YEAR IN CARDIOLOGY SERIES

The Year in Acute Coronary Syndrome

Robert P. Giugliano, MD, SM, Eugene Braunwald, MD
Boston, Massachusetts

In this year’s report on acute coronary syndromes (ACS), we have expanded the scope to include ST-segment elevation myocardial infarction (STEMI) in addition to non–ST-segment elevation ACS. In this report, we review selected highlights across the spectrum of ACS published between June 2012 and September 2013.

Background

It is estimated that there were over 1.1 million patients with diagnoses of ACS discharged from U.S. hospitals in 2010, of whom 74% were classified as having myocardial infarction (MI) (1). Despite improvements in the management of coronary heart disease risk factors, the annual rates of acute myocardial infarction (AMI) have been fairly stable in the United States over the past decade. The impact of enhanced prevention has been offset by the use of more sensitive biomarkers of cardiac necrosis, specifically cardiac troponin (cTn), to define MI (2), as well as the increase in comorbidities that increase the risk for developing ACS, including diabetes, metabolic syndrome, and chronic kidney disease, as well as the overall aging of the population. The percent of patients with ACS classified as having STEMI ranges from 29% to 47% in recent databases and registries, depending on the methods used to identify patients and the population being studied (1). This percent is decreasing relative to non-STEMI (NSTEMI), in part because of temporal changes in the risk factor profile (reductions in “classic” risk factors such as smoking and hypertension but increases in the aforementioned comorbidities (3). With the broader acceptance of the third universal definition of MI (4) (Table 1), we expect these trends to continue.

Indeed, as the sensitivity of cTn measurements has increased, the fraction of patients with unstable angina (UA) (i.e., those with non–ST-segment elevation ACS and no evidence of myocardial necrosis) is steadily declining (2). With the introduction of so-called high-sensitivity cTn (hs-cTn) into clinical practice in a number of countries (other than the United States), almost all patients with ischemic discomfort at rest consistent with ACS have elevations of hs-cTn and are being reclassified as having NSTEMI (5). Patients with chest pain at rest without elevation of hs-cTn on 2 measurements made 2 to 4 h apart most likely have nonischemic chest pain.

New Guidelines

New guidelines for the management of STEMI were released by the American College of Cardiology Foundation (ACCF) and American Heart Association (AHA) (6) and the European Society of Cardiology (7) during the past year. In addition, the ACCF and AHA published an update of the guideline for UA and NSTEMI guideline (8). Key changes in these guidelines are summarized in Table 2.

Two important updates to the STEMI guideline (6) include a new target of no more than 120 min from first medical contact to initiation of fibrinolysis (for those not undergoing primary percutaneous coronary intervention [PCI]) and the early initiation of therapeutic hypothermia in survivors of cardiac arrest, followed by immediate PCI when appropriate. Across the ACS spectrum, these updated guidelines (6–8) now recommend the use of the more potent oral antiplatelet drugs (prasugrel or ticagrelor) as alternatives to clopidogrel and provide specific advice on how to minimize bleeding, particularly among patients who require dual-antiplatelet therapy (DAPT) in addition to oral anticoagulation.

Pathophysiology

Three important reports extended the framework for understanding the basic mechanisms leading to ACS: 1) Libby (9) described an updated model in terms of cellular and molecular pathways that underlie the pathogenesis of ACS, with a central role for inflammation, which drives plaque disruption and thrombosis (Fig. 1). This more nuanced understanding of the pathophysiology of ACS has broadened our approach beyond management of a focal
intracoronary stenosis. 2) Crea and Liuozzo (10) classified ACS into 3 groups (Fig. 2): obstructive atherosclerosis with systemic inflammation, obstructive atherosclerosis without systemic inflammation, and ACS without obstructive atherosclerosis (e.g., Prinzmetal’s angina, amphetamine-induced coronary spasm). 3) Falk and a group of cardiac pathologists (11) described 3 common coronary artery plaque morphologies resulting in thrombosis (plaque rupture, plaque erosion, and disruptive nodular calcifications protruding into the coronary artery lumen, known as “calcified nodules”). These latter investigators described several contributors to the “vulnerable plaque,” including structural determinants of the plaque (size of the necrotic core, thickness and degree of inflammation within the fibrous cap), plaque neorevascularization and infiltration with hemoglobin-stimulated macrophages (both of which increase the risk for intraplaque hemorrhage), and the pattern of calcification (spotty calcification confers higher risk compared with dense localized calcification). It is hoped that continued work on the pathogenesis of ACS will lead to new diagnostic algorithms and therapeutic targets.

The search continues for interventions, other than prompt revascularization, to reduce infarct size in patients with STEMI. An intriguing study in swine in which the left anterior coronary artery was occluded showed that unloading the left ventricle with left atrial–femoral artery bypass when added to coronary occlusion resulted in further reduction of myocardial infarct size (12). Although this approach cannot be applied routinely in the catheterization laboratory in all patients with STEMI, it could be lifesaving in those with large infarctions.

### Risk Factors

Several reports published during the past year explored genetic risk factors for ACS. Micro-ribonucleic acids (miRNAs) are noncoding ribonucleic acid molecules, 21 to 23 nucleotides long, that regulate the expression of target genes. After multivariate adjustment, 3 circulating miRNAs (126, 233, and 197) were found to be risk factors for the development of future MI (13). Other miRNAs have been found to be associated with reduced myocardial salvage, more pronounced reperfusion injury, and left ventricular remodeling after first STEMI (14,15). The discovery of miRNAs represents a major advance in biology that is likely to aid in the elucidation of the pathobiology of many conditions (including ACS), may provide families of new biomarkers, and might open the possibility for the development of new therapies. For example, miRNAs can be “silenced” by specific antagonists, known as antagomirs, that might be designed to modify target proteins that predispose plaques to rupture.

New data on hormonal contraceptives and nonsteroidal anti-inflammatory drugs provided new insights regarding the increased risk for ACS with these classes of medications. In an analysis of over 1.6 million women the use of ethinyl estradiol was associated with increases in the risk for MI (16). A nationwide Danish cohort study of almost 100,000 patients alive at 30 days after first MI found that nonsteroidal anti-inflammatory drugs (prescribed to 44% of the cohort) within 5 years after the index MI increased the risk for coronary death or nonfatal MI by 30% after 1 year and 41% after 5 years (17). These findings provide additional support for the Class III recommendations (i.e., contraindications) for estrogen-containing hormones (6) and nonsteroidal anti-inflammatory drugs (6–8) present in current ACS guidelines.

Two reports call attention to specific groups of patients who are at high risk for initial and/or recurrent ACS events. 1) Mild psoriasis was associated with a 30% increase in the adjusted risk for MI, while severe psoriasis was independently associated with increased risk for MI and cardiovascular (CV) mortality of 70% and 40%, respectively (18).
Because corticosteroids and other immunomodulatory therapies used to manage psoriasis have either shown no benefit or the potential for harm early after MI, identification of the optimal treatment plan for these patients remains an unmet need. 2) In patients with non–ST-segment elevation ACS who experienced ventricular tachycardia (VT) or ventricular fibrillation (VF), either early (within 48 h) or late (>48 h) after admission, the adjusted hazard ratios (HRs) for mortality at 1 year were 7.4 and 15, respectively, compared with no VT or VF during the index hospital stay (19). These findings are important for 2 reasons. They demonstrate that ventricular arrhythmias early after MI may not uniformly represent benign reperfusion arrhythmias, as previously had been thought. Also, the very high risk for VT or VF occurring >48 h after admission raises concern regarding the safety of early discharge for patients who had experienced even brief bouts of VT and the need for risk stratification and better therapies to prevent and treat late ventricular arrhythmias.

We end this section with a brief discussion of a novel dynamic risk score in patients with STEMI (20). Most risk scores for ACS, such as the TIMI (for a list of trial acronyms, see Table 3) risk score for STEMI (21), are based on findings at the time of the patient’s initial presentation. However, they do not take into account events that occur during the hospital stay. The dynamic TIMI risk score for STEMI (20) includes 6 clinical events occurring after admission (reinfarction, stroke, major bleed, congestive heart failure or shock, arrhythmia [VT, VF, or atrial fibrillation], and renal failure) that affect the risk for mortality adversely (Table 4). Addition of these clinical events resulted in a high discriminatory capacity (C-statistics of 0.76 in the derivation set and 0.81 in the validation set) and improved net reclassification (0.33 in the derivation set, 0.35 in the validation set) over the original TIMI risk score for STEMI (21) for the prediction of 1-year mortality. This dynamic score could help clinicians tailor discharge medical regimens and guide decisions regarding discharge location, cardiopulmonary rehabilitation, and timing of follow-up visits.

### Biomarkers

The ACCF released an expert consensus document (22) that focuses on the practical issues related to elevated cTn levels in clinical practice. A conceptual model proposed 3 categories of cTn elevation: 1) ischemic myocardial damage (i.e., MI), 2) nonischemic causes of myocardial damage (e.g., myocarditis), and 3) analytical issues that may be either assay based (e.g., calibration errors) or sample based. In Figure 3, we highlight the importance of nonischemic causes of cTn elevation, including both cardiac diagnoses (e.g., congestive heart failure) and systemic illnesses (e.g., sepsis), because these are frequently encountered in hospital care and account for a large number of unnecessary requests for cardiology consultations. It is essential that healthcare providers incorporate the clinical context of an elevated cTn level to help guide the triage, diagnostic work-up, and treatment plans for these patients, and not reflexively label all cTn elevations as indicating MI. In addition, a prospective analysis of 887 unselected patients with acute chest pain found that a simple algorithm that incorporates ST-segment elevation, the level of hs-cTn (currently not available in the United States) at presentation, and the absolute change in hs-cTn during the first hour performed well (C-statistic = 0.94) in separating AMI from noncoronary diagnoses (23). As increasingly sensitive cTn assays become available, we anticipate that most patients will have detectable levels of cTn after PCI, but the clinical significance of minor releases of cTn in this setting is unclear. One analysis concluded...
that elevations in creatine kinase-MB 3-fold to 5-fold above the upper limit of normal after PCI correlated with cTn elevations of 50-fold to 100-fold in both frequency and risk for mortality 1 year after PCI (24).

Among 2,544 patients presenting with symptoms consistent with ACS, the combination of normal hs-cTn at presentation and 2 h later, no ischemic changes on electrocardiography, and a TIMI risk score for UA or NSTEMI (25) of 0 or 1 identified approximately 40% of patients in whom the rate of major adverse cardiac events through 30 days was <1% and who therefore were good candidates for early discharge (26). It is likely that many of these patients may not actually have had ACS (5). Another study in 1,967 patients presenting to emergency departments with chest pain onset within 6 h demonstrated that the combination of negative cTn (not high sensitivity), copeptin level <14 pmol/l, and nondiagnostic electrocardiographic findings could rule out AMI in the majority of patients without serial blood draws (27). These studies highlight how the incorporation of cTn into a rapid assessment at presentation could help improve efficiency in the diagnosis and risk stratification of patients with chest pain.

From the many reports describing novel biomarkers associated with clinical outcomes in ACS published during the past year, we have selected 4 markers for this year’s review.

1) pregnancy-associated plasma protein–A, a zinc-binding metalloproteinase found in vulnerable plaques that cleaves insulin-like growth factor–4 from insulin-like growth factor–1 and that causes destabilization of the fibrous plaque, was measured at baseline in 3,782 patients with non–ST-segment elevation ACS in the MERLIN–TIMI 36 trial (28). After multivariate adjustment for baseline cTn I and other risk
factors, elevated baseline pregnancy-associated plasma protein–A was found to be independently associated with increased risk for CV death or MI at 30 days (HR: 1.62; \( p = 0.006 \)) and 1 year (HR: 1.35; \( p = 0.012 \)). 2) Ischemia-mediated changes to myocardial cell surface molecule expression render the cell membrane a target for the complement system, leading to the formation of a membrane attack complex (MAC), which leads to cell lysis. In an analysis of 725 patients with STEMI treated with primary PCI, elevated concentrations of soluble MAC (a stable nonlytic form of MAC that can be used to estimate MAC) after multivariate adjustment were associated with all-cause mortality (HR: 1.81; \( p = 0.029 \)) and major adverse CV events (HR: 1.70; \( p = 0.006 \)) \( ^{29} \). 3) Interleukin-17 is produced by a recently described lineage of CD4\(^+\) T cells, plays a role in host immunity and the pathophysiology of

**Figure 2** A New Pathogenetic Classification of ACS

Simple clinical descriptors provide a framework for understanding the basic mechanisms responsible for coronary instability in homogenous groups of patients with acute coronary syndromes (ACS) that might help in the search for new diagnostic algorithms and therapeutic targets: 1) patients with obstructive atherosclerosis (ATS) and systemic inflammation; 2) patients with obstructive atherosclerosis without systemic inflammation; and 3) patients without obstructive atherosclerosis. Reprinted with permission from Crea and Liuzzo \( ^{10} \).

---

**Table 3** Trial Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARCTIC</td>
<td>Assessment by a Double Randomization of a Conventional Antiplatelet Strategy Versus a Monitoring-Guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption Versus Continuation One Year After Stenting</td>
</tr>
<tr>
<td>ATLAS ACS 2</td>
<td>Second Trial of Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome</td>
</tr>
<tr>
<td>CHAMPION PHOENIX</td>
<td>Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition</td>
</tr>
<tr>
<td>COMFORTABLE AMI</td>
<td>Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction</td>
</tr>
<tr>
<td>DAPT</td>
<td>Dual Antiplatelet Therapy</td>
</tr>
<tr>
<td>EMBRACE-STEMI</td>
<td>Evaluation of the Myocardial Effects of Bendavia for Reducing Reperfusion Injury in Patients With Acute Coronary Events–STEMI</td>
</tr>
<tr>
<td>EXAMINATION</td>
<td>Clinical Evaluation of the Xience-V Stent in Acute Myocardial Infarction</td>
</tr>
<tr>
<td>GUSTO</td>
<td>Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries</td>
</tr>
<tr>
<td>HORIZONS-AMI</td>
<td>Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction</td>
</tr>
<tr>
<td>IABP-SHOCK II</td>
<td>Intracoronary Balloon Pump in Cardiogenic Shock II</td>
</tr>
<tr>
<td>MERLIN</td>
<td>Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes</td>
</tr>
<tr>
<td>PARADOX</td>
<td>The Influence of Smoking Status on Prasugrel and Clopidogrel Treated Subjects Taking Aspirin and Having Stable Coronary Artery Disease</td>
</tr>
<tr>
<td>PLATO</td>
<td>Platelet Inhibition and Patient Outcomes</td>
</tr>
<tr>
<td>RIFLE-STEACS</td>
<td>Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome</td>
</tr>
<tr>
<td>RIVAL</td>
<td>A Trial of Trans-Radial Versus Trans-Femoral Percutaneous Coronary Intervention Access Site Approach in Patients With Unstable Angina or Myocardial Infarction Managed With an Invasive Strategy</td>
</tr>
<tr>
<td>TIMI</td>
<td>Thrombolysis in Myocardial Infarction</td>
</tr>
<tr>
<td>TRILOGY</td>
<td>Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes</td>
</tr>
<tr>
<td>TRITON</td>
<td>Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel</td>
</tr>
<tr>
<td>TRIUMPH</td>
<td>Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients’ Health Status</td>
</tr>
<tr>
<td>TWENTE</td>
<td>The Real-World Endeavor Resolute Versus Xience V Drug-Eluting Stent Study in Twente</td>
</tr>
<tr>
<td>WOEST</td>
<td>What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting</td>
</tr>
<tr>
<td>XAMI</td>
<td>Xience V Stent vs. Cypher Stent in Primary PCI for Acute Myocardial Infarction</td>
</tr>
</tbody>
</table>
immune-mediated diseases and may play a role in the development of an unstable plaque. In an analysis of 981 patients enrolled in a French registry of patients with MI, low levels of interleukin-17 were independently associated with increased risk for death or reinfarction at 2 years (HR: 1.40; p = 0.03) after adjustment for CV risk factors (30). Koga et al. (31) reported that higher levels of circulating pentraxin 3, a novel inflammatory marker, were associated with thin-cap vulnerable plaques, as determined by optical coherence tomography.

Imaging

There is an increasing effort to identify noninvasive imaging modalities to predict acute clinical CV events in patients suspected of having coronary artery disease. Coronary magnetic resonance angiography was found to be helpful in the risk stratification of patients with suspected CAD who were followed for 25 months (32). Patients with significant luminal narrowing (≥50% diameter reduction) were at higher risk for cardiac death, MI, UA, or need for revascularization (6.3% vs. 0.3%, p = 0.001) compared with those without significant stenoses.

Building on the prior data supporting a role for computed tomographic angiography (CTA) to assist in the rapid triage of patients presenting with acute chest pain to hospital emergency departments described in last year’s review (33), Ferencik et al. (34) demonstrated that a CTA-based score incorporating morphologic characteristics of coronary lesions (stenosis length, plaque volume and attenuation, remodeling index, presence of spotty calcium) was quite accurate (C-statistic = 0.83) in the detection of ACS in a cohort of patients with acute chest pain and significant stenosis by CTA. A systematic review and meta-analysis of 4 randomized trials of 1,869 patients undergoing CTA and 1,397 managed with usual care showed that CTA reduced the mean cost in the emergency department and shortened lengths of hospital stay (35). Furthermore, in an analysis by Poon et al. (36), routine CTA of patients presenting with chest pain to an emergency department reduced health expenditures largely because the use of this technique reduced the incidence of patients’ return to the emergency department within 30 days.

Two catheter-based imaging techniques are being evaluated for the characterization of coronary plaques in patients with ACS. Using optical coherence tomography, plaque rupture was found to be responsible for the culprit lesion in 44% of 126 patients, while 31% had plaque erosion; the latter was more frequently observed in younger patients with NSTEMI, whose plaques had thicker fibrous caps and less lipid than those with plaque rupture (37). An interesting alternative approach is the use of a catheter designed to provide near-infrared spectroscopy, which allows the detection of lipid in the plaques. Madder et al. (38) reported that use of this catheter in patients with acute STEMI revealed that the lipid core in culprit plaques was larger than those observed in nonculprit arteries, thereby providing a “biochemical signature” of the culprit plaque.

Antiplatelet Therapy

Antiplatelet therapy is one of the cornerstones of the management of ACS. From a large body of research, we have selected 5 areas to highlight in this year’s review.

Table 4 Dynamic TIMI Risk Score for STEMI

| Points |
|------------------|------------------|
| Baseline TIMI risk score for STEMI | 0 to 14 possible points |
| Age, yrs | 2 |
| 65 to 74 | 1 |
| ≥75 | 3 |
| Diabetes, hypertension, or angina | 1 |
| Systolic blood pressure <100 mm Hg | 3 |
| Heart rate >100/min | 2 |
| Killip class II, III, or IV | 2 |
| Weight <67 kg | 1 |
| Anterior ST-segment elevation or left bundle branch block | 1 |
| Time to treatment >4 h | 1 |
| Added index hospitalization events for dynamic score | 0 to 15 possible points |
| Recurrent myocardial infarction | 1 |
| Stroke | 5 |
| Major bleeding | 1 |
| Congestive heart failure or shock | 3 |
| Arrhythmia | 2 |
| Renal failure | 3 |
| Dynamic TIMI risk score | 0 to 29 possible points |

The 6 clinical events after hospital admission (bottom half) are added to the baseline risk factors (top half) of the original TIMI risk score for STEMI to yield the dynamic TIMI risk score, which ranges from 0 to 29 points. Reprinted with permission from Amin et al. (20).

STEMI = ST-segment elevation myocardial infarction.

Table 4 Dynamic TIMI Risk Score for STEMI

| Points |
|------------------|------------------|
| Baseline TIMI risk score for STEMI | 0 to 14 possible points |
| Age, yrs | 2 |
| 65 to 74 | 1 |
| ≥75 | 3 |
| Diabetes, hypertension, or angina | 1 |
| Systolic blood pressure <100 mm Hg | 3 |
| Heart rate >100/min | 2 |
| Killip class II, III, or IV | 2 |
| Weight <67 kg | 1 |
| Anterior ST-segment elevation or left bundle branch block | 1 |
| Time to treatment >4 h | 1 |
| Added index hospitalization events for dynamic score | 0 to 15 possible points |
| Recurrent myocardial infarction | 1 |
| Stroke | 5 |
| Major bleeding | 1 |
| Congestive heart failure or shock | 3 |
| Arrhythmia | 2 |
| Renal failure | 3 |
| Dynamic TIMI risk score | 0 to 29 possible points |

The 6 clinical events after hospital admission (bottom half) are added to the baseline risk factors (top half) of the original TIMI risk score for STEMI to yield the dynamic TIMI risk score, which ranges from 0 to 29 points. Reprinted with permission from Amin et al. (20).

STEMI = ST-segment elevation myocardial infarction.
Phase 3 clinical trial results with novel antiplatelet drugs. Cangrelor, an intravenous, rapidly acting, potent, yet reversible P2Y_{12} inhibitor, was compared with clopidogrel in the double-blind, double-dummy CHAMPION PHOENIX trial of 11,145 patients (44% of whom had ACS) undergoing either urgent or elective PCI (39). Cangrelor significantly reduced the odds of both the primary CV composite endpoint of death, MI, ischemia-driven revascularization, or stent thrombosis at 48 h after randomization by 20% among the 2,810 patients with non–ST-segment elevation ACS and by 25% among the 1,991 patients with STEMI, rates that were statistically similar to the significant 22% reduction observed in the overall trial population (Fig. 4). In addition, cangrelor reduced the odds of stent thrombosis (by 38%) through 48 h without increasing bleeding in the overall population, without heterogeneity across the population stratified by type of ACS at presentation. This trial demonstrated the benefit of intense but short-duration inhibition of P2Y_{12} to reduce periprocedural complications, particularly MI and stent thrombosis. In contrast, the potent oral thienopyridine prasugrel did not reduce the composite of CV death, MI, or stroke among medically managed patients with non–ST-segment elevation ACS compared with clopidogrel, in the TRILOGY ACS trial (40). These 2 trials (CHAMPION PHOENIX and TRILOGY ACS), considered in the light of prior studies of potent P2Y_{12} inhibitors in patients with ACS, suggest that more intensive blockade appears most beneficial in high-risk patients during PCI (as had been observed with prasugrel in the TRITON–TIMI 38 trial [41]), whereas the benefit of such therapy over the long term in those patients who are managed medically deserves further prospective evaluation.

A randomized trial of bedside monitoring to adjust antiplatelet therapy. In the ARCTIC trial (42), 2,440 patients scheduled for coronary stent implantation (30% with prior MI, 27% with non–ST-segment elevation ACS) were randomized to a strategy of platelet-function monitoring using the VerifyNow assay (Accumetrics, San Diego, California), followed by intensification of the antiplatelet regimen in patients with high platelet reactivity, compared with a conventional strategy with no monitoring or adjustment of the antiplatelet regimen. Despite increasing the antiplatelet therapy in over one-third of the patients in the platelet monitoring group, there were no differences in the primary CV composite endpoint (death, MI, stent thrombosis, stroke, or urgent revascularization), the major secondary endpoint of stent thrombosis or any urgent revascularization, or major bleeding. Several potential explanations for the lack of improvement in clinical outcomes in ARCTIC and 3 prior similar studies have been offered, including a suboptimal cut point for high platelet reactivity, a need for even more potent antiplatelet agents in patients with high reactivity, and the observation that some clinical ischemic events (e.g., procedural complications) cannot be influenced by antiplatelet therapy. Until more

![Figure 4 Primary Efficacy and Safety Results From the CHAMPION PHOENIX Trial by Diagnosis at Presentation](https://example.com/figure4.png)

The primary efficacy composite included death, myocardial infarction, ischemia-driven revascularization, or stent thrombosis through 48 h after randomization. The primary safety endpoint was moderate or severe bleeding according to the GUSTO scale. ACS = acute coronary syndromes; HR = hazard ratio; STE = ST-segment elevation; STEMI = ST-segment elevation myocardial infarction. Modified with permission from Bhatt et al. (39).
successful strategies are developed, we agree with the recommendations in the current ACS guidelines that do not endorse routine testing of platelet function (6–8).

**Studies exploring shorter duration of DAPT.** DAPT is recommended for at least 12 months after ACS, whether it is secondary to STEMI (6) or non–ST-segment elevation ACS (8) and whether patients receive intracoronary stents or not. During the past year, new findings regarding the risks and benefits of prolonged DAPT after the placement of a drug-eluting stent (DES) were reported. In a meta-analysis including 8,231 patients (61% with ACS) undergoing PCI with DES from 4 randomized trials, extended use of DAPT (>12 months) significantly increased the risk for TIMI major bleeding by 2.6-fold but did not reduce mortality, MI, or stroke compared with control (3 to 12 months of DAPT) (43). Further support for stopping DAPT >12 months after DES placement come from the TWENTE trial (44), which showed a very low rate of late stent thrombosis (0.3%) between 12 and 24 months among patients who received second-generation DES (either zotarolimus or everolimus), 95% of whom stopped clopidogrel at 12 months. However, interruption of DAPT within the first 90 days after DES placement is not advised.

Certain high-risk subgroups (e.g., patients undergoing intracoronary stent placement into a saphenous vein graft [45]) are at increased risk (adjusted incidence ratio: 1.33) for stent thrombosis within the first 3 months, regardless of stent type, if clopidogrel is stopped before day 90 after stent placement. Although interruptions in DAPT were common within the first year of a registry enrolling 1,622 patients (59% of whom had ACS) at 29 Spanish hospitals, they were typically brief (median 7 days) and not associated with a statistically significant increase in the risk for stent thrombosis (46). The DAPT Study (NCT00977938) enrolled more than 26,000 patients who had received intracoronary stents (either bare-metal stents [BMS] or DES) and were treated with DAPT. After 12 months, patients who were free of major CV events and bleeding were randomized to either placebo (12-month DAPT arm) or an additional 18 months of thienopyridine (30-month DAPT arm). This trial represents the first adequately powered evaluation of the clinical efficacy and safety of differing durations of DAPT; results are anticipated in 2014.

**Reduction of stent thrombosis with ticagrelor.** Analysis of the TRITON–TIMI 38 trial in patients with ACS undergoing coronary stent implantation showed that, compared with clopidogrel, the administration of prasugrel reduced stent thrombosis by 50% (41). In the PLATO trial, which compared ticagrelor with clopidogrel, 11,289 patients with ACS received coronary stents. Definite and probable stent thrombosis were also reduced significantly, by 25% (47). As was the case for prasugrel, this benefit was consistent across all patient subgroups and types of stents.

**Influence of smoking on antiplatelet inhibition.** There have previously been scattered reports on the effects of smoking on the action of clopidogrel. In the PARADOX study, reported by Gurbel et al. (48), patients were randomized to clopidogrel or prasugrel in a crossover design. Inhibition of platelet activation on clopidogrel was lower in nonsmokers than smokers. Inhibition of platelet activity was greater with prasugrel than clopidogrel in both smokers and nonsmokers and was not affected by smoking status in patients receiving prasugrel. These results support the so-called smoker’s paradox, in which the clinical benefits of clopidogrel are greater in smokers than in nonsmokers.

**Oral anticoagulant agents.** Two secondary analyses from the ATLAS ACS 2–TIMI 51 trial (49) that evaluated the oral factor Xa inhibitor rivaroxaban in addition to standard therapy (including DAPT) in patients with ACS provided greater insight into the potential role for oral anticoagulation after ACS. Among the 7,817 patients with STEMI (>70% of whom underwent PCI), the use of rivaroxaban starting on average 4.7 days after the index event was associated with a significant 19% reduction in the composite of CV death, MI, or stroke compared with placebo (49). The benefit began early and was statistically significant at 30 days. Furthermore, the very low-dose regimen of rivaroxaban (2.5 mg twice daily) reduced CV death (2.5% vs. 4.2%, p = 0.006) compared with placebo. However, the addition of rivaroxaban to DAPT significantly increased major bleeding, including intracranial hemorrhage, although rates of fatal bleeding were low and not statistically different from placebo. Among the 9,631 patients with ACS who received stents in ATLAS ACS 2–TIMI 51 and were treated with DAPT, the addition of rivaroxaban compared with placebo significantly reduced definite or probable stent thrombosis (as defined by the Academic Research Consortium) by 35% (95% confidence interval: 7% to 54%; p = 0.017) (50). A mortality reduction of 44% (95% confidence interval: 11% to 65%) was observed in patients who received the lower dose of rivaroxaban (2.5 mg twice daily) compared with placebo. These findings helped shape the European Medicine Agency’s approval of rivaroxaban after ACS in 2013; a similar review by the U.S. Food and Drug Administration is ongoing.

**Bleeding**

One hundred sixteen years after aspirin was first synthesized, a consensus on the use of lower dose aspirin for patients with ACS appears to have developed (6–8). A systematic review of the literature including 136 studies with 289,330 patients concluded that there was no improvement in clinical outcomes with higher (>160 mg/day) maintenance doses of aspirin compared with lower doses in patients with ACS receiving coronary stents or being medically managed (51). However, there was an excess of major bleeding of 23 per 1,000 with these higher doses of aspirin in medically treated patients. An analysis from the HORIZONS-AMI trial in patients with STEMI treated with primary PCI concluded that higher dose aspirin (>200 mg/day) increased major bleeding (adjusted HR: 2.80) and was not more effective than low-dose aspirin in preventing recurrent
ischemic CV events (52). In addition, less severe forms of bleeding, which are also more common with higher doses of aspirin, have a negative impact on the quality of life and may increase the need for re-hospitalization, as shown in the TRIUMPH study of 3,560 patients receiving DAPT after MI (53).

Bleeding complications are particularly elevated in patients requiring “triple therapy” with aspirin, a P2Y12 inhibitor, and a full dose of an oral anticoagulant agent (e.g., patients with ACS and atrial fibrillation). An analysis of nationwide registries in Denmark between 2000 and 2009 of 11,480 patients with atrial fibrillation admitted with MI or for PCI concluded that the excess risk for bleeding with triple therapy begins early (within 90 days) and continues through at least 1 year (54). These findings are important because they suggest that there is no improvement in tolerance over time with triple therapy, at least through 1 year of treatment. Although newer, more potent antiplatelet therapies, such as prasugrel, have been shown to reduce CV events (41), substitution of prasugrel for clopidogrel in a small series of 377 patients with DES receiving triple therapy resulted in a 3.2-fold increase in the hazard of TIMI major or minor bleeding (55). Therefore, we believe that patients who require triple therapy generally should receive low-dose aspirin and clopidogrel for the minimal duration recommended, warfarin with a target international normalized ratio of 2.0 to 2.5, and, if coronary stenting is indicated, a BMS.

A novel approach to avoiding triple therapy was tested in the open-label WOEST trial (56), carried out in 573 patients with long-term indications for oral anticoagulation undergoing coronary stenting. In the experimental arm, aspirin was not administered, and the combination of clopidogrel and an oral anticoagulant agent was compared with triple therapy (aspirin 80 to 100 mg/day plus clopidogrel and an oral anticoagulant agent). The risk for any bleeding was substantially less with clopidogrel plus an oral anticoagulant agent compared with triple therapy (19.4% vs. 44.4%, p < 0.0001). Surprisingly, rates of the combined secondary endpoint of death, MI, target vessel revascularization, stroke, or stent thrombosis also were lower with dual compared with triple therapy (HR: 0.60; 95% confidence interval: 0.38 to 0.94). However, these data are not very robust given the small number of events (81 events in the entire trial). Additional large studies that limit the exposure of patients to long-term triple antithrombotic regimens are needed.

Invasive Management

In this section, we highlight a few of the important publications on the invasive management of ACS and remind readers that a dedicated review on interventional cardiology was recently published in the Journal (57).

Current guidelines for the management of STEMI (6,7) emphasize the importance of well-organized regional systems (58) to ensure rapid reperfusion therapy. For example, in North Carolina, an extension of regional coordination to the entire state resulted in more rapid diagnosis of STEMI, shorter transfer and door-to-device times, and an overall increase in the use of reperfusion therapy (59). After a statewide STEMI strategy to transport patients directly to a PCI-capable hospital (bypassing nearer non-PCI hospitals) was implemented, the mean time to reperfusion (by either PCI or fibrinolysis) was reduced by a mean of 31 min (60).

To reduce further the time to reperfusion therapy in patients with STEMI, the emergency department was bypassed by transferring appropriate patients from the ambulance directly to the catheterization laboratory; this strategy saved 20 to 30 min (61). It is likely that this approach will be used with increasing frequency as patient evaluation in ambulances becomes more precise.

Nevertheless, non-system-related delays that are difficult to anticipate (e.g., delays in providing consent, difficulty with vascular access or crossing the culprit lesion, the need for intubation) are not uncommon, occurring in 1 of 7 patients with STEMI in the National Cardiovascular Registry, and are associated with a 6-fold increase in mortality (62). When delays are expected and primary PCI cannot be performed within 120 min of first medical contact, fibrinolytic therapy is recommended (6–8). The optimal method of reperfusion when the delays are shorter (e.g., 60 to 120 min) is less clear.

Two complications, recurrent infarction and major bleeding, are risk factors for subsequent mortality after primary PCI in patients with STEMI. In an analysis of 2,002 patients, Kikkert et al. (63) found that this excess risk persisted beyond 1 year in the case of recurrent MI. However, in the case of bleeding, excess risk returned to normal levels by 1 month. This observation is consistent with results (for bleeding) observed in TRITON–TIMI 38. Thus, although severe bleeding in patients with ACS undergoing PCI certainly adds to early risk, if the bleeding episode can be managed, it does not cause irreversible damage, and the risk declines. However, recurrent infarction causes irreversible damage to the myocardium and results in persistent elevations of risk.

Although early primary PCI with intracoronary stent implantation remains the gold standard for the treatment of patients with STEMI, 2 new reports compared outcomes in patients receiving BMS and DES. In an analysis of 28 randomized trials including 14,470 patients with STEMI who were followed for a total of 34,068 patient-years, Bangalore et al. (64) reported that, compared with BMS, sirolimus-eluting stents, paclitaxel-eluting stents, and everolimus-eluting stents were associated with significantly reduced need for vessel revascularization, without increasing the risk for stent thrombosis. Palmerini et al. (65) reported that in an analysis of 12,453 patients with STEMI treated with stents, the everolimus-eluting stent (a second-generation DES) showed the most favorable safety and efficacy profile.

Similarly, in the EXAMINATION trial of 1,498 patients with STEMI, everolimus-eluting stents and BMS had
similar rates of the primary composite of death, infarction, and any revascularization at 1 year; however, the rates of repeat target lesion (2.1% vs. 5.0%, p = 0.003) and vessel (3.7% vs. 6.8%, p = 0.008) revascularization were significantly lower in the everolimus-eluting stent group (66). In the XAMI trial in 625 patients with STEMI randomized to everolimus-eluting stents versus sirolimus-eluting stents (first-generation DES), the former significantly reduced major CV events (4.0% vs. 7.7%, p = 0.048) compared with sirolimus-eluting stents (67). Meanwhile in the COMFORTABLE AMI trial, biolimus-eluting stents with a biodegradable polymer reduced the primary endpoint of major adverse cardiac events at 1 year compared with BMS (4.3% vs. 8.7%, p = 0.004) (68). In patients who are not candidates for prolonged courses of DAPT (which is necessary with DES to prevent late stent thrombosis), BMS are preferred; however, most other patients would appear to benefit from newer generation DES.

Results with several adjunctive therapies during primary PCI were reported in the past year. A retrospective analysis of 2,567 consecutive patients with STEMI undergoing primary PCI at a single center in the United Kingdom showed that thrombus aspiration reduced both in-hospital and longer term (mean 10 months) adjusted mortality rates (69). However, the lack of randomization and the absence of large-scale outcome trials comparing thrombectomy with glycoprotein IIb/IIIa inhibition make it difficult to know which strategy is preferred. A meta-analysis of 18 trials including 3,936 patients comparing aspiration thrombectomy with conventional primary PCI demonstrated significant reduction in major adverse cardiac events (risk ratio: 0.76) and all-cause mortality (risk ratio: 0.71) with aspiration thrombectomy (70). However, no differences were found in major adverse cardiac events, mortality, or other individual ischemic events between mechanical thrombectomy and conventional primary PCI in a meta-analysis of 7 trials including 1,598 patients (70). Last, a randomized comparison of manual thrombus aspiration with rheolytic thrombectomy (using high-velocity saline jets in the distal catheter tip) showed that neither technique completed removed the thrombus; no difference in residual thrombus between the groups was observed using optical coherence tomography (71). Both the ACCF and AHA (6) and the European Society of Cardiology (7) STEMI guidelines state that manual aspiration thrombectomy is reasonable for patients undergoing primary PCI (Class IIa, Level of Evidence: B).

Although early myocardial reperfusion is a cornerstone of therapy for STEMI, reperfusion injury is a common adverse effect, and therefore this treatment has been likened to a 2-edged sword (72). Prevention of reperfusion injury in AMI remains a major unmet need. New data suggest that intracoronary microparticles (derived from platelets and from endothelial cells) are correlated with ongoing thrombosis and microvascular dysfunction leading to microvascular obstruction (73). Infusion of exenatide, a glucagon-like peptide-1 analogue, beginning 15 min before primary PCI significantly increased myocardial salvage and reduced infarct size as assessed by magnetic resonance imaging compared with placebo in 172 patients with STEMI and TIMI flow grades of 0 or 1 (74). Intracoronary adenosine was shown to improve ST-segment resolution and angiographic microvascular obstruction in a placebo-controlled 3-arm trial of 240 patients with STEMI treated with PCI and thrombus aspiration (75). In a randomized trial in patients with STEMI undergoing primary PCI, both intracoronary diltiazem and verapamil were more effective than intracoronary nitroglycerin in preventing the no-reflow phenomenon (a manifestation of reperfusion injury), as assessed by the corrected TIMI frame count and by the degree of ST-segment resolution after the intervention (76). Ischemic post-conditioning (i.e., brief repeated periods of ischemia induced by multiple low-pressure coronary artery balloon inflations shortly after reperfusion) reduced infarct size and myocardial edema compared with control in a pilot trial of 50 patients with STEMI undergoing direct stent implantation (77). In 544 patients with NSTEMI undergoing PCI randomized to 1 of 2 doses of the P-selectin antagonist inclacumab versus placebo, the higher dose (20 mg/kg) of inclacumab reduced myocardial damage as assessed by release of cardiac biomarkers (78). The EMBRACE-STEMI trial is comparing Bendavia (Stech Peptides, Newton Centre, Massachusetts), an intravenous mitochondrial targeting peptide, with placebo in 300 patients with anterior STEMI undergoing primary PCI to assess whether limiting reperfusion injury with this agent can reduce infarct size (79). Larger studies are needed with such interventions to determine whether these early benefits result in longer term improvement in left ventricular function and reductions in clinical events.

A meta-analysis of 6 randomized trials including 1,054 patients with cardiogenic shock after MI concluded that intra-aortic balloon counterpulsation did not reduce mortality, heart failure, or reinfarction (80). These findings were subsequently confirmed in the IABP-SHOCK II trial, a randomized, prospective, open-label study of 606 patients with cardiogenic shock complicating AMI, which showed no difference in 30-day mortality or other secondary endpoints (81). In the absence of more positive data in the future, we anticipate that the next update of the STEMI guidelines will downgrade the use of balloon counterpulsation from class IIa to IIb in such patients.

New data continue to support the use of radial arterial access in patients with ACS. In an analysis of 294,769 patients with STEMI undergoing PCI in a U.S. database, procedural success was similar, median door-to-balloon time was only 4 min longer, and the adjusted odds of bleeding were reduced significantly by 38% with a radial compared with a femoral approach (82). In the United States, radial access accounted for 1 in 6 PCIs in 2012 (83) and is used more frequently in Western Europe.
Even more favorable results were observed in the RIFLE-STEACS trial of 1,001 patients with STEMI undergoing primary or rescue PCI. Patients randomized to radial access had a significantly lower rate of the primary net adverse composite endpoint of cardiac death, stroke, myocardial infarction, target lesion revascularization, and bleeding (13.6% vs. 21.0%), with significant reductions in mortality, bleeding, and hospital stay (5 vs. 6 days) (84). A similar significant reduction in mortality was observed with radial versus femoral artery access in the subgroup of patients with STEMI in the RIVAL trial (1.3% vs. 3.2%), whereas no similar reduction was observed among patients with non–ST-segment elevation ACS in RIVAL (1.3% vs. 0.8%) (85). Although radial access was used in only 6.4% of patients undergoing PCI for STEMI in the national U.S. registry in 2011 (82), we expect this number to climb rapidly as operators become more familiar with this approach.

In a registry of 46,128 patients with STEMI undergoing primary PCI in the United Kingdom, after adjustment for baseline variables, radial access (compared with femoral access) was associated with a significantly lower mortality, major bleeding, and site complications (86). In a registry of patients undergoing PCI for ACS or chronic coronary artery disease, hospital costs using radial access were, on average, $830 lower than for femoral access, because of a slightly reduced length of hospital stay (87).

Lipids
A recent observational registry in 24 U.S. hospitals showed that 33% of patients had low-density lipoprotein cholesterol levels higher than 100 mg/dl 6 months after AMI (i.e., they did not meet the standard goal of <100 mg/dl), with fewer than one-third achieving levels <70 mg/dl (the more stringent optional goal) (88). Although no single factor is responsible for the low rate of attainment of the goal level of low-density lipoprotein cholesterol in high-risk patients, underdosing (89) and interruption (90) of statin therapy are frequent issues. In a propensity score–matched analysis in a cohort of 17,080 patients >65 years of age with MIs hospitalized in Ontario, Canada, high-intensity statin use significantly reduced the rate of repeat hospitalizations for ACS without increasing the rate of new diabetes (89).

Quality of care. An analysis of 4 nationwide registries spanning 1995 through 2010 described 4 trends that were responsible for a temporal reduction in mortality in patients with STEMI in France: 1) progressively more favorable patient baseline characteristics over time, including declines in age (from 66.2 to 63.3 years) and frequency of prior CV events (from 26% to 17%); 2) a decrease in time from symptom onset to first medical contact (from 240 to 175 min), in part related to greater use of mobile intensive care units; 3) an increase in the use of reperfusion therapy (from 49% to 75%), largely primary PCI; and 4) more frequent use of guideline–recommended therapies (e.g., statins [from 17% to 22%], angiotensin–converting enzyme inhibitors or angiotensin receptor blockers [from 19% to 28%]) before presentation (91).

Although adherence to guideline-based therapies during hospitalization for ACS continues to increase over time, there is still room for improvement, particularly among patients with NSTEMI, who are less likely than those with STEMI to receive proven therapies at admission and at discharge (92). One of the most successful tools to improve guideline-based performance measures is the use of computer-based physician order entry supplemented by a decision support system. Use of such a computerized system resulted in a higher rate of “perfect care,” defined as achievement of all 9 performance measures (Table 5) recommended by the AHA and the American College of Cardiology (93), compared with a standard paper order set (89% vs. 61%, p < 0.001) in an analysis of 1,321 patients with ACS admitted to a single CV center in New Orleans (94). Referral to outpatient cardiac rehabilitation is the recommendation that is least frequently adhered to among the 9 performance measures, despite evidence that completion of cardiac rehabilitation is associated with adjusted reductions in the risks for death of 41% and cardiac rehospitalization of 32% (95). Another argument for rehabilitation is that a slow gait speed is now recognized as a measure of frailty, and among patients with STEMI, it was independently associated with a 41% increase in the hazard of a CV event (CV death, MI, or ischemic stroke) for each decline of 0.1 m/s in gait speed (96). One approach that appears to be promising to improve attendance at cardiac rehabilitation is to schedule an orientation appointment within 10 days of discharge, rather than the standard approach (mean 35 days) (97). This simple, cost-neutral intervention improved attendance to 77% (an absolute increase of 18% over the standard), although larger studies are needed to determine whether this will translate into a clinical benefit.

Additional strategies are also needed to improve long-term adherence with treatment in the year after ACS. A randomized controlled trial is comparing a 4-step intervention (consisting of a pharmacist–led medication reconciliation and tailoring, patient education, closer collaboration between
pharmacists and treating physicians, and a voice messaging system) with usual care to determine whether the intervention can improve medication adherence and reduce healthcare costs (98).

Reprint requests and correspondence: Dr. Eugene Braunwald, Brigham and Women’s Hospital, Department of Medicine, TIMI Study Group, 350 Longwood Avenue, Boston, Massachusetts 02115. E-mail: ebraunwald@partners.org.

REFERENCES


---

Key Words: biomarkers • coronary stent(s) • myocardial infarction • plaque rupture • platelets • thrombosis • troponin.