This review summarizes publications on non–ST-segment elevation (NSTE) acute coronary syndromes (ACS) between May 2007 and May 2008 with an emphasis on the updated practice guidelines for these conditions published in North America (1) and Europe (2), as well as novel findings from clinical studies. Trial acronyms and abbreviations are listed in Table 1.

Epidemiology and Pathophysiology

Over 1.4 million unique hospitalizations for ACS occur in the U.S. each year (3), of which approximately 70% are classified as either unstable angina or non–ST-segment elevation myocardial infarction (NSTEMI); the remainder are classified as ST–segment elevation myocardial infarction (STEMI). A global registry showed improvements in adjusted 6-month survival between 1999 and 2006 in patients with NSTE-ACS (4). Approximately one-half of the reduction in deaths in the U.S. population from coronary heart disease has been attributed to favorable changes in risk factors, such as the achievement of lower serum cholesterol (5,6) and blood pressure (5,6) and discontinuing smoking (6,7), whereas much of the remainder is attributable to improved treatments. In addition, some of the decline in case fatality rates may be attributed to more sensitive detection of myocardial necrosis (and hence identification of smaller NSTEMIs) with the introduction of sensitive cardiac specific troponin assays (8), the preferred biomarker for diagnosing myocardial necrosis (9).

Several publications in the past year contributed to our understanding of coronary plaque rupture—the underlying pathophysiology of the majority of ACS events. These were discussed in the Year in Atherothrombosis (10). Advances in our understanding of the biology of coronary plaques will hopefully lead to better identification of vulnerable lesions and more effective methods to prevent, diagnose, and treat coronary artery disease.

2007 Practice Guidelines

Within 2 months, both the American College of Cardiology/American Heart Association (ACC/AHA) (1) and European Society of Cardiology (ESC) (2) published updated practice guidelines for patients with NSTE-ACS incorporating new information available since the 2002 versions.

ACC/AHA 2007 guideline. The most important change includes new Class I recommendations broadening the selection of anticoagulants to include fondaparinux and bivalirudin in addition to unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) (Table 2). More aggressive secondary prevention measures are emphasized (low-density lipoprotein cholesterol [LDL-C] target <70 mg/dl, blood pressure <130/80 mm Hg in patients with diabetes or chronic kidney disease [CKD]). The guidelines also explicitly advise against use of therapies that now either seem to be harmful (e.g., initiation of hormone therapy with estrogen plus progestin or estrogen alone, nonsteroidal anti-inflammatory drugs) or of no proven benefit (e.g., antioxidants, folic acid) in the secondary prevention of coronary events.

ESC 2007 guideline. The major new features of the ESC guideline are similar to the ACC/AHA (fondaparinux, bivalirudin, more aggressive secondary prevention). More detailed recommendations for the management of bleeding complications, thrombocytopenia, and anemia were added (Table 3).

Differences between the AHA/ACC and ESC 2007 guidelines. These guidelines are remarkably similar. However, they differ regarding the recommendations and level of evidence that support the use of 3 of the 4 anticoagulants (11) (Table 4), and also regarding the loading dose of clopidogrel. The ACC/AHA update gives a higher Level of Evidence (LOE) to UFH and enoxaparin (Class Ia), but lower LOE for fondaparinux in conservatively managed patients (Class Ib). In a nonurgent situation, the ESC guideline (2) expresses a preference for fondaparinux over enoxaparin (Class Ia). In patients managed with an initial invasive approach, the ACC/AHA guideline includes fondaparinux as 1 of the 4 possible anticoagulants that may be used (Class Ib), whereas the ESC guidelines do not.
Lastly, the ESC guidelines declare that a 600-mg clopidogrel loading dose may be used to achieve more rapid inhibition of platelet function in patients considered for an invasive procedure (Class IIa-B), whereas the ACC/AHA guidelines state that the additive clinical efficacy and safety of loading doses of clopidogrel $>$300 mg have not been rigorously established. Given the current equipoise regarding the optimal loading dose of clopidogrel, the results of the ongoing CURRENT/OASIS-7 trial comparing loading doses of clopidogrel 300 versus 600 mg in patients with ACS managed with an invasive strategy are eagerly awaited.

### Risk Stratification

**Diagnostic tools.** Novel observations with both established and newer noninvasive diagnostic methods were shown to be helpful in assessing risk in NSTE-ACS. Assessment of left ventricular systolic function, even among patients who are troponin negative, is an important predictor of long-term risk (12), and this new finding supports the upgrading of the recommendation to assess systolic function with higher mortality in patients with NSTE-ACS (17).

Risk factors. Diabetes mellitus is independently associated with higher mortality in patients with NSTE-ACS (17). The AHA released a scientific statement for hyperglycemia management in patients with ACS (18) that included the following major recommendations: 1) measure plasma glucose concentrations in all patients with suspected ACS; 2) monitor glucose closely and consider intensive glucose control with intravenous insulin in patients with glucose $>$180 mg/dl in the intensive care unit (ICU); 3) maintain glucose $<$180 mg/dl with subcutaneous insulin in the non-ICU setting; and 4) determine the severity of the metabolic derangement after discharge in patients with no prior history of diabetes mellitus who showed hyperglycemia during hospitalization.

Renal dysfunction, a complication also associated with diabetes and hypertension, was found to be a strong independent predictor of cardiovascular death in a post-ACS population (19). Lastly the presence of noncoronary vascular disease, whether manifested as a carotid bruit (20), stroke (21), or peripheral arterial disease (21), was associated with a doubling of mortality at 6 to 12 months. These findings of multiple overlapping and inter-related risk factors for ACS support a more comprehensive approach to primary and secondary prevention of coronary heart disease.

### Biomarkers.

Elevated levels of neopterin (a marker of monocyte activation) 4 months after ACS were found to be an independent predictor of death and the composite of death or major coronary events over a 2-year period (22). There was a significant lowering of neopterin and attenuation of risk among patients receiving atorvastatin 80 mg compared with pravastatin 40 mg, suggesting that high-dose statin could reduce monocyte activation after ACS, and perhaps that this is responsible in part for enhanced clinical benefit. An elevated baseline concentration of myeloperoxidase, a hemoprotein released during degranulation of monocytes and neutrophils, was associated with a doubling of nonfatal myocardial infarction (MI) or recurrent ACS in patients presenting with NSTE-ACS after adjustment for multiple clinical and biochemical predictors (23). Chemokines ligand-5 and -18 (mediators of monocyte recruitment induced by ischemia) were transiently elevated in unstable angina and were associated with refractory symptoms, adding further to the data supporting a critical role for monocytes in NSTE-ACS (24). Elevated circulating levels of osteoprotegerin (a modulator of immune function and inflammation) were strongly associated with long-term mortality and hospitalization for heart failure across the spectrum of ACS (25). Concentrations of angiotatin (26) (a mitogen of endothelial cells and activator of matrix metalloproteinases and plasminogen-activated plasmin pathways) and circulating endothelial cells (27) were found to be elevated in ACS patients and to be associated with increased risk. Research on myeloid-related protein 8/14 suggests that this marker may permit detection of unstable plaques (28), and that it is an independent predictor of long-term risk of death or MI (29). The findings summarized above underscore the important role of leukocytes and inflammation in the pathogenesis of ACS.

**Table 1 Acronyms**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACUITY</td>
<td>Acute Catheterization and Urgent Intervention Triage Strategy</td>
</tr>
<tr>
<td>CRUSADE</td>
<td>Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines</td>
</tr>
<tr>
<td>CURRENT</td>
<td>Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events</td>
</tr>
<tr>
<td>DISPERSE</td>
<td>Dose confirmation Study assessing anti-Platelet Effects of AZD6140 vs. clopidogrel in non-ST-segment Elevation myocardial infarction</td>
</tr>
<tr>
<td>GRACE</td>
<td>Global Registry of Acute Coronary Events</td>
</tr>
<tr>
<td>ISAR-REACT</td>
<td>Intracoronary Stenting and Antithrombotic Regimen—Rapid Early Action for Coronary Treatment Optimal Antiplatelet Strategy for InterventionS</td>
</tr>
<tr>
<td>OASIS</td>
<td>Optimal Antiplatelet Strategy for InterventionS</td>
</tr>
<tr>
<td>REPLACE</td>
<td>Randomized Evaluation in PCI Linking Angioplasty to Reduced Clinical Events</td>
</tr>
<tr>
<td>SYNERGY</td>
<td>Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIa Inhibitors</td>
</tr>
<tr>
<td>TIMI</td>
<td>Thrombolysis In Myocardial Infarction</td>
</tr>
<tr>
<td>TRITON</td>
<td>Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel</td>
</tr>
</tbody>
</table>

ACC/AHA = American College of Cardiology/American Heart Association; PCI = percutaneous coronary intervention.
Novel observations with platelet and genetic markers were also described during the past year. Plasma concentrations of SCUBE1 (a novel platelet protein) were at or below the minimum detectable level in healthy subjects and patients with stable coronary artery disease, but increased more than 4-fold as early as 6 hours after the onset of symptoms of ACS, a finding consistent with its proposed role as a marker of platelet activation (30). Important new findings with genetic markers in patients after an ACS event include the association of a polymorphism of the kinesin-like protein 6 gene (which regulates intracellular transport of protein complexes, membrane organelles, and messenger ribonucleic acid along microtubules) with higher event rates but better response to high-dose statins, independent of the effects on lipid and C-reactive protein levels (CRP) (31). A second polymorphism (GJA4) that affects macrophage adhesion was associated with increased mortality after ACS (32).

With a growing number of biomarkers associated with adverse clinical outcomes, an important challenge facing investigators is the identification of a parsimonious menu of biomarkers that can be integrated with imaging (33) and other diagnostic modalities to improve the prediction of death and cardiovascular complications in a cost-effective manner (34).

**Antiplatelet Agents**

Research during the past year has focused on variable patient responses to antiplatelet therapy, new strategies and
therapies that deliver a greater degree of platelet inhibition more quickly, and improving safety.

Concomitant therapies (e.g., omeprazole [35]) and genetic polymorphisms of the cytochrome P450 isoforms (36), in addition to differences in patient clinical characteristics, may affect the degree of platelet inhibition achieved with clopidogrel, either by interfering with drug absorption or slowing metabolism of the prodrug to the active form. One simple and effective approach to reduce the number of hyporesponders is to administer a larger loading dose (i.e., ≥600 mg) to all patients, including a reload of 600 mg in patients who were previously receiving the standard 75-mg daily maintenance dose of clopidogrel (37). However, an even more promising strategy seems to be the incorporation of a measurement of platelet inhibition after clopidogrel loading using vasodilator-stimulated phosphoprotein phosphorylation (VASP) index, followed by dose titration to a target level of antiplatelet activity. Such an approach was shown to reduce major adverse cardiovascular events compared with simply administering a 600-mg loading dose without assessment of VASP in all patients undergoing percutaneous coronary intervention (PCI), many of whom were admitted with NSTE-ACS (38). However, VASP assays must be run in specialized coagulation laboratories and therefore are not widely available. Thus, confirmation of similar results using a point-of-care device (39) represents an important goal of ongoing research.

Longer duration of clopidogrel therapy without interruption seems to be important for reducing mortality and mortality after ACS. Rates of death and acute myocardial infarction (AMI) were increased, both in patients treated medically and after stenting, during the first 6 months after cessation of clopidogrel (40) (Fig. 2).

Newer, more potent, faster-acting oral antiplatelet therapies are on the horizon. Prasugrel, a novel thienopyridine that achieves greater platelet inhibition than clopidogrel (41), significantly reduced the composite of cardiovascular
death, nonfatal MI, or nonfatal stroke by 19% through 15 months in 13,608 patients with moderate- to high-risk ACS scheduled to undergo PCI in the TRITON–TIMI 38 trial (42). In addition, prasugrel significantly reduced myocardial infarction by 24%, the need for urgent revascularization by 34%, and stent thrombosis by 52% (43) (Fig. 3). The benefits of prasugrel were seen during both the first 3 days as well as during later follow-up (44). However, these reductions in ischemic complications were achieved at a cost of significant increases in bleeding (hazard ratio 1.32), including absolute excesses of 0.5% and 0.3% in the rates of life-threatening and fatal bleeding, respectively (42).

AZD6140 is a potent oral P2Y12 receptor antagonist that differs from clopidogrel and prasugrel in that its effects are reversible (45). In the DISPERSE-2 trial, this agent showed a favorable trend in reducing MI compared with clopidogrel, a similar rate of major bleeding, but an increase in minor bleeding (46).

The oral protease-activated receptor (PAR)-1 antagonist SCH 53048 was studied in 1,030 patients undergoing nonurgent PCI or coronary angiography with planned PCI in a phase II placebo-controlled, dose-ranging trial (47). The drug achieved >80% inhibition of thrombin receptor agonist peptide-induced platelet aggregation rapidly, with no increase in Thrombolysis In Myocardial Infarction bleeding. Two large outcome trials with this PAR-1 antagonist are now underway.

**Anticoagulant Agents**

The long-term results of the ACUITY trial, a 3-arm, open-label trial comparing UFH or enoxaparin + a glycoprotein Ib/IIIa inhibitor (GPI) versus bivalirudin + GPI versus bivalirudin monotherapy in patients with NSTE-ACS undergoing early invasive management, revealed similar rates of the net outcome of death, MI, unplanned revascularization for ischemia, or non–coronary artery bypass graft major bleeding (15.4%, 16.0%, and 16.2%, respectively) and mortality alone (3.9%, 3.9%, and 3.8%, respectively) across the 3 groups at 1 year. A strategy of switching to bivalirudin monotherapy, either before (48) or at the time of PCI (49), was shown to be safer and as effective as UFH or enoxaparin + GPI regardless of whether preceding anticoagulation had been initiated before randomization or not.

However, as reported in the preliminary results from the ISAR-REACT 3 trial (50), bivalirudin (0.75 mg/kg followed by 1.75 mg/kg/h infusion) was not superior to the much simpler and less expensive strategy of UFH monotherapy (140 U/kg bolus with no infusion) in reducing the net composite outcome (risk ratio [RR]: 0.94, p = NS) in 4,570 biomarker-negative patients with stable or unstable angina who had received 600 mg clopidogrel ≥2 h before scheduled PCI. The incidence of major bleeding was significantly reduced by 33% with bivalirudin, with no statistical difference in the composite of death, MI, or urgent revascularization. These findings add to the growing number of studies that have shown less bleeding and similar rates of ischemic complications with bivalirudin compared with other antithrombotic regimens.

Subgroup analyses from the OASIS-5 trial comparing fondaparinux with enoxaparin in NSTE-ACS yielded important information in 2 high-risk subgroups: patients undergoing PCI and those with renal insufficiency. Among 6,238 patients undergoing PCI, fondaparinux was associated with similar rates of ischemic complications at day 9 (6.3% vs. 6.2%), significantly reduced major bleeding by 54%, but a >2-fold excess in catheter thrombosis (0.9% vs. 0.4%) (51). An analysis of outcomes stratified by renal function revealed greater differences in bleeding between fondaparinux and enoxaparin as renal function declined, particularly in patients with a calculated glomerular filtration rate <58 ml/min/1.73 m² (52). Like bivalirudin, fondaparinux also seems to be associated with less bleeding than heparin or enoxaparin, and fondaparinux is recommended in patients managed with an initial conservative approach who are at high risk of bleeding (ACC/AHA Class Ib, ESC Class Ia) (1,2).

Several new anticoagulants are under development, with a particular interest in short-acting, reversible agents and oral anticoagulants that inhibit factors Xa or IIa (53). Two short-acting, reversible drugs that reported phase I results in the past year included an antidote-controlled modulator of factor IXa activity (54) and an anti–von Willebrand factor aptamer (55). Both are intended for clinical use in ACS and PCI with the hope that their rapid reversibility will reduce bleeding compared with existing anticoagulants.

**Bleeding Complications of Antithrombotic Therapy**

Research exploring the relationship between bleeding and mortality, strategies to reduce bleeding, and the clinical
conundrums that physicians face in combining multiple antithrombotic agents (1,2,56) were important topics reported in the past year and represent major additions to both NSTE-ACS practice guidelines.

New analyses from REPLACE-2 (57) (a trial of 6,010 patients undergoing elective or urgent PCI comparing 2 antithrombotic regimens) and 4 studies with abciximab (58) showed that major bleeding was independently associated with mortality in patients undergoing PCI. However, establishing a causal relationship between bleeding and ischemic complications including death remains elusive because of the number and complex interactions of the other clinical characteristics and events (e.g., thrombocytopenia [59], transfusions [60]) that tend to occur in such patients. Indeed, one comprehensive analysis of 40,087 patients with AMI in the GRACE registry concluded that although bleeding may have been associated with adverse outcomes in some patients, it was more often simply an indicator of patients at higher risk for adverse outcomes (61).

Efforts to reduce bleeding include the use of: 1) weight-adjusted (as opposed to fixed) doses of anticoagulants (62); 2) modified dosing in patients with renal dysfunction (63) and when concomitant GP IIb/IIIa inhibitors are administered (64); and 3) the selection of fondaparinux (conservative strategy) or bivalirudin without GPI (invasive strategy) in patients who are at higher risk of bleeding (1,2).

Because dual antiplatelet therapy with aspirin and clopidogrel is a Class Ia indication in patients with NSTE-ACS (1,2) and the recommended treatment duration has been extended to 1 year in patients with drug-eluting stents (65) and post–NSTE-ACS (1,2), long-term data regarding the safety of dual antiplatelet therapy in patients also receiving warfarin has become increasingly important. Data from both the GRACE (66) and CRUSADE (67) registries reported that most patients on prior warfarin who receive stents are discharged on all 3 agents. Adjusted analyses comparing single versus dual antiplatelet therapy among patients who are also discharged on warfarin show no major differences in outcomes. However, the numbers of patients in these retrospective registry analyses are modest and randomized data are lacking.

### Invasive Versus Conservative Management Strategies

New analyses of key patient subgroups showed a benefit of an early invasive strategy among women, the elderly, and patients with CKD, groups that historically have been less likely to undergo angiography. In a meta-analysis of data from 8 trials involving 3,075 women and 7,075 men, an early invasive strategy reduced the composite of death, MI, or recurrent ACS by 19% in women and 27% in men (Fig. 4) (68). Among women who had a positive biomarker at baseline, an invasive strategy reduced the odds of an event by 33%, whereas in biomarker-negative women there was only a 6% reduction (interaction p = 0.08). In 1,936 elderly (age ≥75 years) patients with NSTEMI enrolled in a German ACS registry, an invasive strategy significantly reduced in-hospital mortality by 45% and the composite of death and nonfatal MI by 49% with a trend toward more bleeding (8.8% vs. 5.8%), adjusted for confounding using a propensity score analysis (69). Pooling data from 5 trials that enrolled 1,453 patients with NSTE-ACS and moderate to severe CKD (stage 3 to 5), an early invasive strategy significantly reducedrehospitalizations by 24% and tended to have favorable effects on all-cause mortality (RR: 0.76), nonfatal MI (RR: 0.78), and the composite of death...
or MI (RR: 0.79) (D. Charytan, personal communication, June 2008).

In parallel with these analyses showing benefit with an early invasive strategy in high-risk groups, an analysis of the temporal trend of the use of PCI, coronary artery bypass graft, and medical management of NSTE-ACS patients in the CRUSADE registry (70) showed a significant increase in the use of PCI from 38% to 53% between January 2002 and June 2005. Furthermore, analyses from the SYNERGY clinical trial showed significantly lower rates of death or MI as the time interval from presentation to angiography decreased, with an adjusted odds ratio of 0.56 for angiography performed <6 h compared with patients who received angiography at any later time or who never received angiography (71). The benefit of an early invasive approach, compared with angiography deferred until later, persisted until angiography was performed at up to 30 h. Finally, data from a Canadian ACS registry identified that the major reason that patients were not referred for angiography was the physician impression that the patients were “not at high enough risk,” although 59% were at intermediate to high risk according to the Thrombolysis In Myocardial Infarction risk score (72). With greater implementation of risk stratification as endorsed in the updated guidelines (1,2) and new information regarding the benefit of an early invasive strategy in subgroups with prior low rates of utilization (e.g., women and patients with CKD), the current trends of more frequent and earlier use of angiography are expected to continue.

**Evaluation of Quality of Care**

A number of publications evaluated the quality of care in selected patient subgroups and health care settings. Sequential Canadian ACS registries documented an increase from 29% to 51% in the use of optimal evidence-based pharmacologic therapies from 1999 to 2001 compared with 2002 to 2003 (73), and use of these optimal therapies was associated with significantly lower adjusted 1-year mortality (odds ratio: 0.54). However, older (74,75), higher-risk (76) patients and those without cardiology follow-up (77) are less likely to receive recommended therapies. From a hospital perspective, the most effective method for improving the quality of care seems to be implementation of quality improvement tools, such as those used in the CRUSADE initiative (78).

With 2008 being an election year in the U.S., we end this review with a proposed solution to the important problem of noncompliance with secondary preventive therapies in patients with ACS. One major barrier to the use of effective secondary prevention is the high out-of-pocket total cost of these therapies. A cost-effectiveness model that compared current U.S. prescription drug coverage with full coverage of proven medical therapies after MI showed greater functional life expectancy (0.35 quality-adjusted life years) and a $2,500 reduction in resource use from a societal perspective with a full-coverage program (79). However, from the perspective of Medicare, such a change in coverage would result in an increased cost of $7,182 per quality-adjusted life year (well below the generally accepted threshold of $60,000 per quality-adjusted life year for a cost-effective intervention), but additional funding would be required to realize this benefit.

**Reprint requests and correspondence:** Dr. Eugene Braunwald, TIMI Study Group, 350 Longwood Avenue, 1st Floor Offices, Boston, Massachusetts 02115. E-mail: ebraunwald@partners.org.

**REFERENCES**


15. Bennett KM, Hernandez AF, Chen AY, et al. Heart failure with preserved left ventricular systolic function among patients with non-
34. Zethelius B, Berglund L, Sundstrom J, et al. Use of multiple
33. Chen WQ, Zhang M, Ji XP, et al. Usefulness of high-frequency
32. Lanfear DE, Jones PG, Marsh S, Cresci S, Spertus JA, McLeod HL.
31. Iakoubova OA, Sabatine MS, Rowland CM, et al. Polymorphism in
27. Boos CJ, Soor SK, Kang D, Lip GY. Relationship between circulating
20. Pickett CA, Jackson JL, Hemann BA, Atwood JE. Carotid bruits as a
17. Donahoe SM, Stewart GC, McCabe CH, et al. Diabetes and
14. Moliterno DJ, Jennings L, Becker RC, et al. Results of a multinational
8. Boos CJ, Soor SK, Kang D, Lip GY. Relationship between circulating
7. Boos CJ, Soor SK, Kang D, Lip GY. Relationship between circulating
6. Cannon CP, Husted S, Harrington RA, et al. Safety, tolerability, and
5. Moliterno DJ, Jennings L, Becker RC, et al. Results of a multinational
4. Boos CJ, Soor SK, Kang D, Lip GY. Relationship between circulating
2. Boos CJ, Soor SK, Kang D, Lip GY. Relationship between circulating
1. Boos CJ, Soor SK, Kang D, Lip GY. Relationship between circulating

Key Words: non–ST-segment • coronary • syndrome.