Antiplatelet therapy for primary prevention in diabetes

P Ambrosi, P Villani, G Bouvenot

ABSTRACT
Aspirin is currently recommended by ADA (American Diabetes Association) for the diabetic patients over 40 years of age and without cardiovascular disease. This recommendation is at odds with drug approval for aspirin. The main explanation is the absence of appropriate trials assessing the usefulness of aspirin in such patients. Two assumptions, central to these guidelines are that diabetes is a coronary risk equivalent, and that aspirin benefit/risk ratio is similar in diabetic patients than in coronary disease patients. Unfortunately, vascular risk level is variable in diabetic patients. Patients with new onset diabetes have lower cardiovascular risk than patients with established cardiovascular disease. Smoking habits markedly increase the risk. Benefits may be lower in diabetic patients since aspirin resistance is common in these patients. Haemorrhagic risk may be higher since diabetes is a risk factor for haemorrhagic stroke. Awaiting trial evidence, aspirin therapy should be considered in diabetic patients with a very high risk, such as smokers, patients with long diabetes duration, or atherosclerotic plaques at echography.

Key-words: Aspirin · Clopidogrel · Diabetes mellitus · Primary prevention.


RÉSUMÉ
Intérêt des antiagrégants en prévention primaire chez le diabétique
L’aspirine est recommandée par l’ADA (American Diabetes Association) chez les diabétiques de plus de 40 ans sans antécédents cardiovasculaires. Cette recommandation n’est pas cohérente avec les indications reconnues par les autorisations de mise sur le marché. La principale explication est l’absence d’essai clinique évaluant de manière adéquate l’intérêt de l’aspirine chez ces patients. Les deux postulats fondant cette recommandation sont d’une part que le diabétique a un risque vasculaire équivalent à celui du coronarien et d’autre part que le rapport bénéfice/risque de l’aspirine est le même chez le diabétique que chez le coronarien. Malheureusement, le risque vasculaire du diabétique est très variable. Les patients avec un diabète récent ont un risque cardiovasculaire plus bas que ceux avec une maladie cardiovasculaire avérée. Le tabagisme augmente considérablement le risque vasculaire. Le bénéfice de l’aspirine est peut-être moins important chez le diabétique, en raison d’une résistance à l’aspirine. Le risque hémorragique est peut-être plus élevé, puisque le diabète est un facteur de risque pour l’hémorragie cérébrale. Dans l’attente du résultat des essais cliniques en cours, il paraît raisonnable de limiter l’indication de l’aspirine aux diabétiques à très haut risque comme les fumeurs, les patients avec un diabète ancien ou avec des plaques d’athérosclérose à l’échographie.

Mots-clés : Aspirine · Clopidogrel · Diabète · Prévention primaire.
Despite the absence of large clinical studies assessing the usefulness of antiplatelet therapy for macrovascular prevention in patients with diabetes, there is a large bulk of evidence supporting aspirin use for secondary prevention of arterial vascular disease in such patients. Secondary prevention trials have reproducibly demonstrated a reduction of vascular events, mainly coronary events, on aspirin therapy in patients with myocardial infarction (MI), stroke or transient ischemic attack [1]. The Anti-Platelet Trialists have performed a meta-analysis of diabetic sub-groups in 145 prospective trials [1]. They have shown that antiplatelet drugs reduce the occurrence of major vascular events by about one-quarter to one-third in diabetic patients with a cardiovascular history. Thus there is no doubt that aspirin and/or clopidogrel are indicated in diabetic patients with established coronary disease, peripheral arterial disease or ischemic stroke, in the absence of contra-indications.

Routine use of antiplatelet drugs for primary prevention in diabetes is more controversial. Drug approval and guidelines are discrepant. For instance FDA and French AFSSAPS have approved low-dose aspirin and clopidogrel only for secondary prevention. In contrast, the American Diabetes Association (ADA) recommends aspirin therapy (75-162 mg/day) as a primary prevention strategy in men and women with type 1 or type 2 diabetes at increased cardiovascular risk, including those over 40 years of age or who have additional risk factors (family history of cardiovascular disease, hypertension, smoking, dyslipidemia, albuminuria) [2]. French ANAES has published similar guidelines. Thus, according to these recommendations, aspirin is indicated in most diabetic patients. Although these recommendations have been published for the first time in 1997, less than one-third of UKPDS (United Kingdom Prospective Diabetes Study) patients without pre-existing cardiovascular disease (CVD) were taking aspirin regularly in 2000 and 2001 [3]. Similarly, regular aspirin use was less than 40% in the USA among diabetics with hypertension, hypercholesterolemia or smoking habits and without cardiovascular disease in 2001 [4]. This may relate to a lack of convincing evidence. In the present review, we examine epidemiological evidences and trial data supporting aspirin efficacy for primary vascular prevention in diabetic patients.

Epidemiological evidence

The main epidemiological argument supporting a wide use of antiplatelet therapy in diabetics without known vascular disease is the high vascular risk level of these patients. Haffner et al have illustrated such a high risk in 1998 [5]. They have found that the risk of death from coronary disease in patients with type 2 diabetes was as high as in patients who have had a prior MI. However their study population was relatively small (2,432 patients), with a diabetes mean duration of eight years, and they were Finnish people i.e. with coexisting major risk factors (figure 1). Another study suggests that diabetes mellitus may be classified a stroke risk equivalent in diabetic women [6].

Several other studies have compared the coronary risks of prior MI and diabetes (Table I). Taken together, these studies show that coronary risk is usually higher in men with MI than in men with diabetes only [7-11]. In women, the excess risk of patients with prior diabetes seems equivalent to that conferred by prior MI. Other studies have compared the vascular risk of established coronary disease (angina and/or MI) and diabetes (Table II), with similar results [12, 13]. The longer the duration of diabetes, the higher is the cardiovascular risk.

The prognosis of incident diabetes has also been compared to incident MI or CVD (Table III). Risk ratios of coronary or cardiovascular death are substantially greater for patients with incident MI than those with incident diabetes alone [9, 14-15].

Table I
Risk for death from coronary heart disease in subjects with diabetes only, myocardial infarction (MI) only and neither diabetes nor MI diagnoses at baseline. Adjusted risk ratios or hazard ratios are given with 95% confidence interval.

<table>
<thead>
<tr>
<th>Study [ref.]</th>
<th>MI only/ diabetes only</th>
<th>Diabetes only/neither diabetes nor MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haffner et al. [5]</td>
<td>0.7 (0.38 to 1.4)</td>
<td>NA</td>
</tr>
<tr>
<td>ARIC* [7]</td>
<td>1.86 (1.35 to 2.56)</td>
<td>2.0 (1.64 to 2.44)</td>
</tr>
<tr>
<td>Kuopio [8]</td>
<td>1.1 (0.66 to 1.66)</td>
<td>7.0 (4.8 to 10.1)</td>
</tr>
<tr>
<td>Hu et al., men [9]</td>
<td>1.43 (1.16 to 1.77)</td>
<td>NA</td>
</tr>
<tr>
<td>Hu et al., women [9]</td>
<td>0.63 (0.47 to 0.84)</td>
<td>NA</td>
</tr>
<tr>
<td>Wannamethee et al. [10]</td>
<td>1.38 (0.7 to 2.6)</td>
<td>2.82 (1.85 to 4.28)</td>
</tr>
<tr>
<td>MRFIT [11]</td>
<td>1.37 (1.26 to 1.48)</td>
<td>NA</td>
</tr>
</tbody>
</table>

MRFIT: Multiple Risk Factor Intervention Trial
*In ARIC (Atherosclerosis Risk In Communities), RR were given for coronary death or non-fatal MI.
Thus vascular risk in type 2 diabetes is variable: older patients, especially women, with long diabetes duration may have a coronary or a stroke risk equivalent. Younger patients or patients with recent diabetes have a vascular risk intermediate between patients with a history of MI and non-diabetic patients without cardiovascular disease. We can speculate that the risk of patients on antidiabetic drugs is often near from that of patients with stable coronary disease in the absence of prior MI. Vascular risk may be calculated in individual diabetic patient from risk tables such as UKPDS risk engine or Framingham equation. These tables highlight the importance of associated smoking habits. However we still lack such risk tables for diabetics living in Southern Europe.

Another lesson from epidemiological studies is that hemorrhagic risk is somewhat elevated in patients with diabetes. Ariesen’s systematically reviewed studies on risk factors for intracerebral haemorrhage. Crude risk ratio for diabetes was 1.30 (95% CI, 1.02 to 1.67) in cohort and case-control studies combined [16].

Primary prevention with aspirin in various populations

Several studies evaluated the value of aspirin for vascular prevention in various populations. Table IV summarises the three major, placebo-controlled, primary prevention studies [17, 18, 19]. All were negative studies. For instance, in the Physicians’ Health Study, 22,071 American physicians, from 40 to 84 years of age, were randomly assigned to take either 325 mg aspirin every other day or placebo for an average follow-up of 5 years [17]. In the 11,037 patients receiving aspirin there were 100 MI less (p< 0.00001), 21 strokes and 20 major haemorrhages (p= 0.02) more than in the placebo group, without significant difference according to primary endpoint. Women’s Health Study showed significant benefits only for secondary endpoint or sub-groups such as major vascular event in women 65 years of age or older [18]. As there is only a trend for benefit with aspirin therapy in men or women over 40 years of age, aspirin should not be prescribed in the general population and should be targeted to selected high risk patients. This hypothesis was tested in HOT (Hypertension Optimal Treatment) study in 18,790 hypertensive patients, aged 50-80 years, mostly in primary prevention [19]. In this study, aspirin did not significantly reduced major cardiovascular events. In a secondary endpoint analysis of this study, excluding silent myocardial infarction, the authors found a statistically significant 15% decrease of major cardiovascular events, with a very large confidence interval. Moreover, severe bleeds were twice as common in the aspirin group.

The meta-analysis of five primary prevention studies showed that aspirin therapy reduced the risk for coronary heart disease by 28% (OR 0.72, 95% CI, 0.60 to 0.87) [20].
However, the absence of significant risk reduction of the primary endpoint in the very large primary prevention studies shows that the benefit, if any, is small. Thus, there is no convincing evidence that aspirin may be effective and safe for primary cardiovascular prevention.

Primary prevention with antiplatelet therapy in diabetic patients

Neither aspirin nor clopidogrel have been appropriately evaluated for primary prevention in diabetic patients. ETDRS (Early Treatment Diabetic Retinopathy Study) was designed to assess the possibility that aspirin may retard the progression of diabetic retinopathy [21]. Diabetic patients (n=3,711) with known retinopathy were randomly assigned to aspirin or placebo. A cardiovascular disease history was present in 49% of them. Macrovascular events were a secondary endpoint and were not significantly decreased on aspirin.

Aspirin efficacy has also been studied in diabetic subgroups of major prevention studies. None have shown a significant advantage for aspirin. For instance in the 1,031 diabetic patients of the Primary Prevention Project (PPP), aspirin therapy was associated with a non-significant 10% decrease of cardiovascular death, stroke or MI [22]. On the other hand, clinical trials have shown that aspirin is usually well tolerated in diabetics, even in patients with retinopathy.

The usefulness of clopidogrel for primary prevention has not been properly evaluated. The CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial [23] has compared clopidogrel (75 mg per day) plus low-dose aspirin (75 to 162 mg per day) to placebo plus low dose aspirin in 15,603 high risk patients, either for primary or secondary prevention, with a median follow-up of 28 months. The rates of major vascular events were not significantly different between the two randomized treatment arms. Subgroup analysis showed that among the 3,284 patients in primary prevention with multiple risk factors, including diabetes in 81%, the rate of the primary end point was 6.6% with clopidogrel plus aspirin and 5.5% with aspirin plus placebo (p=0.20). In the subgroup with clinically evident atherothrombosis, the rate was 6.9% with clopidogrel plus aspirin and 7.9% with aspirin plus placebo (p=0.046). There was a trend toward higher severe bleeding rates among the primary prevention group than in the secondary prevention group. These results suggest that the benefit/risk ratio of antiplatelet therapy may be lower in diabetics than in patients with established vascular disease.

Aspirin resistance in diabetic patients

The possibility that diabetics may have an increased prevalence of aspirin resistance has been raised by several ex vivo studies [24–26]. Platelet aggregation to agonists such as ADP or arachidonic acid is increased in patients with diabetes compared to controls, at baseline and after aspirin or clopidogrel administration. This does not mean necessarily that the absolute reduction in platelet sensitivity to agonists after aspirin is lower in diabetic than in nondiabetic patients. Platelets may be more activated on aspirin in diabetic than in non-diabetic controls because of the high activation state at baseline. Accordingly, previous works have established that platelets are frequently activated in diabetic patients as a result of widespread arterial lesions and various humoral modifications. This hypothesis is also supported by the observation that patients with new onset diabetes do not have so-called aspirin resistance [27]. Another explanation could be that there is a true aspirin resistance in diabetes, related to high rate of entry of new young platelets into circulation or to protein glycation [24].

Conclusion

Therapeutic guidelines should be based on trial evidence, not on epidemiological data. Two assumptions central to ADA guidelines are that diabetes is a coronary risk equivalent and that aspirin benefit/risk ratio is similar in diabetic patients than in other high risk populations. Unfortunately, vascular risk level is variable in diabetic patients. The hazards of aspirin therapy in such patients have not been precisely evaluated and aspirin resistance may blunt part of the aspirin efficacy. Moreover, we have to keep in mind that aspirin usefulness has not been reproducibly demonstrated in other primary prevention populations. This treatment

Table IV
Major double-blind, placebo-controlled primary prevention studies with aspirin.

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<th>Primary endpoint</th>
<th>RR aspirin/no aspirin (95% CI)</th>
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<tr>
<td>Physicians [17]</td>
<td>Men, 40-84 years</td>
<td>22,071</td>
<td>CV death</td>
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<td>Women’s [18]</td>
<td>Women, ≥ 45 years</td>
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<td>CV death + MI + stroke</td>
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HOT: Hypertension Optimal Treatment  
CV death: cardiovascular death; MI: myocardial infarction

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reduces myocardial infarction, but increases gastrointestinal and intracranial bleeding. Thus, we really need studies assessing the usefulness of aspirin for primary prevention in diabetes. ASCEND (A Study of Cardiovascular Events inN Diabetes) study is ongoing in the United Kingdom. Awaiting trial evidence, aspirin therapy should be considered in diabetic patients with a very high risk such as smokers, patients with long diabetes duration (> 10 years), or atherosclerotic plaques at echography.

References