, that provide funds for care) and payers (organizations, such as health plans or insurance companies, that directly contract with purchasers, providers, and practitioners) of how services are purchased, how payments are made, and how accountability is maintained. Currently, there are scarce data on the proportion of STEMI patients transferred from STEMI referral to STEMI-receiving hospitals for primary PCI, and commercial insurers have less influence over data collection and referral in the emergency setting. The complex aspect of payment relates to transferred patients, and different payers have different policies. For Medicare patients, the STEMI referral hospital receives payment only for ED services if the patient is not admitted before discharge and per diem payment for inpatient services at a rate of the diagnosis-related group amount divided by the geometric mean length of stay; the STEMI-receiving hospital is paid the diagnosis-related group amount as if there had been no preceding care. Despite there being 9 standard measures of quality of care for STEMI patients, there are no standard measures for the appropriateness or rate of revascularization. Time to reperfusion is a standard performance measure for patients definitively treated in the initial hospital but not for transferred patients. Although the Centers for Medicare and Medicaid Services completed a demonstration with Premier (an organization owned by not-for-profit hospitals) of a “pay-for-results” model for acute myocardial infarction measures, neither time from onset of symptoms to reperfusion nor appropriateness of revascularization was included.

In the ideal system for payers, once regional coordinated and integrated systems of care for STEMI patients were developed based on existing guidelines, local payers could then apply appropriate financial incentives and disincentives that would reimburse the appropriate amount for the appropriate care at the right time in the right setting. All payer performance data would be available and in the public domain for all STEMI referral and STEMI-receiving hospitals. An integrated single payment that is shared among the referring, transporting, and receiving providers would en-
courage coordination and integration of care, encourage collaboration between providers and practitioners, and allow the 2 hospitals and transfer system to potentially share gains from removing inefficiencies in the transfer process (although the latter strategy has risks that are not fully understood).47

To achieve the ideal system for payers, an organizational structure that accepts integrated payments would need to be developed and would require revisiting prohibitions on paying for referrals. Furthermore, local payer contract arrangements that would result in financial penalties to patients if they were transported to nonparticipating providers would need to be eliminated. Payers should play a leading role in encouraging measures that are consistent across payers and others who require reporting and in promoting consistent and accurate data collection and public availability of all payer data. Payers should also consider adjusting payments to reward reporting of data and participation in performance improvement alliances and review payment policies for situations where the payment system may have the inadvertent and unintended effect of providing a disincentive to provide the best care.

Evaluation and Outcomes
As with any care system, process improvement strategies may not be implemented successfully or, worse, may lead to unintended adverse consequences. As such, it will be critically important to carefully monitor the impact of any new care plans and tactics on clinical outcomes. In fact, as noted above, measurable patient outcomes and an evaluation mechanism to ensure that quality-of-care measures reflect changes in evidence-based research are 2 of the principles guiding this AHA STEMI initiative.

Although there are many approaches to the evaluation of care, the writing group thought that Donabedian’s classic triad of structure-process-outcome48 provides an ideal model that identifies the major domains of health care and defines the programmatic features needed to achieve success. The specific metrics for each domain are detailed in a subsequent section of these conference proceedings25; however, several points should be emphasized. In addition to the outcomes measures of mortality, nonfatal adverse events, and patient-reported health status, the impact of care on non–health-related measures such as patient satisfaction and economic impact should be considered. In addition, outcomes measures should also include potential unanticipated consequences of changes in care, longitudinal measures (at 6 or 12 months), and both positive and negative “halo” effects on other areas of cardiac care.

Moreover, stakeholder providers should participate in national data collection and quality improvement programs that offer standardized tools for data collection and risk adjustment, as well as feedback on how care compares with benchmarks and with care provided by peer groups. As regional STEMI care delivery systems mature, the individual hospital-centered quality improvement program will need to expand to collaborative, community-wide oversight programs. The evaluation of STEMI care at both the hospital and system levels, by plotting the progress of each quality indicator over time, will allow determination of whether the system is moving in the right direction and potentially provide public metrics that could be used for quality assurance, or perhaps to alter provider reimbursement rates (pay-for-quality programs). Finally, metrics for evaluating STEMI care will likely need to evolve as the field evolves.

Gaps, Barriers, and Implications
The underlying premise behind the development of systems (and centers) of care for patients with STEMI is that although primary PCI is superior to fibrinolytic therapy when performed rapidly, timely access to primary PCI is currently limited. The conference reached a consensus that establishment of regional systems of care that include prehospital EMS protocols and emergency interhospital transfer agreements between STEMI referral and receiving hospitals will improve access to primary PCI and thereby improve outcomes; however, as detailed throughout these conference proceedings, it is widely recognized that the development of such systems will be extremely challenging, and their success will depend on the ability to overcome existing barriers and gaps in the evidence base.

Some of the issues that will require careful consideration and additional evaluation and that have been recognized and thoroughly discussed throughout the conference include the impact of the inherent time delay in bypassing non–PCI-capable hospitals or in interhospital transfer on the benefits of primary PCI compared with fibrinolytic therapy in certain subsets of patients (eg, those at low risk), improving EMS and prehospital ECG utilization and integration across wide variation in EMS and community resources, measurement of performance and accountability at a systems level, realignment of financial incentives, and issues specific to rural and underserved communities that relate to disparities in care. These gaps and barriers have served as the underpinnings for the AHA’s recommendations for research, programs, and policies detailed below (Table) and for the initial implementation strategies that will support this initiative.

Policy Considerations and Implications
Clearly, changes in existing policy and consideration of new policy will need to occur to foster the development of optimal care for patients with STEMI. The policy writing group discussed both short- and long-term policy recommendations and focused on maximizing opportunities to enhance the processes that are currently available but not fully implemented. In the near term, each region and state will need to evaluate its resources for STEMI systems and its access to primary PCI. Each state should also evaluate its pending legislation. Standardized protocols and toolkits for assessment across the continuum of care will need to be developed and introduced into practice. In addition, the development of a national STEMI center certification program and of criteria for both STEMI referral and STEMI-receiving hospitals should be a priority.

In the longer term, quality improvement measures for STEMI patients treated with primary PCI must be developed and incorporated into quality improvement programs. It will be important to work with quality improvement organizations to have quality measures included in future scopes of work and to include process-of-care measures in quality improvement initiatives, pay-for-participation programs, and pay-for-performance programs. These measures would need to be sensitive to the interdependence among system constituent...
<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level of Implementation</th>
<th>Time Frame</th>
<th>Writing Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Research</strong></td>
<td></td>
<td></td>
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<tr>
<td>Quantify the characteristics, frequency, natural history, and effectiveness of interventions with patients who have early prodromal symptoms of STEMI</td>
<td>X</td>
<td>X</td>
<td>Patient</td>
</tr>
<tr>
<td>Conduct patient/family surveys about ways to improve management for STEMI before, during, and after PCI for the acute event</td>
<td>X</td>
<td>X</td>
<td>Patient</td>
</tr>
<tr>
<td>Conduct research on patient and family preferences regarding transfer to a STEMI-receiving hospital (ie, outside of their community)</td>
<td>X</td>
<td>X</td>
<td>Patient</td>
</tr>
<tr>
<td>Determine the most-effective communication methods to bring about changes in patient/bystander action (decreased delay and appropriate system access)</td>
<td>X</td>
<td>X</td>
<td>Patient</td>
</tr>
<tr>
<td>Evaluate other options to EMS; for example, does calling a gatekeeper about symptoms (available 24 hours per day/7 days per week) result in less of a time delay than calling EMS?</td>
<td>X</td>
<td>X</td>
<td>Patient</td>
</tr>
<tr>
<td>Assess the role of decision support and information technology in the home and its impact on patient/bystander delay and EMS utilization</td>
<td>X</td>
<td>X</td>
<td>Patient</td>
</tr>
<tr>
<td>Invest in further research and application of information technology to facilitate access to early recognition of symptoms/diagnosis/treatment</td>
<td>X</td>
<td>X</td>
<td>Patient</td>
</tr>
<tr>
<td>Determine the role of health information technology in expediting patient consent and transfer of medical records</td>
<td>X</td>
<td>X</td>
<td>Patient; STEMI referral hospital; STEMI-receiving hospital</td>
</tr>
<tr>
<td>Study the psychological, medical, logistical, social, and financial impact on patients and families of patients transferred out of their community (ie, transfer to a STEMI-receiving hospital directly by EMS or via interhospital transfer)</td>
<td>X</td>
<td>X</td>
<td>Patient</td>
</tr>
<tr>
<td>Determine how realignment of physicians from STEMI referral hospitals to STEMI-receiving hospitals will affect patient care</td>
<td>X</td>
<td>X</td>
<td>Physician</td>
</tr>
<tr>
<td>Determine how STEMI-receiving hospitals will realign their services to accommodate the added volume of STEMI patients</td>
<td>X</td>
<td>X</td>
<td>STEMI-receiving hospital</td>
</tr>
<tr>
<td>Determine whether direct transport of STEMI patients to a STEMI-receiving hospital (that is not the closest hospital) is safe</td>
<td>X</td>
<td>X</td>
<td>EMS/ED</td>
</tr>
<tr>
<td>Evaluate the feasibility of emergency patient transfer in rural communities</td>
<td>X</td>
<td>X</td>
<td>EMS/ED</td>
</tr>
<tr>
<td>Determine the best approach to use of prehospital ECG (ie, interpreted in field, transmitted to ED)</td>
<td>X</td>
<td>X</td>
<td>EMS/ED</td>
</tr>
<tr>
<td>Evaluate 12-lead ECG systems and reliability of data transfer</td>
<td>X</td>
<td>X</td>
<td>EMS/ED</td>
</tr>
<tr>
<td>Determine whether direct transport of STEMI patients to a STEMI-receiving hospital (that is not the closest hospital) is safe</td>
<td>X</td>
<td>X</td>
<td>EMS/ED</td>
</tr>
<tr>
<td>Evaluate the efficacy of extending programs such as “Get With the Guidelines” and “Guidelines Applied to Practice” to include providers, hospitals, and EMS systems in improving adherence to STEMI guidelines</td>
<td>X</td>
<td>X</td>
<td>EMS/ED</td>
</tr>
<tr>
<td><strong>Programs</strong></td>
<td></td>
<td></td>
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<tr>
<td>Establish community networks where constituents (physicians, patients, EMS, administrators, payers) meet to ensure that appropriate referrals occur reliably</td>
<td>X</td>
<td>X</td>
<td>Patient; Physician; Payer</td>
</tr>
<tr>
<td>Provide administrative infrastructure support within the hospital to emergency physicians, nurses, and cardiology leaders that includes protected time for activities related to STEMI system management</td>
<td>X</td>
<td>X</td>
<td>EMS/ED; Physician</td>
</tr>
<tr>
<td>Develop novel and expedited methods of patient consent and medical information transfer</td>
<td>X</td>
<td>X</td>
<td>Patient; Physician</td>
</tr>
<tr>
<td>Develop programs for seamless interface with patients and their local primary care providers after discharge from STEMI-receiving hospitals</td>
<td>X</td>
<td>X</td>
<td>Patient; Physician; Payer</td>
</tr>
<tr>
<td>Develop protocols that allow EMS-diagnosed STEMI patients to bypass the ED and go directly to the cardiac catheterization laboratory when appropriate</td>
<td>X</td>
<td>X</td>
<td>EMS/ED; Physician; STEMI-receiving hospital</td>
</tr>
<tr>
<td>Develop algorithms for standardized treatment protocols and clinical pathways in ED and STEMI referral and receiving hospitals according to ACC/AHA guidelines</td>
<td>X</td>
<td>X</td>
<td>EMS/ED; Physician; STEMI-receiving hospital</td>
</tr>
<tr>
<td>Develop algorithms for EMS care that include point-of-entry plan and role of STEMI referral and receiving hospitals according to ACC/AHA guidelines</td>
<td>X</td>
<td>X</td>
<td>EMS/ED; Physician; STEMI-receiving hospital</td>
</tr>
<tr>
<td>Develop and test the effectiveness of educational campaigns to decrease patient delay and increase the use of EMS based on access to a primary PCI-capable hospital destination (ideally building on current campaigns), including education about hospital capability for PCI and implications for management patients will receive if they access care for symptoms</td>
<td>X</td>
<td>X</td>
<td>Patient; EMS/ED</td>
</tr>
<tr>
<td>Implement prospective education with patients and families about the system of care they will access when seeking evaluation of STEMI symptoms in a regional system of care (based on access to primary PCI for STEMI)</td>
<td>X</td>
<td>X</td>
<td>Patient</td>
</tr>
<tr>
<td>Recommendation</td>
<td>Level of Implementation</td>
<td>Time Frame</td>
<td>Writing Group</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td><strong>Policy</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Assess current state legislation and local policies that impact system of care for STEMI patients</td>
<td>X X X</td>
<td>Short-Term (&lt;6 mo)</td>
<td>Patient; Policy</td>
</tr>
<tr>
<td>Evaluate state regulations and pending legislation</td>
<td>X X X</td>
<td>Mid-Term (&lt;12 mo)</td>
<td>Policy</td>
</tr>
<tr>
<td>Evaluate resources by state and by region and determine access to primary PCI</td>
<td>X X X</td>
<td>Long-Term (&gt;1 y)</td>
<td>Policy</td>
</tr>
<tr>
<td>Provide EMS with sufficient personnel, training, and resources to ensure that a prehospital 12-lead ECG can be acquired from patients with suspected STEMI</td>
<td>X X X</td>
<td></td>
<td>EMS/ED, Physician</td>
</tr>
<tr>
<td>Empower ED physicians in STEMI-receiving hospitals to activate catheterization laboratory resources within a standardized clinical pathway without fear of reprisal for false-positive activation</td>
<td>X X</td>
<td></td>
<td>EMS/ED</td>
</tr>
<tr>
<td>Develop standardized protocols and toolkits for assessment</td>
<td>X X</td>
<td></td>
<td>Policy</td>
</tr>
<tr>
<td>Develop scripted interrogation protocols/prearrival instructions for telephone-guided cardiopulmonary resuscitation and administration of aspirin while EMS is en route to the scene</td>
<td>X X</td>
<td></td>
<td>EMS/ED</td>
</tr>
<tr>
<td>Develop and provide EMS with 1 standard algorithm for prehospital assessment, triage, and treatment of STEMI patients</td>
<td>X X X</td>
<td></td>
<td>EMS/ED, Policy</td>
</tr>
<tr>
<td><strong>Reimbursement</strong></td>
<td></td>
<td></td>
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<tr>
<td>Ensure that reimbursement rates for interfacility STEMI patient transport reflect the increased level of response capability</td>
<td>X X X</td>
<td></td>
<td>EMS/ED; Payer</td>
</tr>
<tr>
<td>Ensure that transferring hospitals and transport systems are fairly paid for the costs of evaluating the patient, arranging the transfer, and providing care</td>
<td>X X X</td>
<td></td>
<td>Payer</td>
</tr>
<tr>
<td>Ensure that care for patients who are determined not to have STEMI, including EMS transport/transfer, is adequately reimbursed without penalty</td>
<td>X X</td>
<td></td>
<td>Patient; Payer</td>
</tr>
<tr>
<td>Ensure alignment of reimbursement policies to encourage providers to participate in a patient-centered integrated system</td>
<td>X X</td>
<td></td>
<td>Patient; Physician</td>
</tr>
<tr>
<td>Align financial incentives with desired outcomes</td>
<td>X X</td>
<td></td>
<td>Physician; Payer</td>
</tr>
<tr>
<td>Work toward addressing reimbursement barriers that affect the implementation of a STEMI system</td>
<td>X X</td>
<td></td>
<td>Policy</td>
</tr>
<tr>
<td>Consider adjusting payments to reflect reporting of data and participation in performance improvement alliances</td>
<td>X X</td>
<td></td>
<td>Payer; Policy</td>
</tr>
<tr>
<td>Include process-of-care measures in quality improvement initiatives/pay for participation/pay for performance</td>
<td>X X</td>
<td></td>
<td>Policy</td>
</tr>
<tr>
<td><strong>Quality/outcomes/data</strong></td>
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</tr>
<tr>
<td>Develop quality measurement(s) to assess the effectiveness of physicians and other healthcare providers in counseling patients on early activation of EMS and long-term adherence to discharge recommendations according to ACC/AHA guidelines</td>
<td>X</td>
<td></td>
<td>Physician</td>
</tr>
<tr>
<td>Develop quality improvement measures for eligible STEMI patients and incorporate into quality improvement programs</td>
<td>X X</td>
<td></td>
<td>Policy evaluation/outcomes</td>
</tr>
<tr>
<td>Develop data collection and quality improvement systems to oversee the continuum of STEMI patient care</td>
<td>X X</td>
<td></td>
<td>EMS/ED; Evaluation/outcomes</td>
</tr>
<tr>
<td>Work with quality improvement organizations to have quality measures included in future scopes of work</td>
<td>X X</td>
<td></td>
<td>Policy</td>
</tr>
<tr>
<td>Provide formal feedback to all participants in a STEMI system as part of an organized quality improvement process</td>
<td>X X</td>
<td></td>
<td>EMS/ED; Evaluation/outcomes</td>
</tr>
<tr>
<td><strong>Training</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Provide (regional) education on STEMI to physician constituents</td>
<td>X X X</td>
<td></td>
<td>Physician</td>
</tr>
<tr>
<td>Provide continued emergency medical dispatcher training and certification requirements</td>
<td>X X X</td>
<td></td>
<td>EMS/ED</td>
</tr>
<tr>
<td>Provide training to ED personnel to interpret ST-segment elevation on ECG</td>
<td>X X</td>
<td></td>
<td>EMS/ED</td>
</tr>
<tr>
<td><strong>Patient education</strong></td>
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<tr>
<td>Partner with managed care plans to help develop explicit language for their patients about what symptoms constitute an “emergency” that requires activation of EMS without preapproval</td>
<td>X</td>
<td></td>
<td>Patient; Payer</td>
</tr>
<tr>
<td>Ensure appropriateness and consistency of instructions that health plans and providers give patients regarding definitions of emergencies and accessing EMS</td>
<td>X X</td>
<td></td>
<td>Patient; Payer</td>
</tr>
</tbody>
</table>
components. Finally, addressing reimbursement barriers that affect the implementation of STEMI systems may require creation of a demonstration project to test the hypothesis that a change in the reimbursement structure could provide incentives for the timely interhospital transfer of STEMI patients. A demonstration could also help to identify additional barriers or unintended consequences of a STEMI system of care.

**Next Steps**

On the basis of the detailed recommendations from each constituent writing group noted in the Table, the AHA has formulated an initial action plan to continue this initiative.

**EMS System Assessment and Improvement**

The AHA will participate in a needs assessment and analysis of the effectiveness of EMS for STEMI patients as part of a STEMI system of care. This assessment and analysis will identify competencies and related gaps for STEMI care in the EMS setting and will include an evaluation of the EMS infrastructure and policies. The identification of resources (eg, number of advanced cardiac life support vehicles per field), the percentage of responders and dispatchers trained in STEMI protocols, the presence and utilization of 12-lead ECGs on EMS vehicles, mandates to deliver patients to the nearest hospital, protocols for interhospital transfers and call system (eg, 9-1-1 versus next available vehicle), and diversion policies to STEMI-receiving hospitals will be determined.

On the basis of the above assessment, the AHA will facilitate the development of an implementation plan to build the appropriate infrastructure to serve STEMI patients that can be tailored, when necessary, to the appropriate region or state. The implementation phase will address funding, training (using AHA emergency cardiovascular care products), and evaluation of existing process measures and patient outcomes. The AHA, with input from stakeholders, will include the identification of key “next steps,” such as the development and testing of future measures, and other activities necessary to further continuous improvement.

**Establishing Local Initiatives**

The AHA will convene stakeholders at the state and/or local levels to identify initiatives that could be undertaken to improve care for STEMI patients and to consider the establishment of STEMI systems. These same stakeholders would help to ensure that there is “buy in” for interested parties and would help to ensure that any efforts undertaken to improve quality of STEMI care are viable.

The stakeholder evaluation will include but will not be limited to the following:

- Analyzing the current STEMI-related activities taking place at a regional or state level
- Assessing the financial impact of STEMI systems implementation
- Determining the current percentage of the population that has access to ideal STEMI care
- Assessing how EMS and hospital regulations or legislation may serve to enable or hinder the development of STEMI systems within a state and identifying how to overcome regulatory or legislative barriers
- Assessing the potential for overutilization of STEMI services or procedures
- Identifying underserved populations and developing strategies to mitigate disparities in access to care
- Determining feasibility of having interstate diversion or transfers where this would lead to ideal care
- Developing action plans to further patient access to ideal STEMI care

**Objective Evaluation of Existing Models**

The AHA will convene a group of thought leaders to review existing STEMI system-of-care regional pilot programs (ie, those in Minnesota; Boston, Mass; and North Carolina) and determine whether additional pilot programs are necessary to develop informed recommendations for what an ideal STEMI system-of-care model should include. The existing pilot programs will be evaluated for the following:

- Financial impact on STEMI referral and STEMI-receiving hospitals and EMS
- Rural implications and inclusion
- Overutilization and potential for false-positives
- Disparate population impact
- Resource allocation in regional area
- Allocation of resources within STEMI-receiving hospital to accommodate additional patient volume
- Other criteria as deemed appropriate

**Explore Development of National STEMI Center Certification Program and/or Criteria**

The AHA, in collaboration with other patient-focused organizations, will develop recommendations for certification of STEMI referral and STEMI-receiving hospitals. Initial steps will include the following:

- Convening an expert advisory working group
- Developing appropriate criteria for certification
- Developing performance and outcomes measurements for use in quality improvement of pay-for-quality/pay-for-participation programs
- Determining the need for possible additional market research
• Exploring a partnership with an accreditation organization for implementation of criteria in STEMI referral and STEMI-receiving hospitals
• Publishing recommendations

Conclusions
The issues inherent to the development of systems of care for STEMI patients are quite complex, with public health, economic, political, and social implications for our society. Yet, few issues are more important with regard to cardiovascular health and outcomes. Improvements in systems of care that increase timely access and adherence to evidence-based therapies, although initially focused on STEMI patients, will ultimately impact the care of all patients with acute coronary syndromes. The gathering of the multiple constituencies involved in the care of STEMI patients at this conference has fostered the realization that there is considerable overlap among stakeholders in the vision of the ideal system and in the strategies needed to achieve it (Figure). A successful endeavor will require a partnership among patients, physicians, nurses, EMS personnel, hospital administrators, payers, and policy makers. With the ideal system of care in clear focus, it is time to forge this partnership and begin to remove the gaps in our knowledge and the barriers to implementation and to improve the outcomes and quality of care for all STEMI patients.
### Writing Group Disclosures*

<table>
<thead>
<tr>
<th>Writing Group Member</th>
<th>Employment</th>
<th>Research Grant</th>
<th>Other Research Support</th>
<th>Speakers’ Bureau/Honoraria</th>
<th>Ownership Interest</th>
<th>Consultant/Advisory Board</th>
<th>Other</th>
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<tbody>
<tr>
<td>Alice K. Jacobs</td>
<td>Boston Medical Center</td>
<td>None</td>
<td>None</td>
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<tr>
<td>Ezra J. Amsterdam</td>
<td>University of California at Davis</td>
<td>Biosite</td>
<td>None</td>
<td>BMIs; Pfizer; Sanofi; GlaxoSmithKline; Biosite</td>
<td>None</td>
<td>Bristol-Myers Squibb; Pfizer; Biosite</td>
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<tr>
<td>Elliott M. Antman</td>
<td>Brigham &amp; Women’s Hospital</td>
<td>Sanofi-Aventis; Bristol-Myers Squibb; Genentech; Merck; Eli Lilly; Centocor</td>
<td>None</td>
<td>None</td>
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<tr>
<td>Thomas Averano</td>
<td>Johns Hopkins</td>
<td>None</td>
<td>None</td>
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<tr>
<td>Eric R. Bates</td>
<td>University of Michigan Medical Center</td>
<td>None</td>
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<td>Barbara J. Drew</td>
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<td>Anthony G. Elliott</td>
<td>Berkshire Medical Center</td>
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<td>William J. French</td>
<td>Harbor-UCLA Medical Center</td>
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<td>W. Brian Gibler</td>
<td>University of Cincinnati College of Medicine</td>
<td>Biosite; Bristol-Myers Squibb; i-STAT/Abbott; Roche Diagnostics; Sanofi-Aventis; Schering Plough; Sooie; Inovise Medical Group; ESP Pharma; PDL BioPharma</td>
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<td>Christopher B. Granger</td>
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<td>AstraZeneca; Procter &amp; Gamble; Sanofi-Aventis; Alexion; Novartis; Boehringer-Ingelheim; Genentech; Berlex</td>
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<td>Richard Gray</td>
<td>Sutter Pacific Heart Centers at California Pacific Medical Center</td>
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<td>American Heart Association</td>
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<td>Agency for Healthcare Research and Quality</td>
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<td>Timothy D. Henry</td>
<td>Minneapolis Heart Institute Foundation</td>
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<td>Loren F. Hiratska</td>
<td>Bethesda North Hospital; Cardiovascular and Thoracic Surgeons, Inc</td>
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<td>Ridgeview Medical Center</td>
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References


Key Words: AHA Conference Proceedings myocardial infarction point-of-care systems angioplasty reperfusion
Since the initial online posting of the article, “Development of Systems of Care for ST-Elevation Myocardial Infarction Patients: Executive Summary,” by Jacobs et al on May 30, 2007 (DOI: 10.1161/CIRCULATIONAHA.107.184043), the Society of Thoracic Surgeons has added its endorsement. This information has been added to the print and current online versions of the article (Circulation. 2007;116:217–230).

DOI: 10.1161/CIRCULATIONAHA.107.185418
Percutaneous Coronary Intervention of Chronic Total Occlusion With Retrograde Approach
Follow-Up by Cardiac Magnetic Resonance Imaging

Didier Locca, MD; Chiara Bucciarelli-Ducci, MD; Alessio La Manna, MD; Sanjay Prasad, MD

A 59-year-old hypertensive male ex-smoker with diabetes mellitus and a family history of coronary artery disease was referred to our center for percutaneous coronary intervention (PCI) of a known chronic total occlusion (CTO) of the proximal right coronary artery. There was no significant disease in the left coronary system. A Tc-tetrofosmin myocardial perfusion scan was performed. The images after stress revealed severe ischemia of the mid and basal inferior wall.

An anterograde approach failed, so recanalisation of the right coronary artery was attempted via a retrograde approach through the septal collateral. The septal perforation is seen in Figure 1A. PCI was successful with implantation of 4 CYPHER stents (Cordis, Miami Lakes, Fl) (2.75×23 mm, 3.0×33 mm, 3.5×22 mm: in the mid segment and 3.15×13 mm at the ostium). There was TIMI 3 flow at the end of the procedure (Figure 1B). The baseline and post procedure ECGs did not show any significant differences (Figure 2A and B). At 24 hours after PCI, there was a peak of cardiac enzymes (troponin I: 1.19 µg/L [0–0.04], CK-MB: 7.8 µg/L [0–6]).

An initial cardiovascular magnetic resonance (CMR) scan was done 48 hours after PCI, and showed evidence of septal mid-wall late gadolinium enhancement (Figure 3A: arrow 1) compatible with the septal perforation. In addition, there was a chronic inferior wall subendocardial infarct (Figure 3A: arrow 2). A follow-up CMR scan was performed 8 weeks after the procedure and showed a small area of focal fibrosis in the mid septum at the site of previous intervention (Figure 3B: arrow 3). This is less prominent than seen on the previous scan and is likely to represent infarct resorption and a reduction in the amount of associated inflammatory changes.1 There was no inducible ischemia on the stress perfusion scan images (Figure 4: stress and correlating rest images).

Among all patients who undergo coronary arteriography, CTO is present in at least 30% of cases.2–3 Coronary CTO remains one of the most challenging lesion subsets in interventional cardiology,2–6 even with the development of medical devices and operator expertise, although the long term outcome of PCI for CTO is currently unknown. This case shows the benefit of CMR, a safe, noninvasive technology, for the follow-up and assessment of the efficacy of a complex PCI procedure like CTO.

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Disclosures
None.

References

From the CMR Unit and Interventional Cardiology, Royal Brompton Hospital, London, UK.
Correspondence to Dr Sanjay K. Prasad, Cardiovascular Magnetic Resonance Unit, Royal Brompton Hospital, Sydney St, London SW3 6NP, United Kingdom. E-mail s.prasad@rbh.nthames.nhs.uk
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Figure 1. A, Septal perforation (arrow). B, Right coronary artery after PCI.

Figure 2. A, ECG before PCI and B, ECG after PCI. There was no major change before and after the procedure.

Figure 3. A, Contrast-enhanced inversion-recovery image in a short axis view showing localized mid-wall late gadolinium enhancement in the region of the septal perforation branch 48 hours after PCI (arrow 1). There is also evidence of the known chronic inferior subendocardial infarct (arrow 2). B, Contrast-enhanced inversion-recovery image in a short axis view showing a very small focus of residual fibrosis (arrow 3) 8 weeks after PCI. Signal due to the known inferior subendocardial infarct (arrow 2).
Figure 4. Postprocedural CMR stress (A) and rest (B) perfusion scan (adenosine). Arrow showing hypoenhancement in the region of the known inferior subendocardial infarct. There is no inducible ischemia on the stress perfusion scan images.
A 68-year-old woman was admitted complaining of exertional dyspnea. Ten years earlier, a diagnosis of diabetes had been made and hearing loss had developed. Echocardiography and cine magnetic resonance imaging (Movie I, left) showed asymmetric septal hypertrophy with a mildly hypokinetic left ventricle (LV) (ejection fraction = 48%); coronary angiography showed no significant stenosis in any major artery. Electron microscopic examination of a LV endomyocardial biopsy specimen revealed mitochondrial enlargement (Figure 1A, arrows) with concentrically arrayed cristae (Figure 1A, arrow head) and crystalline inclusions (Figure 1B, arrow). The patient was diagnosed with mitochondrial disease after a mitochondrial DNA mutation, an A to G transition at nucleotide position 3243 in the tRNALeu gene, was detected in her leukocytes. Treatment with ubiquinone (coenzyme Q10) for the primary disorder and with carvedilol and enalapril for the secondary heart failure was initiated.

Fifteen months later, however, her exertional dyspnea had worsened. In addition, 12-lead ECG showed remarkable changes in QRS-T patterns, including QRS axis deviation and increased duration (Figure 2), and cine magnetic resonance imaging revealed a further decreased LV ejection fraction (35%) due to severely hypokinetic motion in the inferior to lateral region (Movie I, right). Although a recent myocardial infarction in the region was suspected, coronary angiography again showed no significant stenosis in any major artery (Movie II and III). Cardiac magnetic resonance imaging with gadolinium contrast revealed focal perfusion defects at the interventricular septal and lateral walls (Figure 3A, arrows, and Movie IV) and contrast enhancement in the delayed-enhanced images of the corresponding areas (Figure 3B, arrows), indicating scar tissue within the myocardium.

Mitochondrial disorders are degenerative diseases characterized by heterogeneous phenotypes and genotypes; they usually present with multiorgan involvement and follow a chronic, slowly progressive course.1,2 Although various respiratory chain cofactors and vitamins are widely used in the treatment of patients with these disorders, these standard treatments do not have similar effects in all mitochondrial disorders, because of the heterogeneity.3 The current case presented with diabetes, deafness and cardiomyopathy that developed despite medical therapy. Deterioration of cardiac function with marked ECG changes appears to be attributable to mitochondria-derived injury to the myocardium, including the conduction system, eventually leading to the formation of a fibrotic scar revealed by gadolinium-enhanced cardiac magnetic resonance imaging.

Disclosures

None.

References
Figure 1. Electron microscopic examination of a LV endomyocardial biopsy specimen showing mitochondrial enlargement (A, arrows) with concentrically arrayed cristae (A, arrow head) and crystalline inclusions (B, arrow).

Figure 2. Twelve-lead ECGs recorded at the first admission (A) and 15 months later (B) showing remarkable changes in the QRS-T patterns, including left axis deviation and increased QRS duration.

Figure 3. A, Short-axis magnetic resonance first-pass perfusion image showing focal perfusion defects at the interventricular septal and lateral walls (arrows). B, Short-axis magnetic resonance delayed-enhanced image showing contrast enhancement of the corresponding areas (arrows).

To the Editor:

I read with interest the recent article by Rea et al and the editorial by Ornato and Peberdy. Both papers point to the underlying reason for the American Heart Association’s new defibrillation guideline. The change in the defibrillation guideline results from recognition that automated external defibrillators (AEDs) have a serious shortcoming compared with manual defibrillators. Clearly identifying defibrillator type (AED versus manual) as an important confounding variable is necessary to clarify the significance of results from resuscitation research.

AHA guidelines and training materials have promoted AEDs for more than a decade, advocating their use by trained caregivers as well as the lay public, with little acknowledgement of a major disadvantage: the requirement to stop chest compressions for periods of automated rhythm analysis. There is now for the first time a clear statement from the AHA that AEDs should not be used when manual defibrillators and trained operators are available. However, the new defibrillation guideline makes no distinction between manual defibrillators and AEDs—though it is clearly intended to mitigate the effects of pauses in chest compressions when using AEDs, and though no rationale is presented for its application to manual defibrillation.3 This tends to obscure the importance of defibrillator type as a confounding variable in clinical studies, as well as possibly compromising treatment with manual defibrillators.

The study by Rea et al provides important support for using the new guideline with AEDs but not for its use with manual defibrillators. The editorial also touches on the problem of AED use interfering with CPR but leaves the impression that the defibrillation guideline is somehow based on the “3-phase” model of cardiac arrest.5 This is not the case: the new guideline does not call for varying treatment based on time interval from collapse to start of treatment, the central inference from the 3-phase model; rather, the guideline is intended to lessen the problem of AED-required gaps in CPR after treatment has started. It seems likely that the boundary between the “electrical” phase (defibrillation first) and the “circulatory” phase (CPR first) in the model might vary according to defibrillator type. In studies testing this model, and more generally in research on defibrillation, defibrillator type (AED or manual) should be clearly identified as a confounding variable.

Disclosures

None.

John A. Stewart, RN, MA
Swedish Medical Center
Seattle, Wash


To the Editor:

I read with interest the recent article by Rea et al.1 and the editorial by Ornato and Peberdy.2 Both papers point to the underlying reason for the American Heart Association’s new defibrillation guideline. The change in the defibrillation guideline results from recognition that automated external defibrillators (AEDs) have a serious shortcoming compared with manual defibrillators. Clearly identifying defibrillator type (AED versus manual) as an important confounding variable is necessary to clarify the significance of results from resuscitation research.

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The study by Rea et al.1 provides important support for using the new guideline with AEDs but not for its use with manual defibrillators. The editorial2 also touches on the problem of AED use interfering with CPR but leaves the impression that the defibrillation guideline is somehow based on the “3-phase” model of cardiac arrest.5 This is not the case: the new guideline does not call for varying treatment based on time interval from collapse to start of treatment, the central inference from the 3-phase model; rather, the guideline is intended to lessen the problem of AED-required gaps in CPR after treatment has started. It seems likely that the boundary between the “electrical” phase (defibrillation first) and the “circulatory” phase (CPR first) in the model might vary according to defibrillator type. In studies testing this model, and more generally in research on defibrillation, defibrillator type (AED or manual) should be clearly identified as a confounding variable.

Disclosures

None.

John A. Stewart, RN, MA
Swedish Medical Center
Seattle, Wash


John Stewart comments that recent Guideline changes aimed at increasing CPR should consider whether a manual or automated external defibrillator (AED) is used, since interruptions are more common with the AED, and that future studies should consider defibrillator type as a potential confounder. Science suggests that the ideal resuscitation is one where CPR is not interrupted for rhythm analysis, charge, or pulse checks. The benefit of AED achieved by decreasing the interval from collapse to defibrillation may be offset by other AED features that interrupt CPR; specifically the longer duration required for AED rhythm analysis. Evidence indicates that AED resuscitation using past Guidelines does produce longer CPR interruptions before and after shock than manual defibrillation.1 Importantly, CPR interruptions occurring with manual defibrillation may still be clinically important. Moreover, manual defibrillation is associated with more frequent inappropriate shocks compared with AED, underscoring the importance of training and expertise when undertaking manual defibrillation. Whether inappropriate shocks affect outcome is uncertain, though they presumably introduce additional CPR interruption.

By removing the potential for stacked shocks, new Guidelines eliminate AED-specific interruption following shock but still do not address the excess interruption that occurs for AED analysis before a shock. Through engineering, newer AEDs models have decreased the time for AED analysis and charge, which should attenuate this AED-associated limitation. Importantly, other Guideline changes aimed at delivering more (and more timely) CPR should have similar effects for manual defibrillators and AEDs. Guideline changes eliminate post-shock pulse checks and increase CPR intervals from 1 to 2 minutes, changes which should reduce CPR interruption regardless of defibrillator type.

In summary, Guidelines changes should increase CPR for AED and manual defibrillation. The impact will typically be greater for the AED so that past differences in CPR delivery between manual and AED defibrillation should be attenuated. Nonetheless, with optimal use, manual defibrillation still provides efficiencies that could positively influence outcome. Simple measurement of defibrillator type may incorporate multiple differences, since defibrillator type may be a surrogate for other distinct treatments and/or experience. An alternate approach is to measure hands-off intervals before and after shock, or throughout resuscitation. Careful analysis may help quantitate potential outcome advantages of manual defibrillation and in turn provide a more informed framework for how to use limited resources aimed at improving resuscitation.

Disclosures

None.

Thomas D. Rea, MD, MPH
Michele Garcia, MD
Mickey Eisenberg, MD, PhD
Department of Medicine
University of Washington
Seattle, Wash.

Michael Helbock, MICP
Stephen Perry, MICP
Don Cloyd, MICP
Linda Becker, MA
Division of Emergency Medical Services
Public Health–Seattle & King County
Seattle, Wash.

Advances in the treatment of ST-elevation myocardial infarction (STEMI) over the past 20 years have resulted in dramatic reductions in death attributable to STEMI. In large part, this reduction has been due to early reperfusion and advances in medical therapy.1 The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines and the European Society of Cardiology guidelines for STEMI are in agreement that early and complete reperfusion is optimal, with the goal of door-to-balloon times within 90 minutes and door-to-needle times within 30 minutes.2,3 Most disturbing is that as many as one third of patients do not receive any reperfusion therapy in the absence of contraindications to its use.1,4 In the group of patients who do not receive any reperfusion, both short- and long-term outcomes are significantly worse. Advances in medical therapy, including use of aspirin, heparin, β-blockers, and angiotensin-converting enzyme inhibitors, have also dramatically improved outcomes. Hospitals that are most compliant with the guideline recommendations have better outcomes than those that follow the guidelines less well.5–7

In addition, one of the major delays in patients receiving rapid reperfusion is the delay in the patient seeking care and arrival at the emergency department.8 The National Heart, Lung, and Blood Institute, the AHA, and others have initiated a number of programs to attempt to improve public awareness of this problem and to reduce the time between symptom onset and hospital arrival. Despite these programs, little progress has been made.9 The European Society of Cardiology has identified the need for the establishment of networks for reperfusion at regional and national levels with the ready availability of primary percutaneous coronary intervention (PCI) and adequate quality control.10 Although there are some differences in the delivery of STEMI care between the United States and Europe, both locations are characterized by wide variability in care that would be improved by a more effective and uniform system of care

Treatment Rates in the United States and Europe

The most comprehensive source of information concerning the “real world” treatment of patients with STEMI comes from large registries. The National Registry of Myocardial Infarction (NRMI) is an ongoing voluntary registry that was established in 1990 and has collected data on >2.3 million patients from >1600 hospitals in the United States (http://www.nrmi.org). Over time, there has been a substantial reduction in the use of fibrinolytic therapy, from 34% in 1990 to 20% in 1999, and an increase in primary PCI, from 2.45% to 7.3% during the same time period.1 Concomitant with this change, door-to-needle times improved from 61 minutes to 37.5 minutes. Disappointingly, a more recent study from the NRMI showed little change in these rates between 1999 and 2002, with 46% of patients in the fibrinolytic therapy cohort treated within the 30-minute goal, and 35% of the patients in the PCI cohort treated within the 90-minute goal.11 The reasons for a lack of further improvement are unclear but were not related to hospital characteristics other than hospital volume and a New England location. Hospitals performing
>50 PCI procedures per year had better door-to-balloon times over the 4-year period. Variability in care has been seen in relationship to payer status, with Medicare and Medicaid patients receiving reperfusion therapy less frequently. Likewise, black patients have been less likely to receive reperfusion than nonblacks, and significant regional differences in care are also evident, particularly among those located in a rural setting. Not surprisingly, hospitals with cardiac catheterization laboratories compared with those without are more likely to perform primary PCI. Considerable regional variation in the use of invasive strategies has been seen in the Medicare population. In those regions that provide the highest rates of invasive and medical management strategies, there was an improved 7-year survival rate, averaging 6.2%. In addition, greater compliance with the recommended medical therapy was associated with improved outcomes that helped to explain these regional differences.

The limited on-site availability of cardiac procedures in the highly region- alized Veterans Affairs (VA) health system has been cited as the reason for the underuse of needed angiography after STEMI in the VA compared with the Medicare systems. The availability of invasive facilities is often stated as one of the reasons for regional variability, but studies show that nearly 80% of patients live within 60 minutes of a PCI-capable hospital. Rural hospitals may be an exception where long distances make transport difficult. Care in these hospitals has also been shown to be inferior to that in more urban settings.

The information available from large registries outside of the United States confirms the findings seen inside the United States, with significant variation in practice from country to country and from region to region. In Europe, the distances between tertiary medical centers and community hospitals are substantially shorter, which makes it possible to develop regional care more easily. The shorter distance to the hospital may be one reason for a shorter time from the onset of symptoms to hospital presentation in Europe; however, the use of reperfusion therapy in Europe is similar to that in the United States. In a contemporary Euro Heart Survey, 55% of patients received some form of reperfusion therapy, with 35% receiving fibrinolysis and 21% receiving primary PCI. These rates are lower than those reported in the multinational Global Registry of Acute Coronary Events (GRACE). GRACE is an observational registry involving centers in Australia, New Zealand, Canada, Argentina, Brazil, the United States, and Europe. In these countries, the use of reperfusion with PCI and lytic therapy varied tremendously, with primary PCI varying from 1.1% for Australia, New Zealand, and Canada to 16.2% in Europe. Although the use of primary PCI has significantly increased in all countries over the past few years, these regional differences likely are still present. The registry also showed that there were significant geographic variations in the integration of new guidelines into practice. For instance, the use of low-molecular-weight heparin was more common in Europe (63%) than in the United States (20%). In addition, the use of PCI in STEMI was highly related to the presence of on-site catheterization facilities (61% for those with versus 5.8% for those without). However, in this registry of patients with acute coronary syndromes, there was no difference in short-term or 6-month mortality in 9833 patients with STEMI admitted to hospitals with or without catheterization facilities. This differs from an earlier study from the NRMI performed in the United States in a larger number of patients.

Models of Successful Systems

A number of systems have been developed to improve the acute care of STEMI patients. An initial experience with the ACC “Guidelines Applied in Practice” program in Michigan has been shown to be highly effective in achieving treatment goals and reducing mortality. The AHA’s secondary prevention program, “Get With The Guidelines,” has shown similar success. The ACC/AHA guidelines recommend PCI as the preferred strategy in STEMI, particularly in those patients presenting after 3 hours of chest pain; however, implementation has been difficult given the limited number of PCI-capable hospitals in the United States. It is estimated that only 1200 hospitals in the United States are PCI capable among 2200 hospitals with cardiac catheterization laboratories and nearly 5000 acute care hospitals. To convert all hospitals that have catheterization capability to PCI-capable hospitals would only increase the number of patients receiving primary PCI minimally given the geographic location of these hospitals. In addition, the cost of establishing PCI centers at most hospitals is prohibitively expensive. Therefore, a system of referral to a PCI-capable hospital is necessary. Even in those patients in whom fibrinolysis is chosen, the availability of rescue angioplasty at a referral hospital is often needed. Two models for transfer are most common: the emergency medical services bypass model and the hospital transfer model.

The emergency medical services bypass model is being actively used in a number of cities in the United States. One system in Boston, Mass, is part of an active study to investigate the benefit of ambulance bypass of non–PCI-capable hospitals. This pilot study is ongoing, and results are not yet available. Another approach is to transfer patients from community hospitals to a hospital that has 24-hours-per- day/7-days-per-week primary PCI capabilities. This model has been implemented successfully in the Minneapolis/St. Paul, Minn, area, where patients as far as 200 miles away have door-to-balloon times <100 minutes. Strict protocols and efficient communication have enabled this system to be successful. In North Carolina, the Reperfusion of Acute myocardial infarction in Carolina Emergency departments (RACE) project involves 70 hospitals with strict protocols and timely transfer to regional centers. In Europe, it is easier to implement such a system because the distances between PCI centers and community hospitals are shorter; also, in many countries, socialized care makes implementation easier.

National networks have been established in Denmark and in the Czech Republic in which reperfusion therapy is organized in predefined areas with rapid transport to PCI-capable hospitals. In the DANish multicenter randomized study on fibrinolytic therapy versus acute coronary angioplasty in Acute Myocardial Infarction (DANAMI-2) trial, outcomes were better in those receiving primary PCI, but the study was able to achieve door-to-balloon times of <120 minutes. In
the PRImary Angioplasty in patients transferred from General community hospitals to specialized PTCA Units with or
without Emergency thrombolysis (PRAGUE) study, a system of transport from surrounding communities to Prague, Czech Republic, was effective in achieving door-to-balloon times of 96 to 106 minutes.33,34

Such a triage system is not unlike the trauma system in the United States, where hospitals that meet certain criteria are certified to accept patients with severe trauma. The criteria vary by state but are based on guidelines established by the American College of Surgeons Committee on Trauma. These centers are certified in 3 levels, with level I designated for the most critically injured. As of January 2005, there were 190 level I, 255 level II, and 258 level III trauma centers in the United States. A number of studies have shown this system to be highly effective in reducing mortality.35 There are, however, a number of limitations to the current system. Factors such as a higher volume of trauma and effective quality assurance processes are related to improved outcomes.36 One of the most notable problems is that access is not readily available for all residents. A recent survey determined that only 69% of all US residents had access to a level I or II trauma center, and the majority of those who did not lived in rural areas.37 These same limitations will apply for any system that requires transport for STEMI care in the United States.

Conclusions
The effective treatment of STEMI requires an improvement in the current system of care in the United States. Considerable variability in the use of reperfusion and in compliance with guidelines has limited the benefit of these treatments. An organized strategy to make access and therapy more unified is needed. As suggested by others, the organization of networks at both the regional and national levels is key to success.10 There are many factors that influence the development of an optimal system of care for STEMI patients in the United States beyond the establishment of high-volume skilled centers. Geographic location, particularly in rural areas, presents challenges given the transportation issues and less favorable outcomes seen in patients in this setting.15 In addition, socioeconomic factors are important, with race, sex, and insurance status also playing a role.12,14 Any program that is suggested to improve care for patients with STEMI needs to address these considerations in addition to the type of system, its cost, and its feasibility.

Disclosures
Potential conflicts of interest for members of the writing groups for all sections of these conference proceedings are provided in a disclosure table included with the Executive Summary.

References
17. Guadagnoli E, Landrum MB, Normand SL, Ayanian JZ, Garg P, Hauptman PJ, Ryan TJ, McNeil BJ. Impact of underuse, overuse, and discretionary use on geographic variation in the use of coronary...


Key Words: AHA Conference Proceedings ▪ myocardial infarction ▪ point-of-care systems ▪ angioplasty ▪ reperfusion
A major objective for creating an ideal system of care is to be able to do “the right thing, at the right time, in the right way, for the right person—and having the best results possible.” Critical to this endeavor are patients’ beliefs, values, wishes, fears, expectations, perceptions of symptoms, and cognitive and emotional processes. All of these factors play important roles in determining if, when, and how they access these systems of care.3

Creating an ideal system of care to address the care for patients with ST-elevation myocardial infarction (STEMI) is complex from both the system’s and patient/family’s perspectives. In general, this care is unlike most other hospital care. It typically involves very fast and complex decision making and, often, sudden transportation to another facility for percutaneous coronary intervention (PCI). All of this occurs with a potentially critically ill patient and at a time when the family is often not immediately available. In this report, we address key perspectives from the patient and public point of view of the current system of care for STEMI patients and highlight the barriers and gaps that must be addressed by an ideal system of care (Table 1).

Perspectives on the Current System of Care for STEMI Patients

The biggest challenge to developing an ideal system of care for STEMI patients is the inadequate recognition, by patients and bystanders in the community, of the full spectrum of acute myocardial infarction (MI) symptoms and the urgency of activating the emergency medical services (EMS) system by calling 9-1-1.3 The problem of delay in the setting of symptoms has been recognized for decades,4 but it gained greater urgency with the new treatment paradigm created by fibrinolytic therapy. In surveys and focus groups, heart attack patients, family members, and the public reported that they thought presenting symptoms were less dramatic than expected, they perceived these symptoms as not serious or as transient and therefore took a “wait and see” approach until they were more certain of their significance, and they attributed their symptoms to other chronic conditions or common illnesses. Respondents also cited fear of embarrassment for “false alarms,” reluctance to “bother” physicians or EMS providers unless they were “really sick” or had received permission from others to take rapid action, and existing stereotypes of who is at risk for a heart attack as reasons for delay.2 They often did not perceive women or men under a physician’s care for risk factors as persons at risk.5 They were also unaware of the benefits of rapid action, calling 9-1-1, and reperfusion treatment.

In the current system of care, when and how patients and/or those around them recognize and respond to STEMI symptoms influences which parts of the healthcare system are accessed and can impact the resultant treatment and outcome. The Figure illustrates the time windows and reperfusion scenarios recommended by the American College of Cardiology/American Heart Association (AHA) guidelines. Two EMS options are suggested depending on...
whether the patient accesses EMS and is taken to a non–PCI-capable hospital or a PCI-capable hospital (or self-transport to one). The current recommended time-to-treatment system goals start with contact with the medical system (either EMS arrival or presentation at the emergency department [ED]) but acknowledge the critical total ischemic time of 120 minutes (and the ideal of the “golden hour” of 60 minutes).6

Finally, the current system of care is characterized by marked disparities in access to care and significant variations in the quality of care delivered to those who have access. The most recent National Health Care Quality and Disparities Reports, sponsored by the Agency for Healthcare Research and Quality, document that although many Americans have good access to health care, many others face barriers that make the acquisition of even basic essential health services difficult.7,8 Racial and ethnic minorities, persons of low socioeconomic status or educational attainment, those without health insurance, those who live in rural areas, and poor persons are disproportionately represented among those with access problems.7,8 In fact, in Asian/Pacific Islanders and American Indians/Alaska Natives, the quality of care for acute MI is not only worse than that for whites, but the disparity is getting worse rather than better (comparing the most recent and oldest years of data available).8

The current system of care often places a much higher value on technical competence than on “patient centeredness,” although the evidence suggests that patient-centered care not only improves patient satisfaction but can enhance safety.9 Meeting the needs and expectations of patients and their families is not typically seen as a priority,10 nor is cultural competence or the provision of education and support that patients need to make decisions and participate in their own care, especially after hospital discharge.

**Current Barriers and Gaps That Must Be Addressed by an Ideal System**

Access to timely primary PCI hinges on the patient’s/bystander’s ability to expeditiously recognize STEMI symptoms and activate the EMS system. Current barriers and gaps in knowledge that must be addressed by an ideal system of care exist: in the community and among patients, about STEMI symptoms, the importance of time to artery-opening treatment, the need to access EMS, and how hospitals differ in their capabilities to perform PCI; and among providers, about why patients fail to take appropriate action and the need to deliver systematic, evidence-based education to their patients about appropriate recognition and response to heart attack symptoms and about the advisability of accessing EMS, and gaps in demonstrated effective communication/educational interventions.

![Figure](image-url)

**Figure.** Options for transportation of STEMI patients and initial reperfusion treatment: patient transported by EMS after calling 9-1-1. Reprinted, with permission, from Antman et al.6

### TABLE 1. Perspectives on the Current System of Care for STEMI Patients

<table>
<thead>
<tr>
<th>Community knowledge</th>
<th>EMS system</th>
<th>PCI</th>
<th>After PCI</th>
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<tr>
<td>Inadequate recognition of wide range of MI symptoms</td>
<td>Inadequate enhanced 9-1-1 coverage</td>
<td>Quality of STEMI care delivered</td>
<td>Suboptimal coordination of care and postdischarge instructions: secondary prevention, cost of treatment</td>
</tr>
<tr>
<td>Inadequate awareness of reperfusion treatment and the importance of time to artery-opening intervention</td>
<td>EMS: availability, response time, costs, heterogeneity</td>
<td>Challenges in patient involvement in consent and decision making</td>
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<tr>
<td>Suboptimal use of EMS</td>
<td>Prehospital triage and related issues</td>
<td>Delays in diagnosis and treatment in the ED, in interhospital transfer (if done), and in activation of the PCI team (if patient receives PCI)</td>
<td></td>
</tr>
<tr>
<td>EMS system</td>
<td>Patients’ choice, transparency of decisions, patients’ desires (living will)</td>
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![Image](image-url)

**Goals**

- **Onset of symptoms of STEMI:** Call 9-1-1
- **EMS on-scene:** 9-1-1 EMS Dispatch
- **EMS Triage Plan:** Prehospital fibrinolysis: Door-to-Needle within 30 min
- **EMS on-scene:** 9-1-1 EMS Dispatch
- **EMS transport:** EMS transport to PCI capable hospital within 30 min
- **Hospital fibrinolysis:** Door-to-Needle within 30 min

*Golden Hour = First 60 minutes*
<table>
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<tr>
<th>TABLE 2</th>
<th>Recommendations for Needed Research, Programs, and Policies: Patient Perspectives Work Group</th>
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<tbody>
<tr>
<td><strong>Research</strong></td>
<td></td>
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</table>
| Patient, family, and community knowledge | Invest in targeted research on perspectives of informed patients and their family members, especially those with direct experience with the care for STEMI, as consumers and beneficiaries of health care.  
  Conduct research on patient and family preferences regarding transfer to a PCI-capable hospital, ie, outside of their community.  
  Determine the most effective communication methods to bring about changes in patient/bystander action (decreased delay and appropriate system access).  
  Assess the role of decision support and information technology in the home and its impact on patient/bystander delay and EMS utilization.  
  Study the psychological, medical, logistical, social, and financial impacts on patients and families of transfer out of their community to a PCI-capable hospital either directly by EMS or via interhospital transfer.  
  Examine how patient/family awareness of the unique issues associated with a PCI-oriented system of care affect patient delay and use of EMS in response to symptoms.  
  Quantify the characteristics, frequency, natural history, and effectiveness of interventions with patients who have early prodromal symptoms of an MI.  
  Collect and make available data on patient-centeredness, safety, effectiveness, and timeliness in the delivery of care for STEMI, as well as data on patient outcomes, including health status, after discharge.  
  Invest in further research and application of information technology to facilitate access to early recognition of symptoms/diagnosis/treatment. |
| EMS system      | Invest in a formal evaluation of the proposed ideal system of care for STEMI from the perspective of patients and their use of EMS.  
  Evaluate alternate options to EMS; for example, does calling a gatekeeper about symptoms (available 24 hours per day/7 days per week) result in less time delay than calling EMS? |
| PCI/after PCI    | Conduct patient/family surveys about ways to improve management for STEMI before, during, and after PCI for the acute event. |
| Full spectrum of care for patients with MI | Identify the economic impact of a primary PCI system of care for STEMI on patients and their community providers.  
  Identify aspects of a system of care based on access to primary PCI that have an impact on patient satisfaction.  
  Obtain input from STEMI survivors to inform future program and system development.  
  Examine how the tools of information technology (telehealth; diagnosis and treatment decision support; large-scale databases; medical records access; and education of the public, patients, and healthcare providers) affect access to timely primary PCI.  
  Explore outcomes of patients seen for early assessment of prodromal (eg, intermittent, stuttering) symptoms. |
| Programs        |                                                                                         |
| Patient, family, and community knowledge | Develop and test effectiveness of educational campaigns to decrease patient delay and increase use of EMS based on access to a primary PCI-capable hospital destination (ideally building on current campaigns), including education about hospital capability for PCI and the implications for the management patients will receive if they access care for symptoms.  
  Implement prospective education with patients and families about the system of care they will access when seeking evaluation of MI symptoms in a regional system of care (based on access to primary PCI for STEMI).  
  Address what communities should tell patients about where they will be taken (ie, PCI-capable hospital vs non–PCI-capable hospital), including the rationale for transport/transfer and logistical issues associated with the transport/transfer.  
  Convey to patients/families the ramifications of self-transport in a PCI-based hospital system of care. |
| EMS system      | Provide educational and concrete logistical information (eg, directions to PCI-capable hospital; parking; where to find the patient in the hospital) to family members of patients being transferred out of their community to a PCI-capable hospital (ie, direct transfer if EMS was accessed or interhospital transfer).  
  Educate patients at discharge (and those “ruled out” in the ED) about recognizing MI symptoms and accessing the EMS system. |
| PCI/after PCI    | Provide educational and concrete logistical information (eg, directions to PCI-capable hospital; parking; where to find the patient in the hospital) to family members of patients being transferred out of their community to a PCI-capable hospital (ie, direct transfer if EMS was accessed or interhospital transfer) [also under EMS].  
  Educate patients at discharge (and those “ruled out” in the ED) about recognizing MI symptoms and accessing the EMS system. |
| Full spectrum of care for patients with MI | Develop novel and expedited methods of patient consent and medical information transfer.  
  Include patient education and outreach as part of community/regional hospital and system strategies to increase the number of STEMI patients who receive timely reperfusion.  
  Counsel high-risk patients and their families in advance about recognizing and responding to MI symptoms, including patients seen in the ED and “ruled out” for MI, and at discharge for patients admitted to the hospital with a diagnosis of MI.  
  Clarify the difference in presentation between a “heart attack” (eg, with symptoms) and a cardiac arrest in communications with patients/public.  
  Develop programs for seamless interface with patients and their local primary care providers. |
TABLE 2. Continued

<table>
<thead>
<tr>
<th>Policies</th>
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<tr>
<td>Patient, family, and community knowledge</td>
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<tr>
<td>Ensure appropriateness and consistency of instructions that health plans and providers give patients regarding definitions of emergencies and accessing EMS.</td>
</tr>
<tr>
<td>Ensure commitment from lead national agencies (eg, AHA; National Heart, Lung, and Blood Institute; Centers for Disease Control and Prevention) to regularly update the current educational campaign messages/materials on recognizing and responding to an acute MI as the science and the field evolve.</td>
</tr>
<tr>
<td>EMS system</td>
</tr>
<tr>
<td>Ensure that care for patients who are determined not to have STEMI, including EMS transport/transfer, is adequately reimbursed without penalty.</td>
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<tr>
<td>Ensure timely ambulance availability to all STEMI patients for initial access and interhospital transfer.</td>
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<tr>
<td>Full spectrum of care for patients with MI</td>
</tr>
<tr>
<td>Ensure alignment of reimbursement policies to encourage providers to participate in a patient-centered integrated system.</td>
</tr>
<tr>
<td>Broaden the AHA's efforts in health information technology to include the capture of quality and outcomes data to permit assessment of data that address the consumers' perspectives on healthcare needs.</td>
</tr>
<tr>
<td>Assess current state legislation and local policies that have an impact on the system of care for STEMI patients.</td>
</tr>
<tr>
<td>Include representatives of patients and families in community coalitions to plan the local/regional system of care for timely access and optimal care of patients with STEMI symptoms.</td>
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<tr>
<td>Include the optimum way to time the onset of symptoms, because this is the initial critical measure to capture the overarching biologically important time interval of symptom onset to artery opening for quality improvement programs.</td>
</tr>
<tr>
<td>Collect individual- and population-level data as part of quality improvement efforts (ie, quality of care for the patients treated and quality of care of all eligible patients or the population served by the system).</td>
</tr>
<tr>
<td>Help standardize training and protocols around management of patients who call or walk-in/present to physicians' offices/clinics with possible heart attack symptoms.</td>
</tr>
<tr>
<td>Partner with managed-care plans to help develop explicit language for their patients about what symptoms constitute an &quot;emergency&quot; that requires activation of EMS without preapproval.</td>
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Community/Patient Barriers and Gaps

People who experience a heart attack generally do so in their communities, outside of the hospital, such that the community effectively becomes the "ultimate coronary care unit." Prompt patient presentation to the EMS system and ED is the linchpin to successful coronary reperfusion. Reductions in patient delay in the United States have not been seen over time or as an outcome of intervention studies. Such delays compromise the likelihood of patients receiving timely reperfusion treatment. Despite the benefits of accessing EMS in the setting of STEMI (eg, earlier prehospital diagnosis, prehospital triage, and decreased time to fibrinolytic therapy), rates of EMS use by patients experiencing MI symptoms range from 10% to 56%. Most persons with MI are driven to the ED by someone else (60.4%) or drive themselves to the hospital (15.6%). Literacy level, socioeconomic factors, insurance status, and the prepayment systems and preapproval policies of patients’ health plans can impact prompt activation and use of EMS.

Provider Barriers and Gaps

EMS utilization is influenced by instructions provided by primary care physicians and health plan policies. Rates of EMS use are less among patients who contact their physicians than among those who do not. Physicians may prefer that their patients call them before calling 9-1-1 so that they can provide tailored advice to their patients whose histories are known to them. However, few patients report they ever discuss symptoms, responses, or actions for a heart attack in advance with their providers (or their families). Also, there is variability in how much explicit guidance health plans give enrollees in defining an emergency, in particular, listing the key MI symptoms and linking these to calling EMS.

Barriers and Gaps in Effective Communication/Educational Interventions

Although interventions to increase EMS use for MI patients to date have been only modestly successful, they must be an important part of an ideal system of care for STEMI. Most interventions have focused on reducing prehospital delay time and, to a lesser extent, increasing utilization of EMS for MI. In general, it has proven more difficult to reduce delay time than to increase EMS use. There have been 3 randomized trials conducted in the past decade in North America that have demonstrated an increased use of 9-1-1 for MI: the “Call Fast, Call 911” campaign in King County, Wash; Rapid Early Action for Coronary Treatment (REACT) research program; and the “Heart Attack Survival Kit” project. These intervention trials show that it is possible to increase EMS use for MI when (1) a fairly large quantity of mass media messages are disseminated throughout a community, (2) messages are targeted at high-risk audiences, (3) multi-pronged approaches are implemented that target many different stakeholders, and (4) interpersonal counseling sessions are conducted by credible sources. The results of these trials also show that it is difficult to develop an intervention that has a sustained effect over time.

Key Perspectives on the Ideal System

In light of these barriers and gaps, an ideal system of care for STEMI patients first and foremost recognizes the urgency of STEMI symptoms and the importance of time to treatment in
all community settings where patients may present.\textsuperscript{20} Such a system invests in science-based education about recognition and response to MI symptoms, such as the “Act in Time to Heart Attack Signs,” launched by the National Heart, Lung, and Blood Institute, the AHA, and other partners in 2001 based on key findings from the REACT study.\textsuperscript{21} The ideal system invests in culturally competent and specific educational efforts. Therein, lead national organizations (ie, private, public, voluntary, and professional) periodically review and update science-based education campaigns as new research becomes available to ensure clear, consistent messages about appropriate patient recognition and actions. It streamlines patient activation of the system to eliminate any literacy, cultural, language, and precertification barriers.

In a system of care predicated on transfer for PCI, patients and family members are educated with essential information about the community’s hospitals and their capabilities for PCI (ie, thus providing the rationale for interhospital transfers and associated logistical issues) both in advance and at the time the system is accessed. The ideal system further used tested decision support tools for patients to provide early diagnostic support for patients and their families to seek care.\textsuperscript{22} Such a system would have established protocols in EDs around the processes of rapid detection, evaluation, and referral/treatment of patients\textsuperscript{23} within a PCI system of care, incorporating quality improvement measures for ongoing monitoring and process improvement. The ideal system measures overall delay from symptom onset—including the times to presentation at both the referring hospital (“prehospital delay time 1”) and the receiving hospital (“prehospital delay time 2”)—to ultimate reperfusion, to capture process improvement needs in a regional system of care.\textsuperscript{24}

Furthermore, in an ideal system, neither patients nor providers would be penalized if symptoms turn out to be “false-positive.” An optimum system educates high-risk patients and their family members in advance about recognizing and responding to heart attack symptoms,\textsuperscript{25} including patients seen in the ED and “ruled out” for an MI and at discharge for patients admitted to the hospital.

In addition to an expectation of high-quality care, patients and their families expect a well-coordinated care-delivery system, appropriate preparation of the patient for resumption of normal activities before discharge, and evaluation of the need for and strategies for long-term risk factor reduction. Ideal systems of care for STEMI patients should address key dimensions of healthcare experiences such as coordination of care, delivery of information and education, physical comfort, emotional support, respect for patient preferences, involvement of family and friends, and continuity and transition of care.

The ideal system looks beyond STEMI and ensures that programs are available from which patients with early prodromal symptoms of an MI can obtain prompt and appropriate evaluation and referral from a clinical setting/hospital geared to user-friendly evaluation of possible acute ischemic symptoms (eg, a chest pain center). Finally, an ideal system includes patient representatives on community coalitions that can plan the local/regional system of care to ensure timely access and optimal care of patients with MI symptoms.

**Recommendations**

On the basis of perspectives from patients, their families, and the community, the writing group proposes several recommendations for research, practical programs, and public policy to address the above-mentioned gaps and barriers and facilitate the creation of an ideal system of care for STEMI and acute coronary syndrome patients (Table 2).

**Disclosures**

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**References**


**KEY WORDS:** AHA Conference Proceedings myocardial infarction point-of-care systems angioplasty reperfusion
Development of Systems of Care for ST-Elevation Myocardial Infarction Patients
The Physician Perspective

Mark Sanz, MD, Co-Chair; Richard W. Smalling, MD, PhD, FAHA, Co-Chair;
David L. Brewer, MD, FAHA; William J. French, MD; Lynn A. Smaha, MD, PhD, FAHA†;
Henry H. Ting, MD, MBA; Donald E. Casey, MD, MPH, MBA

The physician’s overarching role in the development of systems of care for ST-segment-elevation myocardial infarction (STEMI) is to advocate for achieving the goal of early infarct-artery patency for all patients with STEMI. An effective STEMI care system relies on a team of multiple physicians, nurses, emergency medical services (EMS) personnel, and other providers to work in an efficient, collaborative manner to deliver optimal patient care. Urgent, direct activation of the EMS system by the STEMI patient is ideal.

Successful first response care by EMS or emergency department (ED) personnel followed by rapid access to revascularization requires standardized, evidence-based STEMI treatment protocols in accordance with the most current American College of Cardiology (ACC)/American Heart Association (AHA) guidelines. Physicians participating in the development of these protocols should include both interventional and noninterventional cardiologists, emergency medicine specialists, EMS physicians, and primary care physicians. Furthermore, to more effectively achieve success in developing and implementing these systems and networks, physicians must demonstrate a new paradigm of leadership, including the following:

1. A passionate and credible commitment to the goal of achieving timely infarct artery patency for all patients with STEMI;
2. An ability to obtain the full cooperation, collaboration, and support of hospital senior management and medical staff at local, referral, and regional levels;
3. The development and implementation of innovative team-based methods for overcoming professional, organizational, and regulatory barriers to ideal STEMI treatment;
4. Effectiveness in implementing protocols that are flexible with regard to geographic and other local issues;
5. Mastery of the use of efficient and credible clinical information systems that support timely data collection, quality and outcomes measurement, feedback, and transparency for both internal and public quality improvement initiatives; and
6. Prompt data collection and feedback.

Ideal STEMI Systems
Currently, primary care and specialist physicians tend to work separately rather than in integrated networks in caring for patients with STEMI, particularly at entry into the medical system. The ideal system encompasses multidisciplinary teams to ensure that optimal care according to ACC/AHA guidelines is delivered on entry, in the hospital, at discharge, and over the long term, within the patient’s local system after discharge.1–3 At each step, the physician will play a critical and clearly defined role.
Community Education

It is recognized that major time delays from patient symptom onset to presentation for medical care exist. Physicians, particularly primary care physicians, should pursue a leadership role in community education (Figure 1), promoting early recognition of ischemic chest pain and the need to call 9-1-1 quickly at the onset of chest discomfort.4,5 This could be accomplished during office visits, using posters and pamphlets, and by speaking at community functions regarding the importance of calling 9-1-1 when experiencing severe chest pain or other symptoms of acute myocardial ischemia. Both primary care and emergency physicians could be helpful in training paramedics and ED personnel to accurately interpret 12-lead ECGs. Ongoing training and education of ED and EMS providers should be part of a written regional plan for STEMI care. These requirements for physician leadership are irrespective of the type of center or system.

Non–Percutaneous Coronary Intervention–Capable Hospitals

Non–percutaneous coronary intervention (PCI)–capable hospitals include all centers either without primary PCI capability or without availability of PCI on a 24-hours-per-day/7-days-per-week basis. A regional standardized transfer protocol should be applied consistently for the entire 24-hour period.3,6,7

Initiation of Care

The primary care and emergency physicians should immediately recognize and accurately diagnose ECG signs of STEMI. They should also be comfortable with the differential diagnosis of ECG abnormalities associated with chest pain, including pericarditis, myocarditis, hypertrophic cardiomyopathy, aortic dissection, and other clinical entities.5

Hospital Care

Emergency physicians and cardiologists should promptly initiate care in accordance with published ACC/AHA guidelines based on duration of symptoms, minimizing delays in transport that include but are not limited to those based on weather conditions, severity of patient illness, and bleeding risk. Protocols may include transportation for primary PCI or full-dose fibrinolytic therapy with optional rescue PCI based on current guidelines.9

Transfer Issues

All STEMI patients should be considered for transfer to a PCI–capable center after appropriate, expedited, on-site initiation of care. Patients receiving fibrinolytic therapy should be considered for timely transfer for potential rescue PCI.6,10–14 A referral hospital door-to-receiving hospital balloon time should be a measure of quality.

PCI–Capable Hospitals

EMS and air ambulance medical directors, emergency physicians, and interventional cardiologists should interact in a seamless fashion with a common goal of achieving infarct-related artery patency in STEMI patients as quickly as possible.1–3,7,13–15

Emergency Physicians

Emergency physicians should accurately interpret 12-lead ECGs transmitted from patients with chest pain in the field (eg, EMS, helicopter) or in non–PCI-capable hospitals. They should be knowledgeable about evidence-based treatments for arrhythmias and hemodynamic emergencies. In addition, they should have access to a global STEMI notification system, capable of simultaneously activating the catheterization laboratory and interventional cardiology teams while the patient is still en route from the field or transferring hospital.

Interventional Cardiologists

When on call, interventional cardiologists and staff should respond to the ED within 20 to 30 minutes of activation based on local conditions so as to meet ACC/AHA guidelines on door-to-balloon times.16 They should be familiar with system and network strategies to achieve and sustain reperfusion of the infarct artery. Interventional cardiologists should also be familiar with the treatment strategies for higher-risk patients, including intra-aortic balloon counterpulsation and other left ventricular support, as well as ventilatory support techniques. They must be involved with discharge protocols that ensure short-term and long-term guideline adherence for secondary prevention medications, smoking cessation, cardiac rehabilitation, and screening for depression. Long-term outcome measurement systems should be developed with input from all providers. They should also be aware of the need to optimize patient and family education needs as lengths of stay decrease. Interventional cardiologists must assume responsibility for the seamless transition of the patients and all their information back to the local cardiologist and primary care provider.

Outcomes Reporting and Quality Initiatives

A complete outcomes reporting process should be mandated for all components of STEMI systems. There should be formal benchmarking, case review, and risk-adjusted institutional and provider comparisons (Figure 2).

Physicians should be leaders in continuous quality improvement initiatives for STEMI programs within a clinical team that includes EMS personnel, emergency physicians, nursing staff, and catheterization laboratory teams and should implement strategies to continuously improve chest pain onset-to-reperfusion times. Outcomes, including mortality and morbidity, and time to treatment measures should be
consistent with national databases. Long-term measures such as medication adherence, smoking cessation, and lipid and blood pressure control should be developed and reported in a continuous quality improvement program. It is important to consider care as a continuum that extends beyond the acute in-hospital phase of STEMI care.

Physician Training in Continuous Quality Improvement Techniques
Physicians should be trained in tools for process and system improvement design. This includes education of those in practice and those in residency and fellowship training.

Physician Qualifications
Physicians should meet ACC/AHA guidelines for STEMI care. Interventional cardiologists performing primary PCI should be board-certified or board-eligible in interventional cardiology, comply with published guidelines for procedural volume, and participate in standardized quality registries for PCI and STEMI. 16

Gaps and Barriers
Rural Settings
Rural physicians may lack the volume of STEMI patients to maintain up-to-date knowledge of STEMI care issues. They also may lack easy access to the educational opportunities available in larger cities or larger physician group settings. They are usually full-time family physicians who not only staff the ED but also maintain full office practices. They must be capable of providing care across the spectrum from pregnancy to end-of-life issues and for acute issues such as trauma. In this setting, timely and easy access to educational materials (preferably Internet-based) is critical. Furthermore, written protocols may help address practice variations in real-world practices.

Transfer Policy Issues
Loss of Patients
Hospitals and physicians both may be reluctant and raise concerns about diverting patients to competing institutions. 17 Furthermore, current policies require ambulance services to transport patients with suspected STEMI to the nearest acute care hospital. Cardiac care is often one of the most prestigious, most marketed, and most profitable service lines.

Financial Issues
Resources: Personnel and Data Systems
As hospitals either lose money or shift resources to profitable endeavors, the money for implementing quality programs may not be forthcoming. Information systems, staff to collect and verify data, and a dedicated meeting time for staff and physicians currently are not reimbursed by payers. However, investment in quality infrastructure may ultimately result in cost savings.

Physician Time
Many physicians have experienced decreasing reimburse-
ment for services and must work more to maintain stable incomes. Often, benefits accrue to hospitals and third-party payers rather than physicians. 18 However, physicians are important drivers for both quality care and cost of care. An ideal system should appropriately align the goals and incentives for all stakeholders, including physicians, patients, hospitals, and payers.

Recommendations
Research
1. Determine how movement of patients, and possibly phys-
sicans, from non–PCI-capable hospitals to PCI-capable centers will affect patient care.
2. Determine whether an adequate number of interventional cardiologists will be trained to meet the demand of increased numbers of STEMI patients undergoing primary PCI.
3. Determine whether simulation training for STEMI patient process of care is effective in improving patient outcomes.

Programs
1. Establish community networks where constituents (physi-
sicans, patients, EMS, administrators, and payers) meet to make appropriate referrals occur reliably.
2. Develop programs for a seamless interface with patients and their local primary care providers after discharge from a PCI center. These programs should focus on guideline-based discharge tools (AHA’s “Get With the Guidelines” or ACC’s “Guidelines Applied in Practice”) and include measurement of patient compliance both early and late after discharge with a feedback cycle to effect improvement.

Policy
1. Align financial incentives with desired outcomes. This may include gain-sharing arrangements as in recent Centers for Medicare and Medicaid Services demonstration projects. 19
2. Develop effective quality measurements and tools to assess the effectiveness of physicians and other healthcare providers in counseling patients on early activation of EMS and long-term adherence to discharge recommenda-
tions according to ACC/AHA guidelines. These measure-
ments must be proven to reflect improvement in long-term outcomes.
3. Provide (regional) education on STEMI to physician constituents. Develop tools for education of providers.
Disclosures
Potential conflicts of interest for members of the writing groups for all sections of these conference proceedings are provided in a disclosure table included with the Executive Summary.

References
Development of Systems of Care for ST-Elevation Myocardial Infarction Patients
The Emergency Medical Services and Emergency Department Perspective

Peter Moyer, MD, Co-Chair; Joseph P. Omato, MD, FAHA, Co-Chair; William J. Brady, Jr, MD; Leslie L. Davis, MSN, RN, ANP-C; Chris A. Ghaemmaghami, MD; W. Brian Gibler, MD; Greg Mears, MD; Vincent N. Mosesso, Jr, MD; Richard D. Zane, MD

Central to the development of systems and centers of care for ST-elevation myocardial infarction (STEMI) patients will be the key role played by emergency medical services (EMS) at entry into the system and within the system when emergency interhospital transport is required.

Current System of Care

Emergency Medical Services System Design

Prehospital EMS systems have 3 major components: emergency medical dispatch, public safety (fire and law enforcement) first response, and EMS ambulance response. Each of these operates within a broader emergency care system, which includes acute care facilities and regionalized healthcare services. In most states, an EMS regulatory entity within the state government oversees the emergency care system. Many states have regional EMS councils and advisory boards that function with varying levels of authority.

Emergency Medical Dispatch

Early access to EMS is promoted by a 9-1-1 system currently available to >95% of the US population. Enhanced 9-1-1 systems provide the caller’s location and number to the dispatcher, which permits rapid dispatch of prehospital personnel to locations even if the caller is not capable of verbalizing or the dispatcher cannot understand the location and telephone number of the emergency. Although cellular phones have been problematic because they do not stay in a fixed location, new technology exists that allows triangulation of a cellular phone caller’s location. This technology is being phased in throughout the country at a rapid pace.

In most communities, law enforcement or public safety officials are responsible for operating 9-1-1 centers, because in most locations, 85% of calls are for police assistance, 10% are for EMS, and 5% are for fire-related emergencies. Dispatchers who staff 9-1-1 centers may have minimal medical training, be emergency medical technicians, or on occasion be paramedics trained and certified as emergency medical dispatchers. In any case, dispatchers operate under standardized, written (often computerized) protocols. Such protocols are developed nationally and then modified locally or nationally. The ideal system has intense quality improvement programs to ensure that dispatchers follow protocols and procedures correctly and consistently. This is particularly true for the prearrival instructions that are given to cardiac arrest bystanders to instruct them on how to perform cardiopulmonary resuscitation (CPR) while awaiting arrival of emergency personnel (telephone CPR). Emergency medical dispatchers can also prompt patients with symptoms suggestive of an acute STEMI to take aspirin while awaiting the arrival of EMS personnel.

Public Safety First Responders

To minimize time to lifesaving treatment, most communities have volunteer and/or paid firefighters and/or law enforce-
Ambulance Responders
EMS ambulances are staffed by a variety of different personnel throughout the United States. Most urban and suburban ambulances are staffed with paid or volunteer fire department, third-service EMS, private or hospital-based, and/or volunteer rescue squad personnel. Most EMS systems are “tiered,” which means that some of the ambulances are staffed and equipped at the basic life support emergency medical technician level (which includes first aid, CPR, and early defibrillation with AEDs), and other units (either transporting or nontransporting) are staffed by paramedics or other intermediate-level emergency medical technicians who can, in addition to basic care, start intravenous drips, intubate, and administer medications. In some systems, advanced life support (ALS) providers can also perform 12-lead ECGs, provide external pacing for symptomatic bradycardia, and administer other advanced treatments. A minority of EMS systems provide only ALS ambulance service (an “all-ALS” model).

Rural areas provide primarily basic life support ambulance services, usually by volunteers supplemented by a relatively small number of ALS units. In some cases, ground ambulance paramedics or helicopter personnel respond to the scene (“ALS intercept”) in addition to a basic life support ambulance team to provide the higher level of service. When a ground ambulance is requested for interfacility transfer, a dispatch center may treat the request as a routine transport, which would result in a potentially avoidable delay.

Aeromedical services (helicopters and fixed-wing aircraft) are currently available throughout most of the United States for scene response to trauma and for interhospital transfer. Many communities use helicopter air ambulances to transport STEMI patients from noninterventional community hospitals to regional primary percutaneous coronary intervention (PCI) centers. In some cases, it may be quicker to transport such patients to a PCI center by a ground ALS ambulance (when available).

EMS Assessment, Triage, and Treatment of Suspected STEMI Patients
The American Heart Association (AHA) advanced cardiovascular life support chest pain algorithm importantly contributes to the prehospital assessment, triage, and treatment of patients with suspected STEMI in most EMS systems. This algorithm recommends empirical treatment of suspected STEMI patients with morphine, oxygen, nitroglycerin, and aspirin (“MONA”). The American College of Cardiology (ACC)/AHA STEMI guidelines also recommend that 9-1-1 center emergency dispatchers ask patients with symptoms suggestive of an acute STEMI to take an aspirin (unless allergic) while first-responder and ambulance units are on the way.

Because the majority of STEMI deaths occur in the first 2 hours due to cardiac arrest after the onset of symptoms, it is important for communities to strengthen their “chain of survival” by continued training of laypersons in CPR and the use of AEDs, including the deployment of AEDs in high-risk public locations (“public access defibrillation”).

Prehospital 12-Lead Electrocardiography
It has been reported that approximately 4% to 5% of EMS patients with chest pain are having an acute STEMI. Prehospital 12-lead ECG acquisition is critical for determining which chest pain patients need to be transported to a PCI-capable facility. The ACC/AHA STEMI guidelines, the 31st Bethesda Conference of the ACC, and a recent technology review supported by the National Heart, Lung, and Blood Institute’s National Heart Attack Alert Program strongly encourage the use of 12-lead ECGs by paramedics to evaluate all adult patients with nontraumatic chest discomfort. In a recent survey of EMS systems serving the 200 largest US cities, 84% of EMS systems reported that 12-lead ECGs were “available” in their system; however, in the National Registry of Myocardial Infarction, a prehospital 12-lead ECG was recorded in <10% of STEMI patients. It is not clear why there is such a disparity between reported availability and documented use.

In prehospital 12-lead ECG-equipped communities that permit transport of patients to both non–PCI-capable and PCI-capable hospitals, paramedics may fill out a fibrinolytic “checklist” and relay the ECG and checklist findings to the receiving hospital. The checklist helps to determine the presence of comorbid conditions for which fibrinolytic therapy may be contraindicated. Local protocols usually dictate the destination hospital for such patients. Traditionally, most community protocols have directed EMS teams to bring chest pain patients to the nearest hospital, under the presumption that most hospitals could provide fibrinolysis if the patient was found to have an STEMI. The increasing use of a primary PCI reperfusion strategy is prompting many communities to consider whether it is better to bypass the closest facility in favor of bringing such patients to the nearest primary PCI-capable and available hospital rather than the nearest hospital.

In Boston, Mass, paramedics reliably recognize “definite STEMI” patients on the prehospital 12-lead ECG with high reliability. Such patients are brought directly to the cardiac catheterization laboratory at a primary PCI-capable hospital. Patients with “possible STEMI” are evaluated in the emergency department (ED) before the catheterization laboratory is contacted.

Prehospital Fibrinolysis
Because randomized controlled trials of fibrinolytic therapy have demonstrated the benefit of initiating fibrinolytic therapy as early as possible after the onset of STEMI symptoms, it would seem logical to expect that a greater number of lives could be saved if fibrinolytic therapy could be started by EMS providers. A meta-analysis of prehospital-initiated fibrinolytic trials suggests that there is a
17% relative improvement in outcome associated with prehospital (versus ED) fibrinolysis.20

Most of these trials were conducted in Europe, where physicians staff ambulances, which makes the decision to administer fibrinolysis easier. Fibrinolysis works best in the first few hours after symptom onset when a fresh thrombus is susceptible to pharmacological dissolution.21 The Myocardial Infarction Triage and Intervention (MITI) study in Seattle, Wash, failed to demonstrate a statistically significant overall mortality benefit for prehospital versus ED fibrinolysis. It did, however, show better outcomes with prehospital fibrinolysis in the subset of patients who were seen within 70 minutes of symptom onset.17

In the CAPTIM (Comparison of Angioplasty and Prehospital Thrombolysis In acute Myocardial infarction) study conducted in France, where ambulances are staffed by physicians, prehospital fibrinolysis was equal to or superior to primary PCI when patients were treated within 2 hours of symptom onset. Patients treated after 2 hours of symptom onset had better outcomes with PCI.22

Although there are isolated areas in the United States that have instituted prehospital fibrinolytic programs,23,24 the strategy has not been adopted widely, likely because of the high cost, difficulty in maintaining paramedic skills for an infrequently used treatment, relatively short transport times in many EMS systems, and potential for litigation if a fibrinolytic drug is administered to a patient who does not need it and there is a serious complication.25,26 For these reasons, the ACC/AHA STEMI guidelines do not advocate a national policy of prehospital fibrinolytic therapy. The guidelines do support prehospital fibrinolysis in special settings in which physicians are present in the ambulance or prehospital transport times are ≥60 minutes in high-volume EMS systems.27

ED Issues

Because both challenges in training and equipping EMS systems with 12-lead ECG and patient factors leading to non-EMS presentations will continue to exist in the foreseeable future, there is no realistic plan that can completely exclude the ED from being an integral part of STEMI care systems. Only 24% to 44% of all STEMI patients utilize EMS as the entry point in the medical system.28 Instead, the majority of STEMI patients have their first medical contact on entry into the ED. This poses a special challenge to ED personnel, because STEMI patients arriving by ambulance typically receive attention and treatment faster than patients who transport themselves.10,28,29 This issue is a particular problem in busy, overcrowded EDs.30

The current process for triaging, evaluating, and treating a suspected STEMI patient who presents to the ED includes a large number of potentially avoidable delays.31 After ED arrival, the ambulatory patient typically undergoes a triage process, followed by emergency nurse and physician assessments. Patients presenting via EMS are usually placed immediately in treatment areas and assessed rapidly by emergency physicians and nurses. Emergency physicians and nurses stabilize the patients medically and begin administering adjunctive treatments (eg, aspirin, β-blockers, or anticoagulation). A 12-lead ECG is usually performed per protocol early in the ED course. The ACC/AHA guidelines recommend that the initial ECG be performed within 10 minutes of arrival, but depending on ED capacity, patients presenting with atypical symptoms for STEMI may wait in the waiting room because of their initial triage assessment. ED overcrowding has been demonstrated to result in delays in initiation of reperfusion therapy.32 Depending on local practice patterns, multiple consultations with cardiologists and/or primary care physicians may be required to determine reperfusion strategy and the need for possible transfer to a primary PCI-capable hospital. These disorganized processes routinely cause delays to reperfusion.33

Many hospitals need to organize their response for patients presenting with symptoms suggestive of STEMI to ensure that the diagnosis can be confirmed and reperfusion therapy can be offered in the shortest possible time. The ACC/AHA STEMI guidelines recommend the establishment of multidisciplinary teams (including primary care physicians, emergency physicians, cardiologists, nurses, and laboratory personnel) who can develop guideline-based, institution-specific written protocols for triaging and managing patients who present with signs and symptoms suggestive of STEMI.2

For hospitals that use a primary PCI strategy, these protocols may include criteria and procedures for patients transported by ambulance with prehospital 12-lead ECG–confirmed STEMI to receive expedited emergency care and, when appropriate, to bypass the ED and go directly to the cardiac catheterization laboratory. An increasing number of hospitals are setting up “STEMI alert” teams patterned after “trauma alert” teams used at trauma centers. Each team, typically consisting of representatives from the ED, the cardiology department, the coronary care unit, and the catheterization laboratory, can be alerted by a group telepage either when a STEMI patient is being transported to the hospital by an EMS ambulance team that has performed a prehospital 12-lead ECG or on diagnosis of STEMI by an emergency physician. The process in the non–PCI-capable hospital is nearly identical to that in the primary PCI-capable hospital with the exception that the activation of the STEMI alert system from outside the STEMI-receiving hospital results in the rapid assessment of available transportation options (by conference call or some other means), followed by a decision to either transport the patient or initiate fibrinolysis. This determination must be made soon after the patient arrives in the ED.

The Ideal EMS/ED System of STEMI Care

The ACC/AHA STEMI guidelines suggest that each community should develop a system of STEMI patient care that incorporates non–PCI-capable and primary PCI-capable hospitals. The trauma center model has been used successfully for decades to help communities optimize the care of seriously injured individuals. This model establishes a hierarchy of hospitals based on their 24-hour care capability. The lead trauma hospital in a region has responsibility for helping to coordinate the network and for conducting research and education. There is increasing support for implementation of the trauma center model for STEMI patient care that is integrated with the regional and statewide systems of care.2

The ACC/AHA STEMI guidelines also suggest that there should be a written plan and standards for STEMI patient assessment, treatment, and triage by EMS providers.2 The plan
should be developed with formal input from EMS agencies, cardiologists, emergency physicians and nurses, hospitals, and others. The plan should interface with that of neighboring communities and should include a requirement to track EMS and hospital performance with pre-established goals. EMS data should include sensitivity and specificity in 12-lead STEMI recognition and compliance with standards and protocols (including transport of non-STEMI cardiac patients to non–PCI-capable hospitals). A quality improvement program must be established that identifies a neutral oversight authority (with representatives from non–PCI-capable and primary PCI-capable hospitals) to collect and analyze data and provide feedback to EMS and hospital providers. An excellent model is the Boston (Mass) EMS system, which currently distributes STEMI patients to dedicated primary PCI centers using a predetermined plan and a highly effective quality improvement program.34

EMS systems need to have enough trained personnel and equipment to ensure that a 12-lead ECG can be performed on adults with non-traumatic chest pain or other symptoms suggestive of STEMI. There should be a written “point-of-entry protocol” that can guide EMS providers in determining where to transport suspected STEMI patients. The plan should designate regional primary PCI-capable hospitals where STEMI patients can be treated promptly by experienced operators 24 hours a day, 7 days a week.

In areas that have developed a well-functioning, regional primary PCI network, STEMI patients should be transported directly to the closest regional primary PCI-capable hospital if it can be reached (by ground or air) quickly enough that the time from initial patient contact to PCI is within 90 minutes. If this is not possible, fibrinolysis (prehospital or at the closest hospital ED) should be given unless contraindicated, and arrangements should be made for transport to the nearest primary PCI-capable hospital.

A few large medical centers in the United States have established STEMI alert networks that provide integrated access to PCI services for both non–PCI-capable and PCI-capable hospitals. These systems aim to determine as many elements of strategic decision making as possible before the patient enters the system at all. The STEMI alert model is based on the use of group paging systems to activate parallel processes to shorten the time from initial medical contact to reperfusion therapy. This ideal model provides emergency physicians (and possibly trained prehospital personnel) with the ability to determine resource availability rapidly and mobilize cardiac catheterization laboratories. Time is saved by accelerating the decision-making processes and by having a team of providers performing multiple essential tasks simultaneously rather than sequentially. The STEMI alert model has been shown to reduce door-to-balloon times and promote a strategy of primary PCI.35 Consideration should be given for EMS providers to sound a STEMI alert if they have a patient whose 12-lead ECG indicates the presence of STEMI.

Non–PCI-capable hospitals that receive a STEMI patient by ambulance or that identify STEMI in an ED walk-in patient should strongly consider immediate transfer of such a patient to a PCI-capable center if it can be accomplished promptly based on the above guidelines. Transferring facilities need to have an effective plan in place that ensures prompt response of the ground and/or air ambulance service to effect emergent interfacility transport of a STEMI patient who requires emergency revascularization. This transfer should be based on a 9-1-1 system and not a “next-available ambulance” protocol. If a transfer cannot be accomplished promptly, fibrinolysis should be considered on the basis of the patient’s risk and duration of symptoms, followed by consideration of transfer to a PCI-capable hospital.

Current Barriers and Gaps That Must Be Addressed by an Ideal System

Developing such an organized system of care for identifying, triaging, and treating STEMI patients is not without its challenges. At first glance, it appears that there might be strong economic disincentives for non–PCI-capable hospitals to participate in such a community program, because cardiovascular care is often a lifeline for a hospital’s financial success. It has been estimated that implementation of a prehospital triage strategy for patients with suspected STEMI would result in the diversion of 22% of patients with STEMI from hospitals without primary PCI capability, even if there was perfect specificity of prehospital triage.36 STEMI patients only account for a small percentage (2% to 5%) of EMS chest pain patients, but the diminished prestige of non–PCI-capable hospitals may draw additional non–STEMI cardiac patients away from them. To survive, non–PCI-capable hospitals will need to continue to receive non–STEMI cardiac patients and will need financial support through changes in reimbursement schemes and sharing of finances across systems that include non–PCI-capable and primary PCI-capable hospitals. In addition, it is important to not overburden the EMS system and primary PCI-receiving facilities with non–STEMI patients.

Several other issues will need careful consideration. There is a lack of emergency physician training and leadership in systems of care for cardiovascular disease and a lack of collaboration between EMS, ED, and cardiology groups at individual hospitals. In many institutions, there is also a lack of coordinated curriculum to teach ED staff to care for STEMI patients and a lack of feedback on performance or guideline compliance to EMS and ED personnel. Furthermore, with decreasing length of hospital stay and decreasing bed capacity, hospital overcrowding has resulted in ED overcrowding. The latter results in ED diversion and longer ED length of stay for patients with increasingly complex conditions. Finally, prehospital reimbursement (ie, for provider salary, equipment, training, medication, and interhospital transfer) is inadequate.

Recommendations

Research

EMS

1. Alternative options for modernizing and improving strategies for emergency medical response should be evaluated.
2. Whether transport of STEMI patients to a PCI-capable center (that is not the closest hospital) is safe should be determined.
3. The best approach to use of prehospital ECGs (ie, interpreted in the field or transmitted to the ED) should be determined.
4. The feasibility of emergency patient transfer in rural communities should be determined.
5. The effectiveness of the implementation of a comprehensive STEMI alert system should be evaluated.

6. Community-based research to help identify effective interventions for improving universal utilization of EMS for STEMI and eliminate associated regional variation should be promoted.

7. The efficacy of extending programs such as “Get With the Guidelines” and “Guidelines Applied to Practice” to include providers, hospitals, and EMS systems in improving adherence to STEMI guidelines should be evaluated.

8. Prehospital 12-lead ECG systems and reliability of data transfer should be evaluated.

Programs

**EMS**

1. Public CPR and AED education should be continued.

2. The AHA should partner with other stakeholder organizations to develop a module for EMS providers that addresses acute coronary syndrome/STEMI care, with particular emphasis on 12-lead ECG acquisition, transmission, and interpretation. Consideration should be given to including extension of ECG acquisition training to basic EMS providers.

3. Industry should continue to partner with EMS to enhance technology for ECG acquisition, transmission, and interpretation.

**In All Hospitals**

1. All STEMI hospitals should have written guidelines and standing orders for administration of fibrinolytic therapy and adjunctive treatments.

2. Mock STEMI drills should be encouraged in low-volume centers to maintain skill sets and to help further refine processes that cause delay at these individual institutions.

**In PCI-Capable Hospitals**

1. Designated emergency physician and nurse leaders and cardiologists should be identified and involved in their institution’s STEMI system development, management, quality improvement, and outreach to referring hospitals, physicians, and EMS providers.

2. The hospital administration should provide infrastructure support to the emergency physician and nurse and cardiology leaders, which should include protected time for activities related to STEMI system management.

3. Protocols should be established that allow EMS-diagnosed STEMI patients to bypass the ED to go directly to the cardiac catheterization laboratory when appropriate.

**In Non–PCI-Capable Hospitals**

1. Predetermined clinical pathways should be used that allow for the rapid determination of appropriateness of transfer for primary PCI based on time of symptom onset and projected transport times.

**Policy**

**EMS**

1. There is a critical need for expeditious and systematized transport of patients from non–PCI-capable hospitals to PCI-capable centers. Such requests for transfer need to be handled by the transporting ambulance agency with the same urgency as a 9-1-1 emergency call.

2. Aggressive implementation of public access defibrillation in high-risk public locations should be promoted.

3. Scripted interrogation protocols/prearrival instructions for phone CPR and administration of aspirin while EMS personnel are en route to the scene should be developed.

4. Continued emergency medical dispatcher training and certification requirements should be developed and maintained.

5. EMS agencies need to have sufficient personnel, training, and resources to ensure that a prehospital 12-lead ECG can be acquired from prehospital patients with clinical presentations suggestive of STEMI to assist in triage, treatment, and point-of-entry decisions.

6. Reimbursement rates for interfacility STEMI patient transport must reflect the increased level of response capability.

7. Data collection and quality improvement systems need to be developed to oversee the continuum of STEMI patient care.

**In All Hospitals**

1. All ED-based STEMI protocols should emphasize rapid evaluation and decision making to determine reperfusion strategy and to administer adjunctive medical treatments as appropriate. Process maps are helpful in the development phase of these protocols.

2. Emergency physicians in all STEMI hospitals should be empowered to activate cardiac catheterization laboratory resources within a standardized clinical pathway without fear of reprisal for false-positive activation.

3. All ED staff taking care of STEMI patients should complete specific educational modules adapted to the local process.

4. All participants in a STEMI system should receive formal feedback as part of an organized quality improvement process.

5. ED personnel should be trained to interpret ST-segment elevation on an ECG.

**In Non–PCI-Capable Hospitals**

1. Whenever possible, patients should be transferred directly from the referring hospital ED to the cardiac catheterization laboratory.

2. When a patient is transported to a non–PCI-capable hospital, he or she should remain on the stretcher while being evaluated for possible transport to a PCI facility, and intravenous infusion (tubing) should be minimized.

**Disclosures**

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**References**


Development of Systems of Care for ST-Elevation Myocardial Infarction Patients

The Non–Percutaneous Coronary Intervention–Capable (ST-Elevation Myocardial Infarction Referral) Hospital Perspective

Gray Ellrodt, MD, Co-Chair; Lawrence B. Sadwin, Co-Chair; Thomas Aversano, MD; Bruce Brodie, MD; Peter K. O’Brien, MD; Richard Gray, MD, FAHA; Loren F. Hiratzka, MD, FAHA; David Larson, MD

Developers of systems to improve access to primary percutaneous intervention (PCI) must recognize that most ST-elevation myocardial infarction (STEMI) patients present to hospitals that do not have PCI capability. Indeed, only ≈25% of US hospitals are currently capable of delivering this intervention.1 These non–PCI-capable institutions are often located in rural areas and face real challenges related to distance from PCI centers. In addition, these institutions face significant financial challenges2 in pursuing any of the 3 potential strategies to increase timely access to primary PCI. These 3 strategies include the following3: (1) hospitals currently without PCI capability can develop primary PCI services without cardiac surgery on-site (SOS); (2) non–PCI-capable facilities can rapidly diagnose and transfer STEMI patients to primary PCI-capable hospitals and thereby serve as STEMI referral hospitals; or (3) communities can develop systems that bypass non–PCI-capable hospitals.

Each of these strategies is addressed in this article. For each, we review the current status, the ideal system, gaps in and barriers to development of the ideal system, and recommendations.

Develop Primary PCI Capability Without Cardiac SOS

Current Status

Early observational studies from single institutions demonstrated potential efficacy and safety of primary PCI without SOS. In the Myocardial Infarction, Triage and Intervention (MITI) trial, 233 of 441 primary PCIs were performed at hospitals without SOS. Emergency cardiac surgery was rare (1.4% of patients), and its presence or absence did not affect survival after myocardial infarction.4 In another observational study, among 334 patients undergoing primary PCI at a hospital without SOS, there were no deaths, and no patient required emergency coronary artery bypass grafting (CABG).5

In a nonrandomized comparison of patients undergoing primary PCI at hospitals without SOS with those undergoing primary PCI after transfer to a tertiary hospital, there was no difference in 30-day or 1-year mortality, although time to reperfusion was significantly shorter, and restoration of Thrombolysis In Myocardial Infarction (TIMI) 3 flow occurred significantly more often in patients undergoing primary PCI without transfer to a tertiary site.6 Only 2 patients (0.4%) required emergency CABG.

In a randomized controlled trial in community hospitals, STEMI patients treated with primary PCI had a 42% lower incidence of the composite end point of death, recurrent infarction, or stroke at 6 months (which was driven by a reduced rate of reinfarction), and the median length of stay was reduced by 1.5 days compared with patients treated with accelerated tissue plasminogen activator.7 No patient required emergency CABG for PCI-related complications.

In another study,8 investigators used the National Registry of Myocardial Infarction (NRMI) database to compare qual-
ity of care in 108,132 patients with STEMI treated with primary PCI at 3 different types of hospitals between April 1998 and October 2001: hospitals with diagnostic cardiac catheterization laboratories without SOS, hospitals with PCI capability but without SOS, and those with PCI capability and SOS. Interestingly, door-to-balloon intervals were shorter in hospitals without SOS. In addition, adherence to American College of Cardiology (ACC)/American Heart Association (AHA)—recommended medications, including the use of aspirin, β-blockers, and angiotensin-converting enzyme inhibitors within the first 24 hours, was significantly better in hospitals without SOS. In-hospital mortality rates were comparable between hospital types: 3.2% for diagnostic only, 4.2% for PCI-capable without SOS hospitals, and 4.8% for hospitals with PCI capability and SOS (P=0.07). However, because 5% of patients in non-SOS hospitals were transferred to other facilities and lost to follow-up, conclusions concerning mortality cannot be made with certainty. Of note is the adherence to guideline-directed therapies in the non-SOS facilities. Recently, another large observational study based on Medicare provider analysis and review data confirmed the safety of primary PCI at hospitals without SOS.

**Ideal System**

It is only possible to highlight some important features of an ideal primary PCI program in a hospital without SOS. A firm commitment to development of a safe, effective, consistently and uniformly applied, and sustainable primary PCI program is an absolute requirement. This commitment must be made at administrative, physician, and nursing levels and involves multiple care areas, including the emergency department (ED), coronary care and step-down units, and the cardiac catheterization laboratory at a minimum. Identification of leaders or “champions” at the administrative, physician, and nursing levels is an important feature of this commitment.

The ACC/AHA/Society for Cardiovascular Angiography and Interventions (SCAI) PCI guidelines describe minimum attributes and requirements of a primary PCI program. These include the setting of standards (for physicians, nurses, technicians, facilities, and treatment), development of logistics, training of staff, and creation of a quality- and error-management strategy (data collection, data review, application of benchmarks, and quality improvement). Furthermore, the physician practitioners should satisfy the ACC/AHA guideline requirements for both initial training and competency maintenance for PCI. Formal affiliation with a temporally close tertiary hospital is important to provide off-site surgical backup, to provide a facility to perform more complex or subsequent nonemergency intervention, and, importantly, to provide a site for initial and continuing observational and hands-on training of catheterization laboratory and postprocedure care staff. It is also critical to develop permanent structures within such institutions to provide regular morbidity and mortality review for physicians, which can be a challenge in low-volume institutions. Furthermore, regular meetings of administrators and physician and nursing representatives from the ED, catheterization laboratory, and coronary care and step-down units are important to review outcomes, identify opportunities for improvement, and modify local practice to reflect the most current evidence-based therapies in this rapidly evolving area.

**Gaps and Barriers**

Sustaining a stand-alone primary PCI program (ie, without “elective” PCI) is difficult from a fiscal and personnel point of view. Stand-alone primary PCI programs perform a relatively small number of procedures and yet require staffing 24 hours a day, 7 days a week. A sustainable system requires staff to be on call no more than 1 of 3 and preferably no more than 1 of 4 nights and weekends. Single catheterization laboratory facilities are subject to interruption of service during preventive maintenance or if the laboratory fails. In certain areas, there may not be enough experienced interventional cardiologists to cover these laboratories that perform only emergency primary PCI procedures. In addition, if the majority of non-PCI-capable hospitals had the clinical obligation or financial need to develop primary PCI services, there would be the potential for the emergence of multiple hospitals providing a relatively low volume of procedures. Finally, the ACC/AHA/SCAI PCI guideline considers the performance of primary PCI at non-SOS hospitals a class IIb indication (usefulness/efficacy is less well established by evidence/opinion).

In addition, a number of STEMI patients have coronary pathology that is not amenable to primary PCI, may be better treated with surgery, or may have a mechanical complication of STEMI that requires cardiac surgery. These patients benefit from prompt surgical evaluation and treatment, including CABG, repair of mechanical defects, and/or insertion of circulatory support devices.

**Recommendations**

1. Randomized studies comparing the safety and efficacy of nonemergency PCI at hospitals with and without SOS are important. If nonemergency PCI can be performed without colocated cardiac surgery, then this may influence both the viability of and the expertise applied to primary PCI at those facilities.

2. A comparison of outcomes, most likely by use of risk-adjusted registry data, of patients undergoing primary PCI at hospitals with and without nonemergency PCI programs (which usually means with and without colocated cardiac surgery) would be of significant interest. Outcomes should be measured to at least 30 days or more after the index infarction.

3. There is a need for policy reevaluation at the state level, with recognition of the link between higher surgical volumes (both institutional and operator) and better surgical outcomes in most cases. A clear need is emerging to limit the proliferation of cardiac surgical programs (to support the creation of additional primary PCI programs) at a time when overall cardiac surgical volumes are decreasing.

4. Healthcare policy makers working together with organizations such as the AHA, ACC, and Joint Commission on Accreditation of Healthcare Organizations must develop criteria for primary PCI centers and determine whether SOS will be required.
Transfer of STEMI Patients From Non–PCI-Capable Hospitals to Primary PCI-Capable Hospitals: The STEMI Referral Hospital

Current Status
The results from recent randomized trials (predominantly from Europe) indicate that outcomes are better when patients with STEMI who present to non–PCI-capable hospitals are transferred to an interventional facility for primary PCI than when they are given fibrinolytic therapy at the local hospital (Figure).12–15 The inherent treatment delays associated with primary PCI compared with fibrinolytic therapy in these trials have ranged from 55 to 103 minutes. Unfortunately, in the United States, transfer delays are much longer. Recent data from the NRMI found median delays of 180 minutes from arrival at the non–PCI-capable hospital to balloon inflation at the primary PCI-capable hospital, with only 4.2% of transferred patients achieving door-to-balloon times of <90 minutes.16 The ACC/AHA STEMI guideline recommends primary PCI as the preferred reperfusion strategy for STEMI, but only if it can be performed within 90 minutes of first medical contact. Consequently, most patients presenting to non–PCI-capable hospitals in the United States are not eligible for primary PCI because of the long potential treatment delays. To increase the use of primary PCI as a reperfusion strategy for patients presenting to non–PCI-capable hospitals, much improvement is needed in reducing transfer times.

Ideal System
It has been clearly shown that with well-defined goals, commitment from administrative and clinical leaders, standardized protocols, integrated systems of transfer, and data feedback to monitor progress, door-to-balloon times for patients presenting to non–PCI-capable hospitals can be dramatically reduced and can approach and meet guidelines for timely treatment with primary PCI.17–19 Time delays in the evaluation, treatment, and transfer of STEMI patients from non–PCI-capable hospitals to tertiary centers can be divided into 3 parts: delays at the non–PCI-capable hospital, transportation delays, and delays before PCI is performed at the tertiary center. Recommended targets for time delays for each of these phases are 30 minutes (the “30-30-30 rule”).

Ideal systems will reduce the in-the-door to out-the-door time to within 30 minutes at the non–PCI-capable hospital. In the 20% to 50% of patients who arrive by emergency medical services (EMS), prehospital 12-lead ECGs should be performed, which can result in early initiation of protocols to facilitate transfer. In patients who arrive by private vehicle, an ECG should be obtained and interpreted by the emergency physician within 10 minutes. If the ECG meets criteria for a STEMI, the emergency physician should be empowered to activate the transfer protocol, which includes simultaneous activation of the catheterization laboratory team at the receiving hospital and paging of the interhospital transport service (EMS). At the receiving PCI center, the batch page goes to notify the catheterization laboratory team, interventional cardiologist, and admissions and bed control personnel.

Standardized written protocols with tools such as posters, pocket cards, and STEMI kits that include all needed medications, equipment, and data forms enable evaluation and treatment to be performed in the minimal amount of time. Patients are treated with oxygen, aspirin, clopidogrel, heparin bolus, intravenous β-blockers, morphine, and nitroglycerin according to the ACC/AHA guidelines and standard protocols, but no drips and pumps are used, and the use of glycoprotein IIb/IIIa inhibitors, if associated with substantial delays, is avoided. Chest radiographs are not routinely essential and may cause additional delays. Transfer data sheets (with pertinent clinical and laboratory information), orders, and ECGs are sent with the patient and also faxed directly to the receiving PCI center’s catheterization laboratory. The goal is an in-the-door/out-the-door time at the non–PCI-capable hospital of within 30 minutes.

Transfer of STEMI patients must be given priority by the EMS system and treated as a 9-1-1 call. If the patient is brought into the non–PCI-capable hospital by ambulance, ideally the same crew should transfer the patient to the PCI center, with the patient remaining on the ambulance stretcher while in the ED. If continuous intravenous infusions are required, they are best administered via saline locks to minimize delays when intravenous tubing is changed. For short transfer distances, heparin and nitroglycerin infusions are not required. Approximately 15 minutes before arrival at the PCI center, the transfer EMS crew should alert the catheterization laboratory team of their impending arrival, and the patient should be taken directly to the catheterization laboratory while in the ED. The goal for transport time from departure from the non–PCI-capable hospital to the catheterization laboratory is within 30 minutes. This, of course, will depend in part on the distance from the non–PCI-capable hospital to the PCI-capable hospital; in some systems that involve longer distances, air transport will be required.
The catheterization laboratory technicians and nurses and the interventional cardiologist should be waiting for the patient’s arrival in the catheterization laboratory. The interventionalist reviews the transfer data sheet and performs a brief examination while the staff prepares the patient. The goal is to perform balloon dilation within 30 minutes of arrival.

Data collection and feedback are essential to a successful transfer program. The interventionalist should call the non–PCI-capable hospital emergency physician at the end of the procedure and the nursing staff at the tertiary hospital should call the non–PCI-capable ED head nurse to discuss times, outcomes, and potential points of improvement. Door-to-balloon times and their component parts, as well as outcomes, should be reviewed by all involved personnel in the non–PCI-capable and PCI-capable hospitals on a regular basis.

Gaps and Barriers
In the United States, there are a number of obstacles that must be overcome to achieve this ideal system:

1. Delays in identifying the patient with STEMI are frequent. The ECG may not be obtained in a timely fashion because of atypical symptoms or a busy and understaffed ED. The ECG may be equivocal for the diagnosis of STEMI. For those patients who arrive by EMS, only a minority (10%) have had a prehospital 12-lead ECG performed.
2. Without prespecified, hospital-specific protocols, delays to reperfusion may occur when ad hoc treatment decisions are being considered. For example, there may be delays in the decision regarding who should be transferred for primary PCI and who should receive fibrinolytic therapy. Some physicians routinely perform a chest radiograph to screen for dissecting aneurysm, which increases transfer delays.
3. There is wide regional variation in interhospital transfer systems. Urban areas have relatively short transfer distances and transfer mostly by ground ambulances, whereas in rural areas, there are much longer transfer distances and many transfers occur by air transport. Unlike the 9-1-1 EMS system, interhospital transfer systems in some regions are not well organized. In some areas of the country, EMS vehicles may not have the staffing and capability to respond to interhospital transfer similar to a 9-1-1 response and may not have the authority to cross county lines. Costs for transport may not be covered by third-party payers, which puts a burden on the patient, and the costs of air transport may be prohibitive.
4. Hospital bed capacity is a major issue in many cities today. Lack of bed availability at the primary PCI hospital may inhibit or delay transfer.
5. Loss of revenue for STEMI patients (and other non-STEMI acute coronary syndrome patients) transferred to the primary PCI-capable hospital may be a disincentive for non–PCI-capable hospitals to participate in transfer protocols.

Recommendations
Further research is needed to better understand which patients under what circumstances are best treated with transfer for primary PCI. Such research should focus on the following areas:

1. Studies are needed to clarify when and in whom the inherent difference between door-to-needle and door-to-balloon times will negate the potential advantage of primary PCI compared with fibrinolytic therapy.
2. The results of ongoing randomized trials are needed to define the role of facilitated PCI in patients presenting to non–PCI-capable hospitals when relatively long delays to primary PCI are anticipated.

Policy and logistical changes are needed to address each of the gaps and barriers outlined above to facilitate development of the ideal system for transport of patients for primary PCI.

1. Well-defined hospital-specific protocols should be developed at each non–PCI-capable hospital to define which patients are candidates for transfer for primary PCI and which patients should be given fibrinolytic therapy on the basis of current guidelines, incorporating patient risk, fibrinolytic risk, time to presentation, and delays to primary PCI. These protocols should be agreed on by all and should eliminate time delays in deciding which patients should be transported for primary PCI. Practical issues, such as keeping patients on their EMS stretchers and rapid decision making (eg, <5 minutes at the non–PCI-capable hospital), which permits EMS personnel to stay with the patient and then transport the patient without waiting for another ambulance, must be addressed.
2. Clinical leadership, visible administrative support, and ongoing commitment to achieving explicit goals for door-to-balloon time will be required at both the non–PCI-capable hospital and the PCI-capable hospital to achieve agreement and implementation of protocols by all parties involved.
3. Transport agreements and protocols will need to be negotiated with EMS and other transport systems. Crucial to this is a 9-1-1 type of response to calls for interhospital transfer for STEMI patients.
4. Similar to a level 1 trauma center, primary PCI hospitals will need to accept transfer of STEMI patients regardless of bed availability.
5. For non–PCI-capable hospitals that are not part of the tertiary care system, a legal revenue-sharing arrangement needs to be negotiated between the non–PCI-capable hospital, the primary PCI-capable hospital, and the third-party payers so the financial losses to the non–PCI-capable hospital are minimized.
6. It is critically important that the non–PCI-capable hospital be given incentive to rapidly treat and transfer STEMI patients according to ACC/AHA guidelines and that these hospitals remain an integral part of the STEMI systems of care. They should not be viewed as the “have not” but rather as the “STEMI referral hospital.”

Develop Universal Systems in Which EMS Transfers STEMI Patients Directly to Regional Primary PCI-Capable Hospitals (STEMI-Receiving Hospital)

Current Status
Another potential strategy would involve bypassing the non–PCI-capable hospital for direct transfer to a primary PCI-capable hospital. This might allow more timely access to primary PCI for patients arriving via EMS. Nearly 80% of the
adult population in the United States lives within 60 minutes of a PCI-capable hospital, and three fourths of the remainder would experience <30 minutes of additional delay in direct transfer.21 Unfortunately, there are few published examples of robust universal transport systems in the United States.

Ideal System
This approach would require paramedic identification of patients with a STEMI in the field and diversion to an appropriate primary PCI-capable hospital. EMS personnel would need to have the training and capability to perform and transmit 12-lead ECGs to the participating primary PCI-capable hospital. Paramedics may accurately acquire such information and identify patients eligible for reperfusion therapy.22–27 After appropriate notification, EMS would be empowered to take the patient directly to the cardiac catheterization laboratory at the designated facility. A brief assessment could then be performed by the receiving providers before proceeding with PCI. Such a triage and treatment plan has already been successfully implemented in 1 large urban area.28

Gaps and Barriers
The gaps and barriers to this strategy have been discussed in the EMS and ED perspective in these conference proceedings.29 From the standpoint of the non–PCI-capable hospital, the impact of being bypassed on the hospital’s clinical and financial viability is largely unknown. Non–PCI-capable hospitals may experience a negative financial impact from the loss of STEMI patients and the negative “halo effect” on other service lines. It is also unclear whether it is safe to transport patients longer distances (before they receive initial treatment) and whether the added transport time will negatively impact the mortality benefit derived from the primary PCI strategy.

Recommendations
1. EMS and STEMI-receiving primary PCI hospitals will need to monitor treatment times, volumes, patient outcomes, and associated quality indicators.
2. It will be important to ensure that patients without STEMI continue to be transported to the non–PCI-capable hospital.
3. Further study is needed to determine the feasibility of such an approach in suburban and rural settings.

Conclusions
Non–PCI-capable hospitals face significant challenges in improving care for STEMI patients. Many of these hospitals are located in rural areas and have long transport times to primary PCI-capable institutions. These are the hospitals most likely to suffer a significant financial impact with the development of such systems, and their very survival may be threatened.2 We have described 3 potential strategies available to these institutions. However, given that approximately 50% to 70% of patients arrive at the local hospital without using EMS, the role of the STEMI referral hospital must be embraced and supported. It is equally important that these institutions and their physicians are reconnected with the STEMI patient after discharge from the STEMI receiving hospital, to guide patient recovery and to promote continued adherence to secondary prevention measures. The connection between the STEMI referral and STEMI receiving hospitals will promote the overall success of the system of care for STEMI patients.

Disclosures
Potential conflicts of interest for members of the writing groups for all sections of these conference proceedings are provided in a disclosure table included with the Executive Summary.

References
As noted in the previous section of these conference proceedings, there are 3 potential strategies to increase the number of ST-segment myocardial infarction (STEMI) patients with timely access to primary percutaneous coronary intervention (PCI): (1) hospitals without PCI capability can develop primary PCI services; (2) non–PCI-capable hospitals can rapidly expeditiously transfer STEMI patients to primary PCI-capable hospitals after diagnosis and thereby serve as STEMI referral hospitals; or (3) communities with emergency medical services (EMS) systems can develop prehospital transport protocols that bypass non–PCI-capable hospitals. The best approach for a given community will vary and will be heavily influenced by geographic location and available resources.

In this article, we view these strategies from the perspective of the PCI-capable hospital that “receives” STEMI patients (STEMI-receiving hospital). A primary PCI center is defined as any hospital that performs primary PCI. Patients can present to PCI-capable hospitals through 1 of 3 pathways. Each of these modes of presentation offers opportunities for improving time to treatment and access to primary PCI. The Figure depicts the position of the primary PCI-capable hospital within the system.

The Current System

Patient Presentation to a PCI-Capable Hospital

Door-to-balloon time is a focus for improvement at many hospitals because it is a Centers for Medicare and Medicaid Services quality indicator for STEMI. An efficient emergency department (ED) triage system quickly acquires a 12-lead ECG to diagnose STEMI in patients with suggestive symptoms and rapidly activates the cardiac catheterization laboratory. Door-to-balloon times have been shown to be shorter when the emergency physician is able to activate the cardiac catheterization laboratory without consulting a cardiologist.

Patient Presentation Directly to a PCI-Capable Hospital by EMS

The use of EMS by patients provides the opportunity for prehospital ECG diagnosis of STEMI, as well as notification and activation of the cardiac catheterization laboratory to substantially accelerate door-to-balloon time. Prehospital ECGs can be read by computer algorithms, interpreted by trained paramedics, and/or electronically transmitted to the receiving hospital. Unfortunately, >50% of patients with STEMI arrive at the hospital without using EMS, and prehospital ECGs continue to be underutilized. Diagnosis of STEMI in the prehospital phase potentially allows the use of
destination protocols to bypass non–PCI-capable hospitals and directly transport patients to the nearest PCI-capable hospital, as shown by the dotted line in the Figure.

**Hospital Transfer to a PCI-Capable Hospital**

Several recent randomized trials support the safety and efficacy of transferring STEMI patients for primary PCI from community hospitals that do not have PCI capability.4–7 A recent meta-analysis of these trials demonstrated a significant reduction in the composite end point of death, reinfarction, and stroke (Table), although there was only a trend for reduction in death.8 Most of the benefit was in reducing the risk of reinfarction, but this benefit may have been overestimated compared with what would be achieved in most practice settings in the United States, because there was very low use of rescue PCI in the patients initially treated with fibrinolytics (1.9% in the DANish multicenter randomized study of fibrinolytic therapy versus acute coronary angioplasty in Acute Myocardial Infarction [DANAMI]-2).4 Moreover, patients deemed to be high risk for transfer were excluded, and first door-to-balloon times were faster than in most reports from the United States. In the only randomized trial to compare transfer for PCI to fibrinolytics performed in the United States (a small trial that did not meet its enrollment objectives), the median first door-to-balloon time was 155 minutes despite a mean transfer distance of only 32 miles.7

**Selected Current Model Systems of STEMI Care in the United States**

**“Hub and Spoke” Systems of Transfer to Primary PCI Centers**

The Minneapolis Heart Institute’s level 1 myocardial infarction program has the largest reported experiences designed to integrate the care at non–PCI-capable hospitals (STEMI referral hospitals) with a regional PCI-capable hospital (STEMI-receiving hospital). The program includes rural and community hospitals up to 210 miles away from the STEMI-receiving hospital.10 Key components of the program include (1) empowering the emergency physician (or EMS personnel in certain situations) at the non–PCI-capable hospital to activate the system with a single phone call; (2) the use of a standardized protocol that is simple and systematic; (3) a customized transfer plan for each non–PCI-capable hospital; (4) an in-depth training program for each non–PCI-capable hospital, including EMS, ED, and primary care providers, as well as the local community; (5) a comprehensive quality improvement program; and (6) systems to support the patient and family during the initial hospital stay and on their return to the local community. More than 1345 patients have now been treated with this system, including 297 patients in the STEMI-receiving hospital, 627 patients in 14 hospitals up to 60 miles away (zone 1), and 421 patients in 16 hospitals 60 to 210 miles away (zone 2) from the STEMI-receiving hospital. With this standardized protocol, the median door-to-balloon times from the community STEMI referral hospitals to balloon inflation in the STEMI-receiving hospital were 96 minutes in zone 1 and 118 minutes in zone 2. All patients

<table>
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<th>Trial</th>
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<th>First Door-to-Balloon Time, min</th>
<th>Transport Time, min</th>
<th>Death/Reinfarction/Stroke Composite End Point, %</th>
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<td>97†</td>
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<td>42% Relative risk reduction</td>
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</table>

PRAGUE indicates Primary Angioplasty in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis; SK, streptokinase; DANAMI, DANish multicenter randomized study on fibrinolytic therapy versus acute coronary angioplasty in Acute Myocardial Infarction; tPA, tissue-type plasminogen activator; and Air PAMI, Primary Angioplasty in Myocardial Infarction.

*Times are median when available.
†Randomization to balloon.
‡Dalby et al5 also includes the Maastricht and Comparison of Angioplasty and Prehospital Thrombolysis in acute myocardial Infarction (CAPTIM) trials.
were included in the protocol and database, which led to a high-risk cohort with 15% of patients >0 years of age, 12% with cardiogenic shock, and 11% with cardiac arrest before arrival in the cardiac catheterization laboratory. Despite this high-risk unselected cohort, the in-hospital, 30-day, and 1-year mortality rates were 4.2%, 4.9%, and 7.2%, respectively, with no differences between patients presenting for primary PCI at the PCI center, zone 1 hospitals, and zone 2 hospitals.11

A statewide approach is being used in North Carolina in the Reperfusion of Acute Myocardial Infarction in North Carolina Emergency Departments (RACE) project, which shares many features of the Minnesota model. The project incorporates standardized protocols and integrated systems for the treatment and timely transfer (when appropriate) of patients with STEMI in 5 geographic regions in North Carolina, which include 70 hospitals, 10 of which are STEMI-receiving hospitals. Although regional centers play a key role in the systems, the goal is not to transfer all patients for primary PCI but rather to also administer fibrinolytic therapy when appropriate according to the ACC/AHA STEMI guideline.2 This project has been created with an alliance between national and regional professional societies, a local payer (Blue Cross and Blue Shield), industry, and healthcare providers, including EMS, emergency medicine, cardiology, and hospital administrations. The program includes 70 hospitals (including 10 STEMI-receiving hospitals). For each hospital, data are collected before and after customized interventions to increase the proportion of eligible patients receiving reperfusion therapy and reduce door-to-balloon and door-to-needle times. The plan includes assessment of the impact of various features on both process and outcomes to allow refinement of strategies for improving application of reperfusion therapy.

Destination Protocols for EMS to Triage to PCI Centers
An urban program has been implemented in Boston, Mass, that involves destination protocols to take STEMI patients directly to qualified PCI-capable hospitals. The Boston EMS has established a “point-of-entry” plan that directly transports STEMI patients to the nearest hospital with primary PCI capabilities.11 To foster collaboration and better care in the region, the project includes an oversight committee composed of representation from the 9 participating hospitals and a data assessment of the impact of various features on both process and outcomes to allow refinement of strategies for improving application of reperfusion therapy.

The Ideal System for the STEMI-Receiving Hospital
The current ACC/AHA guideline provides the best available recommendations to guide practice for treatment with primary PCI.2 The 2004 update of the STEMI guidelines placed a strong emphasis on systems development and integration of aspects of care for which coordination is needed. Ideal systems can enable STEMI-receiving hospitals to expand optimal reperfusion therapy to millions of Americans. Criteria for such an ideal center are proposed below.

Criteria for Primary PCI Centers
The following are criteria for ideal PCI centers,12 with or without on-site cardiac surgery.

Institutional Resources
1. Primary PCI should be provided as routine treatment for appropriate STEMI patients 24 hours a day, 7 days a week.
2. Primary PCI should be performed as soon as possible. The Door-to-Balloon: An Alliance for Quality Campaign (http://www.acc.org) goal is to achieve a door-to-balloon time of <90 minutes for at least 75% of nontransfer patients with STEMI.
3. All institutions should be able to provide high-quality supportive care for patients with STEMI and its complications, including respiratory failure, congestive heart failure, cardiac arrhythmias, and cardiogenic shock (including intra-aortic capability) on-site.
4. All institutions should have a written commitment by the hospital administration to support the program and be required to:
   A. Identify a physician director of the primary PCI program accountable for defining, implementing, and directing the overall primary PCI program, including responsibility for equipment, personnel, physician competency, privileges, availability, quality assurance, and case review conferences, and
   B. Create a multidisciplinary group with representation from the ED, the quality improvement team, EMS, the coronary care unit, and the cardiac catheterization laboratory that includes physician and nursing leadership and meets regularly to review operational issues and problems to identify and implements solutions.
5. All institutions should design and implement a formal continuing education program that includes practical implementation training for staff.
6. For institutions without surgery on-site, there must be a formal, written agreement with a tertiary institution that provides for rapid transfer of patients for any required additional care, including elective or emergency cardiac surgery or PCI. Furthermore, there must be a written agreement with an advanced cardiovascular life support EMS provider that provides for transport within the shortest time feasible, ideally within 30 minutes of request for transport.

Physician Resources
1. Interventional cardiologists should meet ACC/AHA criteria for competence.13 These include performing at least 11 primary PCI procedures per year and 75 total PCI procedures per year.
2. Interventional cardiologists should participate in and be responsive to a formal on-call schedule and participate in the other activities described herein.

Program Requirements
1. At least 36 primary PCI procedures and 400 total PCI procedures should be performed annually.
2. The primary PCI program should be described in a “manual of operations.” Included should be the standards contained in the ACC/AHA guidelines for management of patients with acute myocardial infarction and guidelines for PCI. In addition to policy regarding hours of operation, laboratory staff and physician availability and responsibility, and the process for informed consent, plans for treating recurrent ischemia, reinfarction, and PCI complications should be included.

3. A mechanism for monitoring program performance, process measures, and patient outcomes must be established. This will facilitate ongoing quality improvement activities and provide the opportunity to measure program compliance, effectiveness, and safety. Accordingly, a data set will be required that includes patient demographic and clinical characteristics, and times for symptom onset, initial healthcare system contact, ECG acquisition, catheterization laboratory activation, catheterization laboratory availability, procedure initiation and termination, and achievement of reperfusion and balloon inflation. Procedure outcome and complications and patient clinical outcomes should be recorded.

Other Features of an Ideal System

1. Data collection and feedback: Although Centers for Medicare and Medicaid Services quality measures are focusing on PCI-capable hospital door-to-balloon time, first door-to-balloon time for transferred patients and the proportion of eligible patients receiving some reperfusion therapy need to be included. The NRMI has provided important insights into this problem, but only at participating centers that likely represent better-than-average performance. Feedback to participants in the care process should be timely and complete and should have enough detail to identify specific aspects of care. For example, for a patient transferred for primary PCI, feedback should be provided to the initial transferring hospital as to timing of diagnosis and contact with the PCI-capable hospital, to the EMS personnel and other transfer participants as to transfer times, and to the PCI-capable hospital regarding cardiac catheterization laboratory arrival and balloon inflation time. Although the reviewing of aggregate data at periodic meetings is important to track institutional improvement, the provision of prompt feedback to those involved in the patient’s care will enable identification of specific areas for improvement.

2. Prehospital ECG and earliest cardiac catheterization laboratory activation when ST elevation is identified: Linkage of prehospital ECG interpretation (with or without transmission) with cardiac catheterization laboratory activation provides an important opportunity to shorten time delays. Prehospital diagnosis offers the opportunity to bypass non–PCI-capable hospitals and transport patients directly to the PCI-capable hospital. For patients transferred from a non–PCI-capable hospital, a protocol should be in place with defined procedures to minimize the time necessary for the initial diagnosis and transfer to the PCI-capable hospital. Minimizing delay depends on earliest notification within an integrated communication system. This requires EMS training, technology, and communication systems to enable activation to occur as early as possible.

3. ED protocols: Each primary PCI center ED must have standardized STEMI management protocols focused on efficient diagnosis of STEMI, earliest communication, streamlined initial management, and rapid transfer.

4. Single phone call and universal patient acceptance: STEMI referral hospitals should be able to call a single number to notify the STEMI-receiving hospital that a patient needs primary (or rescue) PCI and to activate the cardiac catheterization laboratory. Catheterization laboratory activation and transfer should not depend on cardiology review of the ECG, checking for bed availability, or review with the interventional cardiologist, all of which will result in delays. Ideally, calls should be recorded and reviewed as part of the quality improvement process.

Current Gaps and Barriers

Barriers to Timely Access to Primary PCI

1. Busy PCI hospitals may be required, on occasion, to divert patients to other EDs because of bed availability or lack thereof.

2. Major delays in ED diagnosis of STEMI occasionally occur, especially for patients not using EMS. There needs to be wider application of written protocols for the assessment of all patients with possible ischemic symptoms, early interpretation of the ECG, and initiation of treatment in the ED.

3. Manpower and financial overhead considerations for smaller programs may prevent 24-hours-a-day, 7-days-a-week availability for primary PCI. Even for larger programs, expansion of services to accommodate patients transferred from STEMI referral hospitals or brought directly to the STEMI-receiving hospital by EMS will need to occur.

4. Reimbursements for optimal coordination of EMS services, STEMI referral hospitals, and STEMI-receiving hospitals need to be aligned to reflect the work performed.

5. In most PCI-capable hospitals, cardiac catheterization laboratory physicians and staff are off-site during off-hours. A mandate to assemble the team within 20 to 30 minutes of notification of the impending arrival of a STEMI patient needs to be established.

Recommendations for Research, Programs, and Public Policy

Research

1. Further evaluation of transfer times, cost, and outcomes with interhospital transfer for primary PCI is needed.

2. More information is needed regarding the safety and effectiveness of primary PCI at centers without surgery on-site.

3. Evaluation of the long-term outcome of reducing reinfarction rates after STEMI should be performed. The main advantage of primary PCI compared with fibrinolytic therapy is a reduced rate of reinfarction.

4. Evaluation of the relationship between operator and hospital volumes and patient outcomes should continue.

Programs

1. Novel and expedited methods of patient consent and medical information transfer should be developed.
2. Communication programs for seamless interface with patients and their primary care providers after discharge from the primary PCI center should be developed.

Public Policy

1. Regional transportation systems need to be developed to transport STEMI patients to STEMI-receiving hospitals.

2. Criteria for STEMI-receiving hospitals need to be defined/redefined and included in the ACC/AHA STEMI and PCI guidelines (include protocols, oversight team, competencies of the hospital and caregivers, and collection of process and outcome data).

3. Requirements for a STEMI-receiving hospital need to be defined so that they could be used by payers and possibly The Joint Commission for payment/certification.

4. The public should be educated on the value of calling 9-1-1 and of treatment at STEMI-receiving hospitals.

5. The Centers for Medicare and Medicaid Services should be encouraged to adjust payment to hospitals based on door-to-balloon times of <90 minutes, provision of cardiac rehabilitation services, and prescription for evidence-based medical and lifestyle therapy for STEMI patients.

6. The establishment of regional STEMI-receiving hospitals should be encouraged. The relationship between volume and outcomes is well established for PCI, and it is likely the best results will be obtained when PCI-capable hospitals perform substantial (eg, >100) primary PCI procedures per year.

Disclosures

Potential conflicts of interest for members of the writing groups for all sections of these conference proceedings are provided in a disclosure table included with the Executive Summary.

References


Key WORDS: AHA Conference Proceedings; myocardial infarction; point-of-care systems; angioplasty; reperfusion
Extending revascularization to all ST-elevation myocardial infarction (STEMI) patients who could benefit from it requires both the rethinking of significant aspects of what is being done now and the development of new thinking for patients for whom such care requires system innovations. Such rethinking and restructuring involves how services are purchased, how payments are made, and how accountability is met. This article focuses on the role of purchasers and payers* in providing primary percutaneous coronary intervention (PCI) for STEMI patients.

The Current System

Data
No current national data exist on the percentage of STEMI patients receiving revascularization or the percentage of STEMI patients who are transferred from the hospital where they are initially examined to another hospital that is better able to provide revascularization.

Emergency Services
Because essentially all patients with STEMI present as emergencies, commercial insurers who contract selectively with hospitals have less influence over data collection and referrals than they have over more elective procedures or even less emergent medical admissions.

Community Structures
Community structures and networks for STEMI care are extremely variable and relatively uncommon. We are unaware of any survey of what the existing structures look like or how frequently they occur.

Payment
The complex aspect of payment is payment for transferred patients. It may be that no 2 payers have the same rules, but for Medicare,1,2 the preponderant payer, the following protocol is followed: (1) The initial (transferring) hospital receives payment only for emergency department services if the patient is not admitted before discharge or (b) per diem payment for inpatient services at a rate of the diagnosis-related group amount divided by the geometric mean of length of stay. This rate is doubled for the first day. (2) The receiving hospital is paid the diagnosis-related group amount as if there had been no preceding care. Despite speculation that some hospitals are reluctant to transfer patients because they fear lost revenue, there is little evidence either to support or to reject this idea.
Quality-of-Care Measurement
Although there are 9 standard measures of quality of care for patients with acute myocardial infarction, there is no standard measure of the appropriateness of the decision to perform or not perform revascularization or even a standard measure of the rate at which revascularization is done, even when all care is provided in 1 hospital. Quality measurement is actually applied less often to STEMI patients who are transferred than to those who are not. Admission measures are applicable (aspirin, β-blockers) in the initial hospital if the patient is admitted but not if they are transferred from the emergency department, and discharge measures are applicable in the receiving hospital. Although door-to-needle time and door-to-balloon time are standard performance measures for patients definitively treated in the hospital to which they were initially admitted, there is not a standard measurement process for transferred patients.

“Pay-for-Performance”
The Centers for Medicare and Medicaid Services (CMS) has just completed a demonstration with Premier (an organization owned by not-for-profit hospitals) of a “pay-for-results” model in which startlingly high performance was achieved on acute myocardial infarction measures, but neither time from symptom onset to revascularization nor appropriateness of revascularization decisions was included in the measures.3

The Ideal System
In an ideal system, care is patient-centered and coordinated from the moment 9-1-1 is called throughout the follow-up care that is given after discharge from the hospital that provided definitive treatment. An ideal system should be informed by evidence-based guidelines developed by expert physician organizations. Well-defined standards for hospital care at transferring and receiving facilities should be integrated into existing accreditation programs, such as the Joint Commission on Accreditation of Healthcare Organizations and CMS. Communities should develop a clear road map for implementing an ideal system for their region. Once these elements have been established, local payers can apply appropriate financial incentives and disincentives that would reimburse the right amount for the right care at the right time in the right setting.4 Many communities have attempted to create such an ideal care system, with varying degrees of success, but to the best of our knowledge, no payers other than fully integrated health plans have an integrated payment system. An ideal system should avoid monopolistic pricing and contracting practices.

Community-Level Organization
A system for the care of patients with STEMI should be community-wide, and development should involve all stakeholders (including payers). Communities should evaluate local need and capacity and design an integrated system appropriate for that region. Such a system may have a clearly defined relationship to the trauma system and should be fully coordinated with the emergency medical services system. It should have an explicit plan regarding the need, if any, for adjustment of community capacity.

Transfer Agreements
Every hospital would have a formal structure for transfers to revascularization centers for patients who need revascularization that the hospital cannot provide. Such a structure could probably be required under the existing accreditation guidelines of the Joint Commission on Accreditation of Healthcare Organizations and the “conditions of participation” of CMS, although both would require some development of specifications, which could probably be achieved effectively in a combined American College of Cardiology/American Heart Association statement. The real goal is to ensure that there is a clear protocol for transfer from any hospital with an emergency room or department that does not have revascularization capability to a hospital that has that capability. Such protocols have proven vital to ensuring that patients arrive at the receiving hospital with all necessary information and with adequate notice.

Internal Protocols
Most STEMI patients will continue to receive definitive care in the hospital to which they are admitted. A clear protocol for making the revascularization decision and moving the patient through the system is probably necessary to reduce door-to-balloon/needle time to the target range. Again, requiring that these processes are defined and efficient is an appropriate focus for both payers and accrediting agencies, with the accrediting agencies using standards largely developed by clinical experts and payers supporting the accreditors in their requirements.

Transparency
All payer performance data should be available and public for all hospitals that see STEMI patients. These data should be standardized, and there should be no duplicative or inconsistent reporting requirements.

Paying for Results
Purchasers would like to get value for their money and are deeply skeptical that they can do so without measuring performance. It is likely that the 2 most important performance measures in revascularization for STEMI will prove to be the time from onset of symptoms or entry into the medical system to needle/balloon and the appropriateness of revascularization. Neither endorsed specifications nor data are currently available for either measure. In the interim, door-to-balloon/needle time is useful and would be even more useful if it were applied to transfer patients (some technical specification development would be needed).

Integration of Payment
A single payment that is shared among the referring, transferring, and receiving providers has several theoretical advantages:

1. A system that fragments payments encourages fragmented care. The current payment strategy does nothing to encourage coordination or integration of care across providers or to encourage collaboration between providers and practitioners. This is an issue for transfer from home to hospital
and from hospital to follow-up care even when there is no transfer between hospitals.

2. In treatment of STEMI, when time is life, efficiency across interfaces translates into lives saved, but there is no structure of joint accountability for the total time the system takes to provide care to the patient.

3. As presentations elsewhere in this conference have made clear, the seamless efficiency of a well-developed transfer system requires careful planning and investment in building a system. Fragmented payments discourage such investment even if, totaled across settings, they reduce total resource use.

4. From an efficiency perspective, a single, prospectively determined payment for transferred patients allows the 2 hospitals and the transfer system to share gains from removing inefficiencies in the transfer process.

5. Finally, as the healthcare system increasingly recognizes that it must take care of patients rather than providers, a single payment becomes the outward and visible sign of this focus on the patient.

However, the organizational structures to make such payments rarely exist, and the creation of such a structure would require rigorous accommodation because of prohibitions on paying for referrals (including the Stark rules and other issues). For the moment, because these structures do not yet exist, we should regard integrated payment as an option for demonstrations rather than as a strategy that can be implemented on a large scale today.

Gaps and Barriers

Resistance From Patients
Patients are often reluctant, for various reasons, to be transferred to another facility. This can result both from their fear of being separated from their family or community and from a sense that transfer means that they are terribly sick. Considerable study is needed concerning how to present transfer as a desirable tailoring of care to the individual patient’s needs.

Competition Among Hospitals
To the extent that transfer becomes another element in the ongoing competition between community hospitals and referral centers, there will be general resistance. In addition, unless words are chosen carefully and messages well shaped, hospitals that are not PCI-capable may fear that transferring patients labels them as “low quality.” Certainly, compliance with anti-trust issues will need to be considered.

Competition Among Physicians
There are 3 significant issues for physicians: (1) fear of losing a patient to another provider; (2) a system that deliberately or unintentionally does not include or consider the primary physician (for example, by failing to provide information or coordinate follow-up plans with the primary physician); and (3) fear of being publicly identified as an “inferior” doctor.

Treating the Patient as a “Case” Rather Than a Person
Particularly under the pressure of time and emergency care, it is too easy to disregard the patient’s individuality and right to be consulted about concerns and questions.

Possible Financial Burden on the Patient
Local payer contract arrangements (ie, participating versus nonparticipating providers) may result in financial penalties to patients if they are transferred to nonparticipating providers. For example, a patient might receive care from a nonparticipating physician (eg, an interventional cardiologist) at significant personal out-of-pocket cost. Provider and payer contracting approaches would ideally address these issues to minimize financial penalties on the patient.

Recommendations
Payers should urgently develop a definition of our goals and rough data on the magnitude of the problem, the benefits of fixing it, and the costs of fixing it.

Measures
Payers should play a leading role in making measures consistent across payers and others who require reporting. Payers should also take a leading role in promoting consistent and accurate data collection and public availability of all payer data. This does not mean that every community must collect the same measures; it does mean that there should be a core measure set and that the definition of any measure used should be standardized.

Community Networks
Payers should take a role with other stakeholders in convening community meetings to make clinically appropriate referrals occur reliably. The American Heart Association should invest in the development of resource kits for convening such meetings; kits should include, among other things, what kinds of data should be assembled in advance, who should be invited, and how meetings can be most effective. Involvement of the Alliance for Cardiac Care Excellence and its many members should be considered.

Efficient Payments
Payments for cardiovascular procedures should be prompt and based on efficient costs, not on historical patterns of high-margin payments.

Patient-Centered Care
Payers should assume a leading role in promoting patient-centered care. Patients, and patient reports of experience, should be included in all planning efforts. Payers should help in the effort to make the possibility of referral to a PCI hospital understandable and acceptable to the patient. Payers should strive for a uniform and understandable definition of emergency that will not cause a delay in calling 9-1-1.

Protocols
Professionally developed transfer protocols and internal protocols should be used, and it may be useful to reference them in contracts between payers and providers.

“Pay-for-Results”
Payers should consider adjusting payments to reward the reporting of data and effective participation in performance improvement alliances. Payers should carefully review payment policies to remove areas where the payment system
inadvertently penalizes better care by, for example, creating disincentives for clinically appropriate transfers for STEMI. Finally, payers should consider developing and piloting ways to pay that support good or improved results.

Transferring Hospitals and Transport Systems

Payers should develop and implement mechanisms to pay transferring hospitals and transport systems fairly for the costs of evaluating the patient, arranging the transfer, and providing any needed care.

Certification

The payer group believes that certification of PCI-capable (STEMI receiving) hospitals may be helpful for factors such as volume, 24-hours-per-day/7-days-per-week availability, and practitioner credentialing.

Gain-Sharing

The sharing between payers and providers of the gains that result from improved efficiency is a promising emerging strategy for encouraging efficiency; however, this strategy may have risks that are not yet fully understood, such as aggravating imbalances in the payment system by increasing rewards for services for which payment is already very attractive. Another risk is that asymmetrical situations may be created in which gain sharing encourages disproportionate acceptance of or avoidance of risk. The payer group urges careful consideration of gain-sharing models with an understanding that there is no single appropriate model, that legal prohibitions such as Stark rules and other issues must be considered carefully, and that for many situations, no model has yet been tested.

Payer Image

All parties should make a concerted effort to understand what payers do and to convey that role to patients.

Acknowledgment

The payer writing group and the conference participants gratefully acknowledge Dr Stephen Jencks’ participation and insightful comments during the conference, his review of this manuscript, and his commitment to this American Heart Association initiative.

Disclosures

Potential conflicts of interest for members of the writing groups for all sections of these conference proceedings are provided in a disclosure table included with the Executive Summary.

References


Key Words: AHA Conference Proceedings ■ myocardial infarction ■ point-of-care systems ■ angioplasty ■ reperfusion
The establishment of systems to improve the quality of care for ST-elevation myocardial infarction (STEMI) patients holds great promise to facilitate patients’ access to evidence-based, timely cardiac therapies and, ultimately, to improve patient outcomes. Any evaluation of the quality of STEMI care should be focused squarely on the patient, from initial symptom onset to rapid access to reperfusion therapy and through a coordinated hospital discharge and return to the community. Ideal care therefore requires close collaboration of multiple parties, including the patient, emergency medical services (EMS), emergency physicians, interventional teams, cardiologists, and community-based clinicians. As with any care system, however, attempts to improve the process may not be implemented successfully or, worse, may lead to unintended adverse consequences. As such, it is important to carefully monitor the impact of any new care strategies on clinical outcomes.

**Conceptual Model for Evaluation**

The overall goal of a proposed STEMI system redesign is to improve quality of care and thereby improve patient outcomes. As defined by the Institute of Medicine, STEMI care should be timely, effective, safe, equitable, patient-centered, and cost-effective. Although there are many approaches to guide evaluation of care, Donabedian’s classic triad of structure-process-outcome provides an ideal model. This identifies the major domains of health care and defines the programmatic features needed to achieve success.

**Structure**

Structure refers to component personnel, equipment, and facilities needed to provide ideal STEMI care. At this conference, several model systems provided examples of EMS, emergency department, percutaneous coronary intervention (PCI)–capable hospital, and regional network features associated with improved reperfusion times (Table 1). Although “structure often drives function,” these structural features should be used only as a guide and will often need to be individualized for a particular care setting. Many of these features are described elsewhere in this report, yet require further explanation. First, we believe that providers should participate in national data collection and quality improvement programs. Examples of such programs include those for EMS, myocardial infarction, and PCI. Participation in such programs provides caregivers with standardized tools for data collection and risk adjustment, as well as feedback on how their care compares with peers. Such feedback systems are known to be a critical element in continuous quality improvement.

As regional STEMI care delivery systems mature, the model of an individual hospital-centered quality improvement program will need to expand to that of collaborative, community-wide oversight programs. These may include a regional STEMI steering committee and, potentially, a separate data safety monitoring board. Such oversight should have comprehensive representation that includes the region’s EMS director and EMS medical director, other emergency services leaders (fire and police), representatives from both the STEMI referral and STEMI-receiving hospitals, and regional...
medical and professional society representatives. These committees should share provider process and outcome data in a transparent manner to ensure access and quality of STEMI care.

Process
Process refers to actions performed in the delivery of care to a patient, including timing and technical competency. Table 2 provides a list of potential process metrics that could be tracked to ensure quality STEMI care. Several of these relate to the timeliness of key steps in the reperfusion process. From a patient perspective, “total ischemic time” (defined as the time from symptom onset to successful PCI) is the most important interval. Yet, the exact onset of symptoms can often be difficult to define. As such, other more quantifiable, intermediate measures (eg, time from 9-1-1 call to hospital arrival and time from hospital to cardiac catheterization laboratory arrival) are also recommended. Beyond timely reperfusion, the importance of providing all evidence-based care, as outlined in the American College of Cardiology/American Heart Association guidelines, to eligible patients is also stressed.9

Outcomes
“Outcomes” refers to tangible measures of the consequences of patient care and can be subdivided into categories of mortality, nonfatal adverse events, and patient-reported

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**TABLE 1. Proposed Structural Measures**

<table>
<thead>
<tr>
<th>Structural Characteristics</th>
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<tbody>
<tr>
<td>EMS structural characteristics</td>
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<tr>
<td>Adequate staff, equipment, and training to perform and transmit prehospital ECGs</td>
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<tr>
<td>Single standardized STEMI checklist/algorithm of evaluation and treatment</td>
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<tr>
<td>Prearranged destination protocols</td>
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<tr>
<td>ED structural characteristics</td>
</tr>
<tr>
<td>Adequate staff, equipment, and training to perform ED rapid evaluation, triage, and treatment</td>
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<tr>
<td>Single standardized STEMI care pathway</td>
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<tr>
<td>One-contact STEMI hotline</td>
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<tr>
<td>Primary PCI hospital structural characteristics</td>
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<tr>
<td>24/7 PCI capacity</td>
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<tr>
<td>Interventional cardiologist and staff capable of arriving at the laboratory within 30 minutes</td>
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<tr>
<td>Volume/experience characteristics according to ACC/AHA PCI guidelines</td>
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<tr>
<td>For hospitals without cardiac surgery on-site capabilities, a predefined transfer and management plan for emergency coronary artery bypass surgery</td>
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<tr>
<td>Quality assurance system</td>
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<tr>
<td>Participation in national EMS, MI, and PCI data collection and feedback systems</td>
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<tr>
<td>Regional STEMI oversight committee</td>
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<tr>
<td>ED indicates emergency department; 24/7, 24 hours per day/7 days per week; ACC/AHA, American College of Cardiology/American Heart Association; and MI, myocardial infarction.</td>
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**TABLE 2. Proposed Process Measures**

<table>
<thead>
<tr>
<th>Process Characteristics</th>
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<tbody>
<tr>
<td>EMS process characteristics</td>
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<tr>
<td>Time from symptom onset to 9-1-1 call</td>
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<tr>
<td>Time from 9-1-1 call to ambulance arrival</td>
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<tr>
<td>Proportion of patients for whom adequate ECGs were obtained or transmitted</td>
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<tr>
<td>Predictive accuracy (false-positive and false-negative) of field diagnosis</td>
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<tr>
<td>Emergency department process characteristics</td>
</tr>
<tr>
<td>Door-to-first ECG time</td>
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<tr>
<td>Proportion of STEMI-eligible patients receiving any reperfusion (PCI or fibrinolytic therapy)</td>
</tr>
<tr>
<td>Door-to-catheterization laboratory time (for nontransfer patients) or door-to-disposition time (for patients transferred to PCI center)</td>
</tr>
<tr>
<td>The proportion of patients ineligible for lytics but eligible for PCI (eg, cardiogenic shock, bleeding) who are not transferred acutely from the STEMI referral hospital to the STEMI receiving hospital</td>
</tr>
<tr>
<td>Primary PCI hospital process characteristics</td>
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<tr>
<td>Door-to-balloon time (from arrival at primary PCI center to balloon inflation, nontransfer patients)</td>
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<tr>
<td>First hospital door-to-balloon time (for transfer patients)</td>
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<tr>
<td>Total patient ischemic time (symptom onset to balloon) stratified by transfer status</td>
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<tr>
<td>Proportion of eligible patients administered guideline-based class I therapies</td>
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<tr>
<td>Proportion of suspected STEMI patients undergoing coronary angiography found not to have STEMI</td>
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</tbody>
</table>

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health status measures (symptoms, functional status, and quality of life). Outcomes assessment should also consider the impact of care on non–health-related measures such as patient satisfaction and economic implications. Finally, outcomes measures may also consider potential unanticipated consequences of care changes. For instance, widespread use of prehospital ECGs and prehospital activation of the cardiac catheterization laboratory may lead to an increase in emergency coronary angiography among patients without acute coronary occlusion; this may lead to increased costs of care and patient risks due to unnecessary procedures. Similarly, a policy that leads to proliferation of low-volume, “stand-alone” primary PCI centers may ultimately result in more procedural complications. A list of potential outcomes metrics is provided in Table 3.

Outcomes represent the aggregate effect of all structure and care processes. Thus, improving this end product is the ultimate goal of successful medical care. The use of outcomes metrics for evaluation, however, also presents challenges. In the case of STEMI care, many adverse events rates tend to be uncommon. Thus, estimates of outcomes performance measures are often unstable at the single-center level, particularly when evaluated over a relatively brief time interval. Moreover, multiple factors beyond provider quality affect patient outcomes and must be accounted for before outcomes comparisons are meaningful. Thus, there is a need for collection of detailed clinical data and rigorous risk adjustment of provider outcomes measurements.10

There are several outcomes perspectives that need to be considered. The first is the time frame for evaluation. Data on acute in-hospital STEMI events are the easiest to collect and most directly related to the care delivered; however, it is also likely that longitudinal patient outcomes (ie, 6 months or 1 year) could be impacted if STEMI care were improved. It is often difficult for providers to collect longitudinal data, yet such data collection may be feasible via collaborations with state quality improvement organizations or other payer partners.

Second, changes in STEMI care may have effects on other areas of cardiac care (“halo effects”). On the positive side, the process integration between emergency medicine and cardiology needed to shorten reperfusion times in primary PCI may also stimulate broader improvements in care for all myocardial infarction patients. On the other hand, if a provider focused solely on reperfusion metrics, this could conceivably distract efforts to improve other evidence-based myocardial infarction care processes.

Finally, one must consider the level of aggregation of results. Currently, the standard paradigm of outcome evaluation is generally centered on individual institutional performance; however, in many STEMI situations, patients require timely transport to a center and even transfer between centers to receive reperfusion. Evaluation of such integrated care systems clearly needs to consider the performance of the system as a whole. For example, if the sickest patients with STEMI never reach the tertiary care center, STEMI outcomes for the community may not improve despite measured improvements at an individual center.

**Patient Satisfaction and Economic Impact**

Nonclinical impacts of programmatic changes must also be considered in the evaluation process. From a patient’s perspective, receiving care close to home minimizes the impact on friends and family members and maximizes connection with local care providers. Thus, efforts will be needed to ensure that if patients are diverted or transferred to more distant centers for primary PCI, their subsequent care is coordinated with local providers. Such coordination must occur both at the initial point of contact, as acute treatment plans are formulated, and again at hospital discharge to ensure smooth care transitions and overall patient satisfaction.

Increased delivery of primary PCI will likely have multiple direct and indirect economic impacts. First, the overall cost-effectiveness of such programs should be considered from a societal perspective. Such an evaluation will need to consider the fixed costs associated with implementing

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**TABLE 3. Proposed Outcome Measures**

<table>
<thead>
<tr>
<th>Hospital STEMI outcome measures</th>
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<tr>
<td>In-hospital (risk-adjusted) mortality</td>
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<tr>
<td>Longitudinal outcomes: 30-day, 1-year (risk-adjusted) mortality</td>
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<tr>
<td>Morbidity events (in-hospital stroke, vascular complications)</td>
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<tr>
<td>PCI procedural success</td>
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<tr>
<th>Regional STEMI outcomes (aggregated across regional hospitals)</th>
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<tbody>
<tr>
<td>In-hospital (risk-adjusted) mortality</td>
</tr>
<tr>
<td>Longitudinal outcomes: 30-day, 1-year (risk-adjusted) mortality</td>
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<table>
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<tr>
<th>“Halo effects” outcome measures</th>
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<tbody>
<tr>
<td>In-hospital, 30-day, and 1-year mortality for all myocardial infarction patients (non-STEMI and STEMI)</td>
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<tr>
<td>In-hospital, 30-day mortality for all PCI patients</td>
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<tr>
<th>Patient satisfaction and resource utilization</th>
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<tr>
<td>Patient’s assessment of provider quality and collaboration (eg, Press-Ganey survey)</td>
</tr>
<tr>
<td>Changes in individual hospital STEMI charges</td>
</tr>
<tr>
<td>Changes in aggregated regional STEMI charges</td>
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</tbody>
</table>
Potential Uses of Evaluative Data

The evaluation of STEMI care at the hospital or system level can have several goals. Most importantly, tracking these metrics may help the individual provider or the region to both identify areas that require further improvement and to track trends in care over time as one implements change. As a first step toward this goal, we believe that healthcare systems engaged in STEMI care should develop the collaborative process required for closely following care and outcomes for their patient population. Although some benchmarks may not be readily achieved, by plotting the progress of each quality indicator over time, it should be possible to determine whether the system is moving in the right direction. By using this approach of continuous quality improvement, a community/regional oversight committee can monitor a region’s success.

On a second level, certain STEMI metrics could be made public and used for quality assurance or even to alter provider reimbursement rates (“pay-for-quality” programs). When evaluation measures are tied to financial or nonfinancial incentives, such metrics should meet a higher level of rigor and specificity. Finally, it must be realized that metrics for evaluating STEMI care will need to evolve as the field evolves. Thus, new therapeutic advances or “out-of-the-box” innovations in care delivery may stimulate a need to reevaluate the tools used in the evaluation process itself.

Summary

The optimization of reperfusion therapy for STEMI patients by developing coordinated care systems that include increased access to primary PCI offers a unique opportunity for collaboration in the delivery of care. If implemented correctly, such coordinated care systems have the potential to improve outcomes substantially for patients with acute myocardial infarction, which is still the leading cause of morbidity and mortality in the United States. Although the opportunities for improvements are vast, these can only be achieved by tracking processes of care and outcomes with standardized quality metrics and careful external oversight. Ensuring that appropriate metrics are implemented in a transparent fashion should help to engage the numerous parties involved in STEMI care and will foster the necessary trust and collaboration that such ambitious changes in care will demand.

Disclosures

Potential conflicts of interest for members of the writing groups for all sections of these conference proceedings are provided in a disclosure table included with the Executive Summary.

References


Key Words: AHA Conference Proceedings • myocardial infarction • point-of-care systems • angioplasty • reperfusion
The establishment of ST-elevation myocardial infarction (STEMI) systems of care that are intended to increase timely access to primary percutaneous coronary intervention (PCI) will affect the US healthcare system in a broad and fundamental way. The key reason for establishing STEMI systems of care is that although primary PCI is superior to fibrinolytic therapy when performed rapidly, timely access to primary PCI is currently limited. By establishing these systems, it is believed that patients with STEMI can be directed to PCI-capable hospitals through prehospital emergency medical services (EMS) protocols and emergency interhospital transfer arrangements, and as a consequence, outcomes will be improved. The establishment of STEMI systems of care in the United States will be challenging, however, and their success will be predicated on the ability to overcome a number of practical barriers. In this article, we discuss several of these barriers, as well as the potential for STEMI systems of care to reduce mortality and their overall implications for the US healthcare system.

Clinical Issues
The overall benefit of directing patients with STEMI to PCI-capable hospitals with prehospital EMS protocols or interhospital transfer arrangements has not been demonstrated definitively in the United States and raises concerns from a clinical perspective that need to be considered. First, the inherent delays required for performing primary PCI may limit its effectiveness when long transport times are anticipated and may influence the choice between reperfusion therapies. Thus, STEMI systems of care that divert patients to PCI-capable hospitals may delay the delivery of reperfusion therapy for many patients compared with prompt treatment with fibrinolytic therapy at the closest hospital. At some point, the additional time required to perform primary PCI will eliminate its advantages over fibrinolytic therapy, and in some scenarios it could lead to higher mortality rates. Some studies suggest that primary PCI loses its advantages over fibrinolytic therapy when door-to-balloon times exceed door-to-drug times by 60 to 90 minutes. Unless an improved system can be developed, patients presenting to non–PCI-capable hospitals may be at particular risk, because door-to-balloon times of 3 hours or more occur in 50% of cases when interhospital transfer is needed, based on recent National Registry of Myocardial Infarction data. Although new strategies—so-called pharmaco-invasive approaches with fibrinolytic therapy and/or glycoprotein IIb/IIIa inhibitors before PCI—are being proposed to mitigate the effect of time delays by accelerating recanalization of the infarct artery with an initial pharmacological approach, these treatment strategies remain experimental, and current studies do not support their use.

The superiority of primary PCI over fibrinolytic therapy may also not be consistent across all patient groups, with a minimal difference in mortality rates noted for many patient...
groups.10 With the exception of high-risk patients, such as those with anterior myocardial infarction, cardiogenic shock, or late presentations, low-risk patients and those presenting early after symptom onset may derive little or no benefit from primary PCI compared with fibrinolytic therapy even under ideal settings, such as in clinical trials in which door-to-balloon times and operator experience with primary PCI are optimized. In the DANish multicenter randomized study on fibrinolytic therapy versus acute coronary angioplasty in Acute Myocardial Infarction (DANAMI)-2 trial, for example, primary PCI and fibrinolytic therapy demonstrated similar outcomes in the nearly 75% of patients identified as low risk.11 In the PRimary Angioplasty in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis (PRAGUE)-2 trial, patients presenting within 3 hours of symptom onset had similar outcomes regardless of the type of reperfusion therapy used.12 A recent clinical trial in the very elderly population also showed similarities between the 2 reperfusion strategies.13 Finally, even in patients in whom primary PCI has been proven to be superior to fibrinolytic therapy, the clinical benefits are restricted primarily to reductions in reinfarction and hemorrhagic stroke, with modest improvements in absolute mortality rates (=1% to 2%).14

Operational and Accountability Issues

A key operational challenge will be to improve utilization of EMS by patients. Patients who are transported by EMS have 2 advantages within STEMI systems of care: (1) They may have shorter times to reperfusion therapy because of earlier recognition of their condition, and (2) they may be preferentially directed to PCI-capable hospitals in a timely fashion ifprehospital electrocardiography is performed.15 In addition, there is the ability to provide immediate advanced life support to the patients who sustain sudden cardiac arrest. However, fewer than half of all STEMI patients use EMS.16 The need for electrocardiographic diagnosis by EMS is even more critical because chest pain is a nonspecific symptom, and the vast majority of patients with chest pain who do use EMS do not have an STEMI.16 The 20-city Rapid Early Action for Coronary Treatment (REACT) trial, an intensive, 18-month, community-based intervention to increase awareness of symptoms of myocardial infarction, showed no improvement in patient-related delays in seeking medical care (≈133 minutes after symptom onset) and only a modest increase in appropriate EMS utilization, which demonstrates how difficult it will be to overcome this barrier.17 In addition, prehospital ECGs are rarely performed by EMS providers, potentially because of limited access to these devices and nonspecific symptoms in many patients.16 Without improvements in EMS utilization and the use of prehospital electrocardiography, the potential of STEMI systems of care will be restricted.

Another operational challenge will be the evaluation of STEMI systems of care to ensure that the anticipated changes in outcomes actually occur. This is discussed in detail in the preceding section of these conference proceedings.18 This issue, which relates to both measurement of performance and accountability, will be particularly difficult to control and measure at a “systems” level, where interactions between EMS providers and hospitals become critical for STEMI systems of care to be successful. For example, under ideal circumstances, STEMI systems of care will direct patients with suspected STEMI rapidly and appropriately to PCI-capable hospitals. If done improperly, however, “overtriage,” “undertriage,” or “mistriage” of patients to PCI-capable hospitals may occur, leading to increased costs with no clinical benefit. Undertriage would result in worse outcomes by failing to direct patients with STEMI to available PCI-capable hospitals when possible within rapid time frames. Overtriage would result in wasted resources if a substantial number of patients without STEMI were sent to PCI-capable hospitals. Mistriage would result in worse outcomes by inefficiently triaging patients to PCI-capable hospitals only after substantial delays. As a result, fibrinolytic therapy would be underutilized in clinical scenarios in which it may have resulted in better outcomes than delayed primary PCI. However, in well-developed systems that utilize prehospital ECGs, the rate of such mistriage has been shown to be low.19 The establishment of systems that monitor these potential problems requires a framework for defining denominator populations (ie, at-risk patients with suspected STEMI) and appropriateness. In addition, discussions about who will be ultimately accountable for the developing, collecting, benchmarking, and reporting of these measures are needed.

Resource and Economic Issues

When establishing STEMI systems of care, stakeholders will need to recognize that there is great variation in EMS and hospital resources throughout the United States. Designing systems to best match the needs of a community given its resources will be challenging for policy makers and providers. Clearly, a “one-size-fits-all” strategy is not practical or achievable. For some communities, direct ambulance referral or emergency interhospital transfer protocols may be effective at preferentially directing STEMI patients to PCI-capable hospitals. Such systems have been developed successfully (but to a limited extent) using regional networks19,20; however, whether these approaches can be generalized to broader areas of the United States is unclear. For other communities, large geographic distances may severely restrict rapid access to cardiac catheterization facilities. In these areas, STEMI systems of care may need to selectively refer high-risk patients to PCI-capable hospitals and use fibrinolytic therapy for others.21 Decisions about who will be responsible for (1) assessing local needs and resources and then (2) designing an optimal strategy for a particular community have not yet been resolved.

In addition, it is currently impossible at a national level to evenly match a population’s needs with available resources. There is no population-based surveillance system of STEMI in the United States as in other countries, and it is unclear whether rates of STEMI are actually declining as some have postulated.22,23 We also have very limited data regarding assessments of available resources. According to the 2002 national survey by the Health Resources and Services Administration, basic life support services are available to
>90% of the US population, whereas advanced life support services are available to only 77%. There is also wide variation in training standards for first responders. In the case of hospital-based resources, it appears that nearly 80% of the US population lives within a 1-hour drive of a PCI-capable hospital; however, this means that >43 million US adults do not have timely access to PCI-capable hospitals without the use of air transport. It also does not take into account whether these hospitals have the personnel resources to provide around-the-clock coverage for primary PCI if a patient were to arrive during off-hours or on weekends.

Understanding the current status of needs and resources across communities is a prerequisite to making new investments. Expanded EMS systems will likely be needed in many areas to account for an increased volume of calls associated with a STEMI system of care. Many EMS providers also will need new equipment, such as devices for acquiring prehospital ECGs, and additional training in its use. In a recent survey of 200 large cities across the United States, only 67% of EMS providers had prehospital electrocardiographs as part of their available equipment, although more recent data suggest improvement. The availability of equipment for EMS providers in less-populated cities and rural areas is unknown but may be lower. Because prehospital ECG devices can cost up to $25,000 per machine, supplying them to EMS providers could lead to substantial upfront costs for many communities. Device maintenance, wireless or remote transmission systems, and training for personnel to perform and potentially read prehospital ECGs will add further costs.

New investment in primary PCI programs will add even more to the costs of STEMI systems of care. Primary PCI is highly cost-effective (and potentially cost-saving) compared with fibrinolytic therapy in hospitals with well-established, high-volume elective PCI programs. However, upfront investments in equipment and personnel costs will limit the availability and cost-effectiveness at hospitals where PCI programs need to be initiated or low volumes are expected. From the systems level, it is unclear under what circumstances STEMI systems of care will be cost-effective for a community, but it is likely to depend on several factors, including the community’s existing resources and anticipated STEMI volume. Additional evaluation and discussion will be required to determine how much additional cost will be incurred and who will pay that cost. Although increased costs are a concern, there is the potential to reduce costs by instituting a more efficient system that delivers timely, evidence-based therapy to STEMI patients, particularly those at highest risk.

Complicating these economic issues further is the fact that patients with acute myocardial infarction are typically insured (≈95%) and relatively “profitable” for hospitals that provide cardiovascular services. In fact, for many hospitals, cardiovascular services are responsible for up to 40% of general revenue, and these services are used to subsidize other less profitable but essential services, such as burn care. Reimbursement structures will need to change to avoid the significant pressure for hospitals to keep and care for patients with STEMI at their own facilities to ensure financial viability. If not, these issues will further fragment the healthcare delivery system and prevent the cooperative effort across hospitals that is needed for successful STEMI systems of care. Additional concerns may come from payers as well. As discussed in the “Payer Perspective” section, STEMI systems of care will need to be designed carefully so as not to place patients at financial risk for their hospitalized care if they are directed to noncontracted providers. Issues related to reimbursement, especially those tied to interhospital transport, will also need to be resolved well in advance of patient arrival to prevent additional time delays during treatment.

Finally, in addition to aligning economic incentives for both non-PCI-capable and PCI-capable hospitals to participate in STEMI systems, there needs to be careful monitoring for the potential expansion of interventional cardiology services within communities where nearby providers already exist. Development of cardiac catheterization laboratories and primary PCI programs could lead to greater utilization of these services in a variety of other clinical settings, such as elective PCI, where there is less evidence that outcomes are improved. Safeguards against the proliferation of a “medical arms race” would be needed, including the ability for STEMI systems to potentially limit the expansion of new PCI programs. As noted previously and by others, detailed and evidence-based criteria for the creation of a STEMI-receiving hospital will need to be established.

Policy Issues

There will be significant political challenges to establishing STEMI systems of care at a national level. Regulatory authorities that control EMS and hospital services vary across states, counties, and cities, which makes it difficult to organize care efficiently. Regulations, such as certificate-of-need laws, are also different across regions. The presence or absence of certificate-of-need laws can have an important impact on how systems are designed. Without certificate-of-need laws, it will be difficult for regulatory authorities to organize primary PCI programs based on need. A commonly cited failure of urban trauma system development has been the designation of too many centers because of an inability of regulatory authorities to centralize services. This can potentially weaken the overall system and lead to duplication of services.

Patients also may have strong preferences regarding where they receive care. This may be a problem, especially for patients who are preferentially directed to PCI-capable hospitals that are far away. One solution may be to retransfer individuals who are stabilized soon after their procedure, but the costs associated with this strategy are unknown. Addressing this issue and developing widespread public support for these systems early in the process will be critical for STEMI systems of care to succeed. This will be especially important because there has been a traditional lack of desire for state-sponsored healthcare planning in the United States. Allowing these systems to be designed and implemented in a manner that respects local regulations and cultures will be extremely challenging.

Finally, it will be important for regulators and the public to determine the overall goal of STEMI systems of care more specifically. This will include specific determinations of the...
extent of additional investments that are available and the populations and regions that will be targeted. These issues may raise concerns of equity or rationing, particularly for rural and underserved communities, which could be denied timely access to these systems in portions of the United States. In those areas, alternative strategies for maintaining access to quality of care for patients with STEMI will need to be considered.

Conclusions

Improving outcomes for patients with STEMI in the United States is an important public health goal. Recent data point to significant underutilization of evidence-based therapies in STEMI patients and persistent disparities in the use of treatments across race, gender, and geography. Optimization of the care of STEMI patients through the establishment of systems of care could be of great value. STEMI systems of care need to be designed not only to reduce mortality by increasing timely access to primary PCI but also to promote broader use of reperfusion therapy in all eligible patients and to enhance access and adherence to other important evidence-based therapies. In the United States, there is currently a lack of robust evidence available to support the widespread use of strategies that preferentially direct eligible patients to PCI-capable hospitals through prehospital EMS protocols or interhospital transfer arrangements, although in Europe, such systems have been implemented successfully.

The unstructured and competitive nature of the US health-care system, unlike those of other countries, also raises practical barriers to the implementation of these systems. The heterogeneous nature of EMS providers and hospitals across the United States will require that these systems be flexible enough to adapt to the local needs and resources of different communities. The costs and cost-effectiveness of STEMI systems of care remain unclear. As outlined in the recommendations throughout these conference proceedings, before STEMI systems of care can be implemented on a large scale, there is a clear need for additional evidence of their “real-world” effectiveness gathered from careful study of some pilot implementation communities, as well as a better understanding of their broader implications for the US healthcare system. Ultimately, a well-designed system of care will improve care for patients with STEMI through improved prehospital diagnosis and “smart triage” of patients, with transport to the most appropriate facility for each individual in the shortest amount of time.

Disclosures

Potential conflicts of interest for members of the writing groups for all sections of these conference proceedings are provided in a disclosure table included with the Executive Summary.

References


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The establishment of timely access to primary percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction (STEMI) patients holds great promise for improving quality of care and patient outcomes. As described in other sections of these conference proceedings, there are significant barriers to the establishment of the ideal system. Changes in policy will be required to overcome many of the obstacles that preclude the delivery of optimal care for all STEMI patients. Short- and long-term policy recommendations that can foster an ideal STEMI system environment are described below. These recommendations focus on how to maximize opportunities to improve the care of STEMI patients by enhancing the processes that are currently available but not fully implemented.

**Short-Term Policy Recommendations**

**Evaluation of Resources for STEMI Systems and Access to Primary PCI by State and by Region**

To ensure that states have the resources available to effectively adopt an ideal system will require that a state or region interested in implementing such a system evaluate their existing resources and analyze how many financial and human resources they would be willing to commit. A state or region should evaluate its emergency medical services (EMS) capabilities and identify the number and location of primary PCI-capable hospitals within a safe distance that would allow for timely treatment of a STEMI patient with primary PCI. It should also assess the total number of STEMI patients that their hospitals receive on an annual basis. This information would help to better identify whether the existing primary PCI hospitals could handle the volume of patients who may be eligible for primary PCI.

**Evaluation of State Regulations and Pending Legislation**

Another factor that should be considered when implementing a STEMI system is how existing state regulations and pending legislation may positively or negatively affect the implementation of a STEMI system. For example, in the state of Arizona, the director of the Arizona Department of Health Services, in consultation with the medical director of EMS, can establish protocols related to the transport of patients based on the patient’s condition. This type of regulation can help further the implementation of a STEMI system by allowing advocates to work with the EMS director to implement primary PCI protocols for EMS. In contrast, the Illinois Department of Public Health will investigate a hospital in an EMS system that goes on “bypass status” due to overcrowding in the emergency department to determine whether the action was reasonable. If the Department of Public Health determines the action to have been an improper diversion by the hospital, the hospital incurs a fine. In this instance, it would be important to work together with the Department of Public Health to establish the importance of diversion to primary PCI hospitals.

Similarly, approximately 50% of states in the United States have certificate-of-need programs that may affect how a hospital’s hospitals receive an annual basis. This information would help to better identify whether the existing primary PCI hospitals could handle the volume of patients who may be eligible for primary PCI.
STEMI system is implemented. Cardiac certificate-of-need laws are intended to regulate the number of hospitals that deliver cardiac catheterization and cardiac surgery procedures, and hospitals must justify their community needs, capital expenditures, and staff requirements to the state health planning agency. These needs must consider STEMI patients and ideal systems of care.

Constituents Should Be Brought Together to Develop Strategies for Implementing an Ideal STEMI System
STEMI systems need to be flexible to account for variations in geography and resources that exist among states and regions. Before implementing such a system, constituents involved in STEMI care who represent different interests should discuss how they can or cannot implement the framework discussed in other sections of this article in developing a STEMI system. Constituents should include representation from state EMS, hospital administration, emergency department staff, cardiologists, nurses, and payers. By bringing together the constituents, it will be possible to discuss resource availability, the desired protocols and procedures for diversion or interhospital transfer, whether or not an oversight committee should be established, and how quality improvement for STEMI patients will be assessed.

Constituents should also consider how they might seek to involve patient representatives in this process to achieve patient and family input and support for the STEMI system model. As discussed in “The Patient and Public Perspective” section of these conference proceedings, patients and their families may not understand why a transfer or bypass to a primary PCI-capable hospital is preferable. Identifying some of the consumer concerns with the systems at the onset may help to positively affect the patient and family experience in bypassing their preferred hospital or in interhospital transfer.

Implement the Sharing of “Lessons Learned” From Regions That Have Piloted STEMI Systems
Although some regions have successfully adopted a STEMI systems approach, there currently is no data repository in which to catalog examples of protocols used or transfer policies or to review assessment of why elements of the STEMI system succeeded or failed in a region. Devising a way to share “lessons learned” and best practices could potentially reduce some of the financial costs associated with a systems approach. Ideally, this information could be found in a national data repository.

Develop Standardized Protocols and Tool Kits for Assessment
Although there needs to be flexibility in how states or regions implement a STEMI system, standardized protocols across the continuum of care (EMS, emergency department, and STEMI referral and STEMI receiving hospitals) and tools for assessment should be developed. These tools could serve to create a standard, help reduce some of the financial costs associated with creating a STEMI system, and create some uniformity in how care is coordinated and delivered. These tools could also foster quality assurance and quality improvement initiatives and measurement of structure, process, and outcomes.

EMS Agencies Should Be Encouraged to Upgrade to 12-Lead ECG Field Devices
Ideally, most EMS vehicles should be equipped with 12-lead ECG capability, and EMS personnel should be trained on these devices; however, the uniform adoption of the 12-lead ECG and the appropriate training currently may not be feasible from a financial and staff resource perspective. Some states may require federal or state funding to facilitate the adoption and training of personnel on ECG interpretation. In the interim, it may be possible to encourage state EMS medical directors to upgrade to a 12-lead ECG system when they need to change their equipment. Funding gaps, implementation strategies, and assurance of reliability and adequate training will need to be addressed.

EMS Should Use One Standard Algorithm for Prehospital Assessment, Triage, and Treatment of Patients
As stated in the “Emergency Medical Services and Emergency Department Perspective” section of these conference proceedings, EMS, as part of a multidisciplinary team, should develop protocols for the prehospital assessment, triage, and treatment of patients with suspected STEMI, using the American Heart Association advanced cardiovascular life support chest pain algorithm for guidance. The use of this standard algorithm will facilitate higher-quality patient care and is a necessary component of a STEMI system.

Development of a National STEMI Center Certification Program and Criteria
It will be important to assess the feasibility of developing criteria for both STEMI referral and STEMI-receiving hospital certification in accordance with the American College of Cardiology/American Heart Association practice guidelines to promote timely access to reperfusion therapy and increased access to primary PCI for all STEMI patients. As noted previously, performance and outcomes measures will need to be developed to ensure alignment of anticipated and actual improvement in the quality of care and outcomes for STEMI patients.

Long-Term Policy Recommendations
Quality Improvement Measures for Eligible PCI Patients Must Be Developed and Incorporated Into Quality Improvement Programs
A significant barrier to increasing patient access to primary PCI has been the lack of data regarding the transfer of patients who are eligible for PCI. The diversity of patterns of patient access to primary PCI, including whether the patient was diverted or transferred from another hospital, has served to inhibit the adoption of national standards. Additionally, patient choice concerning where they are treated has complicated this matter further.

Improvement in patient access to primary PCI will require the development and adoption of national standards for the treatment of patients with primary PCI. Examples of process-
of-care measures that could be included in an ideal STEMI system were discussed in the “Evaluation and Outcomes” section of these conference proceedings.\(^5\) Such measures should be part of quality improvement programs and would be consistent with the recently issued Institute of Medicine (IOM) report entitled “Hospital-Based Emergency Care: At the Breaking Point.”\(^6\) This would facilitate efforts to capture accurate and timely feedback of data on STEMI reperfusion and could provide a better understanding of the cost-effectiveness of implementing a systems approach. Additionally, this information will allow healthcare providers and institutions to track their performance improvement. This could also provide the federal or state legislature with compelling data on why the adoption of a STEMI system could provide patients with a higher quality of care, which potentially would lead to better patient outcomes.

**Work With Quality Improvement Organizations to Have Quality Measures Included in Future Scopes of Work**

The Centers for Medicare and Medicaid Services (CMS) has contracts with more than 50 quality improvement organizations (QIOs) throughout the country that are responsible for working with consumers, physicians, hospitals, and other caregivers to refine care-delivery systems. This allows CMS to ensure that patients receive quality care, particularly patients from underserved populations. The QIOs provide technical assistance to hospitals to improve their scores in CMS quality initiatives.

Last year, the IOM published its report entitled “Medicare’s Quality Improvement Organization Program: Maximizing Potential.”\(^7\) In this report, the IOM stated that the QIOs have the potential to play a significant role in improving the quality of health care delivered to patients. According to the IOM, the primary focus of QIO programs should be to provide technical assistance in the area of performance measurement and quality improvement (in light of the increased use of public reporting initiatives, including pay-for-performance), rather than also focusing its efforts on beneficiary education and communication and the protection of the Medicare trust fund. Although CMS officials have stated that the IOM report does include sound ideas to improve the QIO program,\(^8\)\(^9\) the agency has not reported which policy recommendations it may adopt. As the largest payer of cardiac services, inclusion of process-of-care measures for STEMI into future scopes of work set forth by the CMS could play a critical role in the evaluation of the effectiveness of STEMI systems of care.

**Inclusion of Process-of-Care Measures in Quality Improvement Initiatives/Pay-for-Participation/Pay-for-Performance Programs**

The development of process measures for PCI by transfer or direct transport will facilitate the collection of data and reporting of measures. To collect a broad sample of data, it is worthwhile to explore whether these quality initiatives should be linked to financial incentive programs, such as mandatory reporting, pay-for-participation, pay-for-performance, or pay-for-quality programs. Interest in using these programs has increased greatly and could facilitate the steady adoption of quality measures that would form a part of an optimal STEMI system.

Quality indicators that are developed should be incorporated into hospital voluntary reporting programs. In fact, the IOM report “Hospital-Based Emergency Care: At the Breaking Point”\(^6\) does explore the idea of convening a panel of experts to develop measures that could be used in evaluating the performance of individual providers within the system, as well as the system as a whole, to improve the quality of emergency care provided. The report also notes that once these measures are developed and tested, they could be used in pay-for-performance programs. Therefore, one possibility for a more widespread adoption of these measures could be to gradually incorporate them into pay-for-participation programs by both private and public payers. These measures will facilitate the gathering and evaluation of data as to whether or not there is an increase in the number of patients being directed to PCI-capable hospitals. However, these measures would need to be sensitive to the interdependence among system components (ie, EMS transport time is related to whether a STEMI-receiving hospital’s emergency department is on diversion).

Additionally, as STEMI measures for physicians are developed, they could also be incorporated into existing voluntary reporting or pay-for-reporting programs. For example, the Tax Relief and Health Care Act of 2006 authorized the establishment of a physician quality reporting system by CMS.\(^10\) The program, known as the physician quality reporting initiative (PQRI),\(^11\) establishes a financial incentive for eligible professionals to participate in this voluntary quality reporting program. Those eligible professionals who successfully report on the designated set of quality measures on claims for dates of service from July 1, 2007, to December 31, 2007, may earn a bonus payment of 1.5% of total allowed charges for covered Medicare physician fee schedule services. This program, like other quality improvement initiatives, is intended to facilitate the agency’s effort to improve patient health and outcomes by preventing chronic disease complications, avoiding unnecessary hospitalization, and improving the quality of care delivered. The program is voluntary and consists of 74 evidence-based measures, including measures for STEMI.

However, the American Heart Association believes that any measures that are used in pay-for-performance, pay-for-reporting, or pay-for-quality programs must adhere to 4 principles. These principles state that these programs should\(^12\) (1) promote health care that is safe, effective, patient-centered, timely, efficient, and equitable; (2) use rigorous methodological approaches to measure quality of care (quality-of-care measures should be risk-adjusted, standardized, and evidence-based); (3) promote quality-of-care systems and quality infrastructure; and (4) implement evaluation mechanisms to determine whether program goals are achieved or whether inadvertent adverse consequences have resulted.

**Working Toward Addressing Reimbursement Barriers That Affect the Implementation of a STEMI System**

As discussed in the “Gaps, Barriers and Implications” and the “Payer Perspective” sections of these conference proceed-
ings,\textsuperscript{13,14} development of an ideal STEMI system will involve overcoming some significant financial disincentives that are associated with the participation of non–PCI-capable hospitals in such a community program. These hospitals may be concerned that diversion of patients or interhospital transfer will put them out of the “heart business,” which can often provide a lifeline for a hospital’s financial success and may help to subsidize other less lucrative services. Therefore, nationwide adoption of this system approach will necessitate a change in how health care is reimbursed for eligible PCI patients.

The most attractive proposition for payment reform would be to create a single prospective payment that covers care from activation of 9-1-1 to transfer of a patient, which would allow both hospitals and EMS to share gains that would result from the coordination of patient care and would remove the inefficiencies inherent in the payment system. Such a payment system could potentially provide incentive for interhospital transport by EMS to have the same priority as a patient 9-1-1 transport. However, this type of reimbursement change will require a significant restructuring of the payment system.

The first step might be to create a demonstration project that would test the hypothesis that a change in the reimbursement structure could provide an incentive for the interhospital transfer of patients. This demonstration would also provide an opportunity to apply the protocols delineated in other sections of these conference proceedings at a regional level. This demonstration project could pay all key players for their role in facilitating the transfer of eligible patients to a primary PCI-capable hospital and would provide for an evaluation process. Data provided from this demonstration could then provide advocates of a STEMI system with the necessary information to determine whether this type of coordination is in fact possible, whether it can improve the quality of care delivered to patients, and whether the treatment is cost-effective.

A demonstration could also help to identify additional barriers or unintended consequences of a STEMI system of care. For example, such a demonstration could provide a better understanding of whether a non–PCI-capable hospital would lose prestige as a result of transferring a patient to a primary PCI-capable hospital. Moreover, it could provide information on whether the non–PCI-capable hospital will lose future business for other modality services to the primary PCI-capable hospital and whether the primary PCI-capable hospital makes a concerted effort to refer STEMI patients back to their community hospitals and physicians. On the basis of the data that result from this demonstration, one could apply “lessons learned” to advocate for appropriate changes in national reimbursement.

Disclosures

Potential conflicts of interest for members of the writing groups for all sections of these conference proceedings are provided in a disclosure table included with the Executive Summary.

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2. Ill Rev Stat ch 730, §5/5-9; ch 705, §105/27.6; ch 20, §396/06.01.

Key Words: AHA Conference Proceedings, myocardial infarction, point-of-care systems, angioplasty, reperfusion, health policy
Since the initial online posting of the article, “Development of Systems of Care for ST-Elevation Myocardial Infarction Patients: Executive Summary,” by Jacobs et al on May 30, 2007 (DOI: 10.1161/CIRCULATIONAHA.107.184043), the Society of Thoracic Surgeons has added its endorsement. This information has been added to the print and current online versions of the article (Circulation. 2007;116:217–230).

DOI: 10.1161/CIRCULATIONAHA.107.185418
Serbia has undergone many changes in recent years since the breakup of Yugoslavia in the early 1990s. In addition to gaining its independence, the country has made advances in health care and cardiology. The Clinical Center of Serbia, where Dr Milan Nedeljkovic works as professor and cardiologist, is the major healthcare institution in Serbia (Figure 1). Commenting on the transition to being a country of only 8 million people, compared with the former Yugoslavia’s 22 million (Figure 2), he says, “It has to affect your work.” But he adds, “It is more than 10 years since the former country fell apart. So, I think that now something like a steady state has been established in all countries involved, and they are working on their own.”

Fortunately for doctors and patients, the changes have seen more money pumped into the healthcare system. “I think that the transition only improved our system,” says Dr Nedeljkovic, “and that nowadays, after the transition, the part of the annual budget that is distributed to healthcare providers is much more than it was 10 years ago. The government is doing a lot of things to not only improve technology and equipment, but also to provide better services to people in this country.”

In Serbia, people pay for health services indirectly. The health service is a state-owned social service, and Serbians pay a percentage of their income every month to the state-owned insurance company. So, when a patient visits the hospital, he or she does not receive a bill.

In the past 5 years, the government has funded up-to-date cardiology procedures, including modern catheter laboratories. “I think that we have the newest equipment that completely fulfils European and US standards now,” Dr Nedeljkovic says. “I think they are completely comfortable with European Society of Cardiology requirements.”

Coronary artery disease represents the main problem facing cardiologists in Serbia. “After Russia,” says Dr Nedeljkovic, “Serbia has the highest prevalence of coronary

**Figure 1.** The Clinical Center of Serbia, where Dr Nedeljovic works, is the main healthcare institution in the country.
artery disease in Europe.” He puts this down to historical circumstances and unhealthy lifestyles. Smoking has a very high prevalence, especially in women, and other lifestyle problems also factor in. “I think that people in Serbia do not exercise enough. We have to do a lot of things for promoting a healthy way of living,” Dr Nedeljkovic says. “Also, the diet is greasy food, with a high cholesterol intake.”

Traditional diets can be hard to change, but a concerted effort at health promotion is underway. In 2006, the Serbian Heart Foundation began as a nongovernmental, nonprofit organisation with this aim in mind. It has just become a member of the World Heart Federation and the European Heart Network.

For specialist education, cardiologists can undertake all of their training in Serbia. After finishing medical school, each student does a 4-year speciality in internal medicine to become a doctor of internal medicine. A subspeciality in cardiology follows and takes 2 more years. “At the same time, you are working, and you can choose some field in cardiology that you are interested in,” says Dr Nedeljkovic. He chose to specialise in invasive cardiology and interventional cardiology. “I think that’s the best way to treat the main issue in cardiology: coronary artery disease.”

As yet, Serbia offers no formal training in interventional cardiology. “We are waiting for Europe to define the requirements for training in interventional cardiology,” Dr Nedeljkovic says. “But the Cardiology Society of Serbia does have a working group on interventional cardiology, and I am its general secretary.” Although no official figures exist, he estimates that about 20% of Serbian cardiologists go abroad for some training, primarily to countries in Europe. For some, these periods abroad are short, up to 6 months. Dr Nedeljkovic went to the University of Pittsburgh Medical Center Presbyterian Hospital, Pittsburgh, Pa, from November 2001 to May 2002. “I had some personal contacts with people from the hospital,” he explains, “and some of them are friends of mine.”

Serbia also has good cooperation with Italy. “Many of our doctors from the clinical centre work in Italy, doing invasive and noninvasive cardiology, and they do their training in Milan and Pisa.”

“Cardiology research in Serbia is very active,” says Dr Nedeljkovic. “I think Serbian cardiologists are really leading the way in this part of southeastern Europe, with a number of publications.” Many centres do research in Serbia, with articles being published in all fields of cardiology. Funding for research comes partially from the government. The Ministry of Science funds projects for 4 years, with contracts renewed each year, depending on the success of the work. Industry provides some money, depending on the topic, and some research progresses without specific funding. “Some projects are not funded at all but are just the enthusiastic work of our doctors,” Dr Nedeljkovic says.

Cardiologists have a good life in Serbia, Dr Nedeljkovic believes. “I think it’s a good job and a job of opportunities. You can do what you really like to do. You can do research and everything else. And also, you have a lot of contact with international friends. We participate in all the important cardiology meetings in Europe and the United States.”

As for the future, Dr Nedeljkovic says, “There is nothing special planned for cardiology in Serbia. We will follow the trends for the remainder of the world.” He explains, “I think that we will establish other procedures as they are introduced in other countries.” Despite the recent advances in technology, Serbia has yet to see improvements in survival. Dr Nedeljkovic predicts this could take at least 5 to 10 years. “I hope the improvement of lifestyle modification will have some impact on survival,” he says. “It takes a long time just to change the way people feel about lifestyle modification.”

Jennifer Taylor is a freelance medical journalist.
Climbing the Cardiology Career Ladder: Sweden

A Soft System in a Harsh Climate: Sweden Will Be Offering More Opportunities for Cardiologists, Especially in the North

Sweden tries to follow European guidelines for speciality cardiology training, but it has adapted the recommendations for a “soft system” that gives much credence to personal judgement, according to Per Tornvall, MD, PhD, FESC, president of the Swedish Society of Cardiology and a consultant cardiologist and associate professor of cardiology at the Karolinska University Hospital, Stockholm, Sweden. Barry Shurlock, MA, PhD, reports.

Sweden is a country of 2 worlds: a densely populated southern part, where most of the 9 million inhabitants live, and a larger, thinly populated region to the north that extends beyond the Arctic Circle. It is separated from Norway to the west by mountains that reach a height of more than 2000 m. Despite harsh winters, its people enjoy a life expectancy of 80 years—closer to that of a country bordering the Mediterranean than one in northern Europe. Dr Per Tornvall, president of the Swedish Society of Cardiology, says, “The reasons for this are obscure, but diet and lifestyle are probably important.” He comments, “There has been a dramatic fall in smoking—less than 20% of the middle-aged population now smoke, so lifestyle is an important factor. It’s interesting to compare Sweden with the other Nordic countries. In Denmark, for example, where life expectancy is 77.3 years, they smoke a lot, and they are probably less careful with their health.”

Whatever the explanation, the long life expectancy in Sweden suggests that preventive and clinical cardiology have proved effective. The future might depend on a new speciality training schedule for cardiology introduced on July 1, 2006, based on the recommendations of the European Union and the European Society of Cardiology. As in most other European countries, after obtaining an MD (from 1 of the 6 Swedish medical schools), potential cardiology trainees now spend 3 to 4 years working in internal medicine before finally opting for the speciality.

Dr Tornvall explains, “This may be at a university hospital, or it can be in a small country hospital, as long as the doctors then go on to work for 2 to 3 years in a university hospital. It’s a very flexible system, and during training many interns change their minds about the speciality to go for.” He points out, “Young cardiologists who are not doing well can be steered into other areas—they don’t generally need to be told; they realise it themselves. It’s a very soft system, but it works well.”

Dr Tornvall does not know how the new system will work out. He says, “Previously, you could specialise in cardiology without first doing internal medicine—though many trainees did it anyway. We are busy revising all the training books. In general, the ESC recommendations for training include some good ideas, but what works in one country may not work in another.” He explains, “Having to do a certain number of echocardiograms, for example, doesn’t work everywhere. We mention numbers for such procedures, but it’s not mandatory. For someone training in a country hospital, it would be a waste of resources and not in the interests of the patients.”

No formal system exists in Sweden for obtaining a cardiology training post. Many potential trainees take temporary employment in a clinic for 6 to 9 months, and if it works out well, they will continue with training, which takes 5 or 6 years overall. They then spend another 1 or 2 years in a subspeciality area of their choice, such as interventional cardiology or electrophysiology. About 50% of Swedish cardiologists

Figure 1. A simulator for percutaneous cardiac interventions: New speciality training is based on the recommendations of the European Union and the European Society of Cardiology.
have subspecialities. Dr Tornvall comments, “You have to be highly motivated. Quite a few trainees do a PhD in an area of interest. This is supposed to take 4 years of full-time research, so training takes more than the normal 7 years, but you can usually mix subspeciality training with research and, in this way, finish training in about 9 years.”

Dr Tornvall spent some time working in the United Kingdom and Australia during his own training. He regrets that, in contrast, most Swedes tend to stay in the hospital in which they had their basic training, rather than move elsewhere in the country or go abroad. He says, “It’s really good to see how they work in other countries—you can learn quite a lot. Funding is not a problem for gaining clinical experience, since temporary jobs as locums can usually be found. And, for research abroad, funding is usually available from government sources or from the Swedish Heart and Lung Foundation.”

The best way to accredit cardiologists at the end of their speciality training presents an issue on which the Swedish Society of Cardiology (SSC) and the Swedish Ministry of Health do not agree, according to Dr Tornvall. “The ministry sets great store by letters of recommendation from the head of the department in which the fellow has trained and from his supervisor, whom he or she sees regularly—in theory, once a month,” he says. “The ministry also recognises the benefits of small examinations to check progress in individual modules of training, although these are not held for cardiology, but it does not accept the 2-day examination run by the SSC, which is based on the interpretation of case notes and a written paper.” Dr Tornvall and his colleagues would like to make SSC accreditation mandatory, though at the moment only 15% to 25% of cardiologists bother to finalise their training by taking the examination. He comments, “Not as many cardiologists take the exam as we would wish—perhaps 5 a year. We don’t know for certain how many cardiologists are trained each year, as there is not a national scheme, but an educated guess would be about 20 to 30. I’ve taken the exam—it’s a little bit tense, and the problem is that, in a small country, if you don’t do well, everyone will know. There have been a few failures, and some of these physicians had been accredited by the ministry.” Dr Tornvall emphasises, “Our aim has been to make this exam mandatory, but those in government don’t agree. They say that a long training should not be assessed by a single examination—we’ve discussed it so many times.”

After completing their training, most cardiologists obtain posts as senior registrars, but, according to Dr Tornvall, “They quite soon become consultants, especially if they have a PhD.” He points out that many specialists born in the 1940s are about to retire, so cardiologists in Sweden should have promising career opportunities in the next few years, especially in smaller hospitals and in the north of the country (Figure 2). Cardiologists seeking jobs from outside Sweden must, of course, learn Swedish, but the country has a good history of employing foreign specialists, especially those fleeing from less liberal regimes in the Middle East, such as Iran and Iraq.

Although all medical vacancies in Sweden must be advertised by law, most departmental heads have clear ideas about whom they would like to appoint, according to Dr Tornvall, who comments, “At the Karolinska Institute, a strong interest in research is necessary as well as an interest in patients. People tend to come here who have ambitions for a career in clinical research. More generally, if you’re not known in your part of Sweden, you will probably be employed at first for a limited time, probably 6 months. Advertisements don’t always get the right people.”

Dr Tornvall’s area of interest in research is the genetics of inflammation, which he considers a more important factor in coronary heart disease than previously thought. His clinical work and research consume most of his time; he admits that he never has enough time to do all he would like outside medicine. He says, “I wish I had more time to play more tennis. Like most Swedes, I enjoy skiing, but I don’t have the time for golf. In the summer, we enjoy 5 weeks of vacation in our holiday home on the West coast. I used to sail, but not any more.”

Barry Shurlock is a freelance medical writer.

Reference
Viewpoint: Stroke Problems in Wales

The Stroke Service in Wales Is Likened to That of an Underdeveloped Country

The 2006 National Sentinel Audit for Stroke,1 published in May 2007, has revealed that patients in Wales fare worse than those in other parts of the United Kingdom. Hamsaraj Shetty, FRCP, consultant physician and chair of the Stroke Special Interest Group of Wales, offers his views about the situation to Mark Nicholls.

Dr Hamsaraj Shetty, a senior physician with a special interest in stroke at the University Hospital of Wales in Cardiff, believes patients in Wales are putting up with an inadequate service with respect to stroke care. Dr Shetty also fears that Welsh stroke patients have a higher likelihood of dying or becoming disabled than stroke patients elsewhere in the United Kingdom.

His views follow the recent publication of the 2006 National Sentinel Audit for Stroke, which shows that only 28% of patients in Wales receive treatment in a specialised stroke unit, compared with 64% in England and 73% in Northern Ireland.

Tony Rudd, MA, FRCP, chair of the Intercollegiate Stroke Network and associate director of the Royal College of Physicians Clinical Effectiveness and Evaluation Unit, which carried out the survey, has described the situation as “scandalous.”

Dr Shetty says, “I agree totally with Tony Rudd, and so do most of my colleagues in Wales. The situation is clearly very unsatisfactory. I feel frustrated that I am not able to deliver the best possible care for my patients. I and my colleagues in Wales feel demoralised, as we are constantly lagging behind the rest of the United Kingdom.” He says that the audit has identified major gaps in Welsh stroke services. “It is a serious clinical governance issue, because many of our patients are dying or becoming disabled from a potentially preventable or modifiable medical condition.”

Dr Shetty believes the current situation in Wales has arisen because, although stroke represents the leading cause of disability and the third-leading cause of death, the politicians, commissioners, and health trusts do not consider it a priority for healthcare planning and delivery. “This means,” he adds, “that what is accepted as evidence-based care is not being delivered to our patients. Wales does not have a single full-time stroke physician. All the physicians who care for stroke patients in Wales have significant general medical and care-of-the-elderly commitments.” He explains, “Their workload limits their ability to dedicate adequate time to develop and deliver a high-quality stroke service, and the lack of resources has limited the availability of important support services such as neuroradiology and the use of Doppler.

“There are organisations such as the British Geriatrics Society (Wales),” says Dr Shetty, “that formed a Stroke Interest Group in 1998 with the aim of improving stroke services in Wales. The group organises the Welsh Stroke Conferences; members have contributed to the stroke section of the United Kingdom’s National Service Framework, and they have also been working closely with the United Kingdom Stroke Association. They have also met the chief medical officer, and Welsh Assembly members have been approached to seek their support to improve stroke care in Wales.”

The Stroke Interest Group conducted a comprehensive review of stroke services in Wales between August and September 2006. This review identified gaps in services in all the major hospitals in Wales. Some of the local health boards are currently in discussion with trusts and clinicians to implement some of the key elements of an evidence-based stroke service. But Dr Shetty points out, “Lack of resources is likely to be an important limiting factor. The sad fact is that, as things stand, Welsh stroke patients are more likely to die or become disabled than patients elsewhere in the United Kingdom. This was pointed out by the audit.”

Dr Shetty notes that patients admitted to the hospital during the weekend often had to wait until the next working day for a brain scan to determine their treatment (Figure 1); in the

Figure 1. Computerised tomography scan of the brain showing a thrombosis of the right middle cerebral artery. In some Welsh centres such an investigation may be delayed by up to 72 hours.
worst instances, such delays can take as long as 72 hours. None of the major hospitals in North Wales could perform computerised tomography of the brain within 3 hours, according to the Stroke Interest Group’s audit of September 2006, although negotiations are ongoing with neuroradiologists to address the issue of early tomography.

“Stroke care in the wider community is also variable,” says Dr Shetty, “but in some areas general practitioners have developed care pathways for referring transient ischaemic attack and stroke patients to a stroke specialist in the local trust.”

He continues, “On the plus side, some hospitals in Wales do deliver an excellent service, and a stroke research and development group is currently being set up under the aegis of the Old People and Ageing Network.” Plans also are underway to develop a training programme for specialist registrars in stroke medicine in Wales.

“But what I really want to see,” says Dr Shetty, “is the development of specialised stroke units in all major Welsh hospitals and the availability of rapid access stroke prevention clinics in all hospitals.” At present, only 8 out of 20 hospitals have specialist stroke units (Figure 2), and only 10 out of 20 hospitals have some form of stroke prevention service.

“The people of Wales and the politicians need to recognise the importance of stroke as a health issue,” Dr Shetty says. “We know what the gaps are in our service, and we also have evidence-based guidelines that, if implemented, will improve the outcomes of our patients. Support for healthcare providers from the Welsh Assembly government to implement the National Service Framework will certainly go a long way.”

He explains, “As a clinician, I would like to see improvements in services as soon as possible, as our patients are dying and becoming disabled unnecessarily. Realistically speaking, it is probably going to take at least a couple of years before we catch up with the rest of the United Kingdom.

“Compared with the United States and other advanced countries in Europe,” Dr Shetty believes, “Wales is doing very poorly, with only 1 hospital currently planning to start a 9 AM-to-5 PM thrombolysis service.” He also points to a very limited availability of interventional treatments.

Asked whether the people of Wales are putting up with third-world medicine in the United Kingdom for stroke care, he says, “We certainly are. The majority of stroke patients are frail and elderly. Their spouses and carers are often equally frail and elderly. They are neither physically capable nor politically powerful enough to protest about the less-than-optimal care they are receiving.” He continues, “They do not attract the same kind of attention as heart or cancer patients. It is imperative, therefore, that organisations such as the Stroke Interest Group and the Stroke Association fight for their cause, as they are doing.”

Dr Shetty expresses his disappointment that patients in Wales are missing out on treatments that could save them or make them less disabled, and he holds the political devolution process, which gave Wales its own parliament, partly responsible.

Dr Shetty says, “If you look at the progress that has occurred in terms of improvements in stroke care in England, our patients have certainly lost out because of devolution. Lack of political will to make stroke a priority, a delay in implementing the National Service Framework by the health commissioners, and the nonexistence of full-time stroke physicians have all contributed.” And as for the future for stroke care in Wales? “It can only improve,” says Dr Shetty. “I certainly hope that the improvements will happen sooner rather than later.”

Mark Nicholls is a freelance medical writer.

Reference