Antiplatelet agents

David Varon[1] and Galia Spectre[1]

[1]*Hadassah-Hebrew University Medical Center, Jerusalem, Israel*

The introduction of aspirin as an anti-thrombotic agent some 50 years ago has changed the therapeutic approach in cardiovascular medicine. Since platelets play a key role in the development of arterial thrombosis, antiplatelet drugs serve as a cornerstone in the prevention and the treatment of these conditions. After many years of a "monopoly" of aspirin, ADP receptor P2Y12 inhibitors were introduced with a significant improvement in clinical outcome. Nowadays dual antiplatelet therapy is the common practice for both acute events and secondary prevention in selected groups of patients. Another revolution was the development of potent inhibitors of the platelet integrin GPIIbIIIa, which significantly improved the outcome of percutaneous interventions (PCI), in cardiology. The improved efficacy of multiple-drug therapy is associated with an increased risk of bleeding, which raises the issue of the dosing of these drugs. Recently, numerous studies have reported a variable laboratory response to aspirin and clopidogrel, which correlates with clinical outcome. Several mechanisms have been proposed to cause this variable response, including genetic variability, disease burden and others. A major obstacle in this field is the lack of a standardized method for testing these responses, and thus some studies cannot be compared to others. Ongoing studies are currently investigating the potential translation of these observations into clinical practice. Such studies may lead to a change in the paradigm of antiplatelet therapy, where individual dose adjustment may improve efficacy and safety. Finally, a variety of new drugs are currently in different stages of development, including new P2Y12 receptor inhibitors, thromboxane receptor blockers, direct thrombin inhibitors and other signaling pathway inhibitors including oral GPIIbIIIa inhibitors. Thus, antiplatelet therapy is currently under intensive development toward multiple-drug therapy and personal-dose adjustment, which may improve clinical outcome.

Current Practice

Cardiovascular diseases are the leading cause of morbidity in western countries, accounting for an annual worldwide mortality of 17 million, with an annual cost of around half a trillion dollars in the US alone.[1] Platelets play a major role in arterial thrombosis, which is the final event complicating cardiovascular diseases as well as peripheral vascular diseases, and antiplatelet therapy improves survival of patients with these disorders.[2] The multiple pathways of platelet activation limit the effect of specific receptor/pathway inhibitors, resulting in limited clinical efficacy. In contrast, inhibitors of the final common pathway of platelet activation, binding of the major integrin GPIIbIIIa to its ligands (fibrinogen, von Willebran factor and others), have the potential of complete platelet inhibition, which is independent of the activation pathway. Aspirin (acetyl salicylic acid) is the most commonly used drug in western countries and is the drug of choice for cardiovascular diseases due to its good cost effectiveness profile.[3] Although already used in the ancient world as an anti-inflammatory agent, aspirin was adopted for antithrombotic therapy only in the 1960s.[4] Nowadays, 1 out of every 5 US citizens is taking aspirin on a daily basis, mostly for cardiovascular disease prevention. Aspirin improves clinical outcome in all cardiovascular syndromes, including acute events, primary and secondary prevention, with an overall reduction of serious vascular events by about one quarter.[5] In stable coronary heart disease it was found that a low dose of aspirin (50-100 mg/d) is as effective as the higher does of 300 mg/d but is associated with a lower rate of major bleeding.[6] However, in patients with a higher risk of cardiovascular events, aspirin alone is not sufficiently effective. Thus, combining aspirin with clopidogrel (thienopyridine derivative) is the treatment of choice and is also cost effective in patients presenting with acute coronary syndrome (ACS).[7] The introduction of percutaneous intervention (PCI) technology in cardiology was associated with the need to protect the treated vessels against early and late thrombosis as well as against re-occlusion.[8] Again, the combination of aspirin with P2Y12 receptor blockers (first ticlopidine and later clopidogrel) has proved to be effective in preventing some of these complications.[9] This dual antiplatelet treatment should be

extended for a longer period particularly in patients in whom a drug-eluting stent (DES) is placed, where stent thrombosis may occur late after implantation. A more aggressive antiplatelet approach was the development of the intravenous platelet integrin GPIIbIIIa inhibitors, which improved outcome of patients undergoing PCI.[10-13] These potent platelet inhibitors are currently used during PCI procedures. Oral versions of these drugs were developed later but were found to be either ineffective or not safe for secondary prevention application.[9] The beneficial effect of antiplatelet drugs is associated with an increased risk of bleeding. This is true even with the currently used low dose aspirin; thus, the application of these drugs is limited in some patients and often requires gastric protection medications.[14] In a recent evaluation by the Cochrane group it was found that combination therapy of aspirin and clopidogrel is beneficial only in patients with ACS and for those undergoing PCI, whereas in those with a high risk or an established disease without the characteristics of an acute syndrome, bleeding complications may outweigh the protective effect.[15] In addition, some rare cases of thrombotic thrombocytopenic purpura (TTP) were reported in patients receiving clopidogrel, a complication that requires an urgent intervention.[16] Selected recommendations for antiplatelet therapy are summarized in **Table 1**.

Variable Response to Antiplatelet Drugs

Available data regarding efficacy and safety of antiplatelet therapy are based entirely on the clinical outcome. Although platelet aggregation testing was developed in parallel to the introduction of aspirin as an antiplatelet drug,[4] none of the major studies that established the role of aspirin and clopidogrel in cardiovascular diseases was based on the laboratory response of the individual patient to the specific drug. However, evidence of variable laboratory response to aspirin can be found since the 1970s.[17] One reason for the lack of laboratory response of patients treated with antiplatelet drugs is the labor-intensive nature of the original platelet aggregation test, which did not allow massive screening and testing. Recently several point-of-care (POC) methods have been developed, allowing more accessible testing of the effect of these drugs.[18-21] These developments led to several studies where patients under either aspirin or clopidogrel were tested for the laboratory response to these drugs by different methods.[22,23] These early reports have raised the question of whether pharmacological or functional tests are better markers for monitoring the effect of antiplatelet agents. The mechanism of the variable response to aspirin and clopidogrel was extensively studied as well. Data regarding aspirin responsiveness revealed a complete pharmacological response (inhibition of COX-1) in almost every treated patient.[2] However, when functional testing was applied, a variable response was observed among ACS patients, with a significantly higher rate of low laboratory response to aspirin (sometimes referred to aspirin "resistance") among patients in the acute phase as compared with those at a later stable phase. The mechanism of this dynamic response to aspirin was found to stem from platelet activation at the acute phase, associated with residual response to arachidonic acid in spite of a complete COX-1 inhibition.[24] This residual response was proposed to be driven in part by an ADP effect.[25] Thus aspirin "resistance" seems to reflect the disease burden in the acute event rather than reflecting the genetic variability. The compliance of patients who require chronic aspirin therapy is yet another factor that is of concern. Similar studies of the response to clopidogrel have yielded different results. Although a reduced laboratory response is observed among some 20% to 30% of patients during ACS, there is still a significant range of response to the drug in stable patients as well as among healthy volunteers.[26] This variable response seems to reflect in part a genetic polymorphism of cytochrome p-450 where clopidogrel (as a prodrug) is converted into its active

Table 1. Recommendation for antiplatelet therapy.

Indication	Specific features	Recommended therapy
AF/PAF	< 75 y, w/o risk factors 1 risk factor > 2 risk factors or previous ischemic event	ASA 75-162 mg/d ASA or OAC OAC
Primary prevention		ASA 75-100 mg/d
NSTE ACS		ASA 162-325 mg loading then ASA 75-100 mg/d Clop 300/600 mg then 75 mg/d ± GPIIb/IIIa inhibitors
STE ACS	< 12 h of symptoms	PCI/thrombolysis ASA 75-100 mg/d Clop 300/600 mg then 75 mg/d ± GPIIb/IIIa inhibitors
PCI + stent	BMS DES	ASA + Clop (1 m to 1 y) ASA + Clop (at least 1 y) ± GPIIb/IIIa inhibitors
Stroke/TIA		ASA ± dipyridamole ± Clop
PAD		ASA/cilostazol

AF indicates atrial fibrillation; PAF, paroxysmal AF; ASA, acetyl salicylic acid; OAC, oral anticoagulation; STE, ST-segment elevation; NSTE, non-STE; ACS, acute coronary syndrome; Clop, clopidogrel; PCI, percutaneous intervention; BMS, bare metal stent; DES, drug-eluting stent; TIA, transient ischemic attack; PAD, peripheral arterial disease

metabolite.[27] Other factors which may affect responsiveness to clopidogrel include use of other drugs that are metabolized by cytochrome P450 and gastrointestinal absorptions, etc. An early report by Gum et al was the first to document a correlation between aspirin "resistance" among patients with stable angina and clinical outcome.[28] Additional studies came to the same conclusion, demonstrating higher rates of recurrent cardiovascular events among "resistant" patients as compared with those responding to the drugs.[29] A major limitation of these studies was the relatively low statistical power due to low patient numbers. Recent meta analyses of several prospective studies have shown that indeed ACS patients with laboratory resistance to aspirin and clopidogrel are at a higher risk of recurrent cardiovascular events.[30,31] Thus resistance to aspirin in ACS seems to confer an odds ratio of around 3 for recurrent events, whereas in clopidogrel nonresponders, recurrent events are even more frequent. Additional support for the role of disease burden in the development of laboratory resistance to antiplatelet drugs comes from the observation of low responsiveness to these drugs among patients with diabetes mellitus. A subgroup analysis for diabetic patients in the Antithrombotic Trialists collaboration meta-analysis, showed a non-significant reduction of major cardiovascular events in diabetes mellitus (7% reduction; 5000 patients) as compared with the clear benefit of aspirin for high-risk non-diabetic patients (22% reduction).[5] In addition, in two recent studies of patients with diabetes, aspirin given for primary prevention did not decrease the risk of cardiovascular events.[32,33] Platelet reactivity in diabetic patients still remains high under dual antiplatelet treatment with aspirin and clopidogrel.[34]

New Developments

Clopidogrel Reloading

In the search for improved efficacy, and in view of the observed variable responses to clopidogrel, an improved laboratory response was reported upon increasing the loading dose from 300 mg to 600 mg and increasing the maintenance dose from 75 mg/d to 150 mg/d.[35] Increasing the loading dose to 600 mg in laboratory-resistant patients was associated with improved clinical outcome as well.[36] These studies set the stage for the next step where increasing the dose, or changing the drug combination based on individual laboratory response, is evaluated for its potential beneficial effect on clinical outcome. Several such studies, currently underway, together with others will provide valuable information regarding a potential adaptation of individual dosing strategy of antiplatelet drugs.[37]

Improving Drug Efficacy

Another approach taken by the industry was an effort to improve the effect of thienopyridine derivatives. The first example of such a drug is the prasugrel, which was found to be more potent than clopidogrel due to its higher rate of conversion into the active metabolite. This is due to its resistance to plasma esterase inhibition and to the fact that only single oxidative step is needed for its conversion to the active metabolite.[38] In addition, in contrast to clopidogrel prasugrel was found not to be affected by genetic variations in cytochrome P450.[39] A recent study compared the effect of prasugrel with that of clopidogrel in ACS patients.[40] In this study, when clopidogrel was applied at the original loading dose of 300 mg followed by 75 mg/d, prasugrel was found to be more effective with a significant reduction in myocardial infarctions and stent thrombosis, but with a higher rate of major bleeding events. In a subset of diabetic patients the overall benefit of this drug was more significant, with a better efficacy and yet with a lower rate of major bleeding.[41] This finding is in accordance with the relatively high rate of platelet drug "resistance" observed in diabetic patients, suggesting a better effect of the more potent drug in this group as compared with non-diabetic patients with ACS. Several other new P2Y12 inhibitors are currently at different stages of clinical development, including those which reversibly inhibit the P2Y12 receptor, either by oral (Ticagrelor) or intravenous (Cangrelor) administration.[42,43] The observation of better efficacy achieved by applying a more potent P2Y12 inhibitor led to the initiation of numerous clinical trials aiming to compare clinical outcome in ACS patients under standard combination therapy of aspirin and clopidogrel, with those under adjusted higher dose of clopidogrel based on POC functional testing.[37] At the time of the manuscript preparation there are no official reports from these studies, some of which are expected to conclude soon. In view of the available data it seems likely that dose adjustment as well as modification of drug combinations based on functional testing may be adopted at least for several subsets of patients in the near future.

Other Targets for Antiplatelet Treatment

Thrombin Receptor Inhibition

Blockade of the higher affinity receptor PAR 1 is a new target for antiplatelet drugs. SCH530348 is a highly selective PAR-1 inhibitor that does not interfere with thrombin-mediated cleavage of fibrinogen. It has successfully moved into phase III clinical trials after showing a good safety profile, even when added to the combination of clopidogrel and aspirin.[44]

Thromboxane Receptor Inhibitors

Thromboxane receptor inhibitors have certain pharmacological advantages over aspirin: in addition to blocking the effect of TxA_2 on platelets, they also inhibit other throm-

boxane receptor ligands such as endoperoxides, prostanoids and isoprostanes. They antagonize the effects of TxA_2 on thromboxane receptors present on other cells such as monocytes and vascular cells, and preserve the beneficial COX-1 endothelial production of prostacyclin, leading to inhibition of platelet aggregation and vasodilation.[45] Multiple thromboxane receptor antagonists have been developed; however, only a few have progressed beyond phase II trials because of safety concerns.[43]

Oral GPIIbIIIa Inhibitors

As opposed to the clear benefit of intravenous administration, oral GPIIb/IIIa agents given for long-term secondary prevention in ACS and PCI failed to provide protection from recurrent ischemic events and some were paradoxically associated with an increase in adverse events and mortality.[46] The reason behind this paradoxical effect might be that binding of ligand mimetic antagonists to the receptor causes a conformational change of the receptor, which may result in outside-in signaling, platelet activation and possibly paradoxical thrombosis.[47] In addition, the conformational change might expose new platelet epitopes, resulting in antibody formation and thrombocytopenia in some patients. A novel low-molecular-weight compound with unique features was recently developed.[48]

The compound targets the αIIb unit but not β3; when exposed to purified αIIbβ3, it selectively inhibits the αIIbβ3-receptor, without receptor priming and increased fibrinogen binding. Derivatives of this compound with possible higher affinity are now under development. Such a compound could potentially allow chronic application of GPIIbIIIa inhibitors.

PDE Inhibitors

Cilostazol, a phosphodiesterase III inhibitor, is approved by the US Food and Drug Administration for intermittent claudication. In addition to its antiplatelet effects, it was shown to reduce smooth muscle proliferation and intimal hyperplasia after endothelial injury. A recent meta-analysis (only 5428 patients) concluded that the drug is safe and effective in reducing the risk of restenosis and repeated revascularization after PCI. As the authors state, the currently available data should still be cautiously looked upon due to the potential bias effects of small studies.[49]

Several stage IV studies are currently running in patients after PCI, testing the effect of this drug for the treatment and prevention of cerebral infarction, and a few studies are dedicated to diabetic patients (www.clinical trials.gov).

Signaling Pathways Inhibitors

Learning more about platelet signaling pathways has opened new horizons for antiplatelet treatment. Research on G-protein–coupled receptors and their intracellular pathways has recently been summarized.[43] Interactions of the αIIbβ3 cytoplasmic domains with specific regulatory proteins during αIIbβ3 signaling may also provide new targets for antiplatelet drug development. In knockout mice, deletion of 3 C-terminal β3 residues (arginine-glycine-threonine [RGT]) disrupted c-Src–mediated αIIbβ3 signaling, while retaining β3 residues necessary for talin-dependent fibrinogen binding. Unlike control mice, β3 (Δ 760-762) mice were protected from carotid artery thrombosis after vessel injury with $FeCl_3$. However, disruption of integrin signaling at the level of the β3 cytoplasmic domain might also affect the function of αVβ3 in endothelial cells, osteoclasts, and other cells; this should be further tested in animal models in the future.[50]Again, such a development could be translated in the future to a new class of antiplatelet therapy. β-nitrostyrenes may represent a new class of tyrosine kinase inhibitors with potent antiplatelet activity. The first compound that was discovered is 3, 4-methylenedioxy-β-nitrostyrene (MNS), a tyrosine kinase inhibitor of Src and Syk that prevents protein tyrosine phosphorylation and cytoskeletal association of GPIIb/IIIa and talin. It was shown to potently inhibit GPIIb/IIIa activation and platelet aggregation caused by various agonists. New derivatives from this family are now under development.[51]

Conclusions

A better understanding of the individual patient response may pave the way to improve efficacy and safety of antiplatelet therapy. This goal may be achieved by either dose adjustment of the drug based on functional testing, by changing drug combinations or by the introduction of more potent and safer drugs.

Disclosures

Conflict-of-interest disclosure: DV has equity ownership in Matis Medical and receives research funding from Lilly. GS declares no competing financial interests.
Off-label drug use: None disclosed.

Correspondence

David Varon, MD, Coagulation Unit, Department of Hematology, Hadassah, PO Box 12000, Kirat Hadassah, Jerusalem, 91120, Israel; Phone: 972 (2) 6777672; Fax: 972 (2) 6449580; e-mail: dvaron@hadassah.org.il

References

1. Rosamond W, Flegal K, Furie K, et al. Heart disease and stroke statistics—2008 update: a report from the

American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2008;117:e25-e146.
2. Patrono C. Aspirin: new cardiovascular uses for an old drug. Am J Med. 2001;110:62S-65S.
3. Gaspoz JM, Coxson PG, Goldman PA, et al. Cost effectiveness of aspirin, clopidogrel, or both for secondary prevention of coronary heart disease. N Engl J Med. 2002;346:1800-1806.
4. Born GV. Aggregation of blood platelets by adenosine diphosphate and its reversal. Nature. 1962;194:927-929.
5. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002;324:71-86.
6. Berger JS, Brown DL, Becker RC. Low-dose aspirin in patients with stable cardiovascular disease: a meta-analysis. Am J Med. 2008;121:43-49.
7. Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet. 2005;366:1607-1621.
8. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. The EPIC Investigation. N Engl J Med. 1994;330:956-961.
9. Goodman SG, Menon V, Cannon CP, Steg G, Ohman EM, Harrington RA. Acute ST-segment elevation myocardial infarction: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133:708S-775S.
10. Coller BS. Platelet GPIIb/IIIa antagonists: the first anti-integrin receptor therapeutics. J Clin Invest. 1997;99:1467-1471.
11. Tamhane UU, Gurm HS. The chimeric monoclonal antibody abciximab: a systematic review of its safety in contemporary practice. Expert Opin Drug Saf. 2008;7:809-819.
12. Zeymer U, Wienbergen H. A review of clinical trials with eptifibatide in cardiology. Cardiovasc Drug Rev. 2007;25:301-315.
13. van 't Hof AW, Valgimigli M. Defining the role of platelet glycoprotein receptor inhibitors in STEMI: focus on tirofiban. Drugs. 2009;69:85-100.
14. Steinhubl SR, Bhatt DL, Brennan DM, et al. Aspirin to prevent cardiovascular disease: the association of aspirin dose and clopidogrel with thrombosis and bleeding. Ann Intern Med. 2009;150:379-386.
15. Keller TT, Squizzato A, Middeldorp S. Clopidogrel plus aspirin versus aspirin alone for preventing cardiovascular disease. Cochrane Database Syst Rev. 2007:CD005158.
16. Zakarija A, Bandarenko N, Pandey DK, et al. Clopidogrel-associated TTP: an update of pharmacovigilance efforts conducted by independent researchers, pharmaceutical suppliers, and the Food and Drug Administration. Stroke. 2004;35:533-537.
17. Green D, Dunne B, Schmid FR, Rossi EC, Louis G. A study of the variable response of human platelets to collagen: relation to aspirin-induced inhibition of aggregation. Am J Clin Pathol. 1973;60:920-926.
18. Reny JL, De Moerloose P, Dauzat M, Fontana P. Use of the PFA-100 closure time to predict cardiovascular events in aspirin-treated cardiovascular patients: a systematic review and meta-analysis. J Thromb Haemost. 2008;6:444-450.
19. Malinin A, Pokov A, Swaim L, Kotob M, Serebruany V. Validation of a VerifyNow-P2Y12 cartridge for monitoring platelet inhibition with clopidogrel. Methods Find Exp Clin Pharmacol. 2006;28:315-322.
20. Velik-Salchner C, Maier S, Innerhofer P, et al. Point-of-care whole blood impedance aggregometry versus classical light transmission aggregometry for detecting aspirin and clopidogrel: the results of a pilot study. Anesth Analg. 2008;107:1798-1806.
21. Savion N, Varon D. Impact—the cone and plate(let) analyzer: testing platelet function and anti-platelet drug response. Pathophysiol Haemost Thromb. 2006;35:83-88.
22. Cattaneo M. Aspirin and clopidogrel: efficacy, safety, and the issue of drug resistance. Arterioscler Thromb Vasc Biol. 2004;24:1980-1987.
23. Wiviott SD, Antman EM. Clopidogrel resistance: a new chapter in a fast-moving story. Circulation. 2004;109:3064-3067.
24. Frelinger AL, Li Y, Linden MD, et al. Aspirin 'resistance': role of pre-existent platelet reactivity and correlation between tests. J Thromb Haemost. 2008;6:2035-2044.
25. Frelinger AL, 3rd, Furman MI, Linden MD, et al. Residual arachidonic acid-induced platelet activation via an adenosine diphosphate-dependent but cyclooxygenase-1- and cyclooxygenase-2-independent pathway: a 700-patient study of aspirin resistance. Circulation. 2006;113:2888-2896.
26. Michelson AD, Linden MD, Furman MI, et al. Evidence that pre-existent variability in platelet response to ADP accounts for 'clopidogrel resistance'. J Thromb Haemost. 2007;5:75-81.
27. Mega JL, Close SL, Wiviott SD, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. N Engl J Med. 2009;360:354-362.
28. Gum PA, Kottke-Marchant K, Welsh PA, White J, Topol EJ. A prospective, blinded determination of the natural history of aspirin resistance among stable patients with cardiovascular disease. J Am Coll Cardiol.

2003;41:961-965.
29. Matetzky S, Shenkman B, Guetta V, et al. Clopidogrel resistance is associated with increased risk of recurrent atherothrombotic events in patients with acute myocardial infarction. Circulation. 2004;109:3171-3175.
30. Snoep JD, Hovens MM, Eikenboom JC, van der Bom JG, Jukema JW, Huisman MV. Clopidogrel nonresponsiveness in patients undergoing percutaneous coronary intervention with stenting: a systematic review and meta-analysis. Am Heart J. 2007;154:221-231.
31. Snoep JD, Hovens MM, Eikenboom JC, van der Bom JG, Huisman MV. Association of laboratory-defined aspirin resistance with a higher risk of recurrent cardiovascular events: a systematic review and meta-analysis. Arch Intern Med. 2007;167:1593-1599.
32. Belch J, MacCuish A, Campbell I, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. BMJ. 2008;337:a1840.
33. Ogawa H, Nakayama M, Morimoto T, et al. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. JAMA. 2008;300:2134-2141.
34. Serebruany VL, Malinin AI, Pokov A, Barsness G, Hanley DF. Effects of clopidogrel and aspirin in combination versus aspirin alone on platelet activation and major receptor expression in diabetic patients: the PLavix Use for Treatment Of Diabetes (PLUTO-Diabetes) trial. Am Heart J. 2008;155:93.
35. Matetzky S, Fefer P, Shenkman B, Varon D, Savion N, Hod H. Effectiveness of reloading to overcome clopidogrel nonresponsiveness in patients with acute myocardial infarction. Am J Cardiol. 2008;102:524-529.
36. Bonello L, Camoin-Jau L, Arques S, et al. Adjusted clopidogrel loading doses according to vasodilator-stimulated phosphoprotein phosphorylation index decrease rate of major adverse cardiovascular events in patients with clopidogrel resistance: a multicenter randomized prospective study. J Am Coll Cardiol. 2008;51:1404-1411.
37. Price MJ, Berger PB, Angiolillo DJ, et al. Evaluation of individualized clopidogrel therapy after drug-eluting stent implantation in patients with high residual platelet reactivity: design and rationale of the GRAVITAS trial. Am Heart J. 2009;157:818-824.
38. Herbert JM, Savi P. P2Y12, a new platelet ADP receptor, target of clopidogrel. Semin Vasc Med. 2003;3:113-122.
39. Varenhorst C, James S, Erlinge D, et al. Genetic variation of CYP2C19 affects both pharmacokinetic and pharmacodynamic responses to clopidogrel but not prasugrel in aspirin-treated patients with coronary artery disease. Eur Heart J. 2009;30:174401752.
40. 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.
41. Wiviott SD, Braunwald E, Angiolillo DJ, et al. Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes mellitus in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-Thrombolysis in Myocardial Infarction 38. Circulation. 2008;118:1626-1636.
42. Sabatine MS. Novel antiplatelet strategies in acute coronary syndromes. Cleve Clin J Med. 2009;76:S8-S15.
43. Smyth SS, Woulfe DS, Weitz JI, et al. G-protein-coupled receptors as signaling targets for antiplatelet therapy. Arterioscler Thromb Vasc Biol. 2009;29:449-457.
44. 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.
45. Gaussem P, Reny JL, Thalamas C, et al. The specific thromboxane receptor antagonist S18886: pharmacokinetic and pharmacodynamic studies. J Thromb Haemost. 2005;3:1437-1445.
46. Chew DP, Bhatt DL, Sapp S, Topol EJ. Increased mortality with oral platelet glycoprotein IIb/IIIa antagonists: a meta-analysis of phase III multicenter randomized trials. Circulation. 2001;103:201-206.
47. Bassler N, Loeffler C, Mangin P, et al. A mechanistic model for paradoxical platelet activation by ligand-mimetic alphaIIb beta3 (GPIIb/IIIa) antagonists. Arterioscler Thromb Vasc Biol. 2007;27:e9-e15.
48. Blue R, Murcia M, Karan C, Jirouskova M, Coller BS. Application of high-throughput screening to identify a novel alphaIIb-specific small-molecule inhibitor of alphaIIbbeta3-mediated platelet interaction with fibrinogen. Blood. 2008;111:1248-1256.
49. Biondi-Zoccai GG, Lotrionte M, Anselmino M, et al. Systematic review and meta-analysis of randomized clinical trials appraising the impact of cilostazol after percutaneous coronary intervention. Am Heart J. 2008;155:1081-1089.
50. Ablooglu AJ, Kang J, Petrich BG, Ginsberg MH, Shattil SJ. Antithrombotic effects of targeting alphaIIbbeta3 signaling in platelets. Blood. 2009;113:3585-3592.
51. Wang WY, Hsieh PW, Wu YC, Wu CC. Synthesis and pharmacological evaluation of novel beta-nitrostyrene derivatives as tyrosine kinase inhibitors with potent antiplatelet activity. Biochem Pharmacol. 2007;74:601-611.
52. Patrono C, Baigent C, Hirsh J, Roth G. Antiplatelet drugs: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133:199S-233S.