A Simplified Approach to the Management of Non–ST-Segment Elevation Acute Coronary Syndromes

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While ongoing efforts by the American College of Cardiology (ACC) and the American Heart Association (AHA) have led to guidelines for the management of patients with non–ST-segment elevation acute coronary syndromes (NSTE-ACS), implementation of these recommended acute and long-term treatment strategies remains suboptimal. In order to simplify the guidelines, we propose a modification of the “ABC” approach initially developed by the ACC/AHA for patients most likely to benefit from an early invasive vs early conservative strategy, a comprehensive management plan can be assembled through an “ABCDE” approach. The elements of this include “A” for antiplatelet therapy, anticoagulation, angiotensin-converting enzyme inhibition, and angiotensin receptor blockade; “B” for β-blockade and blood pressure control; “C” for cholesterol treatment and cigarette smoking cessation; “D” for diabetes management and diet; and “E” for exercise.

Context While current practice guidelines provide an evidence-based approach to management of acute coronary syndromes (ACS), application of the evidence by individual physicians has been suboptimal.

Objective To assess and synthesize the evidence regarding optimal management of non–ST-segment elevation ACS (NSTE-ACS).

Data Sources Systematic searches of peer-reviewed publications were performed in MEDLINE and the Cochrane Database from January 1990 through November 2004, with consultation by content experts. Search terms included antithrombotic therapy, antithrombotic therapy, angiotensin-converting enzyme inhibition, angiotensin receptor blockade, β-blockade, hypertension, hyperlipidemia, cigarette smoking, diet, diabetes mellitus, exercise, myocardial ischemia, and coronary artery disease.

Study Selection and Data Extraction Criteria for selection of studies included controlled study design, English language, and clinical pertinence. Data quality was based on the publishing journal and relevance to clinical management of NSTE-ACS.

Data Synthesis While outcomes of controlled studies support a comprehensive approach in the management of patients with NSTE-ACS, many physicians perceive existing guidelines as lengthy and complex. After risk stratification to identify those patients most likely to benefit from an early invasive vs early conservative strategy, a comprehensive management plan can be assembled through an “ABCDE” approach. The elements of this include “A” for antiplatelet therapy, anticoagulation, angiotensin-converting enzyme inhibition, and angiotensin receptor blockade; “B” for β-blockade and blood pressure control; “C” for cholesterol treatment and cigarette smoking cessation; “D” for diabetes management and diet; and “E” for exercise.

Conclusion An “ABCDE” approach for the management of NSTE-ACS provides a practical and systematic means to implement evidence-based medicine into clinical practice.
MANAGEMENT OF NON–ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROMES

Box 1. TIMI Risk Score Predictor Variables

Age >65 years
Three or more risk factors for coronary artery disease
Known coronary artery stenosis of >50%
ST-segment deviation on presenting electrocardiogram
Two or more episodes of angina within the preceding 24 hours
Use of aspirin within the preceding 7 days
Elevated serum cardiac biomarker levels

Abbreviation: TIMI, Thrombolysis in Myocardial Infarction.
*As presented in Antman et al.1

DATA SYNTHESIS

Definition and Diagnosis
NSTE-ACS represents one part in the continuum of disease processes resulting from reduced coronary blood flow due to plaque disruption and subsequent thrombus formation. Also known as unstable angina and non–ST-segment elevation myocardial infarction (MI), NSTE-ACS is a more comprehensive term that combines these 2 entities.

NSTE-ACS should be differentiated from ST-segment elevation MI, as the treatment differs substantially. ST-segment elevation MI is typically characterized by complete thrombotic occlusion of a coronary artery and is generally treated with immediate reperfusion therapy. In contrast, NSTE-ACS usually results from a transiently or nearly completely occluded coronary artery and may or may not require revascularization. NSTE-ACS should be suspected in patients with clinical evidence of myocardial ischemia but without electrocardiographic evidence of ST-segment elevation, a true posterior MI, or a new left bundle-branch block.

Update to the Guidelines
The most recent update to the ACC/AHA guidelines for NSTE-ACS was published in 2002.1 In this update, several areas were highlighted, including (1) early risk stratification; (2) new indications for pursuing an early invasive strategy; (3) the early use of aspirin and clopidogrel; (4) the use of glycoprotein (Gp) IIb/IIIa inhibitors, especially in patients undergoing percutaneous coronary intervention (PCI) or those with high-risk features; (5) the preferential use of low-molecular-weight heparin (LMWH); and (6) the early use of lipid-lowering therapy. While these areas still remain important in the treatment of patients with NSTE-ACS, much has been learned over the last 2 years that has helped to better define their roles.

Risk Stratification

Estimation of risk is an integral component in the evaluation of patients with NSTE-ACS. While several risk stratification tools are available, one that is frequently used is the Thrombolysis in Myocardial Infarction (TIMI) risk score.5 This tool combines 7 variables in an evenly weighted scale (Box 1) and can predict short- and long-term risk based on the calculated score.6,7 It also helps to identify patients that benefit most from Gp IIb/IIIa inhibitors8 and an early invasive strategy.9,10 Even without calculating the TIMI risk score, elevated troponin levels and ST-segment depression help to distinguish individuals at increased cardiovascular (CV) risk.11 The identification of these and other important predictors of risk (eg, hemodynamic instability, signs and symptoms of heart failure, renal insufficiency, and elevated levels of C-reactive protein and natriuretic peptides)12-17 can be particularly helpful in stratifying the early delivery of beneficial treatments for patients with NSTE-ACS.

Early Invasive vs Early Conservative Approach

One of the greatest impacts of risk stratification in NSTE-ACS has been whether to pursue an early routine invasive vs early conservative (selective invasive) strategy. The early routine invasive strategy generally consists of diagnostic coronary angiography and angiographically directed revascularization within 48 hours of symptom onset. In contrast, the conservative strategy relies on noninvasive evaluation of ischemia after a period of observation, with catheterization and revascularization recommended only if ischemia recurs or is unresolved. Anti-ischemic and antithrombotic therapy is recommended for all patients regardless of treatment strategy.

Based on several trials,9,10,16,17 the strongest evidence supporting an early invasive strategy has come from its use in individuals with ST-segment depression, elevated troponin levels, and/or intermediate to high (>3) TIMI risk scores.9,16 Accordingly, the ACC/AHA recommends that an early invasive approach be used for patients with high-risk features (Box 2), reserving the early conservative approach for patients at lower risk.1 This strategy is not only cost-effective18 but is of particular benefit in elderly patients, despite an increased risk of bleeding.19

ABCDE Approach to NSTE-ACS

Several years ago, our center addressed the implementation of previous ACC/AHA guidelines by adapting a previously proposed “ABC” approach to risk management.20 Through a modification of this approach, this review intends to provide an overview of medical therapies and lifestyle changes that are useful in NSTE-ACS (Table).

Antiplatelet Therapy
Aspirin. By inhibiting platelet activation and aggregation, aspirin is able to reduce the incidence of death and nonfatal MI in patients with unstable angina21,22 or acute MI,23 with only a small increased risk of major bleeding (0.2%). Higher doses of aspirin (>100 mg) do not provide greater benefit and in fact may be less desirable due to increased bleeding, especially when combined with clopidogrel.24 Current guidelines, therefore, recommend that all patients with NSTE-ACS receive 162 to 325 mg of aspirin initially, followed by 75 to 160 mg daily thereafter.3
Adenosine Diphosphate Receptor Antagonists. For patients unable to take aspirin because of intolerance or hypersensitivity, the thienopyridine clopidogrel (75 mg daily) should be substituted. This is based largely on the results of the Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study, a trial of 19185 patients with known atherosclerotic vascular disease randomized to receive either clopidogrel (75 mg daily) or aspirin (325 mg daily). Because patients receiving clopidogrel experienced a 9% relative risk reduction in adverse CV events (5.3% vs 5.8%, P=0.04), clopidogrel may be used in lieu of aspirin, albeit at much higher cost.

Most patients with NSTE-ACS who are at low bleeding risk should have clopidogrel added to aspirin at hospital admission, with continuation for up to 12 months. Support for this recommendation comes from the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) trial. In this study, 12562 patients with NSTE-ACS were randomized to receive clopidogrel (loading dose of 300 mg followed by 75 mg daily) plus aspirin (75-325 mg daily) vs aspirin alone (75-325 mg daily) for a mean of 9 months. Patients receiving dual antiplatelet therapy experienced a 20% relative risk reduction in the primary combined end point of CV death, nonfatal MI, or stroke (9.3% vs 11.4%, P<.001).

Clopidogrel is also efficacious among patients with NSTE-ACS undergoing PCI. Both PCI-CURE, a subset of the CURE study that included patients undergoing PCI, and the Clopidogrel for the Reduction of Events During Observation (CREDO) study support the long-term use of clopidogrel in patients treated with PCI. Between both studies, 4774 patients were randomized to receive aspirin (75-325 mg daily) or aspirin plus clopidogrel (300 mg loading dose followed by 75 mg daily), with treatment initiated prior to PCI and continued for a mean of 8 to 12 months. Among patients receiving dual antiplatelet therapy, there was a 27% to 31% relative risk reduction in a combined end point that included all-cause mortality, CV death, MI, and/or stroke (P=.002 to P=.02). No significant differences in major bleeding were noted, even among patients who received concurrent Gp IIb/IIIa inhibitors.

For patients undergoing surgical revascularization, clopidogrel offers both benefit and harm. While its early use is associated with significantly improved outcomes, it increases the risk of bleeding if administered within 5 days of surgery. This is of little consequence in surgeries performed electively but may have major implications if urgent revascularization is required. Accordingly, clopidogrel should be withheld in high-risk patients managed with an early invasive strategy if surgery is likely or if coronary angiography is to be performed early (ie, within 12 hours of presentation). For all others, clopidogrel should be started early, with continuation up until 5 days of surgery.

Gp IIb/IIIa Inhibitors. Based on their ability to prevent ischemic complications following PCI, Gp IIb/IIIa inhibitors should be administered to patients with NSTE-ACS managed with an early invasive strategy. In a pooled analysis of 14644 patients undergoing PCI, treatment with a Gp IIb/IIIa inhibitor was associated with a 42% relative risk reduction in MI and urgent revascularization, clopidogrel offers both benefit and harm. While its early use is associated with significantly improved outcomes, it increases the risk of bleeding if administered within 5 days of surgery. This is of little consequence in surgeries performed electively but may have major implications if urgent revascularization is required. Accordingly, clopidogrel should be withheld in high-risk patients managed with an early invasive strategy if surgery is likely or if coronary angiography is to be performed early (ie, within 12 hours of presentation). For all others, clopidogrel should be started early, with continuation up until 5 days of surgery.

For patients undergoing an early invasive strategy, the benefit of Gp IIb/IIIa inhibitors is less pronounced. In a meta-analysis of 31402 conservatively managed patients with NSTE-ACS, treatment with a Gp IIb/IIIa inhibitor was associated with a 9% relative risk reduction in the incidence of death or MI at 30 days (P=.02). This benefit was limited, however, to patients with a positive troponin level or in need of early revascularization. Thus, epifibatide or tirofiban should be used as a continuous infusion for patients with a positive troponin level or with low-level activities despite intensive anti-ischemic therapy or in need of early revascularization. However, these findings are based on trials conducted before the agent was selected. Available data favor the use of abciximab or accelerated-dose epifibatide if PCI is anticipated soon after presentation (<4 hours), reserving tirofiban and epifibatide for patients treated medically during the first 48 hours.

For patients undergoing an early conservative strategy, the benefit of Gp IIb/IIIa inhibitors is less pronounced. In a meta-analysis of 31402 conservatively managed patients with NSTE-ACS, treatment with a Gp IIb/IIIa inhibitor was associated with a 9% relative risk reduction in the incidence of death or MI at 30 days (P=.02). This benefit was limited, however, to patients with a positive troponin level or in need of early revascularization. Thus, epifibatide or tirofiban should be used as a continuous infusion for patients with a positive troponin level or with low-level activities despite intensive anti-ischemic therapy or in need of early revascularization. However, these findings are based on trials conducted before the agent was selected. Available data favor the use of abciximab or accelerated-dose epifibatide if PCI is anticipated soon after presentation (<4 hours), reserving tirofiban and epifibatide for patients treated medically during the first 48 hours.

Box 2. High-Risk Features Favoring an Early Invasive Strategy*

Recurrent angina/ischemia at rest or with low-level activities despite intensive anti-ischemic therapy
Elevated troponin level
New or presumably new ST-segment depression
Recurrent angina/ischemia with symptoms of heart failure, an S3 gallop, pulmonary edema, worsening rales, or new or worsening mitral regurgitation
High-risk findings on noninvasive stress testing
Left ventricular systolic dysfunction (ejection fraction <40% on a noninvasive study)
Hemodynamic instability
Sustained ventricular tachycardia
Percutaneous coronary intervention within 6 months
Prior coronary artery bypass graft surgery

*Adapted from American College of Cardiology/American Heart Association guidelines.
and found no significant difference in the primary end point of death or MI at 30 days. In fact, a trend toward worse outcomes with longer infusions of abciximab was noted, limiting its use in the treatment of patients for whom PCI is not planned. While the exact etiology for this paradoxical effect is not known, it may be related to proinflammatory effects of subthreshold Gp IIb/IIIa receptor blockade.42

Unfortunately, the optimal antiplatelet regimen for patients with NSTE-ACS remains to be defined. Much of this is based on the absence of clinical trial data comparing the combined use of aspirin, clopidogrel, and a Gp IIb/IIIa inhibitor (ie, triple antiplatelet therapy) to treatment with just 2 antiplatelet agents (ie, aspirin plus clopidogrel or aspirin plus a Gp IIb/IIIa inhibitor). While there is in vitro evidence to support triple antiplatelet therapy in patients with NSTE-ACS,43 event-driven studies are needed to clarify the incremental value vs increased bleeding risk associated with this strategy.

Table. ABCDEs of Cardiovascular Disease Management in NSTE-ACS

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Agent(s)/Treatment Modalities</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Antiplatelet therapy</td>
<td>Aspirin</td>
</tr>
<tr>
<td></td>
<td>All patients indefinitely initially with 162-325 mg followed by 75-160 mg daily thereafter</td>
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<tr>
<td>ADP Receptor antagonist (clopidogrel)</td>
<td>All patients, unless anticipated need for urgent CABG surgery or within 5 days of electively scheduled CABG surgery</td>
<td>Duration of up to 1 year</td>
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<tr>
<td>Gp IIb/IIIa Inhibitor (abciximab, eptifibatide, tirofiban)</td>
<td>All patients with continuing ischemia, an elevated troponin level, a TIMI risk score &gt;4, or anticipated PCI</td>
<td>Avoid abciximab if PCI is not planned</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>Unfractionated heparin</td>
<td>Alternative to LMWH for patients managed with an early invasive strategy</td>
</tr>
<tr>
<td></td>
<td>LMWH (specifically enoxaparin)</td>
<td>Preferred anticoagulant if managed conservatively</td>
</tr>
<tr>
<td></td>
<td>Preferred anticoagulant for patients managed with an early invasive strategy</td>
<td>Avoid if creatinine clearance is ≤60 mL/min (unless anti-Xa levels are to be followed) or CABG surgery within 24 hours</td>
</tr>
<tr>
<td>ACE Inhibition</td>
<td>No clear preferred agent</td>
<td>All patients with LVSD (ejection fraction &lt;40%), heart failure, hypertension, or other high-risk features</td>
</tr>
<tr>
<td>Angiotensin receptor blockade</td>
<td>No clear preferred agent</td>
<td>All patients intolerant of ACE inhibitors</td>
</tr>
<tr>
<td></td>
<td>Avoid combination therapy with ACE inhibitors acutely, but consider in patients with chronic LVSD (ejection fraction &lt;40%) and heart failure</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>β-Blockade</td>
<td>No clear preferred agent</td>
</tr>
<tr>
<td>Blood pressure control</td>
<td>ACE Inhibitors and β-blockers first line</td>
<td>Goal BP at least &lt;130/85 mm Hg (&lt;130/85 mm Hg if diabetes or chronic kidney disease present)</td>
</tr>
<tr>
<td></td>
<td>Optimal BP may be as low as 125/75 mm Hg</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Cholesterol treatment</td>
<td>Potent, high-dose statin</td>
</tr>
<tr>
<td></td>
<td>All patients</td>
<td>Goal LDL-C level &lt;70 mg/dL</td>
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<td></td>
<td>Ezetimibe or bile acid sequestrant (resin)</td>
<td>All patients unable to achieve an LDL-C level &lt;70 mg/dL while taking a potent, high-dose statin</td>
</tr>
<tr>
<td></td>
<td>Fibrates or nicotinic acid (niacin)</td>
<td>Consider in patients with an HDL-C level &lt;40 mg/dL or a triglyceride level &gt;150 mg/dL while taking a potent, high-dose statin</td>
</tr>
<tr>
<td>Cigarette smoking cessation</td>
<td>Long-term behavioral support</td>
<td>All patients using tobacco</td>
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<td></td>
<td>Bupropion plus nicotine replacement</td>
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<tr>
<td>D</td>
<td>Diabetes management</td>
<td>Glycemic control (HbA1c &lt;7% [minimum])</td>
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<tr>
<td></td>
<td>All patients with diabetes</td>
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<tr>
<td>Diet</td>
<td>Weight reduction to achieve optimal body mass index</td>
<td>All patients</td>
</tr>
<tr>
<td></td>
<td>Dietary modification</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>Exercise</td>
<td>Aerobic and weight-bearing exercise 4-5 times per week for &gt;30 min</td>
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<tr>
<td></td>
<td>All patients, preferably within a cardiac rehabilitation program</td>
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</table>

Abbreviations: ACE, angiotensin-converting enzyme; ADP, adenosine diphosphate; BP, blood pressure; CABG, coronary artery bypass graft; Gp, glycoprotein; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LMWH, low-molecular-weight heparin; LVSD, left ventricular systolic dysfunction; MI, myocardial infarction; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

SI conversion factors: To convert creatinine clearance values from mL/min to mL/s, multiply by 0.0167; to convert LDL-C and HDL-C values from mg/dL to mmol/L, multiply by 0.0259; to convert triglyceride values from mg/dL to mmol/L, multiply by 0.0113.

*Modified and adapted from American College of Cardiology/American Heart Association guidelines.4 ©2005 American Medical Association. All rights reserved.
**Anticoagulation**

Through its potentiation of circulating antithrombins and ability to inhibit clot propagation, heparin reduces ischemia in NSTE-ACS. When used in its unfractionated form, however, heparin requires frequent monitoring of the partial thromboplastin time and can be associated with delays in achieving therapeutic anticoagulation. By fractionating heparin into molecules of lower molecular weight, an LMWH is produced with better bioavailability, more predictable pharmacokinetics, and a longer half-life. In addition, LMWH is associated with less platelet activation and heparin-induced thrombocytopenia. Regardless, many practitioners have been hesitant to use LMWH (especially if cardiac catheterization with PCI is planned) because of concerns of reduced efficacy, increased bleeding, and an inability to easily monitor anticoagulation in the catheterization laboratory.

Two large trials recently compared the safety and efficacy of LMWH with that of unfractionated heparin in patients with NSTE-ACS. In the A to Z study, 3987 patients were randomized to receive either unfractionated heparin or LMWH (enoxaparin) concurrently with tirofiban and aspirin. While the incidence of the primary outcome, a 7-day composite of death, MI, or refractory ischemia, was similar in both groups (9.4% for unfractionated heparin vs 8.4% for LMWH; 95% CI, 0.71-1.08), major bleeding episodes were more common with LMWH (0.9% vs 0.4%, \( P = .05 \)). In the Superior Yield of the New Strategy of Enoxaparin Revascularization and Glycoprotein Iib/IIa Inhibitors (SYNERGY) trial, 10027 high-risk patients undergoing an early invasive strategy were randomized to receive LMWH or unfractionated heparin. In this analysis, patients receiving LMWH experienced a lower 30-day incidence of death or nonfatal MI (10.1% vs 11.0%; 95% CI, 0.83-0.99), with no significant difference in major bleeding. In spite of substantial differences between these trials with regard to study design, one group in which LMWH consistently provided benefit was those managed with an early conservative strategy. Similar findings were recently demonstrated in a post hoc analysis of the A to Z study, in which conservatively managed patients treated with LMWH had improved outcomes, with no overall increased bleeding risk. Based on this, LMWH (specifically enoxaparin) should be the preferred anticoagulant in patients managed with an early conservative strategy. When used in patients with renal insufficiency (creatinine clearance \(< 60 \text{ mL/min} \ (1.0 \text{ mL/ s})\), however, it is important that anti-factor Xa levels be monitored to ensure appropriate dosing. Given that either anticoagulant may be used in patients managed with an early invasive strategy, it is more important that open dialogue be maintained between emergency departments, coronary care units, and cardiac catheterization laboratories so as to avoid in-hospital changes in the type of anticoagulant administered.

**Angiotensin-Converting Enzyme Inhibition**

While angiotensin-converting enzyme (ACE) inhibitors have emerged as standard care for most patients with atherosclerosis, diabetes mellitus, left ventricular systolic dysfunction (LVSD), or heart failure, they have not been evaluated in placebo-controlled trials of patients with NSTE-ACS. Nonetheless, support for their long-term outpatient use has come from the Heart Outcomes Prevention Evaluation (HOPE) trial and the European Trial On Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease (EUROPA). These trials randomized 22952 high-risk patients with established vascular disease or diabetes to receive ramipril (10 mg daily) or perindopril (8 mg daily) vs placebo for a mean of 4 to 5 years. Treatment with ACE inhibitors in these trials resulted in a 20% to 22% relative risk reduction in the combined end point of CV death, MI, and stroke or cardiac arrest (\( P < .001 \) for all).

When used in low-risk patients, however, ACE inhibitors do not provide the same benefit. In the Prevention of Events With Angiotensin-Converting Enzyme Inhibition (PEACE) trial, 8290 patients with coronary artery disease (CAD) and either normal or mildly depressed left ventricular function (ejection fraction \( > 40\% \)) were randomized to receive trandolapril (up to 4 mg daily) or placebo for a median of 4.8 years. Patients were required to be at least 2 months out from an acute coronary event and in general were well treated—there was excellent control of blood pressure (BP) (mean, 133/78 mm Hg), a high rate of revascularization, and frequent use of other risk-reducing medications (eg, antplatelet therapy, \( \beta \)-blocker, lipid-lowering agent). Unlike the HOPE and EUROPA trials, however, treatment with trandolapril produced no significant improvement in the primary combined end point of CV death, MI, or need for revascularization (\( P = .43 \)). While this suggests a limited value for the long-term use of ACE inhibitors in individuals similar to those in the PEACE trial, ACE inhibitors should remain an important therapy in those at higher risk.

**Angiotensin Receptor Blockade**

The role of angiotensin receptor blockers in NSTE-ACS is not addressed by current guidelines; however, recent data from the Valsartan in Acute Myocardial...
dial Infarction Trial (VALIANT)

suggest that they may be used as an alternative to, but not in combination with, ACE inhibitors in patients with MI and underlying LVSD (ejection fraction <40%) or heart failure. Among the 14,703 patients enrolled, there were no significant differences in mortality between those taking valsartan (up to 160 mg twice daily) compared with captopril (up to 50 mg 3 times daily) (hazard ratio [HR], 1.00; 97.5% CI, 0.90-1.11) or those taking valsartan (up to 80 mg twice daily) plus captopril (up to 50 mg 3 times daily) compared with captopril alone (HR, 0.98; 97.5% CI, 0.89-1.09). While these findings contrast with the benefits derived from the addition of angiotensin receptor blockers to ACE inhibitors in patients with chronic LVSD (ejection fraction <40%) and heart failure, their combined use in the acute setting should still be avoided.

β-Blockade

Through their sympatholytic effects, β-blockers reduce cardiac workload and thus myocardial oxygen demand. Data supporting their use in the acute setting comes from a 13% relative risk reduction in the rate of progression to an acute MI and a 29% relative risk reduction in death among high-risk individuals with a threatened or evolving MI. When used in patients with hypertension, LVSD, or following an MI, β-blockers also produce significant reductions in adverse CV events. These studies form the basis for current recommendations to use intravenous β-blockers in the setting of chest pain, followed by long-term use of oral β-blockers for low- to intermediate-risk patients with angina and for all high-risk patients unless contraindicated.

BP Control

Because high BP increases myocardial oxygen demand, its treatment remains an important goal in the management of patients with NSTE-ACS. Although current guidelines recommend a BP of less than 130/85 mm Hg (reserving <130/80 mm Hg for patients with diabetes or chronic kidney disease), recent evidence from the Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study suggests that the optimal level may be even lower (ie, 125/75 mm Hg) in patients with stable CAD. This study randomized 1991 normotensive patients (mean BP, 129/78 mm Hg) with angiographically proven CAD to receive amlo-
dipine (10 mg daily), enalapril (20 mg daily), or placebo for 2 years. While patients in both active treatment groups achieved modest BP reduction (mean, 5/3 mm Hg), those taking amlo-
dipine experienced a more significant relative risk reduction in adverse CV events (31%, P = .003). Therefore, although ACE inhibitors and β-blockers should be used preferentially in NSTE-ACS, amlo-
dipine represents an important agent for additional BP reduction in those with stable CAD.

Cholesterol Treatment

By inhibiting the rate-limiting step in cholesterol synthesis, the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) have become standard care for most patients with NSTE-ACS. Their sustained use results in a significant reduction in the level of low-density lipoprotein cholesterol (LDL-C), along with more modest but favorable effects on levels of other serum lipids. Based on a recommended LDL-C goal of less than 70 mg/dL (1.8 mmol/L), nearly all patients with NSTE-ACS should begin treatment with a high-dose, potent statin during their hospitalization.

Support for intensive and early LDL-C reduction in patients with NSTE-ACS has come predominantly from the Pravastatin or Atorvastatin Evaluation and Infection (PROVE IT-TIMI 22) study. This trial randomized 14,626 patients hospitalized with NSTE-ACS to receive high-dose atorvastatin (80 mg daily) or moderate-dose pravastatin (40 mg daily) for a mean of 24 months. Patients receiving atorvastatin experienced a 16% relative risk reduction in the composite end point of death, MI, unstable angina re-
quiring rehospitalization, revascularization, and stroke (P < .005), along with a substantially lower posttreatment mean LDL-C level (62 mg/dL vs 95 mg/dL [1.6 mmol/L vs 2.5 mmol/L]). These benefits were seen as early as 30 days after treatment, similar to the effects noted with atorvastatin (80 mg daily) in the Myocardial Ischemia Re-
duction With Aggressive Cholesterol Lowering (MIRACL) study.

More modest differences were noted in the recent A to Z study, which randomized 4,497 patients to receive early intensive therapy (simvastatin 40 mg daily for 1 month followed by 80 mg daily) vs delayed less-intensive therapy (placebo for 4 months followed by simvastatin 20 mg daily) after experienc-
ing an acute coronary syndrome. While intensive therapy only produced a trend toward reduced CV events at 24 months (11% relative risk reduction, P = .14), smaller relative differences in the post-
treatment LDL-C levels of the 2 groups (when compared with PROVE IT-
TIMI 22) may have accounted for this.

For those unable to achieve an LDL-C level less than 70 mg/dL, another lipid-lowering agent (eg, ezetimibe or a bile acid sequestrant) should be added. Similarly, if high-density lipoprotein cholesterol levels are less than 40 mg/dL (1.0 mmol/L) or triglyceride levels are greater than 150 mg/dL (1.7 mmol/L), addition of niacin or a fibrate should be considered. All patients treated with a high-dose, potent statin should have creatine kinase and transaminase levels closely monitored, with dose adjustment or discontinuation of medication should muscle or liver toxicity occur.

Cigarette Smoking Cessation

Smoking has been shown to promote the development and progression of CV disease and is an important predictor of future CV events. Because abstinence from smoking has been found to greatly lower the risk of future coronary events, all smokers with NSTE-ACS should be encouraged to quit smoking immediately. Behavioral support, as well as bupropion with or without nicotine replacement, have
been shown to have the greatest efficacy in helping patients quit and thus should be offered to all patients to improve long-term smoking cessation.

**Diabetes Management, Diet, and Exercise**

Long-term CV risk reduction is a tenantable and necessary step in the treatment of all patients with NSTE-ACS. In addition to the aforementioned therapies, all patients with diabetes should maintain strict glycemic control with a glycated hemoglobin level of less than 7.0%.81 All patients should be strongly encouraged to adhere to a diet enriched with protein, complex carbohydrates, fruits, vegetables, nuts, and whole grains and restricted in saturated fat, cholesterol, and salt.82 Finally, all patients should be encouraged to participate in moderate levels of aerobic and weight-bearing exercise for at least 30 minutes on most days of the week.83,84 Preferably within a cardiac rehabilitation program.85

**Follow-up**

Although substantial advances have taken place in the management of patients with NSTE-ACS, many individuals remain at high risk. Advanced age, heart failure, persistent ST-segment depression and renal insufficiency, as well as elevated levels of troponin, C-reactive protein, and natriuretic peptides, all predict a higher incidence of recurrent CV events.1,86-93 For all others, their risk approaches that of a similar patient with CAD, especially after 1 year. Close follow-up with a physician is nonetheless recommended for all patients within 1 to 6 weeks after discharge, with regular follow-up thereafter. While there is little indication for routine outpatient stress testing85 (especially following successful revascularization86), coronary angiography should be performed in those who develop new or recurrent ischemic symptoms or heart failure, or who are survivors of cardiac arrest.9

**CONCLUSION**

Despite the existence of evidence-based guidelines for the management of patients with NSTE-ACS, implementation of these recommended acute and long-term treatment strategies remains suboptimal. While in part this may be related to a lack of awareness, familiarity, or agreement with guideline recommendations,97 their length and perceived complexity may play a role as well. We have accordingly proposed a modified and simple “ABCDE” approach to NSTE-ACS that allows physicians and hospitals to more effectively create disease management protocols, define roles and responsibilities for different medical personnel, and ensure implementation of short- and long-term medical and risk-reducing strategies.

**REFERENCES**


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