Low-dose Aspirin for Primary Prevention of Cardiovascular Events in Postmenopausal Women with Type-2 Diabetes: The Prescriptive Approach in the Real World

Abstract

**Background:** The long-term efficacy of low-dose aspirin for primary prevention of cardiovascular (CV) events in postmenopausal women with type-2 diabetes is controversial. Therefore, it is recommended only on an individual basis, recommendation of grade C. **Methods:** We enrolled 275 consecutive postmenopausal women with type-2 diabetes, without an increased bleeding risk and without preexisting CV disease as coronary artery disease, stroke, and peripheral vascular disease, but with a high risk assessed by score >10%, aged 60–69 years. All were receiving aspirin (75–100 mg daily), aspirin group (AG). 170 postmenopausal women with type-2 diabetes and without preexisting cardiovascular (CV) disease, but not on aspirin treatment, despite a high risk assessed by score >10%, were control group (CG). Mean age was 66 ± 4 years for AG and 65 ± 7 years for CG. Our goal was to identify the prevalence of low-dose aspirin prescriptions in these populations according to different clinical conditions. **Results:** Women with only high risk were 41/275 (15%) on AG and 74/170 (43%) on CG, Chi-squared 41, Odds ratio 0.2, c.i. 95%, P < 0.0001. Women affected by metabolic syndrome were 111/275 (40.3%) on AG and 44/170 (25.9%) on CG, Chi-squared 5.1, Odds ratio 1.6, c.i. 95%, P < 0.02. Women affected by metabolic cardiomyopathy were 111/275 (40.3%) on AG and 44/170 (25.9%) on CG, Chi-squared 8, Odds ratio 1.8, c.i. 95%, P < 0.004. Women affected by diabetic cardiomyopathy were 18/275 (6.6%) on AG and 7/170 (4.2%) on CG, Chi-squared 1.2, Odds ratio 1.6, c.i. 95%, P < 0.2 n.s. **Conclusions:** Low-dose aspirin in our population is prescribed preferentially in postmenopausal women with type-2 diabetes when affected by metabolic syndrome or metabolic cardiomyopathy, at the opposite women with only high risk have lower chance to receive aspirin.

**Keywords:** Cardiovascular events, low-dose aspirin, postmenopausal women, primary prevention, type-2 diabetes

Introduction

It is well known that diabetic patients are affected by a CV mortality 1.5–4.5 times greater than the general population,[1] therefore suggesting a need of aggressive therapy for CV event prevention. It has been affirmed that diabetic patients without coronary artery disease have the same CV risk than patients without diabetes, affected by coronary artery disease, on secondary prevention,[2] however three further studies: JPAD (Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes), POPADAD (Prevention of Progression of Arterial Disease and Diabetes), and ETDRS (Early Treatment Diabetic Retinopathy Study) did not confirm this outcome.[3-5] A meta-analysis of 9 randomized and controlled trials assessed that aspirin decreases CV events in diabetic patient, but not statistically significant way.[6] This result was confirmed by three further meta-analyses.[7-9] Nevertheless, if aspirin use could prevent CV events in patients affected by diabetes without evidence of CV disease, it causes major bleeding events. The absolute benefits were largely counterbalanced by the bleeding hazard.[10] The same assessment was in a meta-analysis of thirteen trials, where 53% of subjects were women, aged in the range of 53–74 years and 19% were diabetics.[11] There is a considerable variation in the reported efficacy of aspirin across the trials; approximately, 27% of the total variation could be accounted to the gender differences in the population.[12] Usually trials with predominantly male subjects...

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demonstrated large benefits of aspirin in reducing non-fatal MI rates. In contrast, trials with mostly female subjects failed to show any beneficial effect of aspirin on this endpoint. These data are consistent with the assessment that aspirin therapy might be less effective in reducing non-fatal MI in women than in men.\[13\] Another point is that one-dose-fits-all aspirin approach gave only modest benefits in long-term prevention of CV events because of underdosing in patients of large body size and excess dosing in patients of small body size, which might also affect other outcomes.\[14\] Although women were included in only 2 trials and accounted for only 20% of the population studied, the US Preventive Services Task Force\[15\] and the American Heart Association\[16\] deemed aspirin therapy effective in decreasing the incidence of coronary heart disease in adults of both sexes with increased CV risk. Therefore, American Heart Association guidelines on CV primary prevention in women recommend the use of low-dose aspirin therapy in women whose 10-year risk of a first coronary event exceeds 20% and consider the use in women whose 10-year risk is 10% to 20%.\[17\] The Women’s Health Study, a primary prevention trial of aspirin therapy in women,\[18\] demonstrated that aspirin decreased the risk of stroke without affecting the risk of MI or vascular death, a datum different from that found in studies that enrolled exclusively or predominantly men. Thus, a different beneficial effect of aspirin therapy may exist between men and women. Furthermore, the effects of aspirin therapy varied by sex and diabetes status. Aspirin use was associated with a significant reduction in the risk of CV events in both sexes but different reduction in MI in men and in ischemic stroke in women. Aspirin had no significant effect on CVD in the overall diabetic population but was associated with a reduction in MI among men with diabetes.\[19\]

For all the above considerations, the long-term efficacy-safety balance of low-dose aspirin for primary prevention of CV events in postmenopausal women with type-2 diabetes is unclear. Therefore, the prescription is recommended on an individual basis, recommendation of grade C. The aim of our study is to observe, in the real world, the prescription approach of low-dose aspirin by general practitioners, for primary prevention of CV events, in postmenopausal women with type-2 diabetes.

Methods

We enrolled 275 consecutive postmenopausal women with type-2 diabetes and without preexisting CV disease as coronary artery disease, stroke, and peripheral vascular disease, but with an high risk assessed by score >10%, according to SCORE risk charts, from European Guidelines on CVD Prevention in Clinical Practice 2016,\[20\] aged between 60 and 69 years, without an increased risk for bleeding. Women with the history of ulcer, upper gastrointestinal pain, dyspepsia, or on non-steroidal antiinflammatories drugs were excluded. All of them were receiving aspirin (75 mg or 100 mg daily), prescribed by their general practitioner, aspirin group (AG). 170 postmenopausal women with type-2 diabetes and without preexisting CV disease, but not receiving aspirin, despite a high risk assessed by score >10%, (no-aspirin group) were the control group (CG). Mean age was 66 ± 4 years for AG and 65 ± 7 years for CG, Table 1. Our goal was to identify the prevalence of prescriptive approach of low-dose aspirin in these populations according to different clinical conditions, to understand what leads general practitioner to prescribe low dose of aspirin. Metabolic syndrome (MetS) was assessed according to the National-Cholesterol-Education-Program-Adult-Treatment-Panel III definition.\[21\] Metabolic or diabetic cardiomyopathy diagnosis includes different clinical conditions assessed by left atrial and/or left ventricular changes in geometry, mass, and function; they were diagnosed according to the following criteria: concentric remodeling, left ventricular hypertrophy, and/or left atrial volume increase.\[22\]

Statistical analysis

Statistical analysis was performed by IBM SPSS version 20.0 (Chicago, IL, USA). Results are described as mean with 95% confidence interval (CI 95%). Student’s t-test was used for continuous variables and Chi-square test for categorical variables. A P value < 0.05 was statistically significant.

Results

Women with only high risk were 41/275 (15%) on AG and 72/170 (42.3%) on CG, Chi-square 41, Odds ratio 0.2, c.i. 95%, P < 0.0001, therefore highlighting a lower chance to receive aspirin therapy for women with only high risk, Figure 1.

Women affected by diabetic cardiomyopathy were 18/275 (6.6%) on AG and 7/170 (4.2%) on CG, Chi-squared 1.2, Odds ratio 16, c.i. 95%, P < 0.2 n.s., without statistical significant difference between women with cardiomyopathy and women without, receiving aspirin, Figure 1.

Women affected by metabolic syndrome were 105/275 (38.1%) on AG and 47/170 (27.6%) on CG, Chi-squared 5.1, Odds ratio 1.6, c.i. 95%, P < 0.02, with high statistical

| Table 1: Our study populations |
|-------------------------------|
| **Demographic variables**     | **All** | **Aspirin Group** | **Control Group** |
| Age (%)                       | 66±1    | 66±4             | 65±7              |
| Postmenopausal women          | 445     | 275              | 170               |
| Clinical Conditions           |         |                  |                   |
| High-risk women               | 113     | 41               | 72                |
| Diabetic cardiomyopathy       | 25      | 18               | 7                 |
| Metabolic syndrome            | 152     | 105              | 47                |
| Metabolic cardiomyopathy      | 155     | 111              | 44                |
significant difference between women with metabolic syndrome and women without, those have a lower chance to receive aspirin therapy, Figure 1.

Women affected by metabolic cardiomyopathy were 111/275 (40.3%) on AG and 44/170 (25.9%) on CG, Chi-squared 8, Odds ratio 1.8, c.i. 95%, P < 0.004, with high statistical significant difference between women with metabolic cardiomyopathy and women without, those have a lower chance to receive aspirin therapy, Figure 1.

**Discussion**

There is general agreement concerning secondary CV prevention with aspirin, but aspirin role in CV primary prevention is unclear, also because, among all subjects on primary prevention, there is a high variability of CV risk. It is difficult to identify a cut-off value of CV risk for which the efficacy-safety balance is favorable to low-dose aspirin treatment. ESC suggests treating subject with a CV risk ≥2/100 patients-year,[23] giving priority to safety than effectiveness. In our population of women all with diabetes and high CV risk, assessed by score >10%, according to SCORE risk charts, the low-dose aspirin treatment is mandatory for all the subjects. In our real world, women with diabetes and only high CV risk have a lower chance to receive aspirin; however these chance increases when the diagnosis of metabolic syndrome is made. We know that all diabetic asymptomatic women need the assessment of cardiac organ damage due to subclinical atherosclerosis, as cardiomyopathy diagnosis.[22]

In our study, the cardiomyopathy assessment causes an increase in the prescription of low-dose aspirin in women affected, but mainly when affected by metabolic syndrome, less in women affected by diabetes and high CV risk. Low doses of aspirin (75–100 mg) are effective only to prevent vascular events in patients weighing less than 70 kg, and give no benefit in the 80% of men and nearly 50% of all women weighing 70 kg or more. By contrast, higher doses of aspirin were only effective in patients weighing 70 kg or more. Given that aspirin’s effects on other outcomes, including cancer, also showed interactions with body size, a one-dose-fits-all approach to aspirin is unlikely to be optimal, and a more tailored strategy is required.[14] in our population too. The reason why aspirin would be less effective in reducing MI risk in women is actually unclear. However, recent data indicate that women are more likely to demonstrate aspirin resistance compared to men. In a study by Cook and colleagues, women compared to men were 2.3 times more likely to be aspirin-resistant[34] and in the study by Gum and colleagues, women were 2.5 times more likely to demonstrate aspirin resistance.[25] The mechanisms underlying these observations are uncertain, but they influence the aspirin prescription. Differences in platelet reactivity may result from direct platelet effects of sex hormones or indirect effect on vessels walls.[26,27] Furthermore, estrogens decrease blood levels of fibrinogen, antithrombin III, protein S, and plasminogen activator inhibitor 1.[28,29] Instead testosterone increases thromboxane A2 production and its receptors expression.[29,30] These are the reasons for platelets in premenopausal women are less prothrombotic than platelets in age-matched men, although post-menopausal HRT does not exert cardioprotective effects[31,33] and oral contraceptives increase the risk of thrombotic events.[13] Aspirin antiplatelet effect is similar in both sexes, but there are pathways indirectly related to COX-1, stimulated by collagen, adenosine diphosphate (ADP), and epinephrine, less inhibited in female subjects.[34] In vitro, aspirin produces greater inhibition of platelet aggregation in men, while women retained a higher prevalence of “aspirin resistance.”[35,36] Aspirin was less effective in inhibiting platelet aggregation in women with a history of ischemic stroke or transient ischemic attack.[37] In our population, aspirin is prescribed only in low-doses, preferentially in postmenopausal women with type-2 diabetes when affected by metabolic syndrome or metabolic cardiomyopathy, at the opposite women with only CV high risk have lower chance to receive aspirin. There are also emerging data demonstrating major structural and physiological differences in coronary vessels between men and women.[38] For instance, women have smaller coronary vessels, which are generally stiffer than those in men owing to increased deposition of fibrotic tissue and remodeling of the vessel walls. Women are also more likely to demonstrate impaired vasodilatory responses to acetylcholine.[39] Moreover, when women develop atherosclerosis, their lesions are usually more diffuse and extensive than those observed in men.[40] Although in both men and women, the leading cause of morbidity and mortality is ischemic heart disease,[41] women, especially in the younger age groups (less than 50 years of age), have short-term mortality rates that are twice those observed in men.[42] Our findings in the context of the emerging literature regarding possible aspirin resistance in women suggest that clinicians should be cautious in prescribing aspirin in women, especially for primary prevention. Whether or not other antiplatelet agents would be more effective for women is unclear. Future clinical studies specifically powered to evaluate sex-specific differences will be needed to determine whether other antiplatelet agents might be more effective in women compared with aspirin. Thus, inhibition of platelet aggregation in women.

![Figure 1: Postmenopausal women receiving aspirin according to different clinical conditions](image-url)
treated with aspirin may be insufficient, and females might benefit from higher maintenance dosages or the use of alternative antiplatelet drugs.

**Conclusions**

Low-dose aspirin in our population is prescribed preferentially in postmenopausal women with type-2 diabetes when affected by metabolic syndrome or metabolic cardiomyopathy, at the opposite women with only CV high risk have lower chance to receive aspirin. Future clinical studies specifically powered to evaluate sex-specific differences will determine whether all women with a high risk assessed by score >10%, aged between 60 and 69 years, without an increased risk for bleeding, need to be treated with low-dose aspirin, rather than high-dose aspirin or other antiplatelet agents more effective in women compared with aspirin.

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**Conflicts of interest**

There are no conflicts of interest.

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**References**

1. Haffner SM. Coronary heart disease in patients with diabetes. N Engl J Med 2000;342:1040-2.
2. Haffner SM. Epidemiology of type 2 diabetes: Risk factors. Diabetes Care 1998;21(Suppl 3):C3-6.
3. Aspirin effects on mortality and morbidity in patients with diabetes mellitus. Early treatment diabetic retinopathy study report 14. ETDRS investigators. JAMA 1992;268:1292-300.
4. Ogawa H, Nakayama M, Morimoto T, Uemura S, Kanauchi M, Doi N, et al. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: A randomized controlled trial. JAMA 2008;300:2134-41.
5. Belch J, MacCuish A, Campbell I, Cobbe S, Taylor R, Prescott R, et al. The prevention of progression of arterial disease and diabetes (PAPADAD) trial: Factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. BMJ 2008;337:a1840.
6. Pignone M, Williams CD. Aspirin for primary prevention of cardiovascular disease in diabetes mellitus. Nat Rev Endocrinol 2010;6:619-28.
7. De Berardis G, Sacco M, Strippoli GF, Pellegrini F, Graziano G, Tognoni G, et al. Aspirin for primary prevention of cardiovascular events in people with diabetes: Meta-analysis of randomised controlled trials. BMJ 2009;339:b4531.
8. Zhang C, Sun A, Zhang P, Wu C, Zhang S, Fu M, et al. Aspirin for primary prevention of cardiovascular events in patients with diabetes: A meta-analysis. Diabetes Res Clin Pract 2010;87:211-8.
9. 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.
10. ASCEND Study Collaborative Group, Bowman L, Matham M, Wallendszus K, Stevens W, Buck G, et al. Effects of aspirin for primary prevention in persons with diabetes mellitus. N Engl J Med 2018;379:1529-39.
11. Zheng SL, Roddick AJ. Association of aspirin use for primary prevention with cardiovascular events and bleeding events: A systematic review and meta-analysis. JAMA 2019;321:277-87.
12. Yerman T, Gan WQ, Sin DD. The influence of gender on the effects of aspirin in preventing myocardial infarction. BMC Med 2007;5:29.
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;295:306-13.
14. Rothwell PM, Cook NR, Gaziano JM, Price JF, Belch JF, Roncaglioni MC, et al. Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: Analysis of individual patient data from randomised trials. Lancet Lond Engl 2018;392:387-99.
15. U.S. Preventive Services Task Force. Postmenopausal hormone replacement therapy for primary prevention of chronic conditions: Recommendations and rationale. Ann Intern Med 2002;137:834-9.
16. Pearson TA, Blair SN, Daniels SR, Eckel RH, Fair JM, Fortmann SP, et al. AHA guidelines for primary prevention of cardiovascular disease and stroke: 2002 update: Consensus panel guide to comprehensive risk reduction for adult patients without coronary or other atherosclerotic vascular diseases. American heart association science advisory and coordinating committee. Circulation 2002;106:388-91.
17. Mosca L, Appel LJ, Benjamin EJ, Berra K, Chandra-Strobos N, Fablumi RP, et al. Evidence-based guidelines for cardiovascular disease prevention in women. Circulation 2004;109:672-93.
18. Ridker PM, Cook NR, Lee I-M, 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.
19. Xie M, Shan Z, Zhang Y, Chen S, Yang W, Bao W, et al. Aspirin for primary prevention of cardiovascular events: Meta-analysis of randomized controlled trials and subgroup analysis by sex and diabetes status. PLoS One 2014;9:e90286.
20. Authors/Task Force Members, Piepoli MF, Hoes AW, Agewall S, Fortmann SP, et al. Aspirin for the primary prevention of cardiovascular events: A position paper of the European society for cardiovascular prevention and rehabilitation (EACPR). Eur J Prev Cardiol 2016;23:NP1-96.
21. Maiello M, Zito A, Ciccone MM, Palmiero P. Metabolic syndrome and its components in postmenopausal women living in southern Italy, Apulia region. Diabetes Metab Syndr Obes 2018;11:299-309.
22. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018;39:3021-104.
23. Halvorsen S, Andreotti F, ten Berg JM, Cattaneo M, Coccheri S, Marchioli R, et al. Aspirin therapy in primary cardiovascular disease prevention: A position paper of the European society of cardiology working group on thrombosis. J Am Coll Cardiol 2014;64:319-27.
24. Cook NR, Lee I-M, Zhang SM, Moorthy MV, Buring JE. Alternate-day, low-dose aspirin and cancer risk: Long-term observational follow-up of a randomized trial. Ann Intern Med 2013;159:77-85.

25. Gum PA, Kotlik-Marchant K, Poggio ED, Gurm H, Welsh PA, Brooks L, et al. Profile and prevalence of aspirin resistance in patients with cardiovascular disease. Am J Cardiol 2001;88:230-5.

26. Mikkola T, Turunen P, Avela K, Orpana A, Viinikka L, Ylikorkala O. 17 beta‑estradiol stimulates prostacyclin, but not endothelin-1, production in human vascular endothelial cells. J Clin Endocrinol Metab 1995;80:1832-6.

27. Arora S, Caballaro AE, Smakowski P, LoGerfo FW. Estrogen improves endothelial function. J Vasc Surg 1998;27:1141-6; discussion 1147.

28. Mendelsohn ME, Karas RH. The protective effects of estrogen on the cardiovascular system. N Engl J Med 1999;340:1801-11.

29. Capodanno D, Angiolillo DJ. Impact of race and gender on antithrombotic therapy. Thromb Haemost 2010;104:471-84.

30. Ajayi AA, Mathur R, Halushka PV. Testosterone increases human platelet thromboxane A2 receptor density and aggregation responses. Circulation 1995;91:2742-7.

31. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results From the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321-33.

32. Langer RD, Pradhan AD, Lewis CE, Manson JE, Rossouw JE, Hendrix SL., et al. Baseline associations between postmenopausal hormone therapy and inflammatory, haemostatic, and lipid biomarkers of coronary heart disease. The women’s health initiative observational study. Thromb Haemost 2005;93:1108-16.

34. Sex differences in platelet reactivity and response to low-dose aspirin therapy.-PubMed-NCBI [Internet]. [cited 2019 Mar 03]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/16551714.

35. A sex difference in the effect of aspirin on “spontaneous” platelet aggregation in whole blood.-PubMed-NCBI [Internet]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/?term=A+sex+difference+in+the+effect+of+aspirin+on+%22spontaneous%22+platelet+aggregation+in+whole+blood.+Thromb+Haemost+2013%3A1108%22. [Last cited on 2019 Mar 03].

36. Profile and prevalence of aspirin resistance in patients with cardiovascular disease.-PubMed-NCBI [Internet]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/11472699. [Last cited on 2019 Mar 03].

37. Sex difference in the antiplatelet effect of aspirin in patients with stroke.-PubMed-NCBI [Internet]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/?term=Cavallari+LH%2C+Helgason+CM%2C+Brace+LD%2C+Viana+MA%2C+Nutescu+EA.+Sex+difference+in+the+antiplatelet+effect+of+aspirin+in+patients+with+stroke.+Ann+Pharmacother++2006%3A812%E2%80%93817. [Last cited on 2019 Mar 03].

38. Ye X, Fu J, Yang Y, Gao Y, Liu L, Chen S. Frequency-risk and duration-risk relationships between aspirin use and gastric cancer: A systematic review and meta-analysis. PloS One 2013;8:e71522.

39. Cao Y, Nishihara R, Wu K, Wang M, Ogino S, Willett WC, et al. Population-wide impact of long-term use of aspirin and the risk for cancer. JAMA Oncol 2016;2:762-9.

40. Maas AH, Appelman YE. Gender differences in coronary heart disease. Neth Heart J 2010;18:598-602.

41. Sutcliffe P, Connock M, Gurung T, Freeman K, Johnson S, Kandala NB, et al. Aspirin for prophylactic use in the primary prevention of cardiovascular disease and cancer: A systematic review and overview of reviews. Health Technol Assess Winch Engl 2013;17:1-253.

42. Sanchis-Gomar F, Perez-Quilis C, Leischik R, Lucia A. Epidemiology of coronary heart disease and acute coronary syndrome. Ann Transl Med 2016;4:256.