

Post-PCI Selection of Antithrombotic Therapy

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

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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-

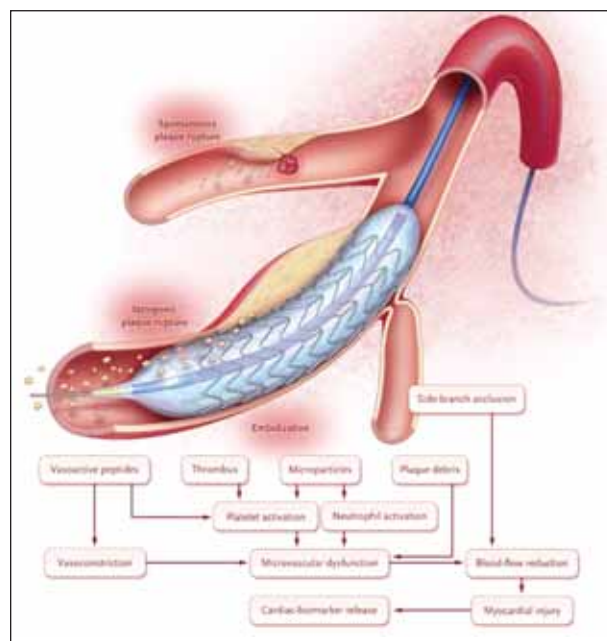


Figure 1. Plaque disruption and vessel injury at the site of PCI causing downstream ischemia. Reprinted with permission from Prasad A et al. Myocardial infarction due to percutaneous coronary intervention. *N Engl J Med*. 2011; 364:453–464.

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

P2Y₁₂ INHIBITORS

Inhibition of the P2Y₁₂ adenosine diphosphate (ADP) receptor attenuates the aggregation of platelets through inhibiting ADP-mediated platelet activation (Figure 2). The oral P2Y₁₂ 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 P2Y₁₂ 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 P2Y₁₂ 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

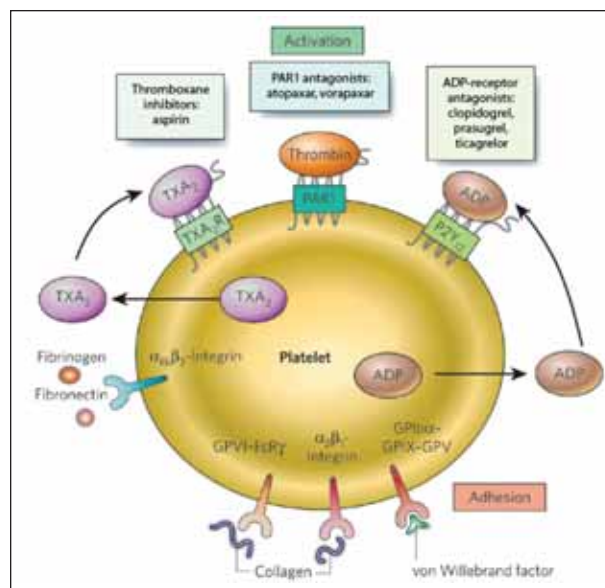


Figure 2. Sites of novel drug development for platelet inhibition. Adapted with permission from Mackman N. Triggers, targets, and treatments for thrombosis. *Nature*. 2008;451:914–918.

(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 P2Y₁₂ 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 1. RECOMMENDATIONS ON ASPIRIN AND CLOPIDOGREL FROM THE MAJOR MEDICAL SOCIETIES

Drug	ACC/AHA/SCAI 2007 PCI Focused Update Recommendations ¹⁰	ESC Recommendations on Antiplatelet Agents ^{11,13}	Antithrombotic Therapy During PCI: 7th ACCP Conference on Antithrombotic and Thrombolytic Therapy ¹²
Aspirin	Class I: Pretreatment for patients on aspirin: 75–325 mg Pretreatment for patients not on aspirin: 300–325 mg 2–24 h prior to PCI 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 Long-term therapy: 75–162 mg daily indefinitely	Class I: Pretreatment with aspirin: 160–325 mg Maintenance aspirin: 75–100 mg long-term	Grade 1A: For patients undergoing PCI: pretreatment with 75–325 mg For long-term treatment after PCI: aspirin 75–162 mg/d Grade 1C: For long-term treatment after PCI for patients receiving antithrombotics such as clopidogrel or warfarin: 75–100 mg/d
Clopidogrel	Class I: Pre-PCI loading dose: 600 mg 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 Class IIb: Clopidogrel beyond 1 year may be considered in patients undergoing DES placement	Class I: Loading dose: 300 mg (600 mg when rapid onset of action is desired) Daily dose: clopidogrel 75 mg/d for 3–4 weeks after bare-metal stenting and 6–12 months after DES placement	Grade 1B: Loading dose at least 6 h prior to PCI: 300 mg Grade 2C: If < 6 h prior to planned PCI: 600 mg loading dose Grade 1A: After PCI: 75 mg/d clopidogrel for at least 9–12 months Clopidogrel 75 mg/d 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)

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.^{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.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 ($P = .02$).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.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.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.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.^{28,29} However, observational analyses from prospective, randomized clinical trials have not corroborated this.^{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.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.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.³⁴ However, the CYP2C19 mutation appears to have no impact on clinical outcomes with the other P2Y₁₂ inhibitors, prasugrel and ticagrelor.^{35,36}

The use of platelet function testing to direct clopidogrel dosing after PCI was prospectively tested in the GRAVITAS trial.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.^{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.⁴⁰ The current guidelines for clopidogrel use are listed in Table 1.

PRASUGREL

Prasugrel is a newer thienopyridine with a more rapid onset and extent of inhibition of platelet activity.⁴¹ 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.⁵² 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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1. Serruys PW, de Jaegere P, Kiemeneij F, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. *N Engl J Med*. 1994;331:489-495.
2. Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. *N Engl J Med*. 1994;331:496-501.
3. Cutlip DE, Baim DS, Ho KK, et al. Stent thrombosis in the modern era: a pooled analysis of multicenter coronary stent clinical trials. *Circulation*. 2001;103:1967-1971.
4. Schomig A, Neumann FJ, Kastrati A, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. *N Engl J Med*. 1996;334:1084-1089.
5. Schwartz L, Bourassa MG, Lesperance J, et al. Aspirin and dipyridamole in the prevention of restenosis after percutaneous transluminal coronary angioplasty. *N Engl J Med*. 1988;318:1714-1719.
6. Barnathan ES, Schwartz JS, Taylor L, et al. Aspirin and dipyridamole in the prevention of acute coronary thrombosis complicating coronary angioplasty. *Circulation*. 1987;76:125-134.
7. Wallentin LC. Aspirin (75 mg/day) after an episode of unstable coronary artery disease: long-term effects on the risk for myocardial infarction, occurrence of severe angina, and the need for revascularization. Research Group on Instability in Coronary Artery Disease in Southeast Sweden. *J Am Coll Cardiol*. 1991;18:1587-1593.
8. Mehta SR, Bassand JP, Chrolavicius S, et al. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. *N Engl J Med*. 2010;363:930-942.
9. Peters RJ, Mehta SR, Fox KA, et al. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study. *Circulation*. 2003;108:1682-1687.
10. King SB 3rd, Smith SC Jr, Hirshfeld JW Jr, et al. 2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: 2007 Writing Group to Review New Evidence and Update the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention, Writing on Behalf of the 2005 Writing Committee. *Circulation*. 2008;117:261-295.
11. Bassand JP, Hamm CW, Ardissino D, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. *Eur Heart J*. 2007;28:1598-1660.
12. Popma JJ, Berger P, Ohman EM, et al. Antithrombotic therapy during percutaneous coronary intervention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126:576S-599S.
13. Silber S, Albertsson P, Aviles FF, et al. Guidelines for percutaneous coronary interventions. The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. *Eur Heart J*. 2005;26:804-847.
14. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol*. 2006;48:193-202.

15. Kotani J, Awata M, Nanto S, et al. Incomplete neointimal coverage of sirolimus-eluting stents: angioscopic findings. *J Am Coll Cardiol*. 2006;47:2108-2111.
16. Pfisterer M, Brunner-La Rocca HP, Buser PT, et al. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. *J Am Coll Cardiol*. 2006;48:2584-2591.
17. Spertus JA, Kettelkamp R, Vance C, et al. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: results from the PREMIER registry. *Circulation*. 2006;113:2803-2809.
18. Airolidi F, Colombo A, Morici N, et al. Incidence and predictors of drug-eluting stent thrombosis during and after discontinuation of thienopyridine treatment. *Circulation*. 2007;116:745-754.
19. Eisenstein EL, Anstrom KJ, Kong DF, et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. *JAMA*. 2007;297:159-168.
20. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). *J Am Coll Cardiol*. 2006;47:e1-121.
21. The Dual Antiplatelet Therapy Study (DAPT Study). *Clinicaltrials.gov* Web site. <http://www.clinicaltrials.gov/ct2/show/NCT00977938>. Accessed February 25, 2011.
22. Leon MB, Baim DS, Popma JJ, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. *N Engl J Med*. 1998;339:1665-1671.
23. Bertrand ME, Rupprecht HJ, Urban P, et al. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting: the clopidogrel aspirin stent international cooperative study (CLASSICS). *Circulation*. 2000;102:624-629.
24. Muller C, Buttner HJ, Petersen J, et al. A randomized comparison of clopidogrel and aspirin versus ticlopidine and aspirin after the placement of coronary-artery stents. *Circulation*. 2000;101:590-593.
25. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet*. 2001;358:527-533.
26. Steinhilber SR, Berger PB, Mann JT 3rd, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2002;288:2411-2420.
27. Gurbel PA, Bliden KP, Hayes KM, et al. The relation of dosing to clopidogrel responsiveness and the incidence of high post-treatment platelet aggregation in patients undergoing coronary stenting. *J Am Coll Cardiol*. 2005;45:1392-1396.
28. Angiolillo DJ, Gibson CM, Cheng S, et al. Differential effects of omeprazole and pantoprazole on the pharmacodynamics and pharmacokinetics of clopidogrel in healthy subjects: randomized, placebo-controlled, crossover comparison studies. *Clin Pharmacol Ther*. 2011;89:65-74.
29. Stockl KM, Le L, Zakharyan A, et al. Risk of rehospitalization for patients using clopidogrel with a proton pump inhibitor. *Arch Intern Med*. 2010;170:704-710.
30. O'Donoghue ML, Braunwald E, Antman EM, et al. Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomised trials. *Lancet*. 2009;374:989-997.
31. Goodman SG, Clare R, Pieper KS, et al. Proton pump inhibitor use is likely a marker for, rather than a cause of, a higher risk of cardiovascular events: insights from PLATO (Abstract). *Circulation*. 2010;122:A12092.
32. Bhatt DL, Cryer BL, Contant CF, et al. Clopidogrel with or without omeprazole in coronary artery disease. *N Engl J Med*. 2010;363:1909-1917.
33. Abraham NS, Hlatky MA, Antman EM, et al. ACCF/ACG/AHA 2010 expert consensus document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. *J Am Coll Cardiol*. 2010;56:2051-2066.
34. Mega JL, Simon T, Collet JP, et al. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. *JAMA*. 2010;304:1821-1830.
35. Mega JL, Close SL, Wiviott SD, et al. Cytochrome P450 genetic polymorphisms and the response to prasugrel: relationship to pharmacokinetic, pharmacodynamic, and clinical outcomes. *Circulation*. 2009;119:2553-2560.
36. Wallentin L, James S, Storey RF, et al. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. *Lancet*. 2010;376:1320-1328.
37. Price MJ. Standard versus high-dose clopidogrel according to platelet function testing after PCI: results of the GRAVITAS trial. *Circulation*. 2010;122:2218.
38. Thrombocyte Activity Reassessment and Genotyping for PCI (TARGET-PCI). *Clinicaltrials.gov* Web site. <http://www.clinicaltrials.gov/ct2/show/nct01177592>. Accessed February 22, 2011.
39. Testing Platelet Reactivity in Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel (TRIGGER-PCI). *Clinicaltrials.gov* Web site. <http://clinicaltrials.gov/ct2/show/NCT00910299>. Accessed February 25, 2011.
40. Holmes DR Jr, Dehmer GJ, Kaul S, et al. ACCF/AHA clopidogrel clinical alert: approaches to the FDA "boxed warning": a report of the American College of Cardiology Foundation Task Force on clinical expert consensus documents and the American Heart Association endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2010;56:321-341.
41. Wiviott SD, Trenk D, Frelinger AL, et al. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 trial. *Circulation*. 2007;116:2923-2932.
42. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357:2001-2015.
43. Wiviott SD, Braunwald E, McCabe CH, et al. Intensive oral antiplatelet therapy for reduction of ischaemic events including stent thrombosis in patients with acute coronary syndromes treated with percutaneous coronary intervention and stenting in the TRITON-TIMI 38 trial: a subanalysis of a randomised trial. *Lancet*. 2008;371:1353-1363.
44. Kushner FG, Hand M, Smith SC Jr, et al. 2009 Focused Updates: ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (updating the 2004 Guideline and 2007 Focused Update) and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention (updating the 2005 Guideline and 2007 Focused Update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2009;120:2271-2306.
45. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:1045-1057.
46. Cannon CP, Harrington RA, James S, et al. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. *Lancet*. 2010;375:283-293.
47. Douglas JS Jr, Holmes DR Jr, Kereiakes DJ, et al. Coronary stent restenosis in patients treated with cilostazol. *Circulation*. 2005;112:2826-2832.
48. Tamhane U, Meier P, Chetcuti S, et al. Efficacy of cilostazol in reducing restenosis in patients undergoing contemporary stent based PCI: a meta-analysis of randomised controlled trials. *EuroIntervention*. 2009;5:384-393.
49. Lee SW, Park SW, Hong MK, et al. Triple versus dual antiplatelet therapy after coronary stenting: impact on stent thrombosis. *J Am Coll Cardiol*. 2005;46:1833-1837.
50. Lee SW, Park SW, Yun SC, et al. Triple antiplatelet therapy reduces ischemic events after drug-eluting stent implantation: Drug-Eluting Stenting Followed by Cilostazol Treatment Reduces Adverse Serious Cardiac Events (DECREASE registry). *Am Heart J*. 2010;159:284-291.
51. Suh JW, Lee SP, Park KW, et al. Multicenter randomized trial evaluating the efficacy of cilostazol on ischemic vascular complications after drug-eluting stent implantation for coronary heart disease: results of the CLON-T (Influence of Cilostazol-Based Triple Antiplatelet Therapy on Ischemic Complications After Drug-Eluting Stent Implantation) trial. *J Am Coll Cardiol*. 2011;57:280-289.
52. Becker RC, Moliterno DJ, Jennings LK, et al. Safety and tolerability of SCH 530348 in patients undergoing non-urgent percutaneous coronary intervention: a randomised, double-blind, placebo-controlled phase II study. *Lancet*. 2009;373:919-928.
53. Goto S, Ogawa H, Takeuchi M, et al. Double-blind, placebo-controlled phase II studies of the protease-activated receptor 1 antagonist E5555 (atopaxar) in Japanese patients with acute coronary syndrome or high-risk coronary artery disease. *Eur Heart J*. 2010;31:2601-2613.
54. Mega JL, Braunwald E, Mohanavelu S, et al. Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46): a randomised, double-blind, phase II trial. *Lancet*. 2009;374:29-38.
55. Alexander JH, Becker RC, Bhatt DL, et al. Apixaban, an oral, direct, selective factor Xa inhibitor, in combination with antiplatelet therapy after acute coronary syndrome: results of the Apixaban for Prevention of Acute Ischemic and Safety Events (APPAISE) trial. *Circulation*. 2009;119:2877-2885.
56. RE-DEEM Dose Finding Study for Dabigatran Etexilate in Patients With Acute Coronary Syndrome. *Clinicaltrials.gov* Web site. <http://www.clinicaltrials.gov/ct2/show/NCT00621855>. Accessed March 2, 2011.
57. Orford JL, Fasseas P, Melby S, et al. Safety and efficacy of aspirin, clopidogrel, and warfarin after coronary stent placement in patients with an indication for anticoagulation. *Am Heart J*. 2004;147:463-467.
58. Khurram Z, Chou E, Minutello R, et al. Combination therapy with aspirin, clopidogrel, and warfarin following coronary stenting is associated with a significant risk of bleeding. *J Invasive Cardiol*. 2006;18:162-164.