Effects of Pioglitazone in Patients With Type 2 Diabetes With or Without Previous Stroke
Results From PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events 04)

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Background and Purpose—Diabetes is an important risk factor for stroke. We conducted analyses in patients who had entered the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) with a history of stroke or without stroke.

Methods—The prospective, double-blind PROactive (mean duration, 34.5 months) randomized 5238 patients with type 2 diabetes and a history of macrovascular disease to pioglitazone (titrated to 45 mg) or placebo, in addition to current diabetes and cardiovascular medications. Cardiovascular end-point events were independently adjudicated. This analysis evaluated the risk of stroke and other cardiovascular outcomes in patients with (n=984) and without (n=4254) prior stroke.

Results—In patients with previous stroke (n=486 in the pioglitazone group and n=498 in the placebo group), there was a trend of benefit with pioglitazone for the primary end point of all-cause death, nonfatal myocardial infarction, acute coronary syndrome, and cardiac intervention (including coronary artery bypass graft or percutaneous coronary intervention), stroke, major leg amputation, or bypass surgery or leg revascularization (hazard ratio[HR]=0.78, event rate=20.2% pioglitazone vs 25.3% placebo; 95% CI=0.60–1.02; P=0.0670) and for the main secondary end point of all-cause death, nonfatal myocardial infarction, or nonfatal stroke (HR=0.78, event rate=15.6% pioglitazone vs 19.7% placebo; 95% CI=0.58–1.06; P=0.1095). Pioglitazone reduced fatal or nonfatal stroke (HR=0.53, event rate=5.6% pioglitazone vs 10.2% placebo; 95% CI=0.34–0.85; P=0.0085) and cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (HR=0.72, event rate=13.0% pioglitazone vs 17.7% placebo; 95% CI=0.52–1.00; P=0.0467). Higher event rates were observed in patients with prior stroke compared with those without prior stroke. In patients without prior stroke, no treatment effect was observed for a first stroke.

Conclusions—In a subgroup analysis from PROactive, pioglitazone reduced the risk of recurrent stroke significantly in high-risk patients with type 2 diabetes. (Stroke. 2007;38:865-873.)

Key Words: clinical trials • pioglitazone • stroke • type 2 diabetes

Patients with diabetes are at increased risk of morbidity and mortality from cerebrovascular disease,1 with a 2- to 6-fold increased risk for first or recurrent ischemic stroke.2-5 Specific and nonspecific risk factors of stroke in the diabetic population include previous cerebrovascular disorders, arterial hypertension, central obesity, smoking, dyslipidemia, hyperglycemia, diabetes duration, diabetic complications, and insulin resistance/hyperinsulinemia.6,7 Hypertension is the strongest predictor for stroke in patients with diabetes as it is in the general population.2

Stroke prevention in patients with diabetes involves multifactorial interventions. The most effective strategies include strict blood pressure control, antiplatelet therapy, and lipid-altering therapy. Although glucose-lowering therapy has been shown to reduce microvascular disease, its effect on macrovascular disease is unclear, and there are no conclusive data showing a benefit in stroke patients8; however, there are data showing a reduction in macrovascular disease in patients with type 1 diabetes managed with a glucose-lowering strategy.9

The PROspective pioglitAzone Clinical Trial In macrovascular Events (PROactive) was a large prospective study that looked at the reduction in macrovascular disease with a glucose-lowering strategy with the peroxisome proliferator--
activated receptor-γ agonist pioglitazone. The primary composite end point included the disease-related end points of death, myocardial infarction (MI), acute coronary syndrome (ACS), and stroke and procedure-related end points of major amputation, coronary and leg revascularization, and coronary artery bypass graft surgery (CABG) or percutaneous coronary intervention (PCI). Pioglitazone was associated with a non-significant 10% risk reduction in this primary composite end point ($P=0.095$) and a statistically significant 16% risk reduction ($P=0.027$) in the main secondary end point, which was a composite of all-cause mortality, nonfatal MI, and nonfatal stroke.$^{10}$ Eighty-six patients (3.3%) in the pioglitazone group versus 107 (4.1%) in the placebo group experienced a stroke; this was associated with a hazard ratio (HR) of 0.81 (95% CIs = 0.61–1.07; $P=0.140$) for the time to first event.

The aim of this subgroup analysis was to investigate the effects on macrovascular events of adding pioglitazone to current medications for dyslipidemia, hypertension, and hyperglycemia compared with placebo in patients who had entered the study with or without a history of stroke (≥6 months before randomization).

### Subjects and Methods

**PROactive** was a prospective, randomized, double-blind, placebo-controlled outcome study in high-risk patients with type 2 diabetes and a history of macrovascular disease. Patients (N=5238) from 321 centers in 19 European countries were randomized and observed for an average of 34.5 months. The protocol, inclusion/exclusion criteria, and methodology have been published previously.$^{10,11}$ The study was approved by the appropriate review boards and is registered as an International Standard Randomized Controlled Trial (ISRCTN NCT00174993). All patients gave written, informed consent.

### Subjects

Male and female patients (35 to 75 years) with type 2 diabetes (glycosylated hemoglobin [HbA$_1c$] above the upper limit of normal; local equivalent of 6.5% for a Diabetes Control and Complications Trial–traceable assay) were randomized to receive pioglitazone at the maximum tolerated dose (increased stepwise from 15 to 45 mg, depending on tolerability) or matching placebo, in addition to their existing cardiovascular and glucose-lowering medications. Investigators were encouraged to treat existing hyperglycemia, dyslipidemia, and hypertension throughout the trial according to the International Diabetes Federation European Guidelines (1999).

Patients who qualified for entry into PROactive on the basis of a previous stroke (≥6 months before randomization; n=984) were included in this analysis and compared with those who did not have a previous stroke (n=4254).

### Measurements

Details of assays and specific methodology have been described previously.$^{10}$ Patients were seen at baseline, at months 1 and 2, every 2 months to the end of the first year, and then every 3 months until the final visit. All patients were followed up until the study end.

### Outcomes

The primary end point in the main PROactive was the time from randomization to the first occurrence of any of the events in the following composite: all-cause mortality, nonfatal MI (including silent MI), stroke, ACS, cardiac intervention (including CABG or PCI), leg revascularization, and amputation above the ankle.

The statistical analysis plan, finalized and submitted to the US Food and Drug Administration before unblinding of the study, prespecified the previous stroke (≥6 months before entry into the study) subgroup and additional analyses of (1) time to fatal or nonfatal stroke and (2) time to cardiovascular death, nonfatal MI (excluding silent MI), or nonfatal stroke.$^{12}$ We describe these analyses together with all-cause mortality. In accordance with the statistical analysis plan, silent MIs were included in the primary composite end point but excluded in all other end points in this subgroup analysis, particularly because they were few and of equal occurrence in both groups.

Stroke was defined as an acute, focal neurological deficit lasting for >24 hours or resulting in death within 24 hours of the onset of symptoms, which was diagnosed as having been due to a cerebral lesion of vascular origin but excluding subarachnoid hemorrhage. Whenever possible, diagnostic neuroimaging was performed, but when unavailable, a clinical diagnosis was accepted. Fatal strokes were identified by the adjudication process (ie, on a case-by-case basis, not by definition). In this analysis, we used an arbitrary 30-day cutoff point to define fatal stroke. Nonfatal MI was defined as a patient with MI who survived for the first 24 hours from onset of symptoms. Cardiovascular deaths were all deaths, excluding those with a proven noncardiovascular cause, and classified as MI, other cardiac, cerebrovascular, or other.

### Statistical Analysis

Statistical methods and power calculations have been published previously.$^{10,11}$ The analysis of outcomes was exclusively an analysis of time to events, and estimated HRs and 95% CIs were calculated by fitting a Cox proportional-hazards survival model with treatment as the only covariate. 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 with a stepwise selection algorithm and a significance level of 0.05.

### Table 1. Baseline Characteristics, Laboratory Values, and Previous Macrovascular Morbidity Data

<table>
<thead>
<tr>
<th></th>
<th>Previous Stroke (n=984)</th>
<th>No Previous Stroke (n=4254)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>596 (61%)</td>
<td>2867 (67%)</td>
</tr>
<tr>
<td>White</td>
<td>973 (99%)</td>
<td>4191 (99%)</td>
</tr>
<tr>
<td>Age, y</td>
<td>62.3±7.5</td>
<td>61.6±7.7</td>
</tr>
<tr>
<td>Time since diagnosis of diabetes, y</td>
<td>9.0 (4–14)</td>
<td>8.0 (4–13)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>30.8±4.8</td>
<td>30.9±4.8</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>819 (83%)</td>
<td>3133 (74%)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>122 (12%)</td>
<td>599 (14%)</td>
</tr>
<tr>
<td>Past</td>
<td>397 (40%)</td>
<td>1961 (46%)</td>
</tr>
<tr>
<td>Microvascular disease (retinopathy, nephropathy, neuropathy)</td>
<td>496 (50%)</td>
<td>1693 (40%)</td>
</tr>
<tr>
<td>HbA$_1c$, %</td>
<td>8.1±1.4</td>
<td>8.1±1.4</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>145±18</td>
<td>143±18</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>84±10</td>
<td>83±10</td>
</tr>
<tr>
<td>Other macrovascular disease criteria, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous MI</td>
<td>177 (18%)</td>
<td>2268 (53%)</td>
</tr>
<tr>
<td>Previous PCI/CABG</td>
<td>102 (10%)</td>
<td>1509 (36%)</td>
</tr>
<tr>
<td>Previous ACS</td>
<td>50 (5%)</td>
<td>665 (16%)</td>
</tr>
<tr>
<td>Symptomatic peripheral arterial obstructive disease</td>
<td>97 (10%)</td>
<td>946 (22%)</td>
</tr>
</tbody>
</table>

Values are mean±SD or n (%).
Results

Baseline Data
Baseline data of the total study population have been published previously.10 There were some differences in baseline data between those with and without previous stroke (Table 1). For example, the proportion of patients with a history of hypertension or previous microvascular disease was higher in the previous-stroke group, and the proportion of men or those with a history of other previous macrovascular disease (MI, PCI/CABG, ACS, and symptomatic peripheral arterial obstructive disease) was higher in the group with no previous stroke. Patient characteristics and previous macrovascular morbidities (as in the entry criteria) were well balanced between the pioglitazone group and the placebo group, irrespective of whether the patient had suffered a previous stroke or not (data not shown). The types of prior, recurrent, or first stroke were not adequately categorized for us to make any pathological groupings.

Baseline laboratory data were also well matched between the 2 treatment groups with respect to baseline blood glucose–lowering treatments (data not shown) and concomitant cardiovascular medications. There were also no differences in baseline glucose-lowering medication in patients with and without previous stroke. Approximately 82% of patients with previous stroke were on antiplatelet medication versus 84% of patients without previous stroke.

| Table 2. Concomitant Medication Use at Baseline and Final Visit in the Pioglitazone and Placebo Groups in Patients With and Without Previous Stroke |
|-----------------|-----------------|-----------------|-----------------|
|                 | Pioglitazone    | Placebo         |                 |
|                 | Baseline (n=486)| Final Visit (n=439)| Baseline (n=498)| Final Visit (n=443) |
| Cardiovascular medications | 445 (94%) | 416 (95%) | 460 (92%) | 420 (95%) |
| β-Blockers       | 195 (40%) | 198 (45%) | 184 (37%) | 201 (45%) |
| ACE inhibitors   | 335 (69%) | 308 (70%) | 327 (66%) | 301 (68%) |
| Angiotensin II antagonists | 27 (6%) | 45 (10%) | 45 (9%) | 51 (12%) |
| Calcium channel blockers | 183 (38%) | 174 (40%) | 218 (44%) | 209 (47%) |
| Nitrates         | 111 (23%) | 100 (23%) | 127 (26%) | 101 (23%) |
| Thiazide diuretics | 104 (21%) | 108 (25%) | 97 (20%) | 93 (21%) |
| Loop diuretics   | 62 (13%) | 89 (20%) | 74 (15%) | 97 (22%) |
| Antiplatelet/anticoagulant medications | 401 (83%) | 379 (86%) | 408 (82%) | 390 (88%) |
| Aspirin          | 322 (66%) | 305 (70%) | 327 (66%) | 302 (68%) |
| Lipid-altering medications | 201 (41%) | 219 (50%) | 211 (42%) | 235 (53%) |
| Statins          | 154 (32%) | 183 (42%) | 161 (32%) | 206 (47%) |
| Fibrates         | 58 (12%) | 41 (9%) | 55 (11%) | 38 (9%) |
| Nervous system medications* | 140 (29%) | 121 (28%) | 150 (30%) | 138 (31%) |
| NSAIDs           | 25 (5%) | 19 (4%) | 22 (4%) | 31 (7%) |

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ACE indicates angiotensin-converting enzyme; NSAIDs, nonsteroidal anti-inflammatory drugs.
*Antidepressant, antipsychotic, hypnotic, anticonvulsant, antiparkinsonism, and other drugs.
patients without previous stroke (including 7% on anticoagu-
lants in both groups); however, only 42% of patients with
previous stroke were on lipid-altering therapy versus 54% of
patients without previous stroke. Overall, 93% of patients
with and 95% without previous stroke were on cardiovas-
cular medications, with differences between groups with respect to
individual treatments (for example, 39% in the previous-
stroke group were on β-blockers versus 58% in the no-
previous-stroke group). Cardiovascular medication use at
baseline and final visit is given in Table 2.

Effect of Pioglitazone Versus Placebo on
Macrovascular Events
Table 3 describes the effect of pioglitazone in patients with
and without previous stroke on the primary and main second-
ary end points from the main PROactive and prespecified end
d points for the stroke subgroup of time to fatal or nonfatal
stroke and time to cardiovascular death, nonfatal stroke, or
nonfatal MI.

Patients With Previous Stroke
In the patients with previous stroke, there were no significant
differences in the primary or main secondary end points defined in the main PROActive, but there was a trend of
benefit (HR = 0.78, 95% CIs = 0.60–1.02; P = 0.067) for the
primary end point. There was a statistically significant
beneficial effect of pioglitazone on the end points of fatal or
nonfatal stroke (HR = 0.53, 95% CIs = 0.34–0.85; P = 0.0085;
Figure 1a) and cardiovascular death, nonfatal stroke, or
nonfatal MI (HR = 0.72, 95% CIs = 0.53–1.00; P = 0.0467).

Patients Without Previous Stroke
The event rates and HRs in the patients without previous
stroke are given in Table 3 and Figure 1b. Pioglitazone had no
effect on reducing the risk of first strokes in this subgroup.
There were no significant differences in any of the end points
(HR = 0.94, 95% CIs = 0.82–1.07; P = 0.3501 for the primary
end point; HR = 0.86, 95% CIs = 0.72–1.03; P = 0.1092 for the
main secondary end point; HR = 1.06, 95% CIs = 0.73–1.52;
P = 0.7671 for fatal or nonfatal stroke; and HR = 0.86, 95%
CIs = 0.71–1.04; P = 0.1289 for cardiovascular death, nonfatal
stroke, or nonfatal MI).

Multivariate Analyses
The interaction test for treatment effect between prior and no
prior stroke groups was positive at P = 0.0216. Multivariate
analysis of all baseline characteristics revealed that among
patients with previous stroke, the only factors with a signif-
icant effect on risk of recurrent stroke were the use of
pioglitazone (P = 0.0076) and statins (P = 0.0126), both of
which were associated with a reduction in risk of ≈50%.
Figure 2a shows the HRs and 95% CIs obtained from this
analysis. None of the other study entry criteria, baseline lipid
measurements, or concomitant medications tested were sig-
nificant predictors of recurrent stroke.

A similar analysis of patients without previous stroke
identified age (P = 0.0002), HbA1c ≥7.5% (P = 0.0038), cre-
tatinine ≥130 μmol/L (P = 0.0468), and peripheral arterial
disease (P = 0.0092) as significant positive predictors of
having a first stroke (Figure 2b). A multivariate analysis of
the entire cohort of patients showed that prior stroke was itself the strongest predictor of recurrent stroke (HR = 2.88,
95% CIs = 2.15–3.86; P < 0.0001).

Laboratory Parameters and Blood Pressure
Changes from baseline to final visit for laboratory parameters
are shown in Table 4. Mean HbA1c decreased significantly
more in the pioglitazone groups than in the placebo groups
(P < 0.0001). There were also marginally greater decreases in
mean blood pressure with pioglitazone than with placebo, but
these differences only reached statistical significance for the
change in systolic blood pressure in patients without previous
stroke (P = 0.0497). There were statistically significant improve-
ments in triglycerides, HDL cholesterol levels, and the LDL-
HDL ratio with pioglitazone compared with placebo, irrespec-
tive of whether the patient had had a previous stroke or not.

Safety and Tolerability
Details of serious adverse events in the total PROactive
population are given in the article by Dormandy et al.10

Patients With Previous Stroke
There was no difference in the proportion of patients with
serious adverse events in the pioglitazone group (237 [49%])

### Table 3. Effects of Add-On Pioglitazone Therapy vs Placebo on Cardiovascular Events

<table>
<thead>
<tr>
<th>End Points</th>
<th>Pioglitazone (n = 498)</th>
<th>Placebo (n = 498)</th>
<th>HR*, 95% CI, P</th>
<th>Pioglitazone (n = 2119)</th>
<th>Placebo (n = 2135)</th>
<th>HR*, 95% CI, P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary†</td>
<td>98 (20.2%)</td>
<td>126 (25.3%)</td>
<td>0.78; 0.60–1.02; P = 0.067</td>
<td>416 (19.6%)</td>
<td>446 (20.9%)</td>
<td>0.94; 0.82–1.07; P = 0.350</td>
</tr>
<tr>
<td>Main secondary‡</td>
<td>76 (15.6%)</td>
<td>98 (19.7%)</td>
<td>0.78; 0.58–1.06; P = 0.110</td>
<td>225 (10.6%)</td>
<td>260 (12.2%)</td>
<td>0.86; 0.72–1.03; P = 0.109</td>
</tr>
<tr>
<td>Total stroke</td>
<td>27 (5.6%)</td>
<td>51 (10.2%)</td>
<td>0.53; 0.34–0.85; P = 0.009</td>
<td>59 (2.8%)</td>
<td>56 (2.6%)</td>
<td>1.06; 0.73–1.52; P = 0.767</td>
</tr>
<tr>
<td>Cardiovascular death, nonfatal stroke, or nonfatal MI†</td>
<td>63 (13.0%)</td>
<td>88 (17.7%)</td>
<td>0.72; 0.53–1.00; P = 0.047</td>
<td>194 (9.2%)</td>
<td>225 (10.5%)</td>
<td>0.86; 0.71–1.04; P = 0.129</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>46 (9.5%)</td>
<td>49 (9.8%)</td>
<td>0.96; 0.64–1.44; P = 0.843</td>
<td>131 (6.2%)</td>
<td>137 (6.4%)</td>
<td>0.96; 0.75–1.22; P = 0.725</td>
</tr>
</tbody>
</table>

*Pioglitazone vs placebo, from a Cox proportional-hazards model (with treatment as the only covariate).
†Excluding silent MI.
‡All-cause mortality, nonfatal MI (including silent MI), nonfatal stroke, ACS, cardiac intervention (including CABG or PCI), leg revascularization, or major leg amputation (above the ankle).
§All-cause mortality, nonfatal MI, or nonfatal stroke.
versus the placebo group (256 [51%]). Heart failure requiring hospitalization was reported in 31 (6.4%) pioglitazone-treated patients versus 20 (4.0%) placebo-treated patients ($P = 0.0946$) and fatal heart failure in 6 (1.2%) in the pioglitazone group versus 4 (0.8%) in the placebo group ($P = 0.5000$).

**Patients Without Previous Stroke**

In patients with no previous stroke, the number with any serious adverse event was 967 (46%) in the pioglitazone group and 1019 (48%) in the placebo group. Heart failure requiring hospitalization occurred in significantly more patients in the pioglitazone group ($n = 118$, 5.6%) than in the placebo group ($n = 88$, 4.1%; $P = 0.0279$ between-group difference); however, fatal heart failure events were similar (19 [0.9%] in the pioglitazone group and 18 [0.8%] in the placebo group; $P = 0.8508$ between-group difference).

**Discussion**

Our results show that pioglitazone significantly reduced the risk of recurrent fatal and nonfatal stroke in high-risk patients with type 2 diabetes but had no effect on first strokes in PROactive. Hyperglycemia is a significant predictor of the risk of fatal or nonfatal stroke, and type 2 diabetes is associated with a 2- to 6-fold increased risk of first or recurrent ischemic stroke. Four case-control studies and 5 prospective, observational, cohort studies have demonstrated an association between insulin resistance and risk for stroke. We decided to look at the effects of pioglitazone in this population of patients with type 2 diabetes and stroke, as pioglitazone also has a number of cardiovascular effects that are considered to be beneficial in arteriosclerotic disease, in addition to its effects on blood glucose.

The addition of pioglitazone to existing cardiovascular medications did not have any effect on preventing a first stroke (incidence 2.6%), but in patients who entered the study having experienced a previous stroke $>6$ months before randomization, pioglitazone reduced the risk of a recurrent fatal/nonfatal stroke by 47% ($P = 0.0085$). The Kaplan–Meier estimates of event rates in this prior-stroke group were 5.6%
in the pioglitazone group and 10.2% in the placebo group at 3 years. There was also a reduction in the end point of cardiovascular death, nonfatal stroke, or nonfatal MI (HR = 0.72, event rate of 13.0% in the pioglitazone group vs 17.7% in the placebo group; \( P = 0.0467 \)). It should be noted that the benefit for this end point was driven primarily by stroke. These data are similar to those obtained in the PROactive subgroup of patients with type 2 diabetes and a previous MI, wherein pioglitazone was effective in preventing a recurrent MI.\(^{15}\)

The magnitude of risk reduction with pioglitazone reported herein is comparable to that of other pharmacological interventions. For instance, in the Heart Protection Study, there was a relative risk reduction in first strokes with statin treatment of 24% (5.0% for simvastatin vs 6.5% for placebo), in addition to the reduction in coronary events in patients with diabetes.\(^{16}\) However, there was no apparent reduction in stroke rate with simvastatin in patients with preexisting cerebrovascular disease in that study.\(^{17}\) In the Collaborative Atorvastatin Diabetes Study, there was a 48% risk reduction
in first strokes with atorvastatin during the 3.9-year study period (event rate of 1.5% in the atorvastatin group vs 2.8% in the placebo group). The recently published data from the Stroke Prevention by Aggressive Reduction in Cholesterol Levels study in patients with recent previous stroke or transient ischemic attack (but no history of coronary heart disease) showed a 10% risk reduction in nonfatal or fatal stroke with atorvastatin relative to placebo after 5 years (P = 0.03). In the Fenofibrate Intervention and Event Lowering in Diabetes study, fibrate therapy was associated with a small, nonsignificant 10% risk reduction in total stroke rate (event rate of 3.2% in the fenofibrate group vs 3.6% in the placebo group over 5 years; P = 0.36).

The reduction in stroke risk with pioglitazone in PROactive is similar to that with tight blood pressure control in 2 large outcome trials in patients with diabetes. The United Kingdom Prospective Diabetes Study suggested that tight blood pressure control (144/82 mm Hg) reduced the risk of stroke by 44% compared with less strict control (154/87 mm Hg) in patients with new-onset type 2 diabetes (event rate over 8.4 years of 5.0% with tight control vs 9.5% with less strict control; P = 0.013). An analysis of the subgroup patients with type 2 diabetes in PROGRESS confirmed the importance of blood pressure lowering in patients with type 2 diabetes at risk of recurrent stroke (relative risk = 28%, event rate over 4 years of 10% in the perindopril group vs 14% in the placebo group).

Long-term follow-up of patients in the United Kingdom Prospective Diabetes Study showed that glycemic control with pharmacological treatment (sulfonylurea or insulin) in patient with type 2 diabetes did not significantly modify the incidence of stroke. In fact, there was an 11% nonsignificant increase in stroke incidence over 10 years in the pharmacologically treated patients (event rate of 5.4%) compared with the lifestyle-managed patients (event rate of 4.8%). A 1% reduction in HbA1c was associated with only a 4% estimated decrease in risk of stroke (P = 0.44). However, in a post hoc analysis of a small subgroup of overweight patients, metformin was more effective in reducing the risk for stroke compared with sulfonylurea and insulin and achieved a 41% stroke reduction (event rate of 12 of 342) compared with lifestyle intervention (event rate of 28 of 411). In the 3.3-year STOP-NIDDM trial in patients with impaired glucose tolerance, there were very low stroke event rates (2 of 682 acarbose-treated patients and 4 of 686 placebo-treated patients).

A recent long-term (17-year) observational study from the Diabetes Control and Complications Trial revealed that intensive treatment of patients with type 1 diabetes reduced the risk of any cardiovascular disease event by 42% (3 events of 113 vs 9 events of 92 in the conventional group; P = 0.02) and the risk of nonfatal MI, stroke, or death from cardiovascular disease by 57% (11 events of 118 vs 30 events of 96 in the conventional group; P = 0.02). The decrease in HbA1c (updated mean at the time of the cardiovascular event during the Diabetes Control and Complications Trial) was significantly associated with most of the positive effects of intensive treatment on the risk of cardiovascular disease, with a 20% reduction in the risk of a cardiovascular event (P < 0.0001).

PROactive was not designed to look at potential mechanisms of action, but other studies have shown that there is a strong relation between plasma lipid and/or lipoprotein concentrations and cerebrovascular atherosclerosis. Pioglitazone is known to have beneficial effects on a number of additional factors, including blood pressure regulation, endothelial function, vascular inflammation, lipid metabolism, smooth muscle cell proliferation, and fibrinolysis. In this analysis, pioglitazone treatment resulted in statistically significant improvements over placebo in glycemic control, HDL cholesterol, triglycerides, and the LDL-HDL ratio in patients with and without previous stroke. There were small decreases in blood pressure in the pioglitazone group in patients with and without prior stroke that may also have contributed to the clinical benefit.

One possible explanation of why pioglitazone affected recurrent stroke, but not first strokes, is simply that the risk of a first stroke was low (2.6% over 3 years) compared with those with previous stroke (10.5%). In addition, there were demographic differences in terms of previous morbidity and risk factors. This risk rate of a first stroke was lower in

| TABLE 4. Change From Baseline Laboratory and Blood Pressure Data |
|-------------------|-------------------|--------|
|                   | Pioglitazone      | Placebo|
|                   | (n=486)           | (n=498) |
| Change From Baseline to Final Visit | Change From Baseline to Final Visit |
| Mean HbA1c, %     | -0.9              | -0.3   | <0.0001 |
| Absolute change from baseline |                      |        |
| Mean systolic blood pressure, mm Hg | -4.4              | -2.7   | 0.2308  |
| Mean diastolic blood pressure, mm Hg | -4.0              | -2.6   | 0.0717  |
| % change from baseline |                      |        |
| Median triglycerides, mmol/L | -11.1             | 8.1    | <0.0001 |
| Median HDL cholesterol, mmol/L  | 21.3              | 10.2   | <0.0001 |
| Median LDL cholesterol, mmol/L | 6.7               | 5.9    | 0.2719  |
| LDL/HDL ratio     | -10.4             | -4.3   | 0.0028  |
| P                  |                    |        | <0.0001 |
| Patients With Previous Stroke | Patients Without Previous Stroke |
| Pioglitazone      | Placebo            |
| (n=2119)          | (n=2135)          |
| Change From Baseline to Final Visit | Change From Baseline to Final Visit |
| Mean HbA1c, %     | -0.9              | -0.3   | <0.0001 |
| Absolute change from baseline |                      |        |
| Mean systolic blood pressure, mm Hg | -4.4              | -2.7   | 0.2308  |
| Mean diastolic blood pressure, mm Hg | -4.0              | -2.6   | 0.0717  |
| % change from baseline |                      |        |
| Median triglycerides, mmol/L | -11.1             | 8.1    | <0.0001 |
| Median HDL cholesterol, mmol/L  | 21.3              | 10.2   | <0.0001 |
| Median LDL cholesterol, mmol/L | 6.7               | 5.9    | 0.2719  |
| LDL/HDL ratio     | -10.4             | -4.3   | 0.0028  |
| P                  |                    |        | <0.0001 |
PROactive than that in population-based studies of similar duration. For example, 6.1% of patients in the 3.5-year study by Kuusisto et al11 had a fatal or nonfatal stroke.

PROactive has some methodological and analytical limitations. The time period of the study may have been too short, and the patients were nearly all white and from European countries. Moreover, the patients were at a very late stage of the disease process. This analysis was of a subgroup of the larger study, and randomization was not stratified by history of stroke. The outcome should be interpreted in this context. Despite the fact that the Executive Committee frequently encouraged the investigators to follow the International Diabetes Foundation European Guidelines, not all of the patients were treated accordingly. Finally, information on the types of prior, recurrent, or first stroke was unavailable for all of the patients who entered the study (ie, ischemic vs hemorrhagic), and hence, no pathological subgrouping was possible. It is unclear, therefore, whether pioglitazone protects in all types of stroke.

Summary
In a subgroup analysis from a large-scale, prospective study, pioglitazone given as an add-on to other existing cardiovascular medications reduced the risk of recurrent stroke in high-risk patients with type 2 diabetes. Further randomized, prospective trials (eg, the National Institutes of Health 4-year Insulin Resistance Intervention after Stroke trial that will use pioglitazone to target insulin resistance as a new approach to preventing recurrent stroke and heart attack)28 are warranted to validate these findings and to address the potential mechanisms of action behind the reduction in recurrent stroke with pioglitazone.

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References


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