Acute coronary syndromes (ACS) now account for approximately 1.6 million hospitalizations as determined by primary and secondary discharge diagnoses (1). The majority of these are without ST-segment elevation (STE), i.e., non–ST-segment elevation-acute coronary syndrome (nSTE-ACS). In this year’s report, we highlight scientific papers that were published or presented between May 2005 and April 2006 in 6 areas: pathogenesis, risk assessment, antithrombotic therapy, percutaneous coronary intervention, lipids, and women and minorities.

PATHOGENESIS

There has been considerable progress in our understanding of the pathogenesis of ACS (2). Sudden luminal thrombosis that is a consequence of either plaque rupture (most common), plaque erosion (in approximately one-third), or a calcified nodule (<10%) is responsible for most cases of ACS (3). Recent research has focused on the detection of “vulnerable” plaques (Table 1). The ideal method to detect such plaques would permit rapid screening of the entire coronary tree (4), because many ACS patients have multiple vulnerable plaques, particularly if systemic inflammation is present (5).

RISK ASSESSMENT

The Thrombolysis In Myocardial Infarction (TIMI) risk index (age² × heart rate/systolic blood pressure) is simple to calculate and was initially developed for patients with STE myocardial infarction (6). It has now also been validated in patients with nSTE-ACS (7). The prognostic capabilities of existing nSTE-ACS risk scores can be improved by adding information from the clinical history (e.g., depression [8], erectile dysfunction [9]), electrocardiogram (ECG) (e.g., STE in aVR [10], quantitative ST-segment deviation [11]), echocardiogram (e.g., left ventricular function and perfusion [12]), and serum markers (e.g., C-reactive protein [CRP] [13]), albeit at the cost of increasing complexity. Among patients with an initial normal troponin concentration, the presence of ST-segment depression, short delay (<8 h) to presentation, and absence of prior percutaneous coronary intervention (PCI) are the strongest predictors of an elevated late troponin (14), while the presence of insulin-dependent diabetes carries a 4-fold increase in the risk of death or reinfarction at 1 year (15).

Biomarkers. The past year added new information regarding markers of necrosis, ventricular stress, inflammation, and metabolic status in patients with nSTE-ACS. Elevated troponin is associated with yellow lipid-rich plaques and thrombus at angioscopy (16). When troponin is detected, even among patients without critical epicardial stenoses, it is associated with higher rates of death and reinfarction (17). Prior studies demonstrated the association of a single B-type natriuretic peptide (BNP) measured after presentation with an ACS with short-term and long-term risk of death and heart failure (18). More recently, changes in BNP over time predicted long-term outcomes, thus providing a tool that could be used to tailor therapy after ACS (19).

Numerous inflammatory biomarkers that may be useful in predicting the risk of patients with nSTE-ACS have been identified. These include cytokines (20) (e.g., interleukin-6, monocyte chemoattractant protein-1), acute phase reactants (21) (e.g., CRP, serum amyloid A), markers of endothelial cell activation and leukocyte adhesion (21) (e.g., soluble intercellular adhesion molecule-1, E-selectin), markers of oxidative stress (22) (e.g., myeloperoxidase, oxidized low-density lipoprotein [LDL], A2 phospholipases), angiogenic growth factors (22) (e.g., vascular endothelial and placental growth factors), matrix metalloproteinases (MMP) (23) (e.g., MMP-1, -2, -9; pregnancy-associated plasma protein A [PAPP-A]), and markers of platelet activation (23) (e.g., soluble CD-40 ligand, P-selectin). Three of the most promising novel markers (PAPP-A [24], placental growth factor [PIGF] [25], secretory phospholipase A2 [sPLA2] [26]) are independent predictors of death or reinfarction in patients with ACS (Table 2).

The overlap of metabolic derangement and cardiac biomarkers is being actively investigated. Using the novel application of metabolomics, changes in citric acid metabolites have been shown to be associated with acute myocardial ischemia (27). In 2 independent cohorts, high blood glucose during ACS was associated with a 1.7-fold increase in mortality, and also was correlated with elevated levels of troponin and BNP (28).
Whether the same applies to glycoprotein IIb/IIIa inhibitors (GPI) remains to be proven, and is further complicated by a difference in antiplatelet effect achieved by each of the 3 GPIs (39).

**Antiplatelet trials.** New data regarding the timing, loading dose, and duration of clopidogrel treatment were published in the past year. In a subgroup analysis from the CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) trial, clopidogrel (compared with placebo) showed consistent treatment benefit over the 9-month follow-up period regardless of the timing of PCI (40). Some of the early benefit of clopidogrel may be explained by its ability to block the rebound hypercoagulable state after heparin discontinuation in patients with ACS (41). Because a 300-mg loading dose of clopidogrel appears to have little benefit when the treatment duration is <12 h before PCI (42), higher doses have been investigated. Data from trials of patients without preceding nSTE-ACS who underwent PCI demonstrated higher levels of active metabolite and platelet inhibition with a 600-mg load (but no further incremental benefit with 900 mg) (43), and less frequent periprocedural myocardial infarction (44).

Three important questions with regard to the role of GPI therapy—efficacy on a background of 600-mg clopidogrel, upstream versus downstream use, and comparison to regimens containing bivalirudin—were explored in clinical trials during the past year. In the ISAR-REACT 2 (Abciximab in Patients with Acute Coronary Syndromes Undergoing Percutaneous Coronary Intervention After Clopidogrel Pre-treatment) trial, abciximab reduced the composite of death, myocardial infarction (MI), or urgent target vessel revascularization within 30 days compared with placebo by 25% (p = 0.03) among 2,022 patients with nSTE-ACS, all of whom received clopidogrel 600 mg at least 2 h before PCI (45). However, the benefit of abciximab was observed only in patients with nSTE-MI (Fig. 2). The EVEREST (Randomized Comparison of Upstream Tirofiban versus Downstream High Bolus Dose Tirofiban or Abciximab on Tissue-Level Perfusion and Troponin Release in High-Risk Acute Coronary Syndromes Treated with Percutaneous Coronary Interventions) trial of 93 patients with high-risk nSTE-ACS compared upstream tirofiban to downstream high bolus-dose tirofiban and downstream abciximab 10 min before PCI. Upstream tirofiban improved TIMI myocardial perfusion before and after PCI, achieved a higher myocardial contrast echocardiographic score, and resulted in

**Table 1. Modalities to Detect Vulnerable Coronary Plaques**

<table>
<thead>
<tr>
<th>Intravascular catheter-based techniques</th>
<th>Noninvasive techniques</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound</td>
<td>Multidetector row computerized tomographic angiography</td>
</tr>
<tr>
<td>Optimal coherence tomography</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>Near-infrared spectroscopy</td>
<td>Radionuclide imaging</td>
</tr>
<tr>
<td>Thermography</td>
<td></td>
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<tr>
<td>Palpography</td>
<td></td>
</tr>
<tr>
<td>Magnetic resonance imaging</td>
<td></td>
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<tr>
<td>Beta-radiation-sensitive catheters</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from J Am Coll Cardiol 2006;47(8)Suppl C.

**ANTITHROMBOTIC THERAPY**

**Variability in antiplatelet response.** The notion that patients exhibit a variable pharmacologic response to antiplatelet therapy is now entering its 5th decade. However, interest in this area has intensified recently in light of the greater ease of assessing pharmacodynamic effects of an increasing number of available antiplatelet therapies, and evidence that now correlates pharmacodynamic effect with clinical outcomes (29). Research on variable antiplatelet pharmacodynamic responses has been hampered by the lack of a universally accepted definition, absence of a gold-standard methodology (30), multiple mechanisms of hyporesponse, and, until recently, an uncertain relationship with pharmacokinetics of the glycoprotein Ia gene (35) each have been speculated to contribute to variability in response to aspirin (32). Some patients who are hyporesponsive to aspirin also may have a lower-than-expected pharmacologic effect after administration of clopidogrel (33), raising the possibility of a common mechanism. Indeed, the glycoprotein IIIa single nucleotide platelet antigen polymorphism PL3a2 (34) and the C807T polymorphism of the glycoprotein Ia gene (35) each have been linked to variability in response to aspirin and clopidogrel. Evidence supports a relationship between an inadequate pharmacologic response to aspirin plus clopidogrel with periprocedural necrosis (36), subacute stent thrombosis (37), and clinical events through 6 months after PCI (Fig. 1) (38). Whether the same applies to glycoprotein IIb/IIIa inhibitors (GPI) remains to be proven, and is further

**Table 2. Novel Inflammatory Markers That Independently Predict Death or Reinfarction**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Ref. #</th>
<th>Timing</th>
<th>HR (95% CI)</th>
<th>Additional Variables Included in the Multivariable Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAPP-A</td>
<td>24</td>
<td>6 months</td>
<td>2.3 (1.3–4.2)</td>
<td>Age, gender, diabetes, hypercholesterolemia, hypertension, prior CAD, ST-segment depression, troponin T, CRP</td>
</tr>
<tr>
<td>PIGF</td>
<td>25</td>
<td>4 yrs*</td>
<td>3.0 (1.4–6.7)</td>
<td>Age, gender, diabetes, ST-segment depression, troponin T, CRP, CD-40 ligand</td>
</tr>
<tr>
<td>sPLA2</td>
<td>26</td>
<td>6 months</td>
<td>3.1 (1.4–6.9)</td>
<td>Age, creatinine, Killip class, prior coronary artery bypass grafting</td>
</tr>
</tbody>
</table>

*Among survivors free of myocardial infarction at 6 months.

CAD = coronary artery disease; CI = confidence interval; CRP = C-reactive protein; HR = hazard ratio; PAPP-A = pregnancy-associated plasma protein A; PIGF = placental growth factor; sPLA2 = secretory phospholipase A2.
lower rates of post-procedure troponin elevation (46). Preliminary results from the open-label ACUITY (Acute Catheterization and Urgent Intervention Triage strategy) timing trial in 9,207 patients randomized to upstream GPI administered on average 6 h before PCI compared with downstream use begun in the catheterization laboratory demonstrated that a downstream strategy was non-inferior for a quaternary net clinical benefit end point (death, myocardial infarction, unplanned revascularization for ischemia, major bleeding), but did not satisfy the non-inferiority criterion for the triple ischemic end point (47). A cost-effective analysis using data from the TACTICS–TIMI-18 (Prognostic Implications of Elevated Troponin in Patients with Suspected Acute Coronary Syndrome but no Critical Epicardial Coronary Disease–Thrombolysis In Myocardial Infarction-18) trial concluded that upstream use of tirofiban was superior to selective use, and was cost-effective in moderate- to high-risk patients (48). Taken together, these studies suggest that upstream GPI therapy may be more effective than downstream use in moderate- to high-risk patients managed with an invasive strategy in whom immediate catheterization is not planned. The EARLY ACS (Early Glycoprotein IIb/IIIa Inhibition in Non-ST-Segment Elevation Acute Coronary Syndrome) study (49) is an ongoing randomized, double-blind, clinical trial comparing upstream double-bolus eptifibatide to downstream selective use in high-risk patients with nSTE-ACS who are not undergoing PCI in the first 12 h and should help shed further light on this issue.

Three new antiplatelet drugs are in phase III clinical trials, including a potent, fast-acting thienopyridine (prasugrel [50]), a reversible oral PGY12 inhibitor (AZD6140, a cyclopentyltriazolopyridimidine [51]), and a potent, short-acting intravenous PGY12 inhibitor (cangrelor [52]). In patients with nSTE-ACS, preliminary data from the DISPERSE 2 (Safety, Tolerability and Preliminary Efficacy of AZD6140, the First Oral Reversible ADP Receptor Antagonist, Compared with Clopidogrel in Patients with Non–ST-Segment Elevation Acute Coronary Syndrome) trial comparing AZD6140 with placebo demonstrated that AZD6140 180 mg twice daily achieved greater and more consistent platelet inhibition and showed favorable effects on clinical outcomes, without an increase in major bleeding (53).

**Anticoagulant trials.** Several studies investigated newer drugs that target more distal factors in the coagulation cascade (e.g., bivalirudin [54]), or more proximal factors (e.g., enoxaparin, fondaparinux) than does the standard anticoagulant, unfractionated heparin [UFH]. In the ACUITY trial, 13,819 patients with moderate- to high-risk
nSTE-ACS were randomized to 1 of 3 arms: heparin + GPI (standard), bivalirudin + GPI (combination), or bivalirudin alone (monotherapy) (55). The primary end point was net clinical benefit (see the preceding text). Combination therapy was non-inferior to the standard (neither arm was superior), while monotherapy was superior to standard therapy, driven by a reduction in bleeding with bivalirudin monotherapy (56). A common theme among the studies evaluating bivalirudin is the marked reduction in bleeding observed when GPI is not routinely administered.

Long-term follow-up from studies comparing enoxaparin to UFH (57) or tinzaparin (58) in patients with nSTE-ACS with relative low rates of early PCI confirmed the superiority of enoxaparin, particularly among patients who presented with ST-segment deviation (59). Selective inhibitors of factor Xa such as fondaparinux have the potential to be safer and easier to use than UFH and low-molecular-weight heparins because they do not bind avidly to other coagulation factors and have a long half-life permitting once daily dosing (60). In the OASIS-5 (Organization to Assess Strategies for Ischemic Syndromes) trial in 20,078 patients with nSTE-ACS, fondaparinux was almost identical to enoxaparin at 9 days for prevention of ischemic complications, but markedly reduced bleeding (hazard ratio 0.52, p < 0.001) (61). Fondaparinux was associated with a significant reduction in death at 30 and 180 days. However, an excess of guiding-catheter thrombus formation was observed with fondaparinux.

Bleeding. Current nSTE-ACS guidelines recommend more intensive antithrombotic therapy for patients at highest risk for ischemic complications; consequently, these patients (particularly the elderly and patients with renal dysfunction) are at a higher risk of bleeding (62). Major bleeding is associated with higher rates of death and reinfarction (62), with worse outcomes among patients with more severe bleeding (63), although it is very difficult to accurately quantify this relationship due to the presence of confounding. Transfusions, which occur more commonly in patients with greater baseline comorbidities, are themselves associated with a higher risk of adverse events (64). The first practical step to minimize the risk of bleeding complications is to avoid excess dosing of antithrombotic agents, which occurred in 42% of patients in the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) registry (65). Reducing the dose of aspirin to 75 to 100 mg reduces bleeding without apparent loss of benefit (66), as does the administration of a proton-pump inhibitor to patients with prior ulcer bleeding (67). There is ongoing controversy regarding the risk-benefit of continuing aspirin (68) and clopidogrel (69) until bypass surgery. Although off-pump surgery reduces hemorrhage, some surgeons are reluctant to forfeit this benefit by operating on patients who have recently received clopidogrel (69). Current practice guidelines recommend continuing aspirin, but withholding clopidogrel for 5 to 7 days, before elective bypass surgery (70).

INTERVENTIONAL CARDIOLOGY IN nSTE-ACS

Updated practice guidelines were released in 2005 by both the European Society of Cardiology (ESC) (72) and the American College of Cardiology (ACC)/American Heart Association (AHA)/Society for Cardiovascular Angiography and Interventions (SCAI) (71,73). New class I recom-
mendations with evidence level A pertaining to patients with nSTE-ACS in the ACC/AHA/SCAI guideline are summarized in Table 3. Recommendations for patients with nSTE-ACS in the updated ESC PCI guidelines (72) are similar, except that a loading dose of 600 mg clopidogrel is considered justifiable (class I, evidence level C) immediately after first medical contact if the time to PCI is 2 to 6 h. Also, the recommended durations of clopidogrel after drug-eluting stents (DES) (6 to 12 months) and after nSTE-ACS (9 to 12 months) are longer (73). Clopidogrel is highly cost-effective through 1 year after PCI (74), and, when given with aspirin for a median of 28 months to patients with clinically evident atherothrombosis, reduced the composite of cardiovascular death, myocardial infarction, and stroke by 12% (75).

In the ICTUS (Invasive Versus Conservative Treatment in Unstable Coronary Syndromes) trial (76) of 1,200 patients with positive troponin but no STE who were managed with intensive medical therapy, as recommended by the nSTE-ACS guidelines, an early invasive strategy did not reduce the primary composite of death, reinfarction, or rehospitalization for angina through 1 year compared with a more selective invasive approach. These findings contrast with those of a meta-analysis of 7 similar prior studies that demonstrated a 25% reduction in new myocardial infarction with a routine early invasive strategy (Fig. 3) (77).

While many studies in the past year compared different intracoronary stents (71), 2 important findings pertain to patients with nSTE-ACS. First, DES were associated with great reductions in periprocedural CRP and troponin (78). Second, patients more likely to receive a DES (compared with bare-metal stent), were younger, with systolic hypertension, dyslipidemia, no prior coronary artery bypass grafting, and absence of ST-segment deviations or markers of myonecrosis at presentation (79).

### LIPID-LOWERING THERAPY

In the past year, ancillary analyses from randomized trials of intensive statin therapy and mechanistic studies provided new insights into the role of lipid lowering in patients with ACS. The case for intensive statin therapy after nSTE-ACS was strengthened by a meta-analysis of 6 randomized controlled trials demonstrating that intensive, but not moderate, statin treatment reduces early recurrent ischemic events, stroke, CRP, and CD40 ligand (80). A detailed comparison of 2 trials comparing intensive to moderate statin therapy emphasized the importance of intensive therapy beginning in the early post-ACS phase, and suggested that the early benefit may be associated with a more

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**Table 3.** New Class I, Evidence Level A Recommendations in Patients With Non–ST-Segment Acute Coronary Syndrome Undergoing PCI (71)

| 1. Aspirin 325 mg for a minimum duration depending on the type of stent utilized: |
| Bare-metal | ≥1 month |
| Sirolimus-eluting | ≥3 months |
| Paclitaxel-eluting | ≥6 months |
| 2. Clopidogrel administered as a 300-mg load at least 6 h prior to PCI followed by 75 mg daily for duration dependent upon the type of stent: |
| Bare-metal | ≥1 month |
| Sirolimus-eluting | ≥3 months |
| Paclitaxel-eluting | ≥6 months |
| 3. Use of drug-eluting stents as an alternative to bare-metal stents in those whom trial data suggest efficacy |

PCI = percutaneous coronary intervention.

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**Figure 3.** Odds of non-fatal myocardial infarction (MI) from randomization to end of follow-up in a meta-analysis of 7 trials of routine versus selective invasive management of acute coronary syndromes (77). p = 0.51 for heterogeneity across the trials. CI = confidence interval; OR = odds ratio. Reproduced with permission from *JAMA* (77).
profound reduction in CRP achieved with earlier intensive therapy (Fig. 4) (81). These results have been rapidly reflected in subsequent changes in the particular statin and dose prescribed. A trend-over-time analysis in Ontario, Canada, documented a greater than doubling in the use of atorvastatin, 80 mg, within months after publication of the PROVE IT–TIMI-22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction-22) and REVERSAL (Reversing Atherosclerosis With Aggressive Lipid Lowering) studies (82).

The benefit of atorvastatin, 80 mg, compared with pravastatin, 40 mg, occurred within 30 days in the PROVE IT–TIMI-22 trial (28% reduction the hazard ratio of death, myocardial infarction, or rehospitalization for recurrent ACS, p < 0.05 (within trial)) consistent with greater early pleiotropic effects (83). A number of potential early benefits of statins that are independent of LDL have been postulated and include favorable effects on inflammation, endothelial function, and the coagulation cascade (84). In a secondary analysis from the PROVE IT–TIMI-22 trial, randomization to intensive statin therapy was associated with a lower CRP level (p < 0.0001) irrespective of the presence of single or multiple uncontrolled cardiovascular risk factors (85). Endothelium-dependent flow-mediated dilation increased between 1 and 4 months after initiating either atorvastatin, 80 mg, or pravastatin, 40 mg, in the BRAVER (Intensity of Lipid Lowering with Statins and Brachial Artery Vascular Endothelium Reactivity After Acute Coronary Syndromes) trial, independent of reduction in LDL and CRP (86).

Two important observations regarding the safety of statins were reported during the past year. An analysis of 15,693 patients from the GRACE (Global Registry of Acute Coronary Events) registry demonstrated that, in general, patients receiving the combination of clopidogrel and statin did not have an increase in clinical events, thus suggesting no adverse interaction exists between these 2 therapies. Indeed, even after adjustment for differences in baseline variables and bias in treatment allocation, an analysis of patients administered aspirin/clopidogrel/statin revealed that the group taking all 3 drugs had the lowest mortality (87). In an analysis of patients who achieved very low LDL concentrations in the PROVE IT–TIMI-22 trial, there was no adverse safety signal while clinical efficacy improved as the LDL was lowered to <40 mg/dl (88), thus suggesting that downward adjustment of the statin dose is not required in patients who achieve very low LDL concentrations.

Despite such favorable results with high-intensity statins, only 44% of patients randomized to atorvastatin, 80 mg, with baseline total cholesterol <240 mg/dl (average LDL 106 mg/dl) achieved the dual goals of LDL <70 mg/dl and CRP <2 mg/l (89). Better control of traditional risk factors (85) and even more potent pharmacologic therapy are necessary to achieve these ambitious targets that have been associated with relatively lower rates of death and recurrent ischemic complications (90).
WOMEN AND MINORITIES

Coronary artery disease has been traditionally considered a disease afflicting men, and studies in nSTE-ACS have predominantly included men. However, 43% of patients with ACS discharged from U.S. hospitals in 2003 were women (1). In the WISE (Women’s Ischemia Syndrome Evaluation) study, gender differences in the onset of disease and risk factor distribution, including variability in the synergy of traditional risk factors and the presence of novel risk factors (e.g., hypoestrogenemia, protracted dysmetabolic state) were demonstrated (91). These differences may result in symptoms that lead to nSTE-ACS despite non-obstructive epicardial disease. Whereas the traditional approach to the patient with nSTE-ACS has focused on the identification of a critical epicardial stenosis, this is not optimal for women, many of whom remain at high risk for poor outcomes despite the absence of obstructive coronary artery disease. Factors such as microvascular dysfunction, endothelial dysfunction, increased oxidative stress, elevated circulating levels of inflammatory markers, and metabolic derangements appear to be more important mediators of ischemic heart disease in women (92). Thus, in women, an alternative approach that focuses on the identification of the culprit patient, rather than culprit lesion is preferred (93).

Despite a near doubling of awareness of cardiovascular disease in women over the past decade (94), gender disparities in the diagnosis and treatment of women with nSTE-ACS persist. Women tend to receive less aggressive acute (95) and chronic (96) treatments than men, and suffer an increased rate of refractory ischemia and rehospitalization (97).

Because a disproportionate percentage of elderly patients are women, it is not surprising that registries of patients with nSTE-ACS in the U.S. (98), Canada (99), and Europe (100) have all found that the elderly are less likely to receive acute and chronic evidence-based medicines and procedures. Similar studies have demonstrated that blacks are less likely than whites to receive evidence-based therapies, particularly invasive procedures (101) and antiplatelet adjuncts to PCI (102). The racial differences appear to be better explained by differences in the quality of care delivered by hospitals treating minorities (103) than variation in procedure volume (104). Paradoxically, elderly and minority patients receive fewer of the proven therapies despite being at higher risk than younger, white patients (99), thus resulting in poorer clinical outcomes (100,101) and quality of life (105).

Conclusions. Advances in the prior decade, which accelerated during the past year, have led to better methods to estimate the prognosis and treat patients with nSTE-ACS, resulting in a decline in mortality over time (106). Surprisingly, some simple measures such as obtaining an electrocardiogram within 10 min after arrival in the emergency department in patients presenting with chest pain (107) and long-term, consistent use of evidence-based secondary preventive therapies in patients post-discharge (108) are sub-optimal. Because each 10% increase in the guideline adherence rates is associated with a 10% decrease in mortality (109), additional interventions that improve compliance with quality measures, such as a computerized physician order entry systems (110), should improve outcomes. These efforts, along with the development of safer and more effective therapies, implementation of uniform clinical performance measures (106), and use of novel strategies (e.g., combination pharmacotherapy [111]), should reduce morbidity and mortality in the future for our patients with nSTE-ACS.

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