

# Effects of picotamide, an antiplatelet agent, on cardiovascular events in 438 claudicant patients with diabetes: a retrospective analysis of the ADEP study

MASSIMO MILANI, ALDO LONGONI<sup>1</sup> & MICHELA MADERNA<sup>1</sup>

Sandoz Prodotti Farmaceutici S.p.A., Cardiovascular Medical Department, Milano and <sup>1</sup>Istituto Ricerche LPB, Milano, Italy

Picotamide is an antiplatelet drug which inhibits thromboxane A<sub>2</sub> (TxA<sub>2</sub>) synthase and antagonizes TxA<sub>2</sub> receptors. In the ADEP (Atherosclerotic Disease Evolution by Picotamide) trial, 2304 patients with peripheral obstructive arterial disease (POAD) were studied in a double-blind, placebo-controlled, 18-month, multicentre trial. In this study, 151 events (13.1%) occurred on placebo and 122 (10.6%) on picotamide (900 mg day<sup>-1</sup>). The relative risk reduction was 19%, ( $P=0.056$ ). This paper reports a *post-hoc* analysis in a subgroup of 438 diabetic patients (picotamide = 230; placebo = 208). There were 32 vascular events on placebo (15%) and 18 on picotamide (8%) (relative risk reduction: 48%; 95% CI = 26, 76;  $P=0.022$ ). The results of this retrospective analysis suggest that a prospective study to investigate events in claudicant patients with diabetes mellitus is warranted.

**Keywords** picotamide antiplatelet drugs peripheral vascular disease secondary prevention

## Introduction

Peripheral obstructive arterial disease (POAD) is often complicated by ischaemic episodes occurring not only in the peripheral circulation but also in coronary and cerebral vessels [1–4]. The mortality rate for POAD patients is 2–3 times higher in comparison with the general population. Diabetes mellitus (DM) is a risk factor frequently associated with vascular deterioration and POAD patients with DM have a higher rate of amputations and an increased risk for myocardial infarction than non-diabetics [5]. Clinical studies have demonstrated an increased platelet aggregation in patients with DM [6]. This suggests that platelet hyperactivity has a role in the progression of the disease and that inhibition of the arachidonic acid pathway might reduce vascular complications in diabetic patients. However, antiplatelet treatment has been given to claudicant patients but the results are less convincing than those obtained in other clinical settings [7–8]. Until now, the effect of an antiplatelet treatment has not been evaluated in claudicant patients with DM. Picotamide (Plactidil® Sandoz PF) is an antiplatelet drug which inhibits platelet TxA<sub>2</sub> and antagonizes TxA<sub>2</sub> receptors [9–11]. Previous studies suggest that picotamide might have a particular benefit in DM [12–14].

Compared with placebo, picotamide reduced exercise-induced microalbuminuria in diabetic subjects with initial nephropathy [12] and halted the progression of carotid atherosclerosis in diabetics with macroangiopathy [13]. In comparison with aspirin, picotamide showed a positive effect on microcirculation in diabetic patients with microangiopathy [14]. A recent multicentre study (ADEP trial), carried out in 2304 POAD patients, demonstrated that picotamide reduced vascular events by 19% on an intention-to-treat basis [15]. Here we report a retrospective analysis of the ADEP study which evaluated the effects of picotamide on vascular events in claudicant patients with DM.

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## Methods

### Study design

The ADEP study was a double-blind, randomized, placebo-controlled multicentre trial, stratified by centre,

carried out in 2304 POAD patients. Full details of the study organization and methods have been previously published [15]. After 1-month, single-blind placebo run-in period, eligible patients, after obtaining their informed consent, were given either picotamide (300 mg three times daily) or placebo and followed for 18 months. The present paper shows the results of a retrospective analysis carried out in a subgroup of 438 diabetic patients.

### Patients

POAD was defined as leg pain on walking that disappeared after 5 min at rest, and an ankle/arm pressure index by Doppler ultrasonography  $\leq 0.85$  or claudication with previous amputation/reconstructive vascular surgery. Exclusion criteria were: treatments with antiplatelet, non-steroidal anti-inflammatory and anticoagulant drugs; pain at rest, skin lesions and myocardial infarction or stroke in the previous 3 months. Patients were examined every 3 months and all vascular event documentations were sent to an independent review committee for event validation which was conducted blind to treatment allocation.

### Outcomes

The events taken into consideration during the ADEP study were the following: vascular and non-vascular death, fatal and non-fatal myocardial infarction (MI), fatal and non-fatal stroke, amputation above the ankle for reasons other than tumours or trauma and excision of ischaemic viscera. MI and stroke were considered fatal if death occurred within 1 month of the qualifying event. These events were defined as major events. Other vascular events included: recently developed angina or unstable angina, possible or probable MI, transient ischaemic attacks (TIA), minor stroke (defined as a focal ischaemic cerebrovascular event resulting in minimal permanent neurologic deficit and at least 80% recovery of function within 3 weeks), and deterioration of vascular disease leading to surgical intervention, angioplasty or local thrombolysis. If a patient had both a major and other vascular event, only the major was counted; each patient contributed only one event.

### Statistical analysis

Event-free analysis was performed on the subset of diabetic patients, establishing survival curves according to the Kaplan–Meier method. The patients lost to follow-up and those who withdrew alive were considered as censored in the intention-to-treat analysis. The null hypothesis  $H_0: \theta = 1$ , where  $\theta$  is the odds ratio of the two curves, was tested by the log-rank test. 95% confidence intervals were also calculated. The Proc Lifetest was used (SAS 6.04) to perform this analysis.

### Results

The characteristics of the patients in the two groups were similar at the time of randomization with mean durations of diabetes of 5.8 and 5.3 years in the picotamide and placebo group respectively; 7% and 5% of the patients in the picotamide and placebo group respectively were using insulin. Oral antidiabetic treatment was used by 20% and 21% of picotamide and placebo patients respectively. Hypercholesterolaemia was present in 36% of picotamide treated patients and in 29% of placebo group. Hypertriglyceridaemia was observed in 33% and 34% of the picotamide and placebo group respectively; 15% on picotamide and 16% on placebo had a clinical history of coronary heart disease, whereas 13% on picotamide and 8% on placebo had previous cerebrovascular disease. Comparable percentages of patients (21% on picotamide and 25% on placebo) had previously undergone surgery or angioplasty for cardiovascular disease. Concomitant treatments were equally distributed in the two groups. During the study, 27 patients were lost to follow-up, 16 (7%) on picotamide and 11 (5%) on placebo. Side effects occurred in 15% of patients on picotamide and 17% of patients on placebo. No difference between the two groups was observed in the frequency of gastrointestinal complaints (10% both in picotamide and placebo). The intention-to-treat analysis for major and other events in diabetic patients is shown in Table 1. Vascular events occurred in 18 (8%) patients of picotamide group and in 32 (15%) in those of placebo group (relative risk reduction: 48%; 95% CI: 26, 76;  $P=0.02$ ; log-rank test). Patients taking picotamide had six major events (3%) and 12 other events (6%), whereas patients taking placebo had 12 major (6%) and 20 minor events (10%) (relative risk reduction for major events: 56%; 95% CI: 21, 143). Event-free survival curves are shown in Figure 1.

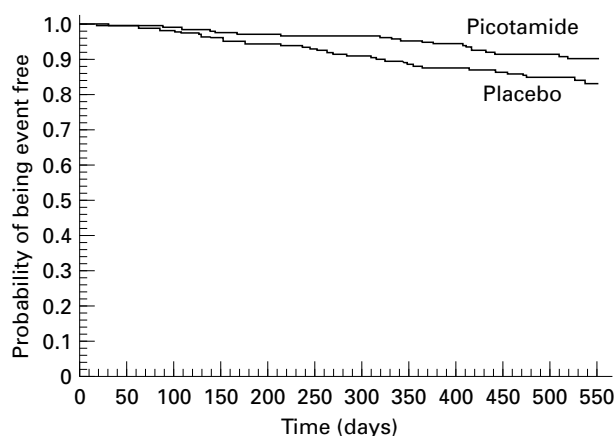
### Discussion

The results of this retrospective analysis of the ADEP study indicated that, in POAD patients with DM, picotamide reduced the relative risk of vascular events by 48%. This effect was greater than that observed in the general POAD population, in which picotamide reduced the risk of vascular events by 19%. These findings are in agreement with other clinical studies which demonstrated a positive effect of picotamide in diabetic patients [12–14]. Taken together, the results of these trials in diabetic patients suggest a potential use of picotamide in preventing vascular disease in this clinical condition. The main limitation of the present study is that it involves a *post-hoc* analysis of the diabetic subgroup patients enrolled in the large scale ADEP trial; therefore these results should be interpreted with caution. Our findings are based on a secondary analysis of the principal study and the potential efficacy of picotamide needs to be further evaluated in a prospective trial planned to analyze its effect in claudicant patients with diabetes mellitus. Therefore our

**Table 1** Cardiovascular events in diabetic patients treated with picotamide or placebo

|                                      | Picotamide<br>n = 230 |     | Placebo<br>n = 208 |      | Total<br>n = 438 |      | Reduction<br>of risk<br>(%) | 95%CI<br>(%) |
|--------------------------------------|-----------------------|-----|--------------------|------|------------------|------|-----------------------------|--------------|
|                                      | n                     | (%) | n                  | (%)  | n                | (%)  |                             |              |
| Total events                         | 18                    | 8.0 | 32                 | 15.3 | 50               | 11.4 | 48*                         | 26, 76       |
| Major events                         | 6                     | 2.6 | 12                 | 5.8  | 18               | 4.1  | 56                          | 21,143       |
| Death                                | 3                     | 1.3 | 6                  | 2.9  | 9                | 2.1  |                             |              |
| Myocardial infarction                | 1                     | 0.4 | 2                  | 1.0  | 3                | 0.7  |                             |              |
| Stroke                               | 2                     | 0.9 | 2                  | 1.0  | 4                | 0.9  |                             |              |
| Amputation                           | 0                     | 0.0 | 2                  | 1.0  | 2                | 0.5  |                             |              |
| Other events                         | 12                    | 5.2 | 20                 | 9.6  | 32               | 7.3  | 46                          | 21, 76       |
| Angina                               | 2                     | 0.9 | 3                  | 1.4  | 5                | 1.1  |                             |              |
| TIA                                  | 3                     | 1.3 | 9                  | 4.3  | 12               | 2.7  |                             |              |
| Minor stroke                         | 1                     | 0.4 | 1                  | 0.5  | 2                | 0.5  |                             |              |
| Peripheral vascular<br>deterioration | 6                     | 2.6 | 7                  | 3.4  | 13               | 3.0  |                             |              |

\* $P < 0.022$  logrank test



**Figure 1** Event-free analysis of diabetic patients treated with either picotamide ( $n = 230$ ) or placebo ( $n = 238$ ) for 18 months. The probability value refers to survival curves developed for picotamide and placebo according to the Kaplan–Meier method.

observations are useful for generating hypotheses and for providing mechanistic insights, and supply clinical information which might be useful in planning future trials.

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## References

- Coffman JD. Intermittent claudication: be conservative. *N Engl J Med* 1991; **325**: 577–578.
- Criqui MH, Langer RD, Frank A, Feigelson HS, Klauber MR, McCann TJ, Browner D. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med* 1992; **326**: 381–386.
- Dormandy J and the Members of Steering and Executive Committees of the Multinational Study on the Prevention of Atherosclerosis Complications by Ketanserin (PACK). Fate of the patients with chronic leg ischemia. *J Cardiovasc Surg* 1989; **30**: 50–57.
- Prevention of Atherosclerotic Complications with Ketanserin Trial Group. Prevention of atherosclerotic complications: Controlled trial of Ketanserin. *Br Med J* 1989; **298**: 424–430.
- Schadt DC, Hines ES Jr, Juergens JL, Barker NW. Chronic atherosclerotic occlusion of the femoral artery. *JAMA* 1961; **175**: 937–940.
- Davi G, Catalano I, Averna M, *et al.* Thromboxane biosynthesis and platelet function in type II diabetes mellitus. *N Engl J Med* 1990; **322**: 1769–1774.
- Antiplatelet Trialists Collaboration. Collaborative overview of randomised trials of antiplatelet therapy-I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *Br Med J* 1994; **308**: 81–106.
- Goldhaber SZ, Manson JE, Stamper MJ, LaMotte F, Rosner B, Buring JE. Low-dose aspirin and subsequent peripheral arterial surgery in the Physicians' Health Study. *Lancet* 1992; **340**: 143–145.
- Violi F, Ghiselli A, Iuliano L, Praticò D, Alessandri C, Balsano F. Inhibition by picotamide of thromboxane production *in vitro* and *ex vivo*. *Eur J Clin Pharmacol* 1988; **33**: 599–602.
- Gresele P, Deckmyn H, Arnout J, Nenci GG, Vermylen J. Characterization of N,N'-bis (3-Picolyl)-4-methoxy-isophtalamide (picotamide) as a dual thromboxane synthase inhibitor/thromboxane A<sub>2</sub> receptor antagonist in human platelets. *Thrombosis and Haemostasis* 1989; **61**: 479–484.
- Modesti P, Cecioni I, Colella A, Costoli A, Paniccia R, Neri Serneri GG. Binding kinetics and antiplatelet activities of picotamide, a thromboxane A<sub>2</sub> receptor antagonist. *Br J Pharmacol* 1994; **112**: 81–86.
- Giustina A, Bossoni S, Cimino A, *et al.* Picotamide, a dual TXB synthetase inhibitor and TXB receptor antagonist, reduces exercise-induced albuminuria in microalbuminuric patients with NIDDM. *Diabetes* 1993; **42**: 178–182.
- Cocozza M, Picano T, Oliviero U, Russo N, Coto V, Milani M. Effects of picotamide, an antithromboxane agent, on carotid atherosclerosis evolution. A two-year,

- double blind, placebo controlled study in diabetic patients. *Stroke* 1995; **26**: 597–601.
- 14 Corsi M, Lacerna F, Laurora G, Milani M, Borzone A. comparison of the effects of picotamide and aspirin on renal albumin excretion and cutaneous microcirculation in patients with type II diabetes mellitus: a pilot study. *Curr Ther Res* 1995; **56**: 1105–1110.
- 15 Balsano F, Violi F and the ADEP Group. Effect of Picotamide on the clinical progression of peripheral vascular disease. A double blind placebo controlled study. *Circulation* 1993; **87**: 1563–1569.

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