Pak Heart J

ASPIRIN - A WONDER

Mohammad Hafizullah[1], Shazia Hafiz[2]

[1,2]Department of Cardiology, Lady Reading Hospital & Khyber Medical University, Peshawar - Pakistan

Address for Correspondence:

Dr.Mohammad Hafizullah,

Professor,

Department of Cardiology, Lady Reading Hospital &
Vice Chancellor,
Khyber Medical University, Peshawar-Pakistan

Email: mhu5555@gmail.com

Date Received: November 10,2013
Date Revised: November 22,2013
Date Accepted: November 28,2013

Contribution
All the authors contributed significantly to the research that resulted in the submitted manuscript.

All authors declare no conflict of interest.

ABSTRACT

Aspirin is in use since 1758. Aspirin has got beneficial anti inflammatory and anti thrombotic effect (inhibition of thromboxane A2). There is a rich data to support its use in acute coronary syndrome and secondary prevention of cardiovascular events. Most studies have shown the side effects of Aspirin as GI upset and bleeding. The exact role of Aspirin in primary prevention awaits further studies currently under process. The biggest challenge that faces the medical community is to identify patients who will derive the greatest benefits yet minimal harm ful side effects.

Key Words: Aspirin, Prevention, ACS, Cardiovascular Disease, Stroke, Aspirin Resistence

INTRODUCTION

Even before earning her name, the predecessor of Aspirin, had established herself as a cure for 'the augues' by Reverend Edward Stone in 1758. He administered ground-up dried willow to ague sufferers and showed that the substance was effective in treating the symptoms.[1] Joseph Buchner, a professor of pharmacy at Munich University, in 1828 identified and synthesize the active ingredient of willow into yellow crystals and labeled it salicin (after salix, Latin for willow).[2] A Dundee Royal Infirmary physician John Maclagan administered salicin to patients with rheumatism and documented remission of fever and joint inflammation in first clinical trial.[3] In 1897 Felix Hoffman, a chemist working in a laboratory owned by Friedrich Bayer formulated a pure and stable form of acetyl salicylic acid simply by mixing acetic and salicylic acids.[2] Hoffman was motivated by the suffering of his father, who had severe arthritis, and could not tolerate salicylic acid due to its irritant action on the stomach.[4] On February 1, 1899, this compound was registered under “aspirin,” A-spirinas a new preparation from acetylation (A-), together with 'spirin' - part of the name for meadowsweet (Spiraeaulmaria), a plant rich in salicylates and in 1904, the original powdered form of aspirin became a stamped tablet.[5]

Aspirin was welcomed with open arms by the medical community and soon recommended for fever, migraine, pain of inoperable cancer, rheumatoid arthritis, gout, rheumatic fever, acute tonsillitis, corns and warts.[6] In1997, the National Library of Medicine listed over 23,000 papers on aspirin, and it was estimated that a paper on aspirin is published on average every two hours! Currently, 40000 tons of aspirin are produced every year worldwide, and in the United States alone, 50 million people take 10 to 20 billion aspirin tablets regularly for the prevention of CVD.[7]

HOW IT WORKS?

It took basic scientists more than half a century to understand the intricate mechanisms through which Aspirin confers the beneficial anti-inflammatory and anti-thrombotic effects. Basic research work on Aspirin entitled Vane, Samuelsson and Bergstrom for Noble prize for medicine in 1971. They described dose dependent inhibition of prostaglandins by Aspirin and other non-steroidal anti-inflammatory drugs.[8] Earlier in 1935, it was revealed that prostaglandins - a product of Arachidonic acid was intricately involved in function of Aspirin.[9] In 1976 Hemler et al, isolated cyclooxygenase (COX) or prostaglandin endoperoxidase synthase as the main target for Aspirin.[10,11] It goes to the credit of Samuelsson to identify 'rabbit aorta contracting substance' as thromboxane A2-a potent vasoconstrictor and stimulator of platelet aggregation. Aspirin was shown to inhibit Thromboxane A2 dependent platelet aggregation and aggregation dependent release of adenosine diphosphate hence claiming recognition as not only an anti inflamma-tory but also an effective anti-thrombotic agent.[12-14]

ASPIRIN IN ACUTE CORONARY SYNDROME AND SECONDARY PREVENTION

In early fifties the possibility of Aspirin as an agent against coronary artery disease was considered but it had to wait for half a century for evidence.[15,16] Considering the patho-physiology of acute coronary syndrome (ACS) Aspirin was shown in many trials to be an effective agent in reducing the risk of death and recurrent myocardial infarction by 50% in patients presenting with unstable angina and non ST elevation MI. The evidence provided led FDA to approve the use of Aspirin in both treatment of acute coronary syndrome and secondary prevention of acute MI.[17-20] Antithrombotic Trialists' Trial (ATT) collaboration supported these findings and conclusively established the role of Aspirin in secondary prevention of occlusive vascular diseases.[21]

Having established itself in the treatment of acute coronary syndrome Aspirin was tried in the setting of acute myocardial infarction in the landmark trial Second International Study of Infarct Survival (ISIS-2). This study conclusively demonstrated the efficacy of Aspirin given to patient within 24 hours of chest pain of AMI. Aspirin on its own or in combination with fibrinolytic agent reduced absolute risk of nonfatal re-infarction by 2.4%, and relative risk reduction of 23% and fatal episodes by 5.2% with relative risk reduction of 42%. Allocation to one month of aspirin was associated with 26 (16 to 35) fewer deaths per 1000 during first 35 days. The early benefit obtained with combination of streptokinase and one month of aspirin also seemed to persist long term.[22]

PRIMARY PREVENTION OF CARDIO-VASCULAR DISEASES

The efficacy and safety of Aspirin in primary prevention of cardiovascular occlusive diseases has been the subject of interest and research in the last few decades. Physicians Health study was the first large reported study employing 22,071 healthy male physicians. After 5 years of treatment risk of first MI reduced by 44% ($p<.00001$).[23] Three other trials reported similar results in risk reduction.[24-7] The Antithrombotic Trialists' Collaboration (ATC) published a meta-analysis including 195 randomized trials of aspirin alone compared with control employing 135,640 patients at high risk of arterial occlusive disease. Combined end point of any serious vascular event reduced by 25%, non-fatal MI by 33%, non-fatal stroke by 25% and vascular mortality by 17%.[28] However meta-analysis on 95,456 low risk patients documented that low dose Aspirin taken for 6.4 years by

1,000 persons will avoid about 3 cardiovascular events-mainly strokes in women and prevent 4 events mainly MI in men. The side effects included 2.5 major bleeds in women and 3 in men, leaving a trivial total benefit of disease minus bleeding of 0.5 per 1000 women 1 per 1000 men over 6.4 years, so protective minimally exceeded the side effects.[29]

The meta-analysis of aspirin did not take into account actual benefit and bleeding risks. Aspirin conferred a modest 12% relative reduction in serious vascular events (0.51%/y for aspirin versus 0.57%/y for control; P<0.001) with an increase in major extracranial and gastrointestinal bleeding (0.1%/y versus 0.07%/y; P<0.001). There was no significant trend in the protective effects of aspirin in persons at very low, low, moderate, and high estimated risk. The conclusion was that the majority of persons in the earlier primary prevention trials were at low absolute risk of coronary heart disease (70% of participants were at very low and low risk) and that, in this population, aspirin is of uncertain net value because the reduction in occlusive events is small and offset by a small increase in serious intracranial and extracranial bleeding.[21,29] The US Preventive Services Task Force recommended encouraging men age 45 to 79 years and women age 55 to 79 years to use Aspirin when the potential benefit of reduction in myocardial infarctions in men and ischaemic strokes in women outweighs the potential harm of an increase in gastrointestinal haemorrhage.[30]

ASPIRIN IN DIABETICS FOR PRIMARY PREVENTION

The role of aspirin in primary prevention of diabetes in still not clear. Evidence from different primary prevention trials done in the past suggest some benefit in patients of diabetes. However more recent randomized trials do not show the same promising results.[31-3] Clavin et al, in a systemic review of randomized clinical trials found no significant benefit from aspirin compared with placebo in terms of mortality, MI, and ischemic stroke (risk reduction, 1.12, 1.19 and 0.70, respectively, in patients with and without diabetes mellitus).[34]

Therefore to date there are conflicting results regarding the effect of aspirin for primary prevention of cardiovascular events in adults with diabetes mellitus. A scientific statement published recently by the American Diabetic Association/American Heart Association/American College of Cardiology Foundation suggests that aspirin should not be used for primary prevention of cardiovascular events in diabetics at low CVD risk. These include men less than 50 years of age and women less than 60 years of age with no other major and additional CVD risk factors (10-year CVD risk less than 5%).[35]

EFFECT OF GENDER ON PRIMARY PREVENTION

In a meta-analysis of the primary prevention trials based on gender was associated with a decrease in major cardiovascular events in both men and women. Before this many randomized trials suggested no difference in response to aspirin in primary and secondary prevention among both genders. In meta-analysis 51,342 women were studied and there was a significant reduction of 12% in cardiovascular events and a 17% reduction in stroke (ischemic stroke) with aspirin therapy. However there was no significant effect of aspirin on MI or cardiovascular mortality in these women. Among the 44,114 men studied, there was a 14% reduction in cardiovascular events and a 32% reduction in MI. However no significant effect was seen on stroke or cardiovascular mortality. The absolute risk reduction calculated during the trials shows that the number needed to treat to prevent 1 stroke among women during the 6.4 years of follow-up was 411, and the number needed to treat to prevent an acute MI in men was 118.[36]

Even in a low-risk population, according to WHS stroke was a more common event than MI (1.4 strokes for every MI), thereby making an argument for recommending aspirin as primary prevention in women.[29] In the updated USPSTF recommendation statement the gender based benefit encourages men 45 to 79 years of age to use aspirin when the benefit of reducing an MI outweighs the harm of bleeding. Similarly it encourages women 55 to 79 years of age to use aspirin when the benefit of a reduction in ischemic strokes outweighs the risk of bleeding.[30] The differences in primary cardio protection between men and women may be related to altered aspirin metabolism, differing event rates among the sexes, and aspirin resistance.[29]

STROKE PREVENTION

A collaborative meta-analysis on effectiveness of aspirin in preventing ischemic stroke was reported by the ATC in 2002.[37] The high-risk patients who were allocated to antiplatelet therapy had reduced combined outcome of any serious vascular event by 25% and nonfatal stroke by 25%. Aspirin was the most widely studied antiplatelet agent and accounted for 25% relative risk reduction in nonfatal stroke compared with placebo. Due to previously mentioned limitations of the initial 2002 meta-analyses, the 2009 Antithrombotic Trialists' (ATT) Collaboration collaborative analysis of all large primary prevention trials with aspirin reexamined the benefit of aspirin prevention for stroke. In this analysis, aspirin in the primary prevention trials had no net effect on strokes of known or unknown cause or on the aggregate of all strokes (0.20%/y versus 0.21%/y;P<0.4).[21] In the secondary prevention trials, however, aspirin significantly reduced the aggregate of all strokes by about

one fifth (2.08%/y versus 2.54%/y; P<0.002). Furthermore, in both the primary and secondary prevention trials, the proportional reduction in stroke did not significantly depend on age or sex, as was suggested by prior analyses.[21]

BENEFIT TO RISK RATIO

The absolute benefit of the antiplatelet prophylaxis with aspirin increases as the risk of experiencing a major vascular event increases.[21] The absolute reduction of serious vascular events resulting from aspirin use was modest and it had no effect on vascular death or overall mortality compared with control subjects in primary prevention. There was an absolute increase in the risk of hemorrhagic stroke and major extracranial hemorrhage (0.01%/y, p<0.05 and 0.03%/y p<0.0001). Conversely, among secondary prevention patients treated with aspirin, the incidence of hemorrhagic stroke of 0.17%/y with aspirin versus 0.09%/y with placebo. Importantly, the patients with higher risk of hemorrhagic stroke were those who had maximal absolute risk reduction of serious vascular events with aspirin. In primary prevention without previous disease, aspirin is of uncertain net value as the reduction in occlusive events needs to be weighed against any increase in major bleeds.[21]

ASPIRIN RESISTANCE

Recently a new phenomenon has emerged called 'Aspirin resistance'. Patients who experience a recurrent cardiovascular event while being on Aspirin should be called treatment failure and not Aspirin resistance. Treatment failure may be due to variable responsiveness to aspirin and involves both pharmacological and pharmacokinetic mechanisms. The term “Aspirin resistance” should be reserved to describe platelet nonresponsiveness or a reduced antiplatelet effect. Aspirin resistance is measured by a number of commercially available in vitro assays but unfortunately they lack sensitivity, specificity, and reproducibility. In our study Platelet aggregability in 105 normal subjects, not taking aspirin was 9.28±3.23 ohms. In 136 cardiovascular patient taking aspirin was 5.81± 5.47 ohms, patients having aggregability ⩾ 6 ohms were 47.1%(n=64). This documents a high percentage of patients with reduced response of Platelet aggregation to Aspirin.[38] Platelet aggregation measured in 201 patients with stable coronary artery disease on aspirin (>80 mg daily) were found to have a wide prevalence of variability and poor correlation among the 6 assays tested.[39] Similar assays employed in assessment of in vitro platelets aggregation using Clopidogrel had conflicting responses.[40-41]

Many factors can possibly contribute to a reduced effect of aspirin on platelet reactivity, and multiple mechanisms have been proposed, including COX-1-related and COX-1-nonrelated pathways. Genetic influences, the type of aspirin preparation, medication compliance, and premature discontinuation of aspirin have all been shown to contribute to the overall observation of aspirin treatment failure and variable responsiveness.[42]

Whether reduction of in vitro responsiveness of platelets to Aspirin has any relationship to subsequent clinical events has been studied. The findings from this meta-analysis showed that the prevalence of reduced aspirin responsiveness ranged from 5% to 65%, with a pooled odds ratio of all cardiovascular events of 3.8 (95% confidence interval, 2.3 to 6.1). But the major criticism of this meta-analysis is the lack of sensitivity and specificity of the methodologies used to assess platelet aggregation, the various doses of aspirin used, and the lack of consistent assessment of participant aspirin compliance.[43]

Treating aspirin nonresponsiveness has been a challenge, and currently there is no established therapeutic approach to manage and overcome aspirin nonresponsiveness in patients treated with low-dose aspirin. In some patients, increasing the dose of aspirin or adding omega-3 fatty acids or Clopidogrel may overcome aspirin-reduced in vitro responsiveness; however, there are limited data supporting this.[44-45]

SIDE EFFECTS PROFILE

In most studies GI upset and bleeding have been noted as the main side effects. Besides severe bleeding, even mild to moderate bleeding in acute setting leads to increased mortality.[46] Aspirin causes 2 to 3 fold increase in the risk of dose-related peptic ulcer bleeding, a risk that does not seem to be reduced by the use of enteric-coated aspirin.[47] Among individuals who had peptic ulcer bleeding, continuous low-dose aspirin use increased the risk of recurrent bleeding but resulted in lower overall cardiovascular and cerebrovascular mortality rates.[48] In the Collaborative analysis of individual data from the 6 primary prevention studies, aspirin use in primary prevention had a borderline absolute increase in the risk of hemorrhagic stroke (0.01%/y; p=0.05) and a significantly increased risk of major extracranial hemorrhage (0.03%/y; p<0.0001), but no net protective effect on stroke or vascular mortality.[21] In patients at very low risk of cardiovascular events, the small absolute benefit is partially offset by the exposure of healthy subjects to an unnecessary bleeding risk. The decision which patients to treat must weigh the benefits of improved protection from cardiovascular events against the risk of bleeding. These observations support that in primary prevention aspirin is of uncertain net value because the reduction in coronary artery obstructive events must be considered against any increase in bleeding.

CONCLUSION

No doubt Aspirin is one of the most commonly used

medications worldwide and its magic continues to dazzle the world of medicine.[49] In quest of understanding the mechanism of action of Aspirin helped the scientific endeavors to discover rather new areas of science like prostaglandin synthesis and platelet inhibition and inspired development of newer antiplatelet agents and antiinflammatory medications. There is rich data to support its use in acute coronary syndrome and secondary prevention of cardiovascular events. The exact role of aspirin in primary prevention awaits further studies currently under progress. The biggest challenge that faces the medical community is to identify patients who will derive the greatest benefits yet minimal harmful side effects.

REFERENCES

1. Stone E. An account of the success of the bark of the willow in the cure of agues. Philos Trans R Soc Lond 1763;53:195-200.
2. Leroux H. Découvert de la salicine. J Chim Med 1830;6:341.
3. Maclagan TJ. The treatment of acute rheumatism by salicin. Lancet 1876;4:342-83.
4. Zundorf U. Aspirin 100 years: the future has just begun. Leverkusen: Bayer AG, Consumer Care Business Group; 1997.
5. Wilthauer J, Wohlgemut J. Uber aspirine (acetylsalicylsaure). Ther Mh (Halbmh) 1899;13:276.
6. Donné A. De l'origine des globules du sang, de leur mode de formationet de leur fin. Compt Acad Sci 1842;14:366-8.
7. Osler W. An account of certain organisms occurring in the liquor sanguinis. Proc R Soc Lond 1874;5:692-734.
8. Piper PJ, Vane JR. Release of additional factors in anaphylaxis and its antagonism by anti-inflammatory drugs. Nature 1969;223:29-35.
9. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nat New Biol 1971;231:232-5.
10. Botting RM. Inhibitors of cyclooxygenases: mechanisms, selectivity and uses. J Physiol Pharmacol 2006;57:113-24.
11. Hemler M, Lands WE, Smith WL. Purification of the cyclooxygenase that forms prostaglandins: demonstration of two forms of iron in the holoenzyme. J Biol Chem 1976;251:5575-9.
12. Roth GJ, Majerus PW. The mechanism of the effect of aspirin on human platelets: acetylation of a particulate fraction protein. J Clin Invest 1975;56:624-32.
13. Hamberg M, Svensson J, Samuelsson B. Thromboxanes: a new group of biologically active compounds derived from prostaglandin endoperoxides. Proc Natl Acad Sci USA 1975;72:2994-8.
14. Vane JR, Botting RM. The mechanism of action of aspirin. Thromb Res 2003;110:255-8.
15. Gibson P. Salicylic acid for coronary thrombosis? Lancet 1948;1:965.
16. Craven LL. Experiences with aspirin (acetylsalicylic acid) in the nonspecific prophylaxis of coronary thrombosis. Miss Valley Med J 1953;75:38-44.
17. Risk of myocardial infarction and death during treatment with low dose aspirin and intravenous heparin in men with unstable coronary artery disease: the RISC Group. Lancet 1990;336:827-30.
18. Cairns JA, Gent M, Singer J, Finnie KJ, Froggatt GM, Holder DA, et al. Aspirin, sulfinpyrazone, or both in unstable angina: results of a Canadian multicenter trial. N Engl J Med 1985;313:1369-75.
19. Lewis HD, Davis JW, Archibald DG, Steinke WE, Smitherman TC, Doherty JE, et al. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina: results of a Veterans Administration Cooperative Study. N Engl J Med 1983;309:396-403.
20. Theroux P, Ouimet H, McCans J, Latour JG, Joly P, Levy G, et al. Aspirin, heparin, or both to treat acute unstable angina. N Engl J Med 1988;319:1105-11.
21. Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009;373:1849-60.
22. Baigent C, Collins R, Appleby P, Parish S, Sleight P, Peto R. ISIS-2: 10 year survival among patients with suspected acute myocardial infarction in randomised comparison of intravenous streptokinase, oral aspirin, both, or neither: the ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. BMJ 1998;316:1337-43.
23. Peto R, Gray R, Collins R, Wheatley K, Hennekens C, Jamrozik K, et al. Randomised trial of prophylactic daily aspirin in British male doctors. Br Med J (Clin Res Ed) 1988;296:313-6.
24. Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk: the Medical Research Council's General Practice Research

Framework. Lancet 1998;351:233-41.

25. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, et al. Effects of intensive blood pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial: HOT Study Group. Lancet 1998;351:1755-62.
26. de Gaetano G. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice: Collaborative Group of the Primary Prevention Project. Lancet 2001;357:89-95.
27. Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med 2005;352:1293-304.
28. Eidelman RS, Hebert PR, Weisman SM, Hennekens CH. An update on aspirin in the primary prevention of cardiovascular disease. Arch Intern Med 2003;163:2006-10.
29. Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, BrownDL. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. JAMA 2006;295:306-13.
30. USPSTF. Aspirin for the prevention of cardiovascular disease: US Preventive Services Task Force Recommendations Statement. Ann Intern Med 2009;150:396-402.
31. Ogawa H, Nakayama M, Morimoto T, Uemura S, Kanauchi M, Doi N, Jinnouchi H, Sugiyama S, Saito Y. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. JAMA 2008;300:2134-41.
32. Belch J, MacCuish A, Campbell I, Cobbe S, Taylor R, Prescott R, 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;337:1-10.
33. Fowkes FG, Price JF, Stewart MC, Butcher I, Leng GC, Pell AC, et al. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. JAMA 303:841-8.
34. Calvin AD, Aggarwal NR, Murad MH, Shi Q, Elamin MB, Geske JB, et al. Aspirin for the primary prevention of cardiovascular events: a systematic review and meta-analysis comparing patients with and without diabetes. Diabetes Care 2009;32:2300 -6.
35. Pignone M, Alberts MJ, Colwell JA, Cushman M, Inzucchi SE, Mukherjee D, et al. Aspirin for primary prevention of cardiovascular events in people with diabetes: a position statement of the American Diabetes Association, a scientific statement of the American Heart Association, and an expert consensus document of the American College of Cardiology Foundation. Circulation 2010;121:2694-701.
36. Aspirin for primary prevention of cardiovascular disease? Drug Ther Bull 2009;47:122-5.
37. 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 2002:12;324:71-86.
38. Faheem M, Ali J, Shah I, Samiullah, Hameedullah, Asghar M, et al. Frequency of aspirin resistance in patients with cardiovascular diseases. J Postgrad Med Inst 2012;26:356-62.
39. Lordkipanidze M, Pharand C, Schampaert E, Turgeon J, Palisaitis DA, Diodati JG. A comparison of six major platelet function tests to determine the prevalence of aspirin resistance in patients with stable coronary artery disease. Eur Heart J 2007;28:1702-8.
40. Khan SB, Hameedullah, Noor L, Hafeezullah M, Awan ZA, ud Din S. Comparison of effect of locally available brands of clopidogrel on platelet aggregation in patients with coronary artery disease. J Ayub Med Coll Abbottabad 2010;22:115-7.
41. Hafizullah M, Bahadur S. Comparison of two loading doses regimen of clopidogrel in patients with coronary artery disease. Pak Heart J 2006;39:33-7.
42. Maree AO, Curtin RJ, Chubb A, Dolan C, Cox D, O'Brien J, et al. Cyclooxygenase-1 haplotype modulates platelet response to aspirin. J Thromb Haemost 2005;3:2340- 5.
43. 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;167:1593-9.
44. Lev EI, Solodky A, Harel N, Mager A, Brosh D, Assali A, et al. Treatment of aspirin-resistant patients with omega-3 fatty acids versus aspirin dose escalation. J Am Coll Cardiol 2010;55:114-21.
45. Faheem M, Ali J, Shah I, Ahmed F, Iqbal MA, Hafizullah M. Does addition of clopidogrel to aspirin decrease platelet aggregability? Pak Heart J 2012;45:141-2.

46. Kelly JP, Kaufman DW, Jurgelon JM, Sheehan J, Koff RS, ShapiroS. Risk of aspirin-associated major upper-gastrointestinal bleeding with enteric-coated or buffered product. Lancet 1996;348:1413-6.

47. Rao SV, O'Grady K, Pieper KS, Granger CB, Newby LK, Van de Werf F, et al. Impact of bleeding severity on clinical outcomes among patients with acute coronary syndromes. Am J Cardiol 2005;96:1200-6.

48. Sung JJ, Lau JY, Ching JY, Wu JC, Lee YT, Chiu PW, et al. Continuation of low-dose aspirin therapy in peptic ulcer bleeding: a randomized trial. Ann Intern Med 2010;152:1-9.

49. Fuster V, Sweeny JM. Aspirin: a historical and contemporary therapeutic overview. Circulation 2011;123:768-78.