Use of antiaggregants in diabetes

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Abstract
The hypercoagulability state present in people with diabetes may contribute to the greater atherosclerotic involvement observed in these patients. Therefore, the use of antiaggregants, besides treatment for other cardiovascular risk factors, seems to be rational in the therapeutic strategy for these patients. Current evidences justify the use of antiaggregants in secondary prevention, although with reduced efficacy in people with diabetes as compared with the general population, probably due to a certain resistance to aspirin effects. Aspirin in primary prevention has been controversial, mainly among the American diabetologists and cardiologists (ADA, AHA) favorable to its use in contrast with the European societies (EASD, ESC) against the use of antiaggregants in this context. The Americans support their position assuming that people with diabetes have a similar risk to those who have had an acute myocardial infarction, while the European opinion is based on the lack of scientific evidence demonstrating the benefit of treatment with aspirin, particularly considering the undesirable effects of this drug. Recent studies seem to support the latter position. Therefore, the use of aspirin in primary prevention is probably only indicated at low doses when numerous cardiovascular risk factors exist, consequently when possible benefits overcome potential risks.

Keywords: aspirin, antiaggregation, diabetes, cardiovascular risk.

Introduction
The diabetes mellitus entails a high atherothrombotic risk, fact that contributes to high cardiovascular (CV) morbimortality coming together with this disease. Therefore, a main objective of the therapeutic scheme should be the reduction of this risk. For this, it is basic to achieve an optimal glycemia and hypertension control, as well as to avoid the classic CV risk factors as the smoking habit, the dyslipidemia and the obesity. However, from a practical point of view this is not generally easy and therefore any other therapeutic option that offers an added value should be taken into account. In this sense, considering that the diabetes induces notable changes in the homeostasis that condition a prothrombotic condition, undoubtedly the antiaggregant treatment should be an option to be considered.

Hypercoagulability and diabetes
The diabetes mellitus, especially if developed with insulin resistance, conditions the existence of a pro-coagulant milieu that might favor the atherothrombosis facilitating the expansion of thrombus generated by the rupture of the plaque. In fact, it is well demonstrated, both clinically and experimentally, that the diabetes induces alterations in coagulation, fibrinolysis and platelet function.
It is well known that the diabetes induces an increase of procoagulant proteins such as the factor VIII, the Von Willebrand factor, the factor VII, the factor X and the fibrinogen, as well as a reduction of coagulation inhibitor factors such as the C protein and the antithrombin III. Some of these abnormalities have been related to the existence of atheromatous disease and of microangiopathic complications such as nephropathy. On the other hand, it is known that the diabetes is associated to a hypofibrinolysis secondary to an increase of inhibitor factor levels of tissue plasminogen activator inhibitor-1 (PAI-1), especially if there is obesity and insulin resistance as already observed in the Framingham Offspring Study\(^1\) and in the Insulin Resistance Atherosclerosis Study.\(^2\) Moreover, it is also known that the diabetes is related to a persistent platelet activation, as deduced from the increase in the biosynthesis of thromboxane A\(_2\) from the higher generation of thrombin dependent from platelets\(^3\) and from the spontaneous platelet aggregation.\(^4\)

It has been demonstrated that the normalization of the glycemia by means of the administration of insulin can correct this pro-coagulant situation, but it is also important to remember that the loss of weight and the physical exercise reduce the levels of PAI-1, as other oral hypoglycemics do, among them the metformin and the thiazolidinediones.

**Antiaggregation in secondary prevention**

The acetylsalicylic acid (ASA) blocks the synthesis of the thromboxane A\(_2\) acetylating the platelet ciclooxigenase, being completely accepted at present that its use has an important role in the therapeutic strategy in order to reduce the CV morbimortality. This is achieved with low doses of ASA, with maximum efficiency in a dose of 75-150 mg/day and an absolute reduction of 4.3 higher of vascular events per each 100 treated patients.\(^5\)

In diabetic population, the most relevant study regarding to the number of patients analyzed in the meta-analysis performed by the group: Antithrombotic Trialists’ Collaboration (ATP),\(^6\) in which 5,126 diabetic patients and CV backgrounds have been included. In this study, the treatment with acetylsalicylic acid at doses associated to the reduction of 7% of the relative risk of vascular events, though this result did not achieve the statistical determination, and was clearly lower than the reduction of 22% observed in the total group. The unique study performed exclusively in diabetic patients is the Early Treatment Diabetic Retinopathy Study (ETDRS),\(^6\) in which 3,711 patients with diabetes were included, from which 48% had a CV disease history, performing the treatment with 650 mg/day of ASA or with placebo in this occasion. The use of ASA was associated to a reduction of 18% in the incidence of myocardial infarction, without increasing the retinopathy risk. Finally, in the study Hypertension Optimal Treatment (HOT),\(^7\) 1,501 diabetic patients were treated with placebo or with 75 mg/day of ASA, observing a reduction of 15% of the CV events in general with this drug, and 36% of myocardial infarctions.

The main limitation of the chronic treatment with ASA is the increase of the hemorrhage risk. According to the findings of the studies ETDRS and HOT, the ASA does not increase the incidence of lethal hemorrhages, cerebrovascular accident or brain or retinal hemorrhage; though the major non-lethal hemorrhages and the inferior hemorrhages are indeed increased in 80%.

**Antiaggregation in primary prevention**

The information we have about primary prevention is scarce and controversial. There are two studies performed in male physicians, one in the United Kingdom using a dose of acetylsalicylic acid of 500 mg/day\(^8\) and another in the United States using a dose of 325 mg/day.\(^9\) The results in 104 diabetic patients that have been included, are not specified, on whom the treatment with ASA was associated to a reduction of 10% in the total mortality, though this was not statistically relevant. In the North American study performed in 22,071 male physicians from whom 533 were diabetic patients, a global risk reduction of 44% was observed after 5 years of follow-up. In the sub-group of diabetic physicians, this reduction of the risk was of 61.1%, compared to 40% in the non-diabetics. The 10.1% of the diabetic physicians in the placebo group showed a myocardial infarction, versus 4.0% in the group treated with acetylsalicylic acid. These differences were statistically relevant.

The data of Primary Prevention Project (PPP)\(^10\) have been published recently. This study performed in 4,495 subjects showed that the administration of 100 mg/day of ASA over 3 years in a general population caused a reduction of 33% of the CV events. However, when 1,031 included diabetic patients were analyzed, a discrete reduction of 10% was only observed and was not statistically relevant.\(^11\) The data of the Women’s Health Study\(^12\) has been published after this study in which it could be observed that the treatment with low doses of ASA was associated to a non-relevant reduction of 10% as regards to CV events higher in the sub-group of 1,027 women with diabetes from a total of 39,876 included. This result was consequence of a reduction of ictus risk of 54% and an increase of the infarction risk of 48%.

In 2008, two randomized studies were published in which the use of ASA in primary prevention was investigated, specifically in diabetic persons.\(^13,14\) In one of them,\(^13\) conducted in Scotland, 1,276 persons with T1D or T2D were included, aged 40 and over and with asymptomatic peripheral vascular disease. After 6.7 years of follow-up, the treatment with 100 mg/day of ASA did not reduce the onset of coronary disease, ictus and amputations. In the other study,\(^14\) performed in Japan, 2,539 patients with T2D without atherosclerosis history were randomized to take a low dose of ASA (81 or 100 mg/day) or not to take it. After 4.3 years of follow-up, there were no differences between the two groups regarding to the onset of cardiovascular events. At present, we are waiting that the ACCEPT-D\(^15\) study ends, which started in 2007, in which a treatment with 100 mg/days of ASA is performed during 5 years to 5,170 patients with T1D and T2D, without CV history and under lipopenic treatment with simvastatin. But, undoubtedly, we count at present with information that does not support the treatment with ASA of the persons with diabetes in primary prevention.
Diabetes mellitus and ASA resistance

It is evident that the results of the clinical trials performed to present show, unlike to what might be expected, a lower efficiency of ASA to prevent the development of CV disease in diabetic population, as regards to the general population. This discrepancy sets out the possibility that the persons with diabetes show a resistance to the ASA action. This concept can be applied in two ways: one clinical, understanding for resistance the onset of thrombotic phenomena in spite of the treatment, and biochemical, defined by the existence of platelet reactivity in spite of existing ASA in this field. In fact, it has been described that between 10% and 40% of the diabetic persons show a biochemical resistance to the ASA.\cite{16}

To present, the causes of the possible resistance to ASA in diabetics are not clear, having postulated three possibilities. The first one would be the higher platelet reactivity, secondary to the lower production of endothelial nitric acid, to structural changes derived from the dyslipidemia, or to a higher concentration of intra-platelet calcium. The second possibility would be the already mentioned existence of a higher activity of the coagulation factors. And the last one, and perhaps the most interesting one, would be the possible glycosylation of the platelet proteins that would interfere in the acetylating process that induces the ASA to achieve the anti-thrombotic effect.\cite{17}

In order to improve this situation as regards to the ASA resistance, it would be very interesting to know if the optimization of the glycemic control or the use of higher doses could increase the efficiency of the treatment in diabetic persons, but unfortunately we do not count with this information at present. Therefore, it seems logical to try assessing other anti-thrombotic therapeutic options, as the thienopyridines that produce their effect blocking the P2Y12 receptor inhibiting the platelet activation dependent on ADP. In this sense, the clinical experience is based mainly in three studies: the CAPRIE,\cite{18} the CURE\cite{19} and the CHARISMA,\cite{20} all of them performed with clopidogrel. In the CAPRIE study the effect of 75 mg/day of clopidogrel versus 325 mg/day of ASA was compared in 19,185 patients with serious CV history, of which 3,866 were diabetic patients. In this study, clopidogrel was superior to ASA in reducing the severe CV episodes (RR: 0.87). In the CURE study has been demonstrated that the addition of clopidogrel to the treatment with ASA produced a reduction of 20% in the relative risk of death, infarction or ictus in 12,562 patients with coronary syndrome without increase of ST (22% with diabetes), though this therapeutic option increased the hemorrhages (8.5 versus 5.0%). However, the results of this trial were not confirmed in the study CHARISMA, where 6,556 patients with diabetes where included in which the addition of clopidogrel to ASA did not offer any advantage, regarding to the treatment only with ASA, considering the reduction of the myocardial infarction rate, ictus or deaths of cardiovascular origin in a population with stable cardiovascular disease or multiple cardiovascular risk factors.

Recommendations of the scientific associations and current situation

As it is logical, since the sanitary importance of the subject, the scientific associations of diabetes and cardiology have done recommendations regarding to the antiaggregant treatment in diabetic persons. The most favorable position to the use of antiaggregants is the one of the American Diabetes Association (ADA), which recommends practically the universal use of ASA. This is based on considering that the diabetes has an equivalent risk to the coronary disease and the risk-benefit of the treatment with ASA is comparable as well. It advised the use of this drug in secondary prevention and in primary prevention in subjects under risk, considering as risk the family history of CV disease, as well as the existence of blood hypertension, smoking habit, dyslipidemia, micro or microalbuminuria or age over 40 years. These recommendations are valid both for men and for women with T1D or T2D, in a dose of 75-162 mg/day. It contraindicates the use in persons under 21 years of age due to the higher risk of showing a Reye’s syndrome, and considers the treatment with clopidogrel in case of ASA contraindication.\cite{21} These recommendations are subscribed totally by the American Heart Association (AHA).\cite{22} At present, these recommendations seem to be based more on the extrapolation of data from other risk groups, assuming that the diabetes has an equivalent CV risk, than in the analysis of the information that the studies performed up to present offer us.

The European opinion is different. Both the European Association for the Study of Diabetes (EASD) as the European Society of Cardiology (ESC) show a disagreement in the treatment with ASA in the primary prevention.\cite{23} They explain, first, that there are no sufficient scientific evidences so as to carry out this recommendation. Second, they consider that the diabetic persons treated with ASA have a high hemorrhage risk as the general population, being the lower the expected therapeutic effect; therefore, the relation risk-benefit would be unfavorable.

Considering this situation, it seems logical to accept that the treatment with ASA should be always used in the secondary prevention unless there is any contraindication. In primary prevention the risk-benefit should be assessed carefully, otherwise said, the possibility of increasing the risk of showing a digestive or brain hemorrhage compared to the reduction of the risk of developing an infarction. In the general population, this approach is set out in the meta-analysis of the US Preventive Task Force,\cite{24} in which it could be observed that the treatment with ASA in patients with 5% coronary risk in 5 years might avoid the onset of 6-20 infarctions and induce between 0 and 2 hemorrhagic ictus and 2-4 gastro-intestinal hemorrhages per each 1,000 cases. If we reduce this risk to a 1% annually, the treatment would avoid between 1 and 4 infarctions, but it would cause between 0 and 2 hemorrhagic ictus and between 2 and 4 gastrointestinal hemorrhages. These data, showing a treatment benefit with coronary risks higher than 10% in 10 years, has been confirmed in other meta-analyses,\cite{25} and in fact this is the recommendation that is carried
out by the AHA\textsuperscript{26} and the ESC.\textsuperscript{27} The decision of including diabetic persons in this therapeutic scheme shall depend on the characteristics of the sick persons and probably on the agreement between the patient and the physician, after the customized analysis of the risk-benefit.

Regardless of what has been commented, it has to be pointed out that the treatment with ASA in diabetic patients in our field is low –considering the existing recommendations– though we would only consider the secondary prevention. In a study performed in 2003 in Catalonia\textsuperscript{28} in 1,718 patients, this treatment was done in 53% of the patients in secondary prevention. At a great extent, this infra-use of ASA at low doses is motivated by the lack of specific recommendations by the professionals, and this is a situation that should be corrected.

Conclusions

To sum up, the diabetes mellitus conditions the existence of a prothrombotic condition that might be implied in the clear increase of CV risk that the diabetic persons show. The treatment with ASA at low doses is effective in secondary prevention and therefore its use should be compulsory, unless in the case there is some contraindication in which clopidogrel should be set out for the treatment. For the situations that there is no previous CV disease, there is no universal consensus regarding to the benefit of the antiaggregant treatment, and it is even questioned in the non-diabetic persons, especially if there is hypertension.\textsuperscript{29,30} Therefore, while we do not count with data from the current ongoing studies, the treatment with ASA should be in consensus with the patient, evaluating carefully the risk-benefit and reserving for patients at high risk, as the smokers could be or those who show a long disease evolution or other risk factors, as for example the microalbuminuria or the existence of atheromatous plaques in the echography.

Declaration of potential conflicts of interest

E. Esmatjes states that there are no conflicts of interest as regards to this manuscript.

References


