The Benefits and Risks of Oral Antiplatelet Therapy in Patients With Acute Coronary Syndrome

Introduction

Patients who have experienced an acute coronary syndrome (ACS) are at a high risk of recurrent ischemic events and death.1-2 ACS encompasses a spectrum of conditions, including ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation ACS (NSTEMI), the latter of which comprises non-STEMI (NSTEMI) and unstable angina (UA). As platelet aggregation plays a key role in ACS pathology, optimizing antiplatelet therapy to achieve adequate platelet inhibition is vital. The benefits of oral antiplatelet therapy in reducing the rate of ischemic events and cardiovascular mortality are well established.3-5 However, the same mechanisms by which antiplatelet therapies confer ischemic benefit also lead to an increased risk of bleeding events. Thus, it is important to balance the anti-ischemic benefit of antiplatelet therapy with the increased risk of bleeding. A range of oral antiplatelet therapies are currently available, each differing in their specific mechanism of action and efficacy and safety profiles. This provides an opportunity to tailor antiplatelet strategies according to an individual patient’s clinical status and benefit-risk profile.

This newsletter aims to provide an overview of the currently available evidence pertaining to the benefits and risks of oral antiplatelet therapies, with a focus on balancing ischemic and bleeding risk to optimize patient outcomes.

Available oral antiplatelet therapies

Aspirin is an irreversible cyclooxygenase-1 inhibitor indicated to reduce the risk of recurrent vascular events in patients with a history of cardiovascular disease.6 As the benefits of aspirin in the secondary prevention of ischemic events are well established, guidelines recommend that a loading dose of aspirin (162–325 mg) be administered as soon as possible following an ACS event.7,8 Aspirin should then be continued indefinitely at a low daily maintenance dose of 81 to 162 mg, although 325 mg may be given under special circumstances.7,8 However, approximately 30% of patients are thought to be ‘nonresponsive’ to aspirin, and recurrent vascular events occur in a significant number of patients prescribed aspirin as the sole antithrombotic therapy.9 Consequently, to achieve adequate inhibition of platelet aggregation following an ACS event, and thereby reduce the risk of recurrent ischemic events, dual antiplatelet therapy with a P2Y12 receptor antagonist and low-dose aspirin is recommended for most patients.7,8,10-14 The choice of P2Y12 receptor inhibitor and the optimal duration of administration require careful consideration of a patient’s individual ischemic and bleeding risk.12

A number of oral P2Y12 receptor antagonists are currently available, including clopidogrel (Plavix), prasugrel (Effient), and ticagrelor (Brilinta) (Table 1).15-18 Clopidogrel, a thienopyridine, is a nonselective, irreversible P2Y12 receptor inhibitor that requires metabolic activation in the liver via the cytochrome P450 (CYP) pathway.5 There is a high degree of variability in patient response to clopidogrel, with around 15% to 40% of patients thought to be poor responders.19,20 The nature of clopidogrel response variability is complex, and precise mechanisms remain unclear. However, both high on-treatment platelet reactivity and CYP2C19 reduced-function phenotypes have been shown to be associated with an increased risk of ischemic events during clopidogrel treatment.21 Proposed mechanisms leading to poor clopidogrel response are summarized in Box 1.22 Several point-of-care platelet function tests and commercial pharmacogenetic tests are available to evaluate individual patient response to clopidogrel (Table 2).22 However, the clinical outcome benefits of these tests are unclear, and there is currently no clear guideline or consensus on the clinical use of these tests in guiding treatment strategies.21

<table>
<thead>
<tr>
<th>Table 1. Oral P2Y12 receptor inhibitors15-18</th>
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<tbody>
<tr>
<td><strong>Indications</strong></td>
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<tr>
<td>Clopidogrel</td>
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<tr>
<td>Patients with ACS, recent MI, recent stroke, or established PAD</td>
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<tr>
<td>Prasugrel</td>
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<tr>
<td>Patients with ACS who are to be managed with PCI</td>
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<tr>
<td>Ticagrelor</td>
</tr>
<tr>
<td>Patients with ACS or a history of MI</td>
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<tr>
<td><strong>Contraindications</strong></td>
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<tr>
<td>Patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage</td>
</tr>
<tr>
<td>Patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage, and patients with a history of TIA or stroke. Not generally</td>
</tr>
<tr>
<td>Patients with a history of intracranial hemorrhage, or patients with active pathological bleeding such as peptic ulcer</td>
</tr>
</tbody>
</table>

Disclosures

Tariq Ahmad, MD, Rhian Davies, DO, and Peter Alagona Jr, MD have no conflicts of interest to disclose.

Acknowledgments

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For patients aged ≥75 years, a loading dose of 300 mg is recommended, followed by a maintenance dose of 75 mg once daily. The loading dose should be increased to 60 mg for the first 12 months, 90 mg twice daily after 12 months of administration.

Bioactivation involves two CYP450-dependent steps, with no effect noted on responsiveness. CYP2C19 polymorphism reduces the responsiveness, and PPI interaction reduces metabolite levels.

Receptor binding is reversible, with a half-life of active metabolite of 9 hours. The presence of genetic polymorphisms associated with reduced active metabolite generation can lead to decreased clopidogrel responsiveness, as measured by platelet function assays, and poor clinical outcomes.

Gene polymorphisms: The presence of genetic polymorphisms associated with reduced active metabolite generation can lead to decreased clopidogrel responsiveness, as measured by platelet function assays, and poor clinical outcomes.

Drug-drug interactions: The coadministration of agents metabolized by CYP2C19 and CYP3A4 isoenzymes, including proton pump inhibitors, lipophilic statins, and calcium channel blockers, can lead to a diminished clopidogrel response.

Clinical factors: Clinical factors such as body mass index, noncompliance, and the presence of diabetes mellitus or ACS have also been associated with an attenuated clopidogrel response.

The "smoker’s paradox" — cigarette smoking has been shown to stimulate CYP1A2 activity, leading to enhanced clopidogrel-mediated platelet inhibition and thus improved clinical outcomes.

Table 2. Methods to assess platelet inhibition in response to clopidogrel

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
<th>Benefits</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>Light transmission agregrometry</td>
<td>Assesses an integrated response of the platelet to ADP through P2Y₁ and P2Y₁₂ receptor function</td>
<td>• Large amount of data available&lt;br&gt;• This method is widely available</td>
<td>• Variable reproducibility&lt;br&gt;• Lengthy processing time</td>
</tr>
<tr>
<td>VerifyNow</td>
<td>A turbidimetric assay measuring aggregation of platelets to fibrinogen-coated beads in whole blood</td>
<td>• Full automation&lt;br&gt;• Good reproducibility&lt;br&gt;• Bedside use</td>
<td>• High cost</td>
</tr>
<tr>
<td>VASP assay</td>
<td>Specific intracellular marker of residual P2Y₁₂ receptor reactivity measured by flow cytometry</td>
<td>• Most specific assay for P2Y₁₂ inhibition (not affected by P2Y₁ inhibition)&lt;br&gt;• High reproducibility</td>
<td>• High cost&lt;br&gt;• Use requires experienced technician</td>
</tr>
</tbody>
</table>

Abbreviations: ADP, adenosine diphosphate; VASP, vasodilator-stimulated phosphoprotein.

The newer oral P2Y₁₂ receptor inhibitors, prasugrel and ticagrelor, are now generally recommended in preference to clopidogrel as first-line therapy (with low-dose aspirin) for the majority of patients following an ACS event. Prasugrel, a third-generation thienopyridine, is a nondirect, irreversible P2Y₁₂ receptor inhibitor with a chemical structure similar to that of clopidogrel. However, it exhibits faster and more consistent pro-drug-to-metabolite conversion and greater inhibition of platelet reactivity, and is less susceptible to variability in response. Ticagrelor, a cyclopentyltriazolopyrimidine, has distinct chemical properties compared with the thienopyridines. It does not require metabolic activation and binds reversibly and noncompetitively to the P2Y₁₂ receptor, resulting in faster and more potent platelet inhibition, and faster reversal of these effects once discontinued, compared with clopidogrel.

In addition, a novel agent, vorapaxar (Zontivity), was approved by the US Food and Drug Administration (FDA) in 2014. It is the first in a new class of drug, a selective antagonist of protease-activated receptor-1, which inhibits thrombin-induced platelet aggregation. It is indicated in combination with clopidogrel or aspirin for the reduction of thrombotic cardiovascular events in patients with a history of myocardial infarction (MI) or with peripheral arterial disease (PAD). However, it is not yet included in US guidelines for the management of patients with ACS.
# Efficacy and safety of available oral antiplatelet therapies

The key efficacy and safety data from major clinical trials for clopidogrel, prasugrel, and ticagrelor are summarized in Table 3.

## Table 3. Key efficacy and safety data from major clinical trials of available oral antiplatelet therapies

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient population</th>
<th>Treatment</th>
<th>Primary efficacy endpoint(s)</th>
<th>Secondary efficacy endpoint(s)</th>
<th>Key safety endpoints(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clopidogrel</strong></td>
<td>Patients with ACS without ST-segment elevation (n=12,562)</td>
<td>Randomized to clopidogrel plus aspirin or placebo plus aspirin for 12 months</td>
<td>Composite of CV death; nonfatal MI, or stroke; significantly lower in clopidogrel group vs placebo group (9.3% vs 11.4%; P&lt;.001)</td>
<td>Severe ischemia: significantly lower in clopidogrel group vs placebo group (2.8% vs 3.8%; P=.003)</td>
<td>Major bleeding: significantly higher in clopidogrel group vs placebo group (3.7% vs 2.7%; P=.001)</td>
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<td>Composite of CV death, nonfatal MI, stroke, or refractory ischemia: significantly lower in clopidogrel group vs placebo group (16.5% vs 18.8%; P&lt;.001)</td>
<td>Heart failure: significantly lower in clopidogrel group vs placebo group (3.7% vs 4.4%; P=.03)</td>
<td>Life-threatening bleeding: no significant difference between treatment groups</td>
</tr>
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<td></td>
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<td></td>
<td>No need for revascularization: no significant difference between treatment groups</td>
<td></td>
<td>Minor bleeding: occurred significantly more in clopidogrel group vs placebo group (5.1% vs 2.4%; P&lt;.001)</td>
</tr>
<tr>
<td><strong>CHARISMA</strong>²⁸</td>
<td>Patients with atherothrombotic risk factors, documented coronary artery disease, cerebrovascular disease, or PAD (n=15,603)</td>
<td>Randomized to clopidogrel plus aspirin or placebo plus aspirin for a median of 28 months</td>
<td>MI, stroke, or CV death: no significant difference between treatment groups</td>
<td>First occurrence of MI, stroke, CV death, UA, TIA, or a revascularization procedure: significantly lower in clopidogrel group vs placebo group (16.7% vs 17.9%; P=.04)</td>
<td>GUSTO-defined severe bleeding: no significant difference between treatment groups</td>
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<td></td>
<td>Moderate bleeding: significantly higher in clopidogrel vs placebo group (2.1% vs 1.3%; P&lt;.001)</td>
</tr>
<tr>
<td><strong>Prasugrel</strong></td>
<td>Patients with ACS with scheduled PCI (n=13,608)</td>
<td>Randomized to prasugrel plus aspirin or clopidogrel plus aspirin for 6 to 15 months</td>
<td>Composite of CV death, nonfatal MI, or nonfatal stroke during follow-up (15 months): significantly lower in prasugrel group vs clopidogrel group (9.9% vs 12.1%; P&lt;.001)</td>
<td>Primary composite endpoint and composite of CV death, nonfatal MI, or urgent target vessel revascularization at 30 and 90 days: significantly lower in prasugrel group vs clopidogrel group (P=.001)</td>
<td>TIMI major bleeding not related to CABG: significantly higher in prasugrel group vs clopidogrel group (2.4% vs 1.8%; P=.03)</td>
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<td>Stent thrombosis: significantly lower in prasugrel group vs clopidogrel group (1.1% vs 2.4%; P&lt;.001)</td>
<td>Non-CABG-related TIMI life-threatening bleeding: significantly higher in prasugrel group vs clopidogrel group (13.4% vs 3.2%; P&lt;.001)</td>
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<td>Composite of CV death, nonfatal MI, nonfatal stroke, or rehospitalization due to ischemic event during follow-up (15 months): significantly lower in prasugrel group vs clopidogrel group (12.3% vs 14.8%; P&lt;.001)</td>
<td>TIMI major or minor bleeding: significantly higher in prasugrel group vs clopidogrel group (5.0% vs 3.6%; P=.002)</td>
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<tr>
<td><strong>TRILOGY-ACS</strong>²⁹</td>
<td>Patients with ACS medically managed without revascularization (n=9326)</td>
<td>Randomized to prasugrel plus aspirin or clopidogrel plus aspirin for 6 to 30 months</td>
<td>Composite of CV death, nonfatal MI, or nonfatal stroke in patients aged &lt;75 years: no significant difference between treatment groups at a mean follow-up of 17 months</td>
<td>CV death, MI, and stroke: no significant difference between treatment groups at a mean follow-up of 30 months</td>
<td>Severe or life-threatening non-CABG-related bleeding or non-CABG-related TIMI major bleeding: no significant difference between treatment groups at a mean follow-up of 30 months</td>
</tr>
<tr>
<td><strong>Ticagrelor</strong></td>
<td>Patients hospitalized for an ACS (n=18,624)</td>
<td>Randomized to ticagrelor plus aspirin or clopidogrel plus aspirin for 12 months</td>
<td>Composite of CV death, MI, or stroke: significantly lower in ticagrelor group vs clopidogrel group (9.8% vs 11.7%; P&lt;.001)</td>
<td>Primary endpoint in invasively treated patients: significantly lower in ticagrelor group vs clopidogrel group (8.9% vs 10.6%; P=.003)</td>
<td>Major bleeding (study criteria and TIMI), and bleeding requiring red blood cell transfusion, or life-threatening or fatal bleeding: no significant difference between treatment groups</td>
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<td></td>
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<td></td>
<td>Non-CABG-related major bleeding (study criteria and TIMI): significantly higher in ticagrelor group vs clopidogrel group</td>
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</table>
Patients with ACS

Compared with clopidogrel, ticagrelor was associated with increased PLATO- and TIMI-defined non-CABG-related thrombolysis in myocardial infarction (TIMI) major bleeding. The rate of non-CABG-related thrombolysis was significantly increased with ticagrelor compared with clopidogrel (7.8% vs 5.1%, P=0.001). No significant difference was observed between ticagrelor and clopidogrel for any of the other secondary safety outcomes.

In the PLATO (Platelet Inhibition and Patient Outcomes) trial, researchers looked at patients hospitalized for an ACS event who were about to receive medical or invasive management. They found that ticagrelor was associated with a significantly greater reduction in the rate of cardiovascular events and cardiovascular death compared with clopidogrel (9.8% vs 11.7%; P=0.003). They also found that ticagrelor reduced the rate of all-cause mortality (4.5% vs 5.9%; P<0.001). Compared with clopidogrel, ticagrelor was associated with increased PLATO- and TIMI-defined non-

PEGASUS-TIMI 54

Patients with previous MI (n=21,162)

| Time to first occurrence of any event from the composite of stroke, MI, or death: no significant difference between treatment groups | Composite of CV death, MI, or stroke at 3 years: significantly reduced with ticagrelor 90 mg (7.9%; P=0.008) and 60 mg (7.8%; P=0.004) vs placebo |
| CV death: no significant difference with either ticagrelor dose vs placebo | All-cause mortality: no significant difference with either ticagrelor dose vs placebo |

Timi major bleeding: significantly higher with ticagrelor 90 mg (2.6%; P=0.001) and 60 mg (2.3%; P<0.001) vs placebo

Intracranial hemorrhage or fatal bleeding: no significant difference with either ticagrelor dose vs placebo

SOCRATES

Patients with nonsevere ischemic stroke or high-risk TIA (n=13,199)

| Time to first occurrence of any event from the composite of stroke, MI, or death: no significant difference between treatment groups | Ischemic stroke: 5.8% in ticagrelor group and 6.7% in aspirin group (P=0.046) |

Net clinical outcome (composite of stroke, MI, death, or life-threatening bleeding): 6.9% in ticagrelor group and 7.7% in aspirin group (P=0.09)

PLATO major bleeding: no significant difference between treatment groups

Intracranial hemorrhage: no significant difference between treatment groups

Vorapaxar

TRACER

Patients with ACS without ST-segment elevation (n=12,944)

| Composite of CV death, MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization: no significant difference between treatment groups | Composite of CV death, MI, stroke, or recurrent ischemia with rehospitalization, or urgent coronary revascularization: no significant difference between treatment groups |

Composite of moderate or severe GUSTO bleeding: higher in vorapaxar group vs placebo group (7.2% vs 5.2%; P<0.001)

TIMI clinically significant bleeding: higher in vorapaxar group vs placebo group (20.2% vs 14.6%; P<0.001)

TRA 2P-TIMI 50

Patients with a history of MI, ischemic stroke, or PAD (n=26,449)

| Composite of CV death, MI, stroke, or recurrent ischemia leading to urgent coronary revascularization: lower in vorapaxor group vs placebo group (9.3% vs 10.5%; P=0.01) |

Composite of CV death, MI, stroke, or death: lower in vorapaxor group vs placebo group (11.2% vs 12.4%; P=0.001)

GUSTO moderate or severe bleeding: higher in vorapaxor group vs placebo group (4.2% vs 2.6%; P=0.001)

Abbreviations: ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CHARISMA, Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilization, Management and Avoidance; CURE, Clopidogrel in Unstable angina to prevent Recurrent Events; CV, cardiovascular; GUSTO, Global Use of Strategies to Open Occluded Arteries; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; PEGASUS-TIMI 54, Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54; PLATO, Platelet Inhibition and Patient Outcomes; SOCRATES, Acute Stroke or Transient Ischemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes; TIA, transient ischemic attack; TIMI, Thrombolysis in Myocardial Infarction; TRA 2P-TIMI 50, Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events – TRACER-Thrombin Receptor Antagonist for Clinical Event Reduction in acute coronary syndrome; TRILIGNY-ACS, Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes; TRITON-TIMI 38, Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38; UA, unstable angina.

Analyses of secondary endpoints were considered to be exploratory and were not used to make conclusions regarding significance.

The pivotal CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) study demonstrated that in patients with NSTE-ACS, the addition of clopidogrel to aspirin was associated with a significant reduction in cardiovascular events and cardiovascular mortality compared with aspirin monotherapy (9.3% vs 11.4%; P<0.001). However, an increased risk of major and minor bleeding events was observed with clopidogrel plus aspirin compared with aspirin therapy alone (5.1% vs 2.4% major bleeding events [P<0.001] and 3.7% vs 2.7% minor bleeding events [P=0.001]).

Also, as mentioned previously, the efficacy of clopidogrel is often limited by suboptimal and delayed platelet inhibition and individual variability in response.

Prasugrel and ticagrelor have both demonstrated achievement of superior clinical outcomes compared with clopidogrel in patients with ACS.4,5 TRITON-TIMI 38 (Trial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibition with prasugrel–Thrombolysis in Myocardial Infarction 38) compared the efficacy and safety of prasugrel and clopidogrel in patients with moderate- to high-risk ACS undergoing percutaneous coronary intervention (PCI). The rate of cardiovascular events and cardiovascular death was significantly reduced with prasugrel compared with clopidogrel over a 15-month follow-up period. However, compared with clopidogrel, prasugrel was associated with an increased risk of noncoronary artery bypass graft (CABG)-related thrombolysis in myocardial infarction (TIMI) bleeding, including life threatening bleeding.6 Conversely, in the TRILOGY-ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) study, researchers looked at patients with ACS intended for medical management without revascularization, and found no significant differences between prasugrel and clopidogrel in terms of cardiovascular events, or non-CABG-related TIMI major bleeding.29
CABG-related major bleeding (4.5% vs 3.8%; \( P = .03 \)). However, the rate of overall major bleeding or fatal/life-threatening bleeding was similar with clopidogrel and ticagrelor. These results were consistent regardless of ACS type and management strategy.5

Ticagrelor therapy has been shown to be associated with an increased incidence of dyspnea compared with clopidogrel.34 This is thought to be partly due to the ticagrelor-mediated inhibition of the cellular uptake of adenosine. The resulting increased extracellular levels of adenosine lead to increased stimulation of the pulmonary vagal C-fibers, mediating the sensation of dyspnea.35 Episodes usually occur early in the course of treatment, and are typically transient and of mild to moderate severity. The discontinuation rate due to dyspnea is low (0.9%).36

Studies investigating the addition of vorapaxar to standard therapy (particularly aspirin and a P2Y\(_{12}\) receptor inhibitor) have produced mixed results. In the TRACER (Thrombin Receptor Antagonist for Clinical Event Reduction in ACS) study conducted in patients with NSTE-ACS, the addition of vorapaxar to standard care did not significantly reduce the composite endpoint of cardiovascular death, MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization.32 However, in the TRA 2P–TIMI 50 (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events) study, the addition of vorapaxar to standard therapy reduced the risk of cardiovascular death, MI, or stroke in patients with a history of MI, ischemic stroke, or PAD.33 This ischemic benefit was most apparent in patients with a history of MI. However, this reduction in cardiovascular events was accompanied by an increased bleeding risk, and no significant difference in net clinical outcome was observed between vorapaxar or placebo treatment groups. Both studies demonstrated that vorapaxar increases the risk of moderate and severe bleeding (1 event in every 26 patients and 1 in every 59 patients receiving vorapaxar, compared with placebo in the TRACER and TRA 2P–TIMI 50 studies, respectively), including intracranial hemorrhage (1 in every 111 patients and 1 in every 200 patients, compared with placebo in the TRACER and TRA 2P–TIMI 50 studies, respectively).32,33

Balancing ischemic and bleeding risk

The same pathways by which antiplatelet therapies confer ischemic benefit also increase the risk of bleeding. Therefore, by identifying patients at high ischemic or bleeding risk, treatment strategies can be tailored to optimize the level of platelet inhibition and improve patient outcomes (Figure 1).12,37 This can be achieved by selecting the appropriate P2Y\(_{12}\) receptor inhibitor and, in particular, by choosing the optimal duration of dual antiplatelet therapy.

Figure 1. Optimizing platelet inhibition according to a patient's ischemic and bleeding risk factors12,37
Abbreviations: ACS, acute coronary syndrome; CAD, coronary artery disease; CKD, chronic kidney disease; DES, drug-eluting stent; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug.


A period of dual antiplatelet therapy, with aspirin and a P2Y₁₂ receptor inhibitor, followed by the indefinite administration of aspirin monotherapy, is recommended in the majority of patients following an ACS. Of note: it is important to differentiate between type-I and type-II MI. Type-I MI usually occurs due to atherosclerotic plaque rupture, whereas type-II MI occurs due to an imbalance in the myocardial oxygen supply or demand, and is estimated to occur in 4.5% of all patients diagnosed with acute MI. Although the management of type-I MI requires antithrombotic therapy and/or revascularization, the management of type-II MI is more varied, and it is unknown whether strategies recommended for ACS would benefit this subgroup of patients.

Lower doses of aspirin are associated with a lower bleeding risk, while conferring comparable cardioprotective benefits, compared with higher aspirin doses. Therefore, when used in conjunction with a P2Y₁₂ receptor inhibitor, the recommended daily dose of aspirin is 81 mg (range 75–100 mg). Guidelines provide specific recommendations for the duration of dual antiplatelet therapy according to clinical status, ACS type, and intended management strategy (Table 4). Although most guidelines agree that a P2Y₁₂ receptor inhibitor should be administered for 12 months in the majority of patients following an ACS event, some recognize that prolonging the duration of dual antiplatelet therapy beyond 12 months may be beneficial for patients with higher ischemic risk and lower bleeding risk. Conversely, a shorter duration of dual antiplatelet therapy may be considered for patients with lower ischemic risk and higher bleeding risk.

**Table 4. Guideline recommendations for the duration of dual antiplatelet therapy**

<table>
<thead>
<tr>
<th>Patients with SIHD</th>
<th>Treated with PCI</th>
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<tbody>
<tr>
<td></td>
<td>• Following BMS implantation, dual antiplatelet therapy should be administered for a minimum of 1 month</td>
</tr>
<tr>
<td></td>
<td>• Following DES implantation, dual antiplatelet therapy should be administered for a minimum of 6 months</td>
</tr>
<tr>
<td></td>
<td>• In patients treated with BMS or DES implantation who have tolerated dual antiplatelet therapy without bleeding complications, and who are not at high bleeding risk, dual antiplatelet therapy should be continued for a minimum of 6 months</td>
</tr>
<tr>
<td></td>
<td>• In patients treated with BMS or DES implantation who have tolerated dual antiplatelet therapy without bleeding complications, and who are at high bleeding risk, dual antiplatelet therapy should be continued for a minimum of 12 months</td>
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</tbody>
</table>

Ischemic risk factors
- Advanced age
- ACS presentation
- History of multiple MIs
- Extensive CAD
- Diabetes mellitus
- Left ventricular ejection fraction <40%
- First-generation DES
- Stent underdeployment
- Small or short lesions
- Stent thrombosis

Bleeding risk factors
- History of prior bleeding
- Oral anticoagulant therapy
- Female sex
- Advanced age
- Low body weight
- CKD
- Anemia
- Chronic steroid or NSAID therapy
risk, continuation of dual antiplatelet therapy beyond minimum recommended treatment duration may be reasonable
- Following DES implantation, in patients who develop a high risk of bleeding, are at high risk of severe bleeding, or develop significant overt bleeding, discontinuation of dual antiplatelet therapy after 3 months may be reasonable

### Undergoing CABG
- Following CABG, dual antiplatelet therapy (with clopidogrel initiated early preoperatively) for 12 months may be reasonable to improve vein graft patency

### Patients with ACS

#### Treated with PCI
- Following BMS or DES implantation, dual antiplatelet therapy should be given for ≥12 months\(^7,8,12\)
- Following BMS or DES implantation, in patients who have tolerated dual antiplatelet therapy without bleeding complications and who are not at high bleeding risk, continuation of dual antiplatelet therapy beyond 12 months may be reasonable\(^7,12\)
- In patients with ACS treated with dual antiplatelet therapy after DES implantation who develop a high risk of bleeding, or develop significant overt bleeding, early discontinuation of dual antiplatelet therapy may be reasonable\(^7,12\)

#### Undergoing CABG
- Nonenteric-coated aspirin (81–325 mg daily) should be administered preoperatively\(^7\)
- Clopidogrel and ticagrelor should be discontinued for at least 5 days before surgery and prasugrel for at least 7 days before surgery\(^7\)
- Dual antiplatelet therapy should be resumed after CABG to complete 12 months of dual antiplatelet therapy\(^12\)

#### Treated with medical therapy alone
- Dual antiplatelet therapy should be continued for at least 12 months\(^12\)
- In patients who have tolerated dual antiplatelet therapy without bleeding complications and who are not at high bleeding risk, continuation of dual antiplatelet therapy beyond 12 months may be reasonable\(^12\)

#### With STEMI and receiving fibrinolytic therapy
- Aspirin should be continued indefinitely, and clopidogrel should be continued for a minimum of 14 days and ideally 12 months in the absence of bleeding\(^8,12\)
- In patients with STEMI treated with fibrinolytic therapy who have tolerated dual antiplatelet therapy without bleeding complications and who are not at high bleeding risk, continuation of dual antiplatelet therapy beyond 12 months may be reasonable\(^8,12\)

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**Abbreviations:** ACS, acute coronary syndrome; BMS, bare metal stent; CABG, coronary artery bypass graft; DES, drug-eluting stent; PCI, percutaneous coronary intervention; SIHD, stable ischemic heart disease; STEMI, ST-segment elevation myocardial infarction.

Certain patient groups have been shown to derive the greatest benefit from prolonged dual antiplatelet therapy (eg, patients with prior MI)\(^30,40\) and risk factors for increased bleeding and thrombotic events have been identified (Figure 1).\(^7,12,37\) Nevertheless, deciding on the optimal treatment duration can be challenging, as patients often possess factors for both ischemic and bleeding risk, and some factors can increase the risk of both types of event. Thus, a clinical decision tool to aid clinicians in identifying which patients would be expected to benefit from prolonged dual antiplatelet therapy may be valuable. Using data from patients undergoing coronary stenting for stable coronary artery disease (CAD) or ACS included in the Dual Antiplatelet Therapy (DAPT) study (n=11,648), a simplified risk score was derived based on ischemic and bleeding risk factors to help identify patients with greater expected benefit vs harm from continuation of dual antiplatelet therapy beyond 1 year. The score ranges from −2 to 10, and assigns points to specific variables such as age, presence of diabetes mellitus, MI at presentation, and cigarette smoking (Table 5).\(^41\) In those with a high score (≥2), the ischemic benefit of prolonged dual antiplatelet therapy outweighs the bleeding risk, and therefore may be beneficial. Conversely, in patients with a low score (<2), the benefit-risk ratio of prolonged dual antiplatelet therapy is not favorable.\(^41\)

**Table 5. Elements of the dual antiplatelet therapy clinical prediction score\(^41\)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td></td>
</tr>
<tr>
<td>≥75</td>
<td>−2</td>
</tr>
<tr>
<td>65 to &lt;75</td>
<td>−1</td>
</tr>
<tr>
<td>&lt;65</td>
<td>0</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>MI at presentation</td>
<td>1</td>
</tr>
<tr>
<td>Prior PCI or prior MI</td>
<td>1</td>
</tr>
<tr>
<td>Paclitaxel-eluting stent</td>
<td>1</td>
</tr>
<tr>
<td>Stent diameter ≤3 mm</td>
<td>2</td>
</tr>
<tr>
<td>CHF or LVEF &lt;30%</td>
<td>2</td>
</tr>
<tr>
<td>Vein graft stent</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total score range:</strong> −2 to 10</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** CHF, congestive heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.
Oral antiplatelet therapy in high-risk patient populations

Specific guideline recommendations pertaining to high-risk patient populations with ACS are summarized in Table 6.

Table 6. Specific treatment recommendations for high-risk patient populations with ACS

<table>
<thead>
<tr>
<th>Patient population</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| Elderly patients (≥75 years) | • Treatment decisions should be made in the context of estimated life expectancy, comorbidities, quality of life, functional and cognitive stress, and patient wishes and preferences.\(^7,^{10}\)  
- The choice of antithrombotic drugs can be tailored and dose can be adjusted by weight and/or CrCl to minimize the occurrence of adverse effects caused by age-related changes in PK/PD, volume of distribution, comorbidities, drug interactions and increased drug sensitivity.\(^7,^{10}\)  
- Prasugrel is not generally recommended in this patient population.\(^15\) |
| History of stroke or TIA | • Aspirin monotherapy or the combination of aspirin and extended-release dipyridamole is recommended.\(^42\)  
- The combination of aspirin and clopidogrel may be beneficial if initiated within 24 hours of a minor ischemic stroke or TIA and continued for 90 days.\(^42\)  
- Prasugrel is contraindicated in this patient population.\(^15\) |
| Renal impairment | • No dose adjustment is required for clopidogrel, prasugrel, or ticagrelor based on renal function.\(^15-17\)  
- Use of clopidogrel, prasugrel, or ticagrelor is not recommended in patients with stage 5 CKD, although clopidogrel may be considered in some selected indications (eg, stent thrombosis prevention).\(^43\) |
| Diabetes | • The management of patients with diabetes and ACS should be the same as that for patients without diabetes.\(^8,^{10}\) |
| PAD | • Antiplatelet monotherapy with aspirin or clopidogrel is recommended,\(^44,^{45}\) with clinical data demonstrating that clopidogrel is more effective than aspirin in reducing the combined risk of ischemic stroke, MI, or vascular death in patients with atherosclerotic CVD, with an overall safety profile similar to that of medium-dose aspirin.\(^46\) |
| COPD | • Current ACS guidelines do not specify which antiplatelet therapy should be used in patients with COPD who have ACS or CAD. |
| Patients with atrial fibrillation receiving oral anticoagulant therapy | • A short period of triple therapy (minimum of 4 weeks and no longer than 6 months), consisting of aspirin, a P2Y\(_{12}\) receptor inhibitor, and an oral anticoagulant is recommended, followed by an oral anticoagulant and a single antiplatelet therapy, preferably clopidogrel, for up to 12 months.\(^47\)  
- Assessment of stroke risk (using the CHA\(_2\)-DS\(_2\)-VASc score) and bleeding risk (using the HAS-BLED score) should be performed regularly.\(^47\)  
- To minimize bleeding risk, the duration of triple therapy should be as short as possible; clopidogrel should be the P2Y\(_{12}\) receptor of choice; and a low daily dose of aspirin (75–100 mg) should be used.\(^7,^{47}\)  
- Proton pump inhibitors can be considered in patients at an increased risk of gastrointestinal bleeding.\(^7,^{47}\) |

Abbreviations: ACS, acute coronary syndrome; CAD, coronary artery disease; CVD, cardiovascular disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; MI, myocardial infarction; PAD, peripheral artery disease; PD, pharmacodynamics; PK, pharmacokinetics; TIA, transient ischemic attack.

Elderly patients (≥75 years)

Elderly patients are at increased risk of ischemic events, and may also have increased bleeding risk during antithrombotic therapy.\(^41,^{46}\)

In COMMIT (CLOpidogrel and Metoprolol in Myocardial Infarction Trial), clopidogrel reduced the primary composite outcome of death, reinfarction, or stroke consistently across all age groups (<60 years, 60–69 years, and ≥70 years).\(^48\) Indeed, as the absolute ischemic risk was greater in patients aged ≥70 years compared with those <60 years, the absolute reduction of risk appeared to be greater in older patients than younger patients. In addition, the risk of major and minor bleeds did not appear to correlate with increasing age.\(^9\) Similar observations have been made for ticagrelor and vorapaxar. In a PLATO substudy, no significant differences in the safety or clinical effectiveness of ticagrelor were observed between elderly and younger patients,\(^50\) and in the TRA 2P–TIMI 50 and...
Conversely, in the TRITON–TIMI 38 trial, prasugrel was not associated with a net clinical benefit in patients aged ≥75 years, with this patient population experiencing less clinical efficacy and greater absolute levels of bleeding than the overall cohort. Consequently, prasugrel is not generally recommended in elderly patients.

Dual antiplatelet therapy with aspirin plus clopidogrel or ticagrelor has generally been shown to provide greater absolute benefits in older patients than younger patients. However, although approximately 32% to 35% of patients with ACS are aged ≥75 years, elderly patients are often under-represented in clinical studies, which is likely due, in part, to an increased risk of bleeding events. Thus, further investigation is required to accurately assess the benefit-risk profile of dual antiplatelet therapy in patients aged ≥75 years.

History of stroke or transient ischemic attack

Patients who experience ischemic stroke or transient ischemic attack (TIA) are at a high risk of recurrent ischemic events, particularly within the first 90 days after the event. Aspirin has been shown to significantly reduce the risk of stroke or TIA in a secondary prevention setting. However, studies investigating the benefits of dual antiplatelet therapy have produced varied results. Two studies showed that among patients with previous stroke, clopidogrel plus aspirin therapy led to an increased risk of bleeding and death compared with aspirin alone, without producing a significant ischemic benefit. Conversely, when clopidogrel was administered within 24 hours of a minor ischemic stroke or TIA and continued for 90 days in 5170 Chinese patients, a significantly greater ischemic benefit was observed with clopidogrel plus aspirin in comparison with aspirin monotherapy, while the rate of moderate or severe bleeding did not differ between the 2 treatment groups.

In a PLATO subanalysis, ticagrelor was associated with reduced ischemic events without an increased risk of PLATO-defined major bleeding in patients with or without prior stroke or TIA. However, in the recent SOCRATES (Acute Stroke Or Transient Ischaemic Attack TReated with Aspirin or Ticagrelor and Patient OutcomEs) trial, in patients with prior acute ischemic stroke or TIA, ticagrelor was not found to be superior to aspirin in reducing the rate of stroke, MI, or death at 90 days. Additionally, prasugrel has been shown to be associated with significant net clinical harm in patients with prior stroke or TIA, and is therefore contraindicated in this patient population.

Current guidelines for the secondary prevention of noncardioembolic ischemic stroke or TIA recommend aspirin monotherapy or the combination of aspirin and extended-release dipyridamole. They also recognize that the combination of aspirin and clopidogrel may be beneficial if initiated within 24 hours of a minor ischemic stroke or TIA and continued for 90 days.

Renal impairment

Patients with renal dysfunction are at a higher risk of bleeding events while receiving anti thrombotic therapy compared with those with normal renal function. Additionally, as aspirin inhibits the synthesis of renal prostaglandins, there is a concern that this may lead to further renal deterioration in patients with chronic kidney disease (CKD). However, as patients with CKD have a high baseline cardiovascular risk, low-dose aspirin therapy is associated with greater absolute cardiovascular risk reduction and lower rates of mortality in patients with CKD than in those with normal renal function.

In addition, although clopidogrel should be used with caution in patients with CKD, a subanalysis from the CURE study showed that levels of ischemic and bleeding risk with clopidogrel plus aspirin were not dependent on renal function. Similarly, in a subanalysis of the PLATO study, in which approximately 25% of the study population met the general definition of CKD (creatinine clearance: <60 mL/min), ticagrelor was shown to significantly reduce ischemic events compared with clopidogrel regardless of renal function. Absolute risk reduction with ticagrelor was greater in those with renal impairment compared with those with normal renal function, due to higher baseline risk levels. In addition, the incidence of major bleeding did not differ significantly between the ticagrelor and clopidogrel groups in patients with normal renal function or those with CKD. However, ticagrelor was associated with a numerically higher rate of nonprocedure-related bleeding compared with clopidogrel in patients with CKD (22% vs 15%; P=.54).

In the TRITON–TIMI 38 trial, prasugrel resulted in superior outcomes to clopidogrel in patients with or without CKD.

No dose adjustment is required for prasugrel, prasugrel, or ticagrelor based on renal function. However, with the exception of clopidogrel in some selected indications (eg, stent thrombosis prevention), use in patients with stage 5 CKD is not recommended due to a lack of data in this patient population.

Diabetes

As patients with diabetes and ACS are at a greater risk of cardiovascular events than those without diabetes, it is vital that they achieve adequate platelet inhibition. However, although dual antiplatelet therapy with clopidogrel and aspirin has been shown to reduce ischemic risk in patients with or without diabetes, some studies have suggested that when insulin resistance or diabetes is present, clopidogrel responsiveness is impaired and clinical efficacy is attenuated. This decreased response does not seem to be apparent with prasugrel and ticagrelor therapy. In fact, in a TRITON–TIMI 38 subanalysis, patients with diabetes achieved a greater net clinical benefit from prasugrel compared with patients without diabetes. Similarly, ticagrelor was shown to exhibit equal efficacy in patients with or without diabetes. Pharmacodynamic studies have also demonstrated that ticagrelor exhibits greater platelet inhibition compared with prasugrel in patients with diabetes. In light of these results, guidelines recommend that the management of patients with diabetes and ACS should be the same as that for patients without diabetes.

Moreover, as part of the PARTHENON Program, the efficacy and safety of ticagrelor treatment in patients with diabetes and CAD will be investigated further in the upcoming THEMIS (A Study Comparing Cardiovascular Effects of Ticagrelor Versus Placebo in Patients With Type 2 Diabetes Mellitus) trial.
Peripheral arterial disease

Patients with peripheral arterial disease (PAD) have increased levels of platelet activity and are at an increased risk of cardiovascular events. However, there is a lack of evidence showing the benefits of antiplatelet agents in this patient population. In a meta-analysis of 18 prospective randomized trials (n=5269), despite a positive trend, aspirin therapy did not result in a significant reduction in cardiovascular events compared with placebo in patients with PAD. That being said, in a subgroup analysis of the CAPRIE (Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events) study, the cardiovascular benefit of clopidogrel was shown to be significantly greater in patients with PAD, with a relative risk reduction of 23.8% (P=0.0028), compared with aspirin therapy. In addition, subanalyses of the PLATO and PEGASUS–TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis In Myocardial Infarction 54) studies show that, in patients with ACS, dual antiplatelet therapy with ticagrelor and aspirin results in consistent relative risk reduction in patients with or without concomitant PAD. However, in the EUCLID (Effects of Ticagrelor and Clopidogrel in Patients with Peripheral Artery Disease) study (n=13,885), in patients with established PAD receiving background aspirin therapy, ticagrelor 90 mg twice daily did not significantly reduce the primary end point of cardiovascular death, MI, or ischemic stroke, compared with clopidogrel 75 mg once daily (10.8% vs 10.6%; hazard ratio = 1.02; 95% CI, 0.92–1.13; P=.65). Additionally, there was no differential increase in the relative risk of limb ischemia and peripheral revascularization, and an increased risk of bleeding events.

In a subanalysis of the TRA 2P–TIMI 50 study, the addition of vorapaxar to standard therapy did not significantly reduce the risk of cardiovascular death, MI, or stroke in patients with PAD, but was associated with a significant reduction in the rate of limb ischemia and peripheral revascularization, and an increased risk of bleeding events.

Consequently, current guidelines recommend antiplatelet monotherapy with aspirin or clopidogrel in patients with PAD, with clinical data demonstrating that clopidogrel is more effective than aspirin in reducing the combined risk of ischemic stroke, MI, or vascular death in patients with atherosclerotic CVD, with an overall safety profile similar to that of medium-dose aspirin.

Chronic obstructive pulmonary disease

Following an ACS event, patients with chronic obstructive pulmonary disease (COPD) are at an increased risk of recurrent ischemic events and all-cause mortality compared with those without COPD. Although ticagrelor has been shown to result in superior outcomes compared with clopidogrel in a number of high-risk patient populations, clinicians may be reluctant to prescribe ticagrelor to patients with COPD due to the increased incidence of dyspnea associated with ticagrelor therapy. However, in a post-hoc analysis of the PLATO study, compared with clopidogrel, ticagrelor substantially reduced absolute ischemic risk in patients with COPD, without increasing overall major bleeding events. Additionally, there was no differential increase in the relative risk of dyspnea in patients with COPD compared with patients without COPD, and no COPD status-by-treatment interactions were observed. Current ACS guidelines do not specify which antiplatelet therapy should be used in patients with COPD who have ACS or CAD.

Patients with atrial fibrillation receiving oral anticoagulant therapy

In patients with ACS, the presence of atrial fibrillation is associated with higher rates of mortality, recurrent ischemic events, and moderate and severe bleeding events. The optimal treatment regimen for patients with atrial fibrillation presenting with ACS is still under debate. Guidelines recommend a short period of triple therapy, consisting of aspirin, a P2Y12 receptor inhibitor, and an oral anticoagulant, followed by an oral anticoagulant and a single antiplatelet therapy, preferably clopidogrel, for up to 12 months. Despite guideline recommendations, only around 17% of patients with atrial fibrillation are discharged on triple therapy following hospitalization with ACS. This may be due, in part, to the fact that compared with oral anticoagulation alone, triple therapy substantially increases the risk of bleeding complications. Additionally, one study demonstrated that clopidogrel monotherapy was associated with a significant reduction in bleeding complications, without an increase in the rate of thrombotic events compared with clopidogrel plus aspirin in patients receiving oral anticoagulants.

The risk of stent thrombosis and recurrent ischemic events vs the potential embolic complications of untreated atrial fibrillation needs to be carefully considered when deciding on the optimal treatment regimen. Guidelines recommend that in patients with ACS and concomitant atrial fibrillation, assessment of stroke risk (using the CHA2DS2-VASc score) should be performed regularly. To minimize bleeding risk in this patient population, the duration of triple therapy should be as short as possible (minimum of 4 weeks and no longer than 6 months); clopidogrel should be the P2Y12 receptor of choice; and a low daily dose of aspirin (75–100 mg) should be used. In addition, proton pump inhibitors should be considered in patients at an increased risk of gastrointestinal bleeding.

In patients at a particularly high bleeding risk, one alternative to anticoagulant therapy is to exclude the left atrial appendage (LAA) using the WATCHMAN device. The device is implanted in the LAA to prevent blood clots from entering the bloodstream and causing a stroke. It was approved by the FDA in 2015 for use in patients with atrial fibrillation at an increased risk of stroke, who are recommended for anticoagulant use, but with an appropriate reason to seek a nondrug alternative, such as those at a high risk of bleeding events. The device has been shown to be noninferior to warfarin in reducing cardiovascular events. Although a higher rate of safety complications was observed with the WATCHMAN in comparison with warfarin, many of these were procedure-related and decreased in frequency with greater operator experience.

Summary

Numerous studies have demonstrated the benefits of antithrombotic therapy in preventing recurrent cardiovascular events following an ACS event, and the increased bleeding risk that accompanies this ischemic benefit. Following an ACS event, a period of dual antiplatelet therapy with a P2Y12 receptor inhibitor and low-dose aspirin is recommended (Table 4), followed by the indefinite administration of aspirin monotherapy. However, as the available
P2Y<sub>12</sub> receptor inhibitors differ in their mechanisms of action and efficacy and safety profiles, the choice of P2Y<sub>12</sub> receptor inhibitor, along with the duration of dual antiplatelet therapy, can be tailored to the individual patient to maximize ischemic risk reduction and minimize bleeding risk.

Newer P2Y<sub>12</sub> receptor inhibitors, prasugrel and ticagrelor, result in faster and more potent platelet inhibition and improved patient outcomes compared with clopidogrel, and are now generally recommended for most patients following an ACS event. However, in certain patient populations in whom bleeding risk is high, such as those with atrial fibrillation receiving concomitant anticoagulant therapy, clopidogrel remains the preferred option. Likewise, although a 12-month period of dual antiplatelet therapy is often recommended, this period can be prolonged or shortened depending on an individual patient's ischemic and bleeding risk.

In conclusion, when considering a patient's antithrombotic treatment regimen, an initial risk assessment is vital. Simple algorithms or risk scores, such as the clinical prediction tool derived and validated using data from the DAPT study, may be of some benefit in aiding clinicians in their treatment decisions. However, further research is required to assess the potential effects of these risk scores on patient outcomes before they are used routinely in clinical practice. In the meantime, a full assessment of a patient's bleeding and ischemic risk factors (including comorbidities, concomitant medication, ACS type, and intended management strategy) should be done, and the treatment strategy should be tailored accordingly to achieve the optimal platelet inhibition for the individual patient.

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**Case Study #1**

**A patient receiving dual antiplatelet therapy following drug-eluting stent placement 4 weeks ago. Presents with significant spontaneous intracranial bleeding.**

Treatment recommendations:

- The risk of complications with continuation of antiplatelet therapy would be very high.
- If the neurosurgical team agrees, withhold all antiplatelet medications, with close monitoring of symptoms, clinical examination, electrocardiograms and laboratory measurements, as appropriate.
- Antiplatelet therapy can be resumed once the patient is stable.

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**Case Study #2**

**A patient with high bleeding risk requires emergency surgery during the time period of suggested dual antiplatelet therapy.**

Treatment recommendations:

- If the surgical team agrees, continue with aspirin peri-operatively, initiate a short acting anticoagulant, such as intravenous heparin, to be stopped temporarily and restarted once bleeding risk improves.
- If the patient is able to tolerate the heparin infusion, dual antiplatelet therapy can be resumed.

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**Case Study #3**

**A patient with a history of gastrointestinal bleeding and chronic atrial fibrillation is receiving warfarin. The patient presents with a complaint consistent with unstable angina, and is found to have an 85% stenosis of the proximal left anterior descending.**

Treatment recommendations:

- **Intervention:** drug-eluting stent.
- **Postintervention:** Give a bolus dose of clopidogrel 600 mg, followed by clopidogrel 75 mg daily in addition to warfarin for approximately 12 months. At 12 months, clopidogrel can be discontinued and aspirin therapy initiated.

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**Case Study #4**

**A patient with advanced liver disease and end-stage renal disease is receiving anticoagulation for acute deep vein thrombosis (4 weeks ago). The patient presents with STEMI requiring PCI.**

Treatment recommendations:

- As the patient has both high bleeding risk and an increased risk of thrombosis, an individualized approach to selection of stent type and triple therapy use is necessary.
- If therapy duration longer than 14 days is warranted, close monitoring for tolerance—in selected patients who are able to reliably participate in their own care—can be considered.
- An interventionalist can consider placing a bare-metal stent, which would require shorter duration of antiplatelet therapy than a drug-eluting stent.
A patient with a history of prior CABG and PCI (4 weeks after bare metal stent or 6 months after drug eluting stent). Presents with atrial fibrillation with a CHA2-D-S2-VASc score of 4.

Treatment recommendations:

- If the patient is at low bleeding risk (according to the HAS-BLED score), triple therapy (aspirin, a P2Y12 receptor inhibitor, and an oral anticoagulant) can be administered for 12 months, followed by aspirin and an oral anticoagulant.
- If the patient is at high bleeding risk, WATCHMAN device placement can be considered.

References


