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Letter by Micheletti and Chevallier Regarding Article, "Hormone Therapy and Venous Thromboembolism Among Postmenopausal Women: Impact of the Route of Estrogen Administration and Progestogens: The ESTHER Study"
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Response to Letter Regarding Article, "Hormone Therapy and Venous Thromboembolism Among Postmenopausal Women: Impact of the Route of Estrogen Administration and Progestogens: The ESTHER Study"
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European Perspectives:

European Perspectives
Circulation 2007 116: 73F - 78F, doi:10.1161/CIRCULATIONAHA.107.186287

Ventricular proarrhythmia is a major hurdle in drug development for therapy for atrial fibrillation. The cardiac sodium current that is a determinant of conduction and excitability in atrium and ventricles is a target for many antiarrhythmic drugs. Sodium-current blockers can suppress atrial fibrillation in some patients, but an adverse impact on mortality rate was observed with some agents administered after myocardial infarction. The recently approved antianginal drug ranolazine is a sodium-channel blocker without adverse mortality effects in human trials. Burashnikov and coworkers compared the electrophysiological effects of ranolazine in canine atrial and ventricular muscle. The drug’s interesting sodium channel-blocking effects and prolongation of action potential duration were greater in the atrium than in the ventricles. Ranolazine had efficacy against atrial fibrillation in tissue models. Selective blockade of atrial sodium channels appears to be a feasible target that warrants further exploration for treating atrial fibrillation without ventricular proarrhythmic effects. See p 1449.

EFFECT OF DISTAL EMBOLIZATION ON MYOCARDIAL PERFUSION RESERVE AFTER PERCUTANEOUS CORONARY INTERVENTION: A QUANTITATIVE MAGNETIC RESONANCE PERFUSION STUDY, by Selvanayagam et al.

The high resolution of cardiac magnetic resonance imaging and the use of the delayed enhancement technique have suggested that after percutaneous coronary intervention (PCI), small new areas of necrosis may be seen in the vascular bed distal to the stented stenosis. In this issue of Circulation, Selvanayagam and colleagues assess changes in perfusion reserve after PCI and the effect of new local myocardial injury on perfusion reserve. They found that at 24 hours after the PCI procedure, perfusion reserve improves in normal myocardium. In segments with new distal injury, however, perfusion reserve is further impaired after PCI although it generally recovers at 6 months. The high resolution of cardiac magnetic resonance allowed the authors to demonstrate that the blunting of perfusion reserve was limited to the local territory showing evidence of new injury, but that was not observed within the same vascular territory upstream to the injury, suggesting a local microvascular process. These data extend the knowledge of post-PCI perfusion and vascular changes, and illustrate how advanced imaging modalities enhance the study of pathophysiology. See p 1458.

CLINICAL CHARACTERISTICS OF DIALYSIS PATIENTS WITH ACUTE MYOCARDIAL INFARCTION IN THE UNITED STATES: A COLLABORATIVE PROJECT OF THE UNITED STATES RENAL DATA SYSTEM AND THE NATIONAL REGISTRY OF MYOCARDIAL INFARCTION, by Herzog et al.

In a comparative analysis of 3049 patients with acute myocardial infarction in the United States Renal Data System and 534 395 patients in the National Registry of Myocardial Infarction, dialysis patients were shown to have less frequent chest pain and ST elevation. Patients on dialysis were less frequently eligible for reperfusion, but of these, only 47% received some type of reperfusion compared with 75% of patients who were not on dialysis. Non-acute percutaneous coronary intervention was performed in 8.2% of patients versus 18.6%, and evidence-based therapies including aspirin, β-blockers, and angiotensin-converting enzyme inhibitors were less frequently used. Renal dialysis patient outcomes were worse than those in non-dialysis patients. In a logistic regression model, the odds ratio for in hospital mortality was 1.498 (95% confidence interval, 1.340–1.674) as compared with 534 395 patients not on dialysis. These data highlight the difficulties of making an initial diagnosis of acute myocardial infarction in patients on dialysis and the under-treatment of this high risk cohort. See p 1465.

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Images in Cardiovascular Medicine

Angiography of an Aneurysmal Aorto–Left Ventricular Tunnel. See p e356.

Vegetation Stalagmite in Left Atrium. See p e358.

Correspondence

See p e361.
Treatment of congestive heart failure by artificial pacing first attracted attention in the early 1990s when reports showed that standard right ventricular apical pacing with a shortened atrioventricular delay improved heart function in a subgroup of patients.\textsuperscript{1} However, few seemed to benefit from this approach,\textsuperscript{2} whereas by altering the pacing site to the left ventricle and using biventricular stimulation in patients with intramyocardial conduction delay, one achieved more consistent functional improvement.\textsuperscript{3,4} The short-term response was greater in patients with a wider QRS complex, typically a left bundle branch pattern,\textsuperscript{5} and subsequent clinical trials that showed biventricular pacing improved morbidity\textsuperscript{6,7} and mortality\textsuperscript{8} principally selected only those patients with a prolonged QRS duration.

However, the story was never that straightforward, as investigators found that the correlation between basal QRS duration and immediate mechanical responses to biventricular pacing was poor\textsuperscript{9} and not predictive of long-term outcome.\textsuperscript{9} QRS narrowing after cardiac resynchronization therapy (CRT) was not useful either.\textsuperscript{10,11} Furthermore, patients without at least a 20% improvement in mechanical dyssynchrony did not respond long term to CRT. The primary conclusion was that you need to have some CR if you are going to benefit from CRT.

The present study by Bleeker et al raises a number of interesting issues. First, the percentage of responding patients defined by a reduced ESV was 85%, higher than the \( \approx 65\% \) rate often reported. Indeed, with the use of more liberal criteria (\( >15\% \) decline in ESV), this same group\textsuperscript{17} and others\textsuperscript{18-19} previously reported 55% to 65% response rates. Furthermore, the magnitude of ESV decline was \( \approx 30\% \), 2 to 3 times the average change reported in prior CRT studies.\textsuperscript{14,20,21} One difference is that patients in the present trial had to have both a long QRS and basal dyssynchrony (\( >65 \) ms delay by tissue Doppler imaging), whereas prior studies only used a long QRS duration as the criterion. This supports the notion that subjects with both electrical and mechanical evidence of intraventricular delay are the most likely to respond to CRT.

What about the actual relationship between resynchronizing the left ventricle and observing a long-term decline in ESV—is the former mandatory as claimed? Perhaps it is, though the magnitude of one does not appear to be very predictive of the magnitude of the other. Although an overall correlation existed between the reduction of mechanical dyssynchrony and long-term lowering of ESV (Figure 4 in the article by Bleeker et al\textsuperscript{15}), this was driven by the patients with \( \leq 30\% \) change in synchronization. For the nearly 90% of patients with change above this level, the results were widely scattered with minimal correlation between variables. Approximately 10 patients fell at or just above the 10% ΔESV cut-off yet had impressive resynchronization. So, although mechanical resynchronization may indeed be required to reverse chronic chamber dilation (ie, reduces ESV), it is not

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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necessarily sufficient. Another issue is that this graph depicts percentage changes, and >80% reduction of dyssynchrony in an individual with a marked basal delay likely means something quite different than in an individual whose basal dyssynchrony was much less.

Another important factor is how one defines a responder. The choice of a ≥10% decline in ESV was based on a recent study of 141 dilated heart failure patients with QRS >120 ms who received CRT. After receiver-operator curve analysis, the authors found that a 9.5% decline in ESV provided the best sensitivity and specificity for all-cause (70% for both) and cardiovascular (89% and 67%, respectively) mortality. This was more predictive than clinical symptoms. However, the latter are ultimately what patients and their doctors must confront, and improvement of symptoms is arguably a primary goal for heart failure treatment. We do not know how the current analysis would look if a clinical end point had been chosen. The ∼10% ΔESV range is similar to that achieved by other therapies that improve mortality, such as β-blockers and angiotensin inhibitors. However, this numeric cut-off is not so black and white, and the presence of another 10% of patients at or just above this cut-off in the present study suggests that fewer clinical responders than presumed may exist even in this group. If so, this would be interesting because it suggests that, even with evidence of mechanical resynchronization, additional complexities exist that ultimately determine how well a patient responds to CRT. These complexities could include the underlying myocardial disease, severity of molecular abnormalities, excitation-contraction coupling, loss of viable myocytes, arrhythmogenicity, fibrosis and/or scar tissue, and other factors.

Although the findings from Bleeker et al support the reduction of mechanical dyssynchrony as a key target for long-term CRT benefit, this reduction is less directly applicable to the identification of candidates because patients must already be treated by CRT to reveal the resynchronization effect. In earlier work, Bax et al reported that simply by use of a tissue Doppler imaging delay of >65 ms (required for inclusion in the present study), one achieved a 92% sensitivity and specificity for prediction of >15% long-term decline in ESV. On the basis of this finding, all but 8% of the subjects in the present study should have had at least a 15% decline in ESV, yet, as seen in Figure 4, ~30% fell below this range. This highlights the continued need for larger, prospective, multicenter, blinded analyses that use several proposed dyssynchrony indexes to determine their ultimate predictive value for CRT outcome. Use of the <20% change in dyssynchrony threshold in the present study improved the negative predictive accuracy to 100%, yet, as noted, this result depended on the exact ΔESV threshold used to distinguish responders from nonresponders. One could argue that the results support more efforts to assess mechanical changes during lead implantation itself with the use of an external stimulator to test the effects. Lack of any demonstrable resynchronization effect despite various left ventricular lead positions would be a criterion not to implant. Efforts have been made to assess regional motion during implantation itself, but this assessment is difficult. New technologies may provide surrogate wall motion signals, but these remain under development. Global hemodynamic surrogates such as arterial pulse pressure change, which reflects, in the short term, improved cardiac output, or change in dP/dt max have also been explored to a limited degree. Change in dP/dt max with CRT correlates with basal values and with the severity of dyssynchrony and perhaps the combination of this measure with electrical and wall timing parameters can improve a predictive index. An ability to vary the left ventricular stimulation site and thus modify implementation would be desirable to make full use of such information.

Finally, the present results pose an interesting contrast to pharmacological treatments for heart failure, where short-term changes have rarely been predictive of long-term efficacy. The prime example is β-blockade, where short-term effects are directionally opposite to those observed over the long term. Although some investigators have made a broad conclusion that short-term responses can never predict treatment efficacy because the disease is simply too complex, the experience with CRT suggests that this may have more to do with what is being targeted. As shown early on, the impact of CRT on resynchronization is immediate, within a single beat, and is achieved by its direct modulation of wall motion timing and mechanics. Although other changes such as reduction of chamber size and exertional improvement undoubtedly involve a more complex interplay between this direct effect and the underlying heart failure pathophysiology, if you do not achieve the first part then it seems very unlikely that you will achieve the second. The present study highlights this and should further efforts to identify optimal candidates. We have a good idea of what we can achieve in the short term, and the new evidence that this effect changes little over time yet predicts long-term remodeling is reassuring. We still need to better standardize measurements of dyssynchrony, make them as objective and reproducible as possible, and consider them in the context of electrical and global mechanical behavior to improve their predictive accuracy. If we can do this, we should be able to improve CRT patient selection.

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Disclosures

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References


Key Words: Editorials ▪ heart failure ▪ pacing ▪ remodeling ▪ Doppler imaging ▪ electrical stimulation
What Exactly Do the Trends Mean?

Bonita Falkner, MD

A lthough the adverse public health and economic consequences of obesity have been reported for some time, little success has been achieved in controlling the progressive increase in population prevalence and severity of obesity. The obesity epidemic in children is especially sobering. More than 17% of children are obese, and these rates have increased with each new survey. A consequence of childhood obesity has been the premature onset of diseases associated with obesity. The chronic disorders of hypertension, type 2 diabetes mellitus, and sleep apnea, which had been considered conditions of middle to late adulthood, now appear in childhood. When the cardiovascular morbidity associated with these conditions is considered, the health impact of childhood-onset hypertension or diabetes mellitus is likely to be enormous.

The extent to which childhood obesity could contribute to an increase in the prevalence of hypertension was studied in a report in this issue of Circulation. Din-Dzietham et al1 conducted a study in which they examined the secular trend in the prevalence of high blood pressure (BP) among children and adolescents to determine if the rise in childhood obesity contributes to an increase in the prevalence of high BP. Data were drawn from serial health surveys conducted by the National Center for Health Statistics between 1963 and 2002 on a representative sample of the noninstitutionalized civilian US population. Data on children between the ages of 8 to 17 years, which included measurement of BP, were the focus of their analysis. The investigators applied the current BP criteria for hypertension and prehypertension in childhood to the data from the participants in each of the 6 survey periods between 1963 and 2002 to determine the prevalence of high BP in each survey period. The representations of non-Hispanic white, non-Hispanic black, and Mexican-American children were sufficient to compare rates and trends across the 3 race/ethnic groups. Childhood obesity markedly increased, from ≈7% in 1976–1980 to >11% in the 1988–1994 examination period, followed by a further increase to 17% in the 1999–2002 examination period. The prevalence of high BP increased between the 1988–1994 and the 1999–2002 examination periods, and the increase appeared to be attributable to the increase in obesity. The analysis by Din-Dzietham and colleagues also demonstrates racial disparities in that the recent unfavorable trends in both obesity and high BP have a substantially greater effect on non-Hispanic blacks and Mexican-Americans.

The most pertinent aspect of the report by Din-Dzietham et al1 is the current upward trend in the prevalence of high BP among children that is concurrent with an increase in childhood obesity. The present report is consistent with a recent report by Munter et al,2 who examined BP level as a continuous variable in adolescents from the same 2 recent National Health Surveys (1988–1994 and 1999–2002). Munter et al found a significant population increase in both systolic and diastolic BP, and they verified that the BP increase was most striking among minority groups. They also demonstrated that the population increase in BP among adolescents was largely, although not entirely, a result of the increase in body mass index. These reports provide evidence for the concept that secular trends in childhood obesity are setting the stage for increasing and premature cardiovascular disease within the US population.

The other intriguing aspect of the Din-Dzietham report is the extremely high rates of high childhood BP detected in the early surveys. As stated in the methods,1 the authors defined high BP according to the guidelines published in 2004 by the most recent Working Group on Hypertension in Children and Adolescents.2 Accordingly, high BP was defined as systolic and/or diastolic BP ≥95th percentile according to sex, age, and height. Prehypertension was defined as systolic and/or diastolic BP ≥90th percentile and <95th percentile; beginning at age 12 years the criteria for prehypertension included BP >120/80 mm Hg if the 90th percentile was >120 mm Hg systolic or >80 mm Hg diastolic. Clinical criteria for diagnosis of hypertension in childhood require the average BP to remain ≥95th percentile in repeat measurement on at least 3 separate visits. The reference population BP data from which the sex-, age-, and height-adjusted BP percentiles were derived are based on >63,000 children. These cumulative childhood BP data were drawn from multiple sources, which included the more recent National Health Surveys. When this current definition of childhood high BP was applied to the earlier surveys, the rates of high BP were astonishingly high. As shown in the Din-Dzietham report, the overall estimated prevalence of high BP among children in the 1963–1970 survey is 37.2%. In the 1971–1975 survey it decreases to 16.9%. The high childhood BP prevalence decreases further to 11.1% in the 1976–1980 survey, then to 4.7% in the 1982–1984 survey, and to the lowest level of 2.7% in the 1988–1994 survey, followed by an increase to 3.7% in the 1999–2002 survey period. On the basis of these results the authors state that a secular trend of decreasing rates of high BP existed among children from 1963–1994, after which...
the prevalence increased. However, it must be noted that the definition of high BP has not changed during that period.

What has changed is the body of normative BP data from which the BP percentiles were derived.

The National Health Surveys between 1963 and 1975 were conducted at a time when BP was rarely measured in healthy children. It was considered difficult to obtain reliable BP measurements, especially in young children, and it was generally believed that hypertension was uncommon in children and adolescents. Because clinicians had little notion of what constituted normal BP in children, when BP was measured, the adult criteria of 140/90 mm Hg were usually applied to define high BP.4,5 Sol Londe was the first clinician who attempted to define high BP in children according to some reference of normal child BP.6 He measured BP in healthy children in his own pediatric practice and observed an increase in BP level with age that was concurrent with growth and development. He then analyzed the BP data to determine the range of systolic and diastolic BP stratified by age and sex. To define high BP, he selected the systolic and diastolic BP at the 90th percentile for each year of age. He reported rates of hypertension that were slightly above 10%, which was consistent with his definition. He also noted that, on repeated measurement among those with high BP, regression toward the mean took place and that the prevalence of persistent systolic or diastolic BP >95th percentile was 1.9%. Moreover, on repeated measurement the children with high BP were often overweight and had a family history of hypertension.6 These observations are remarkably similar to the contemporary characteristics of childhood hypertension established by a larger body of data. What is different is the level of BP used to define hypertension in children.

Early reports on the normal BP range according to age throughout childhood described markedly different results.7 For example, the Londe report in 1966 computed the mean systolic BP for a 13-year-old boy at 120 mm Hg.6 The National Health Survey (1963–1970) described a mean systolic BP for a 13-year-old boy at 132 mm Hg.7 To reconcile the differing data on childhood BP and develop a uniform method to measure BP in the young, the National High Blood Pressure Education Program appointed a Task Force on Blood Pressure Control in Children. The purpose of this Task Force was to examine the available data on BP in children, describe a standard methodology for BP measurement, and define high BP in childhood. The Task Force published its first report in 1977.8 With the use of a statistical definition, the 95th percentile for age and sex was the recommended BP level for ascertainment of hypertension, if verified on repeated measurement. However, on the basis of the data provided in the 1977 report, by 13 years of age in boys the 95th percentile was 140 mm Hg systolic and 90 mm Hg diastolic, and by 18 years of age the 95th percentile was >150 mm Hg systolic and >95 mm Hg diastolic. These numbers seemed to be too high, particularly when considerably lower BP levels were reported from other sources.8 The National Heart, Lung, and Blood Institute recognized the need to obtain a larger body of data on BP in the young within the context of childhood growth and subsequently supported several epidemiological studies that prospectively investigated BP and growth in children and adolescents. These projects were conducted at several sites, applied rigorous detail to the methodology of BP measurement, and examined the anthropometric determinants of BP level relative to physiological development.

As these data emerged, a second Task Force on Blood Pressure in Children and Adolescents was convened to reexamine the data on BP distribution throughout childhood.10 With a substantially larger sample, the normal increase in BP with age remained, but the overall distribution of BP was lower, and the 95th percentile, which defined high BP, was substantially lower than that described in the previous report. In the second report, the 95th percentile for a 13-year-old boy was a systolic BP at 128 mm Hg and diastolic BP at 82 mm Hg. Subsequent to the second Task Force report, additional childhood BP data were developed from the National Health and Nutrition Examination Surveys (1988–1994 and 1999–2002). These data were added to the cumulative childhood BP data and reexamined in the next 2 Task Force Reports.11 With the additional data, the BP distribution curves and the BP levels for the 95th percentiles according to age did not change. However, the BP percentiles were further adjusted for height to define the 95th percentile by age, sex, and height percentile. The Table compares the BP level at the 95th percentile for a 13-year-old boy derived from data in the 1966 study by Londe to the BP level for the 95th percentile for a 13-year-old boy in the 4 Task Force Reports published between 1977 and 2004. As can be seen, the available data that were used to define the 95th percentile in the early surveys resulted in much higher BP levels. The 1987 Task Force Report had the advantage of a large body of data obtained with a uniform methodology and was thus able to create childhood BP distribution curves that have remained stable. Therefore, the downward trend in prehypertension and high blood pressure from 1963 to 1988, described by Din-Dzietham et al.,1 does not reflect a decrease in prevalence of high BP in children and adolescents. Rather, the downward trend reflects a progression toward a more accurate description of the normal BP distribution in childhood, which appears to have been achieved in the 1987 Task Force Report12 and further refined with height adjustments in the 1996 and 2004 reports.2,11 Therefore, the recent upward trend in prevalence of high BP in childhood, which appears to be related to the childhood obesity epidemic, is clearly indicative of a significant emerging public health problem.

### Disclosures

None.

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**BP Levels That Define High BP (95th Percentile) in a 13-Year-Old Boy From 1966 to 2004**

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*95th Percentile for height at median height. Range, 121/79 to 130/84.
References


Key Words: Editorials ■ blood pressure ■ children ■ hypertension ■ obesity
Left Ventricular Resynchronization Is Mandatory for Response to Cardiac Resynchronization Therapy
Analysis in Patients With Echocardiographic Evidence of Left Ventricular Dyssynchrony at Baseline

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Background—Recent studies have demonstrated that a positive response to cardiac resynchronization therapy (CRT) is related to the presence of preimplantation left ventricular (LV) dyssynchrony. The time course and the extent of LV resynchronization after CRT implantation and their relationship to response are currently unknown.

Methods and Results—One hundred consecutive patients scheduled for implantation of a CRT device were prospectively included if they met the following criteria: New York Heart Association class III to IV, LV ejection fraction \( \leq 35\% \), QRS duration \( \geq 120 \) ms, and LV dyssynchrony (\( \geq 65 \) ms) on color-coded tissue Doppler imaging. Immediately after CRT implantation, LV dyssynchrony was reduced from \( 114 \pm 36 \) to \( 40 \pm 33 \) ms \((P<0.001)\), which persisted at the 6-month follow-up (\( 35 \pm 31 \) ms; \( P=0.001 \) versus baseline; \( P=0.14 \) versus immediately after implantation). At the 6-month follow-up, 85% of patients were classified as responders to CRT (defined as \( >10\% \) reduction in LV end-systolic volume). Immediately after implantation, the responders to CRT demonstrated a significant reduction in LV dyssynchrony from \( 115 \pm 37 \) to \( 32 \pm 23 \) ms \((P<0.001)\). The nonresponders, however, did not show a significant reduction in LV dyssynchrony \( (106 \pm 29 \text{ versus } 79 \pm 44 \text{ ms; } P=0.08)\). If the extent of acute LV resynchronization was \( \geq 20\% \), response to CRT at the 6-month follow-up was never observed. Conversely, 93% of patients with LV resynchronization \( \geq 20\% \) responded to CRT.

Conclusions—LV resynchronization after CRT is an acute phenomenon and predicts response to CRT at 6-month follow-up in patients with echocardiographic evidence of LV dyssynchrony at baseline. (Circulation. 2007;116:1440-1448.)

Key Words: cardiac resynchronization therapy ▶ dyssynchrony ▶ imaging ▶ resynchronization

Cardiac resynchronization therapy (CRT) is considered an important breakthrough in the treatment of selected patients with drug-refractory heart failure. Recent large randomized trials have clearly demonstrated the beneficial effects of CRT on heart failure symptoms and left ventricular (LV) systolic function. In addition, CRT resulted in a reduction in heart failure hospitalizations and an improvement in survival.\(^1-4\) Despite these impressive results, a relatively high percentage of patients failed to respond to CRT.\(^1,5-7\) Approximately 30% of patients failed to show improvement in clinical symptoms, and 40% to 50% of patients had no improvement in LV function on echocardiography.\(^1,5-7\) Detailed analysis revealed that none of the established CRT selection criteria (New York Heart Association [NYHA] class III to IV, LV ejection fraction \( \leq 35\% \), and QRS duration \( >120 \) ms) were able to predict a positive response to CRT.\(^5,7\) Recent studies have indicated that the benefit from CRT is related to the presence of LV dyssynchrony before implantation.\(^5-10\) Indeed, patient selection based on echocardiographic detection of LV dyssynchrony resulted in a superior response rate compared with patient selection based on QRS duration alone.\(^5-10\) However, the presence of preimplantation LV dyssynchrony may not be the only determinant of response to CRT because some patients with preimplantation LV dyssynchrony still do not respond to CRT. It is currently unclear whether a reduction in LV dyssynchrony (LV resynchronization) after implantation of the CRT device is man-
datory for a positive response. Accordingly, a prospective analysis in patients with preimplantation LV dyssynchrony on color-coded tissue Doppler imaging (TDI) was performed to answer the following questions: (1) What is the time course of LV resynchronization after CRT; does LV resynchronization occur quickly or develop gradually over time? (2) What extent of LV resynchronization is obtained after CRT? (3) Is LV resynchronization necessary for response to CRT, and if so, which extent of LV resynchronization is the best predictor of response to CRT?

Methods

Study Population and Protocol
Consecutive heart failure patients scheduled for implantation of a CRT device were included in this study. The selection criteria for CRT included moderate to severe heart failure (NYHA class III or IV), LV ejection fraction ≤35%, and QRS duration >120 ms. In addition, patients had to show substantial LV dyssynchrony (≥65 ms) on TDI. Patients with a recent myocardial infarction (<3 months), decompensated heart failure, or unsuccessful LV lead implantation were excluded. Before CRT implantation, clinical status was assessed, and 2-dimensional echocardiography was performed to determine LV volumes and LV ejection fraction. Assessment of LV dyssynchrony with TDI was repeated immediately after CRT implantation and at a 6-month follow-up. The clinical status and changes in LV ejection fraction and LV volumes were reassessed at the 6-month follow-up.

Clinical Evaluation
Evaluation of clinical status included assessment of NYHA functional class, quality-of-life score (using the Minnesota Living With Heart Failure Questionnaire), and evaluation of exercise capacity with the 6-minute hall-walk test. All parameters were reassessed at the 6-month follow-up.

Echocardiography
Patients were imaged in the left lateral decubitus position with a commercially available system (Vingmed System Seven, General Electric-Vingmed, Milwaukee, Wis). Images were obtained with a 3.5-MHz transducer at a depth of 16 cm in the parasternal and apical views (standard long-axis, 2- and 4-chamber images). Standard 2-dimensional and color Doppler data triggered to the QRS complex were saved in cine-loop format. The LV volumes (end systolic, end diastolic) and LV ejection fraction were calculated from the conventional apical 2- and 4-chamber images using the biplane Simpson technique.

Patients with a reduction of >10% in LV end-systolic volume at the 6-month follow-up were considered responders to CRT. In addition, patients who died of progressive heart failure before the 6-month follow-up assessment were classified as nonresponders.

The severity of mitral regurgitation was graded semiquantitatively from color-flow Doppler in the conventional parasternal long-axis and apical 4-chamber images. Mitral regurgitation was characterized as follows: mild = 1+, jet area/left atrial area <10%, moderate = 2+, jet area/left atrial area 10% to 20%, moderately severe = 3+, jet area/left atrial area 20% to 45%, and severe = 4+ (jet area/left atrial area >45%). All echocardiographic measurements after CRT implantation were made with the device in active pacing mode.

LV Dyssynchrony Assessment With Color-Coded TDI
In addition to the conventional echocardiographic examination, TDI was performed to assess LV dyssynchrony. For TDI, color Doppler frame rates were >80 frames per second; pulse repetition frequen-
women with a mean age of 67±11 years. By definition, all patients had preimplantation LV dyssynchrony ≥65 ms (mean, 114±36 ms). The baseline characteristics of the patients are summarized in Table 1.

Immediately after CRT implantation, QRS duration was reduced from 168±27 to 151±25 ms (P<0.001). One patient died at 3 months after CRT implantation as a result of worsening heart failure. Accordingly, this patient did not have the follow-up assessment at 6 months and was classified as a nonresponder to CRT. In the remaining patients, a significant improvement in NYHA class was observed (from 3.0±0.2 to 2.0±0.5; P<0.001) at the 6-month follow-up. In addition, the quality-of-life score decreased from 38±16 to 19±15 (P<0.001), and the 6-minute walking distance increased from 292±108 to 407±100 m (P<0.001). Echocardiography at 6-month follow-up revealed a significant improvement in LV ejection fraction from 23±7% to 33±10% (P<0.001) and significant LV reverse remodeling, with a decrease in LV end-diastolic volume from 243±76 to 204±73 mL (P<0.001) and a decrease in LV end-systolic volume from 188±71 to 136±63 mL (P<0.001).

Eighty-five patients (85%) showed a reduction of >10% in LV end-systolic volume at the 6-month follow-up and were therefore classified as responders to CRT.

LV Resynchronization After CRT

Immediately after CRT implantation, TDI demonstrated a reduction in LV dyssynchrony from 114±36 to 40±33 ms (P<0.001). At the 6-month follow-up, the reduction in LV dyssynchrony by CRT was sustained with an LV dyssynchrony of 35±31 ms (P<0.001 versus baseline, P=0.14 versus immediately after implantation) (Figure 1).

Although the reduction in LV dyssynchrony after CRT was highly significant, with an immediate reduction in LV dyssynchrony of 65% and a 69% reduction at the 6-month follow-up, not all patients experienced a similar extent of LV resynchronization. The distribution of the extent of immediate LV resynchronization after CRT is displayed in Figure 2. In most patients, CRT induced a ≥60% reduction in LV dyssynchrony both immediately after implantation (n=61, 61%) and at the 6-month follow-up (n=67, 67%). In other patients, however, CRT resulted in only a minimal reduction or even an increase in LV dyssynchrony, although this occurred in <10% of all patients (Figure 2). The percentage of acute LV resynchronization was not different between the patients with sinus rhythm or atrial fibrillation (66±30% versus 63±30%; P=0.74) or between patients with ischemic or nonischemic cardiomyopathy (62±29% versus 68±30%; P=0.46).

LV Resynchronization Versus Response to CRT

As indicated above, 85 patients (85%) showed a reduction of >10% in LV end-systolic volume at the 6-month follow-up and were therefore classified as responders to CRT. Fourteen patients (14%) had a reduction ≤10% in LV end-systolic volume.

### TABLE 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67±11</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td>Male 86 (86)</td>
</tr>
<tr>
<td></td>
<td>Female 14 (14)</td>
</tr>
<tr>
<td>Origin, n (%)</td>
<td>Ischemic 59 (59)</td>
</tr>
<tr>
<td></td>
<td>Nonischemic 41 (41)</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>168±27</td>
</tr>
<tr>
<td>Rhythm, n (%)</td>
<td>Sinus rhythm 89 (89)</td>
</tr>
<tr>
<td></td>
<td>Atrial fibrillation 11 (11)</td>
</tr>
<tr>
<td>NYHA functional class, n (%)</td>
<td>III 95 (95)</td>
</tr>
<tr>
<td></td>
<td>IV 5 (5)</td>
</tr>
<tr>
<td>Medication, n (%)</td>
<td>Diuretics 88 (88)</td>
</tr>
<tr>
<td></td>
<td>Angiotensin-converting enzyme inhibitors 92 (92)</td>
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<tr>
<td></td>
<td>β-Blockers 77 (77)</td>
</tr>
<tr>
<td>Quality-of-life score</td>
<td>38±16</td>
</tr>
<tr>
<td>6-Minute walking distance, m</td>
<td>292±108</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>23±7</td>
</tr>
<tr>
<td>LV end-diastolic volume, mL</td>
<td>243±76</td>
</tr>
<tr>
<td>LV end-systolic volume, mL</td>
<td>188±71</td>
</tr>
<tr>
<td>LV dyssynchrony, ms</td>
<td>114±36</td>
</tr>
</tbody>
</table>

Figure 1. Time course of LV resynchronization after CRT implantation in all patients (n=100).
volume, and 1 patient died of progressive heart failure before
the 6-month follow-up; these patients were classified as
nonresponders to CRT (15%).

At baseline, no significant differences were observed
between responders and nonresponders (Table 2). In partic-
ular, baseline LV dyssynchrony was similar between re-

**TABLE 2. Patients With LV Reverse Remodeling at the 6-Month Follow-Up
(Defined as a Reduction in LV End-Systolic Volume >10%; n=85) Versus
Patients Without LV Reverse Remodeling (Reduction in LV End-Systolic Volume
≥10%): Clinical and Echocardiographic Variables at Baseline and the
6-Month Follow-Up**

<table>
<thead>
<tr>
<th></th>
<th>LV Reverse Remodeling Present</th>
<th>LV Reverse Remodeling Absent*</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67±10</td>
<td>66±15</td>
<td>0.65</td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>73/12</td>
<td>13/2</td>
<td>0.74</td>
</tr>
<tr>
<td>Origin, ischemic/nonischemic</td>
<td>47/38</td>
<td>12/3</td>
<td>0.13</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>169±28</td>
<td>158±18</td>
<td>0.13</td>
</tr>
<tr>
<td>LV dyssynchrony, ms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>115±37</td>
<td>106±29</td>
<td>0.49</td>
</tr>
<tr>
<td>Follow-up (acute)</td>
<td>32±23†</td>
<td>79±44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>3.0±0.2</td>
<td>3.1±0.3</td>
<td>0.65</td>
</tr>
<tr>
<td>Follow-up</td>
<td>2.0±0.5†</td>
<td>2.6±0.5†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6-Minute walking distance, m</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>295±110</td>
<td>264±89</td>
<td>0.34</td>
</tr>
<tr>
<td>Follow-up</td>
<td>419±85†</td>
<td>337±151†</td>
<td>0.003</td>
</tr>
<tr>
<td>Quality-of-life score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>37±17</td>
<td>42±13</td>
<td>0.42</td>
</tr>
<tr>
<td>Follow-up</td>
<td>18±14†</td>
<td>28±16†</td>
<td>0.01</td>
</tr>
<tr>
<td>LV end-systolic volume, mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>190±69</td>
<td>170±79</td>
<td>0.43</td>
</tr>
<tr>
<td>Follow-up</td>
<td>130±59†</td>
<td>177±73</td>
<td>0.007</td>
</tr>
<tr>
<td>LV end-diastolic volume, mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>245±75</td>
<td>220±84</td>
<td>0.42</td>
</tr>
<tr>
<td>Follow-up</td>
<td>200±72†</td>
<td>231±80</td>
<td>0.14</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>23±7</td>
<td>24±7</td>
<td>0.57</td>
</tr>
<tr>
<td>Follow-up</td>
<td>34±9†</td>
<td>25±7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*One patient died before the 6-month follow-up.
†\( P<0.05\), follow-up vs baseline value.

**Figure 2.** Extent of the decrease in LV
dyssynchrony immediately after CRT
implantation.
sponders and nonresponders (115±37 versus 106±29 ms; \(P=0.49\)). The prevalence of ischemic cardiomyopathy was higher in the nonresponders, although this difference was not statistically significant (80% versus 55%; \(P=0.13\)). There was a trend toward a lower percentage of reduction in LV end-systolic volume at the 6-month follow-up between patients with ischemic versus nonischemic cardiomyopathy (24±21% versus 30±18% reduction in LV end-systolic volume, respectively; \(P=0.13\)). By definition, LV end-systolic volume did not decrease in the nonresponders at the 6-month follow-up (170±79 mL at baseline versus 177±73 mL at follow-up; \(P=0.19\)). In contrast, the responders showed a significant reduction in LV end-systolic volume from 190±69 to 130±59 mL (\(P<0.001\)). In addition, the nonresponders showed no improvement in LV ejection fraction (from 24±7% to 25±7%; \(P=0.64\)), whereas the responders improved from 23±7% to 34±9% (\(P<0.001\)) (Table 2).

An interesting observation was the difference in immediate LV resynchronization between the responders and nonresponders. The patients without response showed no significant reduction in LV dyssynchrony (from 106±29 to 79±44 ms; \(P=0.08\)), whereas the responders demonstrated a significant reduction in LV dyssynchrony from 115±37 to 32±23 ms (\(P<0.001\)) (Figure 3).

In the multivariable regression analysis, 3 variables were related to the absolute change in LV end-systolic volume at the 6-month follow-up (\(r=0.59\), \(P<0.001\)): the extent of immediate LV resynchronization (\(P<0.001\)), baseline LV end-diastolic volume (\(P<0.001\)), and baseline severity of mitral regurgitation (\(P=0.02\)). In the multivariable logistic analysis including all studied variables (including patient age, gender, cause of heart failure, QRS duration, NYHA class, quality-of-life score, 6-minute walking distance, LV ejection fraction, LV end-systolic volume, LV end-diastolic volume, mitral regurgitation, LV dyssynchrony, and presence or absence of acute LV resynchronization), immediate LV resynchronization was the only variable that was predictive of response to CRT at the 6-month follow-up.

Linear regression analysis demonstrated a significant relationship between the immediate reduction in LV dyssynchrony and the reduction in LV end-systolic volume at the 6-month follow-up (\(y=0.29x+8\); \(r=0.41\); \(n=99\); \(P<0.001\)) (Figure 4).

Of interest, when patients showed <20% LV resynchronization \((n=9)\) immediately after CRT, response to CRT never occurred. In the patient who died of progressive heart failure before the 6-month follow-up assessment, LV dyssynchrony showed an immediate increase from 140 to 160 ms. Conversely, 85 of 91 patients with ≥20% LV resynchronization immediately after CRT implantation...
TABLE 3. Baseline Characteristics in Patients With LV Resynchronization (≥20% Reduction in LV Dyssynchrony; n=91) Versus Patients Without LV Resynchronization (n=9)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Resynchronization Present</th>
<th>Resynchronization Absent*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67±10</td>
<td>65±17</td>
<td>0.64</td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>79/12</td>
<td>7/2</td>
<td>0.81</td>
</tr>
<tr>
<td>Origin, ischemic/nonischemic</td>
<td>53/38</td>
<td>6/3</td>
<td>0.89</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>169±28</td>
<td>157±17</td>
<td>0.24</td>
</tr>
<tr>
<td>LV dyssynchrony, ms</td>
<td>114±37</td>
<td>112±24</td>
<td>0.87</td>
</tr>
<tr>
<td>NYHA class</td>
<td>3.0±0.2</td>
<td>3.1±0.3</td>
<td>0.36</td>
</tr>
<tr>
<td>LV end-systolic volume, mL</td>
<td>187±70</td>
<td>197±79</td>
<td>0.70</td>
</tr>
<tr>
<td>LV end-diastolic volume, mL</td>
<td>241±76</td>
<td>255±84</td>
<td>0.60</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>23±7</td>
<td>23±7</td>
<td>0.87</td>
</tr>
<tr>
<td>LV lead position, n (%)</td>
<td>2 (2)</td>
<td>3 (33)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Anterior</td>
<td>42 (46)</td>
<td>3 (33)</td>
<td></td>
</tr>
<tr>
<td>Posterior</td>
<td>44 (48)</td>
<td>3 (33)</td>
<td></td>
</tr>
<tr>
<td>Lateral</td>
<td>2 (2)</td>
<td>3 (33)</td>
<td></td>
</tr>
</tbody>
</table>

*One patient died before the 6-month follow-up.

responded to CRT at the 6-month follow-up. Applying this cutoff value of 20% immediate LV resynchronization resulted in positive and negative predictive values of 100% and 93%, respectively, for the prediction of response to CRT at the 6-month follow-up, with an area under the curve of 0.84. Importantly, no differences were observed between the characteristics of the patients with and without immediate LV resynchronization, except that in patients without LV resynchronization, the LV lead was located more frequently in the anterior LV segments (2% versus 33%; P<0.01; Table 3). An interesting observation was that all patients without LV resynchronization and a posterior or lateral LV lead position had ischemic cardiomyopathy (n=6), whereas in the 3 patients with nonischemic cardiomyopathy, the LV lead was located in the anterior LV segments. Of the 9 patients without an immediate decrease in LV dyssynchrony (defined as an acute decrease of <20% in LV dyssynchrony), 5 patients showed an acute increase in LV dyssynchrony (from 108±31 to 124±29 ms; P<0.05). The LV lead position was in the anterior LV segments in 2 patients, in the lateral segments in 2 patients, and in the posterior LV region in 1 patient. Immediately after CRT implantation, the patients without acute LV resynchronization did not demonstrate a reduction in QRS duration (from 157±17 to 152±27 ms; P=0.69), whereas the patients with acute LV resynchronization had a significant reduction in QRS duration (from 169±28 to 151±24 ms; P<0.001).

At the 6-month follow-up, the patients with immediate LV resynchronization had a significant reduction in mitral regurgitation grade at the 6-month follow-up (from 1.8±1.3 to 1.9±1.0; P=0.83).

Discussion

The main findings of the present study can be summarized as follows. First, LV resynchronization after CRT occurs acutely and is sustained at 6 months but without further resynchronization over time. Large interindividual variation in the extent of LV resynchronization was observed, but the vast majority revealed >60% reduction in LV dyssynchrony immediately after CRT implantation. Finally, <20% resynchronization never resulted in response to CRT, whereas 93% of patients with ≥20% resynchronization responded to CRT at the 6-month follow-up.

Mechanism of Response to CRT

Recent studies have clearly demonstrated that the presence of substantial LV dyssynchrony before implantation is an important predictor of a response to CRT, which may be superior over the traditional selection criteria (severe heart failure, depressed LV function, and wide QRS complex). For example, Dohi et al demonstrated that the extent of LV dyssynchrony was the only preimplantation parameter that was different between responders and nonresponders to CRT; responders had significantly larger septal to posterior peak wall strain than did nonresponders (249±94 versus 137±136 ms; P<0.05).

In the present study, all patients had echocardiographic evidence of LV dyssynchrony, and the echocardiographic response rate (defined as a decrease of >10% in LV end-systolic volume at the 6-month follow-up) was indeed much higher (85%) than in previous studies that included patients selected according to the traditional CRT selection criteria; these studies reported echocardiographic response rates in the range of 50% to 55%. The present findings strongly support the use of echocardiographic selection of potential candidates for CRT.

The parameter for LV dyssynchrony used in the present study was derived previously from 85 heart failure patients undergoing CRT who were evaluated with color-coded TDI. Receiver-operating characteristics curve analysis revealed that LV dyssynchrony ≥65 ms (as determined from 4 basal LV segments) yielded a sensitivity and specificity of 92% to predict LV reverse remodeling after CRT implantation. On the basis of this predefined cutoff value, only patients with evidence of LV dyssynchrony ≥65 ms on TDI were included in the present study.

The definition of response used in the present study (reduction >10% in LV end-systolic volume at the 6-month follow-up) was derived from a study by Yu et al, who studied 141 patients undergoing CRT and observed that a reduction in LV end-systolic volume after 3 to 6 months of CRT was the most important predictor of all-cause and cardiovascular death, whereas clinical parameters were unable to predict response to CRT. Receiver-operating characteristics curve analysis revealed that a cutoff value of 10% reduction in LV end-systolic...
volume was the optimal cutoff value for prediction of improved survival after CRT.

**Time Course and Extent of LV Resynchronization After CRT**

Various studies have reported on LV resynchronization after CRT. Most studies showed immediate resynchronization after CRT. For example, Breithardt et al. studied the acute effects of CRT on the extent of LV dyssynchrony in 34 patients by using echocardiographic phase analysis. Immediately after implantation, a 37% decrease in LV dyssynchrony was observed (from 104°±41° to 66°±42°; \( P<0.001 \)).

However, the time course of LV resynchronization during follow-up is currently unknown, and the question of whether initial LV resynchronization is followed by a further reduction in LV dyssynchrony is unanswered. The present findings clearly demonstrate that LV resynchronization is an acute phenomenon that occurs immediately after CRT implantation. At a mid-term follow-up, the extent of immediate LV resynchronization is sustained, but a further reduction in LV dyssynchrony could not be demonstrated (Figure 1). An interesting observation is the high interindividual variation in the extent of immediate LV resynchronization after CRT implantation. Although most patients demonstrated ≥60% reduction in LV dyssynchrony, some patients demonstrated only a minimal amount of LV resynchronization or even experienced an increase in LV dyssynchrony.

**Lack of LV Resynchronization**

In search for optimal prediction of response to CRT, previous studies have shown that patients with LV dyssynchrony have a relatively high likelihood of responding to CRT, whereas patients without LV dyssynchrony do not respond, although not all patients with LV dyssynchrony responded to CRT. In the present study, patients were selected on the basis of the presence of LV dyssynchrony before CRT implantation, resulting in a high response rate (85%), but 15% of patients still did not respond. Comparison of responders and nonresponders revealed no differences in baseline clinical and echocardiographic characteristics (Table 2). Interestingly, further analysis of the individual patient data revealed that the extent of immediate LV resynchronization can be used to optimize the prediction of response. Patients with <20% reduction in LV dyssynchrony never responded to CRT. In contrast, patients with LV resynchronization ≥20% had an excellent response rate of 93%.

Although the number of patients without LV resynchronization in the present study is low (n=9), a suboptimal position of the LV pacing lead appears to be related to the lack of LV resynchronization. Rossillo et al. recently demonstrated in 233 consecutive patients that placement of the LV pacing lead in the lateral or posterolateral branches of the coronary sinus was associated with a superior improvement in LV function (LV ejection fraction from 19% to 27%; \( P<0.05 \)) compared with patients with an anterior LV pacing lead location (LV ejection fraction from 18% to 20%; \( P=\text{NS} \)).

Recent data have indicated that in heart failure patients the posterolateral LV segments are usually the latest activated LV segments. Pacing the left ventricle outside the area of latest activation resulted in less improvement in LV ejection fraction and LV volumes than did pacing in the area of latest activation. Murphy et al. demonstrated that pacing the LV in a remote area (eg, the anterior LV segments) even resulted in a worsening of LV volumes, with a 9% increase in LV end-systolic volume during follow-up. The present study demonstrated that minimal or absent LV resynchronization may be a potential mechanism for the lack of benefit from CRT in patients with suboptimal LV lead positioning.

A second potential explanation for a lack of LV resynchronization may be the presence of large areas of scar tissue throughout the left ventricle (total scar burden) or the presence of scar tissue in the area of the LV pacing lead. Bleeker et al. recently demonstrated in 40 patients that CRT is unable to reduce LV dyssynchrony (from 84±46 to 78±41 ms; \( P=\text{NS} \)) in the presence of scar tissue in the posterolateral LV segments. As a result, the (clinical) response rate to CRT in patients with posterolateral scar tissue was poor (11%), whereas patients with severe baseline LV dyssynchrony without posterolateral scar tissue had an excellent (clinical) response rate of 95%. In addition, several studies have recently demonstrated that the amount of LV scar tissue is highly predictive for response to CRT regardless of baseline LV dyssynchrony. The presence of scar tissue most likely prevents a normal activation of the myocardium because the activation front is delayed or stopped by large areas of scar tissue, resulting in lack of LV resynchronization. A potential beneficial treatment strategy in patients without initial LV resynchronization is V-V delay optimization. Previous studies have shown that optimization of the V-V pacing delay may result in a (further) reduction in LV dyssynchrony and may therefore be beneficial in patients without initial LV resynchronization. Interestingly, Leon et al. demonstrated that patients with a history of myocardial infarction more frequently benefit from LV preexcitation during V-V optimization, which may be the additional activation delay caused by large amounts of scar tissue. In the present study, V-V optimization was not performed before the 6-month follow-up assessment, which may be considered a limitation.

In addition, whether repositioning of the LV lead to the area of latest activation or to an area without myocardial scar tissue will result in LV resynchronization in patients without an initial reduction in LV dyssynchrony needs further study.

**Study Limitations**

Although none of the patients with acute LV resynchronization <20% responded to CRT (in contrast to a response rate of 93% in patients with acute LV resynchronization ≥20%), the cutoff value of a 20% acute reduction in LV dyssynchrony needs further validation.

In recent years, a wide variety of echocardiographic techniques, ranging from simple M-mode echocardiography to more advanced techniques such as TDI and strain imaging,
have been introduced for quantification of LV dyssynchrony. All techniques have been evaluated only in small, single-center studies, indicating the clear need for larger multicenter studies directly comparing the different techniques. In addition, the cutoff value of 65 ms for LV dyssynchrony measurement was validated in a single study. Further studies are required to confirm 65 ms as the optimal cutoff value for LV dyssynchrony assessment. Furthermore, the differentiation between passive myocardial motion and active contraction of LV segments is possible with strain or strain rate imaging but not with TDI. Still, TDI is among the most widely studied techniques for LV dyssynchrony assessment, with a high predictive value for response to CRT. The fact that the present study included only patients with echocardiographic evidence of LV dyssynchrony limits the generalizability of the study because the effects of CRT on LV dyssynchrony in patients without preimplantation LV dyssynchrony were not studied. The power to detect changes in the group without immediate response to CRT was limited by the small number of patients in this group.

Conclusions

In the present study, LV resynchronization after CRT is an acute phenomenon without further reduction in LV dyssynchrony during follow-up. Despite the presence of substantial LV dyssynchrony before implantation, patients with a <20% immediate reduction in LV dyssynchrony never showed response to CRT at the 6-month follow-up, which indicates that resynchronization is mandatory for response to CRT.

Source of Funding

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Disclosures

None.

References


CLINICAL PERSPECTIVE

Despite the impressive results of cardiac resynchronization therapy (CRT) in large randomized trials (including ≥4000 patients), ≈30% to 40% of patients who meet established patient selection criteria (New York Heart Association class III to IV, left ventricular [LV] ejection fraction ≤35%, and QRS duration >120 ms) fail to respond. Recent studies have found that the benefit from CRT is related to the presence of LV dyssynchrony before implantation. Indeed, patients who have echocardiographic evidence of LV dyssynchrony before CRT have better response rates. However, the presence of preimplantation LV dyssynchrony is not the only determinant of response because some patients with dyssynchrony before implantation still do not respond to CRT. It is currently unclear whether a reduction in LV dyssynchrony (LV resynchronization) after CRT implantation is mandatory for a positive response. The present study evaluates the effects of CRT on LV dyssynchrony and relates these effects to patient response in a group of patients with echocardiographic evidence of LV dyssynchrony (≥65 ms on tissue Doppler imaging). Our results show that LV resynchronization after CRT is an acute phenomenon. Despite the presence of substantial LV dyssynchrony before implantation, CRT that did not improve dyssynchrony immediately after implantation had a low likelihood of improvement during 6 months of follow-up. Thus, a reduction in LV dyssynchrony appears to be required for a favorable response to CRT. Potential explanations for a lack of LV resynchronization may include the presence of large areas of scar tissue throughout the left ventricle and suboptimal position of the LV pacing lead.
Atrium-Selective Sodium Channel Block as a Strategy for Suppression of Atrial Fibrillation

Differences in Sodium Channel Inactivation Between Atria and Ventricles and the Role of Ranolazine

Alexander Burashnikov, PhD; José M. Di Diego, MD; Andrew C. Zygmunt, PhD; Luiz Belardinelli, MD; Charles Antzelevitch, PhD

Background—The development of selective atrial antiarrhythmic agents is a current strategy for suppression of atrial fibrillation (AF).

Methods and Results—Whole-cell patch clamp techniques were used to evaluate inactivation of peak sodium channel current ($I_{Na}$) in myocytes isolated from canine atria and ventricles. The electrophysiological effects of therapeutic concentrations of ranolazine (1 to 10 $\mu$mol/L) and lidocaine (2.1 to 21 $\mu$mol/L) were evaluated in canine isolated coronary-perfused atrial and ventricular preparations. Half-inactivation voltage of $I_{Na}$ was $-15$ mV more negative in atrial versus ventricular cells under control conditions; this difference increased after exposure to ranolazine. Ranolazine produced a marked use-dependent depression of sodium channel parameters, including the maximum rate of rise of the action potential upstroke, conduction velocity, and diastolic threshold of excitation, and induced postrepolarization refractoriness in atria but not in ventricles. Lidocaine also preferentially suppressed these parameters in atria versus ventricles, but to a much lesser extent than ranolazine. Ranolazine produced a prolongation of action potential duration (APD$_{90}$) in atria, no effect on APD$_{90}$ in ventricular myocardium, and an abbreviation of APD$_{90}$ in Purkinje fibers. Lidocaine abbreviated both atrial and ventricular APD$_{90}$. Ranolazine was more effective than lidocaine in terminating persistent AF and in preventing the induction of AF.

Conclusions—Our study demonstrates important differences in the inactivation characteristics of atrial versus ventricular sodium channels and a striking atrial selectivity for the action of ranolazine to produce use-dependent block of sodium channels, leading to suppression of AF. Our results point to atrium-selective sodium channel block as a novel strategy for the management of AF. (Circulation. 2007;116:1449-1457.)

Key Words: action potentials • antiarrhythmia agents • atrial fibrillation • electrophysiology • pharmacology

Antiarrhythmic drug therapy remains the principal approach for suppressing atrial fibrillation (AF), atrial flutter (AFl), and their recurrence. Among the current strategies for suppressing AF/AFl is the development of antiarrhythmic agents that preferentially affect atrial rather than ventricular electrical parameters. Inhibition of the ultrarapid delayed rectified potassium current ($I_{Kur}$), present in atria but not ventricles, is an example of an atrium-selective approach. $I_{Kur}$ block selectively prolongs atrial repolarization and can suppress AF. The present study examines the hypothesis that sodium channel characteristics differ between atrial and ventricular cells and that atrium-selective sodium channel block is another effective strategy for the management of AF. Our study identifies ranolazine and, to a much lesser extent, lidocaine as agents that apparently can exploit the differences in sodium channel inactivation between atrial and ventricular cells. Ranolazine, an antianginal agent, has previously been shown in experimental models to possess antiarrhythmic properties in the ventricle related to inhibition of late sodium channel current (late $I_{Na}$). Results presented herein show that ranolazine exerts a potent atrium-selective use-dependent inhibition of the maximum rate of rise of the action potential upstroke ($V_{max}$) and other electrophysiological parameters dependent on the sodium channels underlying early $I_{Na}$, making it effective in suppression of AF in 2 experimental models.

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Methods

See the online-only Data Supplement (available with this article at http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.107.704890/DC1) for detailed information about the methods used.

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The online Data Supplement, consisting of expanded Methods with figures, can be found with this article at http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.107.704890/DC1.

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Circulation is available at http://circ.ahajournals.org DOI: 10.1161/CIRCULATIONAHA.107.704890
Experiments were performed using isolated arterially perfused canine right atrial (RA) preparations and left ventricular arterially perfused wedge preparations (∼2 × 1 × 1 cm), as well as superfused left ventricular epicardial and M-cell tissue slices (∼1 × 0.5 × 0.1 cm) and left and right ventricular Purkinje fibers. Transmembrane action potential (AP) recordings were obtained from standard or floating glass microelectrodes. A pseudo-ECG was recorded with 2 electrodes consisting of Ag/AgCl half-cells placed in the Tyrode’s solution, bathing the preparation 1.0 to 1.2 cm from the 2 opposite sides of the atrial or ventricular coronary-perfused preparations. Conduction velocity (CV) was measured in atria on the endocardial crista terminalis with 2 unipolar electrodes placed 1 cm apart. To directly compare atria and ventricles, changes in CV also were approximated by measuring the duration of the P-wave complex in atria and the QRs complex in ventricles on the ECG at a level representing 10% of P-wave or QRs amplitude. Diastolic threshold of excitation (DTE) was determined by increasing stimulus intensity in 0.01-mA steps. Effective refractory period (ERP) was measured by delivering premature stimuli after every 10th regular beat at pacing cycle lengths (CLs) of 500 and 300 ms (with 10-ms resolution; stimulation with a 2×DTE amplitude determined at each CL). Postpolarization refractoriness (PRR) was recognized when ERP exceeded AP duration measured at 90% repolarization (APD90) in the ventricle and APD3 in atria. Ventricular ERP coincided with APD20, whereas atrial ERP generally coincided with APD25.

Voltage Clamp of Atrial and Ventricular Myocytes

Whole-cell peak sodium currents were recorded at 37°C in low-sodium external solution from myocytes isolated from the right atrium and left ventricle of adult mongrel dogs, as previously described. The current–voltage relation was determined in external solution containing 1 mmol/L CaCl2 over a voltage range of −65 to −15 mV from a holding potential of −140 mV. Steady-state inactivation was measured with a standard dual-pulse protocol. Cells were held at −90 mV before evoking a 1-second conditioning pulse immediately followed by a 20-ms pulse to −30 mV to measure sodium current. Conditioning pulses ranged from −120 to −50 mV in increased in 10-ms steps. Current was normalized to the peak current recorded after a conditioning step to −120 mV. The normalized current was plotted as a function of conditioning step voltage and fit to a standard Boltzmann equation.

Drugs

Ranolazine (CV Therapeutics, Palo Alto, Calif), lidocaine, acetylcholine (ACh), and isoproterenol (Sigma, St Louis, Mo) all were dissolved in distilled water and prepared fresh as a stock of 1 to 10 mmol/L before each experiment.

Statistical Analysis

Statistical analysis was performed through the use of a paired or unpaired Student t test and 1-way repeated-measures or multiple-comparison ANOVA followed by Bonferroni’s test, as appropriate. All data are expressed as mean±SD. Statistical significance was assumed at P<0.05.

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

Results

Sodium Channel Inactivation Characteristics in Isolated Atrial Versus Ventricular Myocytes

The I-V relationship recorded from atrial and ventricular myocytes demonstrate both voltage control of the preparation and a greater density of sodium channels in atrial versus ventricular cells (∼−89.59±41.05 versus −50.20±3.34 pA/pF, respectively; P<0.001; n=6 to 8; Figure 1A). Current density peaked at −25 mV in atrial and at −35 mV in ventricular cells. The half-inactivation voltage (V1/2) in atrial myocytes was 16.2 mV more negative than that recorded in ventricular myocytes (−88.80±0.19 versus −72.64±0.14 mV; Figure 1B), indicating that a greater percentage of atrial versus ventricular sodium channels would be inactivated at a given resting or takeoff potential.

Because ranolazine has recently been identified as an inactivated-state blocker with little effect on peak Ina in ventricular myocardium at therapeutic concentrations, we hypothesized that this agent may exert a differential effect on sodium channels in canine atria versus ventricles, in light of the results illustrated in Figure 1B and the well-known fact that resting membrane potential (RMP) in atrial cells is less negative than in ventricular cells (Figure 2).

We first examined the effect of ranolazine on sodium channel inactivation using another set of atrial and ventricular myocytes. Ranolazine (15 μmol/L) caused an apparent shift in both atrial and ventricular inactivation curves, increasing the mean difference in V1/2 between atrial and ventricular cells from 13.82 to 16.57 mV (Figure 1C).

We next contrasted the electrophysiological effects of ranolazine with those of another inactivated-state sodium channel blocker, lidocaine, in ventricular and atrial coronary-perfused preparations. Clinically relevant concen-
trations of ranolazine (1 to 10 μmol/L) and lidocaine (2.1 to 21.0 μmol/L) were used.

Atrial and Ventricular APDs and Their Modulation by Ranolazine and Lidocaine
Ranolazine (1, 5, and 10 μmol/L) prolonged atrial APD₉₀ more so than APD₅₀, but produced no change in APD₉₀ (Figure 2 and Figures I and II in the Data Supplement). Ranolazine abbreviated APD in Purkinje fibers and caused little change in APD in ventricular wedges (Figure 2 and Figures I and II in the Data Supplement). Atrial APs, unlike those recorded from ventricular preparations, displayed a much slower late phase 3 (as previously reported⁸,⁹), resulting in a much more gradual approach to the RMP in atrial than in ventricular APs. These differences in late repolarization were further accentuated after exposure to ranolazine (Figure 2). Lidocaine (2.1, 10.5, and 21.0 μmol/L) abbreviated APD₉₀, APD₅₀, and APD₉₀ in ventricles. In atria, lidocaine abbreviated APD₉₀ and APD₅₀ but did not change APD₉₀ (Figure 2 and Figures I and II in the Data Supplement). Another distinguishing feature⁸,⁹ was a more positive RMP in atrial than in ventricular muscle and Purkinje fiber preparations (−83±2, −86±3, and −91±1 mV, respectively; P<0.05 between all; n=7 to 11; Figure 2). Ranolazine and lidocaine did not change RMP in any of the preparations tested.³

Effects of Ranolazine and Lidocaine on ERP, DTE, Vₘₐₓ, and CV
Under control conditions, atrial ERP corresponded to APD₇₅, whereas ventricular ERP corresponded to APD₉₀ (Figure 3), contributing to a shorter ERP in atria versus ventricles. Ranolazine prolonged atrial ERP much more than APD₇₅ in a rate-dependent manner, leading to the appearance of PRR in atria (Figure 3 and Figure III in the Data Supplement). In contrast, ranolazine produced little change in ventricular ERP; these changes were not rate dependent, and ERP remained equal to APD₉₀ (Figure 3 and Figure IV in the Data Supplement). Lidocaine prolonged atrial and to a lesser extent
ventricular ERP, leading to the appearance of a rate-dependent PRR in both the atria and the ventricles, but preferentially in the former (Figure 3 and Figure IV in the Data Supplement).

Atrial PRR developed cumulatively at faster rates. Ranolazine (10 μmol/L) and lidocaine (21 μmol/L) significantly prolonged the briefest S1-S1 permitting 1:1 atrial activation (see the Table). Ranolazine (10 μmol/L) and lidocaine (21 μmol/L) caused loss of 1:1 activation at a CL of 300 in 66% and 43% atrial, respectively, but in none of the ventricular preparations (Figure V in the Data Supplement).

Ranolazine caused a much greater rate-dependent reduction in the maximum rate of rise of the AP upstroke (Vmax), CV slowing, and increase in DTE (Figures 4 and 5 and Figures VI and VII in the Data Supplement) in atrial than ventricular preparations. Lidocaine also preferentially suppressed these parameters in atria versus ventricles, but to a much lesser extent than ranolazine (Figures 4 and 5 and Figures VI and VII in the Data Supplement).

We evaluated the rate of onset and recovery from use-dependent sodium channel block by measuring Vmax changes during acceleration and deceleration of pacing rate in the

![Figure 3](image_url)

Ranolazine specifically and lidocaine preferentially induce prolongation of the ERP and development of PRR (the difference between ERP and APD_{75} in atria and between ERP and APD_{90} in ventricles; ERP corresponds to APD_{75} in atria and APD_{90} in ventricles). CL=500 ms. Ventricular data were obtained from epicardium; atrial data, from pectinate muscle. The arrows in A illustrate the position on the AP corresponding to the end of the ERP in atria and ventricles (ERP is coincident with APD_{75} in atria and APD_{90} in ventricles) and the effect of ranolazine to shift the end of the ERP in atria but not ventricles. *P<0.05 vs control; †P<0.05 vs APD_{75} values in atria and APD_{90} in ventricles. n=5 to 18.

### Ranolazine (10 μmol/L) Versus Lidocaine (21 μmol/L) to Suppress Atrial Excitability and ACh-Mediated AF in the Isolated Canine Coronary Perfused Right Atria

<table>
<thead>
<tr>
<th>Treatment</th>
<th>APD_{90}, ms</th>
<th>ERP, ms</th>
<th>Shortest S1-S1, ms</th>
<th>Persistent AF, %</th>
<th>Termination of Persistent AF, %</th>
<th>Prevention of AF Recurrence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>204±11</td>
<td>158±17</td>
<td>129±8</td>
<td>0</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>RAN</td>
<td>228±14*</td>
<td>218±37*</td>
<td>295±32*</td>
<td>0</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>LID</td>
<td>193±8*</td>
<td>208±15*</td>
<td>276±39*</td>
<td>0</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>ACh (0.5 μmol/L)</td>
<td>43±10</td>
<td>58±8</td>
<td>73±8</td>
<td>100 (10/10)</td>
<td>0 (0/10)</td>
<td>…</td>
</tr>
<tr>
<td>ACh + RAN</td>
<td>68±18†</td>
<td>115±22†</td>
<td>181±57†</td>
<td>20 (2/10)</td>
<td>66 (4/6)</td>
<td>75 (3/4)</td>
</tr>
<tr>
<td>ACh + LID</td>
<td>57±14†</td>
<td>87±19†</td>
<td>128±42†</td>
<td>43 (3/7)</td>
<td>33 (2/6)</td>
<td>50 (1/2)</td>
</tr>
</tbody>
</table>

RAN indicates ranolazine; LID, lidocaine; and Shortest S1-S1, the shortest CL permitting 1:1 activation (at a DTE ×2 determined at a CL of 500 ms). Experiments to prevent AF and to terminate AF were performed in different atria. APD and ERP data presented in the table were obtained from the pectinate muscle region of coronary-perfused atria at a CL of 500 ms (n=6 to 18).

*P<0.05 vs control; †P<0.05 vs ACh alone; ‡P<0.05 vs ACh + LID.
presence of ranolazine and lidocaine. The rate constant of onset of use-dependent block, as well as its recovery, was significantly slower with ranolazine than lidocaine (Figure 6A and 6B). In the ventricle, the rate of onset of block was 0.12±0.03/AP for ranolazine and >1/AP (n=4 to 6) for lidocaine after acceleration of pacing rate from a CL of 5000 ms. V_{max} was not affected by ranolazine or lidocaine at a CL of 5000 ms. The time constant (τ) of recovery of V_{max} from cumulative use-dependent block developed at a CL of 300 ms in the ventricle was significantly longer in the presence of ranolazine (30 μmol/L) than lidocaine (21 μmol/L) (1.56±0.56 and 0.21±0.04 seconds, respectively; P<0.05; n=4 each; Figure 6C and 6D).

Long CLs could not be tested in atria because of sinus automaticity. To directly compare the differential responses of atria and ventricles, we determined the rate constant (k) of onset of use-dependent block after acceleration from a CL of 500 to 300 ms. The rate of ranolazine (10 μmol/L)--induced block in atria was faster than in ventricles (k=0.37±0.10/AP versus 0.24±0.11/AP, respectively; P<0.05; n=12 for each). Use-dependent block induced by lidocaine (21 μmol/L) developed much faster than that induced by ranolazine in both atria and ventricles (k >1/AP; n=10).

### Antiarrhythmic Effects of Ranolazine and Lidocaine

Premature electrical stimulation (a single premature stimulus) and rapid pacing (CL up to 80 ms for 3 to 10 seconds) did not induce arrhythmias under baseline conditions or in the presence of ranolazine (1 to 50 μmol/L) or lidocaine (2.1 to 21 μmol/L) in atrial (n=6 to 15) or ventricular (n=6 to 7) coronary-perfused preparations. Spontaneous arrhythmias were not observed under these conditions.

ACh (0.5 μmol/L) significantly abbreviated APD_{90} and ERP (see the Table). Both ranolazine and lidocaine blunted the effect of ACh to abbreviate APD, with ranolazine being slightly more effective than lidocaine (Table). In the presence of ACh alone, induction of persistent AF was observed in 100% of RA preparations (10 of 10). Ranolazine was more effective than lidocaine in preventing the initiation of ACh-mediated AF, terminating persistent AF, and preventing its reinduction (Table and Figure 7). In the presence of ACh, the effect of ranolazine to reduce excitability was better preserved than that of lidocaine (Table). Acceleration of pacing rate from a CL of 500 to 200 ms in the presence of ACh plus ranolazine (10 μmol/L) and ACh plus lidocaine (21 μmol/L) reduced V_{max} by 23±8% and 16±10%, respectively (P=0.06 versus by 2±3% with ACh alone; P<0.001 for each; n=8 to 9; Figure 7B). V_{max} reduction occurred despite the maintenance of relatively long diastolic intervals (Figure 7B).

The antifibrillatory effects of ranolazine were further evaluated in another model of AF. In 5 RAs subjected to ischemia (30 to 40 minutes) and subsequent reperfusion (40 to 60 minutes), the addition of isoproterenol (0.2 μmol/L) permitted reproducible induction of nonsustained AF/AFl (<1 minute). Note that β-adrenergic stimulation does not promote AF/AFl significantly in “healthy” atria.11 Ranolazine at a concentration of 5 μmol/L prevented the induction of arrhythmia in 3 of 5 RA preparations (Figure 7C). Arrhythmia induction was prevented by 10 μmol/L in 1 resistant RA preparation and by 20 μmol/L ranolazine in the other. Ranolazine caused a pronounced PRR in the ischemia/reperfusion-damaged RA preparations, which prevented closely coupled extrasystoles or rapid pacing (Figure 7C).

### Discussion

Our study demonstrates very significant differences in the inactivation characteristics of atrial versus ventricular sodium channels and a striking atrial selectivity for the action of ranolazine to produce use-dependent block of the sodium channels, leading to depression of excitability, development of PRR, and suppression of AF.

Our hypothesis that ranolazine could exploit the atrioventricular differences in sodium channel inactivation was derived in part from our previous demonstration that the action of the drug on sodium channel-dependent parameters (V_{max}) in the canine ventricle is negligible at therapeutic concentrations (1 to 10 μmol/L).4,14 and from the recent demonstration that the drug is an inactivated-state blocker.6 In support of the hypothesis that the presence of a greater percentage of atrial sodium channels in the inactivated state would enhance the action of the drug in the atria, we demonstrate a striking atrial selectivity in the actions of ranolazine to induce potent effects...
use-dependent effects on \( V_{\text{max}} \), DTE, PRR, and CV; these parameters are dependent on the sodium channels underlying early \( I_{\text{Na}} \), ie, peak (transient) \( I_{\text{Na}} \). Associated with these actions of the drug is its effectiveness to suppress and/or prevent the induction of AF in 2 experimental models. These data provide support for the hypothesis that atrium-selective sodium channel block may be an effective strategy for the management of AF.

Lidocaine, another predominantly inactivated-state sodium channel blocker,\(^7\) also produced an atrium-selective depression of sodium channel–dependent parameters (\( V_{\text{max}} \), CV, DTE, and PRR), providing support for the hypothesis that inactivated-state sodium channel blockers are likely to be atrium selective. It is noteworthy that lidocaine was much less atrium selective than ranolazine. Further evidence in support of the hypothesis derives from the demonstration that propafenone, a predominantly open-state sodium channel blocker,\(^7\) is not atrium selective.\(^12\)

**Ion Channel Inhibition Profile of Ranolazine and Lidocaine**

In isolated canine ventricular myocytes, ranolazine has been shown to inhibit a number of ion channel currents, including late \( I_{\text{Na}} \) (IC\(_{50}=6\ \mu\text{mol/L}\)),\(^3\) rapidly activating potassium-delayed rectifier (\( I_{\text{Kr}} \), IC\(_{50}=12\ \mu\text{mol/L}\)), and late L-type calcium (late \( I_{\text{Ca,L}} \), IC\(_{50}=50\ \mu\text{mol/L}\)); 25% to 30% reduction of late \( I_{\text{Ca,L}} \) is observed at 5 \( \mu\text{mol/L} \) ranolazine.\(^3\) Other potassium (\( I_{\text{Ks}}, I_{\text{to}}, I_{\text{K1}} \)), calcium (peak \( I_{\text{Ca}} \)), and Na–Ca exchanger currents are not affected by ranolazine or are affected at much higher concentrations, well beyond the therapeutic range of the drug (1 to 10 \( \mu\text{mol/L} \)).\(^3\) Previous studies also have shown that ranolazine blocks \( I_{\text{Na}} \) with an IC\(_{50}\) of 294 \( \mu\text{mol/L} \) in canine ventricular myocytes (at 0.1 Hz)\(^6\) and suppresses \( V_{\text{max}} \) with an IC\(_{50}\) of >100 \( \mu\text{mol/L} \) in Purkinje fibers and M-cell preparations paced at a CL of 500 ms.\(^3,4\) In sharp contrast, the results of the present study demonstrate prominent use-dependent reduction of \( I_{\text{Na}} \) (estimated from \( V_{\text{max}} \)) in atrial preparations at concentrations within the therapeutic range of ranolazine. Lidocaine is a fairly specific sodium channel blocker.\(^7\) Intrinsic atrioventricular differences in RMP and slope of late repolarization are largely explained by a smaller \( I_{\text{K1}} \) in atrial versus ventricular cells.\(^9\)

**Atrioventricular Differences in Sodium Channel Inactivation**

Our demonstration of 14- to 16-mV more negative half-inactivation voltage in atria versus ventricles in the canine heart (Figure 1) is qualitatively similar to that reported in the guinea pig heart, where the difference is 9.6±0.3 mV.\(^13\) These differences in biophysical properties suggest the possibility of tissue-specific cardiac sodium channel isoforms or differences in the stoichiometry of auxiliary subunits. Fahmi et al\(^14\) presented evidence in support of this hypothesis showing that SCN5B, a \( \beta \)-subunit of the sodium channel, is present in the ventricles but not in the atria of sheep hearts.

A larger density of \( I_{\text{Na}} \) in atrial versus ventricular myocytes, similar to that recorded in our study (at the holding potential of ~140 mV; Figure 1A), was reported for guinea pig myocytes.\(^13\) The larger maximum current density may offset
the intrinsically smaller sodium channel availability in atrial versus ventricular cells at physiological RMP (Figure 2).

Ranolazine as a Selective Atrial Sodium Channel Block Antiarrhythmic

In atria, unlike ventricle, ranolazine produces a significant reduction in excitability, leading to the development of a prominent rate-dependent PRR. PRR is a well-known feature of sodium channel blockers or conditions (like ischemia) that reduce excitability. Potassium channel blockers (such as I_Ks and/or I_Kr) prolong repolarization and refractoriness to a similar extent (in a reverse rate-dependent fashion) but do not cause PRR. Ranolazine as a Selective Atrial Sodium Channel Block Antiarrhythmic

There are intrinsic factors that predispose sodium channel current to inhibition by ranolazine and lidocaine in atria more effectively than in ventricular muscle or Purkinje fibers. The intrinsic differences are a more depolarized RMP and a less steep repolarization phase in atria, leading to a shorter diastolic interval at rapid rates (Figure 2). Ranolazine is more atrium selective than lidocaine in suppressing sodium channel–dependent parameters. This may be due in small part to the fact that ranolazine prolongs atrial but not ventricular APD_90, whereas lidocaine abbreviates both atrial and ventricular APD_90. The prolongation of atrial APD_90 by ranolazine leads to elimination of diastolic intervals and more depolarized takeoff potentials at rapid rates (Figure 4C). The more negative h curve in atria and acceleration-induced depolarization of takeoff potential act in concert to increase the fraction of channels in the inactivated state, making sodium channels less available and more sensitive to block by ranolazine. The result is a greater suppression of I_Na-dependent parameters such as V_{max}, DTE, and CV and the development of use-dependent PRR. The effect of ranolazine to prolong atrial repolarization potentiates but does not appear to be a determining factor in the atrial specificity and antiarrhythmic efficacy of ranolazine. Propafenone (I_Na and I_Kr blocker), like ranolazine, selectively prolongs atrial APD_90 but suppresses I_Na-dependent parameters in both the atrial and the ventricular preparations to a similar extent, as does GE 68, a propafenone analog. Lidocaine abbreviates both atrial and ventricular APD_90 but still shows an atrial selectivity in

Figure 6. Use-dependent binding/unbinding kinetics of ranolazine and lidocaine to the sodium channel in the ventricle approximated from depression and recovery of the maximum rate of rise of the AP upstroke (V_{max}). A, B, V_{max} changes after acceleration and deceleration of pacing rate in coronary perfused ventricular wedges. Both development of and recovery of use-dependent block are slower with ranolazine (30 μmol/L) than with lidocaine (21 μmol/L). C, D, Superimposed V_{max} deflections obtained during recovery intervals (pacing coupling intervals up to 5000 ms) after the use-dependent V_{max} depression at a CL of 300 ms. To be better able to discern measurable changes in V_{max} in the ventricles, the concentration of ranolazine was increased to 30 μmol/L for these experiments. Unbinding kinetics of sodium channel blockers are believed to be independent of drug concentration. Under control conditions, there is little to no change in V_{max} within the pacing CL range of 300 to 5000 ms.

Figure 7. Ranolazine suppresses AF and/or prevents its induction in 2 experimental models involving isolated arterially perfused right atria. A, Persistent ACh-mediated AF (0.5 μmol/L) is suppressed by ranolazine. AF is initially converted to flutter and then to sinus rhythm. B, Ranolazine prevents rapid-pacing induction of after pretreatment with ACh (0.5 μmol/L). ERP is 140 ms at a CL of 500 ms (left). Acceleration of pacing rate from a CL of 500 to 200 ms permits a 1:1 response only during the first 7 beats (right). C, Rapid-pacing–induced nonsustained AF (48-second duration) induced after ischemia/reperfusion and isoproterenol (ISO, 0.2 μmol/L) (left) and the effect of ranolazine to prevent pacing-induced AF (right). In both models, ranolazine causes prominent use-dependent induction of PRR.
depression of \( I_{Na} \)-dependent parameters. Also of note is the fact that PRR, the principal factor underlying the antiarrhythmic actions of ranolazine, extends well beyond the end of the AP (Figure 7).

Thus, the \( I_{Kr} \)-blocking effect of ranolazine potentiates the action of the drug to produce inactivated-state block of the sodium channel and thus its effectiveness in the management of AF. This effect of ranolazine also further differentiates it from lidocaine and contributes to its greater potency than lidocaine in the management of AF (Table). This greater potency appears to be due to a greater ability of ranolazine versus lidocaine to suppress atrial excitability when APD is abbreviated (Table).

Previous studies involving sodium channel blockers (quinidine, prajmaline, GE 68), including inactivated-state blockers (lidocaine), have failed to demonstrate atrioventricular differences in \( I_{Na} \) inhibition,\(^{6,16,17} \) comparable to those here reported with ranolazine, suggesting that ranolazine may be unique in this respect. Interestingly, AZD7009, which blocks \( I_{Kr}, I_{Na}, \) and \( I_{Kur} \), prolongs ERP and reduces DTE and CV preferentially in canine atria versus ventricles in vivo but produces similar \( V_{max} \) reduction in isolated superfused atrial and ventricular tissue preparations.\(^{18,19} \)

AVE-0118 and low concentrations of 4-AP (both preferentially block \( I_{Kur} \;/I_{Na} \)) produce an important prolongation of refractoriness in atria of dog and goat but negligible ventricular changes; these differences are explained by the presence of \( I_{Kur} \) in atria but not in ventricles.\(^{1,2} \) AVE-0118 suppresses AF in electrically remodeled atria of the goat.\(^{2} \) Ranolazine does not alter phase 1 magnitude of the atrial AP (Figure 2), suggesting that ranolazine is unlikely to block \( I_{Kur} \). Low concentrations of 4-AP, known to selectively block \( I_{Kur}, \) significantly reduce the magnitude of phase 1 in canine atria.\(^{20} \) \( I_{Kr} \) blockers have been reported to preferentially prolong atrial ERP.\(^{21} \)

We evaluated the potential of ranolazine to prevent the induction of AF/AFl and/or its effect to terminate AF in 2 different models. ACh mimics the conditions that predispose to vagally mediated AF and abbreviates atrial repolarization, mimicking the substrate encountered in electrically remodeled atria. This model generates persistent AF reproducibly,\(^{10,22} \) Ischemia/reperfusion, coupled with isoproterenol, mimics the conditions that prevail during acute myocardial infarction or the substrate encountered postsurgically. This model generates paroxysmal episodes of AF reproducibly.\(^{11} \) Clinically relevant concentrations of ranolazine (5 to 10 \( \mu \)mol/L) were effective in preventing and/or terminating AF/AFl in these models.

**Study Limitations**

The atrial selectivity of ranolazine in this study was recorded in “healthy” atrial and ventricular preparations. Electric abnormalities associated with changes in RMP and/or APD (ie, ischemia or electrical remodeling) in either atria or ventricles may modulate atrial selectivity. It is noteworthy that the strong sodium channel–blocking effects of ranolazine in the atria were well preserved in pharmacologically (ACh) remodeled and post-ischemia/reperfusion atria. The absence of autonomic factors, hormones, and other blood-related factors in our Tyrode’s solution–perfused preparations may alter responses from those observed in vivo.

As always, extrapolation of these results to the clinic must be approached with caution. Although \( V_{max} \) provides the best approximation of peak \( I_{Na} \) in multicellular cardiac preparations, it has long been appreciated that \( V_{max} \) is not a linear function of peak \( I_{Na} \). However, the magnitude of ranolazine-induced differences in \( V_{max} \) between atrial and ventricular tissues cannot be explained by the nonlinearity of \( V_{max} \) and \( I_{Na} \). Moreover, 3 other sodium channel–mediated parameters (CV, PRR, and DTE) are shown to be affected by ranolazine in an atrium-specific manner.

**Clinical Implications**

A number of antiarrhythmic agents have been shown to be effective in terminating and/or preventing clinical AF/AFl. Most of these agents have as a primary action the ability to reduce \( I_{Na} \) (such as propafenone or flecainide) or \( I_{Kr} \) (such as dofetilide) or to block multiple channels (\( I_{Na}, I_{Kr}, I_{Kur}, I_{Ca-L}, I_{Kur} \)), amiodarone). An important limitation of these antiarrhythmic agents is their potential ventricular proarrhythmic actions and/or organ toxicity at therapeutically effective doses.\(^{3,23,24} \)

Ranolazine is a novel antianginal agent with relatively mild adverse effects and no known proarrhythmic effects.\(^{25} \) Previous studies have suggested its utility in reducing arrhythmogenesis associated with acquired and congenital long-QT syndrome.\(^{3,4} \) The present study indicates that ranolazine effectively suppresses AF/AFl at concentrations that cause little change in the electric parameters of the ventricle. Although the actions of ranolazine in producing potent block of the sodium channel in the atria may be comparable to those of class IC antiarrhythmic agents such as propafenone and flecainide, it is apparently distinctly different from these agents in its atrial selectivity and rate dependence.

**Conclusions**

Our study demonstrates important differences in the inactivation characteristics of atrial versus ventricular sodium channels and a striking atrial selectivity for the action of ranolazine to produce use-dependent block of sodium channels, leading to suppression of AF. Our findings suggest that atrium-selective sodium channel block may be a valuable strategy to combat AF.

**Acknowledgments**

We gratefully acknowledge the expert technical assistance of Judy Hefferon, Robert Goodrow, and Kathy Sullivan.

**Sources of Funding**

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**Disclosures**

Dr Antzelevitch received research support from and is a consultant to CV Therapeutics. Dr Belardinelli is an employee of CV Therapeutics.

**References**

1. Nattel S, Matthews C, De Blasio E, Han W, Li D, Yue L. Dose-dependence of 4-aminopyridine plasma concentrations and electrophys-


**CLINICAL PERSPECTIVE**

Effective and safe pharmacological management of atrial fibrillation (AF) is one of the greatest unmet needs in our society today and one that is growing as the prevalence of AF continues to increase with the aging of the baby-boomer generation. Among current pharmacological strategies for suppression of AF are sodium channel blockers, which are contraindicated in patients with coronary artery or structural heart disease because of their potent effect in the ventricles; potassium channel blockers, which predispose to torsade de pointes arrhythmias because of their potent effect to prolong ventricular repolarization; and mixed ion channel blockers such as amiodarone, which are associated with multiorgan toxicity and ventricular arrhythmias. Accordingly, recent drug development for the management of AF has focused on agents that selectively affect the atria but not the ventricles of the heart. Inhibition of the ultrarapid delayed rectifier potassium current, present in atria but not ventricles, is an example of an atrium-selective approach. The present study introduces the concept of atrium-selective sodium channel block as another strategy to manage AF. We demonstrate important differences in the sodium channel inactivation characteristics between atrial and ventricular myocytes and the ability of ranolazine to take advantage of these ion channel distinctions. Ranolazine produces potent use-dependent depression of sodium channel current and related parameters in the atria but not in the ventricle, leading to effective suppression of AF in 2 experimental models. The results of our study suggest that atrium-selective sodium channel block is a potentially novel strategy for the management of clinical AF.
Effect of Distal Embolization on Myocardial Perfusion Reserve After Percutaneous Coronary Intervention
A Quantitative Magnetic Resonance Perfusion Study

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Background—Studies have shown that a subset of patients demonstrate persistent impairment in microcirculatory function after percutaneous coronary intervention (PCI). Distal embolization of plaque contents has been postulated as the main mechanism for this. We sought to investigate this further by evaluating PCI-induced changes in myocardial perfusion reserve index (MPRI) over time in segments with “distal-type” procedure-related myonecrosis using high-resolution quantitative cardiovascular magnetic resonance imaging.

Methods and Results—Forty patients undergoing PCI were studied with pre-PCI and 24-hour post-PCI delayed-enhancement magnetic resonance imaging and first-pass perfusion magnetic resonance imaging at rest and stress. Twenty patients underwent a third magnetic resonance imaging scan at 6 months. For perfusion imaging, 3 short-axis images were acquired during every heartbeat with a T1-weighted turboFLASH sequence. MPRI was calculated as the ratio of hyperemic to resting myocardial blood flow and subdivided according to the presence and location of new delayed hyperenhancement. Twenty-one patients demonstrated new distal hyperenhancement after PCI. Mean MPRI in revascularized myocardial segments not demonstrating new HE was significantly increased after the procedure (2.06 [95% CI, 1.99 to 2.13] before PCI and 2.52 [95% CI, 2.42 to 2.62] after PCI; P<0.001). In contrast, MPRI in segments with distal hyperenhancement was reduced after PCI (2.16 [95% CI, 1.95 to 2.37] before PCI; 2.00 [95% CI, 1.82 to 2.19] after PCI; mixed-model z=-4.82; P<0.001). Changes in mean MPRI 24 hours after PCI in segments upstream to new injury were not significantly different compared with perfusion changes in remote myocardium (z=-0.68; P=0.50). At 6 months after the procedure, mean MPRI in segments with new injury improved significantly compared with MPRI measured in these segments at 24 hours after PCI.

Conclusions—MPRI is reduced in myocardial segments that demonstrate new distal irreversible injury at 24 hours after PCI. These reductions are confined to the segments with injury and do not affect the entire supply territory of the culprit vessel. (Circulation. 2007;116:1458-1464.)

Key Words: coronary disease ■ embolism ■ magnetic resonance imaging ■ percutaneous coronary intervention ■ perfusion ■ stents

Percutaneous coronary intervention (PCI) results in enlarged luminal cross-sectional area and improved myocardial blood flow (MBF). However, despite most patients demonstrating improvement in coronary vasodilatory reserve (as assessed by intracoronary Doppler) and myocardial perfusion reserve index (MPRI; assessed by cardiovascular magnetic resonance imaging) after coronary stenting, a minority demonstrate persistent impairment in microcirculatory function after PCI, even after substantial conduit area enlargement. Several potential mechanisms have been suggested for this observation, including persistently elevated basal blood flow after transient ischemia, microvascular stunning resulting from particulate embolization, or acute/chronic impairment of the microvascular circulatory response.

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Cardiovascular magnetic resonance imaging (CMR) permits assessment of both myocardial scar and myocardial...
perfusion concurrently with high spatial resolution. CMR during first pass of an injected tracer permits assessment of myocardial perfusion both at rest and during pharmacological stress and gives superior spatial resolution compared with nuclear imaging methods. CMR perfusion results from animal experiments have shown a strong correlation with microspheres for the assessment of blood flow, and we have recently used this technique to report resting MBF in patients with hibernating myocardium. Delayed-enhancement MRI (DE-MRI), initially validated in large-animal models, allows assessment of the transmural extent of irreversible injury and is superior to single-photon–emission computed tomography for the identification of subendocardial myocardial infarction. It permits precise quantification of even small areas of myocardial necrosis after surgical or percutaneous revascularization. In the setting of PCI, 2 distinct patterns of new myocardial necrosis have been observed (distal and adjacent-to-stent injury), with distal embolization and ischemia caused by side-branch occlusion speculated to be possible mechanisms.

In the present study, we evaluated PCI-induced changes in MPRI and procedure-related myonecrosis using high-resolution quantitative CMR. We prospectively quantified resting and stress MBF before and after PCI using perfusion CMR and compared it with MBF in remote normal myocardium. We then compared the MPRI changes in myocardial segments with and without PCI-induced myonecrosis. We hypothesized that MPRI would be impaired in myocardial segments with new “distal” PCI-induced injury (ie, new hyperenhancement [HE] occurring in a distal distribution). We also speculated that myocardial segments “upstream” to the injury would not demonstrate evidence of microvascular dysfunction after the procedure.

**Methods**

**Ethics**
The study was approved by our institutional ethics committee. Informed written consent was obtained from each patient.

**Patient Population and CMR Imaging Time Points**
Sixty-eight consecutive patients with either 1- or 2-vessel coronary artery disease who were scheduled for complex PCI (30 mm of stent to a single vessel or treatment of a segment that involved at least 1 major side branch >2.0 mm and patients undergoing planned 2-vessel PCI) were enrolled in the study. We excluded patients with a clinical history of myocardial infarction, chronic total occlusion, and typical MI or adenosine contraindications. In the present study, we analyzed 44 consecutive patients who underwent both the initial CMR scan (consisting of cine, rest/stress perfusion, and DE-MRI) 24 hours before PCI and repeat CMR (cine, rest/stress perfusion, and DE-MRI) imaging 24 hours after PCI who did not have preexisting HE in the initial CMR scan (Figure 1). Twenty patients in this study cohort were included in previous studies comparing troponin I release after PCI and new myocardial HE. A randomly selected group of 20 patients (45%) of the study cohort were reimaged at 6 months.

**CMR Protocol**
Patients were studied in a 1.5-T clinical MR scanner (Siemens Sonata, Erlangen, Germany), and steady-state free-precession cine images were acquired in 2 long-axis and 7 to 9 short-axis views, as previously described. A gadolinium-based contrast agent (Gadodiamide, Omniscan, Nycomed Amersham, Little Chalfont, Buckinghamshire, UK) was then administered intravenously at a dose of 0.1 mmol/kg body weight (injection rate, 6 mL/s), followed by a saline flush of 15 mL at the same rate, for both stress and rest imaging. Perfusion imaging was performed every heartbeat during maximal vasodilation, followed by a second scan approximately 15 minutes later during rest. Vasodilation was induced by intravenous infusion of adenosine 0.14 mg · kg⁻¹ · min⁻¹ for 3 minutes before start of the scan. The adenosine infusion was continued until acquisition of the first 10 to 15 images. After rest perfusion imaging, we gave a “top-up” dose of 0.045 mmol/kg for a total gadolinium-DTPA dose of 0.125 mmol/kg before DE imaging. The DE images were acquired after an 8-minute delay with the use of an inversion-recovery segmented gradient-echo sequence as previously described.
CMR Postprocessing and Data Analysis

For perfusion analysis, the endocardial and epicardial contours were traced by an examiner blinded to angiography (MRI-MASS, Medical Imaging Solutions, Leiden, the Netherlands) and corrected manually for displacements (eg, breathing). The myocardium was divided into 24 corresponding segments; in each segment, the MBF was determined (in mL·min⁻¹·g⁻¹) by deconvolution of the signal intensity curves with an arterial input function measured in the left ventricular blood pool, with explicit accounting for any delay in the arrival of the tracer. Because basal MBF is closely related to the rate-pressure product, an index of left ventricular oxygen consumption, values for rest flow in each patient also were corrected for the respective rate-pressure product. MPRI was calculated as the ratio of MBF during hyperemia to rest. DE after processing has been described previously.12 Hyperenhanced pixels were defined as those with image intensities >2 SD above the mean of image intensities in a remote myocardial region in the same image.19 Furthermore, the transmural extent of infarction in each myocardial segment was calculated by dividing the hyperenhanced area by the total area of that segment and scored with the following system: no HE, grade 0; 1% to 25% HE, grade 1; 26% to 50% HE, grade 2; 51% to 75% HE, grade 3; and 76% to 100% HE, grade 4. The diagnostic coronary angiogram was used as the gold standard in defining affected myocardial segments. Each of the 3 (basal, midventricular, and apical) short-axis slices was ascribed a coronary artery territory according to standard criteria.4 As before,12 we prospectively identified the site of any new HE in relation to the implanted stent. Areas of new HE that occurred in the same short-axis image as the stent were classified as adjacent-to-stent injury, whereas new HE occurring in the myocardium distal to the stent was deemed distal injury. Because the primary purpose of the study was to compare myocardial perfusion changes in segments with distal injury, we excluded patients with adjacent-to-stent injury from the analysis. Segments that did not exhibit new HE were subdivided into 3 groups on the basis of their location: Segments subtended by a vessel with distal injury after revascularization. Mean MPRI in such segments was 2.41 (95% CI, 2.32 to 2.50) in revascularized myocardial segments demonstrated new irreversible injury after revascularization. Mean MPRI in such segments was 2.16 (95% CI, 1.95 to 2.37) before PCI and dropped to 2.00 (95% CI, 1.82 to 2.19) after PCI (z=−2.07; P=0.039). Figure 2 shows an example of MPRI changes in a patient with new distal HE. In contrast, mean MPRI across all patients in revascularized segments and 2.58 (95% CI, 2.48 to 2.69) in unaffected segments (z=−3.35; P=0.001).

Comparison of Changes in MPRI Between Myocardial Segments With and Without Post-PCI Injury

When preprocedural and postprocedural DE-MRIs were compared, 25 patients (63%) had evidence of new myocardial HE. Of these, 21 patients (84%) had distal HE (as previously defined) and are included in the final analysis. In the distal HE group, the mean mass of HE per patient was 5.1±3.0 g. We evaluated the levels of MBF before and early after intervention in only those segments that exhibited new distal HE after the procedure (HE group). Eighty-two of 404 (20%) intervened myocardial segments demonstrated new irreversible injury after revascularization. Mean MPRI in such segments was 2.16 (95% CI, 1.95 to 2.37) before PCI and dropped to 2.00 (95% CI, 1.82 to 2.19) after PCI (z=−2.07; P=0.039). Figure 2 shows an example of MPRI changes in a patient with new distal HE. In contrast, mean MPRI across all patients in revascularized myocardial segments not demonstrating new irreversible injury (no HE) was significantly increased after the procedure (2.06 [95% CI, 1.99 to 2.13] before PCI and 2.52 [95% CI, 2.42 to 2.62] after PCI; z=8.73; P<0.001). When the 2 groups (HE and no HE) were compared, the absolute change in MPRI before and after the procedure was significantly different in the non-HE segments (0.46; 95% CI, 0.36 to 0.55) from the HE segments (−0.16; 95% CI, −0.29 to 0.02; z=−4.82; P<0.001; Table 1, first section).

This relationship also held true when the MPRI changes were compared in only the 21 patients with new distal HE (Table 1, second section). After the procedure, there was a drop in MPRI in segments with HE (−0.16; 95% CI, −0.29...
to 0.02) in contrast to an increase in MPRI in segments without evidence of new HE (0.17; 95% CI, 0.04 to 0.29), and the difference between the 2 groups was significant ($z = -6.85; P<0.001$).

**Comparison of MPRI Changes 24 Hours After PCI Between Segments With New Distal Injury and Subgroups of Segments Without Injury**

We assessed MPRI in myocardial segments upstream to procedural injury (HE) and compared them with MPRI in remote segments (segments that underwent PCI in a second vessel in the same patient but not displaying new injury) and segments with no PCI (segments that were subtended by arteries that did not undergo PCI) (Table 1, third section). Changes in mean MPRI after PCI in segments upstream to new injury were not significantly different compared with perfusion changes in remote myocardium ($z = 0.68; P=0.50$), indicating that there was no significant reduction in perfusion reserve in upstream segments after the procedure. When these MPRI changes were compared with the myocardial segments (in the same patient and vessel) that exhibited new HE after PCI, there was a significant difference in the change in MPRI ($z = -4.88; P<0.001$).

**Comparison of MPRI Changes 6 Months After PCI Between Segments With New Distal Injury and Subgroups of Segments Without Injury**

Of 40 patients in the study cohort, 20 (50%) were rescanned at 6 months after the procedure. At 6 months, mean MPRI in segments with new injury was 2.52 (95% CI, 2.24 to 2.79) compared with 2.04 (95% CI, 1.86 to 2.23) 24 hours after PCI and 2.64 (95% CI, 2.32 to 2.96) before PCI. The initial deterioration of MPRI in segments with new injury observed early after PCI was no longer evident after 6 months, and the change in MPRI for segments with new injury was no longer statistically significant ($z = -1.21; P=0.23$). Overall, the

<table>
<thead>
<tr>
<th>TABLE 1. MPRI Changes Before and Early After PCI in Segments With and Without New Distal HE Across All Patients, Only in Patients With New Distal HE, and Subdivided According to Culprit Vessel Territory</th>
</tr>
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<tbody>
<tr>
<td>Segments, n</td>
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<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Affected segments in all 40 patients</strong></td>
</tr>
<tr>
<td>No HE</td>
</tr>
<tr>
<td>HE (distal)</td>
</tr>
<tr>
<td><strong>Affected segments in 21 patients with distal new injury</strong></td>
</tr>
<tr>
<td>No HE</td>
</tr>
<tr>
<td>HE (distal)</td>
</tr>
<tr>
<td><strong>All segments in 21 patients with distal new injury</strong></td>
</tr>
<tr>
<td>Upstream (reference group)</td>
</tr>
<tr>
<td>Distal</td>
</tr>
<tr>
<td>Remote</td>
</tr>
<tr>
<td>No PCI</td>
</tr>
</tbody>
</table>

Upstream indicates myocardial segments supplied by the culprit vessel proximal to the distal HE; remote, segments that underwent PCI in a second vessel in the same patients but not displaying new injury; distal HE, segments demonstrating new distal injury; and no PCI, segments that are subtended by arteries that did not undergo PCI.
Correlation of Magnitude of New Injury to MPRI
We excluded all segments with no myocardial injury and all segments with adjacent injury. In the remaining segments (distal HE group), the absolute percentages of new injury were measured for each segment. Values were categorized into the 4 predefined levels with the following boundaries: 0% to 25% (grade 1), 26% to 50% (grade 2), 51% to 75% (grade 3), and 76% to 100% (grade 4). Early after PCI, there were no segments in grade 4 (>76% necrosis); 53% of segments were in grade 1; 35% were in grade 2; and 12% were in grade 3. The new variable with the 3 valid categories was entered into the mixed model as a fixed effect with MPRI as the outcome. We could not measure any significant trend between the categories of new injury and MPRI early after PCI ($z = -1.31; P = 0.19$). We did not fit a mixed model for the 6-month data because of the small number of cases (20 valid segments) with the smaller variance. However, a bivariate Spearman correlation analysis did not suggest any correlation between the absolute amount of necrosis and the difference in MPRI after 6 months ($r^2 = 0.12, P = 0.16$).

Changes in Rest and Stress MBF Immediately and 6 Months After PCI
Mean resting MBF did not differ across any of the groups before or after PCI (Table 2). Mean hyperemic MBF was reduced significantly in the segments with new HE immediately after PCI and increased at 6 months (Table 2).

Discussion
This study demonstrates that MPRI is reduced in myocardial segments that demonstrate new myonecrosis at 24 hours after PCI. Furthermore, although MPRI is reduced in such segments, it is not reduced in segments upstream from the injury (in the territory of the culprit vessel) compared with remote myocardial segments. Late after the procedure, we found a normalization of MPRI in myocardial segments that demonstrated new irreversible injury. Our findings have important implications for our understanding of the changes in the coronary microvasculature both early and late after percutaneous coronary intervention.

To the best of our knowledge, this is the first study to concurrently examine myocardial perfusion and necrosis serially after PCI with a validated, quantitative CMR technique. Previous studies using intracoronary Doppler in the setting of PCI have shown a residual reduction of relative coronary flow velocity reserve immediately after PCI (related to elevated baseline flow velocity),1,2,20–22 and a persistent reduction in relative coronary vasodilatory reserve has been associated with cardiac biomarker elevation after the procedure.2 Gibson et al23 demonstrated that patients with impaired Thrombolysis In Myocardial Infarction (TIMI) perfusion grade had a 10-fold-higher incidence of postprocedural creatine kinase-MB elevation. Bolognese et al24 found, using a combination of TIMI flow grade, corrected TIMI frame count, TIMI perfusion grade, and myocardial contrast echocardiography, that post-PCI cardiac troponin I elevation in high-risk patients with acute coronary syndrome is associated with an abnormal tissue-level perfusion. We and others have recently demonstrated that areas of new myonecrosis visualized with DE-MRI are linked to impaired TIMI perfusion grade on angiographic analysis immediately after the procedure.14,25 In the present study, we have extended this by finding that areas of myocardium injured during PCI exhibit reduced myocardial perfusion for at least 24 hours after the interventional procedure.

We found that myocardial MPRI at 24 hours in the segments with new HE was reduced as a result of a lack of increase in hyperemic blood flow rather than an increase in baseline (resting) blood flow. In contrast to experimental models of coronary embolization in which the particulate size is small26 (~42 μm), coronary embolization after PCI of native arteries has been found to result in thrombotic and nonthrombotic embolic material ranging from 100 to 550 μm.27 It is likely that the blunted hyperemic flow response persisting at 24 hours seen in our study is a feature of both myocardial necrosis and extensive macrovascular and microvascular plugging of the distal vascular bed. Our findings are in agreement with those of Dupouy et al,28 who found 2

![Figure 3. MPRI changes before, early after, and late after PCI in all 20 patients, with follow-up (FU) data subdivided according to culprit vessel territory. Upstream indicates myocardial segments supplied by the culprit vessel proximal to the distal HE; HE, segments demonstrating new distal injury; and Control, segments signifying both segments subtended by arteries that did not undergo PCI and segments that underwent PCI in a second vessel without new injury.](image-url)

**TABLE 2. Rest and Stress MBF 24 Hours and 6 Months After PCI**

<table>
<thead>
<tr>
<th></th>
<th>Rest MBF, mL · min⁻¹ · g⁻¹</th>
<th>Stress MBF, mL · min⁻¹ · g⁻¹</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before PCI (HE negative)</td>
<td>1.0 (0.9–1.1)</td>
<td>2.2 (2.0–2.4)</td>
<td>...</td>
</tr>
<tr>
<td>After PCI (HE positive)</td>
<td>1.0 (0.9–1.1)</td>
<td>2.2 (1.9–2.5)</td>
<td>...</td>
</tr>
<tr>
<td>Early after PCI (HE negative)</td>
<td>1.0 (0.9–1.2)</td>
<td>2.8 (2.3–3.3)</td>
<td>0.01*</td>
</tr>
<tr>
<td>Early after PCI (HE positive)</td>
<td>1.0 (0.9–1.2)</td>
<td>1.9 (1.7–2.1)</td>
<td>0.03*</td>
</tr>
<tr>
<td>Late after PCI (HE negative)</td>
<td>1.1 (0.9–1.3)</td>
<td>2.7 (2.3–3.0)</td>
<td>0.8†</td>
</tr>
<tr>
<td>Late after PCI (HE positive)</td>
<td>1.2 (0.9–1.4)</td>
<td>2.8 (2.3–3.3)</td>
<td>0.03†</td>
</tr>
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</table>

*Compared with pre-PCI value; †compared with 24-hour post-PCI value.
patterns of postprocedural coronary flow velocity reserve impairment: The first related to a significantly higher baseline average peak velocities within 10 minutes after the last balloon inflation that normalized within 24 hours after PCI, and the second related to a lack of increase in hyperemic average peak velocity in the setting of a normal postprocedural baseline average peak velocity that persisted over the next 24 hours. In the present study, MPRI improved in the segments with new myonecrosis at 6 months. This was a result of improvement in hyperemic blood flow in these myocardial segments that, in turn, likely was due to a resolution in the microcirculatory impairment from distal embolization. Although all patients with new injury had evidence of scarred myocardium in the 6-month scan (data not shown), this did not adversely affect the MPRI in these segments because the total volume of scar (per segment) was small.

Using a sensitive, high-spatial-resolution technique, we did not find a reduction in MPRI in myocardial segments upstream of the new HE. This implies that detection of impaired antegrade flow is likely to be local to the territory affected by plaque embolization and that the no-reflow phenomenon does not affect the whole territory of the epicardial vessel. This is particularly likely to be the case when the volume of myocardial injury is small, as was the case in most of our cohort. Our findings also suggest that pharmacological therapy administered in the catheter laboratory for the no-reflow phenomenon may be of limited value because perfusion remains abnormal >24 hours after the PCI procedure. Indeed, it is possible to speculate that the apparent benefits of vasodilator therapy for no reflow may reflect dilatation of predominantly unafected vascular beds with minimal impact on territories plugged with atheroembolic debris.

Our findings are in contrast to the preliminary CMR perfusion study of Al-Saadi et al., who found that although MPRI in segments after balloon angioplasty alone did not completely normalize in a subset of patients, the stented group demonstrated a complete normalization of MPRI 24 hours after the procedure. There are, however, important differences between this early study and our present study. First, the stented group was small (only 13 of 35 patients [37%]) in the former study. Second, we enrolled high-risk PCI patients in the present study with at least a 30% rate of new irreversible injury. Although the exact rate of procedure-related myonecrosis is not known in the study by Al Saadi et al (because they did not report on CMR or biochemical markers of myocardial injury), it is likely to be low/negligible because it was in a low-risk PCI group. Hence, the MPRI changes in the stented group in their study might reflect the MPRI changes found in the non-HE segments in our study (ie, significant increase 24 hours after PCI). Third, the measures of perfusion reserve indexes also are not directly comparable between these studies because the former used semiquantitative assessment of MBF and we used a quantitative CMR perfusion method.

This study has a number of limitations. It is a highly selected PCI patient cohort that is not representative of many patients undergoing PCI in the current era. The extremely high rate of PCI-related myonecrosis in this study (60%), greater than seen in our previous consecutive series, is a further reflection of this limitation. We excluded patients with side-branch injury because they were too few for a meaningful statistical comparison. Future studies with more patients need to address this further. Although great care was taken to match the myocardial segments of HE with perfusion segments, some misregistration errors could have occurred. Perfusion measurements in 3 short-axis slices did not give complete coverage of the left ventricular myocardium in this study. However, we were still able to assess 16 of 17 myocardial segments in the American Heart Association model. Furthermore, Nagel and colleagues have shown that evaluating only the 3 inner (ie, excluding the most basal and apical) short-axis slices by CMR perfusion resulted in a higher diagnostic accuracy for the detection of significant CAD than evaluating 5 short-axis slices.

Conclusions

Using quantitative CMR perfusion and DE imaging, we have shown that MPRI is reduced in myocardial segments demonstrating new irreversible injury at 24 hours after PCI. Furthermore, these reductions are transitory, seem to be confined to the segments with injury, and do not affect the entire supply territory of the culprit vessel. The sensitivity of CMR in the assessment of MBF and necrosis makes it a powerful tool in the investigation of pathophysiological mechanism injury in the setting of coronary revascularization.

Sources of Funding

This work was supported by the British Heart Foundation, by the Medical Research Council, and by an unrestricted research donation from Boston Scientific, UK. Dr Selvanayagam is funded by the British Heart Foundation. Dr Jerosch-Herold gratefully acknowledges support for his work by NIH RO1 HL65394–01.

Disclosures

None.

References

Studies have shown that some patients demonstrate impairment in microcirculatory function and new myocardial necrosis after percutaneous coronary intervention (PCI). Distal embolization of plaque contents has been postulated as a possible mechanism. However, the relationship between the extent of PCI-induced myocardial necrosis and the degree of microcirculatory impairment is less clear. We evaluated PCI-induced changes in myocardial perfusion reserve index over time in segments with “distal-type” procedure-related myocardial necrosis using high-resolution quantitative cardiovascular magnetic resonance imaging. Patients at relatively high risk for distal embolization during stenting were studied with pre-PCI and 24-hour and 6-month post-PCI delayed-enhancement cardiovascular magnetic resonance imaging and first-pass perfusion cardiovascular magnetic resonance imaging at rest and stress. We found that the myocardial perfusion reserve index is reduced in the presence of new myocardial necrosis early after PCI. At 6 months, there was normalization of myocardial perfusion reserve index in segments that demonstrated PCI-related myocardial necrosis. There was no relationship between the extent of myocardial necrosis on cardiovascular magnetic resonance imaging and the reduction in perfusion reserve either early or late after PCI. Microcirculatory impairment early after PCI may be due to both new myocardial necrosis and transitory macro/microvascular plugging of the distal vascular bed.
Clinical Characteristics of Dialysis Patients With Acute Myocardial Infarction in the United States

A Collaborative Project of the United States Renal Data System and the National Registry of Myocardial Infarction

Charles A. Herzog, MD; Kathee Littrell, RN, PhD; Cheryl Arko, BA; Paul D. Frederick, MPH, MBA; Martha Blaney, PharmD

Background—Acute myocardial infarction (AMI) is catastrophic for dialysis patients. This study set out to determine the clinical characteristics of dialysis patients hospitalized for AMI in the United States.

Methods and Results—This retrospective cohort study used data from the US Renal Data System (USRDS) database (n=1 285 177) and the third National Registry of Myocardial Infarction (NRMI 3) (n=537 444). AMI hospitalizations from April 1, 1998, through June 30, 2000, were identified using International Classification of Diseases, 9th edition, clinical modification, codes 410, 410.x, 410.x0, and 410.x1. The 9418 unique dialysis patients identified with AMI hospitalizations in the USRDS database were cross-matched with the NRMI registry, creating a cohort for analysis that consisted of 3049 matching patients. Clinical characteristics of dialysis and nondialysis (n=534 395) AMI patients were compared by use of the \( \chi^2 \) test. Of clinical significance, 44.8% of dialysis patients were diagnosed as not having acute coronary syndrome on admission, versus 21.2% of nondialysis patients; 44.4% presented with chest pain, versus 68.3% of nondialysis patients; and 19.1% had ST elevation, versus 35.9% of nondialysis patients. Cardiac arrest was twice as frequent for dialysis patients (11.0% versus 5.0%), and in-hospital death was nearly so (21.3% versus 11.7%). In a logistic regression model, the odds ratio for in-hospital death for dialysis versus nondialysis patients was 1.498 (95% CI, 1.340 to 1.674).

Conclusions—Dialysis patients hospitalized for AMI differ strikingly from nondialysis patients, which possibly explains their poor outcomes. Intensive efforts for early, accurate recognition of AMI in dialysis patients are warranted. (Circulation. 2007;116:1465-1472.)

Key Words: electrocardiography ■ kidney failure, chronic ■ myocardial infarction ■ renal dialysis

A acute myocardial infarction (AMI) in dialysis patients is a catastrophic event associated with dismal long-term survival.\(^1\)\(^-\)\(^4\) We previously reported a 1-year death rate of 59% and a 2-year death rate of 73% in US dialysis patients hospitalized for AMI from 1977 through 1995. Surprisingly, outcomes have not improved over 2 decades. The 2-year death rate of dialysis patients with AMI was 71% for 1977 to 1984 and 74% for 1990 to 1995.\(^2\) The 2-year death rate of dialysis patientsinitiating renal replacement therapy from 1995 through 1999 who subsequently sustained AMI in the modern era of reperfusion therapy was still 73%.\(^5\) We have speculated that the poor outcome of these patients may be attributable to both underdiagnosis (a result of atypical presentations) and undertreatment (ie, therapeutic nihilism).\(^1\)\(^,\)\(^6\)

Clinical Perspective p 1472

The Cardiovascular Special Studies Center of the US Renal Data System (USRDS) has designed an ongoing 3-part study to collect data pertaining to dialysis patients hospitalized for AMI: prehospitalization data obtained from dialysis center medical record abstraction, data on the clinical characteristics of dialysis patients hospitalized for AMI, and data on long-term survival after hospital discharge. Here, we report the results of our collaborative retrospective cohort study with the National Registry of Myocardial Infarction (NRMI) on the clinical characteristics of dialysis patients hospitalized for AMI in the United States.

Methods

This project was performed under a collaborative agreement between the National Institute of Diabetes and Digestive and Kidney Diseases...
Patients were initially identified in the USRDS database (n=1,285,177 at the time of the study). AMI hospitalizations were identified by *International Classification of Diseases*, 9th edition, clinical modification, codes 410, 410.x, 410.x0, and 410.x1. The study period was April 1, 1998, through June 30, 2000, corresponding to the time of enrollment for NRMI 3 (n=537,444 patients, 1,553 hospitals), the third NRMI data collection study. Eligible patients had received renal replacement therapy for at least 90 days and for at least 60 days before AMI. A total of 9,418 unique dialysis patients hospitalized for AMI were identified in the USRDS database. This patient list was then cross-matched with the NRMI 3 registry, which does not identify dialysis dependency, by the Ovation database. This dataset was then cross-matched with the NRMI 3 registry. A 1-way ANOVA and the nonparametric alternative Wilcoxon rank-sum test were used to evaluate continuous variables that were normally distributed or skewed, respectively. (Patient age, systolic and diastolic blood pressures, pulse, weight, number of days in the intensive care unit, and left ventricular ejection fraction were normally distributed, and mean values were compared; onset of symptoms to first admission data in hours were skewed, and median values were compared.) For nonparametric comparisons involving >2 groups, the Kruskal-Wallis test was used. All tests are 2 tailed on the basis of a level of significance set at 0.05. A 2-sided Bonferroni probability value was used to control for experimental type I error rate for multiple comparisons; the reported probability values reflect this adjustment for multiple comparisons. Characteristics included demographics, prior medical history, temporal variables, clinical variables on admission, and in-hospital variables such as therapeutic strategies. A standard NRMI 3 definition of eligibility for acute coronary reperfusion was based on the following characteristics: time from symptom onset to evaluation <12 hours; ST-segment-elevation myocardial infarction (STEMI, which by convention includes both ST elevation and left bundle-branch block) on first ECG; no Killip class IV; and no spontaneous reperfusion, major organ failure, or early death. This definition is problematic for the end-stage renal disease (ESRD) cohort because all patients would be considered to have major organ failure. A more meaningful definition for the ESRD cohort includes tabulation in the registry of the reasons reperfusion was not used, described below.

To further analyze the association of in-hospital death and dialysis, a logistic regression analysis was performed. The logistic regression model included variables pertaining to dialysis (yes or no), demographic characteristics (including age, gender, and race), insurance status, hospital characteristics, medical history (such as congestive heart failure or diabetes), clinical presentation (including ECG findings of STEMI, Killip class, pulse, and blood pressure), medications administered within 24 hours of admission, and any initial coronary reperfusion therapy.

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

**Results**

Detailed data for the comparisons of dialysis (n=3,409) and nondialysis (n=534,395) patients are presented in Tables 1 through 5, with findings of special interest highlighted in this narrative summary. For selected continuous variables of interest, data are presented as mean±SD, with additional inclusion of median values. Probability values for comparisons are included in the tables. Because of the large sample size, clinically insignificant differences in variables of interest may still be statistically significant.

Demographically, the 2 patient groups were of similar age, with 47.5% of dialysis and 48.5% of nondialysis patients ≥70 years of age (Table 1). Proportionately more dialysis patients were female (46.9% versus 39.2% for nondialysis). Reflecting the disproportionate representation of black patients with ESRD, only 63.6% of dialysis patients were white, compared with 85.3% of nondialysis patients. The 2 patient groups differed significantly by prior medical history (Table 1). Dialysis patients had a lower prevalence of current smoking (10.7% versus 26.0%), hypercholesterolemia (18.6% versus 31.2%), and family history of cardiovascular disease (12.9% versus 26.8%). About twice as many dialysis patients were identified as diabetic (57.4% versus 28.8%). Dialysis patients had a greater prevalence of known cardiovascular disease: hypertension (77.8% versus 56.2%), congestive heart failure (30.9% versus 15.7%), prior coronary artery bypass surgery (19.6% versus 12.7%), and stroke (15.3% versus 9.6%). The prevalence of prior AMI (25.9% versus 24.0%) and the prevalence of angina (14.7% versus 12.8%) were minimally higher in dialysis patients than in nondialysis patients.

A trend toward less prehospital delay for nondialysis patients appeared (29.4% presented at <2 hours versus 20.7% of the dialysis group), but the interpretation is muddied by missing data (Table 2). The mean±SD time from symptom onset to evaluation was similar for both groups, 5.8±2.0 hours for dialysis and 5.5±0.9 hours for nondialysis patients, but the median time was less for the nondialysis group (2.3 versus 2.7 hours).

We found a markedly lower diagnostic suspicion of AMI and, notably, of acute coronary syndromes in dialysis patients (Table 3). In the nondialysis group, 43.8% had an admitting diagnosis of AMI, versus 21.8% of dialysis patients. Of clinical significance, 44.8% of dialysis patients were diagnosed as not having acute coronary syndrome on admission, compared with 21.2% of nondialysis patients. Concord with the lower diagnostic suspicion for acute coronary syndrome, fewer than half of the dialysis patients (44.4%) presented with chest pain, compared with 68.3% of nondialysis patients. Fewer dialysis patients were classified as Killip class I (58.4% versus 75.2%).

Another clinically important difference between dialysis and nondialysis patients is ECG data (Table 3) because ECGs are major determinants of selection for acute coronary reperfusion therapy. Among nondialysis patients, 35.9% had ST elevation, compared with only 19.1% of dialysis patients. The prevalence of ST depression was comparable for dialysis and nondialysis patients (27.7% and 28.9%, respectively). Left bundle-branch block was slightly higher among dialysis patients (8.1% versus 5.8%), and nonspecific ECG findings were more common (44.1% versus 35.8%). If we assumed that all of the left bundle-branch block findings were new, only 27.2% of dialysis patients would be deemed ECG eligible for acute coronary reperfusion, compared with 41.7% of nondialysis patients. (Using the NRMI 3 registry STEMI
definition, either ST elevation or new/unknown/old left bundle-branch block, which is a separate data entry field, 26.0% of dialysis patients and 40.0% of nondialysis patients would be ECG eligible for acute coronary reperfusion.)

Because not all of these findings are new, the actual percentage of STEMI is likely to be lower in both groups. The larger proportion of non–Q-wave MI in dialysis patients (77.8% versus 62.6%) reflects this difference.

On the basis of NRMI definitions, only a small proportion of the dialysis patients presenting with AMI were considered eligible for acute coronary reperfusion (Table 4). Only 10.2% of dialysis patients were deemed reperfusion eligible, compared with 24.6% of nondialysis patients. However, the NRMI definition of reperfusion eligibility is problematic for dialysis patients because it excludes on the basis of major organ failure. A less restrictive definition that includes all dialysis patients with STEMI on first ECG and time from symptom onset to evaluation of <12 hours raises the number of reperfusion-eligible dialysis patients from 310 (10.2%) to 408 (13.4%).

In descending order of frequency, STEMI dialysis patients did not receive reperfusion for the following reasons: contraindications to thrombolysis (22.4%), major organ failure (21.3%), quality of life (15.3%), history of cerebral vascular accident (8.2%), Killip class IV (2.0%), early death (0.7%), and spontaneous reperfusion (0.2%). STEMI nondialysis patients did not receive reperfusion for the following reasons: contraindications to thrombolysis (16.6%), quality of life (10.6%), history of cerebral vascular accident (6.5%), major organ failure (2.3%), Killip class IV (2.1%), early death (0.6%), and spontaneous reperfusion (0.7%).

### TABLE 1. Demographic and Medical History of Dialysis and Nondialysis Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dialysis (n=3049)</th>
<th>Nondialysis (n=534 395)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1620 (53.1)</td>
<td>324 944 (60.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>White†</td>
<td>1926 (63.6)</td>
<td>453 112 (85.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age, mean±SD, y</td>
<td>67.3±12.1</td>
<td>68.0±13.9</td>
<td>0.3514</td>
</tr>
<tr>
<td>Age, y†</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&lt;40</td>
<td>64 (2.1)</td>
<td>12 359 (2.3)</td>
<td></td>
</tr>
<tr>
<td>40–49</td>
<td>232 (7.6)</td>
<td>50 001 (9.4)</td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>507 (16.6)</td>
<td>95 656 (17.9)</td>
<td></td>
</tr>
<tr>
<td>60–69</td>
<td>799 (26.2)</td>
<td>117 136 (21.9)</td>
<td></td>
</tr>
<tr>
<td>70–79</td>
<td>1030 (33.8)</td>
<td>143 410 (26.8)</td>
<td></td>
</tr>
<tr>
<td>≥80</td>
<td>417 (13.7)</td>
<td>115 778 (21.7)</td>
<td></td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>327 (10.7)</td>
<td>139 200 (26.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1750 (57.4)</td>
<td>153 910 (28.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>791 (25.9)</td>
<td>128 087 (24.0)</td>
<td>0.5447</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2371 (77.8)</td>
<td>300 114 (56.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>566 (18.6)</td>
<td>166 851 (31.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Family history‡</td>
<td>393 (12.9)</td>
<td>142 960 (26.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Angina</td>
<td>448 (14.7)</td>
<td>68 519 (12.8)</td>
<td>0.1031</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>942 (30.9)</td>
<td>83 952 (15.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Percutaneous transluminal coronary angioplasty</td>
<td>311 (10.2)</td>
<td>54 634 (10.2)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Coronary artery bypass graft surgery</td>
<td>599 (19.6)</td>
<td>68 043 (12.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stroke</td>
<td>468 (15.3)</td>
<td>51 551 (9.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hormone replacement therapy in women§</td>
<td>46 (3.2)</td>
<td>15 117 (7.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>407 (13.3)</td>
<td>73 959 (13.8)</td>
<td>1.0000</td>
</tr>
</tbody>
</table>

Values are given as n (%) unless otherwise indicated.

*Probability values are adjusted for multiple comparisons with the Bonferroni method.

†Patient numbers may vary by row because of missing data.

‡Family history of cardiovascular disease.

§Dialysis, n=1429; nondialysis, n=209 451; excludes male patients.

### TABLE 2. Temporal Variables for Dialysis and Nondialysis Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dialysis (n=3049)</th>
<th>Nondialysis (n=534 395)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prehospital delay, h</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&lt;2</td>
<td>631 (20.7)</td>
<td>157 274 (29.4)</td>
<td></td>
</tr>
<tr>
<td>2–5</td>
<td>507 (16.6)</td>
<td>100 732 (18.8)</td>
<td></td>
</tr>
<tr>
<td>6–12</td>
<td>197 (6.5)</td>
<td>39 541 (7.4)</td>
<td></td>
</tr>
<tr>
<td>&gt;12</td>
<td>152 (5.0)</td>
<td>35 953 (6.7)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>1562 (51.2)</td>
<td>200 895 (37.6)</td>
<td></td>
</tr>
<tr>
<td>Time of presentation†</td>
<td></td>
<td></td>
<td>1.0000</td>
</tr>
<tr>
<td>8 AM to 4 PM</td>
<td>1317 (43.7)</td>
<td>220 548 (43.4)</td>
<td></td>
</tr>
<tr>
<td>4 AM to before midnight</td>
<td>981 (32.6)</td>
<td>167 334 (33.0)</td>
<td></td>
</tr>
<tr>
<td>Midnight to before 8 AM</td>
<td>714 (23.7)</td>
<td>119 794 (23.6)</td>
<td></td>
</tr>
<tr>
<td>Onset to data, h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>5.8±2.9</td>
<td>5.5±9.0</td>
<td>1.0000</td>
</tr>
<tr>
<td>Median</td>
<td>2.7</td>
<td>2.3</td>
<td>0.0020</td>
</tr>
</tbody>
</table>

Values are given as n (%) unless otherwise indicated.

*Probability values are adjusted for multiple comparisons with the Bonferroni method.

†Patient numbers may vary by row because of missing data.
Of the reperfusion-eligible patients, 47% of dialysis patients (n=146) and 75% of nondialysis patients (n=98 528) received some type of coronary reperfusion (*P*<0.0001 for use of coronary reperfusion in reperfusion-eligible dialysis versus nondialysis patients). Overall, only 8.3% of dialysis patients presenting with AMI, regardless of STEMI or reperfusion eligibility status, actually received any acute coronary reperfusion therapy, compared with 28.7% of nondialysis patients (data not shown). Coronary angiography and coronary revascularization (both done in nonacute reperfusion settings) were more common among nondialysis than dialysis patients: coronary angiography, 34.6% versus 28.4%; percutaneous coronary intervention, 18.6% versus 8.2%; and coronary artery bypass surgery, 9.1% versus 4.2%. Evidence-based medical therapies were used less commonly among dialysis patients on admission (aspirin, 69.8% versus 83.3%;

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dialysis (n=3049)</th>
<th>Nondialysis (n=534 395)</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission diagnosis†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>657 (21.8)</td>
<td>229 207 (43.8)</td>
<td></td>
</tr>
<tr>
<td>Rule out myocardial infarction</td>
<td>713 (23.7)</td>
<td>122 752 (23.5)</td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td>291 (9.7)</td>
<td>59 943 (11.5)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1348 (44.8)</td>
<td>110 836 (21.2)</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>143.6±39.3</td>
<td>143.8±32.3</td>
<td>1.0000</td>
</tr>
<tr>
<td>Median</td>
<td>143.0</td>
<td>142.0</td>
<td>1.0000</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>75.5±20.7</td>
<td>80.7±18.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median</td>
<td>74.0</td>
<td>80.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pulse, bpm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>94.7±24.1</td>
<td>86.7±24.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median</td>
<td>92.0</td>
<td>84.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chest pain†</td>
<td>1325 (44.4)</td>
<td>353 442 (68.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Killip class†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I: no congestive heart failure</td>
<td>1775 (58.4)</td>
<td>394 914 (75.2)</td>
<td></td>
</tr>
<tr>
<td>II: rales, jugular venous distension</td>
<td>764 (25.1)</td>
<td>83 433 (15.9)</td>
<td></td>
</tr>
<tr>
<td>III: pulmonary edema</td>
<td>461 (15.2)</td>
<td>40 074 (7.6)</td>
<td></td>
</tr>
<tr>
<td>IV: cardiogenic shock</td>
<td>39 (1.3)</td>
<td>6778 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Electrocardiogram†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST elevation</td>
<td>579 (19.1)</td>
<td>188 099 (35.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ST depression</td>
<td>840 (27.7)</td>
<td>151 492 (28.9)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Nonspecific</td>
<td>1338 (44.1)</td>
<td>187 650 (35.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Q wave</td>
<td>170 (5.6)</td>
<td>46 744 (8.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Left bundle-branch block</td>
<td>244 (8.1)</td>
<td>30 134 (5.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Right bundle-branch block</td>
<td>198 (6.5)</td>
<td>30 485 (5.8)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Normal</td>
<td>193 (6.4)</td>
<td>40 196 (7.7)</td>
<td>0.3294</td>
</tr>
<tr>
<td>Other</td>
<td>760 (25.1)</td>
<td>92 146 (17.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Myocardial infarction type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior/septal</td>
<td>508 (16.7)</td>
<td>126 566 (23.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Inferior</td>
<td>555 (18.2)</td>
<td>163 559 (30.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Posterior</td>
<td>65 (2.1)</td>
<td>23 060 (4.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lateral</td>
<td>293 (9.6)</td>
<td>66 376 (12.4)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Right ventricle involvement</td>
<td>13 (0.4)</td>
<td>3624 (0.7)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Unspecified/other</td>
<td>1892 (62.1)</td>
<td>229 312 (42.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Q wave</td>
<td>78 (22.2)</td>
<td>199 602 (37.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Not Q wave</td>
<td>2371 (77.8)</td>
<td>334 793 (62.6)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values are given as n (%) unless otherwise indicated.

*Probability values are adjusted for multiple comparisons with the Bonferroni method.

†Patient numbers may vary by row because of missing data.
and β-blockers, 45.8% versus 54.7% among nondialysis patients) and at discharge (aspirin, 66.8%; β-blockers, 56.6%; and angiotensin-converting enzyme [ACE] inhibitors, 34.5% for dialysis patients; for nondialysis patients, 80.3%, 63.6%, and 40.7%, respectively).

More dialysis patients had impaired left ventricle systolic performance (27.4% with left ventricular ejection fraction <40%, compared with 18.0% of nondialysis patients; Table 5). Consistent with this finding were greater numbers of dialysis patients with congestive heart failure (25.1% versus 19.1%). From a clinical standpoint, the most striking differences relate to unexpected cardiac arrest and in-hospital death. Cardiac arrest was twice as frequent in dialysis patients as in nondialysis patients (11.0% versus 5.0%). After exclusion of patients transferred to other institutions, the in-hospital death rate of dialysis patients was 21.3%, compared with 11.7% for nondialysis patients.

Dialysis and nondialysis patients in this study showed different demographic and clinical characteristics. In the logistic regression analysis, despite these differences, we found an independent association of dialysis status and in-hospital death. Compared with nondialysis patients, the odds ratio of in-hospital death for dialysis patients was 1.498 (95% CI, 1.340 to 1.674). Although there were significantly more nonwhite patients in the dialysis group, black (versus white) race was not independently associated with in-hospital death; the odds ratio for death was 0.980 (95% CI, 0.934 to 1.027).

### Discussion

The clinical characteristics of dialysis patients hospitalized for AMI are strikingly different from those of nondialysis AMI patients. Although the data are observational and derived from the NRMI 3 database, this is the largest clinical study on AMI in ESRD patients performed so far, and the findings are likely to be representative of real-world clinical practice.

Our work identified several important clinical issues. There is a lower index of clinical suspicion and a higher level of inaccuracy for initial diagnosis of acute coronary syndromes in dialysis patients with AMI because twice as many patients (44.8%, versus 21.2% of nondialysis patients) were incorrectly diagnosed on admission. This diagnostic inaccuracy is understandable if clinicians relied on a history of chest pain, present in only 44.4% of dialysis patients versus 68.3% of nondialysis patients, and presence of diagnostic ECG changes because relatively fewer dialysis patients had ST elevation. Further diagnostic confusion may have resulted from the greater prevalence of hypertension and likely attendant hypertensive heart disease and uninterpretable ST depression in the dialysis cohort. Our finding of a lower prevalence of chest pain in dialysis patients with AMI is concordant with the study by Sosnov et al,9 which reported that patients with chronic kidney disease (estimated glomerular filtration rate <60 mL·min⁻¹·1.73 m⁻²) in the Worcester Heart Attack Study were 43% less likely to report chest pain than patients.
without chronic kidney disease, independently of the presence of diabetes.

The cornerstone of AMI treatment is acute coronary reperfusion, but only a minority of the general population, those with STEMI presenting sufficiently early from symptom onset and no contraindications to treatment, are reperfusion eligible. The ECG (ST elevation or new left bundle-branch block) defines the initial patient population eligible for acute coronary reperfusion. In this study, we found a remarkable difference between ECG findings for dialysis patients with AMI and those for nondialysis AMI patients. Only 19.1% of dialysis patients had ST elevation, versus 35.9% of nondialysis patients. Assuming that all left bundle-branch blocks are new, an assumption that might be unpalatable in the clinical setting, by ECG criteria, 27.2% of dialysis patients and 41.7% of nondialysis patients might be considered for acute coronary reperfusion before exclusions (or 26.0% and 40.0%, respectively, using the definition of either ST elevation or new/unknown/old left bundle-branch block). By NRMI criteria, only 10.2% of dialysis patients and 24.6% of nondialysis patients were reperfusion eligible. Ultimately, only 8.3% of our dialysis cohort and 28.7% of our nondialysis cohort received acute coronary reperfusion.

From the perspective of our original speculations on underdiagnosis and therapeutic nihilism in dialysis patients with AMI, a third distinct category appears necessary: potential differences in pathophysiology. Our data support the concept of underdiagnosis of acute coronary syndromes, including AMI, and less aggressive treatment in dialysis patients with AMI; 47% of reperfusion-eligible dialysis patients and 75% of nondialysis patients received acute coronary reperfusion. However, the ECG data imply that there also may be an important mechanistic difference. A higher proportion of non-STEMI might suggest a greater prevalence of preexisting obstructive coronary artery disease and perhaps attendant increased coronary collateralization.

### Table 5: In-Hospital Laboratory and Clinical Event Variables for Dialysis and Nondialysis Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dialysis (n=3049)</th>
<th>Nondialysis (n=534 395)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac biomarkers†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatine kinase or creatine kinase-MB</td>
<td>1921 (68.7)</td>
<td>389 902 (78.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥2 times normal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Troponin elevated</td>
<td>2452 (92.1)</td>
<td>362 296 (84.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Troponin ≥2 times normal</td>
<td>2227 (85.0)</td>
<td>327 700 (78.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Left ventricular systolic function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction, mean±SD, %</td>
<td>41.7±15.5</td>
<td>46.3±14.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ejection fraction, median, %</td>
<td>40.0</td>
<td>47.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ejection fraction category</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40%</td>
<td>835 (27.4)</td>
<td>95 965 (18.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥40%</td>
<td>1120 (36.7)</td>
<td>242 543 (45.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Missing</td>
<td>1094 (35.9)</td>
<td>195 887 (36.7)</td>
<td></td>
</tr>
<tr>
<td>In-hospital outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive care unit stay, mean±SD, d</td>
<td>3.0±2.5</td>
<td>2.6±2.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Clinical events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death‡</td>
<td>578 (21.3)</td>
<td>49 092 (11.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>434 (14.2)</td>
<td>57 506 (10.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Recurrent ischemia/angina</td>
<td>266 (8.7)</td>
<td>63 856 (11.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Unexpected cardiac arrest</td>
<td>336 (11.0)</td>
<td>26 664 (5.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Congestive heart failure/pulmonary edema</td>
<td>766 (25.1)</td>
<td>101 949 (19.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypotension</td>
<td>734 (24.1)</td>
<td>77 458 (14.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>137 (4.5)</td>
<td>14 966 (2.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Recurrent myocardial infarction</td>
<td>46 (1.5)</td>
<td>9805 (1.8)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Cardiac rupture/pulseless electrical activity</td>
<td>38 (1.2)</td>
<td>3217 (0.6)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>178 (5.8)</td>
<td>24 233 (4.5)</td>
<td>0.0284</td>
</tr>
<tr>
<td>Sustained ventricular tachycardia/ventricular fibrillation</td>
<td>253 (8.3)</td>
<td>34 573 (6.5)</td>
<td>0.0022</td>
</tr>
</tbody>
</table>

Values are given as n (%) unless otherwise indicated.

*Probability values are adjusted for multiple comparisons with the Bonferroni method.

†Patient numbers may vary by row because of missing data.

‡Dialysis, n=2720; nondialysis, n=420 365; excludes transfer-out patients.
and myocardial ischemic preconditioning in dialysis patients, reducing the likelihood of transmural occlusion. Another less likely possibility (for which there are no supporting data) is that diagnostic ST elevation is somehow masked in dialysis patients suffering transmural ischemia; ie, the ECG is less accurate for identifying anatomically appropriate coronary reperfusion candidates. Our ECG findings differ from those reported by Berger at al\textsuperscript{10} using data from the Cooperative Cardiovascular Project (CCP). They found that 31.3% of dialysis patients and 37.4% of nondialysis patients with AMI in the CCP database had ECG findings of ST elevation. The reasons for these discordant findings are unclear. It is plausible, however, that treatment patterns could vary by registry. Berger et al\textsuperscript{10} reported a greater relative underuse of aspirin, \(\beta\)-blockers, and ACE inhibitors in dialysis patients than in nondialysis patients. Consistent themes reported in prior publications include the increased risk of death associated with chronic kidney disease and AMI, the inverse relationship of renal dysfunction and likelihood of receiving evidence-based therapies (aspirin, \(\beta\)-blockers, and ACE inhibitors) for improving survival, and the association with improved survival of these treatments in chronic kidney disease patients who sustain AMI\textsuperscript{10–14}.

The concept of “accelerated atherosclerosis” in dialysis patients was advanced in a classic article by Lindner et al\textsuperscript{15} 3 decades ago that was based on 39 patients. Surprisingly, few systematic attempts have been made in the modern treatment era to obtain coronary angiographic data for dialysis patients to better define the incidence, prevalence, and rate of progression of coronary artery disease in ESRD patients.

On the basis of our reported ECG and other clinical data, we believe that performing a prospective study of coronary angiographic and other clinical findings in dialysis patients with acute coronary syndrome would also be valuable.

Not unexpectedly, we found a markedly increased rate of in-hospital death for dialysis patients (21.3%, compared with 11.7% for nondialysis patients). We previously reported a 26% in-hospital death rate for dialysis patients hospitalized for AMI from 1977 through 1995.\textsuperscript{2} We also found a significant cardiac arrest hazard complicating AMI in dialysis patients; 11% of dialysis patients versus 5% of nondialysis patients sustained an unexpected cardiac arrest. Sudden cardiac death is the single largest cause of death among chronic dialysis patients;\textsuperscript{16} that they would also be at increased vulnerability to cardiac arrest in the setting of acute myocardial ischemia is not surprising.

We have attempted to provide a clinical picture of the special characteristics of dialysis patients with AMI to better understand the potential mechanisms for their poor outcome. Our study is limited by its uncontrolled, observational nature and potential biases inherent in any selective registry. Nevertheless, we believe that our initial impressions are likely to be clinically valid on the basis of the data sources. Ultimately, we hope that these observations will help to increase awareness and understanding of the special characteristics of patients with chronic kidney disease, including ESRD, and to improve their care.

Acknowledgments

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Disclosures

Kathee Littrell and Martha Blaney are employed by Genentech, Inc, which sponsors NRMII. Paul D. Frederick is employed by ICON Lifecycle Sciences Group (formerly Ovation Research Group), which receives research funding from Genentech, Inc. Charles A. Herzog and Cheryl Arko report no conflicts.

References


**CLINICAL PERSPECTIVE**

Acute myocardial infarction (AMI) in dialysis patients is associated with poor long-term survival. Nearly three fourths of US dialysis patients hospitalized for AMI die within 2 years, and this outcome has not improved over 2 decades. Previous speculations have attributed this poor outcome to underdiagnosis (as a result of atypical presentations) and undertreatment (“therapeutic nihilism”). In this study, the clinical characteristics of 3049 dialysis and 534,395 nondialysis patients hospitalized for AMI were compared. The diagnostic suspicion for AMI was lower in dialysis patients: 45% of dialysis patients were not diagnosed with acute coronary syndrome, compared with 21% of nondialysis patients, reflecting in part the lower prevalence of chest pain (in 44% of dialysis patients and 68% of nondialysis patients). The cornerstone of AMI treatment is acute coronary reperfusion, and the ECG defines the initial population eligible for this treatment strategy. Only 19% of dialysis patients had ST elevation, versus 36% of nondialysis patients, and only 10% of dialysis patients versus 25% of nondialysis patients were eligible for reperfusion. In reperfusion-eligible cohorts, 47% of dialysis patients and 75% of nondialysis patients received acute coronary reperfusion. The overall in-hospital death rate was 21% in dialysis patients, versus 12% for nondialysis patients. The poor survival rate of dialysis patients after AMI appears to be attributable to their strikingly different clinical presentations (including lower proportion of ST-segment–elevation MI and attendant reperfusion eligibility) and to undertreatment. A high index of diagnostic suspicion for AMI (and greater use of “evidence-based” therapies) by clinicians is warranted in dialysis patients.
Parental Occurrence of Premature Cardiovascular Disease Predicts Increased Coronary Artery and Abdominal Aortic Calcification in the Framingham Offspring and Third Generation Cohorts

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Background—Parental premature cardiovascular disease (CVD) is a risk factor for coronary heart disease (CHD). We related validated parental premature CVD with the subclinical measures of coronary artery (CAC) and abdominal aortic (AAC) calcification in the community.

Methods and Results—We studied 2 generations of Framingham Heart Study subjects who underwent multidetector computed tomography measurements of CAC and AAC and who had 2 parents in the study. Subjects included 797 Framingham Offspring (mean age, 63 years; 56% women) and 1238 Third Generation (Gen3) (mean age, 46 years; 47% women) participants free of CVD. Generalized estimating equations adjusted for major CVD risk factors were used to relate validated parental premature CVD and CHD to CAC and AAC, defined by >90th percentile age- and sex-specific cut points from a healthy subsample. Parental premature CVD was associated with CAC among Gen3 (odds ratio=2.17 [1.41 to 3.33]; P<0.001) and nonsignificantly among Offspring (odds ratio=1.42 [0.91 to 2.22]; P=0.12). Parental premature CHD was associated with CAC among Gen3 (odds ratio=2.22 [1.22 to 4.01]) but not Offspring. Parental premature CVD was not associated with AAC in either cohort. Parental premature CHD was associated with AAC among Gen3 (odds ratio=1.65 [0.99 to 2.75]; P=0.05) but not among Offspring. The magnitude of risk conferred was greater for paternal than maternal premature CVD.

Conclusions—Parental premature CVD is associated with CAC, and premature CHD is associated with AAC, after adjustment for risk factors, particularly in younger middle-aged adults. Risk conferred by parental premature CVD on vascular calcification may be mediated through novel mechanisms not accounted for by classic CVD risk factors known to cause atherosclerosis. (Circulation. 2007;116:1473-1481.)

Key Words: calcium □ epidemiology □ imaging □ atherosclerosis □ coronary disease □ aorta

A reported “family history” of premature cardiovascular disease (CVD) is an independent risk factor for CVD1–14 and has been a recommended risk stratification marker in US guidelines for hypertension and hyperlipidemia treatment.15,16 US and European Task Force guidelines on CVD risk prevention both highlight that family history information may indicate a higher risk status than would be predicted by Framingham risk score and European SCORE risk tools.17,18

Furthermore, data demonstrate that the addition of family history information to risk prediction based on traditional CVD risk factors may substantially improve the prediction of elevated coronary artery calcium.19 This suggests that parental CVD confers proband risk via increased susceptibility for the occurrence of atherosclerosis in key vascular beds. Indeed, coronary calcium is a well-established measure of atherosclerosis that strongly predicts future CVD events.20–22 Whereas other major risk factors for CVD such as smoking, hyperlipidemia, and hypertension have been shown to be
associated with coronary artery calcification (CAC), few studies have examined the effects of family history of premature CVD on CAC.\textsuperscript{23-26} It remains unclear whether parental CVD confers increased risk for subclinical atherosclerosis in probands independent of shared risk factors. Limitations of previous analyses include selected study samples and the use of unvalidated family history information based on participant recall.\textsuperscript{27}

Familial occurrence of CVD may also predict atherosclerosis in other vascular beds. For example, abdominal aortic calcification (AAC) has been shown to be an independent predictor of CVD.\textsuperscript{28} Previous studies demonstrate that genetic factors account for 52% and 20% of the variability in AAC between parent-offspring and sibling pairs, respectively.\textsuperscript{29} Whereas traditional cardiovascular risk factors such as older age, hypertension, dyslipidemia, and smoking have been reported to be associated with AAC,\textsuperscript{30-32} the relationship between family history of premature CVD and AAC has not been well established.

With the recent completion of vascular calcification measurements with the use of multidetector computed tomography (MDCT) in both the Offspring cohort and Third Generation (Gen3) cohort of the Framingham Heart Study, we had a unique opportunity to examine the association of the validated occurrence of parental CVD with CAC and AAC in offspring in both a younger-adult cohort and a middle-aged cohort, respectively.

**Methods**

Participants for this study were drawn from the MDCT substudy of the community-based Framingham Heart Study, including both Offspring and Gen3 cohorts. The original Framingham Heart Study cohort was enrolled beginning in 1948.\textsuperscript{33} Beginning in 1971, 5124 children and spouses of children of the original cohort were enrolled in the Framingham Offspring Cohort.\textsuperscript{34} Beginning in 2002, 4095 Gen3 participants, who had at least 1 parent in the Offspring cohort, were enrolled into the Framingham Heart Study and underwent standard clinical examinations.

Between June 2002 and April 2005, 3483 participants (\(n=1390\) Offspring participants and \(n=2093\) Gen3 participants) underwent assessment of coronary artery and aortic calcium. Inclusion in this study was weighted toward participants from larger Framingham Heart Study families and those who resided in the Greater New England area. Men were at least 35 years of age and women at least 40 years of age and not pregnant, and all participants weighed <320 pounds. Of these, 1303 Offspring and 2087 Gen3 participants had interpretable CAC measurements. We excluded participants with only 1 parent participating in the Framingham Heart Study (because validated parental CVD information was not available on the other parent who did not participate in the Framingham Heart Study) (Offspring, \(n=425\); Gen3, \(n=558\)); with a father younger than 55 years or a mother younger than 65 years, irrespective of whether they had experienced a CVD event before that age (Gen3, \(n=276\); or with prevalent CVD at the time of the MDCT test (Offspring, \(n=81\); Gen3, \(n=15\)). After these exclusions, 797 Offspring and 1238 Gen3 participants remained eligible for analysis of CAC outcomes.

Among these 3483 participants in the MDCT study, 1384 Offspring and 2093 Gen3 had interpretable AAC measurements. We excluded participants with only 1 parent participating in the Framingham Heart Study (Offspring, \(n=461\); Gen3, \(n=562\)), with a father younger than 55 years or a mother younger than 65 years, irrespective of whether they had experienced a CVD event before that age (Gen3, \(n=274\), or with prevalent CVD at the time of the MDCT test (Offspring, \(n=115\); Gen3, \(n=21\)). After exclusions, 808 Offspring and 1256 Gen3 participants remained eligible for analysis of AAC outcomes.

**MDCT and Calcium Measurements**

All subjects were imaged with an 8-slice MDCT (Lightspeed Ultra, GE, Milwaukee, Wis). Each subject underwent 2 chest scans that were performed according to a sequential scan protocol with a slice collimation of \(8\times2.5\) mm (120 KVP, 320/400 mA for <220 and >220 lb body weight, respectively) during a single end-inspiratory breath hold (typical duration, 18 seconds). Image acquisition (330 ms) was prospectively initiated at 50% of the cardiac cycle. Thirty contiguous 5-mm-thick slices of the abdomen were acquired covering 150 mm above the level of S1. Calcium measurements were performed on an offline workstation (AcuStar, Terarecon, San Mateo, Calif) by 4 experienced observers (3 trained physicians and 1 trained technician). A calcified lesion in either the coronary arteries or the aorta was defined as an area of at least 3 connected pixels with CT attenuation \(>130\) Hounsfield units with the use of 3-dimensional connectivity criteria (6 points). Each scan was evaluated for the presence of CAC and AAC. A modified Agatson score (because the Agatson score was originally devised from electron beam computed tomography (CT) scans and then “modified” to MDCT) was determined, as has been described previously.\textsuperscript{35}

**Definition of CAC and AAC**

The presence of both CAC and AAC was defined as \(\geq90\)th percentile age-, sex-, and cohort-specific cut points based on a healthy referent sample (free of hyperlipidemia, diabetes, hypertension, smoking, and prevalent CVD). In secondary analyses, we defined CAC as \(\geq75\)th percentile age-, sex-, and cohort-specific study sample.

**Risk Factor Assessment**

At the baseline examination cycle (Offspring examination cycle 7 from 1998 to 2001; Gen3 examination cycle 1 from 2002 to 2005), participants underwent a routine physical examination, anthropometry, and laboratory assessment of vascular risk factors. Plasma glucose, total and high-density lipoprotein cholesterol, and triglycerides were measured on morning samples obtained after an 8-hour fast. Diabetes was defined as a fasting plasma glucose \(\geq126\) mg/dL or treatment with either insulin or an oral hypoglycemic agent. Participants were considered to be current smokers if they smoked at least 1 cigarette per day for the last year. Women were considered to be menopausal if their periods had stopped for at least 1 year. The median duration between baseline examination and MDCT measure was 4 years for Offspring participants and 0 years for Gen3 participants.

**Validated CVD Assessment**

For Offspring and Gen3 cohorts, parental CVD and CHD information was drawn from physician-adjudicated outcomes from the Framingham Original cohort and the Offspring Cohort, respectively. Using previously published Framingham Heart Study criteria to validate parental events,\textsuperscript{36} we defined a cardiovascular event as the occurrence of coronary death, myocardial infarction, stable or unstable angina pectoris, atherothrombotic stroke, intermittent claudication, or cardiovascular death. Hard coronary heart disease (CHD) events were defined as coronary death, myocardial infarction, or hospitalized coronary insufficiency only. Parental occurrence of premature CVD was defined as the occurrence of a validated parental event before the offspring MDCT examination and before age 55 years in a father and/or age 65 years in a mother. These age cut points were based on recommendations of the National Cholesterol Education Program Third Adult Treatment Panel\textsuperscript{13} and Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.\textsuperscript{16} We chose to study premature parental CVD in addition to premature parental CHD because we have previously demonstrated that premature parental CVD and premature parental CHD are independent risk factors for offspring CVD.\textsuperscript{37} This study was approved by the institutional review boards of the Boston University Medical Center and Massachusetts General Hospital. All subjects provided written consent.
Statistical Analysis

Parental (either maternal, paternal, or both) occurrence of premature CVD and premature CHD, and the separate paternal and maternal occurrence of these outcomes, were related to dichotomous variables for CAC and AAC. Generalized estimating equation logistic regression analysis was used to assess relations between parental occurrence of premature CHD/CVD and calcification. Generalized estimating equation models were employed to account for related observations given the presence of siblings in both the Offspring and Gen3 cohorts. Multivariable models were adjusted for age, sex, total/high-density lipoprotein cholesterol, lipid treatment, systolic blood pressure, hypertension treatment, body mass index, diabetes, smoking, hormone replacement therapy, and menopausal status. In secondary analyses, among Gen3, we assessed the association between parental premature CVD and CHD with the following mutually exclusive outcomes versus the referent category AAC and CAC: (1) AAC only ≥90th percentile; (2) CAC only ≥90th percentile; and (3) both CAC and AAC ≥90th percentile. All statistical analyses were performed with the use of SAS statistical software (version 9.0). A probability value <0.05 was considered statistically significant.

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 and CAC/AAC Prevalence

Baseline characteristics of the Offspring and Gen3 cohorts, including the prevalence of the occurrence of parental CVD and mean CAC and AAC scores, are shown in Table 1. The mean age of Offspring and Gen3 cohort participants was 63 and 46 years, respectively. Offspring cohort participants tended to have a higher prevalence of CVD risk factors including hypertension, diabetes, and a higher prevalence of hormone replacement therapy and lipid medication use compared with Gen3 participants. Both Offspring and Gen3 participants had mean body mass index values in the overweight range. Current cigarette smoking was reported by 13% of Gen3 and 11% of Offspring cohort participants. The positive parental occurrence of either CVD or CHD was 26% and 9%, respectively, in Offspring participants and 16% and 7%, respectively, in Gen3 participants. As expected, given the substantial difference in ages, the mean and median CAC and AAC scores were higher in Offspring than in Gen3 participants.

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Demographic and risk factor characteristics</th>
<th>Offspring (Total n=797)</th>
<th>Gen3 (Total n=1238)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62.5±8.5</td>
<td>46±5.5</td>
</tr>
<tr>
<td>Female sex, n</td>
<td>444 (55.7)</td>
<td>583 (47.1)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>202.5±35.3</td>
<td>193.8±33.7</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>54.2±15.7</td>
<td>53.8±17.4</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.2±5.1</td>
<td>27.6±6.9</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>124.8±17.3</td>
<td>119.5±18.6</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>75.1±9.3</td>
<td>77.8±24.3</td>
</tr>
<tr>
<td>Diabetes, n</td>
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<tr>
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<tr>
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<td>34.9±167.9</td>
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<td>174 (14.1)</td>
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<tr>
<td>AAC ≥90th percentile cut point</td>
<td>173 (21.7)</td>
<td>230 (18.6)</td>
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</table>

Value are expressed as mean±SD or n where indicated; percentages are in parentheses. HDL indicates high-density lipoprotein.
Table 2 shows the unadjusted prevalence of premature CVD and premature CHD by presence of CAC and AAC (defined by the 90th percentile age- and sex-specific cut point from a healthy referent group). For both Offspring and Gen3, CAC, there was generally a greater proportion of participants with a positive parental occurrence of premature CVD or of CHD above the AAC cut point compared with below the CAC cut point. Similarly, for both Offspring and Gen3, there was generally a greater proportion of participants with a positive parental occurrence of premature CVD or of CHD above the AAC cut point compared with below the AAC cut point (Table 2).

### Odds Ratios for Association of Premature Parental CVD With Vascular Calcification

Among Gen3 participants, parental premature CVD and parental premature CHD were both associated with a 2.2-fold increased odds of CAC (odds ratio [OR] = 2.17 [1.41 to 3.33]; P = 0.009, and 2.22 [1.22 to 4.01]; P < 0.001, respectively), after adjustment for age and other CVD risk factors (Table 3). Among Offspring participants, the multivariable-adjusted ORs were also increased but not statistically significant for association of parental premature CVD with CAC (OR = 1.42 [0.91 to 2.22]; P = 0.12) and for parental premature CHD with CAC (OR = 1.44 [0.80 to 2.59]; P = 0.22).

Among Gen3 participants, parental premature CVD was associated with AAC in age- and sex-adjusted models (P = 0.001 and P = 0.02, respectively); however, the strength and statistical significance of these associations were diminished after further adjustment for CVD risk factors (Table 3). Among Gen3 participants, parental premature CHD was associated with a 1.6-fold increased odds of AAC, of borderline statistical significance (OR = 1.65 [0.99 to 2.75]; P = 0.05). There was a more modest association of parental premature CVD with AAC in Offspring participants (OR = 1.38 [0.78 to 2.45]; P = 0.27), an association that was not statistically significant (Table 3).

We further examined these associations according to the occurrence of premature paternal and premature maternal CVD. Among Gen3 participants, premature paternal CVD was associated with a 2.9-fold increased odds of CAC (P = 0.0001) and a 2.2 increased odds of AAC (P = 0.02) (Table 3). Similarly, among Gen3 participants, premature paternal CHD was associated with a 2.2-fold increased odds of CAC (P = 0.04) and a 2.1 increased odds of AAC (P = 0.009). Premature paternal CHD was not associated with CAC or AAC among Offspring participants. There was no significant association of premature maternal CVD or premature maternal CHD with CAC or AAC in either Offspring or Gen3 participants.

### Adjustment for CVD Risk Factor Subgroups

We further examined the impact of adjustment for specific risk factors subgroups on the association between parental parental CVD outcomes with CAC and AAC in Gen3 (Table 4). The age- and sex-adjusted association between parental premature CVD and CAC among Gen3 was modestly attenuated by the addition of lipid covariates to age- and sex-adjusted models (age- and sex-adjusted OR = 2.39 [P < 0.001]; age-, sex-, total/HDL cholesterol–, and lipid treatment–adjusted OR = 2.29 [P = 0.002]; multivariable-adjusted OR = 2.17 [P = 0.004]). Similar findings of attenuation by lipid covariates were found for the association between premature CHD and CAC among Gen3. The age- and sex-adjusted association between parental premature CVD and AAC among Gen3 was modestly attenuated by the addition of cigarette smoking to the statistical model (age- and sex-adjusted OR = 1.80 [P = 0.002]; age-, sex-, and smoking-adjusted OR = 1.58 [0.02]; multivariable-adjusted OR = 1.39 [P = 0.1]).

### Secondary Analyses

When we utilized age-, sex-, and cohort-specific 75th percentile cut points derived from the entire Offspring and Gen3 samples undergoing MDCT scanning, premature parental CVD and premature parental CHD were both associated with a >2-fold increase in CAC in Gen3 (P < 0.05), but in Offspring participants the odds ratios for association were substantially lower (1.3- to 1.5-fold increase) and not statistically significant for associations with CAC (Table 1 in the online-only Data Supplement).

Among the 1230 Gen3 participants having both AAC and CAC measurements, the prevalence of the following mutually exclusive categories was as follows: both CAC and AAC <90th percentile, 73.7%; only CAC ≥90th percentile, 12.3%; only AAC ≥90th percentile, 7.7%; and both CAC and AAC ≥90th percentile, 6.3%. The ORs for associations of...
premature parental CVD and CHD with only AAC ≥90th percentile, only CAC ≥90th percentile, and both CAC and AAC ≥90th percentile, with the referent category being both CAC and AAC <90th percentile, are shown in the Figure. Premature parental CVD and CHD were most strongly and significantly associated with having only CAC ≥90th percentile.

**Discussion**

**Main Findings**

In 2 contemporary Framingham Heart Study cohorts with mean ages of 63 (Offspring cohort) and 46 (Gen3 cohort) years, respectively, we found that a validated parental occurrence of premature CVD was strongly and significantly associated with an elevated risk of CAC in the younger of the
2 cohorts, even after adjustment for risk factors. The parental occurrence of premature CVD and of premature CHD was also associated with AAC among Gen3 participants, although these associations were largely attenuated and not significant after adjustment for CVD risk factors. Our analyses suggest a stronger relationship of paternal versus maternal premature CVD with both CAC and AAC.

### Parental CVD and CAC in Offspring

Our finding that validated parental CVD is significantly associated with CAC in our younger subjects, using a 90th percentile cut point, substantially extends prior evidence. Our results are similar to recent findings in the Dallas Heart Study that demonstrated a significant association between family history of myocardial infarction and coronary calcium among younger (men ≤45 years, women ≤55 years) but not among older study participants (P for interaction ≤0.02).37 Furthermore, previous epidemiological studies demonstrated larger relative risks of CVD associated with parental myocardial infarction in younger versus older probands.38–40 The multivariable-adjusted 2-fold magnitude of increased risk for parental premature CHD with CAC in Gen3 participants is consistent with prior studies of populations with a similar age distribution (aged 32 to 47 years).41 A previous study of 8549 asymptomatic men and women (mean age, 53 ± 9 years) referred by their physicians for subclinical atherosclerosis screening by electron beam CT demonstrated a very similar association between premature parental CHD and both the presence of CAC, CAC ≥75th percentile, and the presence of at least moderate coronary calcification.26 Because we use validated parental CVD outcome information, our study extends these previous findings, which were recorded in a
higher-risk population that was not drawn from a general population and that utilized retrospective participant reports of family history data.

Use of 75th Percentile Cut Points Derived From the Broad Study Sample
To facilitate comparison of our results with those of Nasir and colleagues from the Multiethnic Study of Atherosclerosis (MESA), we analyzed our data utilizing CAC and AAC cut points similar to the cut points of their study. Among white participants in MESA, a positive family occurrence of CHD conferred an elevated odds of CAC $\geq$75th percentile of 1.97 (95% CI, 1.51 to 2.57). This estimate is nearly identical to our corresponding OR of 2.15 (95% CI, 1.02 to 4.52) for the association of parental premature CHD and CAC among Framingham Heart Study Gen3 participants.

Self-Reported Versus Validated Family History Data
Self-reported family history may be highly inaccurate because of significant reporter bias and/or misclassification compared with a family history validated by a physician adjudication panel. In the Framingham Offspring Cohort, the positive predictive value for a reported myocardial infarction in a father before age 55 years was only 28% when participant report was validated with medical records. Although use of the validated family history provides a state of the art exposure measure for the present study and as such provides the strongest level of evidence for the associations of family history with CAC, the family history in clinical practice is usually elicited by report and not by the use of primary medical records. The association of validated family occurrence of premature CVD with CAC/AAC in the context of aging should be explored in further investigations.

Parental Premature CVD and AAC in Offspring
Our finding that parental premature histories of CVD and CHD are associated with AAC in a younger and relatively low-risk cohort is a relatively novel finding. These associations are largely attenuated by multivariable adjustment except in the younger Gen3 cohort, suggesting that these associations, in older persons in particular, are largely a result of shared CVD risk factors. Future studies are needed to confirm these findings and to determine in other population settings whether family history consistently adds to prediction of AAC above and beyond classic CVD risk factors.

Differences in Association of Paternal Versus Maternal Occurrence of Premature CVD With CAC
Our finding that paternal premature CVD and CHD was associated with CAC and AAC, particularly in Gen3, is consistent with previous data linking paternal CHD with proband CHD. Our finding that maternal premature CVD/CHD was unrelated to CAC is surprising in light of previous data relating maternal premature myocardial infarction to offspring CHD, including some studies that suggest a stronger risk conferred by history of maternal versus paternal CVD. The magnitude and consistency of differences in risk conferred by maternal CVD versus paternal CVD on offspring CVD outcomes are still uncertain, but it may be that the mechanism of association of parental CVD with clinically apparent disease in offspring differs from the mechanism for increased risk for subclinical atherosclerosis in the coronary arteries or aorta. There may be significant sex-related differences between inherited triggers of CVD events versus inherited susceptibility to endothelial damage and atherogenesis. However, it remains uncertain whether maternal CVD confers CHD risk through mechanisms unrelated to atherosclerosis and therefore unrelated to vascular calcification. Further studies are needed to confirm any differential effect of premature paternal and maternal history of CVD/CHD on both outcomes and subclinical atherosclerosis manifested by vascular calcification.

Clinical Implications of Our Findings
The appropriate clinical role for CAC in risk screening is still being defined. Recent expert guidelines recommend coronary artery calcium screening only for individuals specifically having an “intermediate” 10-year CHD risk (ie, those with a 10% to 20%, 10-year CHD risk based on presence of conventional CVD risk factors). Our findings that parental history of premature CVD and CHD is associated with CAC, accounting for major CVD risk factors, suggest that family history information should be further investigated as a simple clinical indicator, in addition to the other risk factors in the Framingham risk algorithm, to identify individuals who might benefit from coronary artery calcium screening. Our study underscores the need for further observational and interventional studies to identify the appropriate patient subgroups in which CAC screening will add incremental information in addition to family history information and established risk factors to identify at-risk individuals in whom effective lowering of risk can be achieved.

Limitations
Several limitations should be acknowledged as well. Our study sample is limited both geographically and ethnically. Because our study sample is of largely white, European descent, generalizability to other ethnic groups may be limited. Because the distribution of CAC differs across various ethnic groups, and the risk of CAC given parental CVD varies across ethnicity, our findings should be confirmed in other populations. Among Offspring participants, the MDCT scans were done a median of 4 years after baseline examination (compared with Gen3, among whom the median was 0 years). Therefore, there was a greater opportunity for covariate misclassification in Offspring participants, which would have biased associations toward the null. Although we adjusted for most known traditional CVD risk factors in our analysis, residual confounding from covariates not measured in our study cannot be excluded. Survival bias could have attenuated associations between exposure and outcome in our study, especially among our older Offspring cohort participants. Additionally, we had limited power to detect very modest effect sizes for maternal and paternal premature CVD and CAC/CAC. We did not have adequate power to undertake sex-specific analyses among our study sample. We did
not analyze sibling history of premature CVD and CHD because sibling information was incomplete for several study participants (not all siblings participated in the Framingham Heart Study in several families). Accordingly, we chose to focus on the premature parental CVD and CHD occurrence. We could not combine the Gen3 and Offspring cohorts to formally assess an age interaction because of insufficient overlap in their respective age distributions.

In this study we used an 8-slice MDCT scanner, and we reported an Agatston score averaged from 2 sequential chest MDCT scans. Since the study inclusion, the temporal resolution and volume coverage of MDCT scanners has improved, with the introduction of 32- and 64-slice scanners from 330 ms to $\approx 165$ to 210 ms and from 18 seconds to $\approx 10$ to 14 seconds, respectively. However, in a recent report from the MESA study, the differences between different CT scanners appear negligible, at least on a population basis, and thus we do not believe that the use of an 8-slice scanner significantly decreased the accuracy of our calcium measurements. Finally, our MDCT coverage of the abdominal aorta significantly decreased the accuracy of our calcium measurement.

Conclusions

A validated parental occurrence of premature CVD and of premature CHD was significantly associated with increased coronary atherosclerosis, independent of traditional risk factors. We found that the relationship between parental premature CVD and CHD with CAC and AAC was strong and significant, particularly in our younger Framingham Heart Study subjects, suggesting possible age-dependent effects of parental premature CVD/CHD on atherosclerosis. The parental occurrence of premature CVD and of premature CHD was associated with AAC, although shared CVD risk factors appear to underlie much of these associations. Our analyses also suggest stronger relationships with CAC and with AAC of paternal premature CVD versus maternal premature CVD. These findings may have clinical implications as further evidence accrues regarding the appropriate use of family history information and subclinical disease screening over and above established risk factors.

Sources of Funding

This work was supported by the National Heart, Lung, and Blood Institute’s Framingham Heart Study (N01-HC-25195).

Disclosures

None.

References


**CLINICAL PERSPECTIVE**

We determined that parental history of premature cardiovascular disease and premature coronary heart disease is associated with high levels of coronary artery calcification after accounting for major cardiovascular disease risk factors. Additionally, we found that a positive history of parental premature cardiovascular disease and coronary heart disease was a risk factor for coronary artery calcification in middle-aged persons compared with elderly individuals. Prospective outcome studies are warranted to confirm that family history information considered in addition to other established cardiovascular risk factors may identify individuals who might benefit from coronary artery calcium screening. Our findings may have clinical implications as further evidence accrues regarding the appropriate use of family history information together with subclinical atherosclerosis screening over and above established risk factors.
Influence of Nonfatal Hospitalization for Heart Failure on Subsequent Mortality in Patients With Chronic Heart Failure

Scott D. Solomon, MD; Joanna Dobson, MSc; Stuart Pocock, PhD; Hicham Skali, MD; John J.V. McMurray, MD; Christopher B. Granger, MD; Salim Yusuf, MD, DPhil; Karl Swedberg, MD, PhD; James B. Young, MD; Eric L. Michelson, MD; Marc A. Pfeffer, MD, PhD; for the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) Investigators

Background—Patients with chronic heart failure (HF) are at increased risk of both fatal and nonfatal major adverse cardiovascular events. We used data from the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) trials to assess the influence of nonfatal hospitalizations for HF on subsequent mortality rates in a broad spectrum of HF patients.

Methods and Results—In the present study, 7599 patients with New York Heart Association class II to IV HF and reduced or preserved left ventricular ejection fraction were randomized to placebo or candesartan. We assessed the risk of death after discharge from a first hospitalization for HF using time-updated Cox proportional-hazards models on 7572 patients for whom discharge data were available. Of 7572 patients, 1455 (19%) had at least 1 HF hospitalization, and 586 of 1819 deaths occurred after discharge from an HF hospitalization. The mortality rate was increased after HF hospitalizations, even after adjustment for baseline predictors of death (hazard ratio, 3.15; 95% confidence interval, 2.83 to 3.50). Longer duration of HF hospitalization enhanced the risk of dying, as did repeat HF hospitalizations. Moreover, risk of death was highest within a month of discharge and then declined progressively over time, particularly for death resulting from HF progression and for sudden cardiac death. We observed a similar pattern of risk associated with all-cause hospitalization, although the magnitude was less than that with HF hospitalization.

Conclusions—In patients with chronic HF, the risk of death is greatest in the early period after discharge after a hospitalization for HF and is directly related to the duration and frequency of HF hospitalizations. These findings suggest a role for increased surveillance in the early postdischarge period of greatest vulnerability after an HF admission. (Circulation. 2007;116:1482-1487.)

Key Words: heart failure □ hospitalization □ mortality □ outcomes □ prognosis

Patients with chronic heart failure (HF) are at increased risk of both fatal and nonfatal major adverse cardiovascular events.1,2 Nonfatal events, including hospitalization for HF, myocardial infarction, and stroke, contribute to increased cost and reduced quality of life and portend increased risk of both additional nonfatal events and death.3-6 Although common, distressing, and expensive, symptomatic worsening of HF leading to hospital admission usually is not associated with a high inpatient mortality rate, but it is associated with an increased risk of subsequent death, although this relationship has not been examined in detail. A better understanding of the relationship between HF hospitalization and postdischarge death in patients with HF is important for a number of reasons. First, there are implications for clinical care and postdischarge surveillance. Second, a better understanding of this relationship may allow improvement of prognostic models. These, in turn, may aid targeting of expensive monitoring technologies and treatments. Clarification of the prognostic importance of HF hospitalization also is important from the perspective of clinical trials in which the use of this nonfatal outcome as a component of composite mortality-morbidity end points has been controversial.7

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The Candesartan in Heart failure: Reduction in Mortality and morbidity (CHARM) Program studied the effect of...
candesartan compared with placebo in a broad spectrum of patients with symptomatic HF and either reduced or preserved left ventricular ejection fraction (LVEF). We used data from the CHARM trials to assess the influence of a nonfatal hospitalization for HF on subsequent death in this broad spectrum of HF patients.

**Methods**

**Patients: The CHARM Program**

The CHARM program consisted of 3 independent, concurrently performed trials in which 7599 patients with New York Heart Association class II to IV chronic HF of ≥4 weeks’ duration were randomized to candesartan (target dose, 32 mg once daily) or matching placebo added to conventional background treatments. Patients were enrolled in the individual CHARM trials according to LVEF and baseline treatment with an angiotensin-converting enzyme (ACE) inhibitor. Patients with an LVEF ≤40% who were not receiving an ACE inhibitor because of intolerance were enrolled in CHARM-Alternative (n=2028). Patients who had an LVEF ≤40% and who were taking an ACE inhibitor were enrolled in CHARM-Added (n=2548). Patients with an LVEF >40% (with or without concomitant ACE inhibitor use) were randomized into CHARM-Preserved (n=3023). Overall, follow-up ranged from a median of 41 months in CHARM-Added and 37 months in CHARM-Preserved to 34 months in CHARM-Alternative (38 months in the overall CHARM Program). The primary outcome in the individual component trials of the CHARM program was the composite of cardiovascular death or hospital admission with worsening HF analyzed by time to first event, and the primary outcome of the overall CHARM Program was all-cause mortality. The design, baseline findings, and primary results of the CHARM program have been reported in detail.8–11

**Statistical Analysis**

First hospitalizations for HF were related to subsequent risk of death by the use of time-updated Cox proportional-hazards models. The time-updated variable for HF hospitalization comes into play at hospital discharge. Thus, HF hospitalizations that led directly to death (ie, the patient never left the hospital) were not attributed to the subsequent mortality risk. The 27 patients for whom the discharge date was missing were excluded, leaving 7572 patients for the present analysis. Only a first hospitalization for HF was considered for the initial analysis. Both unadjusted and covariate-adjusted hazard ratios are reported, with adjustment for those baseline predictors of all-cause mortality identified in previous analyses.5 We further explored the relationship between duration of hospital stay and risk of death after discharge, the relationship between hospitalization for HF and specific causes of death, and the effect of multiple HF hospitalizations on subsequent mortality rates. For the analysis of multiple hospitalizations, only those hospitalizations that investigators had identified as resulting from worsening HF were included, and the sample size was reduced to 7549 patients because of missing data. Death rates by both length of hospital stay and time since HF hospitalization were obtained with a Poisson survival model with covariate adjustment. To determine the prognostic significance of any hospitalization in this population, we also assessed the relation-
ship between all first hospitalizations for any cause and subsequent mortality rates.

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**

Of the 7572 patients included in this analysis, 1455 had at least 1 hospitalization for HF and were subsequently discharged from hospital. Of these, 869 patients survived to the end of the trials, and 586 patients died during the follow-up period. Regardless of whether patients had an LVEF ≤40% or >40%, patients with a hospitalization for HF were older, were more likely to be diabetic, had worse baseline New York Heart Association class, were more likely to have been hospitalized for HF in the 6 months before randomization, and were less likely to have been randomized to candesartan (Table 1). Of the patients who were hospitalized for HF, those who subsequently died during follow-up were older and were more likely to have cardiomegaly, to be underweight, and to have been hospitalized for HF in the 6 months before randomization, also regardless of whether LVEF was ≤40% or >40%.

Of the 1819 overall deaths in the trial, 586 occurred after hospital discharge for a first HF hospitalization. The estimated crude hazard for all-cause mortality after discharge following a first hospitalization for HF (Table 2) was 4.55 times that of patients never hospitalized for HF or yet to be hospitalized and discharged (95% confidence interval [CI], 4.11 to 5.03) and remained elevated after adjustment for baseline predictors of mortality (hazard ratio, 3.15; 95% CI, 2.83 to 3.50).

The mortality risk after a hospitalization for HF subsequently declined over time (Figure 1), with an estimated 6-fold excess risk in the first month after discharge falling to a doubling of risk after 2 years after discharge compared with those not hospitalized for HF. The risk of dying also was related to the length of HF hospitalization, with long HF hospitalizations (≥22 days) carrying more than double the mortality risk of short HF hospitalizations (≤7 days) (Figure 2). Both time from HF hospitalization and duration of HF hospitalization were predictive of death independently of each other (Figure 3).

Patients who died after a hospitalization for HF were at the greatest increased risk of dying of progressive HF, followed by sudden death (Figure 4). For each cause of death, the risk of death decreased with time from discharge, an effect that was most marked for death resulting from progressive HF. The relationships between time from discharge and subse-

<table>
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<th>TABLE 2. Hazard Ratio for All-Cause Mortality After Discharge From Hospitalization for HF and by Baseline Characteristics</th>
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<td>Hazard Ratio (95% CI)</td>
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BMI indicates body mass index.
sequent mortality outcomes and between duration of HF hospitalization and mortality outcomes were similar in patients with LVEF >40% and ≤40% and in patients from different geographic regions, with no interaction observed on the basis of LVEF >40% or ≤40% or geography.

The risk of death increased with each additional HF hospitalization, with a nearly 30% cumulative incremental risk associated with discharge from a second or third HF hospitalization (Figure 5). However, ≥4 HF hospitalizations carried no additional risk. Duration of longest HF hospitalization, time from most recent discharge, and number of HF hospitalizations all contributed substantively to a combined model of mortality based on HF hospitalizations. Hospitalization for any cause similarly increased the risk of subsequent death, with a similar declining risk after hospital discharge, although the magnitude of the risk was less compared with hospitalization for HF (Table 3).

**Discussion**

The CHARM program, which enrolled a broad group of symptomatic HF patients across the full spectrum of LVEF, provides a unique opportunity to assess the influence of an HF hospitalization on subsequent risk of dying after discharge. We found that hospitalization for HF conferred a significantly increased risk of subsequent death. Moreover, this risk was inversely related to the time since discharge, was increased after longer hospital stay, and was further increased after additional HF hospitalizations.

We observed that a number of factors affect the influence of HF hospitalization on subsequent death after discharge, including duration of hospital stay, time from HF hospitalization, and number of HF hospitalizations. Peripheral edema, duration of treatment with intravenous diuretic, renal impairment, concurrent respiratory problems, and factors requiring social intervention have been associated with increased length of stay. The thresholds for the decision to hospitalize and its duration can be influenced by HF severity and comorbidity, as well as local practice patterns. We adjusted for the former by including those baseline covariates that most contributed to death in our overall multivariable mortality model. That we did not observe any heterogeneity based on geography suggests that these findings are valid even accounting for local practice pattern differences.

The finding that the risk of death was highest in the immediate postdischarge period and declined steeply and exponentially thereafter is in contrast to the relatively stable
overall mortality risk over time observed in HF trials in general, including CHARM, and is reminiscent of the initially high mortality risk observed in the post–myocardial infarction setting.15 Indeed, a discrete HF hospitalization event appears to place a patient in a much higher risk category. This was true for patients in CHARM whether they had reduced or preserved LVEF.

That risk is highest in the immediate postdischarge period has potentially important clinical implications. The initially high and subsequently declining risk indicates that patients are particularly vulnerable in the early postdischarge period and require heightened surveillance, especially if the hospital admission has been prolonged or if the patient has had prior admissions for worsening HF. We also observed that the risk of sudden unexpected death was highest in the immediate postdischarge period, a finding that also has been seen in the early post–myocardial infarction period.16 Early intervention at clinic or home visits might help to detect and treat HF patients before decompensation, especially because we found that the greatest increased risk and most likely cause of death after discharge was progressive HF. Similarly, careful monitoring of electrolytes may be important in ameliorating the risk of sudden death, particularly because these patients have generally experienced recent changes in diuretic dose and the addition of other treatments that influence blood chemistry. Indeed, patients identified as being at particularly high risk using these simple measures might represent a selected population in which new but relatively expensive technologies permitting remote monitoring (using either external or internal devices) that have shown promise in clinical trials might play a role.17 Although our findings suggest a relative concordance of hospitalization for HF and mortality risk in the immediate postdischarge period, we cannot say that this would invalidate HF hospitalization as an independent end point in all populations, especially because some therapies might reduce hospitalization without reducing long-term mortality rates.

A number of limitations of this analysis should be noted. Although we had data on length of HF hospitalization and baseline data from randomization on comorbidity, we could not easily incorporate time-updated comorbidity data into our models. It is likely that additional factors beyond HF hospitalization duration and number such as change in New York Heart Association class or weight loss may have contributed to risk and that more detailed knowledge of patient characteristics at the time of HF hospitalization may add to a time-updated predictive model. In addition, we were not able to determine to what extent patients were discharged with the anticipation that they would die soon. Because a number of patients with advanced HF are discharged to hospice or a chronic care facility with the expectation that death is imminent, the increased risk of death observed in the early postdischarge period may be elevated secondary to an over-representation of these types of patients. Finally, we cannot exclude potential bias in categorizing cause of death when death occurred shortly after a HF hospitalization.

In summary, we have found that HF hospitalization, its duration, and its frequency are important predictors of increased subsequent death after discharge in symptomatic chronic HF patients with reduced or preserved LVEF. This risk appears to be greatest in the early postdischarge period and declines over time. These findings may help to identify HF patients at greatest risk of dying and suggest a role for increased surveillance in the early postdischarge period.

Source of Funding

The CHARM program was funded by AstraZeneca.

Disclosures

Drs Solomon, Dobson, Pocock, McMurray, Granger, Yusuf, Swedberg, Young, and Pfeffer have received research funding from AstraZeneca. Drs Pocock, McMurray, Granger, Yusuf, Swedberg, Young, and Pfeffer have consulted for or have received honoraria from AstraZeneca. Dr Michelson is an employee of AstraZeneca. Dr Skali reports no disclosures.

References


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<td>6.18</td>
<td>4.81</td>
</tr>
<tr>
<td>1–3</td>
<td>4.39</td>
<td>3.50</td>
</tr>
<tr>
<td>3–6</td>
<td>3.54</td>
<td>2.86</td>
</tr>
<tr>
<td>6–12</td>
<td>3.11</td>
<td>2.59</td>
</tr>
<tr>
<td>12–24</td>
<td>2.46</td>
<td>2.06</td>
</tr>
<tr>
<td>&gt;24</td>
<td>1.93</td>
<td>1.48</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio.


**CLINICAL PERSPECTIVE**

Patients with chronic heart failure are at increased risk for both fatal and nonfatal cardiovascular events, including hospitalization for recurrent episodes of heart failure. We used data from the Candesartan Heart failure: Reduction in Mortality and morbidity (CHARM) program to elucidate the subsequent risk of death associated with a heart failure hospitalization. We found that the mortality rate was highest early after a heart failure hospitalization and declined rapidly thereafter. Moreover, patients who were hospitalized longer or more frequently had a higher subsequent mortality risk. These data suggest that chronic heart failure patients are most vulnerable in the immediate aftermath of a hospital admission and suggest a potential role for increased surveillance during this period.

Go to http://cme.ahajournals.org to take the CME quiz for this article.
High Blood Pressure Trends in Children and Adolescents in National Surveys, 1963 to 2002

Rebecca Din-Dzietham, MD, MPH, PhD; Yong Liu, MS; Marie-Vero Bielo, MD; Falah Shamsa, PhD

Background—Secular trend data on hypertension in children and adolescents are scarce and inconsistent. In the face of growing obesity, we sought to assess high blood pressure (HBP) secular trends in children and adolescents enrolled in national surveys and to determine whether the HBP trend reversed its course with the rise in obesity.

Methods and Results—National survey data obtained from multistage probability sampling of the US noninstitutionalized population from 1963 to 2002 were examined; 8- to 17-year-old non-Hispanic blacks and whites and Mexican Americans were included. HBP ascertainment was based on age-, gender-, and height percentile–specific systolic and diastolic BPs. Weighted analyses were performed to account for the complex design. The BP, pre-HBP, and HBP trends were downward from 1963 to 1988 and upward thereafter. Pre-HBP and HBP increased 2.3% (\(P=0.0003\)) and 1% (\(P=0.17\)), respectively, between 1988 and 1999. Obesity increase, more so abdominal than general obesity, partially explained the rise in HBP and pre-HBP from 1988 to 1999. BP and HBP reversed their downward trends 10 years after the increase in the prevalence of obesity. Additionally, an ethnic and gender gap appeared in 1988 for pre-HBP and in 1999 for HBP; non-Hispanic blacks and Mexican Americans had a greater prevalence of HBP and pre-HBP than non-Hispanic whites, and males had a greater prevalence than females.

Conclusions—HBP and pre-HBP in children and adolescents are on the rise. These new findings have implications for the cardiovascular disease public health burden, particularly the risk of a new cardiovascular disease transition. They reinforce the urgent call for early prevention of obesity and HBP and illustrate racial/ethnic disparities in this age group. (Circulation. 2007;116:1488-1496.)

Key Words: epidemiology | hypertension | obesity | pediatrics | trends

Hypertension in adults remains a major public health problem. Several studies support the theory that the roots of essential hypertension may extend back to childhood.1 With obesity reaching epidemic proportions2 and obesity in children and adolescents being one of the strongest predictors of young adulthood hypertension,3 along with childhood blood pressure (BP) level and family history of hypertension, it is important to determine whether the prevalence of hypertension is increasing or decreasing in children and adolescents. This question is even more pertinent when we consider that the incidence of type 2 diabetes mellitus in youth is increasing, a direct result of the increase in childhood obesity.4 A recent study in a national sample has documented the BP increase in children and adolescents since the late 1980s.5 However, data on secular trends of BP in children and adolescents are scarce and inconsistent.6,7 Moreover, they are based on samples that are not nationwide. The limited national data on hypertension prevalence in children and adolescents enrolled in the earliest National Health and Nutrition Examination Survey (NHANES) showed a decreasing trend, although the investigators used the adult definition of hypertension.8,9 Trends in adult hypertension in NHANES exhibited an upward slope from 1988 to 1994 after a long period of downward slope.10,11

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We used the US National Health Surveys data (1963 to 2002) (1) to describe the trends of age-adjusted prevalence of high BP (HBP) and mean BP for boys and girls 8 to 17 years of age, (2) to describe these trends by racial/ethnic-gender and age groups, and (3) to examine the impact of increasing obesity on these trends, hypothesizing that the HBP trend would reverse its course in relation to the obesity trend.

Methods

Study Population

The study population consisted of boys and girls aged 8 to 17 years who participated in the National Health Examination (NHES), the Hispanic Health and Nutrition Examination Survey (HHANES), and the NHANES. These surveys were conducted by the National Center for Health Statistics (NCHS) on a nationwide probability sample of the civilian noninstitutionalized US population and based on a
TABLE 1. Measures of Observer Bias: Weighted Prevalence of Matching of Arm Circumference With Cuff Size

<table>
<thead>
<tr>
<th>Cuff Size</th>
<th>1963–1964 n (%)</th>
<th>Correctly Cuffed (SE, %)*</th>
<th>Undercuffed (SE, %)</th>
<th>Overcuffed (SE, %)</th>
<th>1999–2002 n (%)</th>
<th>Correctly Cuffed (SE, %)*</th>
<th>Undercuffed (SE, %)</th>
<th>Overcuffed (SE, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child</td>
<td>2431 (56.3)</td>
<td>63.0 (2.0)</td>
<td>0.3 (0.2)</td>
<td>36.7 (2.0)</td>
<td>807 (22.6)</td>
<td>0.451 (0.029)</td>
<td>92.8 (1.5)</td>
<td>0.02 (0.2)</td>
</tr>
<tr>
<td>Adult</td>
<td>1606 (40.3)</td>
<td>87.5 (1.6)</td>
<td>7.5 (1.1)</td>
<td>5.0 (1.0)</td>
<td>2598 (58.8)</td>
<td>0.468 (0.040)</td>
<td>76.7 (2.8)</td>
<td>21.6 (3.0)</td>
</tr>
<tr>
<td>Large Adult</td>
<td>143 (3.1)</td>
<td>88.0 (4.4)</td>
<td>10.5 (4.3)</td>
<td>1.5 (0.9)</td>
<td>923 (16.2)</td>
<td>0.457 (0.030)</td>
<td>72.1 (3.7)</td>
<td>26.2 (3.7)</td>
</tr>
<tr>
<td>Adult thigh</td>
<td>2 (0.3)</td>
<td>100.0 (0.0)</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
<td>150 (2.4)</td>
<td>0.444 (0.024)</td>
<td>59.4 (6.6)</td>
<td>40.6 (6.6)</td>
</tr>
</tbody>
</table>

AC/CW indicates ratio of arm circumference to cuff width.

*Criteria for AC-CW matching varied: (1) NHANES III: child cuff if AC=18.0 to 26.0 cm, adult cuff if AC=26.1 to 35.0 cm, large adult cuff if AC=35.1 to 47.0 cm, and thigh cuff if AC=47.1 to 66.0 cm; (2) continuous NHANES: child cuff if AC=17.0 to 21.9 cm, adult cuff if AC=22.0 to 29.9 cm, large adult cuff if AC=30.0 to 37.9 cm, and thigh cuff if AC=38.0 to 47.9 cm.

†Cuff size was not recorded for NHANES-NHES.

complex multistage sampling design. The periods of examination were 1963 to 1965 (NHES II; 6 to 11 years of age), 1966 to 1970 (NHES III; 12 to 17 years of age), 1971 to 1975 (NHANES I), 1976 to 1980 (NHANES II), 1982 to 1984 (HHANES), 1988 to 1994 (NHANES III), and 1999 to 2002 (continuous NHANES). However, NHANES II and NHES III were collapsed for the current analyses.

These surveys included an initial household interview, followed by an examination in an equipped mobile examination center. Data on physical measurements and physiological tests were collected through standardized physical examinations. Adjusted sampling weights were computed to account for the complex sampling strategy and to reflect the US civilian noninstitutionalized population at the time of the survey. Details on the surveys design and procedures have been published.12–19 The HHANES is a survey of 3 Hispanic subgroups—Mexican Americans, mainland Puerto Ricans, and Cuban Americans—in selected areas of the United States. It covered ~76% of the 1980 Hispanic-origin population in the United States and used the same data collection techniques as the national surveys.20

English-speaking children who self-reported their race as non-Hispanic black or white or Mexican American (included since 1988) were included. The “other” (other Hispanics, Asians, and Native Americans) racial/ethnic groups were excluded because of small numbers (n = 946). Children with congenital kidney or heart diseases (International Classification of Diseases, ninth revision, clinical modification, code 753 or 745 to 747, respectively, n = 142) were excluded (to exclude secondary hypertension), as were pregnant girls (n = 119) and participants with poor-quality data (as defined by NCHS investigators; n = 6).21 Participants with missing data for BP (n = 1232), weight, and height (n = 468) also were excluded. The final sample sizes were 11 339, 3405, 2985, 2771, 4183, and 4482 for NHES I–III, NHANES I, NHANES II, HHANES, NHANES III, and continuous NHANES, respectively. Informed consent and assent were signed by all participants and parents, and the study was approved annually by the Centers for Disease Control and Prevention (CDC) institutional review board.12–17,19

BP Measurement and HBP Definition

BP measurement methods varied over time and between surveys. On the basis of the NCHS documentation, procedures were similar for 2 consecutive surveys (NHES II and III, NHANES I and II, and NHANES III and continuous NHANES). At all periods, the procedure for measuring BP followed the American Heart Association recommendations; that is, sitting BP was measured several times in only 1 session. To differentiate the outcome of interest in the present study from the rigorous definition of hypertension, this outcome is labeled HBP, but the same cutoff points are used. Therefore, by analogy with the task force classification, the BP categories were defined as normal BP (observed systolic [SBP] and DBP <90th percentile), pre-HBP (observed SBP or DBP ≥90th percentile but <95th percentile or DBP ≥120/80 mm Hg but below 95th percentile), and HBP (observed SBP or DBP ≥95th percentile). Pre-HBP is relevant because clinically, children who chronically have BP values at ≥90th percentile exhibit signs of early target-organ damage in young adulthood.28–30

Pre-HBP is defined as DBP ≥90th percentile but <95th percentile or DBP ≥120/80 mm Hg but below 95th percentile. HBP is defined as DBP ≥95th percentile. Pre-HBP and HBP are both considered high BP. The new definitions are based on the 2000 CDC growth chart values for a child of the same age and gender, and the 2000 CDC growth chart values for a child of the same age and gender using a modified LMS (median [M], standard deviation [S], and the power in the Box-Cox transformation [L]) estimation procedure.27 The new guidelines recommend multiple BP measurements at different times to define persistent hypertension.
Exposure and Covariates

Time, the exposure variable for the trend study, was categorized into 6 levels corresponding to the survey’s period of examination (NHES II and III were collapsed).

The sampling plan for NHANES is based on age at interview. Age was defined as a continuous variable for assessment of confounding and categorized into 8 to 11, 12 to 14, and 15 to 17 years for stratified analyses to proxy the effect of puberty. This categorization is clinical and not data based; it was used because the Tanner index of sexual maturation was not measured at all periods.29,32 The race/ethnicity categories included non-Hispanic blacks (blacks), non-Hispanic whites (whites), and Mexican Americans.

Obesity was assessed by body mass index (BMI; in kg/m²) for age,27 an index of overall obesity, and by waist circumference (in cm; not measured in NHANES I and II), an index of visceral adiposity. Body weight was measured to the nearest 0.05 kg and height to the nearest 0.1 cm.

Statistical Analyses

Analyses were performed with SAS33 and SUDAAN34 to obtain correct variance estimates. NCHS-computed sampling weights were used in the analyses to account for differential probability of selection resulting from the cluster design, planned oversampling of selected subgroups (children, blacks, and Mexican Americans), unit nonresponse, and noncoverage. Estimates derived from a sample size smaller than the recommended sample size for the design effect or the estimated proportion were considered unreliable and reported with a footnote.21,35

For the trends analyses, prevalence of HBP and pre-HBP and distribution of mean BP were standardized to the 2000 census 5-year age distribution by the direct standardization method. These analyses were conducted on the total population and then stratified by age group and gender-race/ethnicity.

Two methods were used to assess the impact of obesity rise on HBP/pre-HBP increase between NHANES III and IV: multivariate logistic regression to establish the likelihood of HBP by obesity status and direct standardization to quantify the magnitude of HBP/pre-HBP prevalence increase accounted for by the increase in obesity during this same period. In the first procedure, NHANES 1988 to 1994 and 1999 to 2002 datasets were pooled, and the original NCHS-computed weight for each survey was used. For HBP, there was a marginally significant 3-way interaction by time and race/ethnicity across time (P = 0.09), mainly because of an interaction of BMI with race/ethnicity in 1988 to 1994 (P < 0.001) and 1999 to 2002 (P = 0.05). For pre-HBP, there was a marginally significantly 3-way interaction between obesity and race/ethnicity across time (P = 0.06), resulting mainly from a significant interaction of BMI with race/ethnicity in 1988 to 1994 (P = 0.03) but not in 1999 to 2002 (P = 0.6). In contrast, the effect of waist circumference was constant across time and racial/ethnic groups. Therefore, subsequent analyses were performed separately for each period to account for the interaction by time. To account for the race/ethnicity-by-BMI interaction, race/ethnicity-specific models were fit that included age, gender, and BMI-for-age z scores. Waist circumference was strongly collinear with BMI; hence, it was analyzed in a separate model.

Second, the impact of obesity on the HBP increase was further quantified by direct standardization using the NHANES 1988 to 1994 distribution of BMI or waist circumference to compute the NHANES 1999 to 2002 estimates.8 The resulting change in HBP and pre-HBP prevalence was evaluated.

The statistical method to obtain variance estimates was Taylor linearization.21 We used the Student t test for 2 independent samples (2-sided) to test whether the difference in HBP/pre-HBP prevalence between NHANES III and NHANES 1999 to 2002 and the impact of BMI rise on this difference were statistically significant.26 The nominal cutoff points for statistical significance were 0.05 for main effect and 0.10 for interactive effects. 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

Study Population Characteristics

Table 2 displays the study population characteristics by race/ethnicity. The age and gender distribution remained almost stable over time. As expected, general and abdominal obesity increased over time in all racial/ethnic groups.

Trends of HBP and BP

High Blood Pressure

Table 3 displays the distribution of HBP. Males tended to have slightly greater HBP prevalence than females. Age-adjusted HBP prevalence tended to decrease between 1963 and 1988 to 1994 and to increase thereafter. In 1999 to 2002, the age-adjusted prevalences of HBP were 4.2% (SE, 0.7%), 3.3% (SE, 0.6%), and 4.6% (SE, 0.6%) for blacks, whites, and Mexican Americans, respectively. The distribution of HBP exhibited many unreliable estimates (Table 3). A gender and ethnic disparity appeared in 1999, whereas it appeared in 1988 for pre-HBP (data not shown).

Table 4 details the increase in prevalence that occurred between 1988 and 2002. Pre-HBP and HBP increased by 2.3 (P = 0.0003) and 1 (P = 0.17) percentage points, respectively. The pre-HBP increase was significant for blacks and Mexican Americans, whereas the HBP increase was significant for Mexican American males and white females. However, we must place a note of caution for the HBP data because in many cases the sample size is too small to yield reliable estimates, even though there were significant differences.

Blood Pressure

Figure 1 displays the BP trends for lean, at risk for overweight, and overweight, along with the prevalence trends for the latter 2 groups. As expected, the trend of SBP and DBP mirrored that of HBP. The mean increase in age-adjusted BP between 1988 to 1994 and 1999 to 2002 was greater for DBP (8.4 mm Hg; SE, 1.1 mm Hg; P < 0.001) than for SBP (1.3 mm Hg; SE, 0.5 mm Hg; P = 0.01). The age-adjusted mean increase in SBP between 1988 to 1994 and 1999 to 2002 was comparable for lean (1.0; SE, 0.4), at-risk-for-overweight (0.9; SE, 1.1), and overweight (0.6; SE, 1.0) children and adolescents, whereas the DBP increase during that same period was greater and significant for lean (9.2; SE, 1.2) than for at-risk-for-overweight (7.4; SE, 1.8) and overweight (4.7; SE, 2.3) children.

Upward Trends of HBP and Obesity

Obesity increased in a monotonic fashion beginning with the earliest survey (1963 to 1970) for blacks and whites (Table 2). However, the trends differed in their patterns: stepwise for at risk for overweight and curvilinear for overweight (Figure 1). The increase in BP/HBP/pre-HBP lagged 10 years behind the increase in obesity (Figure 1 and Table 3; data not shown for pre-HBP).

As expected, both BMI and waist circumference significantly increased the likelihood of HBP. In 1999 to 2002, the odds ratios (ORs) for HBP were 2.1 (95% confidence interval [CI], 1.5 to 3.0), 1.8 (95% CI, 1.2 to 2.6), and 3.2 (95% CI, 2.4 to 4.4) for blacks, whites, and Mexican Americans, respectively, for 1 BMI z-score unit increment. For pre-HBP,
they were 1.6 (95% CI, 1.4 to 1.7), 1.7 (95% CI, 1.4 to 2.1), and 1.7 (95% CI, 1.4 to 2.0). Relative to a child at the median BMI for age and sex, a child 1 z score higher would have a BMI that was between 2.1 and 3.5 kg/m² higher, depending on age and sex. Conversely, the OR for waist circumference was constant for both outcomes. The corresponding ORs were 1.28 (95% CI, 1.26 to 1.31), 1.28 (95% CI, 1.24 to 1.33), and 1.35 (95% CI, 1.32 to 1.38) for HBP and 1.22 (95% CI, 1.21 to 1.23), 1.28 (95% CI, 1.26 to 1.31), and 1.28 (95% CI, 1.24 to 1.33) for pre-HBP among the 3 respective ethnic groups for a 5-cm increment in waist circumference. Obesity rise had the greatest impact in blacks and Mexican Americans for HBP and in Mexican Americans only for pre-HBP (Figures 2 and 3).

Discussion

Summary of Results

The present study explored the trends of HBP in children and adolescents in a nationally representative sample of 8- to 17-year-old subjects over the past 40 years and the impact of obesity increase on these trends in the past 10 years. We found that the prevalence of elevated BP has been on the rise among US children and adolescents since the late 1980s, after a long period of decreasing trend. The BP rise lags behind the increase in obesity. The increase in obesity, more so abdominal obesity than general obesity, accounts for part of the upward trend of HBP. The ethnic divergence in BP distribution paralleled the ethnic changes in obesity. Finally, the racial/ethnic disparity in HBP is a recent phenomenon in this age group. To the best of our knowledge, this is the first report of such findings.

Comparison With Other Studies

The few studies of children that have examined secular BP trends as a function of secular obesity yielded inconsistent results. In the Minneapolis Children’s BP Study of 10- to 14-year-old children, SBP percentiles were significantly higher and DBP percentiles were significantly lower in 1996 than in 1986, whereas in the Bogalusa study, both SBP and DBP decreased at the end of the study periods (1975 to 1981 and 1984 to 1992) but obesity increased in both cohorts. The effect of obesity was evaluated in the former study and explained the SBP secular increase only. That DBP increased more rapidly than SBP in our study may be a reflection of early subclinical vascular disease because impairment of arterial compliance and endothelial function have been linked to weight (ie, low birth weight and excess current weight) in youth.

Despite the BP measurement variation, the downward BP trends seem real and universal; they have been described in a variety of settings. In the 1960s, such a downward trend was reported in children and adolescents by the NCHS investigators using the adult definition of hypertension, that is, BP ≥140/90 mm Hg. The prevalence of hypertension decreased from 0.6% to 0.4% among the 6- to 11-year-old children and from 6.4% to 3.6% among the 12- to 17-year-old adolescents between 1971 to 1975 and 1976 to 1980. The same downward pattern has been described in adults enrolled in NHANES and among young adults in the United King-
dom and Australia.39 Goff et al40 analyzed the BP decline in adults 18 to 74 years of age enrolled in NHES/NHANES 1960 to 1994 by 10-year birth cohorts from 1887 to 1975. They also found that more recent cohorts had lower BPs than 1960 to 1994 by 10-year birth cohorts from 1887 to 1975.

In these studies, obesity rise (as assessed by BMI) accounted for a variable proportion of the BP/hypertension increase: 29% of SBP and 12% of DBP increase in youth5 and 44% of hypertension increase in adults between 1988 to 1994 and 1999 to 2000.11 In the present study, the increase in HBP was attenuated by 27% and 68%, respectively, suggesting that the recent increase in the prevalence of pediatric HBP is explained, at least in part, by the increase in BMI and waist circumference. That the 1984 to 1999 DBP increase is greatest among lean individuals reinforces the fact that obesity is not the sole factor (this observation is not an artifact because the median for lean remained constant over time). The greater impact of abdominal obesity on elevated BP rise is consistent with findings in adult hypertension.41

Another intriguing finding is that the BP/HBP increase lagged 10 years behind the obesity increase. The question then is why the downward BP trends persist in the face of increasing obesity trends. Although this question is beyond the scope of our study, we might speculate on a few reasons. In Figure 1, we notice that in 1963 to 1980, the prevalence of at risk for overweight was stable, whereas that of overweight then is why the downward BP trends persist in the face of increasing obesity trends. Although this question is beyond the scope of our study, we might speculate on a few reasons.

The upward pattern also mirrors the adult hypertension trends in NHANES11 and the BP trends in children and adolescents.5 In these studies, obesity rise (as assessed by BMI) accounted for a variable proportion of the BP/hypertension increase: 29% of SBP and 12% of DBP increase in youth5 and 44% of hypertension increase in adults between 1988 to 1994 and 1999 to 2000.11 In the present study, the increase in HBP was attenuated by 27% and 68%, respectively, suggesting that the recent increase in the prevalence of pediatric HBP is explained, at least in part, by the increase in BMI and waist circumference. That the 1984 to 1999 DBP increase is greatest among lean individuals reinforces the fact that obesity is not the sole factor (this observation is not an artifact because the median for lean remained constant over time). The greater impact of abdominal obesity on elevated BP rise is consistent with findings in adult hypertension.41

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### TABLE 3. Age-Adjusted and Age-Specific Prevalence (%) of HBP by Gender and Race/Ethnicity Over Time

<table>
<thead>
<tr>
<th></th>
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<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1963–1970</td>
<td>37.2 (0.7)</td>
<td>16.9 (1.0)</td>
<td>11.1 (1.1)</td>
<td>4.7 (1.0)</td>
<td>2.7 (0.5)</td>
<td>3.7</td>
<td>5.5</td>
<td>5.5</td>
<td>5.5</td>
<td>5.5</td>
<td>4.0</td>
<td>4.0</td>
<td>4.0</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>1971–1975</td>
<td>34.7 (2.0)</td>
<td>17.8 (2.2)</td>
<td>10.5 (2.1)</td>
<td>...</td>
<td>...</td>
<td>3.7</td>
<td>8.1</td>
<td>8.1</td>
<td>8.1</td>
<td>8.1</td>
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<td>4.2</td>
<td>4.2</td>
<td>4.2</td>
</tr>
<tr>
<td>1976–1980</td>
<td>37.5 (0.8)</td>
<td>16.7 (1.0)</td>
<td>11.2 (1.2)</td>
<td>...</td>
<td>...</td>
<td>2.5</td>
<td>3.3</td>
<td>3.3</td>
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</tr>
<tr>
<td>1982–1984</td>
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<td>...</td>
<td>...</td>
<td>...</td>
<td>4.8</td>
<td>2.5</td>
<td>2.5</td>
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<td>2.5</td>
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<td>1999–2002</td>
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</tr>
</tbody>
</table>

*HBP (≥95th percentile) frequency is <7.
†HBP (≥95th percentile) frequency is 0.
whereas the prevalence of at risk for overweight remained stable, although at a higher level. During 1988 to 2002, we observed the reversed, upward HBP trend. It is therefore conceivable that it may take obesity that amount of time to induce cardiovascular modifications that will lead to HBP years later or that there is a threshold effect at the population level. Only cohort studies can adequately address such a question.

TABLE 4. Increase in Age-Adjusted Prevalence (SE) of Pre-HBP and HBP During 1988 to 2002 by Gender and Race/Ethnicity

<table>
<thead>
<tr>
<th></th>
<th>Total, n</th>
<th>Cases, n</th>
<th>% (SE)</th>
<th>Total, n</th>
<th>Cases, n</th>
<th>% (SE)</th>
<th>Difference (SE)</th>
<th>P*</th>
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<tr>
<td>Pre-HBP</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>All</td>
<td>300</td>
<td>7.7 (0.7)</td>
<td>463</td>
<td>10.0 (0.6)</td>
<td>2.3 (0.6)</td>
<td>0.0003</td>
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<tr>
<td>Non-Hispanic blacks</td>
<td>8.1 (1.0)</td>
<td>12.8 (1.1)</td>
<td>4.7 (0.5)</td>
<td>0.0001</td>
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<td>778</td>
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<td>758</td>
<td>15.9 (1.7)</td>
<td>3.9 (1.8)</td>
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<tr>
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<td>755</td>
<td>3.9 (1.0)</td>
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<td>9.6 (1.1)</td>
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<td>1.4 (1.1)</td>
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<td>637</td>
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<td>617</td>
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<td>0.6 (1.3)</td>
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<td>10.9 (0.9)</td>
<td>4.0 (1.0)</td>
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<td>876</td>
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<td>All</td>
<td>118</td>
<td>2.7 (0.5)</td>
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<td>1.0 (0.4)</td>
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<td>0.8 (0.7)</td>
<td>0.25</td>
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<td>16</td>
<td>3.5 (0.8)</td>
<td>−0.1 (1.1)</td>
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<td>7</td>
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<td>15</td>
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<td>1.9 (0.8)</td>
<td>0.03</td>
<td></td>
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<tr>
<td>Mexican Americans</td>
<td>2.5 (0.7)</td>
<td>4.6 (0.6)</td>
<td>2.1 (0.6)</td>
<td>0.002</td>
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<tr>
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<td>34</td>
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<tr>
<td>Females</td>
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<td>1.9 (0.6)</td>
<td>30</td>
<td>3.9 (0.8)</td>
<td>2.0 (0.8)</td>
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</table>

*P value, pooled t test for H0: $P_{1988-94}=P_{1999-02}$; df=93 (49 for NHANES III + 44 for NHANES 1999 to 2002).

**Figure 1.** Trends of youth anthropometric status-specific BP and prevalence of at risk for overweight (Ov.) and overweight.
A latent factor that may explain the downward BP trend is lifestyle changes. We cannot rule out the effect of increased awareness of cardiovascular disease risk factors and consequent lifestyle changes, as suggested by the study by Goff et al in which the BP downward shift in adults had bearing on the whole BP distribution. Although the interventions were directed mostly at adults, the whole family may have reaped the benefits of healthy behavioral changes. Sodium intake and physical inactivity, which are strong correlates of HBP, were not consistently measured in NHANES. Hence, their potential beneficial effect cannot be evaluated. Current data suggest an increased sedentary lifestyle in children and adolescents, as defined by television viewing time, and increased sodium intake. Thus, these 2 habits would not explain the downward trend either. In their review of secular trends in BP in early life, McCarron et al allude to other factors that may reduce adulthood hypertension prevalence, such as birth weight, childhood growth, and early diet, including salt restriction in infancy, breastfeeding, and increased intake of fruits and vegetables. Further work is required to understand the mechanisms by which SBP and HBP continued to decrease while obesity increased. These protective factors may be promoted in this phase of a reversed, upward BP/HBP trend.

Methodological Issues
The most important methodological issue is the variation of BP measurement across study periods. If the multiplicity of BP measures within a visit attenuates the effect of the child’s anxiety toward this procedure, the lack of repeat BP measurements over time overestimates the individual’s values by not accounting for the effect of regression toward the mean. However, the impact on trends should be minimal, if any, because this emotional component is constant over time.

The improvement in quality-control monitoring measures in national surveys over time is demonstrated by the reduction of prevalence of 0-end-digit preference. Australian investigators found that digit-preference bias tended to overestimate hypertension prevalence. Digit-preference bias

Figure 2. Impact of obesity rise as assessed by BMI and waist circumference (WC) on the rise of HBP in 1988 to 1999 by race/ethnicity and gender. *Standardized (std) by the distribution of BMI or WC in NHANES III.

Figure 3. Impact of obesity rise as assessed by BMI or waist circumference (WC) on the rise of pre-HBP in 1988 to 1999 by race/ethnicity and gender. *Standardized (std) by the distribution of BMI or WC in NHANES III.
would not play a great role in our study because the NHES survey had among the lowest prevalence of digit preference (24%) yet the greatest HBP prevalence.

Another important potential source of error is the use of inappropriate cuff size in relation to arm circumference. It has been demonstrated that undercuffing overestimates and over-cuffing underestimates BP. As a result of the data in Table 1, the 1988 to 1999 HBP prevalence gradient may be smaller than observed.

Finally, we cannot exclude the latent confounding effect of inconsistently measured variables such as physical activity or sexual maturation, which play an important role in hemodynamics and physiological maturation. These limitations do not minimize the strengths of this study. This study uses national representative data that included multiethnic groups to document for the first time the HBP and pre-HBP trends and racial/ethnic disparities in children and adolescents. It also documents the new fact that the cardiovascular risk for the young Mexican-American male is about to surpass that for young non-Hispanic blacks.

Conclusions

HBP and pre-HBP are on the rise in children and adolescents after a long period of decline. This observation has great public health importance because elevated BP is a major risk factor for cardiovascular disease. This rise can be explained, at least in part, by obesity, particularly abdominal obesity. These results point to the need to adopt multiple strategies aimed at preventing the clustering of risk factors, called metabolic syndrome, in children and adolescents, particularly those belonging to racial/ethnic minority groups. Prevention is particularly important in view of the possibility that the current generation of children may be the first to have shorter life expectancies than their parents.50

Source of Funding

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Disclosures

Dr Shamsa has received support from the Georgia Cancer Coalition.

References

28. Jiang X, Srinivasan SR, Radhakrishnamurthy B, Dufierre ER Jr, Bao W, Berenson GS. Microalbuminuria in young adults related to blood pressure...


35. Flegal K, Carroll M, Ogden C, Johnson C. Prevalence and trends in general obesity, partially accounts for the elevated blood pressure trend. For example, had the distribution of waist circumference and trend analyses. *Int J Epidemiol.* 1997;26:122–125.


**CLINICAL PERSPECTIVE**

Using the 1963 to 2002 national survey data, we found that, after a long period of decline, the prevalence of elevated blood pressure has reversed its trends since 1988. However, the increase over the last 2 survey periods (1988 to 1994 and 1999 to 2002) is greater and significant for pre–high blood pressure (2.3%; *P*<0.0003) than for high blood pressure (1%; *P*=0.17). Because this is the beginning of the upward trend, strong action taken now may prevent the progress of such a trend. Therefore, it is advisable to measure blood pressure at every visit with the appropriate technique to rank the child’s measured blood pressure from the Centers for Disease Control and Prevention growth charts and the gender-, age-, and height-specific blood pressure table (published by the National Task Force) and to follow the recommendations proposed by this body for elevated blood pressure management. The second observation was that obesity, more so abdominal than general obesity, partially accounts for the elevated blood pressure trend. For example, had the distribution of waist circumference remained at the 1988 to 1994 level, the prevalence of pre–high blood pressure in 1999 to 2002 would have been lower by almost two-thirds. We draw 3 conclusions: (1) Measurement of waist circumference should become a routine clinical act, along with measurement of height and weight; (2) components of the metabolic syndrome should be monitored; and (3) pre–high blood pressure should be managed as vigorously as high blood pressure, especially because the Bogalusa studies have shown that the former leads to early target-organ damage in young adulthood. Special attention must be paid to minorities, particularly young Mexican American boys. Finally, the Centers for Disease Control and Prevention should consider building growth charts for waist circumference similar to the other anthropometric variables charts.
Effects of Random Allocation to Vitamin E Supplementation on the Occurrence of Venous Thromboembolism

Report From the Women’s Health Study

Robert J. Glynn, PhD, ScD; Paul M Ridker, MD; Samuel Z. Goldhaber, MD; Robert Y.L. Zee, PhD; Julie E. Buring, ScD

Background—Supplementation with vitamin E may antagonize vitamin K in healthy adults, but it is unclear whether intake of vitamin E decreases the risk of venous thromboembolism (VTE).

Methods and Results—The Women’s Health Study randomized 39,876 women ≥45 years of age to receive 600 IU of natural source vitamin E or placebo on alternate days. Before randomization, 26,779 participants gave blood samples, which were used to determine factor V Leiden, G20210A prothrombin, and 677C>T MTHFR polymorphisms. Documented VTE (including deep vein thrombosis or pulmonary embolism) and unprovoked VTE (no recent surgery, trauma, or cancer diagnosis) were prospectively evaluated, secondary end points of the trial. During a median follow-up period of 10.2 years, VTE occurred in 482 women: 213 in the vitamin E group and 269 in the placebo group, a significant 21% hazard reduction (relative hazard, 0.79; 95% CI, 0.66 to 0.94; P=0.010). For unprovoked VTE, the hazard reduction was 27% (relative hazard, 0.73; 95% CI, 0.57 to 0.94; P=0.016). In subgroup analyses, the 3% of participants who reported VTE before randomization had a 44% hazard reduction (relative hazard, 0.56; 95% CI, 0.31 to 1.00; P=0.048), whereas women without prior VTE had an 18% hazard reduction (relative hazard 0.82; 95% CI, 0.68 to 0.99; P=0.040). Women with either factor V Leiden or the prothrombin mutation had a 49% hazard reduction associated with vitamin E treatment (relative hazard, 0.51; 95% CI, 0.30 to 0.87; P=0.014).

Conclusions—These data suggest that supplementation with vitamin E may reduce the risk of VTE in women, and those with a prior history or genetic predisposition may particularly benefit. (Circulation. 2007;116:1497-1503.)

Key Words: venous thrombosis ■ pulmonary embolism ■ randomized controlled trials ■ thromboembolism ■ vitamin E

Venous thromboembolism (VTE) is a common and clinically serious event, with an age-related incidence that increases from ≈1 case per 1000 person-years at age 50 years to ≈5 cases per 1000 person-years at age 75 years. Risk factors for venous thromboembolism include a prior event, surgery, trauma, immobilization, prothrombotic mutations, older age, greater body mass index, and hormone therapy. However, VTE commonly occurs in people without identifiable risk factors, whereas others with multiple factors remain event free.

Clinical Perspective p 1503

Both basic research and observational epidemiological studies support the hypothesis that vitamin E can inhibit oxidative injury and reduce the risk of cardiovascular disease and cancer. However, large-scale randomized trials have not found evidence that vitamin E supplementation prevents cancer or major cardiovascular events. Nonetheless, vitamin E supplementation might influence risk of VTE through alternative pathways. Specifically, animal studies indicate that vitamin E supplementation has an anticoagulant effect in the presence of low vitamin K intake. Although vitamin E intake does not alter coagulation times in humans, experimental evidence indicates that vitamin E supplementation may inhibit vitamin K and hence vitamin K–dependent clotting factors. Vitamin E has also been shown to inhibit platelet adherence. The relevance of these relationships for the risk of VTE is unclear.

The Women’s Health Study tested whether vitamin E supplementation for 10 years decreased the risk of cardiovascular disease or cancer in a large group of women without these diseases at entry. We report here the effect of random-
ized allocation to vitamin E or placebo on the occurrence of VTE, a prospectively evaluated, secondary end point of this trial.

Methods

Study Design

The Women’s Health Study was a randomized, double-blind, placebo-controlled, 2X2 factorial trial evaluating the balance of risks and benefits of low-dose aspirin (100 mg every other day; Bayer Healthcare) and vitamin E (600 IU of α-tocopherol every other day; Natural Source Vitamin E Association) in the primary prevention of cardiovascular disease and cancer.9,14,15 Originally, a third component, beta carotene, was also included. However, this component was terminated early in January 1996 after a median treatment duration of 2.1 years.16 Written informed consent was obtained from all participating women. The trial was approved by the institutional review board of Brigham and Women’s Hospital and monitored by an external data and safety monitoring board.

Details about the study design and relationships of vitamin E treatment with cancer and cardiovascular disease have been described previously.9 Between September 1992 and May 1995, letters of invitation to participate in the trial and baseline health questionnaires were mailed to >1.7 million female healthcare professionals throughout the United States; 453,787 women completed the questionnaires, and 65,169 were willing and eligible to participate. Eligibility criteria included the following: age ≥45 years; no previous history of coronary heart disease, cerebrovascular disease, cancer (except nonmelanoma skin cancer), and other major chronic diseases including dementia, chronic kidney or liver disease, gout, or gastrointestinal bleeding; and no use of individual supplements of vitamin A, E, or beta carotene more than once a week. Before randomization, women were asked whether they ever had deep vein thrombosis or pulmonary embolism, but those with a positive history were not excluded. However, women who currently used anticoagulants were excluded.

Eligible women were enrolled in a 3-month run-in period of placebo administration to identify a group likely to be compliant with long-term treatment; 39,876 women were willing, eligible, and compliant during the run-in period, and they were randomized to vitamin E (n = 19,937) or placebo (n = 19,939) and separately to aspirin or matching placebo.

During the run-in period, women were asked to provide a blood sample, and DNA was extracted from 26,779 randomized participants who provided samples. Genotyping for factor V Leiden, the G20210A prothrombin mutation, and the 677C>T polymorphism in methylenetetrahydrofolate reductase (MTHFR) was performed with the use of multiplex polymerase chain reaction and linear immobilized probe assays as previously described (Roche Molecular Systems, Alameda, Calif.).17,18 Linear array processing was facilitated by the use of AutoRELI-Mark II (Dynal Biotech, UK). To confirm genotype assignment, scoring was performed by 2 independent observers, and discordant results (<1% of all scoring) were resolved by a joint reading and, when necessary, repeat genotyping.

Treatment and Follow-Up

Each year, women received an annual supply of calendar packs that contained active agents or placebo. Every 6 months for the first year and annually thereafter, they also received follow-up questionnaires that inquired about compliance with pill-taking, potential adverse effects, occurrence of end points, and risk factors. Treatment and follow-up continued in a blinded fashion until the scheduled end of the trial (March 31, 2004). At the end of blinded treatment, mortality status was known for 99.4% of participants, and questionnaires reporting morbidity were received from 97.2% of surviving participants.

On the basis of self-reported compliance from follow-up questionnaires, 78.9% of participants reported taking at least two thirds of their vitamin E or matching placebo capsules at 5 years, and 71.6% reported this level of compliance at 10 years. Averaged throughout the trial, 75.8% of women reported this level of compliance, with no difference between active and placebo groups (P = 0.64). Use of vitamin E supplements outside the trial for at least 4 days per month (“drop-ins”) was reported by 10.0% of participants at 5 years and 10.9% of participants at 10 years. Such outside use of vitamin E supplements throughout the trial averaged 8.6% of women in the active group and 8.9% of women in the placebo group (P = 0.07).

End Point Definition

On each follow-up questionnaire, women were asked separately about the new occurrence of deep vein thrombosis and pulmonary embolism. Those reporting events, including next-of-kin of deceased, were asked for permission to obtain medical records. An end points committee of physicians reviewed records in a blinded fashion. Diagnosis of deep vein thrombosis was confirmed by a positive report of venous ultrasound or venography, and diagnosis of pulmonary embolism was considered confirmed in the presence of a positive angiogram or computed tomography scan of the chest or a ventilation-perfusion scan with ≥2 mismatched defects. Deaths due to pulmonary embolism were confirmed when autopsy reports, symptoms, circumstances of death, and medical history were consistent with this diagnosis. Only events confirmed by the end points committee were included.

Unprovoked deep vein thrombosis or pulmonary embolism was defined as occurring in the absence of known malignancy (diagnosed either before or up to 3 months after the VTE), trauma, or surgery within 3 months before the VTE. Provoked VTE included events that occurred in patients with cancer or during or shortly after trauma or surgery.

Statistical Analysis

Primary analyses compared the occurrence of VTE between treatment groups in all randomized subjects classified according to the intention-to-treat principle. The primary end point for this analysis was the first occurrence of VTE after randomization, including women both with and without prior VTE reported at baseline. A second event after randomization was not considered, although women who had both pulmonary embolism and deep vein thrombosis within 3 days at the time of their index event were counted toward each of these specific outcomes. Secondary end points included unprovoked VTE, pulmonary embolism as the first event, and deep vein thrombosis as the first event.

Subgroup analyses considered the effects of vitamin E on the incidence of VTE within categories of risk factors for VTE. Risk factors evaluated were age, body mass index, menopausal status, and use of hormone therapy, prior history of VTE, factor V Leiden, the prothrombin mutation, and the MTHFR 677C>T polymorphism.19 The approach of Kaplan and Meier was used to estimate the overall cumulative incidence of VTE by treatment group, as well as the cumulative incidence of unprovoked VTE and the cumulative incidence among women with reported VTE at baseline and those with prothrombotic mutations. The log-rank test was used for crude comparisons of incidence rates. Estimates of the relative hazard of VTE by vitamin E assignment and associated 95% CIs were based on proportional hazards models that controlled for age and other randomized treatments and stratified on reported VTE at baseline.

Subgroup analyses used proportional hazards models stratified on prerrandomization VTE and adjusted for age and other randomized treatments. Heterogeneity in the relationship between vitamin E treatment and VTE across categories of a risk factor was evaluated by adding interaction terms between vitamin E and the risk factor to proportional hazards models, with tests for trend performed when subgroup categories were ordinal. As a sensitivity analysis to consider the impact of compliance, additional proportional hazards models were fitted with follow-up time censored when a woman reported taking less than two thirds of her study vitamin E (or matching placebo) during the preceding year. The validity of the proportional hazards assumption was tested by inclusion of an interaction between vitamin E and the log of follow-up time, with time centered at the average log follow-up.20 Additionally, separate proportional hazards models were fitted to the experience of the first
5 years of follow-up and the experience after 5 years to estimate the effects of treatment in early and later follow-up.

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 and VTE Occurrence

Women assigned to active vitamin E and those assigned to placebo had comparable distributions of demographic, medical, and genetic determinants of VTE (Table 1). In terms of important risk factors for VTE, 3% of participants reported a prior VTE at baseline, 5% had factor V Leiden, and 3% had the prothrombin mutation. In addition, 10% of women were ≥65 years of age, 30% currently used hormone therapy, and 18% were obese (body mass index ≥30 kg/m²).

During a median follow-up of 10.2 years (interquartile range, 9.7 to 10.6 years), 482 women had a confirmed VTE (Table 2). Half of the cases had unprovoked VTE, and 37% involved pulmonary embolism. The overall incidence of VTE

<table>
<thead>
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<th>TABLE 1. Baseline Characteristics in the Women’s Health Study</th>
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<td>55–64 y</td>
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<tr>
<td>≥65 y</td>
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<tr>
<td>Race, %</td>
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<td>Hispanic</td>
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<td>Asian or Pacific Islander</td>
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<td>Body mass index, %</td>
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<td>25.0–29.9 kg/m²</td>
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<td>Prothrombin mutation, %</td>
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<td>677C→T MTHFR TT, %</td>
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*Among women with blood samples.

<table>
<thead>
<tr>
<th>TABLE 2. Incidence and Relative Rates of VTE According to Treatment Assignment</th>
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<td>Unprovoked VTE*</td>
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<tr>
<td>Provoked VTE*</td>
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<tr>
<td>Pulmonary embolism†</td>
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<td>Deep vein thrombosis only†</td>
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<tr>
<td>VTE, first 5 y</td>
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<tr>
<td>VTE, after 5 y</td>
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</tbody>
</table>

*Six women with confirmed VTE (2 in the vitamin E group and 4 in the placebo group) had insufficient information to determine whether the event was provoked.

†Seventy-six women (30 in the vitamin E group and 46 in the placebo group) had confirmed pulmonary embolism and deep vein thrombosis diagnosed within 3 days of each other, and they are counted with pulmonary embolism only.
per 1000 person-years rose from 0.9 in women 45 to 54 years of age at baseline, to 1.4 in women 55 to 64 years of age, and to 2.5 in women ≥65 years of age at baseline. VTE occurred nearly as often as stroke in this study (487 women had a stroke) and more frequently than myocardial infarction (391 women had a myocardial infarction).

**Vitamin E and VTE**

VTE occurred in 213 women assigned to vitamin E, compared with 269 women in the placebo group (Table 2), a significant 21% reduction in the hazard of VTE associated with vitamin E (relative hazard, 0.79; 95% CI, 0.66 to 0.94; \( P = 0.010 \)). Analyses restricted to unprovoked VTE found a slightly larger 27% reduction in hazard associated with vitamin E (\( P = 0.016 \)). Vitamin E treatment was associated with a 28% reduction in the hazard of pulmonary embolism (\( P = 0.034 \)), whereas the association with deep vein thrombosis only was somewhat weaker and not significant (\( P = 0.10 \)). The relationship of vitamin E with VTE was not significantly modified by either of the other randomized treatments (aspirin or beta carotene), nor did it differ in analyses that censored a woman at the time her compliance was less than two thirds. In particular, among women assigned to active aspirin therapy, the relative hazard of VTE associated with vitamin E was 0.83 (95% CI, 0.64 to 1.07), whereas among women assigned to placebo aspirin, the relative hazard of VTE associated with vitamin E was 0.75 (95% CI, 0.58 to 0.97). Furthermore, no evidence was observed for a varying effect of vitamin E by time: Identical 21% reductions in hazard were observed during the first 5 years of the trial and thereafter. The estimated 10-year risk of VTE was 1.1% in the vitamin E group and 1.4% in the placebo group (Figure).

**Subgroup Analysis**

Examination of the effects of vitamin E on the hazard of VTE in subgroups revealed no significant heterogeneity between groups, either for demographic and medical characteristics (Table 3) or genetic factors (Table 4). The highest subgroup-specific rates of VTE occurred in women who reported a history of VTE at baseline. For them, vitamin E treatment was associated with a significant 44% reduction in the hazard of VTE (relative hazard, 0.56; 95% CI, 0.31 to 1.00; \( P = 0.048 \)). Among women who reported a VTE before randomization, the estimated 10-year risk of a confirmed new VTE was 3.2% in the vitamin E group and 5.5% in the placebo group (Figure). A significant (\( P = 0.040 \)) 18% reduction in the hazard of VTE was observed among women without a history of VTE at baseline.

Women with genetic polymorphisms known to influence VTE had elevated event rates in the placebo group (Table 4). Vitamin E was associated with a significant (\( P = 0.014 \)) 49% reduction in the hazard of VTE among women with either factor V Leiden or the prothrombin mutation. In TT homozygotes for the MTHFR polymorphism, vitamin E was associated with a nonsignificant (\( P = 0.061 \)) 48% reduction in the hazard of VTE.

Altogether, the Women’s Health Study randomized 3097 women at particularly high risk of VTE because of either a history of prior VTE or presence of factor V Leiden or the prothrombin mutation. Vitamin E treatment was associated with a 49% reduction in the hazard of VTE in these women (relative hazard, 0.51; 95% CI, 0.33 to 0.77; \( P = 0.002 \)). Furthermore, the 10-year risk of VTE in these women was 4.1% in the placebo group, compared with 2.1% in the vitamin E group (Figure).
Discussion

In this large-scale, long-term trial, 600 IU of natural source vitamin E on alternate days was associated with a significant 21% reduction in the hazard of VTE, a significant 27% reduction in the hazard of unprovoked VTE, and a significant 28% reduction in the hazard of pulmonary embolism. The effect of vitamin E was uniform over the 10-year follow-up period and did not vary substantially across subgroups. Among women at high risk because of prior history or prothrombotic mutations, vitamin E was associated with significant 40% to 49% reductions in the hazard of VTE. The absolute reduction in the 10-year risk of VTE was modest in the overall population (0.3%) but substantial (2.0% to 2.3%) in women at high baseline risk. The estimated numbers of women who need to be treated with vitamin E for 10 years to prevent 1 VTE were 357 (95% CI, 200 to 1659) in the overall population and 52 (95% CI, 32 to 144) in the high-risk subgroup of women with a history of VTE or prothrombotic mutation.

VTE is a common, potentially catastrophic clinical event with age-specific rates of occurrence in the Women’s Health Study comparable to those observed in population-based

### TABLE 3. Incidence and Relative Rates of VTE in Clinically Important Subgroups, According to Treatment Assignment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Vitamin E</th>
<th>Placebo</th>
<th>Hazard Ratio (95% CI)</th>
<th>P for Interaction*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45–54</td>
<td>102</td>
<td>116</td>
<td>0.88 (0.68–1.15)</td>
<td>0.21</td>
</tr>
<tr>
<td>55–64</td>
<td>69</td>
<td>96</td>
<td>0.71 (0.52–0.97)</td>
<td></td>
</tr>
<tr>
<td>≥65</td>
<td>42</td>
<td>57</td>
<td>0.74 (0.50–1.10)</td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25.0</td>
<td>69</td>
<td>106</td>
<td>0.66 (0.48–0.89)</td>
<td>0.23</td>
</tr>
<tr>
<td>25.0–29.9</td>
<td>85</td>
<td>85</td>
<td>0.98 (0.73–1.33)</td>
<td></td>
</tr>
<tr>
<td>≥30</td>
<td>55</td>
<td>70</td>
<td>0.78 (0.55–1.11)</td>
<td></td>
</tr>
<tr>
<td>Menopause and hormone replacement therapy‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>45</td>
<td>55</td>
<td>0.82 (0.56–1.22)</td>
<td>0.57</td>
</tr>
<tr>
<td>Uncertain</td>
<td>36</td>
<td>35</td>
<td>1.05 (0.66–1.67)</td>
<td></td>
</tr>
<tr>
<td>Postmenopausal, current hormone replacement therapy</td>
<td>73</td>
<td>97</td>
<td>0.76 (0.56–1.03)</td>
<td></td>
</tr>
<tr>
<td>Postmenopausal, no hormone replacement therapy</td>
<td>57</td>
<td>79</td>
<td>0.70 (0.50–0.99)</td>
<td></td>
</tr>
<tr>
<td>Reported VTE at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>195</td>
<td>238</td>
<td>0.82 (0.68–0.99)</td>
<td>0.22</td>
</tr>
<tr>
<td>Yes</td>
<td>18</td>
<td>31</td>
<td>0.56 (0.31–1.00)</td>
<td></td>
</tr>
</tbody>
</table>

*The null hypothesis is that there are no differences between subgroups; for age and body mass index, the interaction is between the continuous variable and treatment.

†Eight hundred twenty women with missing data on body mass index at baseline are excluded.

‡One hundred women with missing data on menopause or hormone replacement therapy status are excluded.

### TABLE 4. Efficacy of Vitamin E Treatment by Genetic Risk Factors

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Vitamin E</th>
<th>Placebo</th>
<th>Hazard Ratio (95% CI)</th>
<th>P for Interaction*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden or prothrombin mutation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>20</td>
<td>39</td>
<td>0.51 (0.30–0.87)</td>
<td>0.11</td>
</tr>
<tr>
<td>Absent</td>
<td>124</td>
<td>147</td>
<td>0.84 (0.66–1.07)</td>
<td></td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>15</td>
<td>22</td>
<td>0.60 (0.31–1.16)</td>
<td>0.59</td>
</tr>
<tr>
<td>Absent</td>
<td>129</td>
<td>164</td>
<td>0.79 (0.63–0.99)</td>
<td></td>
</tr>
<tr>
<td>Prothrombin mutation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>6</td>
<td>19</td>
<td>0.33 (0.13–0.82)</td>
<td>0.063</td>
</tr>
<tr>
<td>Absent</td>
<td>138</td>
<td>167</td>
<td>0.82 (0.66–1.03)</td>
<td></td>
</tr>
<tr>
<td>677C&gt;T MTHFR polymorphism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TT</td>
<td>13</td>
<td>24</td>
<td>0.52 (0.27–1.03)</td>
<td>0.33</td>
</tr>
<tr>
<td>CT</td>
<td>69</td>
<td>88</td>
<td>0.80 (0.58–1.10)</td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>62</td>
<td>74</td>
<td>0.83 (0.59–1.16)</td>
<td></td>
</tr>
<tr>
<td>No blood sample</td>
<td>69</td>
<td>83</td>
<td>0.83 (0.60–1.14)</td>
<td></td>
</tr>
</tbody>
</table>

*The null hypothesis is that there are no differences between subgroups; for the 677C>T MTHFR polymorphism, the interaction is between a trend across number of T alleles and treatment.
studies. As in the Women’s Health Study, previous population-based studies have found an overall rate of VTE comparable to that of stroke and myocardial infarction. The approach used to identify VTE in this and most other clinical studies does not lead to ascertainment of asymptomatic VTE, which occurs frequently in high-risk individuals and is associated with increased risk of death. Thus, results of this trial apply to clinically apparent VTE.

The finding of a reduced rate of VTE associated with vitamin E must be viewed in the context of other randomized evaluation of the risks and benefits of vitamin E. The Women’s Health Study found a nonsignificant 7% reduction in the hazard of a major cardiovascular event (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death) associated with vitamin E supplementation (hazard ratio, 0.93; 95% CI, 0.61 to 1.38). The trial also found no significant difference observed in recent meta-analyses and other trials and supported the recommendation that vitamin E supplementation does not provide overall benefit for major cardiovascular events. The Women’s Health Study also found no significant relationship between vitamin E and the risk of cancer or all-cause death. Whereas secondary analyses of trials of vitamin E supplementation in people with vascular disease or cancer suggest a possibly increased risk of heart failure associated with treatment, the women of the Health Study also found no significant relationship between assignment to vitamin E and the incidence of heart failure.

Evaluation of any strategy to influence platelet function and coagulation requires consideration of possible adverse bleeding effects. In the Women’s Health Study, 44 women in the vitamin E group developed hemorrhagic stroke, compared with 48 women in the placebo group (hazard ratio, 0.92; 95% CI, 0.61 to 1.38). The trial also found no significant differences between active vitamin E and placebo groups in rates of gastrointestinal bleeding, hematuria, or easy bruising. Women in the vitamin E group had a significant 6% increased rate of reported epistaxis (hazard ratio, 1.06; 95% CI, 1.01 to 1.11; P=0.02). Overall, vitamin E was associated with far lower bleeding risks than those observed for low-dose aspirin in this trial.

For patients requiring secondary prevention of VTE, low- or full-intensity warfarin therapy is associated with a >60% reduction in the risk of VTE. However, bleeding risk and monitoring requirements, as well as drug–drug and drug–food interactions, make indefinite-duration warfarin therapy unacceptable for many patients. Thus, a safer strategy that (1) is useful for both primary and secondary prevention of VTE, (2) requires no laboratory monitoring, and (3) is associated with a substantial risk reduction would be of great value for high-risk patients.

The apparent benefit of vitamin E on risk of VTE differs from its lack of efficacy in prevention of cancer and cardiovascular disease. Controversy persists on whether mechanisms for arterial and venous events are shared and whether effective treatments for one condition are equally useful for the other. Prospective cohort studies have found different relationships of risk factors for heart disease and stroke with the risk of VTE. A unique benefit of vitamin E on risk of VTE is possible.

Limitations of our study include its restriction to healthy and generally health-conscious women, the cautious interpretation required for secondary end points in a trial, and the need for further elaboration of potential mechanisms of action of vitamin E on risk of VTE. Additional studies are needed in men and in women with other comorbid conditions associated with increased risk of VTE. Although VTE was a secondary end point, it was prospectively evaluated, and its report required confirmation by the trial’s end point committee blinded to treatment status. We made no measurements of the impact of vitamin E supplementation on coagulation, and therefore biological mechanisms of potential venous thrombophrophylaxis remain speculative.

Overall, vitamin E may be a useful treatment for prevention of a first or recurrent VTE. Because VTE was a prospectively evaluated, secondary end point of the Women’s Health Study, the protective effect observed here requires confirmation in additional studies. Given its lack of efficacy for prevention of cardiovascular disease and cancer, vitamin E may be most appropriate for people at high risk of VTE. In the Women’s Health Study, 20% of the cases of VTE occurred among the 8% (n=3097) of participants with a prior history of VTE at baseline, factor V Leiden, or the prothrombin mutation. Vitamin E treatment in these women was associated with a significant 49% reduction in the hazard of VTE during follow-up. With a 4.1% 10-year risk of symptomatic VTE among women receiving placebo in this group, these women would apparently benefit from vitamin E prophylaxis.

Acknowledgments

We are indebted to the 39 876 participants in the Women’s Health Study for their dedicated and conscientious collaboration and to the entire staff of the study. We thank Roche Molecular Systems, Inc, Alameda, Calif, for providing the genotyping platform used in the present study.

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Disclosures

Dr Buring reports that the Natural Source Vitamin E Association provided vitamin E and matching placebo to the Women’s Health Study. The remaining authors report no conflicts.

References


CLINICAL PERSPECTIVE

Pulmonary embolism and deep venous thrombosis constitute venous thromboembolism (VTE). The death rate from pulmonary embolism is higher than that of acute myocardial infarction. VTE is difficult to diagnose and challenging to treat, with long-term complications that include thromboembolic pulmonary hypertension and chronic venous insufficiency. Low- or full-intensity warfarin effectively reduces the risk of VTE, but bleeding risk, monitoring requirements, and drug–drug and drug–food interactions make indefinite-duration warfarin therapy unacceptable or unfeasible for many patients. Therefore, individuals with permanent risk factors, including factor V Leiden or the prothrombin gene mutation, or a personal or family history of VTE would especially benefit from an effective, low-cost, safe, straightforward strategy to prophylaxis against VTE. Both basic research and observational clinical studies suggest that vitamin E might reduce the risk of cardiovascular disease and cancer. Although an overview of many randomized trials, including the Women’s Health Study, does not find that vitamin E therapy provides overall benefit for these outcomes, vitamin E taken prophylactically may provide the unique benefit of reducing the risk of VTE. We present in this article data from the Women’s Health Study suggesting that prophylaxis with every-other-day vitamin E taken for 10 years reduces the overall risk of VTE by 21%. The observed risk reduction was 44% among those with prothrombotic mutations or a personal history of VTE. The mechanisms of action to explain these selective beneficial effects of vitamin E in reducing VTE require elaboration, and our clinical findings require confirmation.
Acute Ischemic Stroke Treatment in 2007
Larry B. Goldstein, MD

A variety of interventions have proven effective in reducing the risk of a first stroke.1 Nevertheless, each year, more than 700,000 Americans have strokes and more than 150,000 die, making stroke the country’s third-leading cause of death.2 More than 25% of stroke survivors older than age 65 years are disabled 6 months later.2 On the basis of the results of prospective randomized clinical trials and other studies performed over the past decade, the general approach to the management of acute stroke has evolved from nihilism to active intervention.

Principles of Management
A large volume of experimental studies delineates the various aspects of the ischemic cascade. The results of the single laboratory study shown in Figure 1 provide a conceptual framework that guides the current clinical approach to patients with acute ischemic stroke.3 The experiment, performed in awake monkeys, shows that focal symptoms (in this case, paralysis) develop when local cerebral blood flow drops below a certain threshold (in this experiment, <23 mL · 100 g−1 · min−1). In Figure 1, the hatched area between the development of symptoms and infarction is a graphic representation of the so-called penumbra, an area of brain that is functionally inactive but structurally intact and potentially salvageable. Neurological function is completely recoverable if local cerebral blood flow is restored promptly. For a given level of reduced blood flow, the likelihood of sustaining irreversible injury (ie, ischemic stroke) increases as a function of time. This essential biology is the basis of the mantra, “Time lost is brain lost.” Timely restoration of blood flow to ischemic brain offers the chance of reversing or limiting the injury.

Management Algorithm
Figure 2 provides a basic algorithm that outlines a general approach to patients with acute ischemic stroke. It begins with establishing the diagnosis.4 A variety of conditions can mimic stroke, including seizures, tumors, infection, hypoglycemia, and other metabolic abnormalities. Such stroke mimics are common. In one study, 13% of 821 consecutive patients initially diagnosed with stroke were eventually found to have other conditions.5 In another series, 31% of 350 consecutive patients with suspected stroke who were being evaluated in an emergency department did not have strokes.6 Prehospital screening with any of several available diagnostic aids can increase the likelihood of a correct diagnosis in a patient being transported to a hospital because of suspected stroke.7-9 A scale has also been developed to improve the accuracy of stroke diagnosis for patients being evaluated in an emergency department. The Recognition Of Stroke In The Emergency Room (ROSIER) scale includes 7 items.10 Points are assigned depending on the characteristics of the event (loss of consciousness or syncope, −1; seizures, −1; acute onset of asymmetrical facial weakness, +1; asymmetrical arm weakness, +1; asymmetrical leg weakness, +1; speech disturbance, +1; or visual field defect, +1) in patients without hypoglycemia. Stroke is unlikely (but not completely excluded) if the total score is less than or equal to 0. An initial assessment of stroke by ambulance personnel using one of the validated screening instruments followed by use of the ROSIER scale by hospital personnel would be expected to lead to a large increase in the probability of stroke.11 Diagnostic studies including neuroimaging are still required to exclude stroke mimics and, in patients in whom reperfusion therapy is being considered, to exclude the possibility of brain hemorrhage.4

Reperfusion Therapy: Intravenous Recombinant Tissue Plasminogen Activator
Once stroke has been diagnosed, the next step is to determine whether the patient might be a candidate for reperfusion therapy (Figure 2). The US Food and Drug Administration approved intravenous recombinant tissue plasminogen activator (rtPA) as a treatment for acute ischemic stroke in 1996 (Table 1). It remains the only approved pharmacological treatment for this condition. Its use is largely based on the National Institute of Neurological Disorders and Stroke (NINDS) trial that showed treatment with intravenous rtPA 0.9 mg/kg (10% given as a bolus with the remainder given over 1 hour, maximum dose of 90 mg) within 3 hours of the onset of symptoms led to an overall 32% relative (12% absolute) increase in the proportion of patients with minimal or no disability after 3 months.12 Those treated with rtPA were also more likely to have minimal or no disability after 1 year.13 The widespread adoption of treatment with rtPA has not been without controversy, at least in part because other thrombolytic studies in stroke have been negative, because of concern that baseline imbalances might explain the benefit of
treatment, and because the overall benefit in the NINDS trial included a 10-fold increase in the proportion of treated patients having symptomatic intracerebral hemorrhage (6.4% versus 0.6%), which could compromise the benefit when used outside a clinical trial setting.

Negative thrombolytic studies differed from the NINDS trial in fundamental and important ways (eg, different thrombolytic drugs, different doses of rtPA, and longer intervals between symptom onset and treatment). Trials of another thrombolytic, streptokinase, included patients treated beyond 3 hours of symptom onset and generally incorporated the concomitant use of other antithrombotic drugs, which was prohibited in the NINDS trial.14–16 Negative trials of intravenous rtPA included the European Cooperative Acute Stroke Study (ECASS)-I, which used a higher dose of rtPA and randomized patients up to 6 hours after the onset of symptoms.17 In the negative ECASS-II, the dose of tissue plasminogen activator was identical to that used in the NINDS trial, but there was a 6-hour treatment window, with most patients treated after 3 hours.18 The Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) study used a treatment protocol identical to the NINDS trial but randomized patients 3 to 5 hours after stroke.19

Figure 3 gives the results of an intention-to-treat analysis of data pooled from randomized trials of rtPA for ischemic stroke (NINDS, ECASS-I, ECASS-II, and ATLANTIS) that included 2775 patients treated up to 6 hours after symptom onset at more than 300 hospitals located in 18 countries.20 The analysis supports the primary finding of the NINDS trial in that treatment within 3 hours (and possibly up to 4.5 hours) of symptom onset is associated with a greater chance of a favorable outcome at 3 months. Moreover, as expected on the basis of the principles illustrated in Figure 1, the likelihood of benefit diminishes as time after symptom onset elapses (ie, the chances of benefit decrease as time to reperfusion increases).

A second concern was that a baseline imbalance in stroke severity between the rtPA- and placebo-treated groups in the NINDS trial might explain the observed benefit. An independent group reanalyzed the trial data and found a clinically important and statistically significant treatment benefit despite subgroup imbalances in baseline stroke severity.21 Multiple exploratory analyses failed to identify any subgroup of ischemic stroke patients who would be more likely to either benefit from treatment or be harmed by it.

A third concern has been that the benefits of intravenous rtPA found in the NINDS trial would not be generalizable to nonstudy settings. Several observational studies reinforced this fear, because higher rates of bleeding complications occurred more commonly when treatment protocols were
after stroke and not to the seizure. Treatment provided the clinician is convinced that the residual impairments are beyond the currently approved 3-hour treatment window.26 Patients in the United States. The commonest reason that patients are not treated is because they arrive at a hospital beyond the currently approved 3-hour window.26 Many patients who awaken with symptoms (the time of onset is taken from the last time they were known to be symptom free) are excluded, but numerous studies document that patient and bystander knowledge of stroke symptoms is poor, which results in delays in seeking emergency care. There can also be delays in dispatch of emergency responders and in the diagnosis and transport of stroke patients by emergency medical services personnel. Because of the time dependency of reperfusion-related treatment benefits (ie, Figures 1 and 3), it is critical to expedite arrival at a hospital, which has led to the call for the development of systems of stroke care.27 Comprehensive programs of patient and provider education and systematic organization of care are associated with more rapid arrival at hospitals after symptom onset and increases in the proportions of patients receiving treatment.28, 29 The use of telemedicine is being explored as a way of extending stroke treatment expertise to patients arriving at community or rural hospitals where support and experience may be limited.

**Endovascular Therapy**

There have been no direct comparative studies of intravenous thrombolysis and endovascular therapy to assess their relative effects on patient outcomes, and intravenous rtPA is viewed as first-line therapy for those who qualify for the treatment (Figure 2).22 Endovascular treatment, however, offers the potential advantage of real-time visualization of a thrombus while recanalization therapies are administered. The approach requires a skilled neurointerventionalist and the necessary infrastructure support, is technically limited to more proximal occlusions, and logistically requires more time to initiate than intravenous thrombolysis. A prospective randomized trial tested the efficacy and safety of intra-arterial prourokinase plus heparin versus heparin alone in patients with acute ischemic stroke and angiographically proven occlusion of the middle cerebral artery who could be treated within 6 hours of symptom onset (Prolis in Acute Cerebral Thromboembolism Trial [PROACT-II]).30 Although there was no effect on mortality, 40% of the intra-arterial prourokinase–treated patients had mild or no functional limitations (the study’s primary end point) at 3 months compared with 25% of control subjects (P=0.04). Intracranial hemorrhage with neurological deterioration occurred in 10% of patients treated with intra-arterial prourokinase and 2% of control patients (P=0.06). There was no significant difference between the groups with regard to a variety of other secondary outcome measures, although trends

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**TABLE 1. Characteristics of Patients With Ischemic Stroke Who Could Be Treated With rtPA**

<table>
<thead>
<tr>
<th>Diagnosis of ischemic stroke causing measurable neurological deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td>The neurological signs should not be clearing spontaneously</td>
</tr>
<tr>
<td>The neurological signs should not be minor and isolated</td>
</tr>
<tr>
<td>Caution should be exercised in treating a patient with major deficits</td>
</tr>
<tr>
<td>The symptoms of stroke should not be suggestive of subarachnoid hemorrhage</td>
</tr>
<tr>
<td>Onset of symptoms &lt;3 h before beginning treatment</td>
</tr>
<tr>
<td>No head trauma or prior stroke in previous 3 mo</td>
</tr>
<tr>
<td>No myocardial infarction in previous 3 mo</td>
</tr>
<tr>
<td>No gastrointestinal or urinary tract hemorrhage in previous 21 d</td>
</tr>
<tr>
<td>No major surgery in previous 14 d</td>
</tr>
<tr>
<td>No arterial puncture at a noncompressible site in previous 7 d</td>
</tr>
<tr>
<td>No history of previous intracranial hemorrhage</td>
</tr>
<tr>
<td>Blood pressure not elevated (systolic &lt;185 mm Hg and diastolic &lt;110 mm Hg)</td>
</tr>
<tr>
<td>No evidence of active bleeding or acute trauma (fracture) on examination</td>
</tr>
<tr>
<td>Not taking an oral anticoagulant, or if anticoagulant being taken, INR &lt;1.7</td>
</tr>
<tr>
<td>If receiving heparin in previous 48 h, aPTT must be in normal range</td>
</tr>
<tr>
<td>Platelet count &gt;100 000 mm$^3$</td>
</tr>
<tr>
<td>Blood glucose concentration &gt;50 mg/dL (2.7 mmol/L)</td>
</tr>
<tr>
<td>No seizure with postictal residual neurological impairments†</td>
</tr>
<tr>
<td>CT does not show a multilobar infarction (hypodensity &gt;1/3 cerebral hemisphere)</td>
</tr>
<tr>
<td>The neurological signs should not be clearing spontaneously</td>
</tr>
<tr>
<td>The patient or family understands the potential risks and benefits of treatment</td>
</tr>
</tbody>
</table>

†A patient with a seizure at the time of onset of stroke might be eligible for treatment provided the clinician is convinced that the residual impairments are due to stroke and not to the seizure.

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favored treatment. The Food and Drug Administration required a confirmatory study that was not pursued by the study’s sponsor.

No placebo-controlled, randomized studies have evaluated the use of intra-arterial rtPA. It has been used in patients with middle cerebral artery–distribution strokes similar to those included in PROACT-II who do not fulfill the criteria for intravenous rtPA, in selected patients with catheter-associated stroke, and in patients with retinal artery occlusion. Another group of patients in whom intra-arterial rtPA is considered is those with basilar artery occlusion who do not meet criteria for intravenous rtPA because of time.

The effectiveness of intravenous rtPA may be poor in patients with a proximal occlusion. Recanalization occurs in only 10% of occluded internal carotid arteries and 25% of occluded middle cerebral arteries.31–33 In addition, early recouclusion occurs in approximately one third of rtPA-treated patients.34 The pilot Interventional Management of Stroke study investigated the feasibility and safety of sequential intravenous and intra-arterial treatment with rtPA using historical controls from the NINDS intravenous rtPA trial.35 Of 80 enrolled patients, 77 had angiograms, and 62 received combination therapy with results that compared favorably with those of the NINDS intravenous rtPA trial. Further evaluation of this approach and of other means of improving recanalization rates with intravenous rtPA, such as the use of Doppler ultrasound, is in progress.36

Mechanical clot retrieval has the theoretical advantage of avoiding the systemic bleeding risk associated with thrombolytic drugs. The MERCI (Mechanical Embolus Removal in Cerebral Ischemia) clot retriever was approved by the Food and Drug Administration as a tool for the removal of blood clots from brain blood vessels. This approval was based on the results of a noncontrolled case series that involved 151 enrolled patients (141 of whom could be treated) with proximal (internal carotid, middle cerebral, or vertebrobasilar) arterial occlusions treated within 6 hours of symptom onset (mean 4.3 hours to catheterization).37 Adjuvant therapy with intra-arterial thrombolytics was permitted. Recanalization was achieved in 48% of those in whom the device was deployed, with 28% having asymptomatic intracerebral hemorrhages and 8% having symptomatic hemorrhages. Approximately 32% of those who were successfully recanalized died within 90 days, but 46% of those surviving at 90 days had little or no disability. Whether outcomes would be similar, better, or worse than with other reperfusion treatments is unknown because the study had no concurrent control subjects. The approach has the same logistic limitations as intra-arterial thrombolytic therapy but offers the possibility of treatment for selected patients who cannot be given a thrombolytic drug (eg, patients who have undergone a recent operation or invasive procedure).

**Neuroprotective Therapy**

As depicted in Figure 1, a variable amount of brain tissue may be ischemic but structurally intact. Neuroprotective therapies are aimed at preserving this tissue until adequate blood supply can be reestablished, either through spontaneous or therapeutic recanalization or via collateral flow. There have been published reports of >1000 experimental neuroprotective treatments for acute stroke targeting various portions of the ischemic cascade, with >100 coming to clinical trials.38 To date, none has proved efficacious. The potential reasons for these failures are varied, and discussions of the problem have been the subject of numerous reviews, conferences, and commentaries.39 Possible issues focus on limitations of preclinical testing and a host of concerns related to clinical trial design, including patient selection, drug dosing, treatment windows, outcome measures, and data analysis. Trials of neuroprotection, such as hyperacute administration of magnesium during transport to the hospital and the administration of albumin, continue.40,41

Experimental studies strongly support the potential of therapeutic hypothermia as a neuroprotective strategy.38 A recent Cochrane review that included articles published between 1966 and 1998, however, could not identify any completed randomized trials of physical or chemical cooling in acute stroke.42 Several small pilot studies of a variety of approaches for inducing hypothermia in patients with acute stroke, used either alone or in conjunction with surgical procedures for massive infarction, have since been published, but definitive studies have not been completed. Potential complications of induced hypothermia include pneumonia, sepsis, hypotension, cardiac arrhythmias, and coagulopathy, and the approach is still viewed as experimental.

**Radiological Identification of Neuroprotective and Reperfusion Candidates**

As reflected in Figure 1, at any given time point, a patient’s symptoms could result from involvement of infarcted or ischemic but potentially recoverable brain tissue. Although the likelihood of infarction increases with time, clinical features cannot be used to make this distinction. Infarction may already be completed in a subset of patients presenting soon after the onset of stroke symptoms, and others may have considerable areas of ischemic but noninfarcted tissue after the standard 3-hour treatment window has elapsed. Those with completed infarctions would not benefit from recanalization or neuroprotective therapy, whereas those with ischemic but uninfarcted tissue might be helped by treatment after the 3-hour period. The advent of advanced CT and magnetic resonance–based neuroradiological techniques offers the possibility of moving from a purely time-based to a more objective means of selecting patients for recanalization or other acute therapies. CT perfusion techniques use dynamic scanning to measure temporal changes in the density of the brain tissue that result from rapid changes in concentration of a contrast agent.43 Diffusion-weighted MRI assesses water homeostasis, which enables the rapid detection of areas of ischemia, and it can be coupled with perfusion-weighted MRI, which provides a semiquantitative assessment of regional cerebral blood flow.44 Despite experimental studies showing that areas of abnormality on diffusion-weighted MRI may be reversible, permanent tissue injury is generally present.45 It is hypothesized that regions of brain with reduced perfusion that do not show abnormal diffusion may represent salvageable tissue (ie, the penumbra; Figure 1).46 Longitudinal studies show that the area of diffusion abnormality can
expand to involve the area of perfusion abnormality over time. Although the concept of so-called diffusion-perfusion mismatch has limitations,47 the technique has been used in clinical trials in an attempt to identify subgroups of patients who are more likely to benefit from both neuroprotective48,49 and recanalization therapy,50,51 including those presenting >3 hours after symptom onset.

MRI with T2*-weighted sequences can identify remote microhemorrhages that were thought to be a marker of hours after symptom onset.

Micturitional incontinence in patients treated with thrombolytic therapy.52 Prospective studies have not confirmed this risk,53–55 which would also need to be balanced against the potential benefit of reperfusion in patients with acute ischemic stroke.

Perfusion CT and diffusion/perfusion MRI can be helpful diagnostically and are now commonly used in advanced centers to aid in the evaluation of patients with acute stroke. The techniques hold promise as means of identifying patients more or less likely to benefit from hyperacute interventions, but at present, the data are insufficient to support their widespread use for this purpose.56

General Measures

A variety of general measures are relevant to the management of patients with acute ischemic stroke regardless of whether or not they are treated with intravenous rtPA or endovascular therapy (Figure 2).

Blood Pressure

Cerebral blood flow (CBF) is determined by the relationship between cerebral perfusion pressure (CPP) and cerebrovascular resistance (CVR), where CBF = CPP/CVR.57 Cerebral perfusion pressure is determined by the difference between the mean arterial pressure (MAP) and venous pressure, which is generally negligible (ie, CBF = MAP/CVR; exceptions include venous obstruction). Cerebrovascular resistance depends on the degree of cerebral vasodilatation (decreasing cerebrovascular resistance) or vasoconstriction (increasing cerebrovascular resistance). Normally (ie, for mean arterial pressures ranging from approximately 60 to 150 mm Hg), decreases in cerebral perfusion pressure are matched by decreases in cerebrovascular resistance, and increases in cerebral perfusion pressure are matched by increases in cerebrovascular resistance (cerebral autoregulation).57 The lower and upper limits of autoregulation are shifted to higher values in patients with chronic hypertension. As a result, cerebral blood flow decreases at a relatively higher mean arterial pressure in patients with chronic hypertension than in normotensive individuals.

The autoregulatory relationship is disrupted in the setting of acute ischemia, in part because ischemia-related local tissue acidosis leads to maximal vasodilatation.58 Therefore, changes in mean arterial pressure are directly reflected in changes in local cerebral blood flow. The potential consequences of reducing local cerebral blood flow in the setting of acute ischemia are apparent by referring to Figure 1. Nonischemic tissue immediately surrounding the zone of ischemia could become compromised, and further reductions in local cerebral blood flow in already ischemic tissue could lead to infarction. In addition, an acute reduction in blood pressure could further compromise flow through a stenotic artery and collateral vessels.59 Theoretical arguments favoring treatment include reduction in edema and decreasing the risk of hemorrhagic transformation.

Clinical data on the effect of blood pressure alterations on outcome after ischemic stroke come mainly from observational studies. Some show no clear relationship between acute elevations in blood pressure and neurological worsening or outcome after ischemic stroke; however, at least one observational study found that poor outcome 3 months after stroke was independently associated with the degree of systolic blood pressure reduction during the first 24 hours (OR = 1.89 for poor outcome per 10% decrease in blood pressure [95% CI 1.02 to 1.87]).60

The calcium channel antagonist nimodipine was evaluated as a potential neuroprotective agent.61 Nimodipine has antihypertensive properties, and given orally within 48 hours of ischemic stroke, it also reduced blood pressures and was associated with higher 1- and 3-month mortality rates. The Intravenous Nimodipine West European Stroke Trial (INWEST) tested intravenous nimodipine (1 or 2 mg/h) started within 24 hours of acute ischemic stroke.62 Neurological outcomes were better in placebo-treated patients after both 3 weeks and 6 months. Exploratory analysis showed the odds of death or dependency at 21 days were 2.60 (95% CI 0.82 to 8.27) for those with a <10% early decrease in diastolic blood pressure, 2.97 (95% CI 1.16 to 7.63) for those with a 10% to 20% decrease, and 4.36 (95% CI 1.63 to 11.7) for those with a ≥20% decrease.63 In contrast, the Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS) Study randomized 342 hypertensive patients with ischemic stroke to candesartan cilexetil over the first 7 days, targeting a 10% to 15% reduction in blood pressure in the first 24 hours, or placebo.64 Both groups received candesartan cilexetil after 7 days. There were, however, no significant differences in blood pressures between the active-treatment and placebo-treated patients during the first week. There were no differences in outcome between the groups after 3 months, but there was a significant improvement in outcomes in acutely treated patients after 12 months. Because there were no differences in blood pressures between the groups, the study cannot address the relative benefits and risks of acute blood pressure treatment. The mechanism by which acute treatment led to a difference at 12 months is uncertain. A systematic review of studies assessing the effect of vasoactive drugs performed by the Cochrane Collaboration concluded that there was not enough evidence to reliably evaluate the effect of altering blood pressure on outcome in persons with acute stroke.65

Because of the lack of definitive data, current recommendations for the management of blood pressure in patients with acute ischemic stroke remain largely empirical (Table 2).22 On the basis of the issues reviewed, acute treatment is not recommended unless hypertension is severe (ie, systolic blood pressure ≥220 mm Hg or diastolic blood pressure ≥120 mm Hg) or in those with hypertensive encephalopathy, aortic dissection, acute pulmonary edema, or acute myocardial infarction. Abrupt lowering of blood pressure should be avoided.
Another potential exception to the recommendation to avoid lowering blood pressure in patients with acute ischemic stroke is patients who are otherwise candidates for thrombolytic treatment in whom intravenous rtPA should be withheld unless blood pressures are <185/110 mm Hg (Table 1). As shown in Table 1, an attempt can be made to gently lower blood pressure in these patients to below these levels. Postthrombolytic blood pressure management recommendations are given in Table 3. It must be recognized that these recommendations are based on the protocols used in the NINDS rtPA clinical trial, but an independent panel reviewing the trial data could not assess the effects of blood pressure or its management on outcome.21

### Fever

Although the benefit of therapeutic hypothermia is unproven, experimental studies show that even small temperature elevations increase the volume of infarcted brain tissue.66 In patients with acute ischemic stroke, fever is associated with increases in both morbidity and mortality. It is reasonable to treat fevers aggressively, although no prospective randomized trials link treatment of fever with improved stroke outcomes.

### Anticoagulants and Antithrombotics

Potential reasons to provide anticoagulant therapy to patients with acute ischemic stroke include reducing the chances of both reembolization in those with a cardiogenic source of embolism and neurological worsening related to clot propagation in those with stroke related to atheroembolism. These possible benefits need to be balanced against the risk of hemorrhagic complications. In 2000, a Cochrane systematic review based on 21 trials involving >23,000 participants found no evidence that anticoagulant therapy reduced the risk of death, and on the basis of 5 trials that included nearly 22,000 patients, no evidence was found that anticoagulant therapy reduced the odds of death or dependency.67 The International Stroke Trial (IST) contributed 19,435 patients to these analyses.68 Using a factorial design, IST randomized patients to 1 of 2 fixed doses of subcutaneous heparin (5000 or 12,500 IU twice daily) or a strategy to avoid heparin, and aspirin 300 mg/d or a strategy to avoid aspirin. A small reduction in recurrent ischemic strokes was offset by a similar increase in hemorrhagic strokes in heparin-treated patients. The relevance of IST for clinical practice in the United States was questioned because only two thirds of patients had a CT scan before randomization, and as noted, the study did not evaluate dose-adjusted intravenous heparin.

Although the emergent use of anticoagulation in patients with acute ischemic stroke remains a source of some controversy, enthusiasm for treatment with these drugs is increasingly tempered by a lack of data showing that the approach is efficacious. Individual trial reviews published in 2002 (ie, after the Cochrane report) concluded that most patients with

### TABLE 2. Approach to Elevated Blood Pressure in Acute Ischemic Stroke

<table>
<thead>
<tr>
<th>Clinical Situation</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP =&lt;220 mm Hg or diastolic BP =&lt;120 mm Hg</td>
<td>Observe BP unless other end-organ involvement (eg, aortic dissection, acute myocardial infarction, pulmonary edema, or hypertensive encephalopathy). Treat headache, pain, agitation, nausea, vomiting, and other stroke complications.</td>
</tr>
<tr>
<td>Systolic BP &gt;220 mm Hg or diastolic BP 121–140 mm Hg</td>
<td>Labetalol 10–20 mg IV over 1 to 2 min. May repeat or double every 10 min (maximum dose of 300 mg) OR Nicardipine 5 mg/h IV infusion as initial dose; titrate to desired effect by increasing by 2.5 mg/h every 5 min to maximum of 15 mg/h (target 10% to 15% BP reduction)</td>
</tr>
<tr>
<td>Diastolic BP &gt;140 mm Hg</td>
<td>Nitroprusside 0.5 μg·kg⁻¹·min⁻¹ IV as initial dose with continuous BP monitoring (target 10% to 15% BP reduction)</td>
</tr>
<tr>
<td>Patient otherwise candidate for intravenous rtPA</td>
<td>If systolic BP &gt;185 mm Hg or diastolic BP &gt;110 mm Hg, labetalol 10–20 mg IV over 1 to 2 min; may repeat 1 time, or use 1 to 2 inches of nitropaste. If BP is not reduced and maintained at desired levels (&lt;185 mm Hg systolic and &lt;110 mm Hg diastolic), do not administer rtPA.</td>
</tr>
</tbody>
</table>

BP indicates blood pressure.

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### TABLE 3. Recommendations for Blood Pressure Management After Intravenous rtPA

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment frequency</td>
<td>Measure blood pressure every 15 min for the first 2 h, every 30 min for the next 6 h, and then every hour until 24 h from treatment</td>
</tr>
<tr>
<td>Diastolic BP &gt;140 mm Hg</td>
<td>Sodium nitroprusside 0.5 μg·kg⁻¹·min⁻¹ IV as initial dose and titrate to desired BP (systolic &lt;180 mm Hg, diastolic &lt;110 mm Hg)</td>
</tr>
<tr>
<td>Systolic BP &gt;230 mm Hg or diastolic BP 121–140 mm Hg</td>
<td>Labetalol 10 mg IV over 1 to 2 min. May repeat or double labetalol every 10 min to a maximum dose of 300 mg, or give initial labetalol dose, then start labetalol drip at 2–8 mg/min OR Nicardipine 5 mg/h IV infusion as initial dose; titrate to desired effect by increasing by 2.5 mg/h every 5 min to maximum of 15 mg/h; if BP not controlled, consider sodium nitroprusside</td>
</tr>
<tr>
<td>Systolic BP 180–230 mm Hg or diastolic BP 105–120 mm Hg</td>
<td>Labetalol 10 mg IV over 1 to 2 min. May repeat or double labetalol every 10–20 min to a maximum dose of 300 mg, or give initial labetalol dose, then start labetalol drip at 2–8 mg/min</td>
</tr>
</tbody>
</table>

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TABLE 4. Recommendations for the Use of Anticoagulants and Antiplatelet Agents in Patients With Acute Ischemic Stroke\textsuperscript{71}

1. Patients with acute ischemic stroke presenting within 48 h of symptom onset should be given aspirin (160–325 mg/d) to reduce stroke mortality and decrease morbidity, provided contraindications such as allergy and gastrointestinal bleeding are absent and the patient has not been and will not be treated with rtPA. The data are insufficient at this time to recommend the use of any other platelet antiaggregant in the setting of acute ischemic stroke.

2. Subcutaneous unfractionated heparin, LMW heparins, and heparinoids may be considered for DVT prophylaxis in at-risk patients with acute ischemic stroke, with the recognition that nonpharmacological treatments for DVT prevention also exist. A benefit in reducing the incidence of pulmonary embolism has not been demonstrated. The relative benefits of these agents must be weighed against the risk of systemic and intracerebral hemorrhage.

3. Although there is some evidence that fixed-dose, subcutaneous, unfractionated heparin reduces early recurrent ischemic stroke, this benefit is negated by a concomitant increase in the occurrence of hemorrhage. Therefore, use of subcutaneous unfractionated heparin is not recommended for decreasing the risk of death or stroke-related morbidity or for preventing early stroke recurrence.

4A. Dose-adjusted, unfractionated heparin is not recommended for reducing morbidity, mortality, or early recurrent stroke in patients with acute stroke (ie, in the first 48 h) because the evidence indicates it is not efficacious and may be associated with increased bleeding complications.

4B. High-dose LMW heparin/heparinoids have not been associated with either benefit or harm in reducing morbidity, mortality, or early recurrent stroke in patients with acute stroke and are therefore not recommended for these goals.

5. Intravenous, unfractionated heparin and high-dose LMW heparin/heparinoids are not recommended for any specific subgroup of patients with acute ischemic stroke that is based on any presumed stroke mechanism or location (eg, cardioembolic, large-vessel atherosclerotic, vertebralbasilar, or “progressing” stroke) because data are insufficient. Although the LMW heparin dalteparin at high doses may be efficacious in patients with atrial fibrillation, it is not more efficacious than aspirin in this setting. Because aspirin is easier to administer, it, rather than dalteparin, is recommended for the various stroke subgroups.

LMW indicates low molecular weight; DVT, deep vein thrombosis. Data derived from Coull et al.\textsuperscript{71}

Acute ischemic stroke should not be treated with unfractionated heparin or other rapidly acting anticoagulants and that there was no overall benefit of treatment with heparin in patients with acute ischemic stroke and atrial fibrillation.\textsuperscript{69,70} A 2002 guideline statement jointly developed by the American Stroke Association and the American Academy of Neurology was based on a systematic literature review.\textsuperscript{71} Recommendations are given in Table 4 and were reiterated in a subsequent guideline statement from the American Stroke Association.\textsuperscript{72}

Despite the completion of several additional trials, little has changed since these guidelines were issued. The Rapid Anticoagulation Prevents Ischemic Damage in Acute Stroke (RAPID) study compared aspirin and dose-adjusted unfractionated heparin in patients with nonlacunar ischemic stroke started within 12 hours of symptom onset.\textsuperscript{73} The study was halted after only 67 patients were randomized because of poor recruitment, with no effect on the primary end point (no significant disability at 90 days). A single-center trial randomized 418 patients with nonlacunar hemispheric ischemic stroke to dose-adjusted intravenous heparin or saline started within 3 hours of symptom onset and continued for 5 days.\textsuperscript{74} There were more symptomatic intracerebral and systemic hemorrhages in the treated group, but there was an overall increase in the proportion of patients with favorable outcomes after 90 days (38.9% versus 28.6%, \(P=0.025\)). Control subjects, however, were not given aspirin, and whether the results can be generalized to other settings is uncertain. The TOAST trial (Trial of Org 10172 in Acute Stroke Treatment) found no overall benefit of acute anticoagulation with a heparinoid (danaparoid) but a suggestion of benefit in the subgroup of subjects with large-artery-type stroke.\textsuperscript{75} This finding has not yet been replicated in an independent study.

In contrast to acute anticoagulation, aspirin (160 to 325 mg/d) started within 48 hours of symptom onset is recommended for most patients with ischemic stroke (Table 4).\textsuperscript{22,71} This is largely based on a preplanned combined analysis of data from 40,000 patients who participated in IST and the Chinese Acute Stroke Trial (CAST), which found 9 fewer recurrent ischemic strokes or deaths during hospitalization per 1000 patients treated with aspirin.\textsuperscript{76} Alternative oral antiplatelet drugs have not been evaluated in this setting.

Uncontrolled and phase 2 studies suggested that intravenous administration of platelet glycoprotein IIb/IIIa inhibitors might be safe and effective in the emergent treatment of patients with ischemic stroke. The Abciximab in Emergent Stroke Treatment Trial-II (AbESTT-II) trial was a phase 3 study that planned to randomize 1200 patients with ischemic stroke to double-blind treatment with abciximab versus placebo within 6 hours of symptom onset or 2.5 hours of awakening.\textsuperscript{77} Reported in abstract form, the study was stopped prematurely because of safety concerns after 808 patients were enrolled.

Although the use of any therapeutic intervention needs to be individualized, there remain no data showing a net benefit of anticoagulants in most patients with acute ischemic stroke, although the possibility of benefit in some patient subgroups cannot be excluded, and there are only limited data for hyperacute administration. Although the benefits are small, aspirin should be given to most patients. Patients who are treated with intravenous rtPA should not receive any anticoagulants or antithrombotic drugs over the first 24 hours.\textsuperscript{22,71}

Preventing Complications

In addition to the general measures applicable to all stroke patients, prevention of complications, initiation of secondary prevention, and facilitation of functional recovery are integral to the management of patients with acute ischemic stroke (Figure 2). Several common complications of acute stroke are often preventable. One multicenter study found that medical complications were recorded in 85% of hospitalized stroke patients.\textsuperscript{78} The commonest were pain (34%), falls (25%),
urinary tract infections (24%), pneumonia (22%), and pressure sores (21%). These complications can prolong hospitalization, interfere with the recovery process, and lead to further morbidity and mortality.

Indwelling urethral catheters in hospitalized patients are the major risk factor for the development of urinary tract infections. The estimated rate of infection is 3% to 10% per day. Women are at greater risk than men. Avoidance of the use of indwelling catheters or their removal as soon as feasible can lessen the infection risk. Risk is also decreased with the use of condom catheters in men or through the use of intermittent or suprapubic catheterization.

Approximately one third of stroke patients have dysphagia, with 20% developing aspiration pneumonia. Aspiration pneumonia also occurs in 10% of stroke patients without dysphagia. Silent aspiration, without overt signs of dysphagia, can also occur. Although having depression of the level of consciousness increases risk, dysphagia and aspiration also occur in patients with preserved consciousness. Dysphagia has been associated with aspiration in 54% of patients with bilateral hemispheric strokes and 50% of those with brain stem strokes. Aspiration occurs more commonly in patients with bilateral versus unilateral cranial nerve signs; however, it can complicate >40% of unilateral hemispheric strokes and can occur with strokes affecting various brain regions and with strokes of all sizes, including >20% of small-vessel-type strokes.

In addition to depressed consciousness, clinical identifiers of aspiration risk include the presence of dysarthria, dysphonia, a weak voluntary cough, and drooling. Findings on clinical examination, however, have limited sensitivity for identifying patients at risk for aspiration. For example, an absent or diminished gag response is not helpful in discriminating aspirators from nonaspirators. Having the patient attempt to swallow 3 oz of water is a sensitive screening tool for identifying patients at risk for clinically significant aspiration. Patients with dysphagia and those suspected to be at risk for aspiration should be referred to a speech and language pathologist for further evaluation before the initiation of oral feeding.

Deep vein thrombosis (2% to 3%) and pulmonary embolism (1% to 5%) can be major complications in immobilized stroke patients. A prospective study using MRI found 18% of patients with acute ischemic stroke had a proximal deep vein thrombosis after 21 days, with 12% having a pulmonary embolism. The risk of deep vein thrombosis and pulmonary embolism in immobilized stroke patients can be decreased with subcutaneous unfractionated heparin; however, aspirin is not effective for this purpose (Table 4). A Cochrane review based on studies reported through 2003 also found that treatment with either a heparinoid or a low-molecular-weight heparin is associated with a reduction in the risk of deep vein thrombosis. The use of heparinoids but not low-molecular-weight heparin was associated with decreased deep vein thrombosis risk compared with unfractionated heparin. There were too few events to determine whether heparinoids or low-molecular-weight heparins decrease the rate of pulmonary embolism in this setting (Table 4). A trial comparing enoxaparin with subcutaneous heparin was completed recently. The benefit of subcutaneous unfractionated heparin is enhanced by the concomitant use of pneumatic sequential compression devices.

Secondary Prevention and Recovery
Secondary prevention and integrated measures to facilitate and optimize poststroke recovery are separate topics but are integral to the care of patients with acute ischemic stroke. Guidelines were published recently that review the prevention of stroke in patients with prior stroke or transient ischemic attack. Care in comprehensive stroke units incorporating multidisciplinary rehabilitation is associated with lower complication rates and improved functional outcomes after stroke. Organized multidisciplinary rehabilitation is associated with reductions in stroke-related mortality, long-term institutionalization, and dependency such that 5 extra patients are returned home in an independent state for every 100 treated. Functional outcome is improved with adherence to poststroke rehabilitation guidelines.

Conclusions
The management of patients with acute ischemic stroke has become complex. Optimization of care requires systematic organization that extends from primary prevention through poststroke rehabilitation. Treatment will continue to be refined as ongoing clinical trials are completed.

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References


KEY WORDS: stroke □ anticoagulants □ blood pressure □ complications □ imaging □ thrombolysis □ antiplatelets
Interventional Cardiac Electrophysiology

Catheter Ablation for Atrial Fibrillation

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Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with associated deterioration of atrial mechanical function. It is the most common cardiac arrhythmia, becomes more prevalent with age, and is associated with an increased long-term risk of stroke, heart failure, and all-cause mortality. AF can occur in the absence of underlying heart disease but is more frequent in connection with mitral valve disease, heart failure, ischemic heart disease, and hypertension. The most frequent pathological observations in AF are atrial fibrosis and loss of atrial muscle mass. Although the severity of fibrosis reflects the duration of preexisting AF, fibrosis can also occur in association with inflammation in the absence of other cardiac pathology and may contribute to the onset of AF. Molecular, ionic, and genetic influences have all been implicated in AF and are reviewed in detail elsewhere. It is likely that most AF occurs primarily in the context of an interplay between left atrial (LA) electrical and mechanical dysfunction and later becomes self-perpetuating by promoting further electromechanical change during ongoing fibrillation.

AF: Mechanisms and Consequences

A simple and clinically relevant consensus classification recognizes 3 patterns of AF: paroxysmal (lasting <7 days and self-terminating), persistent (lasting >7 days and requiring electrical or pharmacological cardioversion), and permanent (cardioversion failed or not attempted). Although useful, this arbitrary classification does not account for all presentations of AF and is not clearly related to any specific pathophysiology or mechanism of arrhythmogenesis.

Focal activity, multiple reentrant wavelets, and macroreentry have all been implicated in AF, perhaps under the further influence of the autonomic nervous system. The focal source hypothesis, incorporating automaticity and/or local reentry, is consistent with a dominant role for the LA in human AF. AF can be initiated by ectopic beats originating from the pulmonary veins (PVs) and elsewhere, and experimental work has shown that a high-frequency source is capable of maintaining AF. An alternative theory of AF proposes the presence of macroreentrant loops and/or multiple reentrant wavelets meandering throughout the atria seeking nonrefractory tissue, the number of which is related to atrial refractory period, mass, and conduction velocity. This theory provides the rationale for ablation procedures that compartmentalize the LA area available for conduction and therefore reentry. A further intriguing hypothesis is that rather than individual structures, it is the interaction between the LA and its appended structures (PVs, coronary sinus, and LA appendage) that is critical for perpetuation of AF.

The shorter the duration, the more easily AF can be terminated either pharmacologically or by DC cardioversion. In animal models, sustained AF is associated with shortening of the atrial effective refractory period, an increase in LA size, and facilitated induction of AF. In contrast to the rapid recovery of these electrical parameters after restoration of sinus rhythm, recovery of atrial size and transport function occurs more slowly, is often preceded by a period of atrial stunning, and is related to the duration of the preceding AF. ACE inhibitors reduce the incidence of AF in patients with left ventricular dysfunction after acute myocardial infarction. Similarly, pharmacological interruption of the intracellular signaling pathways crucial to remodeling may have important consequences for patient management after restoration of sinus rhythm.

Rapid and irregular ventricular rates during AF can result in left ventricular impairment, which may be wholly or partially reversible with control of the ventricular rate or restoration of sinus rhythm. Atrial remodeling also occurs due to congestive heart failure and is characterized by structural changes, abnormalities of conduction, sinus node dysfunction, and increased refractoriness, all of which may increase the propensity to AF. An ablative approach to achieve sinus rhythm in many patients with heart failure may be warranted whether or not AF is overtly symptomatic.

Patient Selection

Catheter ablation has emerged as a realistic treatment strategy to target pulmonary venous triggers that initiate AF. The feasibility of catheter ablation, with a variety of ablation techniques, has been demonstrated for patients across the entire spectrum of AF from paroxysmal to permanent. There are recent data to support the extension of ablation as a treatment option to patients previously deemed unsuitable, ie, those with persistent and permanent
AF and those with moderate to severe left ventricular impairment.31

**Drug-Refractory Paroxysmal AF**
The greatest body of data supporting catheter ablation exists for patients with paroxysmal AF. This is recognized in the most recent American College of Cardiology/American Heart Association/European Society of Cardiology guidelines on management of patients with AF, in which catheter ablation should be considered after failure of antiarrhythmic medication for recurrent paroxysmal AF.1 Three trials have demonstrated the superiority of catheter ablation either in combination or in direct comparison with antiarrhythmic medication in patients with drug-refractory paroxysmal AF.38–40 In the absence of any large, randomized trial of catheter ablation as a first-line therapy for AF in either symptomatic or asymptomatic patients, a history of symptoms despite therapeutic doses of antiarrhythmic medication (type 1A, 1C, or III according to the Vaughan Williams classification) is widely accepted as the minimum qualifying criterion for catheter ablation. With improved efficacy of ablation techniques, however, the threshold for ablation will continue to fall.

**Persistent and Permanent AF**
Early attempts at catheter ablation of AF were inspired largely by the success of the Maze surgical procedure.19 The first catheter-based, linear-ablation attempt to recreate the Maze III lesion set was accomplished by Swartz et al in 1994.41 Packer et al42 published their experience of this approach in 18 patients with chronic AF, reporting acute termination in 50% and long-term drug-free success in 78%, albeit after long and multiple procedures in 39%. Many groups have now demonstrated proof of concept in extending catheter ablation to patients with persistent or permanent AF, achieving medium-term (1 to 2 years) success rates of 70% to 95% with an acceptable procedural risk.43–44,49 (Table 47–49

At present, the extensive procedures required, coupled with the shortcomings of current energy-delivery systems (non-transmurality of lesions, tissue recovery), represent significant limitations to effective ablation in this patient group. As the long-term follow-up data are gathered and tools and techniques improved, the role of catheter ablation will become more clearly defined. In the meantime, published guidelines recommend catheter ablation for recurrent persistent AF only after failure of at least 1 antiarrhythmic medication and severe symptoms despite rate control.1

**Preinterventional Diagnostic Modalities**
Electrocardiography, both static and ambulatory, remains the primary tool for diagnosis and quantification of AF, with the optimal preinterventional diagnostic evaluation still evolving. Transthoracic echocardiography to assess cardiac structure and function is required in all patients. Preprocedural transesophageal echocardiography is widely practiced to exclude the presence of intra-atrial thrombus before transseptal puncture and catheter manipulation within the LA. Electroanatomic mapping can localize a given electrode position in 3D space and thereby enable the construction of a representation of atrial anatomy while simultaneously gathering activation timing and voltage-amplitude data.21 Magnetic resonance or tomographic cardiac images acquired before the ablation procedure give detailed anatomic information that can be useful to plan the procedure.50 These images can be imported or “merged” into the electroanatomic platform and integrated with the mapping-acquired anatomy to aid catheter manipulation during the ablation procedure. Such techniques are now widely available, can reduce intra-
procedural radiation exposure, and may improve procedural outcomes.

**Techniques for Ablation of AF**

The clinical presentation may provide clues to the mechanism of AF and assist in planning an ablation procedure. Paroxysmal AF, especially of short duration, is frequently a purely trigger-dependent phenomenon, whereas persistent AF and permanent AF are generally mechanistically complex, implicating a more diffuse abnormality of the atrial substrate. Elimination of the influence of triggers of AF in an individual patient requires spontaneous firing to be readily identifiable during an ablation procedure. Although this is unpredictable, the PVs are well established as the dominant sources of triggers in paroxysmal AF, in addition to their contribution to maintenance of AF. On the other hand, there is limited knowledge of how to identify, map, and ablate the culprit atrial substrate in an individual patient, because AF is generally associated with locally complex electrograms of indefinable timing and sequence. Mapping is possible, however, after AF organization (consistent activation sequence) either spontaneously, pharmacologically, or by prior ablation. This heterogeneity of substrate may explain why no single predetermined ablation schema is effective for all patients across the entire spectrum of AF. At present, there are 3 principal techniques for catheter ablation of AF: PV isolation, LA linear ablation, and ablation of LA electrophysiological targets. Each of these has been implicated in modification of the triggers and/or substrate of AF.

**PV Isolation**

Ablation targeting the PV-LA junction is effective in isolating the LA from proarhythmic PV activity. PV or pulmonary antral isolation confirmed by absence or dissociation of PV potentials is easily demonstrated, objective, and an effective end point for treatment of most patients with paroxysmal AF. After PV isolation alone, success rates of 60% to 85% have been reported in patients with paroxysmal AF, who were free of antiarrhythmic drug use at follow-up. Because AF frequently coexists with atrial flutter, additional cavotricuspid ablation has also been shown to improve outcome in patients with typical atrial flutter documented either before or during the procedure. Recurrences of arrhythmia after successful PV isolation are generally related to recovered conducting tissue at the pulmonary venous ostia.

**LA Linear Ablation**

PV isolation alone is insufficient for restoration and maintenance of sinus rhythm in most patients with persistent AF. In these patients, additional linear lesions at the roof and mitral isthmus are intended to eliminate more arrhythmogenic substrate and specifically to prevent large atrial reentrant circuits potentially involved in perpetuation of AF. Complete linear lesions have been shown to improve outcomes. Even if incomplete, they may be effective merely by incorporating other abnormal arrhythmic substrate within their trajectory. PV isolation plus ablation at the roof and mitral isthmus achieved sinus rhythm in 69% of patients with persistent AF compared with only 20% of patients who underwent PV isolation alone. The incremental benefit of mitral isthmus ablation in addition to PV isolation was greater for patients with persistent AF than for those with paroxysmal AF. Circumferential PV ablation and adjunctive roof and mitral isthmus ablation significantly reduced the AF burden at 12-month follow-up as measured by 7-day Holter monitoring. At 18-month follow-up, 91% of patients with paroxysmal AF were free of arrhythmia when adjunctive linear ablation was performed, guided by the presence of persisting or inducible AF after PV isolation. Linear ablation in addition to PV isolation was demonstrated to be effective in preventing atrial tachycardia after circumferential PV ablation for paroxysmal AF, whereas macroreentrant arrhythmias that occur during follow-up are frequently related to gaps in previous linear lesions.

**LA Electrophysiological Targets**

Fractionated potentials are high-frequency, cycle-length-dependent signals, the precise mechanism and significance of which are unclear but likely to be multifactorial, including local areas of slow or anisotropic conduction, continuously reentering impulses, and temporal overlap of different activation waves. Demonstrated that ablation solely targeting areas of complex fractionated electrical activity was effective in treating both chronic and paroxysmal AF. Further studies are needed to improve our interpretation of the mechanistic significance of these electrograms and to differentiate those sites perpetuating AF from those activated passively.

Constant or intermittent sources of rapid activity (with or without 1:1 conduction to surrounding atrium) have been demonstrated to drive AF. With the use of conventional recording techniques in humans, such sources can be identified as (1) sites with the most rapid regional atrial activity or (2) rapid centrifugal atrial activation emanating from a single point source or a small (≈1 to 2 cm in diameter) local reentrant circuit. Ablation at such sites has been shown to prolong AF cycle length and/or change activation sequence and terminate AF organized by prior ablation (Figure 1).

**Combination of Ablation Techniques**

No single ablation strategy is uniformly effective in all patients with AF. The heterogeneous individual mechanisms at work in AF are targeted to greater or lesser degrees by each of the techniques outlined above. Many groups have now incorporated elements of all of the above techniques to optimize the outcome of catheter ablation of AF. Ablation of complex electrograms in patients with paroxysmal AF undergoing PV isolation resulted in freedom from AF in 77% of patients (not taking antiarrhythmic medication). In patients with persistent AF who were taking amiodarone, ablation in the LA roof, septum, anterior wall, mitral isthmus, and atrial aspect of the mitral annulus restored sinus rhythm in 68% of patients not taking drugs. With a stepwise approach that combined all of the aforementioned targets, termination of long-lasting persistent AF by ablation alone can be achieved in 87% of patients, with freedom from AF achieved in 95% of patients.
Safety of Catheter Ablation Techniques

Catheter ablation is not without risk, with a major complication being reported in up to 6% of procedures performed worldwide. Complications may arise as a result of direct injury to cardiac structures, thermal injury to adjacent extracardiac structures, or thromboembolism.

Cardiac tamponade has been reported in 2.2% of cases from high-volume centers that perform AF ablation. Reduction of the power used for radiofrequency ablation has reduced this to 1%. Injury to the phrenic nerve, the right substantially more often than the left, is observed in 0.5% of cases, with complete or partial recovery in the majority. Gastric hypomotility has been described as a result of injury to periesophageal vagal plexus in 4 of 367 patients undergoing AF ablation and may have implications for evolving ablation strategies that target the cardiac vagal plexi. Anecdotal reports exist for injuries to other extracardiac structures, including the recurrent laryngeal nerve and bronchi.

Figure 1. Discrete sites perpetuating AF. A, Electrograms recorded in the coronary sinus (CS) during a sudden acceleration of activity from 210 to 140 ms, with activation continuing in a distal-to-proximal direction. B, Electrograms recorded using the mapping catheter (RF) in 2 patients at 2 distinct sites at the basal portion of the LA appendage (LAA). The temporal gradient of activity recorded at the superior base is consistent with a local small circuit; the continuous activity recorded at the posterior ridge is nonspecific. Arrhythmia was terminated in all patients within 1 minute of radiofrequency application. RFd indicates distal bipole of the ablation catheter; RFp, proximal bipole.

The most significant complication of LA catheter ablation is atrioesophageal fistula formation, with a reported incidence of between 0.05% and 1% and an associated mortality rate in excess of 50%. The position of the esophagus relative to the LA varies considerably between patients and varies even in a single patient during an ablation procedure. Ablation can result in a temperature rise in the esophageal lumen, which may, in turn, be related to an increased risk of fistula formation. Although rare, this devastating complication warrants attention, with possible solutions including development of real-time esophageal location, temperature monitoring, the use of lower-power or alternative energy sources when ablation near the esophagus is necessary, and improved early detection of esophageal injury.

PV stenosis remains an important complication, with reports suggesting an incidence of between 1% and 10% in those undergoing ablation for AF. The incidence may be decreased by a more proximal ablation position when targeting the LA-PV junction, a reduction in power delivery when engaging the anterior aspect of the left PVs, and increased operator experience.

Radiofrequency ablation disrupts the cardiac endothelial surface, activates the extrinsic coagulation cascade, and leads to char and thrombus formation, which in turn may lead to systemic thromboembolism. Intracardiac echocardiography has identified a 10% incidence of LA thrombus during catheter ablation of AF. An increased intensity of heparin anticoagulation (activated clotting time >300 seconds) may prevent LA thrombus formation during radiofrequency ablation of the LA, whereas aggressive heparinization (activated clotting time 350 to 400 seconds) is associated with a reduction of peri procedural embolic events, albeit without affecting char formation. High-flow transseptal sheath perfusion (180 mL of heparinized saline per hour) may further reduce the risk of stroke during complex LA ablation procedures in addition to conventional systemic anticoagulation.

As novel, potentially thrombogenic ablation tools are introduced to the LA for treatment of AF, for example, balloon-based therapies, mesh catheters, and noncontact arrays, we must maintain vigilance to minimize the potential for thromboembolic complications.

A recent study of 755 patients who underwent LA ablation for AF reported a thromboembolic complication after the procedure in 1.2%. Although the findings support the discontinuation of anticoagulation if sinus rhythm is maintained at 3 to 6 months after successful ablation, the advisability of discontinuation of anticoagulation in patients with known risk factors for stroke is not fully settled. The latter study did not extend to patients whose risk factors included age >65 years and previous history of stroke. In addition, the study was relatively small and nonrandomized, and the follow-up was relatively short for a potentially lifelong threat. Of note, three quarters of thromboembolic events in this study occurred within 30 days of the ablation procedure, which underscores the importance of strict therapeutic anticoagulation at least within this window while longer-term follow-up data are awaited.
Controversies in AF Ablation

Optimization of patient selection and development of improved ablation strategies leading to better patient outcomes can only come from a clearer understanding of the shortcomings of current practices. The greatest barrier to meaningful comparison of the current approaches between centers is the lack of standard definitions for technical, procedural, and clinical end points.

Technical End Points of Catheter Ablation

There is near consensus of electrical PV isolation as an end point of ablation targeting the LA-PV junction. Conduction block across linear lesions is associated with an improved outcome after catheter ablation for atrial flutter and fibrillation, whereas incomplete linear-ablation lesions are associated with recurrence of atrial arrhythmias. Conduction block at the mitral isthmus and LA roof can be readily assessed in a manner analogous to that used for the cavitricuspid isthmus and represents an unequivocal end point. Clear reporting of the presence or absence of PV isolation and conduction block for linear lesions is desirable to facilitate more meaningful comparisons between ablation strategies for AF and their outcomes.

Abolition of inducible vagal reflexes has been proposed as an end point of ablation on the basis of experimental data. In 1 series, vagal reflexes induced by radiofrequency energy were seen in up to one third of patients with paroxysmal AF undergoing circumferential PV ablation, and their elimination by further ablation was associated with 99% freedom from AF at 1-year follow-up. The latter finding remains to be verified by others.

End points for ablation at sites of complex fractionated electrograms are more ambiguous and include complete elimination of these activities or local slowing/organization. Furthermore, it is not known whether ablation of all such sites is necessary or if it is possible to target specific locations and thereby limit the extent of unnecessary ablation and resultant tissue damage.

Procedural End Points of Catheter Ablation

There are 3 principal procedural end points advocated for catheter ablation of AF, the applicability and relevance of which may depend on the type of AF: (1) completion of a predetermined lesion set, (2) termination of AF during ablation, and (3) noninducibility of AF after ablation. The clear electrophysiological and pathophysiological differences between trigger-dependent and substrate-dependent AF argue strongly against a single pret-a-porter ablation strategy for all forms of AF; however, certain generalizations can be made for paroxysmal versus persistent AF.

In paroxysmal AF, PV isolation is the basic ablation lesion and is effective alone in ~70% of patients. In the remainder for whom this is insufficient for a satisfactory outcome, whether determined by failure to terminate AF or by persistent inducibility, the precise role of supplementary electrogram-guided versus linear ablation is ill-defined and remains at the discretion of the operator. Although noninducibility is associated with an improved outcome in paroxysmal AF (~20% greater success), persistent inducibility may lead to further unnecessary ablation and associated LA tissue damage. Furthermore, neither the definition of inducibility nor the protocols used to assess it are uniform.

In patients with persistent and permanent AF, the procedural end point is less clear. Although restoration of sinus rhythm by ablation, without the use of antiarrhythmic drugs or DC cardioversion, appears an intuitively ideal end point, as of yet there are few data to support the widespread applicability of such an exacting end point. In the interim, completion of a predetermined lesion set that incorporates PV isolation and LA ablation remains the basic procedure.

Clinical End Points of Catheter Ablation

Freedom from AF, both symptomatic and asymptomatic, at specified intervals after ablation without the use of concomitant antiarrhythmic medication is the ideal clinical end point. Consensus is needed on what constitutes adequate monitoring and what is the minimum acceptable AF burden to satisfy this end point.

Although symptomatic improvement despite continuing AF is a valuable end point from the patient’s perspective, absence of symptoms is clearly not reliable proof of the absence of AF and therefore is of little use in determining future stroke risk and the need for continued anticoagulation. Definitions of freedom from AF include absence of AF, AF episodes lasting no more than 3 to 30 seconds, absence of symptomatic AF of any duration, and others. Many published studies have combined populations of patients with paroxysmal and persistent AF, which makes it confusing to
interpret results. Finally, success rates are not uniformly quoted for patients who have stopped taking all antiarrhythmic medication. After catheter ablation for AF, success rates within a single study differ depending on the duration of ECG monitoring. Examples of follow-up protocols reported in the literature include 3-monthly Holter, event monitor, and ECG recording; event monitor for 1 year with 3-minute daily recordings, 5 days per week when asymptomatic and at any time when symptomatic; continuous 7-day ECG recording at 3, 6, and 12 months after ablation; and continuous inpatient telemetry for 3 to 5 days after ablation and at 1, 3, 6, and 12 months. As of yet, there are few truly long-term data (>5 years) available for corroboration of the short-term clinical efficacy of catheter ablation. Although continuous-loop recording with regular transtelephonic data transmission throughout a uniform period of follow-up would be the “gold standard” for assessment of cardiac rhythm, this is impractical, inconvenient, and expensive.

Recurrences of AF and organized atrial arrhythmias are well described after all catheter ablation techniques for AF, the mechanisms of which include (1) recurrence of PV to LA conduction; (2) gaps in previous linear lesions (manifesting as roof-dependent or perimtrial macronecropy); and (3) locally abnormal conduction at the site of previously ablated tissue or LA scar. Many investigators empirically incorporate a “blanking period” of 1 to 3 months after ablation, during which time antiarrhythmic medication may be continued or modified and DC cardioversion performed for early arrhythmia recurrences without resort to further catheter intervention. This strategy of watchful waiting may prevent unnecessary intervention in up to one third of patients in whom atrial tachycardia resolves spontaneously within 3 to 4 months of ablation. For those in whom tachycardia recurs after electrical or pharmacological cardioversion, repeat electrophysiological study and ablation are invariably recommended and are frequently successful.

**Future Directions**

Ablation is more effective than medical therapy for the treatment of all forms of AF in selected groups of patients and retrospective data are suggestive of a mortality benefit in favor of AF ablation over conventional treatment. Heart failure and AF coexist in up to 40% of patients with heart failure, and restoration of sinus rhythm by catheter ablation of AF in patients with congestive heart failure has been shown to improve cardiac function, symptoms, exercise capacity, and quality of life. Clearly, there is an urgent need for robust, prospective, long-term data to address 2 critical questions: (1) What is the role of ablation in the therapeutic arsenal across all AF patient groups? (2) Is there an associated mortality benefit? The answers would have immense implications for electrophysiology worldwide and are crucial for ablation therapy to be disseminated effectively and safely from the high-volume centers to those centers that wish to establish an AF ablation program. Future trials should include patients with chronic AF, elderly patients (>70 to 75 years), and patients with LA enlargement (parasternal dimension >55 to 65 mm), structural heart disease, and heart failure (left ventricular ejection fraction <30% to 35%). The design of future trials must aim for inclusion rather than exclusion to define appropriate patient selection criteria by incorporating these large patient groups who potentially have the most to gain by restoration of sinus rhythm if acceptable efficacy and safety can be demonstrated.

At a more fundamental level, the limited resolution of current mapping technologies is an obstacle to a more complete understanding of the underlying mechanisms in AF. Although great progress has been made in real-time tracking of catheter position within reconstructed and registered anatomy, interpretation of the significance of recorded activity requires greater development, with an emphasis on online global substrate mapping during AF. This may facilitate the development of an “AF fingerprint” for an individual patient, allow custom selection of ablation targets and tools to optimize the procedural and clinical outcome, and perhaps even thereby shorten the operator learning curve.

Recovery of conduction across previously ablated tissue is responsible for the vast majority of arrhythmia recurrences after catheter ablation for AF. Radiofrequency is the dominant energy source used but remains inadequate to ensure lesion continuity and permanence without an unacceptable increase in procedural time and complications. New, effective, and safe alternative energy sources are needed to achieve the ultimate goal of a single, widely applicable, curative procedure for all forms of AF.

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**References**


Key Words: catheter ablation ■ atrial fibrillation ■ arrhythmia ■ atrium
Angiography of an Aneurysmal Aorto–Left Ventricular Tunnel

Ghassan Chehab, MD; Jean Hayek, MD; Zakhia Saliba, MD; Issam El-Rassi, MD

The aortoventricular tunnel is an abnormal congenital extracardiac communication between the ascending aorta and 1 of the ventricles. 1 Approximately 130 cases have been reported in the literature, 90% being aorto–left ventricular tunnels (ALVTs). 2 Echocardiography is the best diagnostic tool for ALVT, and thus cardiac catheterization is not routinely performed unless more information is needed concerning the coronary arteries. Coronary artery anomalies may be associated with ALVT in 45% of patients. 3, 4 The ostium of the right coronary artery may lie within the tunnel; alternatively, there may be complete absence of the origin of the left or right coronary ostium. In this report, we describe a rare angiographic appearance of an aneurysmal ALVT.

A 2-month-old boy was admitted to our institution with a suspected echocardiographic diagnosis of ALVT (Figure 1). Cardiac catheterization was performed to confirm diagnosis before surgery. It showed the ALVT developing as a large extracardiac aneurysm; the catheter was advanced from the femoral artery to the ascending aorta, then through the aortic opening of the tunnel just above the aortic valves; it looped completely in the extracardiac aneurysm (Figure 2A and 2B) and exited the tunnel through its left ventricular opening. The tunnel and the aneurysm were then injected with dye (Figure 3A and 3B).

In this case, the presence of separate left and right coronary ostia was confirmed on angiography (Figure 3). Surgical inspection revealed an aneurysmal 3-cm tunnel arising from the ascending aorta just above the right Valsalva sinus (Figure 4). The aortic orifice of the tunnel was situated 2 mm above the ostium of the right coronary artery. The ventricular orifice was situated under the right-left commissure of the aortic valve. Both orifices were closed separately with pledgeted interrupted stitches and 2 Gore-Tex patches from inside the opened aneurysmal tunnel. The postoperative course was uneventful, and the child was extubated 24 hours after surgery. Postoperative echocardiography confirmed the absence of any residual leak, with only mild aortic incompetence.

Disclosures

None.

References

Figure 1. Echocardiography showing ALVT. Ao indicates aorta; LV, left ventricle.

Figure 2. Angiography showing the catheter advanced through the tunnel down into the left ventricle. Arrows indicate the aortic entry and ventricular exit orifices of the tunnel. Ao indicates aorta; LV, left ventricle.
Figure 3. Opacification of the tunnel. Arrows indicate right coronary artery (A) and left main coronary artery (B). Ao indicates aorta; LV, left ventricle; LMCA, left main coronary artery; and RCA, right coronary artery.

Figure 4. Surgical views of the tunnel. RCA indicates right coronary artery.
Mitral valve prolapse (MVP) is a common disorder, occurring in 4% of the general population. It is associated with increased risk of infective endocarditis, and antibiotic prophylaxis is suggested in those high-risk patients who have systolic murmurs. The vast majority of cases involve the valve and its accessory apparatus. Herein, we present an unusual location of vegetation in a patient with MVP.

A 45-year-old woman had been diagnosed with MVP 1 month before admission at our institution, after a grade III/VI pansystolic murmur with late systolic click was heard during a regular health checkup. Echocardiography illustrated myxomatous change and prolapse of the anterior mitral leaflet, with severe eccentric mitral regurgitation. Because of intermittent fever, left flank pain, and tender skin erythema of both feet, the patient visited our emergency department, where blood pressure 113/76 mm Hg, heart rate 126 bpm, and body temperature 39.5°C were noted. Blood analysis showed white blood cell count of 11 400/mm³, hemoglobin level of 9.7 g/dL, C-reactive protein level of 12.4 mg/dL, and rheumatoid factor level of 23.7 U/mL. Abdominal computed tomography showed white blood cell count of 11 400/mm³, hemoglobin level of 9.7 g/dL, C-reactive protein level of 12.4 mg/dL, and rheumatoid factor level of 23.7 U/mL. Abdominal computed tomography demonstrated several wedge-shaped low-density lesions in the spleen and both kidneys (Figure 1). Splenic and renal infarctions were diagnosed, which was assumed to be caused by infective endocarditis. Blood culture showed bacterial growth of Staphylococcus aureus. Transthoracic and transesophageal echocardiography subsequently identified vegetations over the anterior mitral leaflet and jet lesion site (1.1×0.9 cm), the latter being a swinging seaweed in the left atrium (Figure 2A and 2B; Movie). Three-dimensional echocardiography illustrated that the vegetation in the left atrium resembled a stalagmite (Figure 2C and 2D). The patient then underwent surgical intervention with replacement of the mitral valve and resection of the large vegetation within the left atrium (Figure 3). Chordae rupture of A1 and A2 areas was noted during operation. The patient was then begun on a complete course of antibiotics with teicoplanin plus ciprofloxacin and was discharged before admission was probably related to septic emboli, too. We have presented this case to demonstrate the nature of the growth of stalagmite-like vegetations and to alert physicians that in patients referred for echocardiography to evaluate eccentric regurgitation jet, more attention should be paid to the knock-on sites of the eccentric jets.

Disclosures

None.

References


Figure 1. A and B, Computed tomography disclosed wedged-shape low-density lesions (arrows) in the spleen and both kidneys.

Figure 2. A and B, In the parasternal short-axis view, the vegetation attached at the knock-on site of the eccentric mitral regurgitant jet (arrow). C and D, Three-dimensional echocardiography showed the vegetation and the eccentric mitral regurgitation jet.

Figure 3. A, Transesophageal echocardiography showed the vegetation with a rocky appearance, which gave the impression that the growth of vegetation resembled the formation of a stalagmite. B, Closer view of the vegetation in the left atrium during operation.
Figure 4. The echocardiography at a health checkup 1 month before admission in parasternal long-axis view (A) and in parasternal short-axis view (B) showed a small, overlooked hyperechogenic lesion (0.5×0.2 cm, arrow in left panel) on the knock-on site of the eccentric mitral regurgitant jet, which was probably the nidus for future vegetation, a stalagmite-like mass (1.1×0.9 cm, arrow in right panel) with obvious growing nature in the left atrium.
Letter by Micheletti and Chevallier Regarding Article, “Hormone Therapy and Venous Thromboembolism Among Postmenopausal Women: Impact of the Route of Estrogen Administration and Progestogens: The ESTHER Study”

To the Editor:

We read with interest the report by Canonico and colleagues that shows a differential association of oral and transdermal estrogen with venous thromboembolism (VTE) risk among postmenopausal women. In addition, their data suggest that norpregnane derivatives may be thrombogenic (with a 4-fold-increased VTE risk), whereas micronized progesterone and pregnane derivatives appear safe with respect to thrombotic risk.

First, we note that in 2 groups, oral estrogens and norpregnane derivatives, the authors reached conclusions about increased VTE risk notwithstanding odds ratios with very large confidence intervals that showed a great deal of heterogeneity. Could they give us the odds ratio variance and the probability value obtained with another statistical test for comparison of qualitative variables?

When progestins were studied, the route of estrogen administration was not shown, whereas an increased VTE risk was noted with oral estrogen. In this case, what type of progestin was involved?

The exposure time to estrogen has not been mentioned. The probability of VTE occurrence is the strongest in the first year of hormone exposure; in this respect, what can justify the cutoff point being fixed at 5 years?

The results do not appear to be in concordance with the already available data about hemostasis and nomegestrol acetate, and in our opinion, no biological plausibility has ever been found to explain the results of this case-control study. Nomegestrol acetate has very strong antagonadotropic and antiestrogenic actions, so it is used particularly in premenopausal women with strong hyperestrogenic symptoms, and hyperestrogenemia is by itself an important VTE risk factor.

Although the results are interesting, we believe that more randomized trial data are needed before conclusions can be made about the thrombogenic properties of nomegestrol acetate.

Disclosures

Drs Micheletti and Chevallier are employed by Laboratoire Théramex, Merck Serono.

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References


We thank Drs Micheletti and Chevallier for their interest in our report. First, we believe that odds ratios (ORs) and 95% confidence intervals (CIs) estimated from logistic regressions provide adequate information about significance and the size and direction of the effect of norpregnane derivatives. Because elevation in venous thromboembolism (VTE) risk is substantial (OR: 4) and significantly different from 1 (with the 95% CI not crossing 1), our results suggest a thrombogenic effect of norpregnanes, and the probability value (P < 0.006) indicates that the probability of the result being due to chance is very small.

Second, only the main effects of the route of estrogen administration and type of progestogens were estimated with a joint model (Table 2 of the original article). Stratified analyses by route of estrogen administration and type of progestogens have also been performed. Among transdermal estrogen users, women received estrogen alone (10 cases and 35 controls; OR: 0.8, 95% CI: 0.4 to 1.8 after adjustment for obesity, family history of VTE, and varicose veins) or combined with either micronized progesterone (13 cases and 63 controls; OR: 0.6, 95% CI: 0.3 to 1.2), progesterone derivatives (16 cases and 51 controls; OR: 0.8, 95% CI: 0.4 to 1.6), or norpregnane derivatives (28 cases and 31 controls; OR: 3.1, 95% CI: 1.7 to 5.9). Among oral estrogen users, women received estrogen alone (4 cases and 5 controls) or combined with either micronized progesterone (6 cases and no controls), pregnane derivatives (23 cases and 28 controls), norpregnane derivatives (12 cases and 6 controls), or nortestosterone derivatives (12 cases and 7 controls). There was no significant difference in VTE risk between any of the progestogen subgroups among current users of oral estrogen (overall OR: 4.5, 95% CI: 2.6 to 7.5).

Third, to allow for adequate numbers of subjects within subgroups, stratified analyses by time of exposure used the median of the distribution (5 years) as a cutoff point. Unlike oral estrogens, there was no significant interaction between the time of exposure to either transdermal estrogens or norpregnane derivatives and VTE risk. Therefore, differences in exposure time to hormone therapy cannot explain our results.

Finally, although our results may be clinically relevant, we acknowledge that interpretation of data may have been biased by the inclusion of women with hyperestrogenic symptoms who were prescribed norpregnane derivatives. This prescription bias was emphasized in the Discussion section. Regarding the absence of thrombogenic mechanism underlying our results, Micheletti and Chevallier quote an inconclusive small trial that failed to also show the well-known activation of blood coagulation among women using oral estrogens. In addition, relevant hemostatic tests such as plasma-activated protein C sensitivity were not included as endpoints in this trial. Because relevant data are lacking, we are presently investigating the impact of norpregnanes on hemostasis among users of hormone therapy in the Study of NorpregAnes on Coagulation (SNAC study).

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References


The Congenital Cardiac Audit Database (CCAD) now collects performance data from the United Kingdom’s specialist centres and publishes them on a Web site, www.ccad.org.uk/congenital (Figure 1). This move comes a decade after an in-depth inquiry into the high death rates of babies treated at Bristol Royal Infirmary, England, in the 1980s and 1990s.1

Leisa Freeman, MB, ChB, FRCP, a consultant cardiologist at the Norfolk and Norwich University Hospital in England with a specialist interest in grown-up congenital heart disease (GUCH) and a trustee of the GUCH Patients Association, welcomed the move to publish online the surgery survival rates for children with congenital heart disease, but she has some reservations. She says, “Based on the validity of the data from coronary artery bypass graft outcomes, I am sure that the data reflect the performance of the centres involved. However, coronary artery bypass graft is a fairly unifying diagnosis, as all patients have coronary artery disease, and it thus makes it possible to predict the risk of surgery based on preoperative risk assessments such as the EuroSCORE.” And she points out, “It is interesting that the data from CCAD have shown a fall in mortality relating to coronary artery bypass graft surgery to 1.8%, despite the pre-operative EuroSCORE assessments rising from 3% to 3.5%. This suggests that the surgeons are operating on more complex patients yet obtaining better results.”

Although Dr Freeman sees the publication of surgical outcome by centre as a good step, she would not consider publishing data specific to each surgeon such a positive move. She says, “The drive to publish the outcomes of individual surgeons began as a result of the Bristol inquiry, which was dealing with surgery for congenital heart disease. The variety of the underlying congenital heart disease is large, and the operations that are done reflect the many different operations that are required.” She continues, “Therefore,
the data for individual surgeons on individual lesions may be relatively small, and the problems regarding small numbers come into play. Surgery under these circumstances requires a team approach involving cardiologists, paediatric cardiac surgeons, anaesthetists, nurses, physiotherapists, and cardiac physiologists, so publication of surgical outcome per centre is good, but specific to each surgeon is not good.”

However, Dr Freeman believes that patients, parents, surgeons, and hospitals will benefit from the transparency of publishing data online. “The coronary artery bypass graft data have shown that operative success has actually improved after publication of data, so I think the surgeons and the hospitals will benefit.” Specialised operations in congenital heart disease such as the Fontan revision to total cavopulmonary connection might eventually be concentrated in single centres in England if the data show survival issues in the most complex cases. Dr Freeman thinks that patients or parents will not likely choose their centre on the basis of results; rather, cardiologists will continue to guide such decisions. “What the people may do, however, is do some research to find out where a particularly complex operation is being performed frequently and ask questions about that operation.” She explains that if a patient needs surgery, she refers them to the surgical centre she considers best for the patient. “In the case of a recent patient with Ebstein’s anomaly of the tricuspid valve, I referred them to Southampton General Hospital, in southern England, which has a cardiac unit with the best outcomes in such patients.”

Paul Schoof, MD, PhD, a surgeon specialising in congenital cardiac surgery, and congenital cardiologist Folkert Meijboom, MD, PhD, of the Nijmegen University Medical Center, the Netherlands, gave their uncompromising assessment of the United Kingdom’s decision to publish the survival rates.

Dr Schoof says, “Without risk adjustment, the publication of raw mortality rates of individual centres is meaningless, of no use to the public, and useless as a quality instrument for the professionals. Since it does not serve its purpose, I would strongly oppose publication of this simplified outcome measurement.” In the Netherlands, congenital cardiac surgeons have recently committed themselves to using the European Association for Cardiothoracic Surgery–Society of Thoracic Surgeons database, developed during the past few years in Europe. This database uses a uniform method of cardiac diagnosis, surgical treatment, outcome parameters, and risk stratification.

Dr Schoof explains, “It allows us to compare our national or centre-specific results to those of other European countries or centres. In contrast to the raw mortality rates, this is considered to be a valuable tool for quality improvement. We in Europe have not yet decided to share our data with the public on a national or European level.” Dr Schoof adds that individual hospitals have already used their data for publication on their own Web sites.

“However,” says Dr Schoof, “We expect that these data will be accessible for both public and professionals within the foreseeable future. But, rather than focussing on individual surgeons, the team performances of all professionals involved in the chain of care will be measured, and the outcomes of overall performance will be published.”

Dr Schoof and Dr Meijboom believe that reporting hospital and surgeon performance in general represents a good move to improve quality of care. Nevertheless, in congenital cardiac surgery, outcomes depend heavily on the quality of the entire system of care and on the ability of all members of the team. “Selective reporting of individual surgeons’ performance is therefore unlikely to help the patient or parents to assess the quality of the complete chain of care,” says Dr Schoof. “We believe that a high-quality database, using audited and validated data, and analysed with a uniform case-complexity score, is mandatory for sensible evaluation of outcomes of surgical treatment.”

Dr Schoof adds, “Sharing this information with our fellow providers of care and the paediatric cardiac surgical patient will undoubtedly improve quality; the reported best results will act as benchmarks for all other centres.” He concludes, “Sharing this information with the public will lead to preferential referral to the centres that present the best results, until other centres catch up in terms of results. Provided these outcome data are regarded as representing all involved professionals, the public reporting of our European data may prove to be of benefit to the public.”

Stephen Westaby, PhD, FRCS, FESC, a consultant cardiac surgeon at the Oxford Heart Centre, United Kingdom, who has a large number of patients who are children and a reputation for operating on high-risk patients, expresses
concerns over the validity of the online data for congenital heart disease. “The publication of UK cardiac surgical mortality statistics followed emotional demands by bereaved parents after the Bristol Inquiry,” he says, pointing out that whereas most surgeons support the publication of accurate, risk-stratified, independently verified information, UK government agencies and the media have employed administrative data sets for hospital profiling because such data sets are inexpensive and accessible. In general, these have a poor track record on both sides of the Atlantic.

The Bristol inquiry and subsequent UK investigations used unverified hospital episode statistics collected from raw data submitted by non–clinically aware hospital coding clerks. A recent comparison with the clinical CCAD showed between 5% and 38% (median 15%) of operations missed by hospital episode statistics, together with a 40% median shortfall (range, 0% to 73%) in deaths reported. CCAD information comes from clinicians in the congenital heart units and is linked to the Office of National Statistics to track deaths, irrespective of location. Even so, from 2000 to 2003, CCAD had between 1% and 23% missing outcome data for 11 English centres. Publication of inaccurate statistics detracts from, rather than enhances, public confidence.

Dr Westaby says, “It is imperative that public reporting is based upon data of the highest quality derived from prospectively gathered, validated, and audited data supplied by clinicians. Precise database definitions and uniform training of data managers are essential.” He believes that the National Health Service has not invested sufficient resources to make this happen, and he senses outstanding questions about the motives and effects of public reporting. “In its present form, the public reporting of cardiac deaths cannot increase the safety of surgery, but it may reduce mortality rate if the system discards high-risk patients,” says Dr Westaby. “Surgeons would not wish to take this route, but many will follow their self-preservation instinct in order to avoid hostile media attention.”

Dr John Gibbs, FRCP, president of the British Congenital Cardiac Association and consultant paediatric cardiologist at Leeds General Infirmary, has a differing view. For the past 11 years, he has served as clinical lead for congenital heart disease at CCAD and has participated actively in the process with the CCAD database set up jointly between the British Congenital Cardiac Association, the Society of Cardiothoracic Surgeons of Great Britain and Ireland, the British Cardiovascular Society, and the UK Department of Health.

Dr Gibbs says that clinicians have driven the whole project from the word go. “It has been a gradual process bringing all, or the vast majority, of congenital heart doctors round to agreeing that publication of centre-specific mortalities is a good thing, but we did achieve that. And, before we went public, we had agreement from every centre to do so.” He explains, “Naturally, cynics remain, but they are in a small minority, and most cardiologists and surgeons now think it is helpful to them as well as to the public. It is the first time that doctors, let alone the public, can see national outcomes—both perioperative and at 1 year—for the major congenital cardiac procedures.” Dr Gibbs continues, “We think it is a crude indicator of performance for specific procedures—but note that we do not give overall mortality for any centre, only results for individual procedures. This is because the case mix varies, and there is no validated risk stratification for congenital heart disease.”

Dr Gibbs personally feels that operator-specific data will come eventually, but the consensus view at present does not regard such data as potentially helpful. “The reasons given are that no individual operator works alone, and that a team’s results are the most appropriate to place in the public domain. The current message to patients and parents is that they should discuss individual operator results with their surgeon/cardiologist.” He says, “I’m sure patients and parents will find the information useful, although there can be no doubt that such data can be alarming rather than reassuring. For the purposes of counselling parents and patients on risk and longer-term outcome, it is clearly invaluable to doctors as well. I am optimistic that, in the longer term, doctors may use the data to identify best practices and learn from that.”

Dr Gibbs considers the figures relevant because they stick to specific procedure outcomes. He concludes, “There are future plans to publish national and centre-specific actuarial survival curves for each major condition, and freedom from reintervention from selected surgical and catheter interventions.”

Mark Nicholls is a freelance medical writer.

References
The mission of the Hungarian National Heart Foundation (HNHF) is to reduce the prevalence and impact of cardiovascular disease in Hungary’s population of 10 million people. The task is immense. The number of deaths caused by cardiovascular disease is more than twice the European Union average (see Table). Life expectancy at birth in Hungary for women is 5.6 years lower, and for men 7.8 years lower, than the European Union average. About 37% of adults are overweight, 23% are obese, and the proportion of overweight children and adolescents has been rising.

The HNHF concentrates on influencing the general public and opinion leaders, leaving scientific research and the education of hospital doctors to its parent organisation, the Hungarian Society of Cardiology. However, the HNHF does work with both general practitioners and hospital doctors on prevention strategies.

Although the HNHF was founded in 1993 by the Hungarian Society of Cardiology, in its early years it had to exist without full-time staff and attracted only a small income. Dr Nagy is a full-time cardiologist at Bács-Kiskun County Hospital in Kecskemét, Hungary, where he runs the cardiology department. His research interests there are cardiovascular prevention and ischaemia-reperfusion injury.

In recent years, the Foundation has grown in authority in Hungary. Dr Nagy sees the key to that growth as being participation in European Heart Network and European Union projects, especially those that relate to children, obesity, and associated avoidable chronic disease, and the EuroHeart project on prevention of cardiovascular disease. For the past 2 years, the Foundation has been able to afford 1 full-time employee, and this also has hugely increased the viability and effectiveness of the organisation.

The HNHF has developed 2 strong coalitions within the country. The first is a coalition of 14 nongovernmental organisations to combat obesity; 10 of these have now contributed to the development of a national guideline. The second, arranged together with the Hungarian Society of Cardiology, was the endorsement of the European Heart Health Charter by the Hungarian Minister of Health and the leaders of 18 professional and civic organisations.

Funding the Foundation
Dr Nagy explains how the Foundation is currently resourced. “At present, we are involved in an automated external defibrillator programme, and this brings in some funds from a partner in industry. The other source of funds is the European Heart Network.” Government funding has been small, but he expects that to become larger in scale as the reputation of the HNHF increases and with the Health Ministry’s commitment to the European Heart Charter. In the future, the HNHF intends to develop corporate partnerships to bring in funds and support its mission, but Dr Nagy stresses that the HNHF will be careful to maintain its independence and will not enter into a relationship or accept sponsorship that harms its reputation.

Public donations and legacies are unlikely to be a large source of funds in his country. Dr Nagy says, “In Hungary, and generally in Eastern Europe, there is no tradition of giving to charities. People also have the ingrained attitude that the government is responsible for paying for their care.”

The Defibrillator Programme
Dr Nagy is enthusiastic about the success of the automated external defibrillator programme. “The Foundation plays a leading role among civil society organisations fighting
against sudden cardiac death,” he says. We have supplied health providers, mainly general practitioners, with life-saving defibrillator equipment in unprecedented numbers through our Every Minute Counts programme. We are leaders in providing such life-saving devices for public areas and other areas where there are high concentrations of people.”

Healthy Food Campaign
The Healthy Food Campaign and the Children and Obesity Campaign are 2 of the HNHF’s most important campaigns. The top priorities of the Healthy Food Campaign are the mandatory labelling with nutritional information of all processed foods and pursuing a government restriction on trans fats. Whereas labelling was enforced when Hungary joined the European Union, the ruling has been diluted to the minimum European level. Hungarians had previously been used to rather more detailed labels on a wide range of food products, so in some ways the recent changes have left the population less well informed.

Action on healthy eating at schools started during 2006. Dr Nagy says, “The control of the sale of foods, especially fatty snacks, confectionery, and sweet drinks in schools has already been implemented in Hungary. This was undoubtedly the most important development in the country since the start of the Children and Obesity Campaign.”

Dr Nagy describes the approach to reforming food outlets in schools. “Rather than directly banning certain food categories at school kiosks, the National Institute for Food Safety and Nutrition first issued a scientifically based set of recommendations,” he explains. “Contracts with school food outlet providers were then revised, and renewals were not allowed if the vendors failed to comply with these recommendations. In addition, the school health service and parents boards must confirm that the vendor has complied.”

European Heart Health Charter
The European Heart Health Charter, launched in June 2007, is in Dr Nagy’s view a massive opportunity for his country. He says, “This is an unprecedented opportunity to reach our own national consensus. That consensus was the starting point for other countries in their struggle against heart diseases. Neither individuals, nor professional societies, nor politicians are able to bring about radical change alone.”

The roundtable of the signatories of the Charter in Hungary prioritised 3 key areas for immediate action, and these are:

- Heart-healthy lifestyles should be incorporated into the curriculum of school education.
- Forceful regulatory and taxation measures should be implemented against active and passive smoking. Smoking should be forbidden at all workplaces.
- Appropriate incentives combined with strong media involvement are needed to reach at least the minimum recommended level of 400g fruit and vegetable consumption for adults.

Robert Short is a freelance medical journalist.

References

History of Cardiology: Eduardo de Araýjo Coelho, MD, PhD

An Overlooked European Pioneer of Cardiac Research

Eduardo Coelho (1896–1974), a professor cardiology, appears to be an overlooked pioneer in cardiac research. In 1952, at the First European Cardiology Congress in London, United Kingdom, he revealed to the medical world the first coronary angiography in a living patient. Diana Berry tells his story.

Eduardo Coelho was born in Guimarei, Portugal, in 1896. His early medical studies were undertaken in Portugal at Coimbra University, and his final year was spent at the Lisbon Faculty of Medicine, from which he graduated in 1922, producing his PhD thesis a year later. In 1925, he attended the Department of Clinical Practice at the University of Berlin, Germany, under the tutelage of Rudolph Kraus, MD. After studying electrocardiography under Dr Kraus, he set up a department of electrocardiography at the Santa Marta Hospital, Portugal, in 1925.
Dr Coelho married the niece of Egas Moniz, MD, a Portuguese psychiatrist and neurosurgeon who in 1927 developed cerebral angiography using x-rays to visualise arteries and veins transiently opacified with a radio-opaque high-density agent. Dr Coelho was in the darkroom during the experiment and shouted out excitedly on first seeing the cerebral veins in a living patient.

In 1933, he took the necessary examinations to take up the position of assistant professor in internal medicine. In 1934, his monograph *L’infarctus du Myocar* was published in France by Masson of Paris. It was the first European monograph on myocardial infarction.

Dr Coelho’s observations on the correlation between the pathological alterations of the coronary arteries and myocardial infarction led him to propose the coexistence of a number of pathological possibilities. These included obstruction of a coronary artery with myocardial infarction, obstruction without infarction, and multiple scars or infarction with normal arteries. He was able to show that the development of collateral circulation was proportional to the extent of coronary occlusion, and that thrombosis, obstruction, and infarction may occur silently, whereas symptoms of angina pectoris may coexist with normal coronaries.

Dr Coelho’s activities extended to other pioneering studies, including work on endocardial electrocardiography presented in 1948 to the Third Inter-American Cardiology Congress in Chicago, IL. In 1948, he was also able, through catheterisation of the right heart, to embark on the study and evaluation of acquired cardiopathies and chronic cor pulmonale. These studies were undertaken by the radiology department of Santa Marta Hospital and represented the beginning of paediatric cardiology in Portugal.

Dr Coelho’s article *L’artériographie des coronaires chez l’homme vivant* was presented in 1952 at the First European Cardiology Congress in London, United Kingdom, and was published a year later. It sets out in detail the work undertaken in producing the first coronary angiographies in living humans. In the article, Dr Coelho and his colleagues first outline the then current situation with respect to available methods for diagnosing coronary lesions such as sclerosis and thrombosis using clinical data and electrocardiography. They go on to discuss the failings in such diagnostic methods, pointing out that many patients with an apparently normal electrocardiogram are found at autopsy to have obstruction, stenosis, or other abnormalities of the coronary arteries. They also state that simple radiography without a contrast medium reveals little in most cases of arteriosclerosis and that only the technique of arteriography employing a contrast medium can give useful information about the anatomical state of coronary artery disease in the living person.

The article recalls previous attempts to visualise the coronary arteries in vivo and then presents a detailed account of Dr Coelho and colleagues’ research, including the techniques employed. A key paragraph reads: “We began with giving the low concentration injections of diodrast (20 to 30%) of 20, 30, 40, and 50cc in 7 seconds. The patients did not present any problems; with this concentration of diodrast the cardiographies did not show the slightest trace of the coronaries and therefore these first cases were unsuccessful. An injection of 50–60cc of diodrast at 70% concentration finally allowed us to see the opacification of the two coronaries. The injections took 4-5 seconds to administer using a Lauerlock syringe and we were able to get ten x-rays in a few seconds. In order to avoid too high a concentration of diodrast in the blood from tenderising the brain we compressed the carotids during the injection process. The electrocardiograms taken during and after the injections did not show any changes. The patients were sedated the day following the radiography and over the following two days received injections of heparin, controlled by the level of clotting time.”

The authors conclude that coronary arteriography in live humans is a risk-free procedure provided that the carotid arteries are firmly compressed during the injection of the diodrast and that the catheter is placed facing the coronary arteries and not within them. “Despite the technical difficulties in filling the coronaries with a sufficient concentration of the opaque substance,” they comment, “one cannot deny the importance of this method, the only means by which we are able to see a stenosis or an obstruction of the coronaries.”

F. Mason Sones Jr, MD, of the Cleveland Clinic, Ohio, is considered the father of selective coronary angiography. When, on October 30, 1958, an aortic root catheter accidentally entered the right coronary artery, he envisioned a technique that, once perfected, was to revolutionise the diagnosis of coronary artery disease, but this well-known story does not detract from Dr Coelho’s contribution to the field.

Despite Dr Coelho’s research not perhaps having received the full acclaim that it deserves, recognition has arrived from some quarters. Godofredo Gensini, MD, writing in 1972, felt that “Eduardo Coelho and his colleagues were pioneers in searching for new methods specifically intended for deliberate, satisfactory, human coronary visualisation,” and in 1980, Willis Hurst, MD, confirmed that, in his opinion, “While Dr Sones should be credited for developing the technique and moving on to its clinical usage… Dr Coelho should be credited with originating the technique.” And in a personal letter to Dr Coelho’s son, Eugene Braunwald, MD, wrote in April 2004 that “clearly Professor Coelho’s work was groundbreaking.”

*Diana Berry is a freelance medical historian.*

**References:**


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