PROactive: time for a critical appraisal

D. John Betteridge¹*, Ralph A. DeFronzo², and Robert J. Chilton³

¹Department of Medicine, Royal Free and University College Medical School, University College Hospital, Third Floor, 250 Euston Road, London NW1 2PQ, UK; ²Division of Diabetes, The University of Texas Health Science Center at San Antonio, San Antonio, TX, USA; and ³Division of Cardiology, The University of Texas Health Science Center at San Antonio, San Antonio, TX, USA

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The PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) remains the only completed cardiovascular (CV) outcomes study with a thiazolidinedione. It has provided valuable information on the impact of pioglitazone on CV outcomes in a high-risk population of patients with type 2 diabetes and established macrovascular disease. The investigators in PROactive chose a challenging primary composite endpoint that included events in multiple vascular beds (cerebral, cardiac, and peripheral), as well as both disease-related and procedural endpoints. They also pre-specified a more conventional main secondary composite endpoint of all-cause mortality, myocardial infarction, and stroke. Since the results of PROactive were first presented, there has been much debate on the relative merits of the statistically non-significant 10% decrease in the primary endpoint vs. the statistically significant 16% decrease in the main secondary endpoint seen with pioglitazone. However, PROactive includes more information than just these two main endpoints and has provided an extensive safety data set, as well as new insights into the impact of pioglitazone in different patient subpopulations. In this article, we consider all the results from PROactive presented to date and offer our own appraisal of how these findings shape the CV efficacy and safety profile of pioglitazone.

Keywords Cardiovascular disease • Clinical trial • Pioglitazone • PROactive • Type 2 diabetes

Introduction: rationale for the PROactive study

Type 2 diabetes mellitus (T2DM) markedly increases the risk of cardiovascular disease (CVD), including myocardial infarction (MI), stroke, peripheral vascular disease, and CV death.1–8 Patients with T2DM who have not previously experienced an MI are more likely to experience an MI than non-diabetic individuals who have had a previous MI.9 Thus, the importance of reducing CV risk in people with T2DM is well established.7,10,11

Although both primary and secondary intervention studies with metformin, antihypertensives, or statins in people with diabetes and/or CVD show consistent improvements in CV outcomes in people with T2DM,12–20 they also reveal a significant residual risk compared with those without diabetes (for review, see reference 21). Furthermore, improvements in long-term mortality after a CV event have been harder to achieve in people with diabetes.22 This underscores the need for better strategies and novel interventions in this high-risk patient group.

In addition to hyperglycaemia, dyslipidaemia, hypertension, obesity (especially visceral), endothelial dysfunction, and hypercoagulability,23,24 multiple prospective studies have demonstrated that insulin resistance per se is an independent risk factor for atherosclerotic CVD.25–31 At the molecular level, impaired insulin signalling is a characteristic feature of T2DM, obesity, hypertension, and dyslipidaemia (Figure 1).22,33 Despite the defect in insulin-stimulated glucose uptake in skeletal and arterial smooth muscle, the MAP kinase pathway retains normal sensitivity to insulin, and the compensatory hyperinsulinaemia (to the underlying insulin resistance) leads to the stimulation of multiple pathways involved in the development of atherosclerosis. Because thiazolidinediones are the only glucose-lowering agents that improve insulin signalling/sensitivity in muscle and inhibit the MAP kinase pathway, while improving dyslipidaemia, reducing elevated blood glucose levels, inhibiting inflammation (decreased hsCRP), enhancing endothelial function, and ameliorating the hypercoagulable state, thiazolidinediones may provide an opportunity to address the excess burden of atherosclerotic disease in this high-risk group.34 Individual thiazolidinediones have beneficial, but differing, effects on established and emerging risk factors for CVD. For example, there is a notable difference between the two currently approved thiazolidinediones on their effect on lipids. Thus, rosiglitazone increases LDL cholesterol and apo B100 and tends to raise triglycerides, whereas pioglitazone is
neutral with respect to LDL cholesterol, lowers apo B100, and reduces plasma triglyceride levels.\textsuperscript{35–37} Pioglitazone also is more effective in raising HDL cholesterol and converting LDL lipid subfractions to larger, more buoyant particles, possibly due to a decrease in atherogenic Apo B particles (each LDL particle contains one Apo B particle).

The PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) was designed to ascertain whether the potential metabolic and CV benefits described earlier for pioglitazone would translate into a significant reduction in the risk of macrovascular events in patients with type 2 diabetes and established macrovascular disease (MI, stroke, prior coronary intervention procedure, acute coronary syndrome (ACS), other objective evidence of coronary artery disease, or obstructive arterial disease in the leg) above and beyond the benefit achieved with that obtained with a regimen adherent to contemporary guidelines for the treatment of hyperglycaemia, hypertension, dyslipidaemia, etc.\textsuperscript{38} The underlying hypothesis in PROactive was that pioglitazone would confer benefits in multiple vascular beds (i.e. cerebral, cardiac, and peripheral) beyond standard guideline-driven therapy. These considerations reflected the choice of the primary composite endpoint. Another key objective of PROactive was to characterize further the safety of pioglitazone in this high-risk T2DM population.

As a double blind, randomized, placebo-controlled study with only one interventional therapy (pioglitazone), it was anticipated that PROactive would provide an answer to the question—does treatment with pioglitazone improve macrovascular outcomes over and above guideline-driven therapy? However, both the statistical and clinical significance of the macrovascular benefit of pioglitazone reported in PROactive have been—and continue to be—an area of active debate.\textsuperscript{39–46} In this article, we provide our appraisal of the key findings from PROactive now that further analyses have been made available to address some of the unanswered questions that have arisen since PROactive was first presented.\textsuperscript{47}

What was the main outcome of PROactive?

The pre-specified primary endpoint in PROactive was time from randomization to all-cause mortality, non-fatal MI (including silent MI), stroke, ACS, endovascular or surgical intervention on the coronary or leg arteries, or amputation above the ankle. The predefined main secondary endpoint was time to the first event of death, MI (excluding silent MI), or stroke. Pre-defined secondary endpoints (in order of priority after the main secondary endpoint) also included CV mortality and time to individual components of the primary endpoint. Other pre-specified endpoints were time to fatal/non-fatal MI and the composite of CV death, non-fatal MI (excluding silent MI), and non-fatal stroke. It should be noted that the definition of the main secondary endpoint was not included in the baseline characteristics paper.\textsuperscript{38} In late 2004 and early 2005, a working party comprising members of the PROactive Executive Committee and the sponsors prepared a formal statistical analysis plan for the study. During these meetings, it was recognized that the clinically important composite of death, MI, and stroke was not part of intended analysis. Thus, it was included in statistical analysis plan in March 2005. The final version of the statistical plan was signed and released on 13 May 2005 and a copy was registered as received by the Food and Drug Administration (FDA) on 17 May 2005. The study database was formally locked on 25 May 2005 and statistical analysis of unblinded data was commenced following that date.

PROactive was an event-driven study. With a predicted placebo event rate of 6% per year, a minimum of 760 first events were required to achieve the requisite statistical power: 91% power to detect a reduction of at least 20% in the primary endpoint event rate. The study was expected to last 4 years. However, enrolment proceeded faster than expected (completion in <12 months), drop out was less than expected (16.5% discontinued study medication before death or final visit, 6% withdrew consent, and only two patients were lost to follow-up), and the event rate was higher than expected (~8% per year). Consequently, the stop-point of 760 events was reached earlier than projected and the protocol was amended to allow a minimum of 30 months of treatment. At study end, 1086 first events contributed to the primary endpoint after a mean follow-up of 34.5 months. In total, there were 1703 total events in PROactive, but the primary endpoint was based upon the 1086 first events.

Kaplan–Meier estimates of the 3 year event rates were calculated for all endpoints. All time-to-event analyses were carried out by calculating hazard ratios (HRs) and 95% confidence intervals (CIs) from a Cox proportional hazards survival model with treatment as the only covariate. Linear models or logistic regression models were used for other endpoints, if appropriate. Multivariate models were used to investigate the effect of treatment after adjustment for baseline factors identified as prognostic of outcome. Variable selection was carried out using a stepwise selection algorithm and a significance level of 0.05. All analyses were by intention to treat.

The final analysis revealed a 10% relative risk reduction (RRR; 195 with pioglitazone vs. 240 with placebo) in the primary
Table 1 Reported number of total outcomes from PROactive (entire population)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Pioglitazone (n = 2605, n (%))</th>
<th>Placebo (n = 2633, n (%))</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
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<tr>
<td>All-cause mortality, MI (including silent MI), stroke, ACS, coronary revascularization, major leg amputation, leg revascularization</td>
<td>514 (19.7)</td>
<td>572 (21.7)</td>
<td>0.90 (0.80–1.02), P = 0.095</td>
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<tr>
<td><strong>Main secondary outcome</strong></td>
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<tr>
<td>All-cause mortality, MI (excluding silent MI), stroke</td>
<td>301 (11.6)</td>
<td>358 (13.6)</td>
<td>0.84 (0.72–0.98), P = 0.027</td>
</tr>
<tr>
<td><strong>Other secondary outcomes</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CV mortality</td>
<td>127 (4.9)</td>
<td>136 (5.2)</td>
<td>0.94 (0.74–1.20), P = 0.62</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>177 (6.8)</td>
<td>186 (7.1)</td>
<td>0.96 (0.78–1.18), P = 0.68</td>
</tr>
<tr>
<td>Non-fatal MI (including silent MI)</td>
<td>119 (4.6)</td>
<td>144 (5.5)</td>
<td>0.83 (0.65–1.06), P = 0.13</td>
</tr>
<tr>
<td>Stroke</td>
<td>86 (3.3)</td>
<td>107 (4.1)</td>
<td>0.81 (0.61–1.07), P = 0.14</td>
</tr>
<tr>
<td>ACS</td>
<td>56 (2.1)</td>
<td>72 (2.7)</td>
<td>0.78 (0.55–1.11), P = 0.17</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>169 (6.5)</td>
<td>193 (7.3)</td>
<td>0.88 (0.72–1.08), P = 0.23</td>
</tr>
<tr>
<td>Major leg amputation</td>
<td>26 (1.0)</td>
<td>26 (1.0)</td>
<td>1.01 (0.58–1.73), P = 0.98</td>
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<tr>
<td>Leg revascularization</td>
<td>80 (3.1)</td>
<td>65 (2.5)</td>
<td>1.25 (0.90–1.73), P = 0.19</td>
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<tr>
<td><strong>Other pre-specified outcomes</strong></td>
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<tr>
<td>Fatal/non-fatal MI (excluding silent MI)</td>
<td>108 (4.1)</td>
<td>140 (5.3)</td>
<td>0.77 (0.60–1.00), P = 0.046</td>
</tr>
<tr>
<td>CV mortality, MI (excluding silent MI), stroke</td>
<td>257 (9.9)</td>
<td>313 (11.9)</td>
<td>0.82 (0.70–0.97), P = 0.020</td>
</tr>
<tr>
<td><strong>Post hoc analyses</strong></td>
<td></td>
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<tr>
<td>All-cause mortality, MI (excluding silent MI), stroke</td>
<td>339 (13.0)</td>
<td>409 (15.5)</td>
<td>0.83 (0.72–0.96), P = 0.010</td>
</tr>
<tr>
<td>CV mortality, MI (excluding silent MI), stroke</td>
<td>295 (11.3)</td>
<td>367 (13.9)</td>
<td>0.80 (0.69–0.94), P = 0.005</td>
</tr>
<tr>
<td>Fatal heart failure</td>
<td>25 (0.96)</td>
<td>22 (0.84)</td>
<td>1.15 (0.65–2.03), P = 0.639</td>
</tr>
</tbody>
</table>

Because the endpoint analysis was based upon time to first event, the total number of events exceeds that used to determine the primary, main secondary, and other pre-specified outcomes. Data are from Dormandy et al.,47 Wilcox et al.,77 Erdmann et al.,86,53 and Takeda, data on file.

The number of individual first events in the pioglitazone and placebo groups, respectively, contributing to the primary endpoint were all-cause mortality (n = 110 vs. 122), non-fatal MI (excluding silent MI) (n = 85 vs. 95), silent MI (n = 20 vs. 23), stroke (n = 76 vs. 96), major leg amputation (n = 9 vs. 15), and ACS (n = 42 vs. 63). Contrary to expectations, there was an increase in leg revascularization procedures in the pioglitazone group (n = 71 vs. 57). Coronary revascularization was unaltered by pioglitazone (101 events in each group). Of the composite endpoints, ‘disease-related’ endpoints (mortality, MI, stroke, ACS, leg amputation) decreased significantly (n = 372 vs. 446; P = 0.0087), whereas ‘procedure-related’ endpoints increased (leg revascularization) or were similar (coronary revascularization) in the pioglitazone and placebo groups (Table 1).

For the main secondary endpoint (pre-defined prior to unblinding), i.e. the MACE or all-cause mortality, non-fatal MI, or stroke, there was a statistically significant 16% RRR (P = 0.027) with pioglitazone. The number of individual first events contributing to the main secondary endpoint in the pioglitazone and placebo groups, respectively, were all-cause mortality (n = 129 vs. 142), non-fatal MI (excluding silent MI) (n = 90 vs. 116), and stroke (n = 82 vs. 100). No statistical adjustment for multiple testing for the main secondary endpoint took place since, as a composite component of the primary endpoint, any adjustment would be extremely conservative and suffer from lack of power because the two endpoints are highly correlated.86 Much of the discussion of the strength of the results from PROactive revolves around considerations of the relative value of the statistically insignificant decrease (P = 0.095) in the primary endpoint and the statistically significant (P = 0.027) decrease in the main secondary endpoint.

The other pre-defined secondary outcome in PROactive—CV mortality—showed a small, non-statistically significant decrease in events in the pioglitazone group [n = 127 (4.9%) vs. 136 (5.2%)] (Table 1) (data on file). The number of non-CV deaths was identical in each group (n = 50 each). Other pre-defined and post hoc outcomes for other composite CV endpoints are displayed in Table 1. Of note, all of these composite endpoints showed significant reductions in risk with pioglitazone.

Subgroup analyses by baseline statin use suggested that the benefit of pioglitazone on the composite of all-cause mortality, non-fatal MI, or stroke was observed in those not receiving a statin at baseline [HR = 0.77; 95% CI 0.64–0.93; P = 0.008], but was not evident in those receiving statins at baseline [HR = 0.97; 95% CI 0.75–1.26; P = 0.845] (data on file). The interaction between baseline statin use and the effect of pioglitazone did not reach statistical significance for this endpoint (P = 0.1547), indicating that the effect of pioglitazone relative to placebo was similar regardless of baseline statin use or not. In addition, multivariate analyses did not reveal evidence...
of heterogeneity and the attenuation was no more than expected by chance alone.\textsuperscript{47} Thus, the best estimate of pioglitazone treatment effect for the statin subgroup is the same as that for the entire PROactive cohort as a whole.

**Beyond the main outcomes in PROactive**

PROactive incorporated several pre-specified analyses in two pre-defined patient subgroups—those with previous MI and those with previous stroke (Table 2). Among the 2445 patients with a previous MI, there was a statistically significant 28% RRR for recurrent fatal/non-fatal MI in those treated with pioglitazone (Figure 2C).\textsuperscript{49} Effects on two pre-specified CV composite endpoints (i) CV mortality and MI and (ii) CV mortality, MI, and stroke were not statistically significant, but trended in the same direction (Table 2). Similarly, among the 984 patients with a previous stroke (secondary prevention), there was a statistically significant 47% RRR for recurrent fatal/non-fatal stroke with pioglitazone, as well as a decrease in the composite of CV mortality, MI, and stroke (Figure 2D).\textsuperscript{50} There was no decrease in risk among those patients with no previous history of stroke (primary prevention).

In subsequent post hoc analyses (Table 3), patients with evidence of occlusive peripheral arterial disease (PAD) at baseline had a significantly elevated risk of major CV events (based on either the primary or main secondary composite endpoints) and mortality compared with those without PAD, and the risk associated with PAD alone was equivalent to that associated with previous MI alone.\textsuperscript{51} Pioglitazone was less effective in decreasing the primary composite and main secondary outcomes in these 1274 PAD patients and there was a significant increase in leg revascularization in the pioglitazone-treated group (Table 3). However, among those patients with no evidence of PAD ($n = 3964$), the risk of both the primary composite and main secondary endpoints was significantly reduced with pioglitazone, and there were numerically fewer leg revascularization first events.

Renal dysfunction [glomerular filtration rate (GFR) $< 60 \text{ ml/min/1.73 m}^2$] was evident in 12% of patients in PROactive, and these patients had a significantly increased risk of major CV events.\textsuperscript{52} Pioglitazone significantly reduced the risk of major CV events based on the main secondary endpoint in patients with renal dysfunction (Table 3). However, the decrease was not statistically significant in those without renal dysfunction. The interaction between GFR and the effect of pioglitazone on CV event rates was not significant for either the primary ($P = 0.19$) or the main secondary endpoints ($P = 0.18$), indicating that the effect of pioglitazone relative to placebo was similar regardless of GFR.

In patients with T2DM treated with pioglitazone vs. placebo, there was a significant increase in the number of patients with serious heart failure (SHF; defined as heart failure that required hospitalization or prolonged a hospitalization stay, was fatal or life threatening, or resulted in persistent significant disability or incapacity): 149 vs. 108 or 5.6 vs. 4.1%, respectively. However, there was no increase in fatal heart failure cases (25 vs. 22, respectively), or CV events or all-cause mortality (Table 3).\textsuperscript{53} When pioglitazone-treated patients who developed SHF are compared with placebo-treated individuals who developed SHF, the risk of the main secondary endpoint was reduced ($P = 0.025$) and there was a trend towards reduced risk for the primary endpoint and all-cause mortality (Table 3).

Metabolic (glycaemic control and favourable lipid changes) and other benefits of pioglitazone over placebo also were seen in PROactive, even though both groups were treated with other glucose-lowering and CV medications according to 1999 IDF guidelines. First, pioglitazone significantly reduced A1C compared with placebo ($−0.8 \text{ vs. } −0.3\%$, $P < 0.001$), and this occurred despite pioglitazone delaying the need for insulin therapy and reducing insulin requirements in those already receiving insulin.\textsuperscript{47,54,55} Treatment with pioglitazone also significantly improved triglyceride and HDL cholesterol levels compared with placebo and reduced the LDL cholesterol/HDL cholesterol ratio.\textsuperscript{56} Liver enzyme levels also were improved with pioglitazone in PROactive.\textsuperscript{49}

**What governed the choice of main composite endpoints in PROactive?**

Complex CV endpoints are increasingly used in order to increase statistical precision by allowing the collection of more events.\textsuperscript{58} The need for such composites reflects continual improvements...
in therapy (e.g. statin use), which inevitably lead to lower event rates. The use of composite CV endpoints also permits the design of a shorter study with a smaller number of participants, thereby reducing both the study time and costs. However, the use of such a composite endpoint can lead to uncertainty when interpreting the results if benefits are not seen for all components. This is a particular concern when the major pathogenic mechanisms responsible for the composite endpoint differ. Thus, dyslipidaemia is the major risk factor for coronary artery disease, hypertension is the major risk factor for stroke, and smoking and diabetes are the major risk factors for peripheral arterial disease. Furthermore, one has to consider the impact of including different endpoints across a steep gradient of clinical importance, which may dilute the clinical relevance of the overall findings.

The primary composite endpoint chosen for PROactive was unconventional and based on the hypothesis that pioglitazone would confer benefits in multiple vascular beds (i.e. cerebral, cardiac, and peripheral). It also included both disease-related (patient-determined) and less objective procedural endpoints (physician-determined). However, the higher-than-expected event rate and rapid enrolment allowed the investigators of PROactive to define a second principal endpoint (all-cause...
mortality, stroke, and MI) prior to unblinding. In the final analysis, 659 first events contributed to the main secondary endpoint (811 events in total). This more conventional endpoint is clinically important, since it (i) includes just the major hard events of death, MI, and stroke, (ii) is patient/disease (not physician/procedure)-determined, and (iii) facilitates comparison with other outcome trials that used a similar endpoint. The process of adjusting endpoints in outcome studies is not an unusual occurrence—an analysis on the nature of outcome reporting in clinical trials revealed formal amendments to primary or secondary endpoints in seven out of 102 studies.63 A good example is provided by the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study,64 during which the primary endpoint was amended from coronary heart disease death to coronary heart disease events (through the addition of non-fatal MI) in order to maintain the study’s power. Similarly, a low event rate in the recent Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) trial65 prompted amendment of the primary outcomes to include an additional analysis of the combination of both macro- and microvascular events, rather than just the separate analyses defined originally in the protocol.

Figure 2. Continued
In PROactive, the assumption that clinical trial is somewhat artificial and mainly a clinical, rather than of what constitutes the primary or main secondary endpoints in a primary endpoint. First, it should be emphasized that the decision on the main secondary endpoint in the context of a statistically

The relative value of the primary and main secondary endpoints in PROactive

Pioglitazone failed to produce a statistically significant effect on the primary composite endpoint in PROactive. Nevertheless, there was an apparent trend towards benefit (P = 0.095) that was consistent across all individual components, with the exception of those reflecting peripheral vascular disease. Furthermore, the treatment groups continued to diverge at the study end, and it remains unknown whether a longer study (e.g. the estimated 4 years) would have led to a statistically significant result. With a minimum and mean follow-up of 30 and 34.5 months, respectively, with >80% of patients completing the trial on study medication, and with >25% of the total first events contributing to the third year of the analysis, this latter part of the Kaplan–Meier relationship is likely to retain a considerable amount of integrity, although caution is required when making such visual interpretations.

The key issue is how to interpret the statistically significant effect on the main secondary endpoint in the context of a statistically insignificant (but consistent) trend towards benefit in the primary endpoint. First, it should be emphasized that the decision of what constitutes the primary or main secondary endpoints in a clinical trial is somewhat artificial and mainly a clinical, rather than statistical issue. In the case of PROActive, the assumption that pioglitazone would confer benefits in multiple vascular beds may have been unfounded and the inclusion of peripheral vascular endpoints was clearly responsible for the failure to achieve statistical significance. Interestingly, all of the unexpected increase in frequency of leg revascularizations in the pioglitazone-treated group occurred in the subset of patients with PAD at baseline or within 12 months of starting treatment. The reasons underlying this observation remain unclear. Furthermore, there was no increase in amputations (either as first or total events) during the study. Nevertheless, it appears that the inclusion of peripheral vascular events in the primary composite endpoint, along with the inclusion of patients with evident PAD, reduced the impact of pioglitazone on the primary outcome. Whether the inclusion of less objective coronary revascularization procedural endpoints also may have favoured the null hypothesis remains unclear.

In retrospect, it is likely that the main secondary endpoint (more conventional and more clinically relevant) would have been a more appropriate choice as the primary outcome and most consistent with its widespread use in other CV intervention studies.

Other CV outcome studies also have encountered similar problems with the clinical and statistical significance of primary and secondary endpoints. The approval of carvedilol for heart failure (although without a mortality claim) was based on the strong clinical and statistically significant finding with mortality (the more clinically relevant secondary endpoint), even though the effect on the primary endpoint (exercise ability) was not statistically significant.

Since the main secondary endpoint in PROactive represented the most clinically relevant components of the primary composite, this might provide an exception where the secondary endpoint might assume primacy over the primary endpoint. Furthermore, in the light of the unpredicted lack of effect on peripheral vascular outcomes, it may be necessary to view the results in a more flexible manner, rather than focusing entirely on what may have been an inappropriate choice of primary endpoint.

Are the results of PROactive clinically relevant?

Statistical arguments aside, the effect sizes reported in PROactive would appear to be clinically significant. The number needed to treat (NNT; a reciprocal of the absolute RR) allows clinicians to...
Table 4 Number needed to treat in major placebo-controlled trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient population</th>
<th>Patient number</th>
<th>Duration</th>
<th>Interventions</th>
<th>Endpoint</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROactive</td>
<td>Secondary prevention in type 2 diabetes and macrovascular disease</td>
<td>5238</td>
<td>34.5 months</td>
<td>Pioglitazone</td>
<td>Primary: composite of all-cause mortality, non-fatal MI (including silent MI), non-fatal stroke, major leg amputation, ACS, cardiac intervention (bypass graft or percutaneous coronary intervention), and leg revascularization&lt;sup&gt;a&lt;/sup&gt;</td>
<td>120/year</td>
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<td></td>
<td>Main secondary: composite of all-cause mortality, MI, or stroke</td>
<td>143/year</td>
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<td></td>
<td>Pre-specified: recurrent MI</td>
<td>149/year</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>Pre-specified: recurrent stroke</td>
<td>63/year</td>
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<tr>
<td>ADVANCE&lt;sup&gt;65&lt;/sup&gt;</td>
<td>Primary and secondary prevention in type 2 diabetes and macrovascular disease or one other risk factor</td>
<td>11 140</td>
<td>4.3 years</td>
<td>Perindopril + indapamide</td>
<td>Primary: composite of macrovascular (CV mortality, MI, or stroke) and microvascular (nephropathy, retinopathy) events</td>
<td>331/year</td>
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<td></td>
<td>Major vascular events: composite of major coronary events, stroke, and coronary/ non-coronary revascularizations</td>
<td>672/year</td>
</tr>
<tr>
<td>Heart Protection Study&lt;sup&gt;71&lt;/sup&gt;</td>
<td>Primary and secondary prevention in patients with CVD (diabetes + occlusive arterial disease subgroup)</td>
<td>3051 (out of 20 536)</td>
<td>5 years</td>
<td>Simvastatin</td>
<td>Major vascular events: composite of major coronary events, stroke, and coronary/ non-coronary revascularizations</td>
<td>75/year</td>
</tr>
<tr>
<td>HOPE&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Primary and secondary prevention in high-CV risk patients (diabetes subgroup)</td>
<td>3577 (out of 9541)</td>
<td>4.5 years</td>
<td>Ramipril</td>
<td>Primary: CV death, MI, and stroke</td>
<td>91/year</td>
</tr>
<tr>
<td>4S&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Secondary prevention in patients with CHD (diabetes subgroup)</td>
<td>483 (out of 4398)</td>
<td>5.4 years</td>
<td>Simvastatin</td>
<td>CHD death, MI</td>
<td>42/year</td>
</tr>
<tr>
<td>CARE&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Secondary prevention in patients with previous MI (diabetes subgroup)</td>
<td>586 (out of 4159)</td>
<td>5 years</td>
<td>Pravastatin</td>
<td>CHD death, MI, cardiac intervention (main endpoint used for subgroup analyses)</td>
<td>54/year</td>
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<td></td>
<td>Recurrent MI&lt;sup&gt;a&lt;/sup&gt;</td>
<td>135/year</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Primary: CHD death, MI&lt;sup&gt;a&lt;/sup&gt;</td>
<td>189/year</td>
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<td>MI</td>
<td>150/year</td>
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*The effect of intervention on this endpoint was not statistically significant.*

assess more adequately the potential clinical utility by providing an estimate of the number of patients (with a particular baseline level of risk) that would have to be treated over a given time period in order to prevent one event.70 i.e. if the NNT is 120, then treating 120 patients would save one from an event. Conversely, the number needed to harm (NNH) indicates the number of patients (with a particular baseline level of risk) that would need to be exposed to a risk factor over a given time period in order to harm one patient who would not otherwise have been harmed. Looking at the 3 year placebo event rate of 23.5% and pioglitazone event rate of 21.0% for the primary endpoint (RRR = 10%) in PROactive, 1000 patients with T2DM would have to be treated with pioglitazone to prevent 25 first primary composite endpoint events. In other words, 40 patients would need to be treated for
3 years in order to prevent one first event. Thus, the NNT is $\sim 120$ per year, if one assumes that the effects of drug treatment are evenly distributed over time during the study. For the main secondary endpoint (placebo event rate 13.6% and pioglitazone event rate 11.6%), pioglitazone would need to be used in 1000 patients in order to avoid 21 first MIs, strokes, or deaths over 3 years (NNT is $\sim 48$ or 143 per year). Unfortunately, such estimates are not available for subsequent events during the study, which would improve this value further.

Comparison of these NNTs with interventions in patients with diabetes in other outcomes studies is complicated due to differences in the nature of pre-existing CVD in the study population, the absolute baseline CV risk, and the composite endpoints used (Table 4). For the primary endpoint, perhaps the best comparison with an effective treatment can be made with the Heart Protection Study71 using the subgroup of over 3000 patients with both diabetes and occlusive arterial disease at baseline. In this study, the placebo event rate for the secondary outcome of major vascular events (composite of major coronary events, stroke, and coronary/non-coronary revascularizations—which included amputations) was 36% over 5 years (similar to the 3 year estimated event rate of 23.5% seen in PROactive). Intervention with simvastatin was associated with a significant 18% RRR for major vascular events and it was estimated that 5 years of simvastatin therapy would prevent such events in 66 people for every 1000 who are treated (i.e. NNT is approximately 75 per year).

The HOPE study17 also used a primary composite endpoint (CV death, MI, or stroke) that was similar to the main secondary outcome in PROactive. Patients with diabetes (two-thirds of whom had a history of coronary artery disease, peripheral vascular disease, or stroke) had a placebo event rate for this composite of 19.8% over 4.5 years (similar to the 14.4% over 3 years with the main secondary endpoint in PROactive). Ramipril therapy was associated with a 25% RRR compared with placebo, which translates into an NNT of approximately 91 per year.

The clinical relevance, however, extends beyond the primary and main secondary endpoints. In the subgroup of patients with previous MI, large effect sizes were seen for reduced risk of recurrent MI. With a placebo event rate of 7.2% over 3 years and a RRR of 28%, this translates into an estimated NNT of 50 or approximately 149 per year. Subgroup analyses from statin trials using similar patient populations and various coronary endpoints reveal NNT values in the region of 40–190 per year.15,16 In the UKPDS, which is the only other completed CV outcomes study investigating intervention with glucose-lowering agents, metformin therapy was associated with an NNT for fatal/non-fatal MI of approximately 150 per year, although it should be emphasized that this was mainly a primary prevention study in a lower risk population and the RRR with metformin was only significant relative to the diet and lifestyle group and not to the insulin/sulfonylurea groups.20 Furthermore, the UKPDS72 compared glucose management policies with different glycaemic targets (‘intensive’ vs. ‘conventional’), and its stepwise design led to considerable therapeutic overlap between intervention groups, undermining its ability to determine the effect of individual therapies. In PROactive, the only difference between treatment groups was the use of either pioglitazone or placebo, thus avoiding such interpretational issues. Similarly, in the previous stroke subgroup, a placebo event rate of 10.2% over 3 years and an RRR of 47% translate into an NNT of approximately 21 (63 per year) to prevent one fatal/non-fatal stroke. By comparison, a recent placebo-controlled trial looking at secondary stroke prevention with atorvastatin obtained an NNT for fatal/non-fatal stroke of approximately 227 per year, although the analysis was not performed specifically among the 17% of patients with diabetes.73

It also should be emphasized that the metabolic benefits of pioglitazone—notably the improved glycaemic and lipid control and delayed need for insulin use—are highly clinically relevant. This demonstrates the additional advantage of including a thiazolidinedione in a glucose control regimen, even when all other contemporary glucose-lowering options are available in the effort to achieve glycaemic goals. Considerable data also have accumulated to indicate a benefit of thiazolidinediones on the durability of glycaemic control and preservation of β-cell function.74–78

![Figure 3](https://academic.oup.com/eurheartj/article-abstract/29/8/969/1745991) Pioglitazone FDA meta-analysis of clinical trials (www.fda.gov).85
Thiazolidinediones and cardiovascular safety

Recently, discussions about thiazolidinedione therapy have shifted from potential CV efficacy to concerns over CV safety. A meta-analysis by Nissen and Wolski suggested that rosiglitazone significantly increased the risk of MI and trended to increase CV death. Although questions have been raised about the statistical approach used by Nissen and Wolski, two subsequent analyses of the rosiglitazone results, which have taken into account some of these statistical deficiencies, have demonstrated a significant increase in CV events, whereas a third demonstrates trend towards significance (HR = 1.31 for MI and 1.36 for CV death). A GSK retrospective analysis of data from pooled clinical studies that is included in the EU summary of product characteristics found that the overall incidence of events typically associated with cardiac ischaemia was 31% higher with rosiglitazone than comparators (HR = 1.31; 95% CI 1.01–1.70). The Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) study remains the only other CV outcomes trial with a thiazolidinedione for which data (although interim) are available. This study was designed to assess the non-inferiority of rosiglitazone plus metformin or sulfonylurea (plus insulin as needed) compared with metformin plus sulfonylurea (plus insulin as needed) in terms of overall CV risk. The primary endpoint of RECORD is hospitalization or death due to CV causes (including heart failure). An interim analysis, which is underpowered to show statistical significance, also shows a trend towards increased overall CV risk and MI. Most recently, the FDA has completed a Kaplan–Meier time-to-first event analysis for all available rosiglitazone data and demonstrated a significant increase in all ischaemic events (HR = 1.4 vs. all comparators and 1.8 vs. placebo). As a consequence, on 14 November 2007, the FDA added a new black box warning for ischaemic heart disease on the rosiglitazone label. A similar analysis performed by the FDA for pioglitazone demonstrated a significant decrease in CV events (HR = 0.83, 95% CI 0.72–0.95) (Figure 3). If PROactive is deleted from this analysis, the HR declines to 0.75 (95% CI 0.55–1.02), but the decrease is of borderline significance because of the smaller number of subjects. A summary of the HRs for CV events from these recent meta-analyses is shown in Figure 3.

The implications of PROactive for clinical practice

Although subanalyses may have more limited value from a statistical viewpoint, they nonetheless (in the absence of further prospectively designed studies) can provide valuable clinical insights into which patients might benefit most (in terms of CV outcomes) from pioglitazone therapy. In PROactive, patients with a history of MI and stroke derived the greatest reduction in the risk of recurrent events with pioglitazone therapy, whether or not they were receiving statin therapy. Furthermore, the presence of renal dysfunction, an important microvascular complication in patients with T2DM, did not impact on the ability of pioglitazone to prevent secondary CV events.

It is notable that pioglitazone did not have any impact on first stroke, but unfortunately similar analyses have not been reported for first MI. Patients with evidence of occlusive PAD would appear not to be good candidates for secondary prevention therapy with pioglitazone. Any potential role for pioglitazone in
primary CVD prevention in diabetes remains unclear. SPARCL is the only other study to show a direct effect on secondary prevention of stroke. The Heart Protection Study failed to show a benefit of simvastatin on secondary prevention. The increase in treatment-emergent signs of heart failure has been a key area of debate when considering the overall CV benefit of pioglitazone. In those individuals who developed SHF while on pioglitazone, there was no increased risk of adverse CV outcomes. In fact, patients with T2DM in PROActive who were treated with pioglitazone and developed SHF had fewer MIs/stroke/CV death than placebo-treated patients who developed SHF. In a recent meta-analysis of CHF, the HR for CHF was 1.32 (95% CI 1.04–1.68) for pioglitazone and 2.18 (95% CI 1.44–3.32) for rosiglitazone. Most notably, CV death in these studies was not increased, indicating that thiazolidinedione-associated CHF does not have the same ominous significance that CHF has in the general population of patients with T2DM. The authors suggest that CHF associated with thiazolidinediones results from volume overload in individuals with diastolic dysfunction and responds well to diuretic therapy (figure 4). Diastolic dysfunction is more common in patients with diabetes, hypertension, and obesity than systolic dysfunction (decreased ejection fraction). In contrast, CHF that occurs as part of the natural history of type 2 diabetes is more likely related to systolic dysfunction and low ejection fraction and is associated with high CV risk: ~50% mortality over 5 years.

It should be emphasized, however, that the use of pioglitazone in patients with pre-existing symptomatic heart failure (NYHA classes II–IV) remains less clear, as these patients were excluded from PROActive. It should be noted that the EU licences for both thiazolidinediones contra-indicate their use in people with any NYHA class of heart failure. In the USA, the thiazolidinediones are contra-indicated in NYHA class III and IV heart failure.

Pharmaco-economic factors can be important determinants of access to therapies in the clinic, and analyses based on PROActive provide new insights into the potential long-term cost-effectiveness of pioglitazone. Using the CORE diabetes model, it has been estimated that pioglitazone would provide an incremental cost-effectiveness ratio (cost per quality-adjusted life year gained) of $44 105 in the USA, £4060 in the UK, €13 294 in Germany, and CHF60 596 in Switzerland (all 2005 values).

Conclusions

PROActive remains the only large-scale, prospective, secondary prevention trial carried out entirely in patients with T2DM. Moreover, only a handful of primary and mixed primary/secondary prevention studies have been carried out specifically in individuals with T2DM. PROActive provides good evidence of a macrovascular benefit with pioglitazone, particularly in terms of major adverse CV events (all-cause mortality, MI, and stroke), despite only showing a statistical trend towards benefit for the primary composite outcome. Most importantly, it is notable that the impact of pioglitazone on macrovascular outcomes was evident despite contemporary guideline-driven attention to classical risk factors, although it should be noted that treatment of these risk factors remained sub-optimal. The driver of the favourable effects of pioglitazone is unknown, but favourable lipid, glucose, and/or blood pressure changes may have contributed to the outcome.

From a safety perspective, pioglitazone does not increase the risk of macrovascular events or worsen outcomes in those who develop signs of heart failure in a high-risk population with T2DM with macrovascular disease. Even when the increased incidence of signs of heart failure (with a normal ejection fraction) is taken into account, the overall CV benefit of pioglitazone remains. In total, 41 more patients experienced at least one event of SHF on pioglitazone, whereas 58 fewer patients on pioglitazone experienced at least one primary endpoint event and 57 fewer patients experienced at least one secondary endpoint first event during the study. In total (including both first and subsequent events), there were nine fewer deaths, 26 fewer MIs (including three fewer silent MIs), 27 fewer strokes, 13 fewer ACS, and 45 fewer coronary revascularizations (alongside no difference in amputations and 23 more leg revascularizations) during the study. The overall benefit is even more compelling when one considers that the increase in SHF events was not associated with any absolute increase in adverse outcomes (mortality or subsequent macrovascular events). It should be emphasized that, like other robust, well-controlled studies, PROActive provides more information than simply the primary outcome. It would be unfortunate to reject the clinical significance of these findings when the trial provides such a wealth of information in this understudied group of patients. Despite all of the statistical arguments regarding the failure of the primary endpoint to reach conventional statistical significance, doubts over the clinical significance of PROActive are a consequence of the wrong choice of composite endpoint (i.e. one including PAD events, specifically leg revascularization). If the main secondary endpoint had been chosen as the primary endpoint, then, no doubt, the macrovascular benefits of pioglitazone in secondary prevention would be more universally accepted.

Conflict of interest: D.J.B. has served as a consultant to, and/or received travel expenses and/or payments for speaking at meetings from, Takeda and is a Principal National Investigator for PROActive. R.A.D. has received grants from, and serves on the Advisory Boards of, Bristol Myers Squibb, Amylin, Eli Lilly, Novartis, Pfizer, Takeda, and Roche. He is also on the Speakers’ Bureau for Amylin and Takeda. R.L.C. has received honoraria from Pfizer, MSD, GSK, Takeda, Medtronics, and Boston Scientific for lectures.

References


19. Hedblad B, Nilsson P, Janzon L, Berglund G. Relation between insulin resistance and carotid intima-media thickness and stenosis
60. Stokes J, Kannell WB, Wolf PA, Cupples LA, D’Agostino RB. The relative importance of selected risk factors for various manifestations of cardiovascular disease among men and women from
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