Post-PCI Selection of Antithrombotic Therapy

Improvements in antithrombotic pharmacotherapy have led to important reductions in complications after percutaneous coronary intervention.

BY JOHN P. VAVALLE, MD, AND ROBERT A. HARRINGTON, MD

Since the introduction of percutaneous coronary intervention (PCI) more than 3 decades ago, the rates of procedural success and associated ischemic complications have substantially improved. This is due, at least in part, to advancements in antithrombotic pharmacotherapy targeted at inhibiting platelet activation/aggregation and thrombin generation/activity that occurs at the site of vessel injury after plaque disruption with balloon and stent procedures (Figure 1). Early studies with bare-metal stents used a potent antithrombotic regimen of aspirin and anticoagulants like vitamin K antagonists, but they demonstrated a significant bleeding risk, with in-hospital stent thrombosis rates as high as 3% to 4%.1,2 The introduction of thienopyridines ushered in a new era of dual-antiplatelet therapy (DAT; aspirin plus a thienopyridine) and resulted in substantial reductions in the rates of stent thrombosis and myocardial infarction (MI), as well as decreased bleeding risk compared with use of oral anticoagulants after the procedure.3,4

DAT is now the standard of care after PCI. However, antithrombotic therapy after PCI is becoming increasingly more complex with the introduction of new therapies that have shown promise in further reducing ischemic complications, although often with a risk of increased bleeding (Figure 2). In this article, we review the antithrombotic agents that are currently available or are being investigated for use after PCI and highlight the challenges in selecting the optimal therapy.

ASPIRIN

Aspirin inhibits platelet aggregation by irreversibly inhibiting cyclooxygenase and blocking the production of thromboxane A2 (Figure 2). Early studies aimed at showing a reduction in restenosis rates with aspirin after balloon angioplasty failed to demonstrate this but did show a beneficial effect in reducing ischemic events.5,6 As a result of these findings and aspirin’s proven effect on reducing cardiovascular events among a broader group of coronary artery disease patients, aspirin represents the cornerstone of antiplatelet therapy before and after PCI.7

The optimal dose of aspirin before and after PCI remains uncertain. The CURRENT-OASIS 7 trial investigated high-dose aspirin (300–325 mg) versus low-dose aspirin (75–100 mg) in the treatment of acute coronary syndrome (ACS) in patients undergoing an invasive strategy.8 Among those undergoing PCI, there was no difference in the composite primary or secondary ischemic endpoints between patients who received high- or low-dose aspirin.9

dose aspirin. There was also no difference in major bleeding, but a higher risk of gastrointestinal bleeding (0.4% vs 0.2%; \( P = .04 \)) was observed with high-dose aspirin.

A post hoc analysis of the CURE study evaluated the impact of different aspirin doses in the treatment of ACS.\(^9\) Although not all patients underwent PCI, this study suggested that when used in combination with clopidogrel, there was no incremental anti-ischemic benefit to using doses of aspirin > 100 mg. The investigators did note an increase in bleeding risk associated with doses > 100 mg. This led the authors to recommend an optimal daily aspirin dose for long-term treatment after an ACS event of between 75 and 100 mg. The recommendations from major medical societies for aspirin use after PCI are listed in Table 1.\(^{10-13}\)

**P2Y\(_{12}\) INHIBITORS**

Inhibition of the P2Y\(_{12}\) adenosine diphosphate (ADP) receptor attenuates the aggregation of platelets through inhibiting ADP-mediated platelet activation (Figure 2). The oral P2Y\(_{12}\) inhibitors include the thienopyridine derivatives ticlopidine, clopidogrel, and prasugrel, as well as the nonthienopyridine agent, ticagrelor. These have a more potent antiplatelet effect than aspirin monotherapy and are used in conjunction with aspirin for their complementary mechanism of action.

DAT with aspirin and a P2Y\(_{12}\) inhibitor has resulted in consistent reductions in PCI-related ischemic complications and is the standard of care after PCI. This has been shown in several large clinical trials and in a meta-analysis of more than 6,000 patients in which treatment with aspirin plus a thienopyridine reduced the incidence of stent thrombosis to < 1% as compared with 3% to 4% in previous studies using systemic anticoagulation.\(^1-3\)

The optimal duration of P2Y\(_{12}\) inhibitor therapy after PCI remains undefined but may depend on the type of stent implanted (Table 1). The implantation of a drug-eluting stent (DES), as opposed to a bare-metal stent, appears to portend an increased risk of late stent thrombosis due to impaired endothelialization and increased inflammation at the site of stent deployment.\(^{14,15}\) In this setting, premature discontinuation of DAT appears to be the most significant risk factor for late stent thrombosis.\(^{16-18}\) In a nonrandomized study by Eisenstein and colleagues, extended therapy with aspirin and clopidogrel reduced the risk of death and MI in patients who received DES, with benefit extending as far out as 24 months after DES implantation.\(^{19}\)

The understanding of the benefits of prolonged DAT, especially in the setting of DES, led the 2007 American College of Cardiology (ACC)/American Heart Association (AHA) PCI guidelines committee to recommend “at least” 12 months of DAT, a change from the 2005 guidelines recommendation of “ideally up to” 12 months (Table 1).\(^{10,20}\) The ongoing Dual Antiplatelet Therapy Study, which is a large, prospective, randomized trial of more than 20,000 patients evaluating the role of DAT beyond 12 months after stent implantation, will provide insight into optimal DAT duration.\(^{21}\) Until these data are available for patients with high-risk features for stent thrombosis, such as bifurcation lesions, diabetes, or multiple overlapping stents, current guidelines state that it is reasonable to continue DAT beyond a year as long as the risk-benefit ratio of prolonged DAT is carefully considered.\(^{20}\)

**TICLOPIDINE**

Ticlopidine, the first thienopyridine available, demonstrated significant reductions in ischemic events after PCI. In the STARS study, aspirin with ticlopidine reduced the incidence of death, target lesion revascularization, vessel thrombosis, or MI at 30 days to 0.5% as compared to 3.6% with aspirin monotherapy and 2.7% with aspirin plus warfarin.\(^{22}\)

Ticlopidine has now largely been replaced by other available P2Y\(_{12}\) inhibitors like clopidogrel due to the incidence of serious adverse side effects, such as thrombotic thrombocytopenic purpura and agranulocytosis. In two randomized trials, clopidogrel and ticlopidine showed similar efficacy in terms of major adverse car-
<table>
<thead>
<tr>
<th>Drug</th>
<th>ACC/AHA/SCAI 2007 PCI Focused Update Recommendations&lt;sup&gt;10&lt;/sup&gt;</th>
<th>ESC Recommendations on Antiplatelet Agents&lt;sup&gt;11,13&lt;/sup&gt;</th>
<th>Antithrombotic Therapy During PCI: 7th ACCP Conference on Antithrombotic and Thrombolytic Therapy&lt;sup&gt;12&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>Aspirin</td>
<td>Class I: Pretreatment for patients on aspirin: 75–325 mg</td>
<td>Class I: Pretreatment with aspirin: 160–325 mg</td>
<td>Grade 1A: For patients undergoing PCI: pretreatment with 75–325 mg</td>
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<td>Pretreatment for patients not on aspirin: 300–325 mg 2–24 h prior to PCI</td>
<td>Maintenance aspirin: 75–100 mg long-term</td>
<td>For long-term treatment after PCI: aspirin 75–162 mg/d</td>
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<td>After PCI: 162–325 mg daily for at least 1 month after bare-metal stent, 3 months after sirolimus DES, 6 months after paclitaxel DES</td>
<td>Grade 1C: For long-term treatment after PCI for patients receiving antithrombotics such as clopidogrel or warfarin: 75–100 mg/d</td>
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<td></td>
<td>Long-term therapy: 75–162 mg daily indefinitely</td>
<td>Grade 1B: Loading dose at least 6 h prior to PCI: 300 mg</td>
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<tr>
<td>Clopidogrel</td>
<td>Class I: Pre-PCI loading dose: 600 mg</td>
<td>Class I: Loading dose: 300 mg (600 mg when rapid onset of action is desired)</td>
<td>Grade 2C: If &lt; 6 h prior to planned PCI: 600 mg loading dose</td>
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<td>Post-PCI: clopidogrel 75 mg daily for at least 12 months after DES and a minimum of 1 month and ideally up to 12 months after bare-metal stenting</td>
<td>Daily dose: clopidogrel 75 mg/d for 3–4 weeks after bare-metal stenting and 6–12 months after DES placement</td>
<td>Grade 1A: After PCI: 75 mg/d clopidogrel for at least 9–12 months</td>
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<td>Class IIb: Clopidogrel beyond 1 year may be considered in patients undergoing DES placement</td>
<td>Grade 1C: After PCI: 75 mg/d clopidogrel for at least 2 weeks after bare-metal stenting, 2–3 months after sirolimus DES placement (grade 1C), and 6 months after paclitaxel DES placement (grade 1C)</td>
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Abbreviations: ACCP, American College of Chest Physicians; ESC, European Society of Cardiology; SCAI, Society for Coronary Angiography and Intervention.
diac events, but clopidogrel was associated with significantly fewer side effects than ticlopidine.\textsuperscript{23,24}

**CLOPIDOGREL**

Clopidogrel has been extensively studied for use in the setting of PCI and after stent implantation. The PCI-CURE trial demonstrated the beneficial effect of clopidogrel plus aspirin in reducing cardiovascular death or MI for up to 1 year after stenting among patients presenting with a non–ST-elevation acute coronary syndrome.\textsuperscript{25} In this study, the rate of cardiovascular death or MI was reduced from 12.6\% in those receiving aspirin plus clopidogrel for 4 weeks after PCI to 8.8\% in those receiving DAT for up to 1 year. Similarly, the CREDO study evaluated a pre-PCI clopidogrel load of 300 mg followed by 12 months of daily clopidogrel (75 mg/d) against no clopidogrel loading followed by daily clopidogrel for 28 days only. In this study, patients who were assigned to the clopidogrel load followed by 12 months of daily therapy had a 26.9\% relative reduction in the 12-month incidence of the composite of death, MI, or stroke ($P = .02$).\textsuperscript{26} Data from this study suggest that a 300-mg load should be given at least 6 hours before PCI to allow adequate platelet inhibition; however, with a 600-mg load, administration 2 hours prior to PCI may be a safe interval. In patients on long-term clopidogrel who are undergoing PCI, maintenance doses alone may not be sufficient. Reloading is recommended and is usually accomplished with a 300-mg load.\textsuperscript{20}

Higher doses of clopidogrel after PCI (600-mg load, 150 mg/d for 6 days) have been examined in the CURRENT-OASIS 7 trial.\textsuperscript{8} Although the overall trial results showed no incremental benefit to high-dose clopidogrel, in the prespecified (although postrandomization) subgroup analysis of the more than 17,000 patients who underwent PCI, there was a reduction in the secondary outcome of stent thrombosis at 30 days with the higher dose (1.6\% vs 2.3\%; hazard ratio [HR], 0.68; 95\% confidence interval [CI], 0.55–0.85; $P < .001$). However, this was at a cost of increased major (2.5\% vs 2\%; HR, 1.24; 95\% CI, 1.05–1.46; $P = .01$) and minor bleeding.

Significant interindividual variability in the response to clopidogrel has been well described.\textsuperscript{27} Interactions with drugs, such as proton pump inhibitors, have been associated with a decreased pharmacodynamic response to clopidogrel, and in observational studies, they have been associated with worse clinical outcomes.\textsuperscript{28,29} However, observational analyses from prospective, randomized clinical trials have not corroborated this.\textsuperscript{30,31} The COGENT trial prospectively randomized patients to an omeprazole-clopidogrel combination drug or clopidogrel alone and showed a reduction in gastrointestinal bleeding without an increase in cardiovascular events.\textsuperscript{32} Although COGENT was limited by its modest sample size, relatively brief duration of follow-up, and its premature termination due to financial considerations, it is the only source of randomized data that examines this drug-drug interaction. A consensus statement from the ACC, AHA, and American College of Gastroenterology recommends the use of proton pump inhibitors with a thienopyridine antiplatelet agent in those at high risk for gastrointestinal bleeding.\textsuperscript{33}

Loss of function mutations in the CYP2C19 allele that metabolizes the clopidogrel prodrug have also been associated with worse clinical outcomes for patients taking clopidogrel after an ACS event. In a meta-analysis of patients on clopidogrel after stenting, there was an HR for stent thrombosis of 2.67 (95\% CI, 1.69–4.22; $P < .0001$) for heterozygotes versus wild-type, and 3.97 (95\% CI, 1.75–9.02; $P = .001$) for homozygotes versus wild type.\textsuperscript{34} However, the CYP2C19 mutation appears to have no impact on clinical outcomes with the other P2Y\textsubscript{12} inhibitors, prasugrel and ticagrelor.\textsuperscript{35,36}

The use of platelet function testing to direct clopidogrel dosing after PCI was prospectively tested in the GRAVITAS trial.\textsuperscript{37} In this study, clopidogrel nonresponders, as defined by and assessed with the use of a point-of-care platelet function test, were randomized to high-dose clopidogrel at 150 mg per day versus standard dose clopidogrel (75 mg/d). No reduction in the primary outcome of MI, cardiovascular death, or stent thrombosis was observed with high-dose clopidogrel as compared with standard dose despite demonstrating modest reductions in platelet reactivity. Whether the hypothesis underlying GRAVITAS was incorrect or there were methodological limitations to the trial (including a modest sample size with fewer endpoint events than originally assumed) is under debate.

Further studies are ongoing to test whether platelet function testing or genotyping should play a role in selecting the dose of clopidogrel or in selecting alternative agents such as prasugrel to reduce ischemic events after PCI.\textsuperscript{38,39} Until these data are available, the ACC/AHA writing committee for the Clinical Expert Consensus Document on the use of clopidogrel concluded that “the evidence base is insufficient to recommend either routine genetic or platelet function testing at the present time” and that “there is no information that routine testing improves outcome in large subgroups of patients.” However, they do state that for those at high risk for adverse events who are also identified as poor metabolizers of clopidogrel, other agents such as prasugrel should be considered.\textsuperscript{40} The current guidelines for clopidogrel use are listed in Table 1.

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**Table 1:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Use</th>
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<tr>
<td>Clopidogrel</td>
<td>Secondary prevention of cardiovascular events</td>
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<tr>
<td>Prasugrel</td>
<td>For patients at high risk for cardiovascular events</td>
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<tr>
<td>Ticagrelor</td>
<td>For patients at high risk for cardiovascular events</td>
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PHARMACOLOGY
PRASUGREL

Prasugrel is a newer thienopyridine with a more rapid onset and extent of inhibition of platelet activity.51 In the TRITON-TIMI 38 study, patients with ACS and planned PCI were randomized to clopidogrel (300-mg load, 75 mg daily) or prasugrel (60-mg load, 10 mg daily) in addition to aspirin and followed for up to 15 months.42 In this trial, prasugrel was associated with a lower rate of cardiovascular death, MI, or stroke than clopidogrel (9.9% vs 12.1%; HR, 0.81; P < .001); this was mostly driven by a reduction in nonfatal MI that was also associated with an increase in TIMI major bleeding unrelated to coronary artery bypass grafting (2.4% vs 1.8%; HR, 1.32; P = .03). There was also increased fatal and life-threatening bleeding, seen especially in those with a history of transient ischemic attack or stroke. In the TRITON-STENT substudy of more than 12,000 patients who received at least one stent, prasugrel showed a reduction in both early and late stent thrombosis in both DES and bare-metal stents as compared with clopidogrel (1.13% vs 2.35%; HR, 0.48; P < .0001).43

The 2009 updated ACC/AHA ST-elevation myocardial infarction (STEMI) guidelines included prasugrel as an acceptable adjunctive therapy in the setting of primary PCI.44 However, as noted by the US Food and Drug Administration, which approved the drug for use in the United States in 2009, prasugrel is contraindicated in patients with a history of transient ischemic attack or stroke and should generally be avoided in patients older than 75 years.

TICAGRELOR

Ticagrelor is a reversible, direct-acting, nonthienopyridine inhibitor of the P2Y12 ADP receptor. It too is a more rapid and potent inhibitor of platelets than clopidogrel and was compared to clopidogrel head-to-head in an international, double-blind, randomized controlled trial in more than 18,000 patients with ACS in the PLATO study.45 Ticagrelor showed a reduction in the composite primary endpoint of vascular death, MI, or stroke when compared to clopidogrel (9.8% vs 11.7%; HR, 0.84; P < .001), and there was no difference in the rate of major bleeding (11.6% vs 11.2%; P = .43). However, there was both a higher rate of bleeding unrelated to coronary artery bypass grafting (4.5% vs 3.8%; P = .03) and more fatal intracranial bleeds with ticagrelor than with clopidogrel.

In the PLATO trial, more than 10,000 patients received a stent, and ticagrelor was associated with a reduced rate of stent thrombosis: definite (1.3% vs 1.9%; P = .009); probable or definite (2.2% vs 2.9%; P = .02); and possible, probable, or definite (2.9% vs 3.8%; P = .01). The PLATO-Invasive analysis examined 13,408 patients with a planned early invasive strategy and demonstrated results that mirrored the overall study, with a reduction in the primary composite endpoint but without an increase in major bleeding, suggesting that ticagrelor may be an attractive option for ACS patients being managed with a planned early invasive strategy.46 The agent is approved for use in the European Union but not yet in the United States, as the US Food and Drug Administration continues to review data from the trial concerning a difference in observed treatment effect in the United States compared with the overall trial.

OTHER ANTITHROMBOTIC AGENTS

Cilostazol

Cilostazol selectively inhibits 5’3’-cyclic nucleotide phosphodiesterase III and has antiplatelet and vasodilating effects. It has been shown to reduce restenosis rates with coronary stents.47,48 Two single-center, nonrandomized studies showed that cilostazol, when added to aspirin and a P2Y12 inhibitor, reduced stent thrombosis and other ischemic complications.49,50 However, in a randomized multicenter clinical trial of patients receiving DES, there was no benefit of adding cilostazol to aspirin plus clopidogrel in the reduction of death, MI, ischemic stroke, target lesion revascularization, or stent thrombosis despite a statistically significant reduction in platelet reactivity levels.51 The routine use of adjuvant cilostazol after PCI is not currently recommended by the major medical societies.

Elinogrel

Elinogrel is a novel P2Y12 inhibitor that is available in both oral and intravenous formulations and is the first reversible and competitive inhibitor of the ADP P2Y12 receptor. It is a more potent antiplatelet agent than clopidogrel, with a more rapid onset and offset of action. Its enhanced platelet inhibition, competitive binding nature, and rapid reversibility make it a potentially attractive option. Large clinical trials will be required to test this hypothesis.

Thrombin Receptor Antagonists

Atopaxar and vorapaxar are two novel agents that target thrombin-induced platelet activation by inhibiting the protease-activated receptor 1 and are being studied in patients with ACS and coronary artery disease (Figure 2). Early-phase clinical trials of these drugs have been promising, suggesting a reduction in ischemic events when added to standard therapy.52,53 In the setting of nonurgent PCI, vorapaxar was well tolerated in a phase 2 study.54 More data are needed to evaluate the role of these agents after PCI to define which patients may have the greatest benefit (balanced against tolerable side effects) with these drugs.
Oral Anticoagulants

Since the early trials with warfarin showing a reduction in ischemic events after PCI, there has been hope for a role of oral anticoagulants, in addition to standard of care, to further drive down thrombotic complications after PCI.22 Phase 2 trials of novel oral anticoagulants, such as the factor Xa inhibitors, apixaban and rivaroxaban, as well as the oral direct thrombin inhibitor, dabigatran, have all shown some reductions in ischemic complications after an ACS event at the risk of increased bleeding.54-56 However, this additional bleeding risk remains a significant concern and may limit their applicability. Data are forthcoming from large clinical trials that will clarify their role in this setting.

ANTITHROMBOTIC TREATMENT AFTER PCI FOR PATIENTS REQUIRING LONG-TERM ANTICOAGULATION

The optimal antithrombotic therapy after coronary stenting for patients with an indication for long-term anticoagulant therapy is not clear. The risk of thrombotic and thromboembolic complications must be weighed against the risk of bleeding when considering the addition of DAT on top of chronic oral anticoagulation (so-called triple therapy). Small registry analyses suggest a significant increase in hemorrhagic complications with triple therapy as opposed to DAT alone.57,58 Selecting the appropriate patients for triple antithrombotic therapy involves understanding their indications for oral anticoagulation and the risks associated with discontinuation of anticoagulation, as well as their risk factors for bleeding. Avoiding triple therapy in the elderly, using bare-metal stents with a shortened duration of DAT, and careful monitoring of the international normalized ratio (aiming for the lower end of the target therapeutic range) are reasonable strategies to mitigate bleeding risk.

CONCLUSION

As a result of a better understanding of the pathophysiology of ischemic complications after PCI, significant improvements in antithrombotic therapy have translated into important reductions in the ischemic complications of the procedure. With multiple newer and more powerful antithrombotic agents available, selecting the optimal therapy has become increasingly more challenging. Although use of the more potent antiplatelet and anticoagulant therapies has resulted in a reduction in ischemic events such as stent thrombosis, this is almost always at the cost of increased bleeding. Choosing the optimal therapy for a patient after PCI depends on factors such as the type of stent implanted and comorbidities of the patient and must be tailored to balance the ischemic and bleeding risk of that individual. Ongoing trials will help to define the most appropriate regimen for these patients.

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