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YEAR IN CARDIOLOGY SERIES

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

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Acute coronary syndromes (ACS) account for approximately 1.6 million annual inpatient hospital discharges in the U.S. (1). Approximately 80% of these are due to non–ST-segment elevations ACS (NSTE-ACS). In this year's review, we highlight publications and presentations between May 2006 and April 2007 in 6 areas: risk assessment, antithrombotic therapy, anti-ischemic therapy, percutaneous coronary intervention (PCI), lipid management, and selected patient subgroups.

Risk Assessment

Although several risk scores that predict short-term outcomes have been developed and validated, research in the past year has focused on the assessment of risk at the time of discharge and on longer-term prediction of outcome. The GRACE (see Table 1 for clinical trial acronyms) hospital discharge risk score incorporates 9 historical and clinical variables, and was demonstrated to predict mortality at 6 months to 4 years with accuracy (c-statistics 0.76 to 0.80) (2). Modifications of the score (Otago-Southland model) (2) and a simplified GRACE risk calculator (3) provide further refinements to predict long-term mortality and the composite of death or myocardial infarction (MI), respectively. Future models may need to incorporate more information regarding disease in noncoronary vascular beds (e.g., cerebrovascular [4], peripheral arterial [4], and systemic arterial [5]), because patients with disease in these territories also are at increased risk for late cardiovascular events. Such risk scores are important, because patients with NSTE-ACS continue to experience higher mortality than patients with ST-segment elevation myocardial infarction (STEMI) for up to 10 years (6), and risk stratification at hospital discharge may be very useful in guiding post-discharge management in such patients.

New data on depression in patients with ACS described an 18% prevalence of moderate/severe depressive symptoms (of which only 25% of cases had documented recognition of depressive symptoms in the medical record) (7). Elderly patients and those who live alone were at highest risk for depression (8), and these patients were the most likely to suffer the adverse consequences of depression, such as noncompliance to proven therapies (9) and delayed return to work (10).

Biomarkers. A new model of risk stratification based on a panel of molecular and genetic factors is shown in Figure 1 (11). As the investigation of novel biomarkers (especially circulating serum and plasma markers) continues to accelerate, such a construct helps to organize the various classes of biomarkers and highlights their role in the pathogenesis of ACS. To evaluate the clinical utility of new biomarkers (12–23), 3 fundamental questions have been proposed by Morrow and de Lemos (24) to serve as benchmarks (Table 2).

1. Can the clinician measure the biomarker?
2. Does the biomarker add new information?
3. Will it help the clinician manage patients?

One of the most promising novel markers is growth differentiation factor (GDF)-15, a member of the transforming growth factor-beta cytokine superfamily. Growth differentiation factor-15 is released from cardiomyocytes after ischemia and reperfusion injury. Circulating serum levels of GDF-15 were shown to be a strong independent marker of 1-year mortality (Fig. 2), providing additional prognostic information beyond that attained by existing biomarkers and clinical features of patients with NSTE-ACS (12). Further characterization of GDF-15 along with improved understanding of the role it may play in the pathogenesis of ACS is needed before GDF-15 joins other established biomarkers such as troponin (25), B-type natriuretic peptide (BNP) (25,26), C-reactive protein (27), ST-segment depression (28), and alterations in myocardial perfusion (29).

Other promising biomarkers with new data are summarized in Table 2 and include new markers of ischemia/necrosis, inflammatory/metabolic status, lymphocyte subsets, modulators of atherothrombosis, and markers of intracellular signaling. Additional research evaluating the relevant value of novel biomarkers to predict initial ACS (30) and recurrent ACS events (31) are needed.

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Table 1 Clinical Trial Acronyms

ACUITY	Acute Catheterization and Urgent Intervention Triage Strategy
ANTHEM	Anticoagulation With rNAPc2 to Help Eliminate MACE
ARMYDA	Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty
CHARISMA	Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance
CRUSADE	Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines
ELISA	Early or Late Intervention in Unstable Angina
FRISC	Fast Revascularization During Instability in Coronary Artery Disease
GRACE	Global Registry of Acute Coronary Events
GUSTO	Global Utilization of Streptokinase and TPA for Occluded Arteries
ICTUS	Invasive Versus Conservative Treatment in Unstable Coronary Syndromes
MERLIN	Metabolic Efficiency With Ranolazine for Less Ischemia in NonST-Segment Elevation Acute Coronary Syndromes
MIRACL	Myocardial Ischemia Reduction With Aggressive Cholesterol Lowering
PROTECT	Randomized Trial to Evaluate the Relative PROTECTion Against Post-PCI Microvascular Dysfunction and Post-PCI Ischemia Among Antiplatelet and Antithrombotic Agents
PROVE IT	Pravastatin or Atorvastatin Evaluation and Infection Therapy
SYNERGY	Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa Inhibitors
TIMI	Thrombolysis In Myocardial Infarction
TRITON	Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel

ACC/AHA = American College of Cardiology/American Heart Association; MACE = major adverse cardiac events; PCI = percutaneous coronary intervention; rNAPc2 = recombinant nematode anticoagulant protein c2; TPA = tissue plasminogen activator.

Antithrombotic Therapy

Clopidogrel, in addition to aspirin, is now considered to be part of the standard antithrombotic regimen for all patients with NSTE-ACS who do not have a contraindication (e.g., active bleeding) (32). However, limitations to the clinical effectiveness of clopidogrel include a delayed onset of action after the standard 300-mg loading dose and inter- and intrapatient variability in antiplatelet effect (so-called "clopidogrel response variability") (33), both of which have been associated with recurrent ischemic complications. To overcome these limitations, investigators have explored loading doses >300 mg in patients with NSTE-ACS and have observed a more rapid onset of action, a higher level of platelet inhibition, and a greater reduction in platelet activation with 600 mg compared with 300 mg (34,35), with only modest further incremental benefit after a 900-mg load (34).

Prasugrel is a novel thienopyridine with greater potency, faster onset of action, and more consistent inhibition of platelet aggregation than even 600-mg clopidogrel (36). It is being studied in the phase III clinical trial TRITON–TIMI 38, an event-driven study that has completed enrollment of over 13,600 patients with ACS undergoing PCI, which will be reported during the next year (37).

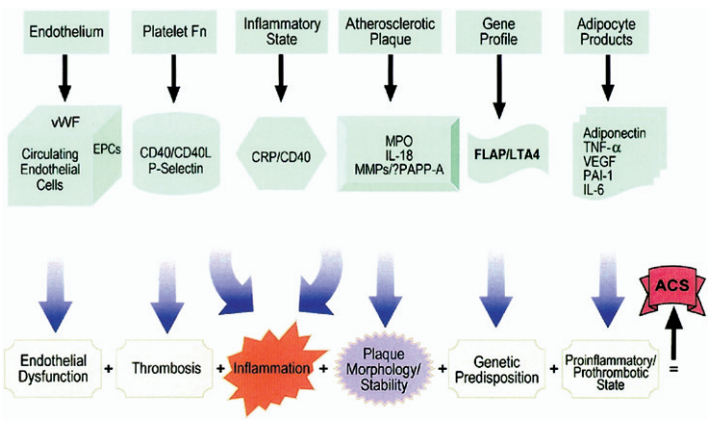

Figure 1 Panel of Cellular and Molecular Components Involved in the Pathogenesis of Acute Coronary Syndrome

ACS = acute coronary syndrome; EPC = endothelial progenitor cell; FLAP = 5-lipoxygenase–activating protein pathway; IL = interleukin; LTA4 = leukotriene A4 pathway; MMP = matrix metalloproteinase; MPO = myeloperoxidase; PAI-1 = plasminogen activator inhibitor; PAPP-A = pregnancy-associated plasma protein A; sCD40L = soluble CD40 ligand; TNF = tumor necrosis factor; VEGF = vascular endothelial growth factor; vWF = von Willebrand factor. Adapted from Anwaruddin et al. (11).

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Table 2 Novel Biomarkers

	Measurable	Informative	Clinically Useful
Ischemia/necrosis markers			
Heart-type fatty acid binding protein (13)	+++	++	++
Ischemia-modified albumin (14)	++	++	++
Inflammatory/metabolic markers			
Growth differentiation factor-15 (12)	++	+++	+
C-reactive protein gene polymorphisms (15)	+	+	?
Adiponectin (16)	++	+½	+
Lymphocyte subsets			
$CD4^{+}CD28^{null}$ (17)	+	+	+
$CD4^{+}CD25^{+}$ (18)	+	+	+
Modulators of thrombosis			
Lipoprotein-associated phospholipase A^2 (19)	+++½	+++	++½
Myeloperoxidase (20)	+++	+++	++
Matrix metalloproteinase-3 polymorphism (21)	+	+	+
Markers of intracellular signaling			
Platelet collagen receptor glycoprotein VI (22)	+	+	+
Soluble intercellular adhesion molecule-1 (23)	++	+	+

+ = preliminary; ++ = modest supportive data; +++ = multiple sources of supportive data; ++++ = extensive data, widely accepted; ? = unknown.

An alternative method to increase the inhibition of platelet function is to add a third agent to the standard combination of aspirin and clopidogrel. The ELISA-2 trial compared the effect of adding the glycoprotein (GP) IIb/IIIa receptor antagonist tirofiban (so-called "triple antiplatelet therapy") to standard dual therapy in patients with NSTE-ACS treated with an early invasive approach and found a trend toward less (166 IU/l vs. 192 IU/l; p = 0.2) lactate dehydrogenase release over 48 h, and fewer (46% vs. 57%; p = 0.052) infarcts with triple therapy (38).

The final results of the ACUITY trial, a trial of 13,819 patients with NSTE-ACS managed with an early invasive strategy, were published in 2006. The ACUITY trial randomized patients to 1 of 3 antithrombotic regimens: 1) bivalirudin monotherapy; 2) bivalirudin + a GP IIb/IIIa receptor antagonist; or 3) heparin + a GP IIb/IIIa antagonist (39). The principal findings were that bivalirudin monotherapy reduced the net clinical composite of bleeding + ischemic complications compared with either of the 2 arms that included a GP IIb/IIIa receptor antagonist and that this difference was driven by a markedly lower rate of bleeding when routine GP IIb/IIIa blockers were not given. There were similar rates of ischemic complications through 1 year across the 3 arms (40). The combination of bivalirudin + GP IIb/IIIa inhibitor did not appear to offer any substantial advantage over the other regimens. The optimal timing of GP IIb/IIIa inhibitor use also was evaluated in the ACUITY Timing trial (41), which demonstrated that a strategy of initiating GP IIb/IIIa inhibitor therapy in the catheterization laboratory (i.e., "down-

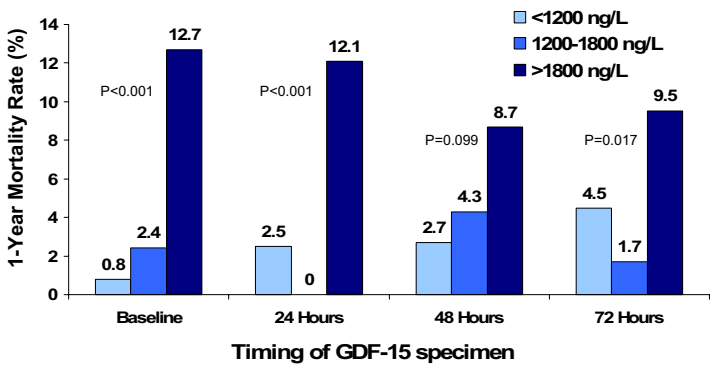

Figure 2 Tertiles of GDF-15 at Baseline and Follow-Up Predict 1-Year Mortality in Non–ST-Segment Elevation Acute Coronary Syndrome

Patients enrolled in the GUSTO IV-ACS trial were stratified according to tertiles of growth differentiation factor-15 (GDF-15) levels at baseline and at 24, 48, and 72 h after randomization. Mortality at 1 year was highest for the patients in the upper tertile (>1,800 ng/dl) of GDF-15 measured at all time points. Data from Wollert et al. (12).

stream") compared with upstream initiation (i.e., on initial presentation) an average of 4 h earlier was associated with a 20% reduction in bleeding ($p = 0.009$). However, patients randomized to downstream initiation tended to experience more ischemic complications (7.9% vs. 7.1%; $p = 0.13$). Of note, the average time from hospital arrival to PCI in the CRUSADE registry was approximately 24 h (42), and the delay is even longer for patients who are admitted on weekends (43). An ongoing trial (EARLY-ACS [44]) is comparing early versus deferred GP IIb/IIIa blockade in patients with a longer duration of upstream therapy that more closely reflects the median delay to catheterization in the U.S.

The PROTECT–TIMI 30 trial (29) also compared bivalirudin monotherapy with heparin + GP IIb/IIIa receptor antagonist (eptifibatide) and revealed a similar trade-off between a decrease in bleeding and an increase in ischemic complications when bivalirudin without a GP IIb/IIIa blocker is substituted for the standard regimen of heparin + GP IIb/IIIa receptor antagonist (Fig. 3). However, the ACUITY and PROTECT–TIMI 30 trials differed in the direction of the absolute net benefit (defined as the MI rate minus the TIMI major bleeding rate), with the net benefit favoring bivalirudin monotherapy in the ACUITY trial (39) but favoring heparin + GP IIb/IIIa antagonist in the PROTECT–TIMI 30 trial (29). Based on these findings, an individualized approach that considers the patient's risk of bleeding and ischemic complications in the light of other clinical features, such as the use and timing of other adjunctive therapies (e.g., clopidogrel, PCI), to determine the optimal antithrombotic regimen appears most reasonable.

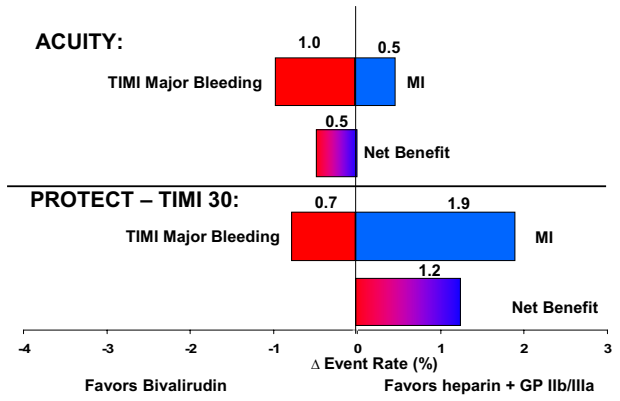

Figure 3 **Trade-Off of Efficacy and Safety in the ACUITY and PROTECT–TIMI 30 Trials**

The absolute difference in the rates of myocardial infarction and TIMI major hemorrhage are shown for each trial, as well as the composite (myocardial infarction [MI] minus TIMI major bleeding). In the ACUITY trial (n = 13,819), there were more TIMI major hemorrhages prevented with bivalirudin than there were MIs prevented by heparin + glycoprotein (GP) IIb/IIIa inhibitor, and thus the net benefit (0.5%) favored bivalirudin. In the PROTECT–TIMI 30 trial (n = 857), the net benefit went in the opposite direction, favoring heparin + GP IIb/IIIa inhibitor by 1.2%. Data from Gibson et al. (29) and Stone et al. (39).

The safety of oral antiplatelet therapy was reported in 2 high-risk subgroups of patients with ACS: those undergoing coronary artery bypass graft (CABG) surgery and those with cancer. The CRUSADE trial investigators reported that current guideline recommendations (32) to delay CABG surgery for at least 5 days after the last dose of clopidogrel generally are not followed, despite demonstrating that CABG surgery within 5 days of clopidogrel is associated with increased rates of red cell (65% vs. 57%), large quantity (≥4 U) (28% vs. 18%), and platelet (34% vs. 20%) transfusions (45). Meanwhile, a single-center review of patients with cancer who developed ACS demonstrated the efficacy and safety of aspirin, whether or not thrombocytopenia was present (46).

A prespecified subgroup analysis examining the efficacy and safety of extended clopidogrel (median 28 months) in the CHARISMA trial demonstrated that patients with a documented prior MI had a 23% reduction ($p = 0.031$) in cardiovascular death, MI, or stroke compared with placebo, with no increase in severe bleeding (47). These findings, coupled with the latest recommendations to administer at least 12 months of clopidogrel after implantation of drug-eluting stents (DES) (48), are likely to extend the duration of clopidogrel that clinicians recommend to patients with NSTE-ACS.

The safety and efficacy of rNAPc2, a proximal inhibitor of the coagulation cascade that targets the tissue factor/factor VIIa complex, were studied in the phase II ANTHEM–TIMI 32 trial (49) of moderate-high risk patients with NSTE-ACS managed with an early invasive strategy and standard antithrombotics (aspirin, heparin or enoxaparin, clopidogrel, and GP IIb/IIIa antagonists). Doses of ≥7.5 μg/kg rNAPc2 administered intravenously every 48 h during hospitalization reduced new thrombin generation and ischemia on ambulatory electrocardiography, suggesting a link between the proximal target of this drug and recurrent ischemia that follows plaque rupture.

Detailed analyses of the nonrandomized subgroups of patients undergoing post-randomization PCI were reported for the SYNERGY (50) and ACUITY (41) trials. In the former, enoxaparin was as efficacious (no difference in death or MI) as unfractionated heparin (UFH) but was associated with more bleeding (3.7% vs. 2.5%; $p = 0.028$). In the latter, bivalirudin was associated with less bleeding than heparin + GP IIb/IIIa blocker (3% absolute reduction; $p < 0.0001$), with a similar rate of ischemic complications (9% vs. 8%; $p = 0.48$).

Bleeding. Further efforts to minimize bleeding complications were identified in subsequent analyses from the SYNERGY and PROTECT–TIMI 30 trials. Patients treated consistently with enoxaparin in the SYNERGY trial (i.e., no crossing over between UFH and enoxaparin either before or after randomization) had a significantly lower incidence of death or MI at 30 days (adjusted $p = 0.041$) but a trend toward increased bleeding compared with patients randomized to UFH (51). In the PROTECT–

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TIMI 30 trial, a reduced creatinine clearance (CrCl) was strongly associated with bleeding (52). Among patients with CrCl <50 ml/min, 45% did not have the proper downward adjustment of the infusion of eptifibatide (from 2 μg/kg/min to 1 μg/kg/min), and these patients had a 20% rate of bleeding compared with 0% for patients with proper down-titration of the infusion. Because several analyses have shown a correlation between bleeding and increased mortality (53), clinicians should routinely incorporate steps to minimize bleeding, such as dose adjustment of renally cleared antithrombins as determined by renal function assessed at admission and periodically thereafter.

A promising approach to limit bleeding that is in very early stages of development involves the use of aptamers, i.e., single-stranded nucleic acids that adopt a specific shape, enabling high-affinity binding and specificity to target proteins. Dyke et al. (54) reported phase I results in healthy volunteers with a protein-binding oligonucleotide to factor IXa and its complementary antidote. Future clinical use of such anticoagulants with desirable pharmacologic features, including high selectivity, ease of titration, rapid onset/offset, and ready reversibility, could lead to a substantial reduction in bleeding complications.

Anti-Ischemic Therapy

Ranolazine is a novel antianginal agent that inhibits the late sodium current in myocardial cells, thereby reducing some of the deleterious effects attributed to the overload of intracellular sodium and calcium during ischemia. This drug was studied in 6,560 patients within 48 h of NSTE-ACS who were followed for a median of 348 days in the MERLIN–TIMI 36 trial (55). The addition of ranolazine to standard ACS therapies did not reduce the primary composite of cardiovascular death, MI, or recurrent ischemia, because ranolazine had no effect on death or MI. However, ranolazine did reduce recurrent ischemia by 13% ($p = 0.03$) and appeared to be safe, thus providing further evidence to support its current indication as an antianginal agent.

Interventional Cardiology in NSTE-ACS

(See also Dixon et al. [56].) The use of an early invasive therapy (catheterization within 48 h of admission) in NSTE-ACS has increased (from 53% to 61% in the CRUSADE registry [57]) over the 3 years since the class Ia recommendation given by the 2002 American College of Cardiology/American Heart Association guideline update (32). This trend is likely to continue, given the preponderance of positive data favoring an early invasive approach in NSTE-ACS that were reported during the past year. The most recent meta-analysis confined to patients in the stent and GP IIb/IIIa antagonist era (58) compared an early invasive strategy with a more conservative approach and concluded that the former reduced all-cause mortality by 25% and nonfatal reinfarction by 17% at 2 years. Five-year data from the FRISC-II trial (59) were directionally similar, although the relative reduction in mortality was more modest (5%; p = NS) and the benefit of an early invasive therapy in that trial was most evident in men, nonsmokers, and patients with at least 2 risk factors. Furthermore, in a retrospective propensity-matched analysis, multivessel stenting was associated with a 20% reduction in ischemic complications compared with stenting of only the culprit vessel (60).

A report on the long-term (3- to 4-year) outcomes in the ICTUS trial (61), a Dutch study which compared an early invasive with a selective invasive treatment strategy, does not support an early invasive approach in all patients. The latter was, in fact, associated with a trend toward higher rates of the composite of death, recurrent MI, or rehospitalization for angina at 3 years (hazard ratio [HR] 1.21; $p = 0.09$) driven by higher rates of MI, largely PCI-induced release of biomarkers (HR 1.61; $p = 0.002$), although rates of all-cause and cardiovascular mortality at 4 years were similar between the 2 strategies. Potential explanations for the findings in the ICTUS study include a liberal definition of periprocedural MI that led to a higher early event rate with the early invasive strategy, a relatively high rate (40%) of predischarge revascularization in the comparator arm with a narrowing of the difference in revascularization rates between strategies with time (i.e., a higher rate of cross-overs), and frequent use of high-intensity lipid-lowering regimens (62).

The optimal type of stent (DES vs. bare-metal stents) in patients with NSTE-ACS remains controversial. Implantation of DES appears to reduce periprocedural markers of inflammation and necrosis (63) and to reduce restenosis. However, their use in patients with NSTE-ACS is considered to be "off-label," because most DES trials have focused on patients with stable coronary artery disease (CAD). Given the limited data with DES in patients with NSTE-ACS, and the observation that "off-label" use of DES is associated with increased risk of stent thrombosis (64), we do not endorse the widespread use of DES in patients with NSTE-ACS until additional data are available. Of note, to reduce the risk of late stent thrombosis, patients should be instructed to continue dual antiplatelet therapy for at least 1 year, without interruption, after DES implantation (48).

Statins

Statins are among the most thoroughly studied drugs and have a very favorable risk-benefit relationship. A systematic overview of 74,102 patients enrolled in 35 randomized placebo-controlled clinical trials across a wide range of populations concluded that statins (excluding cerivastatin, which is no longer available) were associated with an excess of elevated transaminases (4.2 ± 1.7 per thousand; $p < 0.01$) but no significant differences in myalgias, creatine kinase elevation, rhabdomyolysis, or discontinuation due to any adverse event (65). This mild increase in the risk of

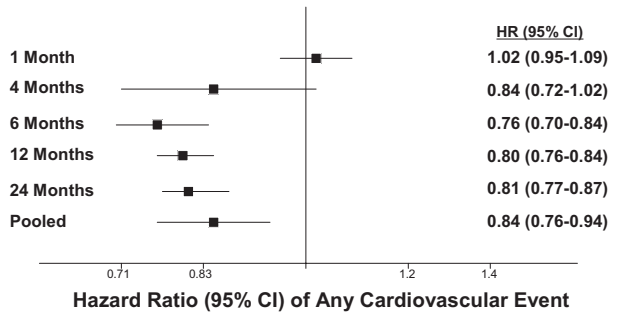

Figure 4 **Meta-Analysis of Early Intensive Statin Therapy in ACS**

By 4 months, the use of an early intensive statin (compared with placebo or low-dose statin control) reduced the risk of overall cardiovascular events in this analysis of 17,963 patients within 14 days of hospitalization for acute coronary syndrome (ACS) among 13 trials. Estimates to the **left** of the line of unity favor intensive statin therapy and those to the **right** favor the control (either placebo or low-dose statin). CI = confidence interval; HR = hazard ratio. Data from Hulten et al. (66).

"transaminitis" is outweighed by a reduction in cardiovascular events that begins to appear after 4 months after ACS (Fig. 4) and in cardiovascular mortality at 2 years (66). Although the mechanism of early benefit with intensive statin treatment (regimens achieving >40% reduction in low-density lipoprotein [LDL]) remains incompletely understood, reductions in tumor necrosis factor- alpha and interferon-gamma production in stimulated T lymphocytes 72 h after treatment with 20 mg rosuvastatin in patients with ACS suggest that rapid immunomodulation may play an important role (67).

The results of one important trial of intensive statin therapy in patients with NSTE-ACS who were undergoing early PCI, the ARMYDA study, were published after the previously described meta-analysis (68). That trial compared 80-mg atorvastatin ≥12 h before PCI followed by another 40 mg preprocedure with placebo. All patients received a 600-mg loading dose of clopidogrel and were treated with 40-mg atorvastatin daily after PCI. The 30-day composite of death, MI, or unplanned revascularization was reduced from 17% to 5% ($p = 0.01$) in patients receiving pre-PCI atorvastatin; this difference was attributed mostly to a reduction in MI (15% vs. 5%; $p = 0.04$). This benefit of short-term pretreatment with high-dose atorvastatin in patients with NSTE-ACS undergoing PCI suggests the presence of a non–LDL-mediated early benefit of high-dose statin.

Intensive statin therapy with 80 mg atorvastatin was also more effective than standard-dose statin (40 mg pravastatin) in reducing the risk of hospitalization for heart failure (HR 0.55; $p = 0.008$) in patients after ACS enrolled in the PROVE IT–TIMI 22 trial (69). The benefit was independent of recurrent MI or a history of heart failure and was particularly prominent in patients with an elevation of circulating BNP. The mechanism of benefit remains unexplained, although data continue to accrue regarding so called "pleiotropic" effects of high-dose statins, such as the favorable effects on C-reactive protein (27) and vitamin D (70).

An evaluation of current treatment guidelines in patients enrolled in a recent clinical trial suggests that nearly two-thirds of patients admitted with ACS who had an indication for statin therapy before the development of the ACS were, in fact, not treated before admission (71). Even after initiation of therapy, poor adherence to statin therapy remains a challenge, and patients who miss their statin dose frequently appear to be at increased risk for mortality with a dose-response adherence-mortality relationship that is even stronger than that observed with beta-blockers (72).

Specific Patient Subgroups

Women. Gender-based differences in cardiovascular diseases long have been recognized, and in the past year an updated evidence-based guideline for primary and secondary prevention of cardiovascular disease in women was released (73). Among the gender-based differences described in that guideline are: 1) a narrower role for aspirin in primary prevention of coronary events in women than in men; 2) recognition of the underestimation of risk in women whose calculated Framingham global risk score is in the low or moderate ranges (74); 3) contraindication of certain drugs (statins, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers) during pregnancy/lactation; and 4) identification of pre-eclampsia/eclampsia as a risk factor for the development of cardiovascular disease.

The need for a guideline dedicated to women is easily justified, because substantial gender differences in ACS have been observed. Women and men have different cardiac risk factors (high-density lipoprotein and C-reactive protein are particularly important coronary heart disease risk factors in women [75]), presenting symptoms (e.g., women are more likely to experience nausea and less likely diaphoresis [76]), and cardiovascular history (women are less likely to have had prior MI or revascularization [77]). Women with chest pain are more likely than men to have nonobstructive CAD at catheterization (78), and these women require fewer procedures and rehospitalizations than women with obstructive CAD (79). However, because nonobstructive CAD requires more intensive anti-ischemic drug therapy, the average lifetime cost estimates for women with nonobstructive CAD is nearly equal to that of women with obstructive 3-vessel CAD (79). Finally, compared with men, women with NSTE-ACS are at increased risk for bleeding, in part owing to lower CrCl (women tend to be older and lighter than men) which results in more frequent excessive dosing of antithrombotic agents (80). Because recent analyses in patients with NSTE-ACS demonstrated a strong, consistent, temporal, and dose-related association between bleeding and death (81), proper dose adjustment of antithrom-

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botic therapy could simultaneously improve safety and efficacy.

Disorders of glucose metabolism. Several observations over the past year highlight the importance of abnormal glucose metabolism in association with NSTE-ACS and identify opportunities to improve care. Nearly one-third of diabetic patients do not have a hemoglobin A_1C assessed during hospitalization. When assessed, 60% of diabetics with ACS were found to have suboptimal control (hemoglobin A_1C >7.0%) (82). Diabetics with higher baseline plasma glucose levels have more severe platelet dysfunction, which can be reversed by acute aggressive glycemic control with intravenous insulin (83). Unfortunately, diabetics also are less likely to achieve goal levels of LDL and C-reactive protein (84), which may indicate the need for more intensive treatments to reduce the risk of subsequent events. One approach to accomplish this would be a higher maintenance dose of clopidogrel (150 mg daily) (85). However, the effect of this higher dose of clopidogrel, when given for prolonged periods, on the risk of bleeding remains to be defined.

Milder forms of impaired glucose metabolism are common in NSTE-ACS and are associated with an increased risk. Metabolic syndrome was present in 25% of patients with ACS in a comprehensive survey conducted in Israel and carried a 2-fold increased risk in 1-year mortality even after multivariate adjustment (86). Hyperglycemia at presentation, as measured by a random glucose measurement, was associated with an adverse biomarker panel (higher troponin and BNP) and increased mortality at 10 months (87).

Elderly. Elderly patients with NSTE-ACS tend more often to be female and have a higher risk profile (88). International variation exists in the management provided to the elderly with NSTE-ACS, particularly with regard to the use of cardiac catheterization and subsequent revascularization (88). Although the risks of most treatments in the elderly are increased, so are the potential benefits. For example, elderly patients (≥70 years) who achieved the optional LDL goal of <70 mg/dl after ACS experienced an 8% absolute and 40% relative lower risk of events, reductions substantially greater than those observed in younger patients (89). Data from the MIRACL study in patients 24 to 96 h after ACS confirmed the lack of an age-treatment interaction among older (≥65 years of age) versus younger patients who were randomized to 80-mg/day atorvastatin versus placebo, and the safety of 80-mg/day atorvastatin was similar between the 2 age groups (90). Further research to understand the reasons for underuse of proven therapies in the elderly and to define more precisely the risk-benefit relationship is necessary.

Quality Improvement

A number of efforts are ongoing to improve the quality of care delivered to patients with NSTE-ACS. The CRUSADE registry collected data from >165,000 patients with NSTE-ACS admitted to >400 U.S. hospitals (91) and now has merged with the National Registry for Myocardial Infarction. Hospitals previously participating in these registries will now report to the National Cardiovascular Data Registry under the auspices of the American College of Cardiology. On a more global front, the GRACE registry (92) continues to collect important data reflecting worldwide practice and outcomes in NSTE-ACS. Real-time monitoring of key quality indicators represents a new advance in quality improvement. Use of a system that reviews and implements key quality-of-care indicators in real time in the hospital has resulted in greater use of evidence-based therapies that improved outcomes more rapidly than the traditional annual cycle of quality improvement (93).

Data from the CRUSADE (94) and GRACE (95) registries demonstrate that, unfortunately, patients with NSTE-ACS at highest risk are least likely to receive guideline-recommended therapies, even after exclusion of those patients with contraindications for proven therapies. Meanwhile, use of complementary and alternative medications that are *not* evidence based are increasingly prevalent in patients with ACS after hospital discharge and, in particular, are more common in high-risk subgroups of patients, including minorities, the uninsured, the economically disadvantaged, and patients with depression (96). Novel approaches to deliver more evidence-based therapies to these patients and others with ACS who are most likely to benefit are needed.

Author Disclosures

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Dr. Giugliano is a Study Investigator for Merck and Co., Novartis, Nuvelo, and Schering-Plough. He serves as a Consultant/Advisory Board Member for CV Therapeutics, Merck and Co., National Institutes of Health, Sanofi-Aventis, and Schering-Plough. He is on the Speakers'

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Dr. Braunwald is the Chairman of the TIMI Study Group at the Brigham and Women's Hospital. He has consulted or participated in symposia or advisory board meetings for which he received honoraria (<$10,000) from the following companies: AstraZeneca Pharmaceuticals, Bayer, Daiichi Sankyo, Merck and Co., Momenta, Pfizer, Sanofi-Aventis, and Schering-Plough.

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