Low-dose aspirin for primary cardiovascular prevention in diabetic patients: the issue to believe it or not

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Primary prevention is addressed to forestall the outbreak of cardiovascular disease by facing its natural causes and risk factors. At a different level, secondary prevention involves strategies and therapies targeting preclinical or clinical verification of cardiovascular disease development. Both primary and secondary prevention of atherothrombosis—a key mechanism of nonfatal myocardial infarction, ischemic stroke, and death—involve the use of pharmacologic agents that counteract the process of clot formation. Acetylsalicylic acid, also known simply as aspirin, has been manufactured and marketed since 1899, but it took around 60 years to appreciate its antithrombotic potential as an antiplatelet agent. The significance of aspirin for primary cardiovascular disease prevention is contentious in light of concerns that increased bleeding may counteract the overall humble benefits of the drug in adults with no clear manifestation of atherothrombosis (1). In contrast, secondary prevention is a setting where the efficacy of aspirin has been regularly and compellingly demonstrated to overshadow the risk of bleeding (2).

The individual likelihood of life-long cardiovascular events may act as a significant modifier of the net benefit of aspirin in both the primary and secondary prevention settings. Diabetes mellitus has been related with an increased risk of both first and recurrent atherothrombotic events. The total amount of individuals with diabetes mellitus is considered to rise from 171 million in 2000 to 366 million in 2030, which poses substantial and urgent questions on how to impact the anticipated additional burden of new onset or recurrent cardiovascular disease (3). Because the benefit of aspirin for secondary prevention in diabetes mellitus is currently undisputed (2), the larger area of controversy is represented by the topic of aspirin for primary cardiovascular disease prevention.

Diabetes mellitus is a significant risk factor for cardiovascular events (4,5), and cardiovascular disease is the principal cause of mortality in diabetic patients with diabetes (6,7). As a result, prevention of cardiovascular disease represents one of the most imperative therapeutic goals in diabetes management. Nonetheless, the clinical trial records for aspirin in primary prevention are restricted, and even if several extensive trials of aspirin for primary prevention have evaluated its effects in subgroups with diabetes, these subgroup analyses did not reveal a noteworthy effect on reducing vascular events because they were underpowered. Consequently, as a matter of fact the role of low-dose aspirin therapy for primary prevention of cardiovascular disease lasts as inconclusive and controversial also in high-risk diabetic patients.

The JPAD study included 2,567 patients with type 2

diabetes mellitus and no history of atherosclerotic disease (i.e., cardiovascular disease, stroke, and peripheral vascular disease) randomly assigned to low-dose aspirin (81 or 100 mg/d) or no aspirin with an initial median follow-up period of 4.4 years, and once again low-dose aspirin as primary prevention failed to reduce the risk of cardiovascular events and was not found to reduce the risk of the primary outcome measure (i.e., fatal or nonfatal ischemic heart disease, fatal or nonfatal stroke, and peripheral arterial disease); in addition, the composite of hemorrhagic stroke and significant gastrointestinal bleeding did not significantly differ between the aspirin and no-aspirin groups (8). Then again, the patients were stratified into high- or low-risk groups, according to the US recommendation concerning age (older-younger) and coexisting cardiovascular risk factors (i.e., smoking, hypertension, dyslipidemia, family history of coronary artery disease, and proteinuria), and for the most part patients were assigned to the high-risk group, made up of older patients with risk factors (n=1,804). The incidence of cardiovascular events was higher in the high-risk group, but aspirin failed to reduce cardiovascular events [hazard ratio, 0.83; 95% confidence interval (CI): 0.58–1.17]. In the low-risk group including older patients without risk factors and younger patients (n=728), aspirin even failed to reduce cardiovascular events (hazard ratio, 0.55; 95% CI: 0.23–1.21); these results were unaffected after adjusting for potential confounding factors, thus indicating that low-dose aspirin is unhelpful even in diabetic patients at high risk (9).

Finally, in light of the evidence that post-trial observational studies can be helpful to evaluate the effect of an intervention on the cardiovascular events prevention and that long-term follow-up can increase statistical power, and considering that the possible explanations of the unclear motivation why the results did not reveal a benefit of aspirin (e.g., observed event rate lower than expected, allowing limited statistical power, chance for type II error, inadequacy of low-dose aspirin in lowering cardiovascular events in patients with type 2 diabetes mellitus in a primary prevention setting), the follow-up period was extended to a median of 10.3 years with no endeavour to change the formerly assigned therapy aiming to clarify the efficacy and safety of long-term low-dose aspirin therapy in patients with type 2 diabetes mellitus, in such a combination of the JPAD trial and of its follow-up period in the JPAD2 study (10). Low-dose aspirin failed to lower cardiovascular events in the per-protocol cohort (hazard ratio, 1.14; 95% CI: 0.91–1.42), and multivariable Cox proportional hazard model adjusted for age, sex, glycemic control, kidney function, smoking status, hypertension, and dyslipidemia revealed comparable findings (hazard ratio, 1.04; 95% CI: 0.83–1.30), with no heterogeneity of efficacy in subgroup analyses stratified by each factor (all interaction P>0.05). Sensitivity analyses on the intention-to-treat cohort allowed reliable results (hazard ratio, 1.01; 95% CI: 0.82–1.25). Gastrointestinal bleeding was observed in 25 patients (2%) in the aspirin group and 12 (0.9%) in the no-aspirin group (P=0.03), and the incidence of hemorrhagic stroke did not differ between groups. To reassume, JPAD 2 confirmed that low-dose aspirin did not influence the risk for cardiovascular events in patients with type 2 diabetes mellitus in a primary prevention setting and reported an increased risk for gastrointestinal bleeding (10). Although these results were surely significant and noteworthy, a few specific concerns should however be recognized.

First, some evidence revealed a difference in aspirin effect by gender: aspirin reduced cardiovascular events in men, but not in women; and reduced stroke in women, but not in men. Nevertheless, the possibility of a gender bias must be interpreted with caution, as these results were essentially driven by only one study (11), were characterized by borderline statistical significance, and were not confirmed in secondary-prevention studies. Use of aspirin in primary prevention is less clear in women compared with men. Previous trials have highlighted important sex differences in the effects of this therapy: in healthy women, low-dose aspirin for primary prevention resulted in a significantly decreased risk of stroke but demonstrated no significant effect on the risk of myocardial infarction (11), whereas the opposite was found in men (12). In both of these studies, aspirin increased the risk of gastrointestinal bleeding and the risk of hemorrhagic stroke; in women, however, this risk was strongly related to the woman's age. A subgroup analysis of participants >65 years of age in the Women's Health Study (11) showed a clear association of benefit for both stroke and myocardial infarction. These studies highlight not only the importance of sex-specific reporting of outcomes, but also the need to consider age as a marker of the menopause effects on cardiovascular risk in women. In this era of precision medicine, reporting of sex differences in outcomes in the scientific literature is critical to deliver effective healthcare interventions. With increasing evidence that aging and menopausal status increase many more cardiovascular risk factors in women than aging in men (13), highlighting to whom the research results apply is an ethical obligation of the scientific community. In the

JPAD2 study (10) the performed separate subgroup analyses stratified by sex and age did not detect any differences between groups and the authors concluded that the overall study results apply to women and men of all ages equally. However, the potential effects of menopause in women were not considered, which is important given their large, albeit not statistically significant, difference in outcome by age. As recently outlined (14), analysis by sex in addition to using age as a proxy of menopausal status would provide clinicians with important information on the potential benefits of aspirin for cardiovascular disease prevention in women. In any case, albeit the meta-analysis of early randomized controlled trials studies indicated that low-dose aspirin may be helpful for reducing the risk of stroke in women (15), whereas it may be advantageous for the risk of myocardial infarction in men (15), in the JPAD2 cohort study (10) and in three further randomized trials (16-18) low-dose aspirin did not reduce the risk of cardiovascular events in the total group of patients with high risks or in any subgroups of patients divided by sex, diabetes mellitus, or no diabetes mellitus. Thus, in a contemporary setting, the sex-related effect of low-dose aspirin is still uncertain.

Second, it should be borne in mind that the use of aspirin in adults without diabetes can increase the risk of intracranial and extracranial, primarily gastrointestinal, bleeding events. The lack of statistical significance for these endpoints on diabetes meta-analyses (when reported) is most likely related to the small number of events, reflecting a power issue, although the risk is nonetheless numerically increased twofold. It should also be noted that randomized trials of aspirin for primary prevention have generally excluded patients at increased risk of gastrointestinal bleeding (including those with a history of peptic ulcer), and the elderly are underrepresented; therefore, these results may not represent the true hazards of routine aspirin use in everyday practice. Also, whether patients have sufficient risk to warrant aspirin depends on their use of other effective strategies for cardiovascular disease risk reduction, including statins, antihypertensive agents and smoking cessation. At the opposite, it may be argued that the widespread adoption of evidence-based drug prevention with these other agents may render the use of aspirin futile by lowering overall cardiovascular disease risk. In the end, there may be a diminished rationale to support the role of aspirin in preventing the onset and progression of cardiovascular disease rather than its thrombotic complications. Low-dose aspirin has been consistently found to reduce the risk of serious ischaemic events and non-fatal myocardial infarction in patients without diabetes or overt myocardial infarction, although this benefit is generally small. With diabetes, evidence of the efficacy and safety of aspirin is lacking or, at best, inconclusive, except for the more recent meta-analysis suggesting a 10% reduction in serious vascular events (relative risk, 0.90; 95% CI: 0.81–0.99) (19). However, this modest yet significant risk reduction of major adverse cardiovascular events with aspirin therapy, compared with placebo or no treatment, was no longer significant whit the exclusion of the ETDRS trial (20). Moreover, there was no significant risk cutback of individual cardiovascular endpoints or all-cause mortality and, excluding myocardial infarction, the heterogeneity in analyses of relevant outcomes was low or absent (19). In stratified analyses, the suggested differences in the effect of aspirin driven by baseline cardiovascular disease risk, medication compliance and gender on major adverse cardiovascular events were observed; on the other hand, because these stratified analyses did not show statistically significant evidence of effect modification, the results should be deciphered with carefulness. For all other explored specific endpoints, a significant reduction in risk with aspirin therapy in either men or women was not observed (19). Aspirin significantly lowered the risk of myocardial infarction by 30% with a treatment duration ≤5 years, but this benefit was not observed with treatment durations >5 years. Additionally, the risk of stroke was significantly decreased in trials using minor interventional doses and major average intervention periods (21). As for the adverse events related to aspirin therapy, there was a suspicion of an augmented risk of bleeding and gastrointestinal symptoms with aspirin in diabetes patients, albeit such assessments were indefinite and not significant (19). In fact, nearly all the available meta-analyses indicate that the relevant trials of aspirin in diabetes are still limited by small patient numbers and low event rates. On such a basis, it may be speculated that aspirin probably exerts a modest risk reduction of cardiovascular disease, whereas the limited data specific to diabetes patients preclude any firm estimate of effect size. As for the risk of bleeding, with the exception of intracranial bleeds, a non-fatal major bleed is more likely preferable to non-fatal myocardial infarction or stroke. It is also important to note that aspirin has been associated with beneficial non-cardiovascular effects, including prevention of venous thromboembolism, chemoprevention of colorectal (and other) cancers and neuroprotection with a reduced risk of dementia (19).

Lastly, there is an ongoing problem due to the relative dearth of data in type 1 diabetes. Although an increased cardiovascular risk is common to both type 1 diabetes and type 2 diabetes, the pathophysiology underlying early atherothrombosis in the former is less well understood than in the latter; likewise, whether the same evidence and findings apply has remained unexplored. Interestingly, in a recent study (22), the authors found that patients with type 1 diabetes and stable glycaemic control display enhanced platelet activation correlating with female gender, and microvascular and oxidative damage. Moreover, aspirin responsiveness is unimpaired in type 1 diabetes, suggesting that metabolic disturbances per se are not related to the altered pharmacodynamics, and thereby indicating a need for further clinical investigations and empirical studies on the efficacy and safety of low-dose aspirin in type 1 diabetes.

In conclusion, as the advantage of aspirin in patients with cardiovascular disease clearly outweighs the risk of bleeding, making its role in secondary prevention undisputable, and given the post-trial follow-up of the JPAD study (10), including observations during and after the trial over more than a decade (mean duration) indicating that long-term therapy with low-dose aspirin is not associated with fewer cardiovascular events in Japanese type 2 diabetes patients in a primary-prevention setting, but is linked to and significantly increases the incidence of gastrointestinal bleeding, it is essential to take into account that, albeit only a humble benefit has been confirmed in primary prevention, the bargain of aspirin initiation *vs.* the augmented risk of intracranial and gastrointestinal bleeds is more ambiguous in patients with no overt cardiovascular disease (23). There is a general consensus across clinical guidelines that aspirin in primary prevention should be highly personalized and founded on an assessment of the given patient's benefit-risk ratio, and on a clinician-patient discussion of the potential benefits, potential harms and patient's preferences (23). While patients with diabetes are at a heightened risk of cardiovascular disease, the simple presence of diabetes is seemingly not sufficient for aspirin to award an advantage that considerably counteracts the risk of bleeding (23). However, additional evidence on this issue is essential, and the currently ongoing clinical trials were designed to meaningfully address whether diabetes is a modifier of net benefit of aspirin in patients free of overt cardiovascular disease (23).

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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