Platelet Antiaggregants in Primary and Secondary Prevention of Atherothrombotic Events

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Abstract

Atherothrombosis and its complications are currently the leading cause of worldwide mortality and its incidence is increasing. Platelets play an essential role in the pathogenesis of atherothrombotic events, justifying the use of antiplatelet agents in their prevention. Thus, it is essential to know the efficacy and safety profile of these drugs in primary and secondary prevention of atherothrombotic events. In this context, this review was performed with the aim of describing and summarizing the outcomes of the main trials involving the use of antiplatelet agents in the two levels of prevention, and evaluating the effectiveness and major adverse events related to therapy.

Introduction

Atherothrombosis is associated with a number of complications and the most important are Coronary Artery Disease (CAD), of which main manifestations are unstable angina and acute myocardial infarction (MI), with or without ST-segment elevation; ischemic cerebrovascular disease (CVA) and transient ischemic attack, in addition to Peripheral Obstructive Arterial Disease (POAD)[1]. Such complications currently correspond to the leading cause of mortality worldwide and it has been estimated that they were responsible for 17.3 million deaths in 2008, with 80% of these deaths in low and middle-income countries.

According to projections of the World Health Organization (WHO), in 2030, approximately 23.6 million people will die every year only due to cardiovascular complications[2]. Due to the key role played by platelets in the pathogenesis of atherothrombotic events, the use of platelet antiaggregants is essential in primary and secondary prevention of such events. Risk factors associated with the development of these events are closely associated with the exacerbation of platelet activation which, in turn, favors the formation of platelet aggregates and

thrombin generation, resulting in platelet-rich thrombi (white thrombi). Thus, the use of platelet antiaggregants has shown to be beneficial in primary and secondary prevention of thrombus-mediated events.

The characteristics of the main platelet antiaggregants used in clinical practice and undergoing study are described in Table 1[3-9], and the membrane proteins they interact with and their metabolic pathways are shown in Figure 1[10].

Platelet antiaggregants as primary prevention

Acetylsalicylic Acid (ASA) or aspirin is the most commonly used platelet antiaggregant in the primary prevention of cardiovascular events caused by atherothrombosis and its use in patients with moderate risk of coronary heart disease and as primary prevention in elderly individuals has been recommended by several guidelines. However, the efficacy and safety of ASA therapy for primary prevention are still controversial, as the literature data have not demonstrated that such efficacy is as marked as in secondary prevention[11].

Six randomized controlled trials have evaluated the benefits and risks of using low-dose ASA in CVD prevention. The description and results of these trials are summarized in Table 2[11-13].

A meta-analysis of six clinical trials performed by the Antithrombotic Trialists' (ATT) Collaboration[12] reported that the use of ASA in primary prevention resulted in a 12% reduction in the occurrence of severe cardiovascular events (0.51% in patients treated with ASA vs. 0.57% in the control group, per year, p = 0.0001), mainly due to a decrease in myocardial infarction (MI) incidence (0.18% vs. 0.23% per year, p <0.0001). The reduction in CVA incidence (0.20% vs. 0.21% per year, p = 0.4) was not significant, nor was the increase in hemorrhagic CVA incidence (0.04% vs. 0.03% per year; p = 0.05). CVD mortality as a whole did not change (0.19% vs. 0.19% per year, p = 0.7)[12].

According to the ATT Collaboration[12] meta-analysis, as a result of the studies, there is no solid evidence to justify the use of ASA in primary prevention, mainly due to the fact that risk of adverse effects (mostly gastrointestinal bleeding) offsets the benefit of ASA therapy. Thus, the choice of therapy should be individualized, and ASA use is indicated or not according to each patient's characteristics. Additional studies should be performed to assess which factors influence the success of ASA therapy and to define risk thresholds below which its use is indicated.

In a meta-analysis by Berger et al[13] involving six clinical trials, there is evidence that men and women respond differently to ASA therapy. In female subjects,

Table 1 – Major platelet antiaggregants available for use and in testing

Drug	Action mechanism	Dose	Administration route	Half-life	Excretion	Main adverse reactions
ASA	Inhibits COX-1 enzyme in platelets, leading to reduction in the synthesis of TXA2, potent platelet aggregation agonist	50-100 mg/day	Oral	15-20 minutes	Hepatic by deacetylation to salicylic acid	Bleeding, gastrointestinal erosion
Ticlopidine	Inhibition of ADP-receptors (P2Y$_{12}$ receptors) on platelet surface resulting in platelet aggregation inhibition	250 mg/day	Oral	24-36 hours	Hepatic, through metabolization by cytochrome P450 enzyme (CYP2CD19), originating an active metabolite	Bleeding, neutropenia
Clopidogrel	Similar to ticlopidine	Loading dose of 300 mg; daily maintenance dose of 75 mg	Oral	8 hours (active metabolite)	Hepatic through metabolization by cytochrome P450 (CYP3A5/2CD19), originating an active metabolite	Bleeding
Prasugrel	Similar to ticlopidine	Loading dose of 60 mg; daily maintenance dose of 10 mg	Oral	7 hours (active metabolite)	Hepatic, through metabolization by cytochrome P450 (CYP3A4) enzyme, originating an active metabolite	Bleeding
Dipyridamole	Inhibits the phosphodiesterase enzyme within the platelet, thus increasing intracellular cAMP levels, which prevent platelet aggregation by inhibiting the release of intracellular Ca2+	300-400 mg/day	Oral	10 hours	Hepatic, with enterohepatic recirculation	Bleeding, headache
Abciximab	Inhibits GPII$_b$III$_a$, membrane protein responsible for platelet aggregation via fibrinogen	Bolus of 0,25 mg / kg, followed by infusion of 0.125 µg / kg / minute for 12 hours or more	Intravenous	30 minutes	Catabolism or proteolytic degradation, with minimal renal excretion	Bleeding
Ticagrelor	Similar to ticlopidine	Loading dose of 180 mg; maintenance dose of 90 mg twice a day	Oral	6-13 hours	Hepatic, originating an active metabolite	Bleeding, increase in incidence of dyspnea
Elinogrel	Similar to ticlopidine	Studies involving this drug showed that doses up to 60 mg were tolerated	Oral, intravenous	12 hours	Hepatic, renal and fecal	There may be allergic reactions in patients sensitive to sulphonylureas
Cangrelor	Similar to ticlopidine	4 µg/kg/minute	Intravenous	<9 minutes	Dephosphorylation (in plasma)	Bleeding, increase in incidence of dyspnea
Atopaxar	Inhibits the binding of thrombin to its platelet surface receptor (PAR-1 receptor), preventing thrombin-dependent platelet aggregation	Studies involving this drug used doses of 50-200 mg / day	Oral	23 hours	Mainly fecal, with little renal excretion and hepatic metabolization	Bleeding
Vorapaxar	Similar to atopaxar	Studies involving this drug used doses of 5-40 mg/day	Oral	311 hours	Mainly fecal, with little renal excretion and hepatic metabolization	Bleeding

ASA: Acetylsalicylic acid; COX-1: Cyclooxygenase 1; TXA2: thromboxane A2, ADP: adenosine diphosphate; cAMP: cyclic adenosine monophosphate; Ca2 +: Calcium; GPII$_b$/III$_a$: II$_b$/III$_a$ glycoprotein.

there was a 12% reduction (p = 0.03) in the occurrence of cardiovascular events and 17% in the occurrence of CVA (p = 0.02), mainly due to the reduction in the occurrence of ischemic CVA. There was no significant effect on the reduction of MI or in CVD mortality. In male subjects, there was a 14% reduction in the incidence of
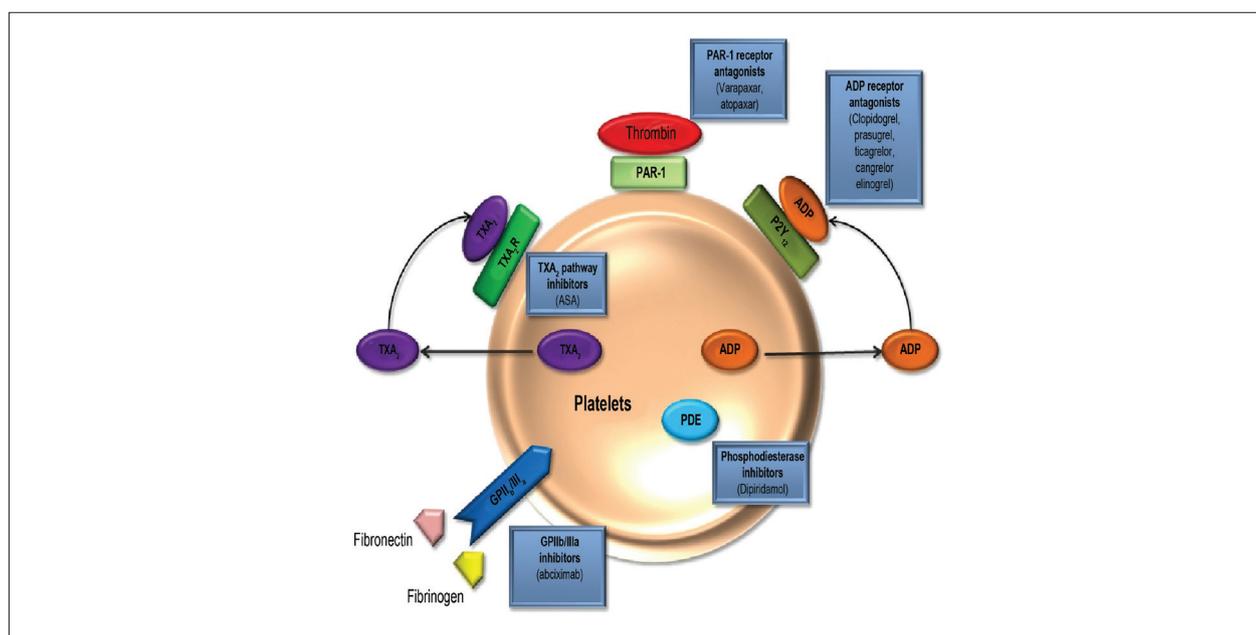
Clinical Update

Figure 1 – *Receptors of main antiplatelet agents and metabolic pathways in which they operate. PAR1: PAR-1 receptor (protease-activated receptor 1); ADP: adenosine diphosphate; $P2Y_{12}$: $P2Y_{12}$ receptor; PDE: phosphodiesterase; GPIIbIIIa: glycoprotein IIbIIIa; TXA2: thromboxane A2; TXA2R: thromboxane A2 receptor; ASA: acetyl salicylic acid.*

Table 2 – Clinical trials involving acetylsalicylic acid (ASA) in primary prevention

Study	n	Description	Women (%)	Dose	Results (ASA *versus* placebo)
Physician's Health Study (PHS)	22.071	Apparently healthy male physicians	0	325 mg on alternate days	ASA resulted in 44% reduction in risk of MI
British Doctor's Trial (BDT)	5.139	Apparently healthy male physicians	0	500 mg/day	Significant reduction in the incidence of death, MI or CVA in individuals treated with ASA
Thrombosis Prevention Trial (TPT)	5.085	Men at high risk of ischemic heart disease	0	75 mg/day	ASA resulted in 32% reduction in the incidence of nonfatal cardiovascular events
Hypertension Optimal Treatment Trial (HOT)	18.790	Hypertensive individuals	47	75 mg/day	ASA resulted in a 15% decrease in the incidence of MI, CVA, and CVD death (p = 0.03) and MI specifically, 32% (p = 0.002)
Primary Prevention Project (PPP)	4.495	Individuals with at least one cardiovascular risk factor	58	100 mg/day	An 8.2% to 6.3%, reduction was observed in the incidence of CVD and a decrease in CVD mortality from 1.4% to 0.8% in individuals treated with ASA
Women's Health Study (WHS)	39.876	Apparently healthy health professionals	100	100 mg on alternate days	Significant efficacy of ASA in preventing cardiovascular events was observed only in women ≥ 65 years

MI: myocardial infarction; CVA: cerebrovascular accident; CVD: cardiovascular disease.

cardiovascular events (p = 0.01) and 32% in the incidence of MI (p = 0.001), and there were no significant differences regarding the occurrence of CVA or CVD mortality.

Platelet antiaggregants as secondary prevention

The Antithrombotic Trialists' Collaboration developed a meta-analysis involving 16 randomized controlled trials, which sought to evaluate the efficacy of aspirin in secondary prevention. The occurrence of cardiovascular events was significantly reduced (6.7% vs. 8.2% per year, p < 0.0001), with a 20% reduction in the risk of CVA (2.08% *versus* 2.54% per year; p = 0.002) and coronary events (4.3% *versus* 5.3% per year, p < 0.0001), whereas the risk of hemorrhagic CVA was not significantly increased (0.04% vs. 0.03% a year, p = 0.05). According to this meta-analysis, the benefits of aspirin in secondary prevention are more pronounced than in primary prevention, thus showing more solid evidence to support its use[14].

The "Clopidogrel versus Aspirin in Patients at Risk of Ischemic Event" (CAPRIE) trial compared the efficacy of aspirin and clopidogrel in secondary prevention of atherothrombotic events. In patients treated with clopidogrel (75 mg daily), there was a relative reduction of 8.7% (p = 0.0043) in the occurrence of ischemic events (CVA, MI or CVD death) compared to patients treated with aspirin (325 mg daily), with a lower incidence of gastrointestinal bleeding in clopidogrel users[15].

The "Ticlopidine Versus Aspirin After Myocardial Infarction (STAMI)" trial showed no evidence of differences in the efficacy of ticlopidine (325 mg/day) and ASA (160 mg /day), whereas the "Ticlopidine Aspirin Stroke Study (TASS)" trial showed that, in one year, the incidence of ischemic CVA in patients treated with ticlopidine (500 mg/day) was 17%, *versus* 19% in those treated with ASA (1,300 mg/day) (p = 0.048)[14].

As there are different processes that lead to platelet aggregation, it is supposed that therapy combined with platelet antiaggregants is beneficial in cardiovascular event prevention. In order to test this hypothesis, several clinical trials have been developed to test the efficacy of other platelet antiaggregants combined with ASA.

In the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial, patients with CVD or multiple risk factors were randomly assigned to therapies with ASA (75-162 mg daily) + clopidogrel (75 mg daily) or ASA (7-162 mg daily) + placebo. The events tested in this study were CVA, MI and death from cardiovascular disease. As a result, cardiovascular events occurred in 6.8% of individuals in the group receiving ASA + clopidogrel *versus* 7.3% in the group receiving ASA + placebo (p = 0.22), which is not considered statistically significant.

The "Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE)" trial evaluated dual antiplatelet therapy in patients with acute coronary syndrome without ST-segment elevation, and its results showed that therapy with ASA (75-325 mg daily) + clopidogrel (75 mg daily) led to a lower incidence of myocardial infarction and CVD death than ASA alone (9.3% vs. 11.4%, p <0.001), with most of the beneficial effects related to the reduction in nonfatal myocardial infarction (5.2% *versus* 6.7% p <0.001)[14,16,17].

A meta-analysis performed by Helton et al[18] assessed the efficacy and safety of combined therapy with aspirin and clopidogrel using the results of five randomized controlled trials, involving a total of 79 624 patients. The analyzed studies were: CURE, Clopidogrel for the Reduction of Events During Observation (CREDO), Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction 28 (CLARITY-TIMI 28), Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) and CHARISMA. All studies compared dual antiplatelet therapy with efficacy and safety of aspirin alone.

It was observed that, in patients undergoing adjuvant therapy, mortality was 6.3% against 6.7% in ASA users alone (OR: 0.94, 95% CI: 0.89 - 0.99, p = 0.026). The incidence of myocardial infarction and CVA were 2.7%

versus 3.3% (OR: 0.82, 95% CI: 0.75 to 0.89, p <0.0001) and 1.2% *versus* 1.4% (OR: 0.82, 95% CI: 0.73 - 0.93, p = 0.002), respectively. The incidence of major bleeding was significantly higher with the combined therapy, being 1.6% *versus* 1.3% (OR: 1.26, 95% CI: 1.11-1.41, p < 0.0001), as well as of fatal bleeding, which was 0.28% vs. 0.27% (OR: 1.04, 95%CI: 0.76-1.43, p = 0.79), with the event latter not being statistically significant.

The meta-analysis by Berger et al[13], using the same trials, compared the clinical efficacy and safety of combined therapy in men and women. According to this meta-analysis, the combined therapy resulted in a relative decrease of 14% in the risk of cardiovascular events (OR: 0.86 95%CI: 0.80-0.93), when compared with monotherapy with ASA. Apparently, although the relative risk in women is lower, it does not reach statistical significance (11.0% *versus* 11.8%, OR: 0.93, 95% CI: 0.86-1.1).

It was observed that, in women, the effect was significant in relation to MI prevention (OR: 0.81, 95%CI: 0.70-0.93), whereas the effects on CVA (OR: 0.91, 95%CI: 0.69-1.21) and mortality (OR: 0.99, 95%CI: 0.90-1.08) were not statistically significant. In men, it was observed that combined therapy resulted in a lower risk of cardiovascular events (7.8% versus 9.0%, OR: 0.84, 95%CI: 0.78-0.91), with this reduction being significant for MI (OR: 0.83, 95% CI: 0.76-0.92), CVA (OR: 0.83, 95% CI: 0.71-0.96) and overall mortality (OR: 0.91; 95% CI: 0.84-0.97). The incidence of major bleeding was higher with the combined therapy, both in women (OR: 1.43 95%CI: 1.15-1.79) and in men (OR: 1.22, 95%CI: 1.05 -1.42).

The TRITON-TIMI 38 trial, a randomized, double-blind, phase III study, showed significant risk reduction in the study primary endpoints (nonfatal MI, nonfatal CVA and cardiovascular death) in patients treated with Prasugrel (10 mg daily) when compared to those treated with clopidogrel (75 mg daily) (9.9% *versus* 12.1%, p <0.001). Prasugrel was also associated with a decrease in thrombosis related to expandable prosthesis placed inside blood vessels (stents), when compared to clopidogrel (1.1% vs. 2.4%, p < 0.001). It was observed that Prasugrel also resulted in a higher risk of severe bleeding than clopidogrel, which leads to an increased risk for its use in patients with increased susceptibility to hemorrhage[16].

The use of dipyridamole in the secondary prevention of cardiovascular events remains controversial, as several clinical trials did not demonstrate adequate efficacy of dipyridamole or its association with ASA in preventing cardiovascular events. After the development of controlled-release formulations of dipyridamole, new studies, such as the ESPS-2 and the European Stroke Prevention Reversible Ischemia Trials (ESPRIT) evaluated the efficacy and safety of dipyridamole in the secondary prevention of cardiovascular events. The ESPS-2 concluded that the dipyridamole + ASA association (50 mg daily + 400 mg daily) is associated with a 22% reduction in cardiovascular events compared with ASA monotherapy. This study, concluded that dipyridamole results in 16% reduction (p = 0.039) in the risk of CVA, when compared to placebo, and a 24% reduction (p <0.001) when associated with ASA. Dipyridamole alone led to a reduction

of CVA in patients with a history of ischemic brain disease, when compared to placebo (OR: 0.82, 95% CI: 0.68-1.0), and that there was an even greater benefit when ASA was added to therapy (OR: 0.61, 95% CI: 0.51-0.71). There is no evidence to suggest that dipyridamole may be useful in the treatment of CAD, being indicated for the prevention of CVA and transient ischemic attack[19-21].

GPIIb/ IIIa inhibitors have established efficacy in reducing ischemic events, both in the management of acute coronary syndromes and as adjunctive therapy during coronary angioplasty. The "Abciximab Before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long Term Follow-Up (ADMIRAL)" trial concluded that patients undergoing coronary angioplasty, together with abciximab therapy (bolus of 0.25 mg/kg, followed by infusion of 0.125 μg / kg / min for 12 hours), showed a 59% reduction in the incidence of death, myocardial infarction or urgent revascularization, when compared to patients only submitted to angioplasty (6% vs. 14.6%, p = 0, 01)[21].

The studies on the efficacy of GPIIb / IIIa receptors are not yet conclusive, as even though most of the trials have shown a significant beneficial effect of using these drugs in secondary prevention, others, such as the "Controlled Abciximab Device Investigation to Lower Late Angioplasty Complications (CADILLAC)" have shown no such benefits. The "Intracoronary Stenting and Atherothrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT2) trial showed that in patients with acute coronary syndrome without ST segment elevation, the use of abciximab had a benefit restricted to patients with high plasma levels of troponin[22].

New platelet antiaggregants

Several antiplatelet drugs are currently undergoing testing, some with completed clinical trials and with others with ongoing.

Ticagrelor

The efficacy of ticagrelor was evaluated by the "Platelet Inhibition and Patient Outcomes (PLATO)" trial, a multicenter, randomized, double-blind phase III trial comparing the efficacy of ticagrelor (loading dose of 180 mg followed by administration of 90 mg twice daily) compared to clopidogrel (loading dose of 300 mg followed by daily administration of 75 mg). The study results showed that the primary outcome (a compound rate of death from cardiovascular disease, CVA and MI) occurred in 9.8% of patients in the group using ticagrelor *versus* 11.7% in the group using clopidogrel (HR: 0.84, 95%CI: 0.77-0.92, p < 0.001), and the secondary outcomes (transient ischemic attack, recurrent ischemia and other atherothrombotic events) were also significantly reduced in the group receiving ticagrelor.

The incidence of major bleeding was higher in ticagrelor users, but there was no statistically significant difference between the groups (11.6% vs. 11.2%, p = 0.43)[23].

Elinogrel

Phase I studies demonstrate that elinogrel inhibits platelet aggregation within 20 minutes after administration, in a dose-dependent form and shows synergistic effect with ASA. According to the "*Early Rapid Reversal of Platelet Thrombosis with IV Elinogrel before PCI to Optimize Reperfusion in Acute Myocardial Infarction* (ERASE-MI)" trial, there were no results that would significantly compromise drug safety at the doses used (10-60 mg, administered intravenously), which led to the continuation of the studies[24].

Cangrelor

In a randomized clinical trial involving patients with myocardial infarction, in which the combined therapy with Cangrelor and Alteplase (a thrombolytic agent) was compared to therapy with each drug alone, it was observed that the combined therapy was better than with either drug alone. The CHAMPION PLATFORM and CHAMPION PCI studies, which sought to determine the efficacy of combined therapy with Cangrelor and Clopidogrel compared to therapy with Clopidogrel alone, were canceled due to lack of efficacy of the combined therapy[24].

Atopaxar and Vorapaxar

Atopaxar and Vorapaxar, PAR-1 receptor inhibitors, are undergoing clinical trials (Atopaxar at phase II and Vorapaxar at phase III), of which results should be published soon. The "Thrombin Receptor Antagonist for Clinical Event Reduction in Coronary Syndrome (TRA-CER)" trial, which involves Vorapaxar, recommended the exclusion of individuals with a history of CVA, due to excess risk of intracranial hemorrhage. In the phase-II Atopaxar trial "Japanese-Lesson from Antagonizing the Cellular Effect of Thrombin" (J-LANCELOT), it was observed that this drug does not lead to significant risk of bleeding[25].

Conclusion

Information related to the participation of platelets in atherothrombotic diseases allows us to imply that antiplatelet therapy plays a crucial role in the prevention of cardiovascular events. The use of antiplatelet agents, especially in secondary prevention is supported by several studies that evaluated their efficacy and safety. In primary prevention, the potential benefit of the preventive use of ASA should be carefully assessed and individualized.

Advances in understanding of mechanisms by which platelets participate in atherothrombotic processes have led to the search for the development of new drugs capable of consistently inhibiting platelet activity with maximum safety. Several ongoing studies suggest that, in the coming years, currently available strategies for the prevention of cardiovascular disease will be optimized and new pharmacological options will be available for clinical use.

Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Statistical analysis, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Silva MVF, Dusse LMS, Vieira LM, Carvalho MG.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Study Association

This study is not associated with any post-graduation program.

References

1. Viles-Gonzalez JF, Fuster V, Badimon JJ. Atherothrombosis: a widespread disease with unpredictable and life-threatening consequences. Eur Heart J. 2004;25(14):1197-207.

2. Organização Mundial da Saúde (OMS). [citado 2012 abril 10]. Disponível em: url: http://www.who.int

3. Patrono C, Baigent C, Hirsh J, Roth G; American College of Chest Physicians. Antiplatelet drugs: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). Chest. 2008;133(6 Suppl):199S-233S.

4. Wallentin L. P2Y(12) inhibitors: differences in properties and mechanisms of action and potential consequences for clinical use. Eur Heart J. 2009;30(16):1964-77.

5. Fuchs FD, Wannmacher L. Farmacologia clínica: fundamentos da terapêutica racional. 4ª ed. Rio de Janeiro: Guanabara Koogan; 2010.

6. Born G, Patrono C. Antiplatelet drugs. Br J Pharmacol. 2006;147 Suppl 1:S241-51.

7. Michelson AD. Advances in antiplatelet therapy. Hematology Am Soc Hematol Educ Program. 2011;2011:62-9.

8. Mager DE, Mascelli MA, Kleiman NS, Fitzgerald DJ, Abernethy DR. Simultaneous modeling of abciximab plasma concentrations and ex vivo pharmacodynamics in patients undergoing coronary angioplasty. J Pharmacol Exp Ther. 2003;307(3):969-76.

9. Tello-Montoliu A, Tomasello SD, Ueno M, Angiolillo DJ. Antiplatelet therapy: thrombin receptor antagonists. Br J Clin Pharmacol. 2011;72(4):658-71.

10. Mackman N. Triggers, targets and treatment for thrombosis. Nature. 2008;451(7181):914-8.

11. Dai Y, Ge J. Clinical use of aspirin in treatment and prevention of cardiovascular disease. Thrombosis. 2012;2012:245037.

12. Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, et al; Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomized trials. Lancet. 2009;373(9678):1849-60.

13. Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. JAMA. 2006;295(3):306-13.

14. Bollati M, Gaita F, Anselmino M. Antiplatelet combinations for prevention of atherothrombotic events. Vasc Health Risk Manag. 2011;7:23-30.

15. Faxon DP, Nesto RW. Antiplatelet therapy in populations with high risk of atherothrombosis. J Natl Med Assoc. 2006;98(5):711-21.

16. Eshaghian S, Shah PK, Kaul S. Advances in antiplatelet treatment for acute coronary syndromes. Heart. 2010;96(9):656-61.

17. Berger PB, Bhatt DL, Fuster V, Steg PG, Fox KA, Shao M, et al. Bleeding complications with dual antiplatelet therapy among patients with stable vascular disease or risk factors for vascular disease: results from the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial. Circulation. 2010;121(23):2575-83.

18. Helton TJ, Bavry AA, Kumbhani DJ, Duggal S, Roukoz H, Bhatt DL. Incremental effect of clopidogrel on important outcomes in patients with cardiovascular disease: a meta-analysis of randomized trials. Am J Cardiovasc Drugs. 2007;7(4):289-97.

19. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002;324(7329):71-86. Erratum in BMJ. 2002;324(7330):141.

20. Patrono C, Andreotti F, Arnesen H, Badimon L, Baigent C, Collet JP, et al. Antiplatelet agents for the treatment and prevention of atherothrombosis. Eur Heart J. 2011;32(23):2922-32.

21. Meadows TA, Bhatt DL. Clinical aspects of platelet inhibitors and thrombus formation. Circ Res. 2007;100(9):1261-75.

22. Steg PG, Dorman SH, Amarenco P. Atherothrombosis and the role of antiplatelet therapy. J Thromb Haemost. 2011;9 Suppl 1:325-32.

23. Marczewski MM, Postula M, Kosior D. Novel antiplatelets agents in the prevention of cardiovascular complications – focus on ticagrelor. Vasc Health Risk Manag. 2010;6:419-29.

24. Hall R, Mazer CD. Antiplatelet drugs: a review of their pharmacology and management in the perioperative period. Anesth Analg. 2011;112(2):292-318.

25. White HD. Oral antiplatelet therapy for atherothrombotic disease: current evidence and new directions. Am Heart J. 2011;161(3):450-461. Erratum in Am Heart J. 2011;162(3):569.