The Year in Non–ST-Segment Elevation Acute Coronary Syndrome

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This review summarizes publications on non–ST-segment elevation acute coronary syndromes (NSTE-ACS) from June 2008 to May 2009. Table 1 lists trial acronyms.

Epidemiology

Mortality following acute myocardial infarction has declined by approximately 30% over the past 2 decades (1), although the burden of coronary heart disease (CHD) remains high. This year, it is estimated, on average, approximately 1 American will have an acute coronary event every 25 s, resulting in 1 death per minute (2). The prevalence of NSTE-ACS is increasing relative to ST-segment elevation myocardial infarction (STEMI) due to changes in the distribution of risk factors in the population (e.g., older age, predominance of females, higher rate of diabetes) (1), use of preventative medications (3), and increasingly sensitive troponin assays (4). Two risk factors heading in opposite directions are smoking and obesity. Smoke-free legislation appears to have reduced hospitalization for ACS (5), whereas the obesity-diabetes pandemic has resulted in a disproportionate increase in non–ST-segment elevation myocardial infarction (NSTEMI) among young patients (each 5 kg/m² increase of body mass index is associated with a 3-year decrease in age of first NSTEMI) (6).

Pathophysiology

Our understanding of the pathophysiology of ACS continues to improve, particularly with advances in imaging techniques and biomarkers. Two invasive imaging techniques—optical coherence tomography and intravascular ultrasound—can identify vulnerable plaques with thin-capped fibroatheromas (TCFA) and positive remodeling in patients with ACS (7). These plaque morphologies have been associated with subsequent adverse cardiac events (8). Interestingly, different stressors may cause a plaque to rupture in different locations (e.g., exertion: thick shoulder [9], diabetes: thin midportion [10]). This raises the hope that information regarding plaque morphology could be helpful in prioritizing risk factors and setting treatment goals.

In addition to the well-known risk factors leading to lipid-rich vulnerable plaques, a number of intriguing studies have linked nontraditional factors such as panic disorder (11), physical distress (12), and insufficient sleep (13) to incident CHD. Evaluation of both pharmacologic (e.g., with serotonin reuptake inhibitors [14]) and nonpharmacologic therapies (e.g., use of music [15] and patient information sheets [16]) directed at reducing anxiety, depression, and stress are needed.

Although plaque rupture and intraluminal obstruction are the most common mechanisms underlying an ACS, in the CASPAR study (17), nearly 25% of patients with ACS prospectively undergoing coronary angiography did not have a culprit lesion. Furthermore, nearly one-half of these patients without culprit lesions exhibited ischemic ST changes after administration of intracoronary acetylcholine, suggesting that these patients may benefit from therapies (e.g., calcium-blockers, nitrates) directed at preventing spasm. Although the notion of coronary artery spasm serving as one of the important mechanisms underlying ACS is not new (18), the findings of the CASPAR study remind us that coronary artery endothelial function, in addition to vessel morphology, can play a critical role in the development of ACS.

Noninvasive Assessments

A variety of noninvasive techniques in patients with NSTE-ACS have improved the ability to establish the diagnosis and provide accurate prognostication. Contrast-enhanced computed tomographic angiography (CTA) can identify
features of a vulnerable plaque (positive remodeling, low plaque density consistent with lipid-rich lesions), and in a prospective study (19), categorized patients into high risk (22%), intermediate risk (6.5%), or low risk (0.5%) of developing an ACS event over the next 27 months based on the presence of 2, 1, or none of these features. By imaging plaque morphology CTA permits greater diagnostic sensitivity beyond that possible with the evaluation of calcium-scoring alone (20).

In the MESA study (21), the left ventricular mass-to-volume ratio measured using cardiac magnetic resonance imaging (MRI) was strongly associated with incident CHD. In another study of MRI in NSTE-ACS, diagnostic accuracy rose from 84% using conventional MRI alone to 93% using an MRI protocol that included T2-weighted imaging, assessment of left ventricular (LV) wall thickness, and delayed enhancement (22). Edema detected on T2-weighted images in dogs with transient coronary occlusions correlated with acute ischemic injury prior to necrosis (23), thus representing another potentially useful marker identifiable by MRI early following symptom onset.

Both coronary CTA (24) and magnetocardiography (25) are also helpful in rapidly establishing the diagnosis of NSTE-ACS, with the former having high negative and the latter high positive predictive value. In the ROMICAT trial of patients with acute chest pain and low-intermediate risk of ACS, 64-slice coronary CTA was able to identify the 50% of patients who were free of coronary artery disease and did not have ACS (26).

Two studies evaluated the ability of continuous electrocardiography (cECG) to predict future ischemic events. In MERLIN-TIMI 36, 20% of 6,355 patients experienced at least 1 episode of ischemia on cECG within 7 days of NSTE-ACS, and such patients experienced a nearly 3-fold increase in mortality and 2-fold increase in recurrent myocardial infarction (MI) over the next year (27). Furthermore, high morphologic variability in the shape of the entire heart beat signal on 24-h cECG monitoring within 48 h post NSTE-ACS in DISPERSE-2 TIMI 33 trial was associated with a marked increase in the risk of death at 90 days (adjusted hazard ratio [HR]: 6.9, p < 0.001) (28).

**Biomarkers**

An American Heart Association (AHA) scientific statement on the criteria for evaluation of novel markers of cardiovascular risk (29) set forth standards for the critical appraisal of risk assessment methods. Among the key concepts identified were: 1) the need to demonstrate the degree to which a novel marker adds to the prognostic information provided by standard risk markers (both in terms of discrimination and accuracy); 2) the clinical value of the marker as measured by the effect on patient management and outcome; and 3) the cost-effectiveness of the marker.

Table 2 highlights a selected sample of biomarkers that have been associated with the development of NSTE-ACS (30–34) or prediction of future events following NSTE-ACS (35–37) published in the past year.
Therapy

Anticoagulants. Additional analyses from prior trials investigating enoxaparin, fondaparinux, and bivalirudin, as well as 2 phase II studies with oral factor Xa inhibitors (rivaroxaban, apixaban) were highlighted in the past year. These data provide additional support for the use of alternatives to unfractionated heparin (UFH) and vitamin K antagonists (e.g., warfarin).

Patients age ≥75 years enrolled in the SYNERGY trial (UFH vs. enoxaparin in high-risk NSTEACS patients managed with an early invasive strategy) experienced higher rates of adverse events compared to younger patients. However, the relative efficacy and safety of enoxaparin compared with UFH were similar across age groups (38).

Fondaparinux, an indirect, selective, reversible, parenteral factor Xa inhibitor, demonstrated similar efficacy and less bleeding than enoxaparin regardless of the level of risk of patients with NSTE-ACS in the OASIS-5 study (39). In a combined analysis of the OASIS-5 and -6 studies, fondaparinux also reduced the net composite of bleeding and ischemic events compared with a heparin-based strategy with either an invasive or conservative management strategy (40). A cost analysis from the OASIS-5 study estimated that fondaparinux would save an average of $547 (95% confidence interval [CI]: $207 to $924) per patient through 180 days, and over the longer term, was dominant (i.e., fondaparinux was less costly and improved quality-adjusted life-years) under most scenarios (41).

The oral direct factor Xa inhibitors rivaroxaban and apixaban were studied in 2 similarly designed phase II placebo-controlled dose-ranging studies of patients with ACS known as ATLAS ACS-TIMI 46 (42) and APPRAISE (43). In both trials, the factor Xa inhibitors were associated with dose-related increases in bleeding compared with placebo (particularly on a background of aspirin with clopidogrel), and a tendency toward fewer ischemic events (Fig. 1). In the APPRAISE trial, the 2 highest dosages of apixaban (10 mg twice daily, 20 mg once daily) were prematurely terminated due to excess major bleeding.

In the ACUITY trial, bivalirudin, a direct-acting antithrombin (with or without glycoprotein IIb/IIIa inhibitor) was associated with a similar rate of stent thrombosis through 30 days as heparin with a glycoprotein IIb/IIIa inhibitor (1.6% vs. 1.1%, p = 0.28) (44). Overall, the rates of mortality alone and an ischemic composite through 1 year with bivalirudin-based strategies in patients undergoing percutaneous coronary intervention (PCI) were similar to those with heparin and glycoprotein IIb/IIIa inhibitors (45). Although the drug costs are higher in bivalirudin-based strategies, an economic analysis of aggregate hospital and 30-day costs demonstrated lowest costs with bivalirudin monotherapy compared with several alternative strategies that included glycoprotein IIb/IIIa inhibitors (whether administered routinely early or selectively in the catheterization laboratory) in combination with either UFH or bivalirudin (mean differences in costs ranged from $123 to $1,091, pairwise p values each ≤0.005 compared with
bivalirudin monotherapy) (46). If bivalirudin monotherapy is selected, it appears important to administer clopidogrel before or within 30 min of PCI to ensure protection from periprocedural ischemic complications (47).

In the ISAR-REACT 3 trial (48), bivalirudin and UFH were compared in patients with stable or unstable angina who had received clopidogrel 600 mg 2 h prior to PCI and no glycoprotein IIb/IIIa inhibitor. In this setting, bivalirudin and UFH achieved similar net clinical benefit (ischemic and bleeding complications: 8.3% vs. 8.7%, p = 0.57). A lower rate of major bleeding with bivalirudin (3.1% vs. 4.6%, p = 0.008) was largely offset by a numeric increase in ischemic events (death, MI, urgent target-vessel revascularization due to myocardial ischemia: 5.9% vs. 5.0%, p = 0.23). These data, when interpreted in the context of prior studies with heparin and bivalirudin with versus without glycoprotein IIb/IIIa inhibitors, demonstrate a reduction in bleeding with bivalirudin monotherapy that is counterbalanced by an increase in ischemic complications when glycoprotein IIb/IIIa inhibitors are omitted (even when 600 mg of clopidogrel is administered).

Antiplatelet agents. A large number of publications in the past year reported on the limitations of currently available platelet inhibitors and the promise of novel antiplatelet agents. Identification of patients with a suboptimal antiplatelet response is important to minimize recurrent events (49,50). For example, stent thrombosis is associated with a high rate of mortality or recurrent ST-segment elevation at 30 days (18%) and at 3 years (28%) (51). Patients who either discontinue clopidogrel (52) or exhibit residual platelet reactivity (49) are at highest risk for stent thrombosis. In addition, patients with poor response to chronic clopidogrel therapy also appear to be at risk for other ischemic complications such as MI (53). Factors that are associated with suboptimal response to clopidogrel include patient characteristics (e.g., advanced age, increased body mass index, diabetes mellitus) (54), presence of aspirin resistance (54), use of proton pump inhibitors (55), coadministration of...
calcium-channel blockers (56), and polymorphisms of the hepatic cytochrome P450 (CYP) enzymes (57).

Clopidogrel is a prodrug that requires activation by CYP-dependent hepatic enzymes. Polymorphisms of the CYP2C19 (and also CYP3A4) genes encoding these enzymes may result in loss of function (i.e., less inhibition of adenosine-induced platelet activation). Therefore, such carriers are at increased risk for ischemic events compared with patients with the normally functioning wild-type allele (Fig. 2). In contrast, prasugrel, a novel thienopyridine that does not require hepatic activation by CYP-dependent enzymes, is unaffected by these polymorphisms (58).

Three approaches to manage hyporesponsiveness to clopidogrel that are being investigated are: 1) administration of higher doses of clopidogrel; 2) use of drugs with more effective PGY12 antagonism; and 3) inhibition of other platelet receptors. One trial of 256 patients with NSTE-ACS did not show any difference (HR: 1.00, p = 0.99) in ischemic complications between 600 mg and 300 mg of clopidogrel loading pre-PCI. However, only 33 events were observed in this underpowered trial (59). The much larger (n = 25,087) CURRENT-OASIS 7 trial (60) comparing 2 different regimens of clopidogrel (load/maintenance dose regimens of 300/75 mg vs. 600/150 [1 week] to 75 mg) and aspirin (75 to 100 mg vs. 300 to 325 mg) in a 2 × 2 design is due to report results this year. Additional data with higher-dose clopidogrel are also forthcoming from the GRAVITAS trial (61), which is randomizing patients with stable angina or NSTE-ACS undergoing drug-eluting stent implantation and who have high residual platelet reactivity to either standard maintenance dosing of clopidogrel (75 mg daily) or high-dose therapy (additional loading followed by 150 mg daily for 6 months).

Alternative PGY12 inhibitors in development include the oral drugs prasugrel and ticagrelor, the intravenous agent cangrelor, and elinogrel (PRT060128); the latter is being developed in both oral and intravenous formulations (62). Primary results of the TRITON-TIMI 38 trial, which compared prasugrel to clopidogrel, were covered in last year’s report (63). New data in the past 12 months with prasugrel include analyses that demonstrated the ability of prasugrel, compared with clopidogrel, to reduce recurrent cardiovascular events by 45% (p = 0.016) and cardiovascular death by 54% (p = 0.008) following an initial nonfatal event (64). Also, the net treatment benefit with prasugrel, compared with clopidogrel, tended to be even greater among diabetic patients (65), which appears to be related to increased levels of active metabolites observed with prasugrel relative to clopidogrel among diabetic compared with nondiabetic patients (66). The long-awaited results of 3 phase III trials—PLATO (A Study of Platelet Inhibition and Patient Outcomes) (67) (investigating ticagrelor in patients with NSTE-ACS and STEMI) and 2 CHAMPION (Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition) studies (investigating cangrelor in patients undergoing PCI)—are expected to be unveiled in full later this year. Top-line results announced in press releases reported that ticagrelor reduced the composite rate of vascular death, nonfatal MI, or nonfatal stroke compared with clopidogrel in the PLATO trial (68), whereas both CHAMPION trials were terminated early due to lack of efficacy with cangrelor (69). Finally, preliminary results in patients with high residual platelet reactivity despite clopidogrel, demonstrated that a single 60-mg oral dose of elinogrel was effective in profoundly inhibiting platelet function using 4 different functional assays (70). Further studies with elinogrel are underway.

A third option to overcome hyporesponsiveness to clopidogrel is to achieve more effective platelet inhibition through inhibition of a target other than the PGY12 receptor. Cilostazol, a selective phosphodiesterase inhibitor, was superior to 150 mg of clopidogrel daily in reducing the rate of high post-treatment platelet reactivity in patients with ACS undergoing PCI who were hyporesponsive to a 300-mg clopidogrel loading dose (71). This finding may explain why cilostazol, when added to aspirin and clopidogrel, reduced the primary composite of cardiac death, nonfatal MI, stroke, or target vessel revascularization at 1 year from 15.1% to 10.3% (p = 0.011) without increasing bleeding compared with standard dual antiplatelet therapy (72). Ongoing studies with 2 selective platelet protease-activated receptor (PAR)-1 antagonists are exploring the efficacy and safety of these novel agents in patients with ACS (73). Antagonism of the PAR-1 receptor on the platelet surface interferes with the cellular actions of thrombin, the most potent known physiologic agonist of platelets. Thus, PAR-1 antagonists exert an antiplatelet effect when
thrombin-stimulated platelet activation is present. Since they do not interfere with collagen or ADP-induced platelet activation, or with fibrin generation by thrombin, PAR-1 antagonists may be less disruptive to normal hemostasis compared with other potent antiplatelet agents.

Two randomized trials explored alternative dosing regimens with eptifibatide, a reversible intravenous glycoprotein IIb/IIIa inhibitor. In the BRIEF-PCI trial (74), the standard 18-h infusion of eptifibatide was compared with an abbreviated infusion of 2 h. There were no differences in periprocedural myonecrosis or clinical ischemic events through 30 days between the 2 treatment groups, whereas bleeding was reduced from 4.2% to 1.0% (p < 0.02) with the shorter infusion.

In the EARLY ACS trial (75), a strategy of early, routine double-bolus eptifibatide followed by an infusion was compared with a strategy of initial placebo followed by provisional eptifibatide (at the physician’s discretion) just prior to PCI in 9,492 patients with high-risk NSTE-ACS undergoing angiography at 12 to 96 h. Routine early eptifibatide was not superior to delayed provisional use and increased the odds of major bleeding and red-cell transfusions by 42% (p = 0.015) and 31% (p < 0.001), respectively (Fig. 3). The data from EARLY ACS do not support routine upstream use of eptifibatide, but additional analyses are ongoing to determine whether specific high-risk groups of patients with NSTE-ACS may benefit from such a strategy. Taken together, these 2 trials suggest that a shorter infusion of eptifibatide initiated just prior to PCI reduces bleeding and could become the preferred regimen, provided that similar clinical efficacy to the standard 18- to 24-h infusion post-PCI could be demonstrated in an adequately powered study.

Bleeding complications of antithrombotic therapy. Numerous publications continue to explore the relationship between bleeding and adverse outcomes, as well as strategies to reduce bleeding complications of antithrombotic therapies and invasive procedures in ACS. Analyses from 2 trials

Table 3 CRUSADE Bleeding Risk Score Estimating In-Hospital Major Bleeding

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Baseline hematocrit, %</td>
<td></td>
</tr>
<tr>
<td>&lt;31</td>
<td>9</td>
</tr>
<tr>
<td>31–33.9</td>
<td>7</td>
</tr>
<tr>
<td>34–36.9</td>
<td>3</td>
</tr>
<tr>
<td>37–39.9</td>
<td>2</td>
</tr>
<tr>
<td>&gt;40</td>
<td>0</td>
</tr>
<tr>
<td>2. Creatinine clearance, * ml/min</td>
<td></td>
</tr>
<tr>
<td>≤15</td>
<td>39</td>
</tr>
<tr>
<td>&gt;15–30</td>
<td>35</td>
</tr>
<tr>
<td>&gt;30–60</td>
<td>28</td>
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<tr>
<td>&gt;60–90</td>
<td>17</td>
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<tr>
<td>&gt;90–120</td>
<td>7</td>
</tr>
<tr>
<td>&gt;120</td>
<td>0</td>
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<tr>
<td>3. Heart rate, beats/min</td>
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<tr>
<td>≤70</td>
<td>0</td>
</tr>
<tr>
<td>71–80</td>
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<td>101–110</td>
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<tr>
<td>111–120</td>
<td>10</td>
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<tr>
<td>≥121</td>
<td>11</td>
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<td>4. Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0</td>
</tr>
<tr>
<td>Female</td>
<td>8</td>
</tr>
<tr>
<td>5. Signs of CHF at presentation</td>
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</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>7</td>
</tr>
<tr>
<td>6. Prior vascular disease†</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>6</td>
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<td>7. Diabetes mellitus</td>
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<td>No</td>
<td>0</td>
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<td>Yes</td>
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<td>8. Systolic blood pressure, mm Hg</td>
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<td>≤90</td>
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<td>181–200</td>
<td>3</td>
</tr>
<tr>
<td>≥201</td>
<td>5</td>
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Risk of Bleeding

<table>
<thead>
<tr>
<th>Total Score (Range 1–100)</th>
<th>Predicted Risk of Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤20 (very low)</td>
<td>3.1%</td>
</tr>
<tr>
<td>21–30 (low)</td>
<td>5.5%</td>
</tr>
<tr>
<td>31–40 (moderate)</td>
<td>8.6%</td>
</tr>
<tr>
<td>41–50 (high)</td>
<td>11.9%</td>
</tr>
<tr>
<td>&gt;50 (very high)</td>
<td>19.5%</td>
</tr>
</tbody>
</table>

*Creatinine clearance was estimated with the Cockcroft-Gault formula. †Prior vascular disease was defined as history of peripheral artery disease or prior stroke. To calculate the CRUSADE bleeding score, total the points associated with the above 8 factors and use the bottom part of the table to predict the risk of bleeding (see text for details).

CHF = congestive heart failure.
concluded that bleeding was closely associated with an increase in fatal and nonfatal adverse outcomes (76,77), although assessing causality is extremely challenging given the complex relationships that exist between bleeding, antithrombotic therapies, ischemia, and invasive procedures. Indeed, there may be multiple mechanisms by which bleeding contributes to poor outcomes, such as the development of ischemia due to supply–demand mismatch during bleeding and the premature discontinuation of oral antiplatelet therapy that occurs in response to the bleeding (73).

The relationship between the use of thienopyridines and perioperative bleeding remains controversial. More judicious use of transfusions (e.g., changing the transfusion hematocrit threshold to 24% in stable patients) may provide

![Figure 4 Hazard Ratios for the Primary and Secondary Outcomes in Pre-Specified Subgroups in the TIMACS Study](image)

Panel A shows hazard ratios for the composite primary outcome of death, myocardial infarction, or stroke in the early-intervention group, as compared with the delayed-intervention group, in selected subgroups of patients. Panel B shows hazard ratios for the composite secondary outcome of death, myocardial infarction, or refractory ischemia in the same subgroups. The size of the squares is proportional to the size of the corresponding subgroup. CI = confidence interval; GRACE = Global Registry of Acute Coronary Events. Reproduced with permission from Mehta et al. (95).
a better balance between risk and benefit (78). Fortunately, reversible thienopyridines may prove to be safer in patients who may need coronary artery bypass grafting (CABG). In the DISPERSE-TIMI 33 trial, the reversible PGI2 inhibitor ticagrelor was associated with less bleeding post-CABG compared with clopidogrel (79), an observation that was most evident when the drugs were continued until ≤5 days before CABG.

Efforts to reduce bleeding have included modifications of the medical therapies and access site management. Greater attention to appropriate dose adjustment of UFH (80), avoidance of concomitant nonsteroidal anti-inflammatory drugs, which increase the risk of gastrointestinal bleeding (81), and efforts to develop safer anticoagulant regimens, such as bivalirudin, fondaparinux, and low-dose UFH (82), may also reduce bleeding.

A validated risk score (Table 3) that predicts major in-hospital bleeding was developed from the CRUSADE registry (83). By summing points assigned to 8 readily available clinical factors, patients can be classified into 1 of 5 bleeding categories with predicted bleeding risks ranging from very low (3.1%) to very high (19.5%) (c-statistic = 0.71).

Two additional factors deserve consideration in the evaluation of bleeding risk. First, thrombocytopenia, even if mild (i.e., <150,000/mm3 or >50% decline from baseline) is a common complication in ACS and is associated with increased bleeding, mortality, and ischemic complications (84,85). Thus, antithrombotic therapies that increase the risk of thrombocytopenia may have an even greater propensity for increased bleeding. Second, with the aging of the population, more patients with ACS experience atrial fibrillation or flutter requiring so-called triple antithrombotic therapy with aspirin, clopidogrel, and an oral anticoagulant (86), placing them at 9-fold increased odds for bleeding compared with those on dual antiplatelet therapy (87).

Intervention. Since this topic has been reviewed in the “Year In Interventional Cardiology” (88), we provide below a few of the key highlights pertaining to patients with NSTE-ACS.

With the majority of studies in the past 15 years showing better outcomes with an invasive strategy over medical management, the current debate has shifted to the comparison of a strategy of early, routine use of angiography with the less costly alternative of selective, deferred use (89). Disadvantages of the latter strategy include the potential for deterioration of left ventricular function while awaiting coronary angiography (90), and longer delays (91) or even discharge without angiography (92) in the highest risk patients such as those with congestive heart failure (93) or renal dysfunction (94).

Two studies published in the past year (95,96) failed to show a significant reduction in their primary composite ischemic end points with an immediate invasive strategy compared with delayed angiography, and a third small study reported higher rates of peri-procedural necrosis with immediate angiography (96). In the largest of the three trials (95), early coronary angiography (median 14 h after randomization) and delayed intervention (median 50 h) achieved similar rates of the primary composite of death, MI, and stroke at 6 months (9.6% vs. 11.3%, HR: 0.85 [95% confidence interval: 0.58 to 1.06], p = 0.15). However, early angiography was associated with a 28% reduction in the secondary end point of death, MI, or refractory ischemia, and also reduced the primary composite end point in the one-third of patients at highest risk (GRACE risk score >140) (Fig. 4).

Several new angiographic observations have added to our understanding of the prognosis with PCI. First, because ischemia in the left circumflex territory is not well represented on the standard 12-lead ECG, the proportion of patients with a culprit lesion in the circumflex is higher among patients with NSTE-ACS than with STEMI (97).

A related observation was that an occluded artery (incidence 25%) in a patient with NSTE-ACS was more likely to be
supplying the postero lateral wall, consistent with the presence of an undiagnosed “true posterior” MI. This suggests a large unmet need for better methods to detect transmural infarction in the postero lateral wall, such as may be possible with body surface mapping (98). Lastly, impaired microvascular flow post-PCI is also common in patients with NSTE-ACS and can be predicted from the presence of increased lipids in the culprit plaque as visualized by pre-procedural optical coherence tomography (99). Thus, detailed evaluation of the culprit lesion and flow pre- and post-PCI may identify patients who require more aggressive adjunctive therapies to reduce the risk of subsequent complications.

**Lipids.** In patients with ACS, current guidelines recommend early initiation of statin therapy to lower the low-density lipoprotein cholesterol (LDL-C) level to well below 100 mg/dl (and preferably to <70 mg/dl). In 2 recent studies utilizing intravascular ultrasound imaging, aggressive statin therapy regressed coronary artery disease following ACS (100), particularly when an LDL-C <70 mg/dl was achieved (101). In addition, high-dose atorvastatin normalized the circulating levels of prostaglandin E2 and metalloproteinase-9 activity in patients with NSTE-ACS, thereby reversing the plaque destabilizing effects resulting from elevated levels of these inflammatory mediators (102). These findings support the notion of using even more intensive lipid-lowering therapies post-ACS, as is being evaluated in the IMPROVE-IT trial (103), which is designed to achieve an LDL of 50 to 55 mg/dl with the combination of ezetimibe and simvastatin. Although this is now approaching the level of LDL-C in newborns, analyses from the PROVE IT-TIMI 22 trial demonstrated continued benefit of intensive lipid lowering (compared with standard therapy) among patients with baseline LDL-C values as low as 66 mg/dl (104,105).

In addition to the benefits observed with achieving lower LDL-C levels post-ACS, other studies suggest targeting C-reactive protein (106), high-density lipoprotein cholesterol (107), and lipoprotein-associated phospholipase A2 may further improve outcomes. These additional markers may be identifying other adverse processes (e.g., inflammation, endothelial dysfunction, plaque instability) that are not completely addressed by dramatic lowering of the LDL with statins.

**Quality of Care**

Use of evidence-based medical therapies continues to increase with implementation of guideline-based critical care pathways (108), even during weekends and holidays with reduced staffing (109). However, there remain subgroups of patients, such as those with low-level troponin elevation (110), renal dysfunction (111), and multiple medical comorbidities (112), in whom guideline therapies are not optimally administered. Furthermore, there is an inverse relationship between the amount of copayment and adherence to outpatient prescriptions (113), confirming that these patients represent a particularly vulnerable group. In addition, pre-authorization programs serve as a barrier for patients to receive timely access to some proven therapies. In an analysis of patients age ≥65 years with acute MI who underwent PCI in Ontario, Canada, between April 1, 2000, and March 31, 2005, removal of a prior-authorization program for clopidogrel in 2003 increased the rate of clopidogrel use within 30 days (from 35% to 88%) and shortened the time to first dispensed dose (from 9 days to 0 days) (114). More importantly, the adjusted 1-year composite of death, recurrent MI, PCI, and CABG declined from 15% to 11% (p = 0.02). We continue to endorse wider access for all patients to evidence-based therapies that have been demonstrated to improve clinical outcomes.

We end this year’s review by summarizing in Table 4 the major changes to the ACC/AHA 2008 Performance Measures as they apply to patients with NSTE-ACS (115). Given the new information summarized in this year’s review and the large number of ongoing studies nearing completion, it can be anticipated that future guidelines and performance measures in NSTE-ACS will require updating in the next 2 years.

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