*For debate***Diabetes mellitus and peripheral vascular disease: is aspirin effective in preventing vascular events?****C. Cimminiello¹, M. Milani²**¹ Thrombotic and Vascular Pathology, 4th Medical Department, Ospedale San Carlo, Milan, Italy² Cardiovascular Department, Sandoz Prodotti Farmaceutici S.p.A., Milan, Italy

*“All that glisters is not gold”
W. Shakespeare. The Merchant of Venice.
Act II, Scene VII*

The combination of diabetes mellitus and peripheral vascular disease (PVD) is a common feature in clinical practice. Epidemiologic studies confirm the high prevalence of intermittent claudication in diabetic men and women who are respectively 3.4 and 5.7 times more frequently affected than are healthy subjects [1]. The prevailing involvement of leg vessels in diabetic patients is revealed by the fact that gangrene or amputation of lower limbs are 20 times more frequent in diabetic than in control subjects, whereas the prevalence of myocardial infarction (MI) in the same patients is only 3 times more frequent than in control subjects [2]. The progression of PVD appears to be more pronounced in diabetic patients who also show a higher amputation rate than non-diabetic patients [3]. The risks of fatal and non-fatal MI and stroke are also increased in diabetic PVD subjects [4]. Therefore, since PVD patients are at elevated risk of subsequent vascular events [5], patients with both diabetes and PVD appear to be at an even higher risk, and it is mandatory for clinicians to try to reduce such excessive risk. Aspirin treatment is currently recommended for PVD patients to decrease their cardiovascular mortality and morbidity [6]; however, in diabetic patients with PVD, the protective role of aspirin is largely unknown. Is aspirin effective in this set of high-risk patients? This article will attempt to elucidate the issue by analysing and evaluating the current

available scientific literature, first concerning the role of aspirin in treatment of both PVD patients and of diabetic patients and finally, the evidence of aspirin efficacy in subjects with both PVD and diabetes.

Efficacy of aspirin in patients with PVD

PVD and especially its second clinical stage according to Fontaine – that of intermittent claudication – are the most common manifestations of atherosclerosis of the lower limbs. The incidence is approximately 0.3% per year with increasing rates in the elderly (0.65%) [7]. Several studies in recent years have improved our knowledge on the prognosis of affected limbs which is relatively benign compared to the increased cardiovascular risk of these patients, who experience a high rate of subsequent coronary and cerebrovascular events. Vascular mortality is in fact 5 times higher in patients with claudication over a period of 10 years [8] while the annual rate of fatal and non-fatal cardiovascular events ranges from 3.5 to 8% per year [9]. Therefore, there is no doubt that patients with claudication are at high risk of future stroke, MI and premature death and this is the reason why consensus statements strongly recommend lifelong treatment with aspirin (325 mg/day) in order to reduce this risk [6]. This recommendation was based on the results of the first report of the Antiplatelet Trialist's Collaboration (APT) [10] describing a 25% risk reduction with antiplatelet drugs in high-risk categories for cardiovascular events, including patients with prior transient ischaemic attack, stroke, unstable angina or MI. However, the appropriateness of extrapolating the aforementioned benefit of antiplatelet therapy (i.e. treatment with aspirin) to patients with intermittent claudication is questionable, as it is potentially biased. In

Corresponding author: M. Milani, MD, Cardiovascular Medical Department, Sandoz PF, Via C. Arconati 1, I-26135 Milano, Italy

Abbreviations: PVD, Peripheral vascular disease; MI, myocardial infarct; ATS, accelerated atherosclerosis.

the second report by the APT [11] studies performed specifically in patients with PVD were also included in the analysis but only a trend, odds ratio, (OR), 0.80, confidence interval, (CI), 0.64–1.0; relative risk reduction 17.8%, 32.5/–0.2%) in favour of antiplatelet therapy (encompassing aspirin, aspirin plus dipyridamole, ticlopidine, suloctidil and indobufen) was observed in the 3295 subjects treated in 22 trials. Moreover, if we consider only the studies (or their subgroups) employing aspirin alone in patients with claudication, then four studies exist (one using only aspirin in combination with dipyridamole) totalling 849 subjects and 112 vascular events. If the data of the patients are recalculated, an OR for cardiovascular events of 0.92 (CI 0.62–1.37) in favour of aspirin is noticeable, with a non-significant relative risk reduction of 6.7% (33.9/–31.8%) due to active treatment. Vascular mortality is reduced by 13.3% (44.9/–36.5%); NS. Therefore, the benefits of long-term aspirin use in patients with PVD remain, so far, unproven.

Diabetes and cardiovascular risk: role of aspirin and other antiplatelet agents

Diabetes is characterized by accelerated atherosclerosis (ATS) and enhanced tendency to thrombosis [12]. Macrovascular and microvascular diseases are common complications of long-standing diabetes [13]. Diabetes is associated with an increased risk of ATS complications. The risk of stroke, MI, PVD and vascular death is increased twofold to fourfold in the majority of the diabetic population [14]. Diabetic patients have an incidence of brain infarction 2–3 times higher than non-diabetic subjects [15]. The mortality from cerebrovascular diseases is also 2–5 times greater in diabetic subjects [16]. Several studies have shown an increased platelet adhesiveness and aggregability, with a concomitant increased release of thromboxane, in diabetic subjects [17]. As mentioned previously, antiplatelet therapy has been shown to reduce the risk of MI and thrombotic stroke in patients at high risk of vascular death. Therefore, a strong rationale supports the prophylactic use of antiplatelet agents in diabetes. The APT collaboration meta-analysis demonstrated that the use of antiplatelet agents in high-risk diabetic patients could significantly reduce the risk of major cardiovascular events. The diabetic patients had 17% fewer vascular events while taking antiplatelet drugs, compared with a 22% reduction in those without diabetes [11]. Unfortunately, there is no indication in the APT report of the specific effect of aspirin in the different subgroups of diabetic patients treated with this drug. On the contrary, data from single studies and published data concerning the efficacy of aspirin in diabetic subjects are controversial. In the Early

Treatment of Diabetic Retinopathy Study (ETDRS) performed on 3711 diabetic subjects followed up for 7 years, primary prevention with aspirin (650 mg/day) did not reduce the incidence of major vascular events in comparison to administration of placebo [18]. Also in the DAMAD Study which evaluated the ability of aspirin (990 mg/day) or aspirin plus dipyridamole (225 mg/day) to prevent the progression of diabetic retinopathy in 475 patients during a follow-up of 36 months, the rate of vascular events was higher in treated (7.5%) than in control groups (5.1%) [19].

In addition, the European Stroke Prevention Study showed that the protective effect of aspirin (990 mg/day) in combination with dipyridamole was greater in non-diabetic patients in comparison to the diabetic population. The authors concluded that the effect of aspirin therapy in the prevention of stroke or vascular death was weaker in diabetic subjects [20]. In the TASS trial comparing ticlopidine and aspirin (1300 mg/day) in patients with prior TIA or minor stroke, the subgroup of 231 diabetic patients treated with aspirin suffered from 38 strokes (17.2%) which were significantly more ($p = 0.003$) than those recorded for the remaining 1214 non-diabetic subjects (121; 10%) treated with the same drug [21]. Finally the ISIS 2 study did not show any benefit of aspirin at a dose of 165 mg/day in the acute phase of MI in the diabetic subgroup [22]. In a recently published trial, aspirin did not have significant long-term protective effects on vascular events in 372 asymptomatic patients with carotid stenosis, of whom 25% suffered from diabetes [23].

Effect of aspirin in patients with diabetes and PVD

The only prospective study so far reported which evaluates the efficacy of 5 years of aspirin treatment in diabetic patients with PVD is the Veterans Administration Cooperative Study which enrolled a total of 231 patients [24]. This study assessed the efficacy of aspirin (650 mg/day) and dipyridamole in preventing the progression of cardiovascular and PVD in diabetic men with limb gangrene or recent amputation for ischaemia. At the end of the follow-up there were no differences in major endpoints such as atherosclerotic vascular death (21.8 and 19%, respectively) in treated and control subjects, or amputation of the opposite extremity (20% in aspirin group vs 24% in control subjects). Stroke and TIA were the only endpoints favourably, though not significantly, affected by treatment (8.2% in active treatment vs 19% in the placebo arm; NS). A large secondary prevention trial of aspirin and/or other antiplatelet drugs in diabetic subjects with PVD is therefore urgently needed.

Discussion

The data on the efficacy of aspirin in PVD patients and in diabetic subjects are conflicting and somewhat disappointing. The main limitation is the lack of a large trial with aspirin in patients with intermittent claudication, aiming to reduce cardiovascular mortality and morbidity. The studies so far reported on the effect of aspirin in PVD patients are unreliable since the majority were designed and sized to detect end-points different from those conventionally used by the APT (non-fatal MI and stroke plus vascular death). The pooling of such studies in a meta-analysis could be biased and inappropriate and might produce misleading conclusions. Even so, the apparent slight protection afforded by aspirin in PVD patients compared to that seen in MI subjects could rely on the fact that the former category is usually older: age seems to be a limiting factor of the efficacy of aspirin owing also to its reduced safety (and compliance) in elderly people [25]. The problem of aspirin efficacy in diabetic subjects deserves comment: even if one credits the 17% reduction described in the APT report entirely to aspirin, by looking at the absolute risk of vascular events in treated patients which still amounts to 18.5% after 2 or 3 years of therapy, it must be pointed out that in the control group of high-risk patients the absolute risk is 16.4%, i.e. 11% less than that obtained by antiplatelet therapy in diabetic subjects. Are these results satisfactory? Are these reductions adequate or do we need better therapeutic strategies than those currently available, i.e. aspirin? In his recent review article on aspirin as an antiplatelet drug, Patrono [26] claimed that doses of aspirin (50 mg/day) lower than those usually employed might have a better effect in diabetic patients, basing his suggestion on the fact that such a dose is able to completely suppress thromboxane synthesis in platelets from diabetic patients. On the basis of the results of clinical trials it is reasonable to conclude that if 30, 300 or 1300 mg of aspirin per day offer equivalent protection in non-diabetic patients, the same could also be expected for diabetic patients, even with a dose of 50 mg of aspirin/day. There is urgent need for newer antiplatelet agents of greater efficacy in patients at very high risk, such as PVD subjects with diabetes.

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