Antiplatelet Therapy for Every Diabetic Person?

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Until recently, aspirin was recommended by most guidelines for the primary prevention of cardiovascular events in people with diabetes. Recommendations were primarily based on indirect evidence from large trials of populations at high risk of cardiovascular (CV) events. Evidence supporting the efficacy of aspirin therapy in trials of diabetic subjects only is scant. A previous meta-analysis on the efficacy of antiplatelet therapy in the prevention of major CV events found a clear benefit of aspirin overall, but no statistically significant benefit in the subgroup of people with diabetes. No significant reduction in the risk of major CV events with low dose aspirin compared with placebo was found in three additional trials published after that meta-analysis. New meta-analyses incorporating the results of more recent trials agree in indicating that the use of aspirin is associated with a 10% reduction in the risk of major CV events, with no significant effect on CV or all-cause mortality. A differential sex effect is also suggested. The lower-than-expected benefits of antiplatelet therapy make particularly important the evaluation of the risk-benefit balance. Aspirin use is associated with an excess risk of major bleedings of one or two cases for 1,000 individuals treated for 1 year. Such a risk is even higher in the real world setting, exponentially increases with age and is probably increased in the presence of diabetes. Given the currently available limited evidence, it seems reasonable to suggest aspirin treatment only for patients with a 10-year risk >15%, and without contraindications for aspirin.

CV disease (CVD) is the leading cause of morbidity and mortality in patients with diabetes (1). In addition to the concomitant presence of multiple classical CV risk factors that increase atherothrombotic risk (2), diabetes is a "prothrombotic state" associated with accelerated atherosclerosis and inflammation that contribute to the pathogenesis and progression of vascular complications (3). For this reason, interventions to block one or multiple pathways modulating platelet activation and aggregation processes are considered as an essential component of diabetes care to reduce ischemic risk (4).

The use of aspirin for secondary prevention of CV events in patients with coronary or cerebrovascular disease is well established and is supported by solid evidence from the Antithrombotic Trialists' (ATT) Collaboration meta-analysis (5). This meta-analysis found that aspirin was beneficial in patients with previous myocardial infarction (MI) or stroke or transient cerebral ischemia. In these high risk populations, aspirin decreases the risk of future events by about one-fifth.

In contrast, the role of aspirin for primary prevention of CV events in individuals with diabetes is controversial, and the debate has been recently refueled by the publication of the results of two randomized clinical trials and several meta-analyses.

In this review, we will examine the pros and cons of aspirin use in the primary prevention setting in individuals with diabetes.

ASPIRIN FOR PRIMARY PREVENTION OF CV EVENTS

Con

Until recently, aspirin was recommended by almost all existing guidelines for the primary prevention of CV events in people with diabetes, although with some inconsistencies (6). Recommendations seemed to be mainly based on indirect evidence extrapolated from large trials of populations at high risk of CV events, under the assumption that aspirin was effective in individuals at high CV risk and that the presence of diabetes undoubtedly confers an elevated risk of major CVD events. Though correct in principle, this reasoning was not supported by solid evidence derived from trials specifically conducted in people with diabetes (7–13). In 2002, a meta-analysis (287 trials, 135,000 participants) on the efficacy of antiplatelet therapy in the prevention of major CV events found a clear benefit of aspirin overall (22% risk reduction), but no statistically significant benefit in the subgroup of 5,126 participants with diabetes (7% risk reduction) (14). After the publication of the meta-analysis, no significant reduction in the risk of major CV events with low dose aspirin was found in a subgroup analysis of the Primary Prevention Project (10) as well as in three additional trials (11–13). Results of the most recent trials have been considered by some as definite proof on the lack of aspirin's efficacy in the primary prevention of CV events (15), but others have raised claims that data are still inconclusive and more trials are warranted (16,17). The persistence of a substantial uncertainty was further confirmed by the publication of two meta-analyses summarizing the results of the trials testing aspirin in individuals with diabetes (18,19). Overall, aspirin use in primary prevention was associated with a 10% relative reduction in the risk of major CV events (CV death, nonfatal MI, nonfatal stroke), with no clear effect on CV and overall mortality. These findings were further

confirmed by the recent ATT meta-analysis (5), based on individual patient data derived from six large primary prevention trials.

The lower-than-expected benefits of antiplatelet therapy make it particularly important to perform a careful evaluation of the risk-benefit balance. Aspirin use is associated with an increased risk of intracranial and gastrointestinal bleeding. The excess risk associated with the use of low-doses of aspirin is estimated to be one or two cases of major bleedings for 1,000 individuals treated for 1 year (20). Such a risk is even higher in the real world setting (21) and exponentially increases with age, being particularly elevated in the elderly. Further, the recent ATT meta-analysis suggests that diabetes may be associated with individuals having a 55% higher risk of gastrointestinal bleeding and a 70% higher risk of intracranial bleeding compared with individuals without diabetes (5). Therefore, given the lack of specific safety data in individuals with diabetes, the assumption that major side effects of aspirin are rare should be taken with caution.

How should we use this information in clinical practice? From recent studies it can be estimated that the incidence of major CV events in people with diabetes and without prior CV events is between 10 and 20 per 1,000 person-years. Assuming a relative risk reduction associated with aspirin treatment of about 10%, as suggested by the different meta-analyses, 1,000 people need to be treated for 1 year to prevent one or two major CV events. Therefore the expected benefits might not exceed the risk of major bleedings, particularly among people at low-intermediate CV risk or among older patients (aged >70 years) at high risk of bleeding. One can argue that preventing one episode of MI or ischemic stroke is more important than provoking a transient episode of gastrointestinal bleeding; on the other hand, the lack of evidence of benefit of aspirin use on CV mortality might also suggest that antiplatelet therapy only prevents the less severe forms of MI or stroke. We are simply missing too many pieces of crucial information in order to draw definite conclusions.

The more recent data have also led scientific societies to review existing guidelines. Until 2009, the American Diabetes Association (ADA) recommended low doses of aspirin for primary prevention in any individual aged ≥40 years or with additional CV risk factors (22). In 2010, the recommendation has been changed, with the identification of individuals with a 10-year risk of CVD events over 10% as candidates for primary prevention. The ADA further specifies that this includes the vast majority of men aged >50 years and women aged >60 years with an additional risk factor (23). The same recommendation was recently made by a panel convened by the ADA, the American Heart Association, and the American College of Cardiology Foundation (24). On the other hand, opposite conclusions were reached by the Scottish Intercollegiate Guidelines Network, which considered existing evidence as insufficient to recommend the use of aspirin for primary prevention in individuals with diabetes (25). The Canadian Diabetes Association also acknowledged the substantial uncertainty surrounding the role of aspirin, leaving the prescription of the drug to individual clinical judgment (26).

Pro

Despite the progress in the treatment of major CV risk factors, diabetes is still associated with a marked increase in the risk of CV morbidity and mortality. Existing epidemiological data are suggestive of a harmful effect of hyperglycemia on CVD risk not only for type 2, but also for type 1 diabetes (27,28). Recent randomized trials, as well as the ATT Collaboration meta-analysis, document that the average 10-year risk of major CV events in individuals with diabetes without established CV disease is around 18%, as compared with 5% in individuals without diabetes (5,28). Given the persisting elevated CV risk and the substantially lower than expected benefits of intensive metabolic and blood pressure control in individuals with long-lasting diabetes and advanced atherosclerotic disease (29–32), all efforts should be devoted to early and intensive intervention on all known CV risk factors. Because of the prothrombotic state associated with diabetes and the variety of documented platelet alterations associated with it, antiplatelet therapy is usually considered as a cornerstone of CVD prevention, and is recommended by the vast majority of existing guidelines. Though supported by a strong pathophysiological rational, the evidence for the efficacy of aspirin in the primary prevention setting in diabetes is still being debated. Recently, results of the Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes trial showed that, after a median follow-up of 4.37 years, aspirin therapy was associated with a (nonsignificant) 20% reduction (hazard ratio 0.80 [95% CI 0.58–1.10]) in the risk of the primary composite end point, including fatal or nonfatal ischemic heart disease, fatal or nonfatal stroke, transient ischemic attack, and peripheral arterial disease (12). In a subgroup analysis restricted to individuals aged ≥65 years, a significant reduction in the incidence of the primary end point was documented in patients treated with aspirin as compared with controls (hazard ratio 0.68 [95% CI 0.46–0.99]). Compliance to aspirin therapy at study end was 90%. A major limitation of the study was the inadequate statistical power, determined by a rate of events much lower than expected.

The lack of adequate statistical power also hampered the results of the Prevention of Progression of Arterial Disease and Diabetes study involving patients with asymptomatic peripheral arterial disease (13). The study found no evidence of the benefit of aspirin on CV events and mortality, despite a baseline CVD risk in the study population close to 3% a year. In this trial, the observed event rate was less than half of the anticipated one and the recruitment of 1,276 patients fell short of the planned 1,600. Further to this, only 50% of the patients were still taking aspirin after 5 years.

The results of more recent trials, pooled with previous evidence in two meta-analyses (18,19), suggest that overall aspirin use reduces the risk of major CV events by about 10%. Though of moderate magnitude, this effect would translate into thousands of major CV events avoided if a large proportion of individuals with diabetes were treated. In particular, data from several trials consistently show that antiplatelet therapy substantially reduces the risk of MI in men and is probably beneficial in reducing the risk of ischemic stroke in women. This differential sex effect, initially documented in broader populations (33), has been recently confirmed in individuals with diabetes by two meta-analyses (18,19). In particular, in the meta-analysis by De Berardis et al. (18) the risk of MI was reduced by 43% in men, while a suggestion of benefit for stroke emerged for women, though statistical significance was not reached.

Based on this differential sex effect, the U.S. Preventive Services Task Force has recently updated its guidelines to encourage men aged 45–79 years to use aspirin when the potential benefit on MI

outweighs the potential harm and women aged 55–79 years when the potential benefits on ischemic stroke outweighs the potential harm (34).

It remains to be established why the beneficial effect on specific CV outcomes does not translate into a reduction in CV mortality. One plausible explanation is the lack of statistical power of the trials so far conducted and the need for a longer follow-up period. As an example, assuming a mortality rate of 1% a year, 25,000 patients need to be followed-up for 10 years in order to detect a relative risk reduction of 10% (α=0.05; $1-\beta$=0.90).

The role of aspirin in the primary prevention of CV disease in people with diabetes will probably be clarified by ongoing trials, involving overall more than 20,000 individuals with diabetes (Table 1). The large number of events and participants should allow adequately powered subgroup analyses for specific populations such as elderly patients, women, or people with different severity of diabetes.

CONCLUSIONS—As clearly documented by the existing debate and the divergent conclusions of recent guidelines, the role of aspirin for the primary prevention of CV events in individuals with diabetes is far from being elucidated. Ongoing trials are expected to make a great contribution in clarifying whether and for whom antiplatelet therapy is effective in preventing major CV events. Meanwhile, a better understanding of the pathophysiological mechanisms involved in the response of platelets to aspirin, especially in diabetes, may also contribute to the identification of those who are more likely to benefit from antiplatelet treatment. In particular, it remains to be established whether diabetes represents a specific case of "aspirin resistance," related to accelerated platelet turnover making the 24-h dosing interval inadequate to completely suppress platelet COX-1 (35). Furthermore, to what extent additional factors, such as poor metabolic control, degree of insulin resistance, or duration of diabetes could play role in modulating platelet response to aspirin remains a key priority for our future research agenda in diabetes and CV diseases (3). The safety profile of aspirin in individuals with diabetes also needs to be evaluated with greater attention to the real world setting. Randomized clinical trials are often inadequate to provide reliable information on safety (36,37), and observation of very large populations is

Table 1—*Characteristics of randomized trials investigating the efficacy of aspirin in the primary prevention of cardiovascular events in individuals with diabetes*

Study	Study design	Men (%)	Diabetic patients (n)	Aspirin dose	Duration of therapy	Primary outcome	Effect of aspirin on major CV events (RR aspirin vs. control)			
							Major CV events	MI	Stroke	All-cause mortality
PHS (7)	R, DB, PC	100	533	325 mg every other day	5 yrs	CV mortality	—	0.40 (0.20–0.79)	—	—
ETDRS (8)	R, DB, PC	56.5	3,711	650 mg/day	5 yrs	All cause mortality	0.90 (0.78–1.04)	0.82 (0.69–0.98)	1.17 (0.87–1.58)	0.91 (0.78–1.06)
HOT (9)	R, DB, PC	53.0	1,501	75 mg/day	3.8 yrs	Major CV events	0.87 (0.59–1.26)	0.61 (0.29–1.28)	0.91 (0.50–1.64)	1.11 (0.71–1.72)
PPP (10)	R, OL, F	48.2	1,051	100 mg/day	3.6 yrs	CV death+MI+stroke	0.90 (0.50–1.62)	0.49 (0.17–1.43)	0.89 (0.36–2.17)	1.23 (0.69–2.19)
WHS (11)	R, DB, PC, F	0	1,027	100 mg every other day	10.1 yrs	CV death+MI+stroke	0.90 (0.63–1.29)	1.48 (0.88–2.49)	0.46 (0.25–0.85)	
POPADAD (13)	R, DB, PC, F	44.1	1,276	100 mg/day	6.7 yrs	CVdeath+MI+stroke+ amputation above ankle for critical limb ischemia	0.97 (0.76–1.24)	1.10 (0.83–1.45)	0.74 (0.49–1.12)	0.93 (0.72–1.21)
JPAD (12)	R, OL	55.0	2,539	81 or 100 mg/day	4.37 yrs	Fatal and nonfatal ischemic heart disease, fatal and nonfatal stroke, peripheral arterial disease	0.80 (0.59–1.09)	0.87 (0.40–1.87)	0.89 (0.54–1.86)	0.90 (0.57–1.14)
Ongoing trials										
ASCEND	R, DB, PC, F		10,000	100 mg/day	Event driven	CV death+MI+stroke				
ACCEPT-D	R, OL		5,000	100 mg/day	Event driven	CV death+MI+stroke				
JPPP	R, OL		4,903	100 mg/day	Event driven	CV death+MI+stroke				

Data are hazard ratio (95% CI) unless otherwise indicated. ACCEPT-D, Aspirin and Simvastatin Combination for Cardiovascular Events in Diabetes; ASCEND, A Study of Cardiovascular Events in Diabetes; DB, double-blind; ETDRS, Early Treatment Diabetic Retinopathy Study; F, factorial design; HOT, Hypertension Optimal Treatment; JPAD, Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP, Japanese Primary Prevention Project with Aspirin in the elderly with one or more risk factors of vascular events; OL, open label; PC, placebo controlled; PHS, Physicians' Health Study; POPADAD, Progression of Arterial Disease and Diabetes; PPP, Primary Prevention Project; R, randomized; WHS, Women's Health Study.

needed to better estimate the risk profile in different patient subgroups.

In conclusion, while awaiting the results of new studies, we believe that aspirin is not indicated for individuals with a 10-year risk below 10%, although the decision to prescribe it in individuals with a moderate risk (i.e., 10–15%) must be made on an individual patient basis after careful evaluation of the balance between the expected benefits and the significant risk of major bleeding. Finally, given the currently available limited evidence, it seems reasonable to suggest that patients at high intermediate risk (i.e., >15%) and higher, and without contraindications for aspirin, probably warrant treatment.

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