Antiplatelet Therapy, Cardiac Surgery, and the Risk of Bleeding: The Surgeon's Perspective

Mariano E. Brizzio, MD, Alex Zapolanski, MD

Valley Heart and Vascular Institute, Ridgewood, NJ

Antiplatelet therapy is widely accepted in the contemporary management of patients with coronary syndromes. Effective platelet inhibition can cause an increased risk of bleeding, which is more evident when patients are referred to surgical coronary revascularization. The cardiac surgeon should be familiar with all new antiplatelet drugs. In this article we compile the latest information about antiplatelet therapy and its impact on cardiac surgery.

[Rev Cardiovasc Med. *2011;12(suppl 1):S40-S46 doi: 10.3909/ricm12S1S0005*]

Key words: Antiplatelet therapy • Cardiac surgery • Bleeding complications

Coronary artery bypass grafting (CABG) is the most common surgical procedure performed by cardiac surgeons in the United States, with close to 300,000 procedures annually.[1]

Perioperative bleeding is not uncommon during cardiac surgical procedures. Approximately 50% to 60% of cardiac surgical patients require blood transfusions perioperatively.[2] There is significant evidence that blood transfusions during cardiac procedures are associated with inferior short- and long-term outcomes.[2-4] Antiplatelet therapy is widely accepted in the contemporary management of patients with coronary syndromes; however, effective platelet inhibition can cause an increased risk of bleeding, particularly in patients who eventually require surgical revascularization.[5]

The Role of the Platelet in the Atherosclerotic Process

Platelets play a critical role in the normal coagulation system by preventing bleeding after blood vessels are damaged. In addition, they contribute to different phases of the atherosclerotic process.[6] Rupture of a previously formed atherosclerotic plaque exposes collagen, smooth-muscle cells, and von Willebrand factor (vWF), all of which trigger platelet activation and massive aggregation.[7] The result of this accumulation of platelets is thrombosis. Acute coronary syndrome (ACS) is a consequence of the occlusion of an atherosclerotic vessel by the thrombotic process. As described, collagen and vWF, in addition to thromboxane A_2 (TxA_2), thrombin, and adenosine diphosphate (ADP), are the most powerful platelet activators.[8] When a platelet is activated, a conformational change occurs in a receptor located in the platelet membrane called glycoprotein (GP) IIb/IIIa, which promotes platelet aggregation.[9]

Antiplatelet agents that target critical steps of the thrombotic mechanism described above have been developed over the past three decades. However, treatment with these agents can sometimes increase the risk of undesirable bleeding complications.[10]

Antiplatelet Agents

Many antiplatelet agents have been tested and used as an effective treatment in arterial thrombosis. Acetyl salicylic acid (commonly known as aspirin) was the first antiplatelet agent used and proven to be effective to reduce the incidence of myocardial infarction (MI) and stroke in many high-risk vascular patients.[10] The recurrence of vascular events in patients treated with aspirin alone ranges between 10% and 20% within 5 years of the initial event.[10]

Aspirin is effective by blocking the synthesis of TxA_2, a powerful platelet activator.[9] In the past decade, thienopyridines (such as clopidogrel) have been used to improve outcomes in the treatment of ACS. This antiplatelet agent irreversibly blocks the $P2Y_{12}$ receptor, precluding the platelet activation by ADP.[10] Its antiplatelet mechanism of action clearly differs from aspirin. In the majority of cardiovascular patients, the combination of clopidogrel and aspirin has additive beneficial effects when compared with clopidogrel or aspirin alone.[10] Clopidogrel also has some limitations, which has prompted the development of newer antiplatelet agents that interact at different sites of the coagulation cascade. Figure 1 and Table 1 reflect the site of action of the common antiplatelet agents.

Antiplatelet Therapy and Cardiac Surgery

It has been estimated that more than 50% of patients undergoing CABG have been exposed to clopidogrel.[11,12] Many studies demonstrate that the risk of postoperative bleeding is higher when clopidogrel is discontinued

In the majority of cardiovascular patients, the combination of clopidogrel and aspirin has additive beneficial effects when compared with clopidogrel or aspirin alone. Clopidogrel also has some limitations, which has prompted the development of newer antiplatelet agents that interact at different sites of the coagulation cascade.

Figure 1. *Platelet activation cascade and site of action of antiplatelets agents. ADP, adenosine diphosphate; GP, glycoprotein; PAR_1, protease-activated receptor 1; TxA_2, thromboxane A_2.*

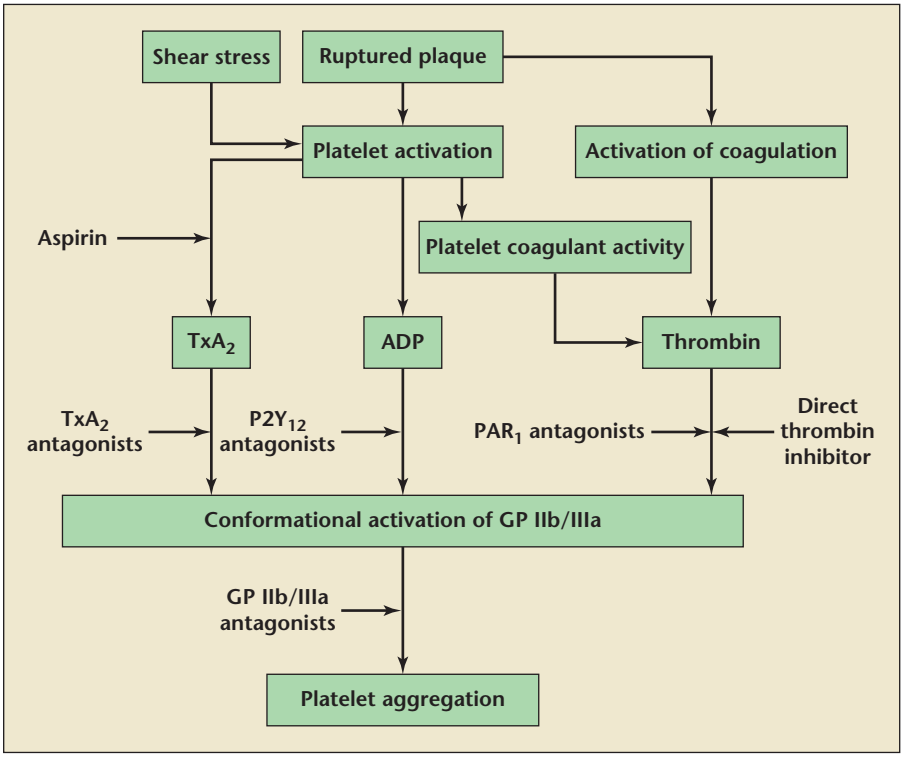

Table 1
Antiplatelet Agents

Inhibits Synthesis of TxA_2
Aspirin
Protease-Activated Receptor 1 Antagonist
Vorapaxar
TxA_2 Antagonists
Dipyridamole
Terutroban
Direct Thrombin Inhibitor
Bivalirudin
$P2Y_{12}$ Antagonists
Ticlopidine
Clopidogrel
Prasugrel
Ticagrelor
Cangrelor
Glycoprotein IIb/IIIa Antagonist
Abciximab
Tirobiban
Eptifibatide

TxA_2, thromboxane A_2.

within < 5 days of surgery.[12] Based on the current evidence, the American College of Cardiology/American Heart Association guidelines for managing patients with coronary artery disease who undergo CABG recommend withholding clopidogrel for 5 to 7 days before the surgical procedure.[13]

The risk of bleeding in CABG patients who are receiving dual antiplatelet therapy (DAPT) has been extensively described.[12-15] In a recent published study in which a cohort of 596 patients was analyzed, significant bleeding complications occurred in those who received clopidogrel within 5 days of CABG.[12] A more recent study including 4794 such patients reported no significant increase of bleeding risk.[15] Despite the conflicting results, neither of these studies considered the potential of clopidogrel resistance and the possible effects in efficacy impacting bleeding outcomes. In a recent publication, Cuisset and Cayla[16] summarized many reported studies in which clopidogrel nonresponse was evaluated. According to these studies, 20% to 30% of patients demonstrate some level of resistance to clopidogrel; however, not all patients on DAPT bleed excessively following CABG. Recent studies have shown much variation in post-CABG bleeding.[17] Perhaps there is a relationship between this variance in bleeding outcomes and clopidogrel resistance. Further studies are needed to address this hypothesis.

In a recent report by the Society of Thoracic Surgeons regarding blood conservation guidelines, point-of-care PI tests are considered a reasonable tool to identify clopidogrel nonresponders. This identifies candidates for early CABG avoiding the usual waiting time.[18] At the Valley Heart and Vascular Institute (Ridgewood, NJ), the VerifyNow P2Y12 Assay® (Accumetrics, San Diego, CA) is used routinely in every patient referred to cardiac surgery with previous exposure to any thienopyridine (clopidogrel or prasugrel).

At the Valley Heart and Vascular Institute (Ridgewood, NJ), the VerifyNow P2Y12 Assay is used routinely in every patient referred to cardiac surgery with previous exposure to any thienopyridine (clopidogrel or prasugrel).

The VerifyNow P2Y12 Assay

The VerifyNow P2Y12 Assay is a rapid platelet function cartridge-based assay designed to measure directly the effects of drugs on the $P2Y_{12}$ receptor. This assay uses prostaglandin E_1 in addition to ADP to increase intraplatelet cyclic-3′,5′-adenosine monophosphate (cAMP), making the assay more sensitive and specific to the effects of ADP mediated by the $P2Y_{12}$ receptor. When the whole blood sample contacts the fibrinogen-coated microparticles included in the cartridges the available platelet receptors activate and aggregate. The VerifyNow P2Y12 Assay measures platelet-induced aggregation as an increase in light transmittance. $P2Y_{12}$ reaction units (PRUs) indicate the amount of ADP-mediated aggregation specific to the $P2Y_{12}$ receptor. PRU is calculated as a function of the rate and extent of platelet aggregation. Percent of inhibition is the change from baseline aggregation, and is calculated from the PRU result and the base result. Expected values are in the range of 0% to 100%. Higher percentage values of inhibition are reported if the thienopyridines have produced the expected antiplatelet effect.

The VerifyNow P2Y12 Assay measures the platelet-induced aggregation as an increase in light transmittance. $P2Y_{12}$ reaction units indicate the amount of adenosine diphosphate-mediated aggregation specific to the $P2Y_{12}$ receptor.

Based on manufacturer recommendations a test result of ≤ 20% is considered a very low grade of platelet inhibition. This result is also consistent

with previous reports demonstrating platelet inhibition after discontinuation of clopidogrel for 5 days and, therefore, may represent an acceptable bleeding risk for a patient to undergo a surgical procedure.[19,20]

Our Experience With the VerifyNow P2Y12 Assay

In a recent study conducted in our institution (Valley Heart and Vascular Institute, Ridgewood, NJ), we sought to determine the utility of the VerifyNow P2Y12 Assay in measuring the PI in patients receiving preoperative clopidogrel. Between June 2007 and July 2009, 482 isolated CABG procedures were performed. We divided the cohort into four subgroups. Group 1 (n = 205) consisted of patients who were not taking clopidogrel. Group 2 (n = 117) included patients who were taking clopidogrel but in whom the test was not performed. Group 3 (n = 122) included patients in whom the test was performed, resulting in a ≤ 20% platelet inhibition. Group 4 (n = 38) included patients in whom the test was performed, resulting in a ≥ 21% platelet inhibition. Patient demographics were comparable in all groups. The median waiting time for surgery from the last dose of clopidogrel was 6 days for the control groups and 3 days for the groups in whom the test was performed ($P < .001$)

Reoperation for bleeding occurred more often in Group 4 (7.9%; $P = .003$). Blood utilization was reduced in Group 1 (24.4%) when compared with Group 2 (34.2%), Group 3 (40.2%), and Group 4 (55.3%) ($P < .001$). Major complications and postoperative length of stay were similar in all groups. This study concluded that the utilization of the VerifyNow P2Y12 Assay in the preoperative assessment of CABG patients previously exposed to clopidogrel significantly reduces the waiting time for elective surgery. Platelet inhibition ≥ 21% is associated with an increased risk of reoperation for bleeding and blood usage.[5]

Other Agents in Use

Dipyridamole

Dipyridamole inhibits the uptake of adenosine into platelets. This inhibition results in an increase in local concentrations of adenosine, which acts on the platelet A_2 receptor, thereby stimulating platelet adenylate cyclase and increasing platelet cAMP levels. Via this mechanism, platelet aggregation is inhibited in response to various stimuli such as platelet activating factor, collagen, and ADP.[21] Modified-release dipyridamole is used in conjunction with aspirin in the secondary prevention of stroke and transient ischemic attack.[22]

Because its half-life is 12 hours, it takes approximately 2.5 hours for the antiplatelet effect to dissipate completely; therefore, discontinuing this drug 2 days before surgery should reduce potential bleeding risks. A triple therapy of aspirin, clopidogrel, and dipyridamole has been investigated, but this combination led to an increase in adverse bleeding events and its use is not approved.[23]

Terutroban

Terutroban is a selective antagonist of the thromboxane receptor. It blocks thromboxane-induced platelet aggregation and vasoconstriction. As of 2010, it is being tested for the secondary prevention of acute thrombotic complications in a phase III clinical trial. However, the recent publication of the finalized Terutroban Versus Aspirin in Patients With Cerebral Ischaemic Events (PERFORM) trial showed no clinical advantage in patients with aspirin monotherapy in preventing strokes. At the time of this publication, its use in clinical practice is not approved in the United States.[24]

Ticlopidine

Ticlopidine is an antiplatelet drug in the thienopyridine family, which inhibits platelet aggregation by altering the function of platelet membranes by irreversibly blocking ADP receptors. This prevents the conformational change of GP IIb/IIIa, which allows platelet binding to fibrinogen.[25] It is used in patients in whom aspirin is not tolerated, or in whom DAPT is desirable (in combination with aspirin). Because it has been reported to increase the risk of thrombotic thrombocytopenic purpura and neutropenia, its use has largely been supplanted by the newer drug, clopidogrel, which is felt to have a much lower hematologic risk.[26] As with other thienopyridines, it is recommended to discontinue its use 5 to 7 days before surgery.

Prasugrel

Prasugrel, a novel thienopyridine, was approved for clinical use in 2010 by the US Food and Drug Administration (FDA). Unlike clopidogrel, which undergoes a two-step, cytochrome P-450–dependent conversion to its active metabolite, prasugrel only requires single-step activation. Prasugrel is a more potent platelet inhibitor with faster action and inhibition. Also, it has been estimated that, due to its easy metabolism, genetic resistance is less likely.[27] In other words, prasugrel has a significantly lower incidence of hyporesponsiveness in comparison with clopidogrel.[27] Prasugrel activity can be measured using the VerifyNow P2Y12 Assay. In our own clinical experience, it has much higher levels of inhibition than clopidogrel, reached in a shorter period of time. A recent publication by Bonello and colleagues[28] corroborates our impression. The risks of bleeding in cardiac surgery patients is greater with prasugrel than with clopidogrel.[29] This

drug should be discontinued at least 7 days before a surgical intervention and the measurement of platelet inhibition is always recommended.

Ticagrelor

Ticagrelor is the most novel class of antiplatelet drugs, the cyclopentyltriazolo-pyrimidines, which also inhibit the $P2Y_{12}$ receptor as do the thienopyridines. However, it has a simpler and faster metabolism (rapid onset of action) high potency and, most importantly, reversibility.[30] In the Dose Confirmation Study Assessing Antiplatelet Effects of AZD6140 Versus Clopidogrel in non–ST-segment Elevation Myocardial Infarction (DISPERSE-2) study, patients who received either clopidogrel or ticagrelor within the first 24 hours of the last dose had similar risks of bleeding. However, if the surgery was performed 1 to 5 days after the last dose, the risks were significantly lower in the ticagrelor-treated group.[31] The drug was as safe as clopidogrel from a surgical standpoint, despite its more potent initial antiplatelet effect.[31] This drug was recently approved by the FDA for clinical use. Ticagrelor should be discontinued 5 days prior to surgery.[32]

Cangrelor

Cangrelor, an adenosine triphosphate analog, is an investigational intravenous (IV) antiplatelet drug. This agent has biphasic elimination and possesses the advantages of high potency, very fast onset of action, and very fast reversibility after discontinuation.[27] This offers a considerable advantage over other ADP antagonists in patients who might need immediate surgery. However, after initial treatment, patients who received IV cangrelor often require continued treatment with one of the oral $P2Y_{12}$ antagonists, which must be taken into consideration.[27]

Abciximab

Abciximab is an antibody against the GP IIb/IIIa receptor. It was popular with interventional cardiologists 10 years ago. In many catheterization laboratories it was replaced by newer IV agents. Abciximab has a plasma half-life of approximately 10 minutes, with a second phase half-life of approximately 30 minutes. However, its effects on platelet function can be seen for up to 48 hours after the infusion has been terminated, and low levels of GP IIb/IIIa receptor blockade are present for up to 15 days after the infusion is terminated.[33]

Tirofiban

Tirofiban is a synthetic, nonpeptide inhibitor acting on GP IIb/IIIa receptors. It has a rapid onset and short duration of action after proper IV administration. Platelet activity returns to normal 4 to 8 hours after the drug is withdrawn.[34]

Eptifibatide

Eptifibatide is a newer antiplatelet drug that inhibits the GP IIb/IIIa inhibitor. It belongs to the class of the so-called arginine-glycine-aspartate mimetics and reversibly binds to platelets. Eptifibatide has a short half-life of 3 to 5 hours, and after discontinuation platelet activity recovers to normal levels.[35] The drug is the third inhibitor of GP IIb/IIIa that has found broad acceptance with interventional cardiologists.

Vorapaxar

Vorapaxar is a protease-activated receptor 1 antagonist based on the natural product himbacine. It is an experimental pharmaceutical treatment of ACS as a very powerful platelet inhibitor.[36] Interestingly, one of the findings in the Thrombin Receptor Antagonist Percutaneous Coronary Intervention (TRA-PCI) trial was a nonsignificant increase in CABG-related bleeding with vorapaxar despite its very long half-life.[37] In January 2011 the clinical trial was halted; it is unknown if it will continue.

Bivalirudin

Bivalirudin is a specific and reversible intravenous direct thrombin inhibitor. Clinical studies demonstrated consistent positive outcomes in patients with stable angina, unstable angina, non–ST-segment elevation MI, and ST-segment elevation

Main Points

- Antiplatelet therapy plays a very important role in the treatment of coronary syndromes. The effectiveness of these agents warrants optimal outcomes in percutaneous coronary intervention and coronary artery bypass graft patients.
- Bleeding complications in cardiac surgery patients are widely demonstrated even with the newest and most developed antiplatelet agents.
- The implementation of any tool available to identify high-risk bleeding patients warrants the best postoperative outcomes.
- The cardiac surgeon should be familiar with the latest antiplatelet therapies and be ready to face new challenges.

MI undergoing PCI in seven major randomized trials.[38] Coagulation times and platelet activity return to baseline approximately 1 to 6 hours following cessation of bivalirudin administration.[39] However, in clinical practice, the bleeding effect in cardiac surgery patients could be much longer, especially if cardiopulmonary bypass has been used.

Conclusions

Antiplatelet therapy plays a crucial role in the treatment of coronary patients. The continuous introduction of new agents is geared to improve results in patients ongoing PCI. These new drugs have significant repercussions in patients requiring CABG. The cardiac surgeon should be familiar with all these new drugs and be ready to face new challenges. In the end, the ideal management of these patients has to be a collaborative effort between cardiologists and surgeons. We should use all the tools available to assure the best possible outcomes. ■

Drs. Brizzio and Zapolanski report no real or apparent conflicts of interest.

References

1. Epstein AJ, Polsky D, Yang F, et al. Coronary revascularization trends in the United States, 2001-2008. *JAMA*. 2011;305:1769-1776.
2. Spiess BD. Blood transfusion: the silent epidemic. *Ann Thorac Surg*. 2001;72:S1832-S1837.
3. Engoren MC, Habib RH, Zacharias A, et al. Effect of blood transfusion on long-term survival after cardiac operation. *Ann Thorac Surg*. 2002;74:1180-1186.
4. Koch CG, Li L, Sessler DI, et al. Duration of red-cell storage and complications after cardiac surgery. *N Engl J Med*. 2008;358:1229-1239.
5. Brizzio ME, Shaw RE, Grau J, et al. Use of an objective tool to assess platelet inhibition prior to off-pump coronary surgery to reduce blood usage and cost. *J Invasive Cardiol*. In press.
6. Hoffman M, Monroe DM 3rd, Roberts HR. Activated factor VII activates factor IX on the surfaces of activated platelets. *Blood Coagul Fibrinolysis*. 1998;9(suppl 1):S61-S65.
7. Heemskerk JW, Siljander P, Vuist WM, et al. Funtion of glycoprotein VI and integrin alpha2beta1 in the procoagulant response of single, collagen-adherent platelets. *Thromb Haemost*. 1999;81:782-792.
8. Jin J, Kunapuli SP. Coactivation of two different G protein-coupled receptors is essential for ADP-induced platelet aggregation. *Proc Natl Acad Sci U S A*. 1998;95:8070-8074.
9. Hechler B, Léon C, Vial C, et al. The P2Y1 receptor is necessary for adenosine 5′-diphosphate-induced platelet aggregation. *Blood*. 1998;92: 152-159.
10. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet*. 1996;348:1329-1339.
11. Ebrahimi R, Dyke C, Mehran R, et al. Outcomes following pre-operative clopidogrel administration in patients with acute coronary syndromes undergoing coronary artery bypass surgery: the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) trial. *J Am Coll Cardiol*. 2009;53:1965-1972.
12. Berger JS, Frye CB, Harshaw Q, et al. Impact of clopidogrel in patients with acute coronary syndromes requiring coronary artery bypass surgery: a multicenter analysis. *J Am Coll Cardiol*. 2008;52:1693-1701.
13. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *J Am Coll Cardiol*. 2007;50:e1-e157.
14. Mehta SR, Yusuf S, Peters RJ, et al; Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE) Investigators. 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.
15. Kim JH, Newby LK, Clare RM, et al. Clopidogrel use and bleeding after coronary artery bypass surgery. *Am Heart J*. 2008;156:886-892.
16. Cuisset T, Cayla G. Aspirin and clopidogrel resistance: should we worry about? *Minerva Med*. 2010;101:35-47.
17. Kapetanakis EI, Medlam DA, Boyce SW, et al. Clopidogrel administration prior to coronary artery bypass grafting surgery: the cardiologist's panacea or the surgeon's headache? *Eur Heart J*. 2005;26: 576-583.
18. Ferraris VA, Brown JR, Despotis GJ, et al. 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. *Ann Thorac Surg*. 2011;91:944-982.
19. Price MJ, Coleman JL, Steinhubl SR, et al. Onset and offset of platelet inhibition after high-dose clopidogrel loading and standard daily therapy measured by a point-of-care assay in healthy volunteers. *Am J Cardiol*. 2006;98:681-684.
20. Chen L, Bracey AW, Radovancevic R, et al. Clopidogrel and bleeding in patients undergoing elective coronary artery bypass grafting. *J Thorac Cardiovasc Surg*. 2004;128:425-431.
21. Harker LA, Kadatz RA. Mechanism of action of dipyridamole. *Thromb Res Suppl*. 1983;4:39-46.
22. Halkes PH, van Gijn J, Kappelle LJ, et al; ESPRIT Study Group. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. *Lancet*. 2006;367:1665-1673.
23. Sprigg N, Gray LJ, England T, et al. A randomised controlled trial of triple antiplatelet therapy (aspirin, clopidogrel and dipyridamole) in the secondary prevention of stroke: safety, tolerability and feasibility. *PLoS ONE*. 2008;3:e2852.
24. Bousser MG, Amarenco P, Chamorro A, et al; PERFORM Study Investigators. Terutroban versus aspirin in patients with cerebral ischaemic events (PERFORM): a randomised, double-blind, parallel-group trial. *Lancet*. 2011;377: 2013-2022.
25. Berger PB. Results of the Ticlid or Plavix Post-Stents (TOPPS) trial: do they justify the switch from ticlopidine to clopidogrel after coronary stent placement? *Curr Control Trials Cardiovasc Med*. 2000;1:83-87.
26. Bennett CL, Davidson CJ, Raisch DW, et al. Thrombotic thombocytopenic purpura with ticlopidine in the setting of coronary artery stents and stroke prevention. *Arch Intern Med*. 1999;159:2524-2528.
27. Raju NC, Eikelboom JW, Hirsh J. Platelet ADP-receptor antagonists for cardiovascular disease: past, present and future. *Nat Clin Pract Cardiovasc Med*. 2008;5:766-780.
28. Bonello L, Pansieri M, Mancini J, et al. High on-treatment platelet reactivity after prasugrel loading dose and cardiovascular events after percutaneous coronary intervention in acute coronary syndromes. *J Am Coll Cardiol*. 2011;58:467-473.
29. Wiviott SD, Braunwald E, McCabe CH, et al; TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patient with acute coronary syndromes. *N Engl J Med*. 2007;357:2001-2015.
30. Cannon CP, Husted S, Harrington RA, et al; DISPERSE-2 Investigators. Safety, tolerability, and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome: primary results of the DISPERSE-2 trial. *J Am Coll Cardiol*. 2007;50:1844-1851.
31. 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.
32. Brilinta (ticagrelor) [package insert]. Wilmington, DE: AstraZeneca; 2011.
33. Tcheng JE, Kandzari DE, Grines CL, et al. Benefits and risks of abciximab use in primary angioplasty for acute myocardial infarction: the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial. *Circulation*. 2003;108:1316-1323.
34. Shanmugam G. Tirofiban and emergency coronary surgery. *Eur J Cardiothorac Surg*. 2005; 28:546-550.
35. Mann H, London AJ, Mann J. Equipoise in the enhanced supression of the platelet IIb/IIIa receptor with integrilin trial (ESPRIT): a critical appraisal. *Clin Trials*. 2005;2:233-241.

36. Chackalamannil S, Wang Y, Greenlee WJ, et al. Discovery of a novel, orally active himbacine-based thrombin receptor antagonist (SCH 530348) with potent antiplatelet activity. *J Med Chem*. 2008;51:3061-3064.
37. 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.
38. 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. *J Am Coll Cardiol*. 2009; 54:2205-2241.
39. Stone GW, McLaurin BT, Cox DA, et al; ACUITY Investigators. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med*. 2006;355:2203-2216.