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DEBATE

Is aspirin effective in diabetic patients? No

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Acetylsalicylic acid (ASA) is a strange antiplatelet drug. It is credited with efficacy and safety records that have still not been documented in some clinical situations. Nevertheless, it seems to be 'politically correct' among many opinion leaders to sustain the efficacy of ASA even when the evidence points are elsewhere. There are complaints that ASA is not used according to guidelines, and that it is denied to a surprisingly large percentage of patients [1]. Fortunately, physicians usually manage to apply some discretion in transferring the official recommendations into clinical practice, and where there is any lack of convincing evidence they try to avoid risks for their patients.

Whether ASA is useful in diabetic patients is good example of this situation. About 10 years ago, I raised this query, citing the data available at the time [2]. In the intervening years, however, doubts about ASA utility in diabetics have not been quelled. There are some basic points that must be recalled on this topic: ASA is certainly effective in some settings, such as coronary artery disease. In patients with an index coronary event, diabetic or non-diabetic, ASA prophylaxis significantly reduces atherothrombotic aftermaths.

The extent of this effect was summarized by the Antiplatelet Trialists' Collaboration (APTc) in 1994 [3], where the cumulative analysis of all the subgroups of diabetic patients who entered the antiplatelet trials (multiplication of a methodological error, perhaps ?) confirmed that active treatment – including ASA among others – was more effective than control. However, the relative risk reduction in diabetics was 17% compared with 22% in non-diabetic patients. This difference was not significant, but as the absolute risk is very high in diabetics we all hoped that antiplatelet therapy would have given more-striking results in these patients. In addition, when talking about antiplatelet therapy, the authors of the APTc report do not – quite rightly – make a distinction between ASA and non-ASA drugs. From the physician's practical viewpoint, however, it is hardly a secondary matter to distinguish the effects of ASA from those of alternative antiplatelet treatments in a diabetic patient.

Up to 1996, a series of data were published on the poor efficacy of ASA as an antiplatelet agent in subgroups of diabetic patients with various vascular diseases [4–7]. These must be assessed with some caution, though, because such *post hoc* analysis can – at most – inspire hypotheses for new prospective trials. The example of those born under the sign of Libra or Gemini in the ISIS-2 trial has become a classic illustration of how chance can show up differences in subgroups in clinical trials [6]. However, the fact that in recent years ASA has shown its limits, often in subgroups of diabetic patients, arouses suspicion. A *post hoc* analysis has been reported on diabetics in the Primary Prevention Project (PPP). This was a randomized open-label trial designed to assess the efficacy of ASA, 100 mg daily (and Vitamin E) in 4495 subjects with no cardiovascular disease but with at least one risk factor [8]. The PPP found positive results for ASA in the general population, with a significant reduction – 23% – in vascular events and a 44% reduction in cardiovascular mortality. However, looking closely at the subgroup of 1031 diabetics in the trial, it was noted that vascular events and cardiovascular mortality not only were reduced, but also cardiovascular mortality was actually higher [9]. In the CAPRIE trial, which enrolled 19 185 patients with recent myocardial infarction or ischemic stroke, or with symptomatic peripheral arterial disease (PAD), and compared two antiplatelet agents, (ASA 325 mg daily and clopidogrel 75 mg daily), 3866 of the patients had not only the index disease, but also diabetes [10]. In this subgroup, the advantage of clopidogrel over ASA seemed greater than in the general population, and bleeding was significantly more frequent with ASA.

Interest in these findings from subgroups is purely academic, but studies of primary and secondary prophylaxis with ASA in case series including only diabetics are certainly more significant. In the ETDRS trial of 3711 diabetics followed for 7 years, primary prevention with ASA 650 mg daily did not reduce the incidence of major cardiovascular events in comparison with placebo [11]. In the DAMAD trial, that assessed whether ASA (990 mg daily) or ASA + dipyridamole (225 mg daily) prevented the progression of diabetic retinopathy in 475 patients followed for 36 months, the frequency of the secondary endpoint, which included vascular events, showed that these were indeed more frequent (7.5%) among treated patients than among controls (5.1%) [12].

The latest report of the Antithrombotic Trialists' Collaboration has summarized the findings of nine primary prevention trials that recruited only diabetics (about 5000 patients); the

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efficacy of antiplatelet therapy, mainly either ASA alone or ASA + dipyridamole, was not encouraging, with a non-significant risk reduction of 7% [13].

The scenario is not much better for secondary prophylaxis. The Veterans Administration Cooperative Study enrolled 231 diabetics who had recently been amputated or had ischemic gangrene in a leg, in order to evaluate whether or not ASA (650 mg daily) + dipyridamole prevented the clinical progression of the vascular disease in the lower limbs. At the end of a 5-year follow-up, antiplatelet therapy gave no protective effect compared with placebo-treated controls, in terms of either new amputations or cardiovascular mortality [14].

Someone will perhaps raise the criticism that these trials are now dated, using ASA doses perhaps too high. However, recently the DAVID (Drug Evaluation in Atherosclerotic Vascular Disease in Diabetics) trial was published in which 1209 patients with Type 2 diabetes and PAD were assigned antiplatelet therapy with picotamide (600 mg daily) or ASA (320 mg daily). At the end of the 2-year follow-up, total mortality was significantly higher in the ASA (5.5%) than in the picotamide arm (3%) [15]. The physiopathological explanation of this lack of efficacy of ASA compared with other antiplatelet agents might involve aspirin resistance that seems more frequent among diabetics [16,17].

The widespread habit of testing new antiplatelet drugs on top of aspirin might need reconsidering in diabetic patients. In the recent MATCH trial, a combination of ASA and clopidogrel was evaluated in patients with ischemic stroke or TIA, 68% of whom had diabetes. The combination was no more effective than clopidogrel alone but the two drugs together caused significantly more frequent life-threatening and major bleeding [18]. The CHARISMA trial [19], now in progress, is comparing the combination of ASA + clopidogrel with ASA alone in patients with already manifest cardiovascular disease or risk factors, including diabetes; I suspect that this trial may well be exposing diabetic patients to an excess risk of bleeding because of the dual antiplatelet regimen, with no foreseeable advantage.

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