Original Article

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

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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 72/170 (42.3%) on CG, *Chi-squared 41, Odds ratio 0.2, c.i. 95%*, $P < 0.0001$. 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%*, $P < 0.02$. 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 16, 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-squared 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	p=n.s.
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	

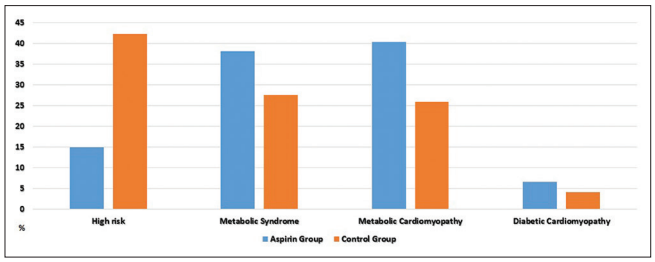

Figure 1: Postmenopausal women receiving aspirin according to different clinical conditions

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[24] 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.[33] 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

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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