Antithrombotic therapy is an essential part of the management of the full spectrum of acute coronary syndromes (ACS). Both antiplatelets and anticoagulants seem to be necessary in the management of ACS (Figures 1 and 2), although the exact proportion of antithrombotic effect that each drug and class should ideally provide remains a matter of ongoing study. As a general principle, more potent antithrombotic effect is associated with a decreased risk of ischemic events, particularly among patients who are appropriately risk-stratified. However, there is a tipping point beyond which more potent antithrombotic effect leads to major bleeding complications that diminish or exceed the benefit on ischemic end points. Finding the so-called sweet spot of antithrombotic therapy remains a major challenge. Risk stratification remains problematic because the most powerful predictors for ischemic complications are essentially the same as for bleeding risk. The American College of Cardiology/American Heart Association guidelines provide a useful framework for thinking about antithrombotic choices in ACS (Tables 1 and 2).

**Abstract:** The past 2 decades have witnessed the introduction and demise of several different antithrombotic medications for acute coronary syndromes. Part of the assessment of these compounds has been their effect on thrombotic events relative to the degree of increase in bleeding events. This review will outline the data supporting various antiplatelet and anticoagulant therapies and their combinations in patients with acute coronary syndromes and related disorders in both the acute and chronic phases of therapy. (Circ Res. 2014;114:1929-1943.)

**Key Words:** acute coronary syndrome ■ hemorrhage ■ myocardial infarction

Antithrombotic therapy is an essential part of the management of the full spectrum of acute coronary syndromes (ACS). Both antiplatelets and anticoagulants seem to be necessary in the management of ACS (Figures 1 and 2), although the exact proportion of antithrombotic effect that each drug and class should ideally provide remains a matter of ongoing study. As a general principle, more potent antithrombotic effect is associated with a decreased risk of ischemic events, particularly among patients who are appropriately risk-stratified. However, there is a tipping point beyond which more potent antithrombotic effect leads to major bleeding complications that diminish or exceed the benefit on ischemic end points. Finding the so-called sweet spot of antithrombotic therapy remains a major challenge. Risk stratification remains problematic because the most powerful predictors for ischemic complications are essentially the same as for bleeding risk. The American College of Cardiology/American Heart Association guidelines provide a useful framework for thinking about antithrombotic choices in ACS (Tables 1 and 2).

**Oral Antiplatelet Agents**

**Aspirin**

Randomized trials have consistently demonstrated a substantial reduction (40–50%) in the risk of death or myocardial infarction (MI) among patients with ACS who were treated with aspirin. The beneficial effects of aspirin seem present at a dose of 75 mg daily, with no additional benefit provided by higher doses. Bleeding events are increased by aspirin and seem to be further elevated with doses >100 mg. During long-term use, the rate of hemorrhagic stroke is slightly increased with aspirin use, although is offset by a greater decrease in MI and ischemic events.
stroke. Bleeding events with aspirin are more commonly of gastric origin and occur at a frequency of ≈2% per year.

The Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events—Organization to Assess Strategies in Ischemic Syndromes (CURRENT-OASIS 7) trial is the only large-scale ACS randomized study to compare outcomes with lower-dose (75–100 mg daily) versus higher-dose (300–325 mg daily) aspirin. In a 2-by-2 factorial design (lower-dose versus higher-dose clopidogrel was also tested), 25,086 patients with ACS received lower-dose versus higher-dose aspirin, and there was no difference in the composite of death, MI, or stroke at 30 days (4.4% versus 4.2%, respectively). There was also no difference in overall bleeding events (2.3% for both aspirin doses) with this short duration of follow-up, although an increased rate of gastrointestinal bleeds in the higher-dose group (0.2% versus 0.4%; \( P=0.04 \)) was observed.

Much had been written about aspirin resistance in the previous decade. The most recent research suggests that biochemical aspirin resistance is rare in patients who are actually taking and absorbing aspirin, and routine testing is not indicated.

**Clopidogrel Monotherapy**

The Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial tackled the question of whether it was possible to have a better antiplatelet than aspirin for secondary prevention. A total of 19,185 patients with previous MI, ischemic stroke, or symptomatic peripheral artery disease (PAD) were randomized to clopidogrel (75 mg per day) or aspirin (325 mg per day). Clopidogrel monotherapy emerged as the superior antiplatelet, although the 8.7% relative risk reduction (\( P=0.04 \)) was modest.

A subsequent analysis of the CAPRIE trial examined rehospitalization and found that clopidogrel reduced the rate of ischemic rehospitalizations compared with aspirin. Interestingly, there was also a reduction in hospitalization for gastrointestinal bleeding with clopidogrel versus aspirin. Whether this difference would have been observed had lower aspirin dosing been used is unknown.

Subgroup analyses of the CAPRIE trial showed that enrolled patients at the higher end of the risk spectrum benefited the most. For example, patients with previous ischemic events (before their qualifying event), with diabetes mellitus, or with a history of previous cardiac surgery had larger reductions in ischemic events than seen in the overall trial.

**Dual Antiplatelet Therapy: Clopidogrel Plus Aspirin**

The efficacy and safety of clopidogrel added to aspirin among patients with non-ST-elevation (NSTEMI)-ACS was established in the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) trial. Among 12,562 patients, the combination of clopidogrel and aspirin lowered the composite of death, MI, or stroke by 21% at 30 days compared with aspirin alone (3.9% versus 4.8%; \( P=0.007 \)), although it caused a significant increase in major bleeding events (3.7% versus 2.7%, respectively; \( P=0.001 \)). The early benefit was maintained throughout the 12-month follow-up. An even greater risk reduction (30%) was seen in the 2658-patient angioplasty subgroup, PCI-CURE, where death, MI, or urgent target vessel revascularization at 30 days occurred in 4.5% of those receiving dual antiplatelet therapy (DAPT) versus 6.4% among those receiving aspirin alone. Bleeding rates were similar between the treatment groups at 30 days, although more minor bleeding events occurred in the DAPT group at an average follow-up of 8 months. A nonrandomized analysis of aspirin dose from the CURE trial found that bleeding was less likely to occur with lower doses of aspirin.

In patients with ST-elevation (STE)-ACS and receiving fibrinolytic therapy, the Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)-Thrombolysis in Myocardial Infarction (TIMI) 28 trial randomized 3491 patients to clopidogrel plus aspirin or aspirin alone. The primary end point, an occluded infarct-related artery at cardiac catheterization or death or MI before angiography, was reduced by 36% (21.7% versus 15.0%; \( P<0.001 \)) among those receiving DAPT. At 30 days, the rates of major and minor bleeding were similar between the 2 groups. CLARITY also had a planned subgroup analysis for the 1863 patients who underwent percutaneous coronary intervention (PCI). Among the PCI-CLARITY patients who received DAPT at enrollment, the 30-day composite of cardiovascular death, MI, or stroke was reduced by 46% (6.2% versus 3.6%; \( P=0.008 \)). There was no difference in major or minor bleeding between the 2 groups.

The Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) study assessed whether the addition of clopidogrel to aspirin would be beneficial among STE-ACS patients who were not undergoing PCI. Among 45,852 patients with STE-ACS in China, the simple addition of daily clopidogrel (without a loading dose) to aspirin resulted in a 9% reduction in death in recurrent MI, or stroke at 28 days (9.2% versus 10.1%; \( P=0.002 \)). No differences in the rates of intracerebral or major bleeding were observed between the 2 groups with approximately half of patients receiving fibrinolytic therapy. Two separate studies addressed questions concerning the timing and duration of DAPT, although not exclusively among patients with ACS. The Clopidogrel for the Reduction of Events during Observation (CREDO) study randomized patients to a 300-mg loading dose of clopidogrel or placebo.
before elective PCI.22 All patients received aspirin and a 75-mg daily dose of clopidogrel. There was a nonsignificant 19% risk reduction in the primary composite end point of death, MI, or stroke at 28 days with the loading dose, and a 39% reduction if clopidogrel was given ≥6 hours before PCI ($P=0.05$).

After the first month, those randomized to the loading dose of clopidogrel remained on a daily maintenance dose for 1 year, whereas the group not receiving a loading dose received daily placebo. At 1 year, there was a 27% relative reduction in the composite of death, MI, or stroke in the DAPT group versus the aspirin-alone group (8.5% and 11.5%; $P=0.02$). There was a trend toward increased major bleeding in the combination therapy group (8.8% versus 6.7%; $P=0.07$).

The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial sought to determine whether prolonged DAPT may be beneficial outside of patients with recent ACS or stenting.23 A total of 15,603 patients were randomized to aspirin plus clopidogrel or aspirin plus placebo and followed for a median of 28 months. There was no difference in the primary end point of cardiovascular death, MI, or stroke, although the secondary end point, which included hospitalizations for ischemia, was significantly reduced. Of note, CHARISMA enrolled 2 major strata of patients: those with secondary prevention indications for antiplatelet therapy (12,153 patients with coronary artery disease, cerebrovascular disease, or PAD) and those who were primary prevention patients. The results were divergent in these 2 subgroups, such that there was a statistically significant benefit in the secondary prevention patients, with a positive subgroup interaction term as well. Of course, one can debate the strength of a positive subgroup in an overall neutral trial, although that subgroup was large. Nevertheless, the results in the large, prespecified secondary prevention subgroup were in line with previous trials of aspirin plus clopidogrel.

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**Figure 1.** Platelet activation and aggregation in response to endothelial injury are an important part of the pathophysiology of acute coronary syndromes. Different platelet receptors are activated by various agonists and serve as the target of various antiplatelet therapies, which have been evaluated in large randomized clinical trials. GP indicates glycoprotein; PAR, protease activated receptor; and TxA$_2$, thromboxane A$_2$. Adapted from Meadows and Bhatt with permission of the publisher. Copyright 2007, American Heart Association. (Illustration credit: Ben Smith.)

**Figure 2.** Site of action of various oral anticoagulants. Activated coagulation factors are in orange squares. Vitamin K antagonists impair the synthesis of coagulation factors. Drugs that are reported in green are used clinically for various conditions such as atrial fibrillation and venous thromboembolic disease and, in some cases, have been studied in acute coronary syndromes; those reported in blue have not shown their efficacy and safety in acute coronary syndromes; those reported in red have been withdrawn from clinical use. GP indicates glycoprotein. (Illustration credit: Ben Smith.)
Table 1. Class I and IIa American College of Cardiology/American Heart Association Guideline Recommendations for Antiplatelet and Anticoagulant Therapy in Patients With Unstable Angina or Non-ST Segment Elevation Myocardial Infarction

<table>
<thead>
<tr>
<th>Guideline Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Prasugrel (in PCI-treated patients)</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Patients at medium or high risk in whom an initial invasive strategy is selected should receive, in addition to aspirin, a second antiplatelet agent on presentation</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Before PCI, an intravenous GPIIb/IIIa inhibitor can be added on presentation</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Before PCI, the second antiplatelet therapy to be added to aspirin on presentation can be clopidogrel or ticagrelor, or if an intravenous GPIIb/IIIa inhibitor, specifically eptifibatide or tirofiban</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>At PCI, clopidogrel if not started before PCI or an intravenous GPIIb/IIIa inhibitor</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>At PCI, prasugrel or ticagrelor</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>With an initial noninvasive strategy, add a loading dose followed by daily maintenance dose of clopidogrel or ticagrelor to aspirin and anticoagulation as soon as possible after admission and up to 12 mo</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>With an initial conservative strategy, if recurrent symptoms/ischemia, heart failure, or serious arrhythmias occur, then perform diagnostic angiography and add 1 of the following:</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Eptifibatide or tirofiban: on top of aspirin and anticoagulant therapy before diagnostic angiography</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Clopidogrel or ticagrelor (loading dose and maintenance dose): on top of aspirin and anticoagulant therapy before diagnostic angiography</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>A loading dose of 1 of the following should be used if PCI is planned:</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Clopidogrel 600 mg as early as possible before or at PCI</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Prasugrel 60 mg promptly and no later than 1 h after PCI once coronary anatomy defined and a decision to proceed with PCI</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Ticagrelor 180 mg as early as possible before or at the time of PCI</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>In patients undergoing PCI, give clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg twice daily for at least 12 mo</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>With the risk of bleeding outweighs the benefits, consider earlier discontinuation</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>With an initial conservative strategy and recurrent ischemic discomfort on aspirin, clopidogrel, or ticagrelor, and anticoagulation, it is reasonable to add a GPIIb/IIIa inhibitor before diagnostic angiography</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>With an initial invasive strategy, it is reasonable to omit an intravenous GPIIb/IIIa inhibitor if bivalirudin is the anticoagulant and at least 300 mg of clopidogrel was administered at least 6 h earlier than planned catheterization or PCI</td>
<td>I</td>
<td>B</td>
</tr>
</tbody>
</table>

COR indicates Class of Recommendation; GP, glycoprotein; LOE, Level of Evidence; and PCI, percutaneous coronary intervention.

Bolstering the results of the secondary prevention subgroup was an even more targeted subgroup analysis, albeit a post hoc analysis.24 A CAPRIE-like high-risk secondary prevention subgroup of 9478 patients with previous MI, previous ischemic stroke, or symptomatic PAD was defined. In this cohort, the primary end point was significantly reduced from 8.8% to 7.3% (P=0.01), with a consistent benefit observed in each of those 3 atherothrombotic subgroups. The patients with previous MI had their event on average 2 years before randomization, so it was a really stable patient population being studied.

Interestingly, in an instantaneous hazard analysis, patients who tolerated DAPT with clopidogrel and aspirin for 9 to 12 months without bleeding seemed to have no greater risk for severe bleeding or transfusions compared with patients on aspirin alone.24,25 It is important to realize that this type of analysis excludes patients who either self-discontinued therapy or whose doctor discontinued therapy because of bleeding, including potentially minor degrees of bleeding. Nevertheless, this analysis provides some reassurance that if a patient passes a bleeding stress test with no bleeding while taking aspirin plus clopidogrel for several months, the subsequent risk of a catastrophic bleed is low (although not zero, of course). These results may be relevant in those patients in whom the physician elects to continue aspirin plus clopidogrel beyond the guideline recommendations. However, these results should not be extrapolated to more potent antiplatelet agents in the absence of long-term data assessing bleeding risk in a stable patient population.

The genetic analysis from CHARISMA did not show any impact of reduced function alleles on potential benefits of clopidogrel plus aspirin in this population.26 If the polymorphisms had been really important, one might have expected patients with gain of function to have a benefit, but this was not the case. Even in the large subgroup of patients from CHARISMA who were enrolled in the secondary prevention category or in the risk-enriched cohort with previous ischemic events, there was no evidence that the genotype was associated with clopidogrel efficacy. There was also no association with severe or moderate bleeding. More minor degrees of bleeding did seem to be associated with CYP2C19 polymorphisms. Overall, though, the CHARISMA genetics study found no real value to clopidogrel genotyping in patients with stable disease, corroborating the similarly negative findings noted in the CURE genetic analysis.27

There are many sources of clopidogrel variability in addition to genetics, and any one factor in isolation may have minimal clinical impact.28 Besides genetics, another source of clopidogrel variability has to do with purported drug–drug interactions. Pharmacokinetic and pharmacodynamic data suggested that proton pump inhibitors (PPIs) attenuate the antiplatelet effect of clopidogrel.29 Some observational analyses supported this, although not ones that were done with more careful statistical techniques.30 COGENT did not find evidence for a significant clinical interaction.31 Importantly, COGENT did find that PPIs given prophylactically do reduce the risk of gastrointestinal bleeding with DAPT, even in patients who are not at particularly high gastrointestinal bleeding risk.32 Although the current guidelines do not recommend routine use of PPIs with DAPT in patients at low gastrointestinal bleeding risk, trials such as COMPASS (see below) are ongoing to test the value of routine PPI use in patients on potent antithrombotic therapy.33,34
have criticized the statistical validity of postrandomization subgroup analysis, although the finding that more potent antiplatelet therapy reduces MI and stent thrombosis in patients with ACS undergoing PCI has been consistent (as reviewed below). However, a more practical limitation to the application of the data is that it is impossible to know which patients in the emergency department will go on to PCI, as opposed to medical therapy or coronary artery bypass grafting (CABG). No risk score has yet been developed that is sufficiently accurate for that type of triaging. Thus, although the higher clopidogrel dosing regimen is useful in patients who ultimately undergo PCI, it is not useful in those who receive medical therapy and may even be harmful in those who undergo CABG, because of increased risk of surgical bleeding.

Prasugrel, also a thienopyridine but more potent than clopidogrel, was studied in patients with ACS undergoing PCI in the Trial to Assess Improvement in Therapeutic Outcomes By Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38). A total of 13608 patients were randomized to either clopidogrel or prasugrel (60 mg loading dose, 10 mg daily maintenance dose). There was a significant reduction in cardiovascular death, nonfatal MI, or nonfatal stroke in favor of prasugrel (from 12.1% to 9.9%; HR, 0.81; P<0.001). There was also a small, but statistically significant, excess in fatal bleeding. The bleeding risks of prasugrel were particularly notable in older or overweight patients and in those with previous cerebrovascular disease, although the remainder of the population had a favorable net clinical benefit.

The TRITON-TIMI 38 genetics analyses did not find that CYP2C19 polymorphisms had any significant effect on prasugrel metabolism or clinical outcomes, nor did it modify the benefit of prasugrel versus clopidogrel. Thus, in choosing between clopidogrel and prasugrel, the knowledge of genotype has not been demonstrated to be clinically useful.

The Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) trial randomized patients with ACS who were initially medically managed with prasugrel or clopidogrel. The trial was meant to complement the TRITON-TIMI 38 trial, which had focused on ACS managed by PCI. The event rate in TRILOGY was lower in the prasugrel arm, although this difference was not statistically significant. The patients enrolled in TRILOGY were high risk, as evidenced by their high event rate, but potentially some of this risk was because of their degree of comorbidities and not just their ACS presentation per se.

A subgroup analysis from the TRILOGY trial compared patients who underwent prerandomization angiography versus those who did not. In the subgroup that had undergone angiography, prasugrel was superior to clopidogrel. Potentially, the patients with ACS with confirmed angiographic coronary artery disease (CAD) were the most likely to have had plaque rupture and, therefore, were the most likely to derive benefit from an intensification of their antiplatelet regimen. Because the overall TRILOGY trial was neutral and prasugrel is currently more expensive than generic clopidogrel, this subgroup analysis should not be used to justify prasugrel use in medical management of ACS. However, this analysis is consistent with

### Table 2. Class I and IIa American College of Cardiology/American Heart Association Guideline Recommendations for Antiplatelet and Anticoagulant Therapy in Patients Receiving Primary PCI for ST-Elevation Myocardial Infarction

<table>
<thead>
<tr>
<th>Guideline Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin 162 to 325 mg load before procedure</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Aspirin 81 to 325 mg daily maintenance dose</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Clopidogrel load: 600 mg as early as possible or at time of PCI</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Prasugrel load: 60 mg as early as possible or at time of PCI</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Ticagrelor load: 180 mg as early as possible or at time of PCI</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Clopidogrel after DES or BMS: 75 mg daily for 1 y</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Prasugrel after DES or BMS: 10 mg daily for 1 y</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Ticagrelor after DES or BMS: 90 mg twice a day for 1 y (recommended maintenance dose of aspirin with ticagrelor is 81 mg daily)</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>UFH with planned GP IIb/IIIa receptor antagonist: 50 to 70 U/kg intravenous bolus to achieve therapeutic ACT (200–250 s)</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>UFH with no planned GP IIb/IIIa receptor antagonist: 70 to 100 U/kg bolus to achieve therapeutic ACT (250–300 s with the HemoTec device or 300–350 s with the Hemochron device)</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Bivalirudin: 0.75 mg/kg intravenous bolus, then 1.75 mg/kg per h infusion with or without prior treatment with UFH; an additional bolus of 0.3 mg/kg can be given if needed (if estimated CrCl &lt;30 mL/min, reduce infusion to 1 mg/kg per h)</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Aspirin 81 mg daily: preferred maintenance dose IIa</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>Abciximab 0.25 mg/kg intravenous bolus, then 0.125 μg/kg per min (maximum 10 μg/min) IIa</td>
<td>A</td>
<td></td>
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<tr>
<td>Tirofiban (high-bolus dose): 25 μg/kg intravenous bolus, then 0.15 μg/kg per min (if CrCl &lt;30 mL/min, reduce infusion by 50%) IIa</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>Eptifibatide (double bolus): 180 μg/kg intravenous bolus, then 2 μg/kg per min; a second 180 μg/kg bolus is administered 10 min after the first bolus (if CrCl &lt;50 mL/min, reduce infusion by 50%; avoid in patients on heparin) IIa</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>Bivalirudin preferred over UFH with GP IIb/IIIa receptor antagonist in patients at high bleeding risk IIa</td>
<td>B</td>
<td></td>
</tr>
</tbody>
</table>

ACT indicates activated clotting time; BMS, bare-metal stent; COR, Class of Recommendation; CrCl, creatinine clearance; DES, drug-eluting stent; GP, glycoprotein; LOE, Level of Evidence; PCI, percutaneous coronary intervention; and UFH, unfractionated heparin.

### Moving Beyond Standard Dose Clopidogrel Plus Aspirin

Multiple reports of clopidogrel response variability demonstrated an association with worse clinical outcomes. This led to an evaluation of more potent dual antiplatelet regimens. The second factorial randomization in the CURRENT-OASIS 7 trial compared standard dosing of clopidogrel (300 mg loading dose, followed by 75 mg daily) with double dosing for the first week. The overall trial of 25086 patients with ACS did not find any significant benefit of the higher dose, but in the large subgroup of >17000 patients who underwent PCI after randomization, the rate of cardiovascular death, MI, or stroke was significantly lower with the higher clopidogrel dosing regimen (3.9% versus 4.5%; adjusted hazard ratio [HR], 0.86; P=0.039). It is unknown whether that benefit was predominantly due to the higher loading dose or whether the increased dose that entire first week is also necessary. Some
the theme that appropriate patients with ACS do benefit from more intense, long-term antiplatelet therapy.

Ticagrelor is the first nonthienopyridine ADP blocker approved for use in patients presenting with both STE-ACS and NSTE-ACS. It is a reversible, direct-acting P2Y12 inhibitor that has a more rapid onset of action compared with clopidogrel, while also allowing a higher level of platelet inhibition and more rapid reversal compared with clopidogrel as well.40 The Platelet Inhibition and Patient Outcomes (PLATO) study was a large, global, randomized clinical trial comparing ticagrelor (180 mg loading dose, followed by 90 mg twice daily) and clopidogrel (300–600 mg loading dose at investigator discretion, followed by 75 mg daily) for the reduction of major ischemic events in 18,624 patients presenting with either STE-ACS or NSTE-ACS. With a median duration of follow-up of ≈9 months, ticagrelor use was associated with a 16% reduction in the first occurrence of vascular death, MI, or stroke compared with clopidogrel (9.8% versus 11.7%; HR 0.84; P<0.001). PLATO major bleeding (the primary safety end point) was not different between the study arms. There was more non-CABG–related major bleeding observed in the ticagrelor group compared with clopidogrel (4.5% versus 3.8%; HR, 1.19; P=0.03), whereas CABG-related major bleeding was similar between the treatments.41

One hypothesis as to why there was only a modest increased risk of bleeding associated with the use of the more potent platelet inhibitor ticagrelor versus clopidogrel has to do with its reversible nature. This suggests that although there is typically an increased risk of bleeding when using more potent anti-thrombotics, perhaps this increase can be blunted with the use of agents with more rapidly reversible mechanisms of action. Data on this balance between efficacy and bleeding are consistent across multiple PLATO subgroups, including the group of patients with the intent to be managed invasively as declared at the time of randomization.42 Interestingly, in patients undergoing CABG after randomization into PLATO, there was no increased risk of bleeding among ticagrelor-treated patients compared with those randomized to clopidogrel, despite having a shorter time of drug discontinuation before the surgical procedure.43 In the PLATO trial, there was an observation that patients enrolled in the United States had outcomes favoring clopidogrel and qualitatively different from the overall results of the trial. Extensive analyses suggested that a different dose of aspirin used in the United States compared with the rest of the world (325 mg versus ≤100 mg) explained much of this difference.44 This is clearly a hypothesis but an intriguing one, especially if one considers the risk–benefit balance when using combination anti-thrombotic therapies, because higher doses of aspirin given with ticagrelor are associated with increased bleeding risks with the possibility of reduced efficacy as well.

Ticagrelor is not a thienopyridine and not a prodrug. It does not require metabolism via the CYP2C19 pathway to have biological activity as an antiplatelet agent; consequently, the challenges of having marked variability in drug antiplatelet effects based on CYP2C19 genotypes are avoided with ticagrelor.45

The Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared with Placebo on a Background of Aspirin (PEGASUS-TIMI 54) trial is randomizing >20,000 patients with previous MI to 1 of 2 doses of ticagrelor or to placebo, in addition to aspirin.46 The trial is designed to examine those patients who seemed to derive the largest benefit from prolonged DAPT in the CHARISMA trial. One dose of ticagrelor is the approved ACS dose (90 mg twice daily), and the other dose (60 mg twice daily) is one that provides less antiplatelet effect than the higher dose of ticagrelor but more effect than would be expected with standard clopidogrel dosing. The evaluation of 2 doses may allow optimization of the net clinical benefit of ticagrelor in this stable patient population.

The optimal duration of DAPT in stented patients has been studied in several trials.47 Each of these trials has individually been underpowered for the rare outcome of stent thrombosis. Most have not enrolled high-risk patients with ACS, although some have included low-risk ACS. The results have been surprisingly consistent with no suggestion of superiority of longer durations of DAPT, in particular when second-generation drug-eluting stents are being used. Many have shown an increase in major or minor bleeding. Several trials are ongoing examining durations of DAPT longer and shorter than 1 year, and these studies should bring greater clarity as to which patient subsets might benefit from different durations of DAPT. Likely, stent type, procedural characteristics, patient characteristics, and ACS status all influence the optimal duration of DAPT, and it is unlikely that the duration should be the same for all patients. In particular, previous troponin-positive ACS seems to signal benefit from more protracted durations of DAPT, regardless of whether stenting is performed or the patient is managed noninvasively. Separately from stent-centered trials, several ongoing trials are testing the hypothesis that longer duration and more intense DAPT may further reduce ischemic events in patients with a history of previous ACS, although it will be important to examine the net clinical benefit because the risk of ischemic events does decline after ACS, although the risk of bleeding on potent anti-thrombotic therapy does not decline as steeply.

An additional challenge with DAPT has been premature cessation. Recently, it has been shown that the clinical circumstance of DAPT cessation is associated with outcome in a time-dependent manner. Physician-recommended discontinuation seems to be less problematic than disruption because of patient nonadherence or bleeding complications.

Interruption because of surgery raises the much debated issue of the need for bridging DAPT at the time of surgery. It is important to acknowledge that there are no large trials that support the value of bridging with an antiplatelet (or anticoagulant). It is intuitive that substituting an oral antiplatelet agent with an intravenous one might provide some protection against perioperative ischemic events, but the obvious concern is that perioperative bleeding rates would rise. Single-center reports of use of eptifibatide and tirofiban have been published, and bridging algorithms have been devised, but there are no meaningful outcome data.48 A small multicenter trial with the short-acting intravenous ADP receptor antagonist, cangrelor, in patients awaiting cardiac surgery demonstrated the feasibility and relative safety of this approach, although the trial was not powered to examine efficacy.49
Protease-Activated Receptor-1 Antagonists

Modulation of other platelet receptors may also be potentially important to improve clinical outcomes. The protease-activated receptor-1 antagonist, atopaxar, was studied in a series of phase II trials. LANCELOT CAD, LANCELOT ACS, and J-LANCELOT examined atopaxar at various doses. There was a trend toward liver function test abnormalities and QT interval prolongation at the highest doses. Although the drug increased bleeding, the degree of excess seemed to be at an acceptable level within the context of a phase II program. A Holter monitor substudy found that the drug reduced recurrent ischemia, thereby providing a strong signal of efficacy that would support phase III evaluation. An analysis of biomarkers from the LANCELOT program did not find any clear effect on markers of inflammation, although some preclinical data had suggested that there might be anti-inflammatory properties of protease-activated receptor-1 antagonism. Thus, any benefit of this class of agents would likely be because of the anti-thrombotic effects. Although the data from the LANCELOT program looked promising with respect to lower doses of atopaxar, at present, because of commercial considerations, there is no planned phase III program.

Vorapaxar is the only protease-activated receptor-1 antagonist to be studied extensively in large, phase III randomized clinical trials, one in patients presenting with NSTE-ACS as well as one in a CHARISMA-like population of CAD (previous MI), cerebrovascular disease (cerebrovascular attack, prior stroke), or PAD. These trials enrolled almost 40,000 patients comparing vorapaxar with placebo in addition to contemporary standards of care.

Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER), randomizing 12,944 patients with ACS without ST-segment elevation to vorapaxar versus placebo, was terminated before its full completion by an independent data safety and monitoring board (DSMB) because of the observation of an increased risk of serious bleeding, including intracranial hemorrhage, among patients treated with vorapaxar compared with placebo. This trial had sufficient events for an evaluation of efficacy when it was stopped by the DSMB. The primary outcome of the composite of cardiovascular death, MI, stroke, recurrent ischemia with revascularization, or urgent coronary revascularization occurred in 18.5% of patients treated with vorapaxar compared with 19.9% treated with placebo (HR, 0.92; P=0.07). The secondary composite of cardiovascular death, MI, or stroke occurred in 14.7% of patients treated with vorapaxar compared with 16.4% treated with placebo (HR, 0.89; P=0.02). Moderate or severe bleeding occurred in 7.2% of vorapaxar-treated patients compared with 5.2% treated with placebo (P<0.001). Intracranial hemorrhage was more commonly observed with vorapaxar compared with placebo (1.1% versus 0.2%; P<0.001). The increased risk of serious bleeding outweighed the modest finding of efficacy in the trial and was contrary to what was observed in the phase II trial of vorapaxar use during PCI.

TRA 2P-TIMI 50 (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events [TRA 2P]-TIMI 50) examined the use of vorapaxar in the subacute to chronic secondary prevention setting, enrolling >26,449 patients with CAD, cerebrovascular attack, or PAD to treatment with vorapaxar or placebo in addition to standard therapy. At the same DSMB meeting where TRACER was recommended to be prematurely terminated because of safety concerns, the DSMB recommended that treatment be stopped in the cohort of patients with previous cerebrovascular attack because of an increased risk of serious bleeding, most notably intracranial hemorrhage. At the same time, the DSMB recommended that the trial otherwise continue until its planned conclusion. The primary end point in the overall population (composite of cardiovascular death, MI, or stroke) occurred in 9.3% of vorapaxar patients compared with 10.5% among placebo-treated patients (HR, 0.87; P<0.001). Results were consistent among several subgroups. Again, in contrast to the phase II data, serious bleeding (including Global Utilization of Streptokinase and tPA for Occluded Arteries [GUSTO] severe or moderate bleeding) was more common among patients treated with vorapaxar compared with those treated with placebo on top of standard therapy, with moderate or severe bleeding in 4.2% of vorapaxar-treated patients versus 2.5% of placebo-treated patients (P<0.001). Notably, when the analyses were confined to the population of those with previous CAD (excluding those with previous cerebrovascular attack), the efficacy findings were maintained while the bleeding risk was attenuated, including the risk of intracranial hemorrhage.

How to reconcile the differences between these 2 trials is unclear because there are differences in trial design (acute inpatient versus chronic ambulatory settings), drug dosing (loading dose versus none), and patient characteristics between the studies (increased age and comorbidities in TRACER versus TRA 2P-TIMI 50). If and how to use vorapaxar in the setting of ACS will require more investigation because the current risk–benefit balance precludes the consideration of use in this clinical setting, although it seems to have utility in secondary MI prevention and in PAD. Use of vorapaxar with prasugrel or ticagrelor has not been studied and given potentially synergistic bleeding risks should likely be avoided.

Intravenous Antiplatelet Agents

Intravenous Glycoprotein IIb/IIIa Inhibition

Several early, large-scale NSTE-ACS trials tested glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors. Most did not include thienopyridines, but rather were studied in combination with aspirin and unfractionated heparin. Pooling data from 6 trials with 31,402 patients, Boersma et al reported a 9% relative reduction in 30-day death or MI (11.8% versus 10.8%; P=0.015) with GPIIb/IIIa inhibitors, although this 1% absolute decrease in ischemic events came at a cost of a 1% absolute increase in major bleeding events (2.4% versus 1.4%; P<0.001). The treatment benefit was found irrespective of many patient baseline characteristics, and the largest benefit was among those who were troponin-positive at admission and those who underwent early PCI. Most of the benefit from GPIIb/IIIa inhibitors among patients with ACS was a reduction in MI, although in a post hoc pooling of trial data, patients with diabetes mellitus were found to receive mortality benefit at 30-day follow-up.

Given the benefit of GPIIb/IIIa inhibitors among patients with ACS undergoing an early invasive strategy, the natural question emerged regarding the relative benefit of
preprocedural or upstream therapy versus procedural or in-laboratory benefit. The Early Glycoprotein IIb/IIIa Inhibition in Non-ST-Segment Elevation Acute Coronary Syndrome (EARLY-ACS) trial\(^6\) randomized 9492 patients with ACS intended to undergo PCI to receive eptifibatide early (≤12 hours before angiography) versus during the procedure. The 30-day occurrence of death or MI was not different between the early treatment and delayed treatment groups (odds ratio [OR], 0.89; \(P=0.08\)). The early treatment group did have more bleeding events and red cell transfusions. Data from EARLY-ACS, a meta-analysis of related studies, and another large-scale timing trial, Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY)\(^6\), support the selective rather than the routine use of upstream GPIIb/IIIa therapy for patients with ACS. This is because the reduction in ischemic events is modest, yet the increase in bleeding events is marked.\(^6\)

Among patients with STE-ACS, multiple placebo-controlled studies were completed testing GPIIb/IIIa inhibitors, although again without the routine use of thienopyridines. These studies demonstrated a significant reduction in 30-day ischemic events, but with less robust evidence for durable benefit at 6 months. In comparison, the Bavarian Reperfusion Alternatives Evaluation-3 (BRAVE-3) trial\(^6\) tested upstream abciximab against placebo among 800 patients after preloading with 600 mg of clopidogrel. The study failed to show a reduction in infarct size or clinical benefit with abciximab. Preprocedural (upstream) administration of abciximab was compared with in-laboratory administration (downstream) in the Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events (FINESSE) trial of 1624 patients undergoing primary PCI for STE-ACS.\(^6\) No difference in the composite ischemic end point was observed, but upstream abciximab increased the risk of bleeding in patients.\(^6\)

**Intravenous ADP Receptor Inhibition**

Limitations of currently available oral antiplatelet therapies for use in the acute care setting have led to a search for more rapidly acting, more predictable, and more readily reversible agents. Cangrelor is a novel, intravenous, direct-acting, P2Y12 receptor antagonist that blocks ADP-induced platelet activation and aggregation with a pharmacokinetic half-life of 3 to 6 minutes.\(^6\) These characteristics might overcome some of the limitations of current therapies and be an effective adjunct to treating patients in the acute setting, including those unable to take oral medications (because of shock, respiratory failure, sedation, hypotension, nausea, etc). Cangrelor has been studied (and compared with current therapy) in 3 large outcome studies in patients with a broad spectrum of clinical presentation undergoing PCI: Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition (CHAMPION) PLATFORM, CHAMPION PCI, and CHAMPION PHOENIX. The 3 trials enrolled >25,000 patients in a program to compare cangrelor with standard clopidogrel therapy as an adjunct to PCI as a way to decrease the periprocedural ischemic complications of PCI while minimizing the most serious bleeding complications of more potent antiplatelet therapy.

PLATFORM and PCI were performed as companion trials to examine the strategy of using clopidogrel (pre- or post-PCI) as a periprocedural antiplatelet agent.\(^6\) Both of these trials were terminated prematurely by an independent committee for futility regarding the primary efficacy end point (death, MI, or ischemia-driven revascularization), although being associated with no increased risk of transfusion. As expected, cangrelor provided a more rapid, sustained, and readily reversible level of platelet inhibition than did clopidogrel.\(^6\) Both the trials, on post hoc evaluation, showed some hints of efficacy, especially concerning the most objective outcomes of clinically important MI and stent thrombosis. A reassessment of the MI end point, using the evolving Universal Definition of MI, provided additional support of cangrelor’s efficacy while also recognizing that this was a hypothesis-generating finding.\(^6\)

PHOENIX was designed to validate the post hoc findings of the previous 2 trials while providing a substantial level of evidence of its own to support use of cangrelor in the peri-PCI setting.\(^6\) The trial enrolled almost 11,000 patients presenting with stable CAD (55%), NSTE-ACS (25%), and STE-ACS (20%) in a randomized comparison of cangrelor with the contemporary standard use of oral clopidogrel (pre- or post-PCI; 300 mg [26%] or 600 mg [74%]). The primary composite included stent thrombosis and the definition of MI was more rigorously defined to better allow the specific distinguishing between pre- and post-PCI MIs. At 48 hours, the primary composite of death, MI, ischemia-driven revascularization, or stent thrombosis was significantly reduced with cangrelor compared with clopidogrel (4.7% versus 5.5%; OR, 0.78; \(P=0.005\)). Both MI and stent thrombosis were significantly reduced among patients treated with cangrelor compared with clopidogrel. These efficacy findings were consistent across multiple subgroups, including region, clinical presentation, and dosing strategies of clopidogrel. The 48-hour results were preserved through 30-day follow-up. GUSTO severe or life-threatening bleeding (primary safety end point; 0.16% versus 0.11%; \(P=0.44\)) as well as GUSTO moderate bleeding were not significantly increased with cangrelor. Milder bleeding was increased in patients treated with cangrelor, although the need for blood transfusions was similar between the treatment groups.\(^7\)

A pooled analysis of the 3 trials was published using the PHOENIX MI definition for all 3 trials and reporting on the PHOENIX primary composite of death, MI, ischemia-driven revascularization, and stent thrombosis in the pooled sample.\(^7\) In this analysis of 24,910 patients undergoing PCI, cangrelor reduced the 48-hour incidence of the composite end point from 4.7% to 3.8% (OR, 0.81; \(P=0.0007\)). Stent thrombosis, MI, and Q-wave MI were all reduced with cangrelor compared with clopidogrel. The 48-hour outcomes were consistent across multiple subgroups and maintained at 30 days without degradation of the early effect. There was no increase in GUSTO severe or life-threatening bleeding nor in the need for blood transfusions associated with cangrelor, but there was an increase observed in GUSTO mild bleeding with cangrelor compared with clopidogrel (16.8% versus 13.0%; \(P<0.0001\)). These data support the notion that cangrelor reduces periprocedural ischemic complications of PCI with a modest increased risk of bleeding compared with standard strategies and doses of clopidogrel. Cangrelor has not been studied with prasugrel or ticagrelor in large outcome trials, thus it is not possible to comment what the incremental clinical benefit of
cangrelor may be if these more potent oral ADP receptor antagonists are used, although additional antiplatelet effect with cangrelor has been demonstrated.

**Oral Anticoagulant Therapy**

**The Case for Long-Term Anticoagulant Therapy in ACS**

Patients with ACS exhibit an increased basal level of activation of the coagulation system. Plaque disruption and the exposure of tissue factor–bearing cells activate the process of coagulation through a cascading pathway (Figure 2). Activation of Factor VII and then Factor X results in an initial production of small amounts of thrombin, a reaction that is then amplified by platelets that accumulate activated cofactors on their surfaces. The large amounts of thrombin generated on the platelet surface convert circulating fibrinogen to fibrin, which leads to thrombus formation and continues to activate platelets.72,73

The dependence of platelet activation and coagulation in response to plaque disruption has supported the combined use of antiplatelet and anticoagulant therapies in the acute phase of ACS. However, some observations support the existence of excessive thrombin generation and a persistent hypercoagulable state beyond the acute period.74 In addition, recurrent ischemic complications have been reported in the days after cessation of intravenous anticoagulation with heparin.75 This has suggested a potential role for long-term anticoagulation in the management of ACS.

In a first meta-analysis including 10 clinical trials with a total of 5938 patients with ACS,76 the use of the vitamin K antagonist, warfarin, in addition to aspirin was associated with a significant decrease in the rate of ischemic complications (ie, MI, ischemic stroke, or revascularization) but with a significant increase in major bleeding as compared with aspirin alone. In a second meta-analysis of 14 randomized controlled clinical trials including 25307 patients,77 it was shown that the benefit of warfarin plus aspirin on the reduction of MI or stroke was restricted to studies with an international normalized ratio target from 2.0 to 3.0 (OR, 0.73; P<0.0001). The widespread use of long-term warfarin in post-ACS patients has been challenged by the narrow therapeutic margin, the wide interpatient variability, the need for routine coagulation monitoring, and the individual risk of bleeding that can outweigh the net clinical benefit. Genetic testing does not seem to improve the safety or efficacy of warfarin.

A second line of evidence supporting a role for long-term anticoagulation in ACS came from the Efficacy and Safety of the Oral Direct Thrombin Inhibitor Ximelagatran in Patients with Recent Myocardial Damage (ESTEEM) trial.78 In this placebo-controlled, double-blinded, multicenter study, a total of 1883 patients who had had a recent ACS were randomized to either a Factor IIa (thrombin) inhibitor, ximelagatran, or placebo in addition to aspirin. There was a significant reduction of all-cause mortality, nonfatal MI, or severe recurrent ischemia with ximelagatran. Interestingly, there was no dose response in the prevention of recurrent thrombotic events suggesting that the maximal therapeutic effect was already achieved with the lowest of 4 evaluated doses. The drug was, however, unsuitable for use because of drug-induced liver injury.

**Novel Direct Factor Xa Inhibitors**

Recently, novel oral anticoagulants have become available. The Factor Xa inhibitors directly and selectively inhibit Factor X, the immediate proximate step that is required for thrombin production (Figure 2). The new drugs have a stable pharmacokinetic profile and can be administered without requiring anticoagulation monitoring. This has created a window of opportunity for the management of ACS, and 3 direct Factor Xa inhibitors (apixaban, darexaban, and rivaroxaban) have been evaluated in patients with ACS.

The Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE)79 trial investigated a range of doses of apixaban (2.5 mg twice daily, 10 mg once daily, 10 mg twice daily, and 20 mg once daily) compared with placebo in 1715 patients with a recent ACS (<7 days). The 2 higher-dose arms were discontinued because of excess bleeding. A dose-related increase in bleeding and a trend toward a reduction in ischemic events were observed in the 2 lower apixaban dose arms. It was suggested that the safety and efficacy of apixaban were more favorable in patients not receiving clopidogrel, but these data deserve cautious interpretation because of the small sample size of these subgroups.

The 10-mg daily dose was selected for further investigation in a phase III clinical trial. The Apixaban for Prevention of Acute Ischemic and Safety Events 2 (APPRAISE 2)80 trial was a double-blinded, placebo-controlled, randomized clinical trial comparing apixaban (5 mg twice daily) with placebo in addition to standard antiplatelet therapy in patients with recent (<7 days) ACS and at least 2 additional risk factors for recurrent events. A majority of patients (81%) were on DAPT with aspirin plus a P2Y12 receptor antagonist, predominantly clopidogrel. The dose of apixaban was reduced to 2.5 mg twice daily in patients with renal impairment (creatinine clearance, <40 mL/min). The study was prematurely stopped after enrolling 7392 patients because of an excess in major bleeding events without any decrease in ischemic events. TIMI major bleeding was observed in 1.3% of patients receiving apixaban and 0.5% of patients on placebo (HR, 2.59; P=0.001). The primary outcome of cardiovascular death, MI, or ischemic stroke occurred in 7.5% of patients receiving apixaban and 7.9% of patients receiving a placebo (HR, 0.95; P=0.51). The selection of higher-risk patients in this clinical trial might have played an important role in its negative results, because many clinical factors that predict recurrent ischemic events are also predictors of bleeding complications. It is possible that in high-risk patients excess bleeding would overwhelm the benefit.

DAREXABAN is another Factor Xa inhibitor that was tested in the phase II Study Evaluating Safety Tolerability and Efficacy of YM150 in Subjects with Acute Coronary Syndromes (RUBY-1) trial.81 Six different darexaban regimens were compared with a placebo on top of DAPT in 1279 patients with a recent ACS. A dose-dependent increase in bleeding events was observed with darexaban. Bleeding rates were higher in all 6 darexaban arms as compared with placebo (pooled HR, 2.27; P=0.02). On the contrary, there was no clear effect on...
ischemic complications with darexaban, and the development of darexaban in patients with ACS was abandoned.

In the phase II Anti-Xa Therapy for Lower Cardiovascular Events in Addition to Aspirin with or without Thienopyridine Therapy in Subjects with Acute Coronary Syndrome-TIMI 46 (ATLAS ACS-TIMI 46) trial, 82,83 3941 patients with recent ACS were randomized to placebo or escalating doses of rivatebraban (5–20 mg given once daily or the same total daily dose given twice daily). Interestingly, the randomization was stratified on the use of thienopyridine (mostly clopidogrel) in addition to aspirin. As with the other Factor Xa inhibitors, a dose-dependent increase in bleeding was noted, with higher rates when the drug was used in addition to DAPT. There was no significant difference in the incidence of ischemic events (death, MI, stroke, or severe ischemia requiring revascularization) in the overall cohort (HR, 0.79; P=0.10). A nonsignificant trend for a reduction in ischemic events was, however, noted for all rivaroxaban doses, and the 2 lowest doses were considered for a phase III study.

ATLAS ACS 2-TIMI 51 85 was a double-blinded, placebo-controlled, phase III trial in which 15 526 patients with a recent ACS were randomized to receive twice-daily doses of either 2.5 or 5 mg of rivaroxaban or placebo. Most of the patients (93%) were taking DAPT (aspirin plus thienopyridine). As compared with APPRAISE-2, there were no specific inclusion criteria to select high-risk patients. In addition, patients with previous stroke or transient ischemic attack were excluded if they were taking DAPT. The 2 doses of rivaroxaban were associated with a significant reduction in the rates of death, MI, or stroke as compared with placebo. TIMI major bleeding complications were higher in both rivaroxaban arms as compared with placebo, but the rates tended to be lower with the lowest rivaroxaban dose. Importantly, the 2.5-mg dose (but not the 5-mg dose) decreased the risk of death from cardiovascular causes and from any cause.

In a recent meta-analysis including the 7 published phase II or III studies of new oral anticoagulants in ACS, 84 a significant but modest decrease in major cardiovascular events was found with new oral anticoagulants. There was, however, a substantial increase in bleeding complications, especially when new oral anticoagulants are combined with DAPT. Of all the new direct Factor Xa inhibitors, rivaroxaban shows the most promising results in the management of ACS. In part, patient selection criteria might explain some of the differences between studies. However, the dosing regimen tested in the ATLAS ACS-2 study represented only a quarter (2.5 mg twice daily) or a half (5 mg twice daily) of the dosing regimen developed for stroke prophylaxis in patients with atrial fibrillation or for the treatment of venous thromboembolism. Potentially, patients with ACS only need low doses of oral anticoagulants when used for long-term therapy if added to 2 antiplatelet agents.

Another question that will be addressed in the Rivaroxaban for the Cardiovascular OutcoMes for People using Anticoagulatlon StrategieS (COMPASS) trial concerns the use of oral anticoagulation to prevent ischemic events in a population somewhat similar to CHARISMA. A total of >20000 patients with coronary or peripheral artery disease will be randomized into 3 arms to evaluate the impact of rivaroxaban plus aspirin versus aspirin alone or rivaroxaban alone on MI, stroke, or cardiovascular death. In a factorial design, prophylactic PPIs will also be tested in COMPASS to extend the findings of COGENT and attempt to mitigate gastrointestinal bleeding risks from various antithrombotic approaches.

Combining Oral Antiplatelet Therapy With Oral Anticoagulants

Defining the best combination between all the available antiplatelet agents and oral anticoagulants is challenging. The question is, however, particularly important for patients who experience an ACS event and have an indication for long-term anticoagulation (ie, those with atrial fibrillation, previous venous thromboembolism, or mechanical heart valves). Current guidelines recommend the addition of a vitamin K antagonist to existing antiplatelet therapy with a target international normalized ratio of 2.0 to 3.0. 85,86 The What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting (WOEST) 86 trial evaluated a strategy of clopidogrel alone (double-therapy arm) versus clopidogrel plus aspirin (triple-therapy arm) on top of oral anticoagulants. The study showed that among the 573 enrolled patients, there was a significant reduction in bleeding episodes in the double-therapy arm as compared with the triple-therapy arm (HR, 0.36; P<0.0001). On the contrary, there was no excess in the rate of thrombotic events in the double-therapy arm, although the trial power was limited in this regard. Current consensus recommendations advise different durations of triple antithrombotic therapy ranging from 1 to 12 months after PCI depending on bleeding risk, thromboembolic risk, and type of stent. 87

Clinical trials are ongoing and will help define the optimal strategy in patients who require combined antiplatelet and anticoagulant therapies. The PIONEER AF-PCI study (exploring 2 strategies of rivaroxaban and 1 of oral vitamin K antagonist in patients with atrial fibrillation who undergo PCI) is exploring 2 different rivaroxaban treatment strategies and 1 vitamin K antagonist treatment strategy with various combinations of DAPT in patients with atrial fibrillation who undergo PCI. The study will include 2100 patients. The RE-DUAL PCI study examining dabigatran (at 2 doses) plus antiplatelet therapy versus warfarin plus antiplatelet therapy is also planned in patients undergoing PCI who need anticoagulation for atrial fibrillation.

Injectable Anticoagulant Therapy

Unfractionated Heparin

Anticoagulation with unfractionated heparin became a foundational therapy for ACS based on several small randomized trials. A meta-analysis of 6 randomized trials comparing treatment with heparin plus aspirin versus aspirin alone among 1353 patients with ACS showed that combination treatment led to a borderline significant 33% relative reduction in the risk of death or MI versus aspirin alone (7.9% and 10.4%, respectively) during 1 to 3 months of follow-up. The combination resulted in a near doubling in the rate of major bleeding, although this also did not reach statistical significance. 88
Low-Molecular-Weight Heparin
With the introduction of low-molecular-weight heparins, particularly enoxaparin, and their superior and more consistent bioavailability compared with unfractionated heparin, several head-to-head trials were initially performed among patients with ACS treated conservatively (ie, without an early invasive strategy). A meta-analysis of 2 larger studies, Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events (ESSENCE) and TIMI-11B,99 demonstrated an 18% relative reduction in the occurrence of death or MI (8.6% versus 7.1%; \( P=0.02 \)) with enoxaparin at 6 weeks of follow-up. Although no difference in major bleeding was found between treatment groups, the odds of minor bleeding was 2.4 times higher with enoxaparin (10.0% versus 4.3%; \( P<0.001 \)).

Separately, enoxaparin was tested versus unfractionated heparin in nearly 10 000 high-risk patients with ACS undergoing early PCI in the Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial.100 In contrast to ESSENCE and TIMI-11B, the duration of antithrombin therapy was shorter, because it was discontinued in nearly all SYNERGY patients immediately after the early PCI procedure. No difference in the primary end point of death or MI was observed between the treatment groups at 30 days (14.0% with enoxaparin versus 14.5% with unfractionated heparin). TIMI major bleeding, however, was higher with enoxaparin (9.1% versus 7.6%; \( P=0.008 \)), particularly among patients who received \( >1 \) antithrombin therapy (ie, crossover).

In patients with STE-ACS, randomized comparisons of enoxaparin and unfractionated heparin have also been made. In Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment (EXTRACT)-TIMI 25, a total of 20 506 fibrinolytic-treated patients received enoxaparin (median duration, 7 days) versus unfractionated heparin (median duration, 2 days).101 The primary end point of 30-day death or MI was 17% lower with enoxaparin (9.9% versus 12.0%; \( P<0.001 \)), whereas major bleeding was increased (2.1% versus 1.4%; \( P<0.001 \)).

Fondaparinux
The shortest effective heparin fragment, the pentasaccharide fondaparinux, has also been studied among patients with ACS because it has several unique pharmacological features including a particularly long half-life and consistency of effect. The OASIS-5 and OASIS-6 trials tested fondaparinux among 20 078 NSTE-ACS and 12 092 STE-ACS patients.102,103 In OASIS-5, fondaparinux was tested against enoxaparin with both agents given an average of 6 days. The primary end point of 9-day death, MI, or recurrent ischemia occurred at virtually the same rate (5.8%) in the 2 treatment groups, whereas the rates of major bleeding were nearly halved by fondaparinux (2.2% versus 4.1%; \( P<0.001 \)). Interestingly, mortality rates were also reduced by fondaparinux at early (30 days) and late (6 months) follow-up.

In OASIS-6, unfractionated heparin for \( \leq 2 \) days was used as the comparator (for patients receiving a fibrin-specific thrombolytic agent) or placebo versus fondaparinux for \( \leq 8 \) days. The primary end point of 30-day death or MI was lowered by 14% with fondaparinux (9.7% versus 11.2%; \( P=0.008 \)), and mortality was lower with fondaparinux at early and late follow-up. A consistent superior effect was seen with fondaparinux considering the different comparator groups and subgroups, the exception being that no benefit was seen in the minority of patients who underwent primary PCI. Despite being tested against a short course of unfractionated heparin or against placebo, the rates of bleeding events were similar or less with fondaparinux.104

Bivalirudin
Bivalirudin is a specific and reversible direct thrombin inhibitor that is approved as an alternative to unfractionated heparin in patients undergoing PCI. In contrast to heparins, bivalirudin does not need mediation of antithrombin III for its action because it directly binds and inhibits thrombin (Factor II).

Bivalirudin has a low oral bioavailability and a short half-life (ie, 25 minutes), requiring administration as an intravenous infusion. The efficacy and safety of bivalirudin was evaluated in the ACUITY trial.105 The study enrolled 13 819 patients with moderate to high-risk ACS undergoing PCI. Three different antithrombotic regimens were compared: heparin (either unfractionated heparin or enoxaparin) plus a GPIIb/IIIa inhibitor versus bivalirudin plus a GPIIb/IIIa inhibitor versus bivalirudin alone. Bivalirudin use (either with GPIIb/IIIa inhibitor or alone) resulted in noninferior rates of the composite ischemic end point (death from any cause, MI, or unplanned revascularization for ischemia). When used alone, bivalirudin was, however, associated with lower rates of major bleeding as compared with the other groups. Subgroup analyses emphasized the importance of clopidogrel pretreatment before PCI in patients given bivalirudin without GPIIb/IIIa inhibition.

Two large, open-label, randomized trials have compared bivalirudin to a heparin in patients undergoing primary PCI in acute MI. The Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial randomized 3602 patients to either bivalirudin (a bolus and an intravenous infusion that was discontinued after PCI) or to unfractionated heparin. A GPIIb/IIIa inhibitor was administered before PCI in all patients receiving heparin but was only used in 7.5% of patients with no reflow or a giant thrombus after PCI in the bivalirudin group. Most of the patients received DAPT before catheterization. The rate of death, reinfarction, target vessel revascularization, or stroke was similar in both groups (5.4% versus 5.5%, risk ratio, 0.99; \( P=0.95 \)). However, there was a significant reduction in the rate of major bleeding (4.9% versus 8.3%; risk ratio, 0.60; \( P<0.001 \)). Treatment with bivalirudin was associated with a reduction in the rates of death from cardiac and all causes, but in patients with stent implantation, bivalirudin was associated with a higher rate of stent thrombosis at 24 hours. In the European Ambulance Acute Coronary Syndrome Angiography (EUROMAX) trial,106 2218 patients with ST-segment elevation MI who were being transported for primary PCI were randomized to the prehospital administration of either bivalirudin or a heparin (89.9% received unfractionated heparin, and 8.5% enoxaparin). Optional use of a GPIIb/IIIa inhibitor was left to physician preference and was actually administered in 69.1% of the heparin group versus 11.5% of the bivalirudin group. The bivalirudin dose was similar to the one used in the HORIZONS-AMI trial, but the infusion had to be continued for 4 hours after PCI. The 30-day rate of death or major bleeding not associated with CABG was significantly lower in the bivalirudin group (5.1%}.
versus 8.5%; risk ratio, 0.60; \( P=0.001 \). The result was mainly because of a significant reduction in the rate of major bleeding, whereas there was no significant difference in the rate of death at 30 days. However, as in the HORIZONS-AMI trial, there was a significant increase in the risk of early stent thrombosis in the bivalirudin group (1.1% versus 0.2%; risk ratio, 6.11; \( P=0.007 \)). The results of these 2 clinical trials are overall consistent with each other and support bivalirudin use as a means to reduce bleeding, although concomitant potent antiplatelet therapy is likely needed to address the early stent thrombosis risk. Other smaller trials of bivalirudin versus heparin alone are ongoing, including trials with concomitant use of prasugrel and ticagrelor and trials with predominant radial artery access.

The choice of anticoagulant is influenced by the clinical situation. For a conservative approach in ACS without ST-elevation, fondaparinux seems to provide the best balance of reduction in ischemic risk without excess bleeding, but this agent is not approved for use in ACS in countries such as the United States. Enoxaparin seems like a reasonable choice as well, although care must be used with dosing in patients with renal insufficiency. In non–ST-elevation MI or ST-elevation MI patients being managed invasively, bivalirudin seems to provide similar protection from ischemic events compared with heparin plus a glycoprotein IIb/IIIa inhibitor, but with a decreased risk of bleeding. The guidelines specifically recommend consideration of bivalirudin use when bleeding risk is high.

**Conclusions**

As reviewed above, there is an abundance of data supporting several antiplatelet and anticoagulant drugs. Numerous combinations are possible, although many have not been studied. This is a major challenge in the field, that there are several approved, guideline-recommended therapies, but potentially hundreds of combinations of how to use antithrombotic drugs although with limited clinical evidence comparing combinations of drugs. It is clear that adding more antithrombotic drugs to the ACS regimen increases the potential for serious bleeding complications, but with appropriate dosing, combination antithrombotic therapy seems useful in carefully selected patients. Though routine bedside platelet function or genetic testing does not seem useful at the present time, assessment of patient phenotype remains a key. Although many risk factors for ischemic events and bleeding (such as advanced age) overlap, some predictors of bleeding (previous stroke) and some predictors of recurrent ischemia (previous MI) do seem useful for allocating less or more antithrombotic therapy. Future challenges include monitoring patient adherence with multiple antithrombotic regimens. Development of a global assay of antithrombotic effect is a major challenge in the field, that there are several approved, guideline-recommended therapies, but potentially hundreds of combinations of how to use antithrombotic drugs although with limited clinical evidence comparing combinations of drugs.

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