Recommending aspirin for primary prevention in diabetic patients: what may we conclude from the data?

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Cardiovascular (CV) disease is the leading cause of morbidity and is responsible for premature mortality in patients with diabetes [King *et al.* 1998]. In addition to its association with multiple classical CV risk factors, diabetes is associated with accelerated atherosclerosis and inflammation that contribute to the pathogenesis and progression of vascular complications [Evangelista *et al.* 2005]. For this reason, antiplatelet therapy is considered an essential component of diabetes care to reduce ischemic risk [Angiolillo, 2009].

Aspirin has been on the market since 1899, and is still one of the most widely used medications for the treatment and prevention of CV disease. Despite such a long history of use, the role of aspirin for the primary prevention of CV events in individuals with diabetes is still a matter of debate. The new evidence made available in the last few years seems to have increased, rather than resolved, all the doubts regarding the risk–benefit profile of antiplatelet therapy. The uncertainty surrounding this topic is clearly demonstrated by the extreme heterogeneity in the recommendations issued by different scientific societies. As an example, until 2008, the American Diabetes Association recommended the use of aspirin for primary prevention of CV events in all individuals aged over 40 years or with additional risk factors [American Diabetes Association, 2008]. This recommendation was graded as A, that is, supported by evidence of the highest quality. In 2009, while maintaining the same

recommendation, grading was changed to C (evidence from poorly controlled studies) [American Diabetes Association, 2009]. In 2010, the recommendation to use aspirin in the primary setting was changed to include individuals with a 10-year risk of CV events >10% (i.e. most men over 50 years of age and most women over 60 years with at least one additional risk factor). The recommendation was attributed a C grading [American Diabetes Association, 2010]. A completely different conclusion was reached by the Canadian Diabetes Association in its 2008 recommendations, where it was concluded that there is no clear evidence to support the prescription of aspirin to the vast majority of patients with diabetes, leaving aspirin use to individual clinical judgment [Bhattacharyya *et al.* 2008]. Guidelines issued by the Scottish Intercollegiate Guidelines Network (SIGN) in 2010 go even further, by considering the evidence on the lack of efficacy of aspirin strong enough not to recommend its use for primary prevention of CV events (A grading) [SIGN, 2010].

Then the question is: ‘what is the body of evidence leading to such divergent conclusions regarding the efficacy of aspirin in individuals with diabetes?’

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

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subgroup of 5126 participants with diabetes (7% risk reduction) [Antithrombotic Trialists' Collaboration, 2002]. Consistent with the findings of the meta-analysis, a subgroup analysis of the Primary Prevention Project in 1031 diabetic patients showed that low-dose aspirin only marginally reduced the risk of major CV events after 3 years of follow up (relative risk [RR] = 0.90; 95% confidence interval [CI] 0.50–1.62) [Sacco *et al.* 2003]. On the same line, results of the Women's Health Study documented in 1027 women with diabetes that treatment with low-dose aspirin was associated with a nonsignificant 10% reduction in the risk of major CV events when compared with placebo (RR = 0.90; 95% CI 0.63–1.29) [Ridker *et al.* 2005]. This overall effect was the net result of a reduction in the risk of stroke (RR = 0.46; CI 0.25–0.85), associated with an increased risk of myocardial infarction (MI) (RR = 1.48; CI 0.88–2.49).

Controversies about the role of aspirin have been refueled by the results of two recent trials. The Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial was specifically designed to address the issue of aspirin therapy for the primary prevention of CV events in diabetes [Ogawa *et al.* 2008]. The trial, including 2539 patients with type 2 diabetes, showed that after a median follow up of 4.37 years, aspirin therapy was associated with a nonsignificant 20% reduction (hazard ratio [HR] = 0.80; CI 0.58–1.10) in the risk of the primary composite endpoint, including fatal or nonfatal ischemic heart disease, fatal or nonfatal stroke, transient ischemic attack, and peripheral arterial disease. In a subgroup analysis restricted to individuals aged 65 years or older, a marginally significant reduction in the incidence of the primary endpoint was documented in patients treated with aspirin compared with controls (HR 0.68; CI 0.46–0.99). A major limitation of the study was represented by the inadequate statistical power, determined by a rate of events much lower than expected.

The Prevention of Progression of Arterial Disease and Diabetes (POPADAD) study involved 1276 patients with asymptomatic peripheral arterial disease, followed up for a median of 6.7 years [Belch *et al.* 2008]. The study found no evidence of benefit of aspirin on CV events and mortality, despite a baseline CV disease risk in the study population close to 3% a

year. Nevertheless, the POPADAD trial was largely underpowered, due to an observed event rate less than half that hypothesized and the recruitment of 1276 patients instead of 1600 as planned. Further to this, only 50% of the patients were still taking aspirin after 5 years.

The persistence of a substantial uncertainty was further confirmed by the publication of two meta-analyses summarizing the results of trials testing aspirin in individuals with diabetes [Zhang *et al.* 2010; De Berardis *et al.* 2009]. 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). Such an effect was mainly attributable to a significant reduction in the risk of nonfatal MI in men, and to a reduction in nonfatal stroke in women. No clear effect on CV and overall mortality was documented. These findings were further confirmed by the recent Antithrombotic Trialists' Collaboration (ATT) meta-analysis [Antithrombotic Trialists' Collaboration, 2009], based on individual patient data deriving from six large primary prevention trials. The meta-analysis showed that both in patients with and without diabetes aspirin decreased the risk of major CV events by about 10%.

Overall, these findings suggest that the benefits of aspirin in the primary prevention setting could be lower than expected on the basis of the results obtained in secondary prevention. It is therefore important to weigh the documented benefits against the risks of intracranial and gastrointestinal bleeding. It is estimated that low doses of aspirin cause one or two cases of major bleedings for 1000 individuals treated for one year [McQuaid and Laine, 2006]. Such a risk is probably higher in the real-world setting [Hernandez-Diaz and Garcia Rodriguez, 2006], and exponentially increases with age, being particularly elevated in the elderly. Further to this, the recent ATT meta-analysis suggests that diabetes *per se* may be associated with a 55% higher risk of gastrointestinal bleeding and a 70% higher risk of intracranial bleeding compared with individuals without diabetes [Antithrombotic Trialists' Collaboration, 2009]. 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? Taken together, existing evidence does not support strong recommendations to use aspirin in the primary prevention of CV events in all people with diabetes. 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 1000 person years. Assuming a RR reduction associated with aspirin treatment of about 10%, as suggested by the different meta-analyses, 1000 people need to be treated for one 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 (i.e. <15% over 10 years), or among older patients (>70 years) at high risk of bleeding. Although preventing one episode of MI or ischemic stroke can be considered far more important than provoking a transient episode of gastrointestinal bleeding, 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.

Further to this, we completely lack information regarding the possible differential role of aspirin in individuals with type 1 and type 2 diabetes. Epidemiological data suggest a harmful effect of hyperglycemia on CV risk, not only for type 2, but also for type 1 diabetes [Turnbull *et al.* 2009; Juutilainen *et al.* 2008]. Nevertheless, given the profound differences in the pathophysiology of type 2 diabetes compared with type 1 diabetes, particularly as far as insulin resistance is concerned, the extrapolation of trials results, including mainly or exclusively individuals with type 2 diabetes, to type 1 diabetes is not warranted.

As for the dose of aspirin, evidence from the ATT collaboration meta-analysis suggests that the benefits obtained with low doses (75–162 mg/day) are similar to those obtained with higher doses (500–1500 mg/day) [Antithrombotic Trialists' Collaboration, 2002]. Although platelets from patients with diabetes have altered function, it is unclear if higher doses of aspirin are required in the patient with diabetes [Pignone *et al.* 2010]. In fact, many alternative pathways exist for platelet activation and aggregation that are independent of thromboxane A₂ and thus not sensitive to the effects of aspirin [Evangelista *et al.* 2005]. Therefore, while platelet activation appears higher in patients with diabetes when

measured by a variety of *ex vivo* and *in vitro* methods, these observations alone are insufficient to recommend empirically higher doses of aspirin [Pignone *et al.* 2010]. Furthermore, it remains to be established whether diabetes represents a specific case of 'aspirin resistance', related to accelerated platelet turnover making the 24-hour dosing interval inadequate to suppress completely platelet cyclo-oxygenase [Davi and Santilli, 2010].

The role of aspirin in the primary prevention of CV disease in people with diabetes will probably be clarified by ongoing trials. Two trials, A Study of Cardiovascular Events in Diabetes (ASCEND, International Standard Randomized Controlled Trial Number ISRCTN60635500) and the Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D) [De Berardis *et al.* 2007], will enroll more than 15,000 participants. In addition, the Japanese primary prevention project [Teramoto *et al.* 2010], involves 14,466 elderly patients, one third of which have diabetes. While awaiting new, firm data, it seems prudent to consider aspirin not indicated for individuals with a 10-year risk below 10%, while the decision to prescribe it in individuals with a moderate risk (i.e. 10–15%), must be taken on an individual patient basis, after a 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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Conflict of interest statement

None declared.

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