The Effect of Pioglitazone on Recurrent Myocardial Infarction in 2,445 Patients With Type 2 Diabetes and Previous Myocardial Infarction

Results From the PROactive (PROactive 05) Study

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Objectives
This analysis from the PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events) study assesses the effects of pioglitazone on mortality and macrovascular morbidity in patients with type 2 diabetes and a previous myocardial infarction (MI).

Background
People with type 2 diabetes have an increased incidence of MI compared with the general population. Those with diabetes and MI have a worse prognosis than nondiabetic patients with cardiovascular disease.

Methods
The PROactive study was a prospective, multicenter, double-blind, placebo-controlled trial of 5,238 patients with type 2 diabetes and macrovascular disease. Patients were randomized to either pioglitazone or placebo in addition to their other glucose-lowering and cardiovascular medication. Treatment of diabetes, dyslipidemia, and hypertension was encouraged according to the International Diabetes Federation guidelines. Patients were followed for a mean of 2.85 years. The primary end point was the time to first occurrence of macrovascular events or death. Of the total cohort, the subgroup of patients who had a previous MI (n = 2,445 [46.7%]; n = 1,230 in the pioglitazone group and n = 1,215 in the placebo group) was evaluated using prespecified and post-hoc analyses.

Results
Pioglitazone had a statistically significant beneficial effect on the prespecified end point of fatal and nonfatal MI (28% risk reduction [RR]; p = 0.045) and acute coronary syndrome (ACS) (37% RR; p = 0.035). There was a 19% RR in the cardiac composite end point of nonfatal MI (excluding silent MI), coronary revascularization, ACS, and cardiac death (p = 0.033). The difference in the primary end point defined in the main PROactive study did not reach significance in the MI population (12% RR; p = 0.135). The rates of heart failure requiring hospitalization were 7.5% (92 of 1,230) with pioglitazone and 5.2% (63 of 1,215) with placebo. Fatal heart failure rates were similar (1.4% [17 of the 92] with pioglitazone versus 0.9% [11 of the 63] with placebo).

Conclusions
In high-risk patients with type 2 diabetes and previous MI, pioglitazone significantly reduced the occurrence of fatal and nonfatal MI and ACS. (PROspective pioglitAzone Clinical Trial In macroVascular Events; http://www.clinicaltrials.gov/ct/show/NCT00174993?order = 1; ISRCTN NCT00174993). (J Am Coll Cardiol 2007;49:1772–80) © 2007 by the American College of Cardiology Foundation

People with diabetes are more than twice as likely to have a myocardial infarction (MI) than are those without diabetes (1–3). Type 2 diabetes has also been suggested to be “risk equivalent” to an MI: that is, those with type 2 diabetes and no previous MI have a similar risk of MI as nondiabetic patients with previous MI (1). Prognosis of MI is worse in patients with type 2 diabetes than in those

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without diabetes (4–7). It is therefore particularly important to improve the unfavorable outcome of people with diabetes and MI. A subanalysis from the UKPDS (United Kingdom Prospective Diabetes Study) looked at differences in risk factors between those with diabetes and fatal versus nonfatal MI and showed that the risk of MI being fatal in type 2 diabetes increased with increasing hemoglobin A1c (8). This is supported by data from DECODE (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) and other studies (9,10). The cardiovascular risk in patients with type 2 diabetes who have had at least 1 MI is increased further if they have coexisting dyslipidemia, arterial hypertension, or type 2 diabetes who have had at least 1 MI is increased further if they have coexisting dyslipidemia, arterial hypertension, or coronary artery disease (11). Current guidelines recommend if they have coexisting dyslipidemia, arterial hypertension, or type 2 diabetes who have had at least 1 MI is increased further if they have coexisting dyslipidemia, arterial hypertension, or coronary artery disease (11). Current guidelines recommend aggressive management of these cardiovascular risk factors, including hyperglycemia (using glucose-lowering agents), dyslipidemia (using statins), hypertension (using angiotensin-converting enzyme [ACE] inhibitors or angiotensin II receptor blocker therapy), and lifestyle factors (12–15). However, there are few outcome studies that look at the effect of glucose-lowering agents on end points related to macrovascular disease.

Pioglitazone, a thiazolidinedione, is an established oral therapy for the management of type 2 diabetes. In addition to its effects on fasting and postprandial hyperglycemia, pioglitazone also increases insulin sensitivity and is known to have positive effects on high-density lipoprotein (HDL) cholesterol, triglycerides, and low-density lipoprotein (LDL) particle size (16–21). There is some evidence to support the view that pioglitazone may also have other beneficial antiatherogenic properties, such as regulating the levels of mediators involved in inflammation and endothelial dysfunction (22). Indeed, data now suggest that combining pioglitazone with other medication for cardiovascular risk factors may have complementary effects in patients with type 2 diabetes (23–25). Therefore, it was anticipated that pioglitazone in addition to current therapy would reduce the recurrence of cardiovascular events in a population with diabetes at high risk of macrovascular events.

The PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events) study is one of a series of studies evaluating the effects of pioglitazone on the progression of atherosclerosis in patients with type 2 diabetes. It was the first large prospective study to look at the reduction in total mortality and macrovascular morbidity using thiazolidinedione. The primary composite end point included both disease (e.g., death, MI, acute coronary syndrome [ACS], and stroke) and procedure-related end points (e.g., coronary and leg revascularization). Data from the total study population showed that there was a 10% risk reduction (RR) in the primary composite end point of macrovascular events in the pioglitazone group compared with the placebo group. This did not reach statistical significance (p = 0.095) (26). However, there was a statistically significant 16% RR (p = 0.027) in the main secondary end point. This included only disease-related end points—the composite of all-cause mortality, nonfatal MI, and nonfatal stroke (26). An analysis of the patients entering the study with a previous MI was prespecified in the Statistical Analysis Plan, as these patients tend to have the worst prognosis. We have further explored the basis of the findings using post-hoc exploratory analyses. Although this investigation includes both prespecified and post-hoc analyses, it involves one of the largest groups of patients with type 2 diabetes and previous MI to be examined in a prospective randomized study.

## Methods

**Patients.** PROactive was a randomized, double-blind, placebo-controlled outcome study in patients with type 2 diabetes (ages 35 to 75 years) who were at increased macrovascular risk. The study randomized 5,238 patients from 19 European countries and observed them for an average of 34.5 months. The study protocol, inclusion and exclusion criteria, and analytical methods have been described previously (26,27).

**Treatments.** Patients were randomized to receive pioglitazone (increased stepwise from 15 to 45 mg within the first 2 months, depending on tolerability) or matching placebo, in addition to their existing medication for management of hyperglycemia, dyslipidemia, and hypertension.

### Table 1: Baseline Characteristics and Previous Macrovascular Morbidity in Patients With Type 2 Diabetes and Previous Myocardial Infarction

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Pioglitazone (n = 1,230)</th>
<th>Placebo (n = 1,215)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>909 (73.9%)</td>
<td>895 (73.7%)</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>1,211 (98.5%)</td>
<td>1,198 (98.6%)</td>
</tr>
<tr>
<td>Age (yrs), mean (SD)</td>
<td>61.8 (7.8)</td>
<td>61.8 (7.6)</td>
</tr>
<tr>
<td>Time since diagnosis of diabetes (yrs), median (IQR)</td>
<td>8 (4, 13)</td>
<td>8 (4, 13)</td>
</tr>
<tr>
<td>Body mass index (kg/m²), mean (SD)</td>
<td>30.9 (4.6)</td>
<td>31.2 (4.7)</td>
</tr>
<tr>
<td>History of hypertension, n (%)</td>
<td>865 (70.3%)</td>
<td>894 (73.6%)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current, n (%)</td>
<td>146 (11.9%)</td>
<td>154 (12.7%)</td>
</tr>
<tr>
<td>Past, n (%)</td>
<td>636 (51.7%)</td>
<td>595 (49.0%)</td>
</tr>
<tr>
<td>Microvascular disease, n (%)</td>
<td>507 (41.2%)</td>
<td>465 (38.3%)</td>
</tr>
</tbody>
</table>

**Other macrovascular disease criteria**

- **Previous stroke, n (%)** 91 (7.4%) 86 (7.1%)
- **Previous PCI/CABG, n (%)** 528 (42.9%) 495 (40.7%)
- **Previous ACS, n (%)** 158 (12.8%) 169 (13.9%)
- **Symptomatic peripheral arterial obstructive disease, n (%)** 99 (8.0%) 106 (8.7%)

*Retinopathy, nephropathy, neuropathy.

**Abbreviations and Acronyms**

- **ACE** = angiotensin-converting enzyme
- **ACS** = acute coronary syndrome
- **CABG** = coronary artery bypass graft
- **ECG** = electrocardiogram
- **HDL** = high-density lipoprotein
- **HF** = heart failure
- **IDF** = International Diabetes Federation
- **LDL** = low-density lipoprotein
- **MI** = myocardial infarction
- **PCI** = percutaneous coronary intervention
- **ACS** = acute coronary syndrome
- **CABG** = coronary artery bypass graft
- **IQR** = interquartile range
- **PCI** = percutaneous coronary intervention
Investigators were encouraged to treat these conditions throughout the trial according to the International Diabetes Federation (IDF) Europe Guidelines (1999) (28).

The analysis presented here investigates the effects of treatment with pioglitazone versus placebo in patients who qualified for entry into the PROactive study on the basis of a previous MI 6 months or more before randomization (n = 2,445). The 6-month restriction was applied to ensure that all patients were in a stable myocardial condition before entry into the study.

**End points.** The primary end point, as described by Dormandy et al. (26), was the time from randomization to the first occurrence of any of the following events: all-cause mortality, nonfatal MI (including silent infarction), nonfatal stroke, ACS, cardiac intervention (including coronary artery bypass graft [CABG], or percutaneous coronary intervention [PCI]), leg revascularization, and amputation above the ankle. The main secondary end point was time to the first event of death from any cause, nonfatal MI (excluding silent MI), or nonfatal stroke. This secondary “hard” end point was analyzed because these disease-related components are the most robust and objective. Other secondary end points included time to individual components of the primary composite and time to cardiovascular death. These are the main study end points (26).

The statistical analysis plan, finalized before the unblinding of the study, prioritized this previous-MI subgroup (as well as the previous-stroke subgroup) for analysis of the following prespecified composite end points: 1) fatal or nonfatal MI (excluding silent MI), 2) cardiovascular death or nonfatal MI (excluding silent MI), and 3) cardiovascular death, nonfatal MI (excluding silent MI), or stroke. In this article, we describe these prespecified end points. Furthermore, we were interested in the outcome of ACS, which was defined by objective clinical criteria, and a further composite cardiac end point of nonfatal MI (excluding and including silent MI), coronary revascularization, ACS, or cardiac death.

**Definitions.** The definition for nonfatal MI was survival for >24 h from onset of symptoms and, in the absence of PCI or CABG, at least 2 of the following: 1) symptoms suggestive of MI (ischemic chest pain or discomfort) lasting >30 min, 2) electrocardiographic (ECG) evidence of MI, or 3) elevation of cardiac serum markers, or following PCI.

### Table 2

<table>
<thead>
<tr>
<th>End Point</th>
<th>Level at Baseline</th>
<th>Change From Baseline</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pioglitazone</td>
<td>Placebo</td>
<td>Pioglitazone</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>Absolute change</td>
<td>% change</td>
</tr>
<tr>
<td>HbA1c, median (IQR)</td>
<td>7.9 (7.1, 9.0)</td>
<td>0.8 (–1.6, –0.1)</td>
<td>1.3 (–25.5, 35.2)</td>
</tr>
<tr>
<td>mmol/l</td>
<td>1.8 (1.3, 2.6)</td>
<td>–11.1 (–34.7, 17.9)</td>
<td>18.8 (6.6, 33.3)</td>
</tr>
<tr>
<td>Triglycerides, median (IQR)</td>
<td>1.1 (0.9, 1.3)</td>
<td>7.8 (–11.6, 27.7)</td>
<td>4.5 (–14.2, 24.1)</td>
</tr>
<tr>
<td>HDL cholesterol, median (IQR)</td>
<td>2.8 (2.3, 3.5)</td>
<td>–9.1 (–27.1, 9.3)</td>
<td>–4.4 (–22.5, 16.1)</td>
</tr>
<tr>
<td>LDL/HDL median (IQR)</td>
<td>2.6 (2.1, 3.2)</td>
<td>2.5 (2.0, 3.3)</td>
<td>–2 (–15, 10)</td>
</tr>
<tr>
<td>Blood pressure: systolic, median (IQR)</td>
<td>140 (130, 150)</td>
<td>–2 (–10, 4)</td>
<td>–2 (–10, 3)</td>
</tr>
<tr>
<td>Blood pressure: diastolic, median (IQR)</td>
<td>80 (73, 85)</td>
<td>21.2 (16.0)</td>
<td>232 (20.8)</td>
</tr>
</tbody>
</table>

**Table 3**

| Glucose-Lowering Therapies in Patients With Type 2 Diabetes and Previous Myocardial Infarction |
|---------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| At Baseline                                       | At Final Visit                                                                            |
| Metformin only, n (%)                             | Pioglitazone (n = 1,220) Placebo (n = 1,215)                                            |
|                                                   | 128 (10.4%) Placebo 119 (9.8%)                                                            |
|                                                   | 127 (11.1%) Placebo 109 (9.8%)                                                            |
| Sulfonylureas only, n (%)                         | 260 (21.1%) Placebo 256 (21.1%)                                                           |
|                                                   | 209 (18.3%) Placebo 138 (12.4%)                                                           |
| Metformin + sulfonylureas, n (%)                  | 306 (24.9%) Placebo 280 (23.0%)                                                           |
|                                                   | 240 (21.1%) Placebo 251 (22.5%)                                                           |
| Insulin + metformin, n (%)                        | 216 (17.6%) Placebo 228 (18.8%)                                                           |
|                                                   | 182 (16.0%) Placebo 232 (20.8%)                                                           |
| Insulin + sulfonylureas, n (%)                    | 91 (7.4%) Placebo 102 (8.4%)                                                             |
|                                                   | 62 (5.4%) Placebo 79 (7.1%)                                                              |
| Insulin + metformin + sulfonylureas, n (%)        | 41 (3.3%) Placebo 47 (3.9%)                                                              |
|                                                   | 43 (3.8%) Placebo 54 (4.8%)                                                              |
| Other combination, n (%)                         | 134 (10.9%) Placebo 128 (10.5%)                                                           |
|                                                   | 108 (9.5%) Placebo 93 (8.3%)                                                             |
| Diet only, n (%)                                  | 50 (4.1%) Placebo 52 (4.3%)                                                              |
|                                                   | 83 (7.3%) Placebo 41 (3.7%)                                                              |
| Any metformin, n (%)                              | 749 (60.9%) Placebo 716 (58.9%)                                                           |
|                                                   | 639 (56.1%) Placebo 681 (61.1%)                                                            |
| Any sulfonylurea, n (%)                           | 760 (61.8%) Placebo 743 (61.2%)                                                           |
|                                                   | 604 (53.0%) Placebo 568 (51.0%)                                                            |
| Any insulin, n (%)                                | 396 (32.2%) Placebo 419 (34.5%)                                                           |
|                                                   | 410 (36.0%) Placebo 517 (46.4%)                                                            |
Concomitant Cardiovascular Medication in Patients With Type 2 Diabetes and Previous Myocardial Infarction

<table>
<thead>
<tr>
<th>Table 4</th>
<th></th>
<th>At Baseline</th>
<th></th>
<th>At Final Visit</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beta-blockers, n (%)</td>
<td>806 (65.5%)</td>
<td>791 (65.1%)</td>
<td>778 (68.2%)</td>
<td>784 (70.4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ACE inhibitors, n (%)</td>
<td>783 (63.7%)</td>
<td>804 (66.2%)</td>
<td>740 (64.9%)</td>
<td>769 (69.0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Angiotensin II antagonists, n (%)</td>
<td>74 (6.0%)</td>
<td>78 (6.4%)</td>
<td>107 (9.4%)</td>
<td>115 (10.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Calcium channel blockers, n (%)</td>
<td>372 (30.2%)</td>
<td>402 (33.1%)</td>
<td>367 (32.2%)</td>
<td>407 (36.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nitrates, n (%)</td>
<td>606 (49.3%)</td>
<td>640 (52.7%)</td>
<td>517 (45.4%)</td>
<td>496 (44.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thiazide diuretics, n (%)</td>
<td>163 (13.3%)</td>
<td>174 (14.3%)</td>
<td>185 (16.2%)</td>
<td>214 (19.2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Loop diuretics, n (%)</td>
<td>207 (16.8%)</td>
<td>198 (16.3%)</td>
<td>282 (24.7%)</td>
<td>225 (20.2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antiplatelet medication, n (%)</td>
<td>1,118 (90.9%)</td>
<td>1,065 (87.7%)</td>
<td>1,044 (91.6%)</td>
<td>1,016 (91.2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aspirin, n (%)</td>
<td>988 (80.3%)</td>
<td>947 (77.9%)</td>
<td>915 (80.3%)</td>
<td>862 (77.4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Statins, n (%)</td>
<td>614 (49.9%)</td>
<td>639 (52.6%)</td>
<td>704 (61.8%)</td>
<td>707 (63.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fibrates, n (%)</td>
<td>127 (10.3%)</td>
<td>131 (10.8%)</td>
<td>91 (8.0%)</td>
<td>105 (9.4%)</td>
<td></td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme.

or CABG if there was ECG evidence of MI. Silent MI was defined as new Q waves in 2 contiguous leads or R-wave reduction in the precordial leads without a change in axis deviation. All potential end point events were adjudicated centrally by an independent committee of clinical experts. Cardiovascular deaths were all deaths excluding those with a proven noncardiovascular cause. Cardiac death was defined as death attributable to MI or other cardiac diseases.

**Procedures.** Patients were seen at months 1 and 2, then every 2 months for the first year, and every 3 months until the last visit. All patients were followed until the end of the study. Vital signs and body weight were measured at each visit. Standard ECGs were obtained at baseline, at yearly intervals, and at the last visit. Blood samples for various analyses were taken at baseline and every 6 months. Details of assays and specific methodology have been described previously (26).

**Statistical analysis.** Statistical methods and power calculations have been reported previously (26,27). Time-to-event analyses were carried out by fitting proportional hazards survival models with treatment as the only covariate and previous testing of the validity of the assumption of proportional hazards. 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. The study is registered as an International Stan-

**Table 5** Effects of Add-On Pioglitazone Therapy Versus Placebo on Cardiac-Related Events in Patients With Type 2 Diabetes and Previous MI

<table>
<thead>
<tr>
<th>Event</th>
<th>Pioglitazone (n = 1,230)</th>
<th>Placebo (n = 1,215)</th>
<th>Hazard Ratio*</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>End points prespecified for the previous-MI subgroup</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal/nonfatal MI (excluding silent MI)</td>
<td>65 (5.3%)</td>
<td>88 (7.2%)</td>
<td>0.72</td>
<td>0.0453</td>
</tr>
<tr>
<td>Cardiovascular death or nonfatal MI (excluding silent MI)</td>
<td>115 (9.3%)</td>
<td>132 (10.9%)</td>
<td>0.85</td>
<td>0.2013</td>
</tr>
<tr>
<td>Cardiovascular death, nonfatal MI (excluding silent MI), or stroke</td>
<td>137 (11.1%)</td>
<td>158 (13.0%)</td>
<td>0.85</td>
<td>0.1493</td>
</tr>
<tr>
<td>Main PROactive end points</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary end point</td>
<td>263 (21.4%)</td>
<td>292 (24.0%)</td>
<td>0.88</td>
<td>0.1351</td>
</tr>
<tr>
<td>Main secondary end point†</td>
<td>148 (12.0%)</td>
<td>178 (14.7%)</td>
<td>0.81</td>
<td>0.0585</td>
</tr>
<tr>
<td>Individual end points from the primary end point</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>82 (6.7%)</td>
<td>94 (7.7%)</td>
<td>0.85</td>
<td>0.2873</td>
</tr>
<tr>
<td>Cardiac death‡</td>
<td>51 (4.1%)</td>
<td>60 (4.9%)</td>
<td>0.83</td>
<td>0.3231</td>
</tr>
<tr>
<td>Nonfatal MI (including silent MI)</td>
<td>72 (5.9%)</td>
<td>85 (7.0%)</td>
<td>0.83</td>
<td>0.2333</td>
</tr>
<tr>
<td>ACS</td>
<td>35 (2.8%)</td>
<td>54 (4.4%)</td>
<td>0.63</td>
<td>0.0346</td>
</tr>
<tr>
<td>Coronary revascularization§</td>
<td>99 (8.0%)</td>
<td>121 (10.0%)</td>
<td>0.80</td>
<td>0.1000</td>
</tr>
<tr>
<td>Fatal/nonfatal stroke</td>
<td>35 (2.8%)</td>
<td>36 (3.0%)</td>
<td>0.95</td>
<td>0.8380</td>
</tr>
<tr>
<td>Other composite end points</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite end point of all cardiac events, excluding silent MI</td>
<td>180 (14.6%)</td>
<td>217 (17.9%)</td>
<td>0.81</td>
<td>0.0336</td>
</tr>
<tr>
<td>Composite end point of all cardiac events, including silent MI</td>
<td>192 (15.6%)</td>
<td>224 (18.4%)</td>
<td>0.83</td>
<td>0.0651</td>
</tr>
</tbody>
</table>

*Pioglitazone versus placebo from a Cox proportional hazards model. †This was the main secondary end point in the main study—death, nonfatal myocardial infarction (MI) (excluding silent MI), and nonfatal stroke (26). ‡Cardiac death was defined as death classified as MI and “other cardiac” (any death associated with cardiac disease adjudicated by the independent adjudication committee). §Percutaneous coronary intervention and coronary artery bypass graft. | Nonfatal MI, coronary revascularization, acute coronary syndrome (ACS), or cardiac death.

CI = confidence interval; Est = estimated value.
Results

Baseline data. Baseline data of the total study population have been published previously (26). Baseline data of the patients with type 2 diabetes and previous MI are given in Tables 1 and 2. Patient characteristics, baseline laboratory data, and previous macrovascular morbidities were well balanced between the patients in the pioglitazone group and those in the placebo group. A high proportion of patients (more than two-thirds) in both groups had other evidence of macrovascular disease (stroke, peripheral arterial obstructive disease, PCI/CABG, or ACS).

There were also no differences between the pioglitazone and placebo groups with respect to baseline blood glucose-lowering treatments and concomitant cardiovascular medication (Tables 3 and 4). Approximately 90% of patients were receiving antiplatelet therapy; 51% were receiving statins at entry, and 63% were receiving statins at the end of the study (Table 4). The final mean dose of pioglitazone was 43.9 mg/day in the 953 patients with previous MI who completed the study on medication. Eighteen patients (1.9%) were receiving 15 mg/day, 34 (3.6%) were receiving 30 mg/day, and 901 (94.5%) were receiving the maximum dose of 45 mg/day.

Effect of pioglitazone versus placebo. Table 5 describes the effect of pioglitazone on the 3 end points prespecified for the previous-MI subgroup, the primary end point, the main secondary end point, and other cardiac-related end points. There was a significant beneficial effect of pioglitazone on the end points of fatal/nonfatal MI, excluding silent MI (RR = 28%; p = 0.045) (Fig. 1), ACS (RR = 37%; p = 0.035) and the composite cardiac end point (nonfatal MI [excluding silent MI], coronary revascularization, ACS, or cardiac death; RR = 19%; p = 0.034) (Fig. 2).

There were no significant differences in the end point of cardiovascular death or nonfatal MI, the end point of cardiovascular death, nonfatal MI, or stroke, the primary or main secondary end points defined in the main PROactive study, and the individual end points of the primary composite; however, there was a consistently lower number of events in the pioglitazone-treated patients for all of the end points (Table 5). The number of silent MIs was similar: 14 in the pioglitazone group and 11 in the placebo group. Deaths from any cause occurred in 82 patients (6.7%) in the pioglitazone group and 94 patients (7.7%) in the placebo group (RR = 15%; p = 0.287).

We performed multivariate analyses including other factors that could affect the likelihood of having either a recurrent MI or an event from the cardiac composite. Baseline characteristics that were significant risk factors for total MI included elevated LDL cholesterol, insulin use,
and increased age. In contrast, prior revascularization reduced the risk of a MI. We found that pioglitazone was still associated with a hazard ratio (HR) of 0.72 after adjusting for these significant risk factors (Table 6). The baseline factors that had a major impact on the cardiac composite were elevated LDL cholesterol, long duration of diabetes (≥10 vs. <5 years), ACE inhibitor use, and high triglyceride levels (Table 6). Similar to the total MI end point, previous revascularization reduced the risk for the cardiac composite (Table 6).

Changes from baseline to final visit for laboratory parameters are shown in Table 2. Median HbA1c decreased in the pioglitazone group to a greater extent than in the placebo group. Median HDL cholesterol increased (8.8%) and median triglycerides decreased (12.4%) to a greater extent in the pioglitazone group relative to placebo.

Safety and tolerability. Details of serious adverse events in the total PROactive population are given in the paper by Dormandy et al. (26). As with the total PROactive study population, there were fewer patients with serious adverse events in the pioglitazone group versus the placebo group (580 [47.2%] vs. 620 [51.0%]) in the patients with type 2 diabetes and previous MI.

Heart failure (HF) occurred in a greater proportion of patients in the MI subgroup (11.6%) than in those without previous MI (7.0%; p < 0.0001). The HR for any HF event in the previous-MI subgroup versus those who did not have a previous MI was 1.68 (p < 0.0001). A similar significant difference was noted for the category of HF requiring hospitalization (HR = 1.75; p < 0.0001). Fatal HF occurred in 28 patients (1.1%) in the previous-MI subgroup and 19 (0.7%) in the no-previous-MI subgroup (HR = 1.66; p = 0.089). In those with a previous MI, there was an increase in serious HF (requiring hospitalization) in the pioglitazone group (Table 7); however, there was no statistically significant difference in fatal HF (1.4% in the pioglitazone group vs. 0.9% in the placebo group).

Median alanine aminotransferase decreased in the pioglitazone group from 25 IU/l at baseline to 24 IU/l (4.2%) at the final visit, whereas there was an increase from 25 to 27 IU/l (8.3%) in the placebo group (p < 0.0001 between groups).

Discussion

PROactive was the first prospective, double-blind outcome study to look specifically at the effects of a glucose-lowering agent, pioglitazone, on the secondary prevention of macrovascular disease in patients with type 2 diabetes. The patients included in this subanalysis of the study all had previous MI and thus were at a very high risk for a subsequent macrovascular event. The results indicate that pioglitazone reduces the risk of adverse cardiac outcomes, including MI, in these patients.
Optimal management of patients with diabetes and MI requires a multifactorial approach to delay or prevent progression of macrovascular disease. Antiplatelet agents, ACE inhibitors, beta-blockers, and lipid-altering agents have all been shown to decrease long-term mortality and cardiovascular morbidity in patients with coronary artery disease. However, prevention of these outcomes with glucose-lowering agents in patients with type 2 diabetes has not been demonstrated in large-scale studies (with the exception of a significant improvement in macrovascular events in a small subgroup analysis of 342 newly diagnosed obese patients with diabetes treated with metformin in the UKPDS) (29).

The effect of pioglitazone was investigated because, in addition to lowering blood glucose, it has a number of cardiovascular effects that are considered to be beneficial in especially high-risk patients. With pioglitazone is also beneficial in patients with type 2 diabetes and previous MI (26). Here, we present a subgroup analysis of 342 newly diagnosed obese patients with diabetes treated with pioglitazone in the pioglitazone arm of the PROactive study (26).

The effect of pioglitazone was investigated because, in addition to lowering blood glucose, it has a number of cardiovascular effects that are considered to be beneficial in atherosclerotic disease. Of special interest are pioglitazone’s effects on lipid levels (increasing HDL cholesterol, lowering triglycerides, and benefiting the composition of LDL particles) and blood pressure and its regulation of levels of mediators involved in inflammation and endothelial dysfunction (e.g., C-reactive protein) (16–22,26,30). In fact, it has been shown (31,32) that one of the widely accepted indicators of coronary atherosclerosis and risk of cardiovascular events, intima–media thickness of the carotid artery, is decreased by pioglitazone. Therefore, there was good reason to consider the use of pioglitazone in patients with macrovascular disease and diabetes. The main results of the PROactive study showed a significant RR of the disease-related end points of all-cause mortality, nonfatal MI, and nonfatal stroke in these patients (26). Here, we confirm through a subgroup analysis that intervention with pioglitazone is also beneficial in especially high-risk patients.

### Table 6

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal/Nonfatal MI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL &gt;4 mmol/l (vs. &lt;3 mmol/l)</td>
<td>2.04</td>
<td>(1.346–3.093)</td>
</tr>
<tr>
<td>Insulin use</td>
<td>1.59</td>
<td>(1.147–2.193)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>1.03</td>
<td>(1.010–1.056)</td>
</tr>
<tr>
<td>Previous PCI/CABG</td>
<td>0.56</td>
<td>(0.392–0.810)</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>0.72</td>
<td>(0.521–0.998)</td>
</tr>
</tbody>
</table>

### Table 7

<table>
<thead>
<tr>
<th>End Points</th>
<th>Previous MI, Number of Events (%)</th>
<th>Time to Heart Failure*</th>
<th>No Previous MI, Number of Events (%)</th>
<th>Time to Heart Failure*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pioglitazone (n = 1,230)</td>
<td>Placebo (n = 1,219)</td>
<td>Placebo (n = 1,375)</td>
<td>Placebo (n = 1,418)</td>
<td></td>
</tr>
<tr>
<td>Any report of heart failure</td>
<td>166 (13.5%)</td>
<td>117 (9.6%)</td>
<td>115 (8.4%)</td>
<td>81 (5.7%)</td>
</tr>
<tr>
<td>Heart failure leading to hospitalization</td>
<td>92 (7.5%)</td>
<td>63 (5.2%)</td>
<td>57 (4.1%)</td>
<td>45 (3.2%)</td>
</tr>
<tr>
<td>Fatal heart failure</td>
<td>17 (1.4%)</td>
<td>11 (0.9%)</td>
<td>8 (0.6%)</td>
<td>11 (0.8%)</td>
</tr>
</tbody>
</table>

*Pioglitazone versus placebo. HR = hazard ratio; other abbreviations as in Table 6.
Key findings. The addition of pioglitazone to existing medication for management of hyperglycemia, dyslipidemia, and hypertension reduced the risk of the end point of a recurrent fatal/nonfatal MI in patients with type 2 diabetes and MI by 28% (p = 0.045). The Kaplan–Meier estimates of event rates were 5.3% in the pioglitazone group and 7.2% in the placebo group at 3 years. There was also a significant benefit in preventing ACS in these high-risk patients treated with pioglitazone (37% reduction in risk; p = 0.035). In addition, we looked at a composite cardiac end point (nonfatal MI, coronary revascularization, ACS, and cardiac death) and found that there was a statistically significant 19% decrease in risk (p = 0.034). All of the other end points trended similarly, but did not reach the conventional level of 0.05 for statistical significance.

Although pioglitazone treatment also resulted in improvements in HDL cholesterol and triglycerides, the specific mediators of pioglitazone’s benefit with regard to cardiac outcomes are unknown, and this study was not designed to determine the mechanisms of cardioprotection.

This particular high-risk subgroup with a MI at the entry into the study would be prone to develop HF as a consequence. There was an increase in reports of serious HF leading to hospitalization (7.5% vs. 5.2%) in the pioglitazone group, but the rate of fatal HF was similar in the 2 groups (1.4% with pioglitazone vs. 0.9% with placebo). A recent analysis of more than 23,000 patients does not support the view that pioglitazone may cause HF (33). The higher relative HF risk shown in the pioglitazone group in PROactive does not appear to be related specifically to the prior myocardial function impairment present in the previous-MI subgroup. The proportion of reports of any HF and serious HF in this MI subgroup were higher than those in the no-previous-MI subgroup, regardless of treatment group. There were increased risks of 68% for any HF event and 75% for HF leading to hospitalization in the previous-MI subgroup relative to the no-previous-MI subgroup (both p < 0.0001).

Study limitations. The main limitation of this analysis is that it includes both prespecified and post-hoc end points. It is an analysis of a subgroup of a larger study, and randomization was not stratified by history of MI. Nevertheless, the sample size is substantial, and the 2 treatment groups within this subgroup were very well balanced at baseline. Furthermore, these data represent one of the largest groups of patients with type 2 diabetes and previous MI randomized as part of a diabetes outcome trial.

Although the protocol specified that investigators follow the IDF Europe guidelines and the executive committee reinforced that, not all of the patients were treated accordingly. For example, according to the guidelines, all of the patients should have been receiving a statin. At baseline, approximately 50% of patients received a statin. By 3 years this had risen to 63%. Recent surveys also show that, in current practice, there is an underuse of statins in people with cardiovascular disease and/or diabetes, with 22% to 55% usage in European countries (34–38). However, the beneficial effect of pioglitazone in this previous-MI subgroup was independent of baseline use of a statin based on a multivariate analysis.

The time period of the study was relatively short, considering the chronic nature of treatment. The benefit of pioglitazone is clear from the Kaplan–Meier curves for both time to fatal/nonfatal MI and time to the composite cardiac end point. If the study duration had been longer, continued divergence of the curves (if it occurred) would have strengthened our findings.

Conclusions. In this analysis of a subgroup of high-risk patients with type 2 diabetes and a previous MI from a large prospective study, pioglitazone appears to be effective in reducing the risk of recurrent MI and other serious cardiovascular events.

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REFERENCES


For a list of the PROactive Investigators, please see the online version of this article.