AHA/ADA vs. ESC/EASD recommendations on aspirin as a primary prevention strategy in people with diabetes: how the same data generate divergent conclusions

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Recently, major scientific societies in Europe and USA have issued guidelines on diabetes and cardiovascular (CV) disease. The conclusions of the two panels of experts regarding the use of aspirin for the primary prevention of CV disease in individuals with diabetes are totally divergent. The US statement recommends the use of aspirin for primary prevention in all individuals aged $\geq 40$ or with additional risk factors. In contrast, in the European guidelines there is no mention of aspirin for the primary prevention of myocardial infarction or CV death, while it is recommended for the prevention of stroke. Both recommendations seem mainly based on extrapolations from data on other high-risk groups, rather than on a comprehensive review of pertinent data. Actually, a body of evidence suggests that the efficacy of aspirin in patients with diabetes is substantially lower than in individuals without diabetes. Nevertheless, existing knowledge is mainly derived from dated trials, including small numbers of patients, and hardly representing current strategies for the management of CV risk factors. The high level of uncertainty regarding the balance between benefits and risks of aspirin therapy have important implications for clinical practice, auditing activities, and the design and conduct of randomized clinical trials.

KEYWORDS
Aspirin; Diabetes mellitus; Primary prevention; Cardiovascular disease

The need for a comprehensive and integrated approach to diabetes and cardiovascular (CV) diseases, increasingly recognized over the last several years, has been further underlined by the joint efforts of diabetes and cardiology societies both in USA and Europe, leading to the development of recent recommendations. Last January, a statement on primary prevention of CV diseases in people with diabetes mellitus has been issued jointly by the American Heart Association and the American Diabetes Association. Simultaneously, the guidelines on diabetes and CV diseases developed by the European Society of Cardiology and the European Association for the Study of Diabetes have also been published.

Both guidelines cover a number of major questions which are most likely facing practicing physicians. The use of aspirin for the primary prevention of CV disease in individuals with diabetes is certainly one of the most relevant, and at the same time controversial, of these themes. The comparison of the approaches utilized by the European and the US panels of experts provides an interesting model case on how perfectly divergent recommendations could be derived from the same information databases. In the elaboration and qualification of guidelines, only the European panel has specifically adopted the criteria of classifying the strength of the evidence available, while more implicit criteria have been adopted by the U.S. experts.

In the ESC/EASD guidelines, defined as 'evidence-based' by their authors, there is no mention of aspirin for the primary prevention of myocardial infarction or CV death, while it is recommended for the primary prevention of stroke. The recommendation is classified as Class I (general agreement that the treatment is beneficial, useful, and effective), based on level of evidence B (evidence derived from a single trial or large non-randomized studies). It is not clear which evidence has been used to sustain this recommendation, that appears in open contrast with the recent guidelines on the prevention of ischaemic stroke issued in 2006 by the American Heart Association and the American Stroke Association. The latter formally acknowledge the lack of benefit of aspirin for the primary prevention of ischaemic stroke in men (Class III, level of evidence A), and only leave the possibility of using it in women, while warning that no clear overall benefit in terms of CV morbidity and mortality has been documented.
The AHA/ADA statement on primary prevention of CV diseases in people with diabetes mellitus recommends the use of low-doses of aspirin as a primary prevention strategy in all individuals aged >40 or who have additional risk factors. The statement is in line with previous recommendations on this topic issued in USA, and share the same non-systematic approach in reviewing the existing evidence. Actually, the recommendation seems mainly based on extrapolations from data on other high risk groups, under the assumption that diabetes is a CV disease risk equivalent, rather than on a comprehensive review of pertinent data.

Then the question is: 'what is the body of evidence sustaining the efficacy of aspirin in individuals with diabetes?' Among the selected pieces of evidence mentioned by AHA/ADA to support its recommendation are the results of the ETDRS trial, the only specifically conducted in diabetic patients. In this trial, including 3711 patients with and without previous CVD, treatment with a daily dose of 650 mg of aspirin for an average of 5 years was associated with a non-significant 9% reduction in the primary endpoint (vascular death, non-fatal MI, non-fatal stroke). It is interesting to note that the same study is cited by the European guidelines to recommend aspirin for the secondary prevention of CV events.

Other results usually mentioned are those of the US Physicians' Health Study, suggesting a 60% reduction in the risk of myocardial infarction associated with the use of aspirin. Nevertheless, such a risk reduction was not statistically significant, due to the very small number of events among individuals with diabetes (11/275 in the aspirin group vs. 26/258 in the placebo group; P = 0.22), and no information on the overall effect on major CV endpoints is available. Furthermore, results refer only to male physicians and, as in the ETDRS trial, participants were enrolled in the early 80s, when other effective strategies for CVD prevention (i.e. ACE-inhibitors, statins) were not yet available.

The results of the previous studies have been included in the last meta-analysis on the efficacy of antiplatelet therapy in the prevention of major CV events. The meta-analysis showed a clear benefit for the whole population of over 140,000 subjects (22% reduction in the risk of major CV events), but no statistically significant benefit was documented in the subgroup of about 5000 diabetic patients (7% risk reduction). These results are not discussed in the AHA/ADA recommendation, but simply mentioned as a reference to support the statement that 'Aspirin is widely regarded as the most cost-effective intervention to reduce CVD in the general population and in patients with diabetes.' The European guidelines provide the overall figures of the meta-analysis to support the recommendation of using aspirin for the secondary prevention, but the quantitative outcome regarding diabetes is omitted. The authors only tell us that 'the benefits experienced among diabetic patients were somewhat lower'.

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 = 0.90; 95% CI 0.50–1.62). More recently, results of the Women's Health Study documented in 1027 women with diabetes that treatment with low-dose aspirin was associated with a non-significant 10% reduction in the risk of major CV events when compared with placebo (RR = 0.90; 95% CI 0.63–1.29). This overall effect was the net result of a reduction in the risk of stroke (RR = 0.46; 0.25–0.85), associated with an increased risk of myocardial infarction (RR = 1.48; 0.88–2.49).

In contrast with prevailing beliefs, existing data thus suggest that the clinical efficacy of low-dose aspirin in patients with diabetes is substantially lower than in individuals without diabetes, despite the higher CV risk conferred by the presence of glucose metabolism abnormalities. Indeed, a growing body of evidence supports the hypothesis that diabetes might represent a special case of aspirin resistance, mainly related to the presence of an up-regulated vascular inflammatory-thrombogenic reaction. Therefore, there are sufficient reasons to suppose that diabetes should be considered as a separate entity, not just one of the many subgroups at high CV risk, at least with respect to the prognostic definition of benefits associated with aspirin.

We believe that the use of aspirin for the primary prevention of CV events in diabetic patients cannot be assumed to be an evidence-based recommendation. On one side, existing knowledge is mainly derived from relatively old trials, including small numbers of patients, and which hardly represent current strategies for the management of CV risk factors. In particular, it is not clear whether aspirin adds any benefit over and above that conferred by statins, ACE-inhibitors, and strict metabolic control. On the other side, there is the plausibility of pathophysiologic mechanisms leading to reduced clinical efficacy.

Some reflections seem appropriate to make good use of this model case of dissociation within the scientific community.

The first one has to do with the ongoing large-scale clinical trials in diabetic patients (ASCEND, POPADAD, ACCEPT-D, JPAD). What reference criteria and data have, and are being used by investigators and Ethics Committees on the two sides of the Atlantic to define inclusion and exclusion criteria, to justify the use of placebo, and to inform patients accordingly?

A second implication touches the normative significance of recommendations with respect to clinical decision for prescribers. In an era of Evidence-Based Medicine, the decision to prescribe such an old drug like aspirin for a common clinical condition 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. Several studies have demonstrated an absolute excess of approximately one to two major bleeding complications per 1000 patients treated with low doses of aspirin for 1 year. Will aspirin benefits outweigh the risk of major bleeding in patients younger than 50, without additional CV risk factors? Should aspirin be prescribed to patients over 70, considering the lack of reliable information in this age group and the sharp increase in the risk of upper gastrointestinal bleeding? If the lower than expected benefit of aspirin in individuals with diabetes will be confirmed by ongoing trials, its use for primary prevention of vascular disease in unselected people could result in net harm. Recent studies, more closely reflecting the actual practice in terms of CV risk factors control, suggest that the incidence of major CV events in individuals with diabetes and without previous CV events be between 10 and 20/1000 person years. Assuming a relative risk...
reduction associated with aspirin treatment of about 10%, as suggested by existing data, 1000 patients need to be treated for 1 year in order to prevent one to two major CV events. Therefore, the expected benefit does not clearly exceed the risk of major bleedings, particularly among older individuals.

A third and last point must be made with respect to the growing emphasis placed by authorities on appropriateness and auditing practices. As soon as a problem is not clear-cut (as it could be said to be in our case, where CV prevention interplays with another clinical condition), the probability of uncertainty is high. The under-use of aspirin in clinical practice among individuals with diabetes is in this sense very 'appropriate', not to be blamed, as it reflects the contradictory recommendations delivered by authoritative scientific societies, as well as indirectly by regulatory bodies, like FDA, not supporting the indication of aspirin for the primary prevention of heart attacks in moderate-risk patients, that is, those whose 10-year risk for heart attack is 10% or greater. The societies who have so beautifully documented that we are facing a perfect case of uncertainty, would greatly contribute to the credibility of the scientific methods in guiding practice if they would agree on a joint, sobering statement recommending that all diabetic patients with no history of CV disease should be considered (except those with documented contraindications, or perceived indications) as candidates for randomized clinical trials.

Conflict of interest: G.T. is at present member of the Executive Committee of a trial sponsored by Bayer which is planned to test ASA in non diabetic moderate risk patients; A.N., G.D.B., M.S., G.T. received a grant for research from Bayer.

References