The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive)

Can pioglitazone reduce cardiovascular events in diabetes? Study design and baseline characteristics of 5,238 patients

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OBJECTIVE — The PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) assesses the effect of pioglitazone, a peroxisome proliferator–activated receptor agonist, with anti-inflammatory and vascular properties, on the secondary prevention of macrovascular events in type 2 diabetes.

RESEARCH DESIGN AND METHODS — PROactive is an on-going randomized, double-blind outcome study in patients with type 2 diabetes managed with diet and/or oral blood glucose–lowering drugs (combination of oral agents with insulin is permitted) who have a history of macrovascular disease. Patients are randomized to receive pioglitazone (forced titration from 15 to 30 to 45 mg, depending on tolerability) or placebo in addition to existing therapy. The primary end point is the time from randomization to occurrence of a new macrovascular event or death. Follow-up is estimated to span 4 years.

RESULTS — A total of 5,238 patients have been randomized from 19 countries. At entry into the study, patients enrolled are a mean age of 61.8 years, with type 2 diabetes for a mean of 9.5 years; 60.9 and 61.5% are taking metformin or a sulfonylurea, respectively; and 33.6% are using insulin in addition to oral glucose-lowering drugs. The majority of patients are men (66.1%). Patients are required to meet one or more of entry criteria, as follows: >6 months' history of myocardial infarction (46.7%); coronary artery revascularization (30.8%), stroke (18.8%), or acute coronary syndrome for >3 months (13.7%); other evidence of coronary artery disease (48.1%); or peripheral arterial occlusive disease (19.9%). One-half (48.5%) of the patients have two or more of these risk factors. Three-quarters (75.4%) have hypertension, and 58.8% are current or previous smokers.

CONCLUSIONS — The cohort of patients enrolled in PROactive is a typical type 2 diabetic population at high risk of further macrovascular events. The characteristics of this population are ideal for assessing the ability of pioglitazone to reduce the cardiovascular risk of patients with type 2 diabetes.

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I t is estimated that 115 million people worldwide suffered from diabetes in 1995 and that this figure will increase to 215 million by 2010 (1) and 300 million by 2025 (2). The social and economic consequences of the management of diabetes and its complications make it a major public health issue. Patients with diabetes have an increased risk of micro- and macrovascular disease, with an overall 25% reduction in life expectancy compared with the general population. This is mainly due to cardiovascular deaths; the risk of coronary heart disease is increased two- to fourfold in this population (3,4). Furthermore, the risk of cardiovascular complications in patients with diabetes is equivalent to that of people without diabetes who have suffered previous acute myocardial infarction (MI) (5).

Recent studies have shown that intensive glycemic control significantly improves microvascular complications in type 1 and type 2 diabetes, although to date glucose-lowering intervention studies have failed to demonstrate a marked effect on the incidence of cardiovascular events (6–9). However, in the U.K. Prospective Diabetes Study (UKPDS), the reduction in the risk of cardiovascular disease and decrease in total mortality, although less prominent than the improvements in microvascular disease, reached significance in a subgroup of overweight patients receiving metformin (6,10). The UKPDS also demonstrated the importance of reducing HbA_{1c}, which is a risk factor for vascular disease in patients with diabetes (6). Other risk factors that predispose to cardiovascular complications include: smoking, dyslipidemia (low HDL cholesterol and elevated plasma triglycerides), hypertension, and central obesity, all of which may be linked by insulin resistance (6,11,12).

Pioglitazone is a thiazolidinedione (TZD) approved for the treatment of type

2 diabetes. As a nuclear peroxisome proliferator–activated receptor-γ agonist, pioglitazone affects insulin resistance by increasing insulin sensitivity in the liver, muscle, and adipose tissue (13,14). Pioglitazone has proven glucose-lowering efficacy, as reflected by improvements in plasma glucose levels and HbA_{1c} (15–28). Insulin resistance is a major determinant of hyperglycemia. To overcome insulin resistance, the β-cell is forced to produce more insulin, with the consequent functional stress (29). Treatments that provide effective decreases in the workload of the β-cell and stabilize its function may improve its longevity (30). Accumulating evidence (for example, evaluations by homeostasis model assessment) also suggests that β-cell function may be preserved (30–34) with TZDs, thus the antihyperglycemic efficacy of pioglitazone or any other concomitant oral glucose-lowering agent could be prolonged.

Insulin resistance, together with hyperinsulinemia, plays a part in the pathogenesis of the metabolic syndrome, and hyperinsulinemia is an independent risk factor for cardiovascular disease (35,36). Agents that address the underlying pathology in the liver, muscle, and fat can also have an impact on markers of the metabolic syndrome. A number of studies suggest that pioglitazone confers clinical benefits beyond a glucose-lowering effect, such as improvements in dyslipidemia and atherosclerosis (22–28,37,38).

Type 2 diabetes is associated with dyslipidemia characterized by increased triglycerides and low levels of HDL cholesterol (39). Pioglitazone has been shown to improve specific lipid abnormalities commonly associated with insulin resistance. Treatment with pioglitazone significantly elevates HDL cholesterol levels, decreases triglyceride levels, and changes the size of LDL particles from small and dense to large and buoyant (less atherogenic) particles that are less susceptible to oxidation (22–27). Microalbuminuria is an independent risk factor for cardiovascular disease (40). Treatment with TZDs decreases microalbuminuria in patients with type 2 diabetes and as such may have a role in treating diabetic nephropathy (41–43).

Inflammation within the vascular wall is at the core of atherosclerosis and gives an indication of vascular risk. Studies (37,38,44–50) suggest that the development or progression of atherosclerotic disease in patients with type 2 diabetes may be modulated using TZDs by their ability to inhibit vascular smooth muscle cell proliferation and migration and to decrease vascular inflammation (as measured by C-reactive protein), carotid intima-media thickness (as measured by B-mode ultrasonography), and plasminogen activator inhibitor-1 levels, reflecting improved hemostatic function. Taken together, these findings suggest that pioglitazone has the potential to slow the progression of cardiovascular disease in addition to lowering glucose.

The PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) is one of a series of studies evaluating the effects of pioglitazone on the progression of atherosclerosis and testing the hypothesis that pioglitazone lowers the incidence of macrovascular complications in high-risk patients with type 2 diabetes. In this double-blind, placebo-controlled study, pioglitazone is used as "add-on" therapy to current treatment, which is to be continuously optimized throughout the trial to allow patients to receive the best possible therapy available. Further studies to compare the effects of pioglitazone on the progression of atherosclerosis include a study evaluating Carotid intima-media tHICkness in Atherosclerosis using pioGlitazOne (the CHICAGO study) and the Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation (PERISCOPE) study. The design and baseline data of PROactive are presented in this article.

RESEARCH DESIGN AND
METHODS — Male or female patients with type 2 diabetes, aged 35–75 years, were included in the study if they had an HbA_{1c} level above the upper limit of normal (i.e., local equivalent of 6.5% for a Diabetes Control and Complications Trial–traceable assay), despite management of diabetes with diet alone or with oral blood glucose-lowering agents. Patients currently using pioglitazone or any other TZD were excluded. Insulin was allowed only if previously given in combination with oral blood glucose–lowering agents. Patients are at increased risk of macrovascular disease as determined by the presence of one or more of the following criteria: MI or stroke at least 6 months before entry into the study, percutaneous coronary intervention or coronary artery bypass graft at least 6 months before study entry, acute coronary syndrome (defined as treatment in a hospital as a consequence of one or more episodes of ischemic discomfort at rest and characterized by electrocardiogram changes and/or elevation of a cardiac serum marker to an extent not indicative of MI) at least 3 months before study entry, objective evidence of coronary artery disease (defined as positive exercise test, angiography with at least one stenosis of >50%, or positive scintigraphy), or history of symptomatic peripheral arterial obstructive disease (as evidenced by current claudication, confirmed by an ankle [or toe] brachial pressure index <0.90 or an amputation).

The main exclusion criteria were any signs of type 1 diabetes (including any history of ketoacidosis or requirement for insulin therapy within 1 year of diagnosis); insulin as sole therapy for diabetes; planned revascularization; symptomatic heart failure (New York Heart Association class II or above); leg ulcers, gangrene, or pain at rest; hemodialysis; or significantly impaired hepatic function (defined as serum alanine aminotransferase >2.5 times the upper limit of normal).

PROactive is a randomized, double-blind, placebo-controlled outcome study. Pioglitazone or placebo is given as add-on therapy to existing diabetes management (including diet and exercise). The investigators are encouraged to maintain glycemia within the limits outlined in the International Diabetes Federation (IDF) Europe Guidelines (<6.5%) (51), which was highlighted and circulated to all investigators. Study medication is assigned using a central interactive voice-response system. During a forced-titration phase in the first 2 months of treatment, the pioglitazone dose is increased stepwise from 15 to 30 mg and then up to 45 mg, with the objective of maintaining patients on the maximum-tolerated dose. At any time during the study, the dose of pioglitazone can be increased or decreased within the 15- to 45-mg range, based on tolerability. Any other medication required (including non-TZD oral glucose-lowering agents) may be administered concomitantly. Throughout the study the investigators were encouraged to optimize all therapy according to the IDF Europe Guidelines, in particular lipid-lowering and antihypertensive therapy. Patients who discontinue the study medication are

followed until the end of the study. It is expected that the study will finish during the course of 2005.

Following randomization, patients attend visits after 1 and 2 months, then every 2 months for the first year and quarterly until the final visit. Vital signs and body weight are measured at each visit. Lipids, HbA$_{1c}$, creatinine, and liver tests are analyzed at a central laboratory. Blinded follow-up of all patients continues until both of the following targets are achieved: *1*) the last patient recruited has been followed for at least 30 months, and *2*) the number of patients with one or more end point events is at least 760.

Efficacy evaluations
A composite cardiovascular disease end point is used because the aim of the study is to evaluate the overall effects on macrovascular disease. The primary end point variable is the time from randomization to the first occurrence of any of the events in the following composite: all-cause mortality; nonfatal MI; acute coronary syndrome; cardiac intervention, including coronary artery bypass graft, or percutaneous coronary intervention; stroke; major leg amputation (above the ankle); bypass surgery; or revascularization in the leg. The end points are adjudicated by an independent panel. Secondary end points include the individual components of the primary end point and cardiovascular mortality.

Other measurements comprise cause of death, time to start of permanent insulin use, transient ischemic attack, treatment with retinal photocoagulation, carotid intervention, number of days of hospitalization for any cause, and use of antihypertensive, lipid-lowering, and blood glucose–lowering medications.

Safety evaluations
The incidence of serious and nonserious adverse events will be reported. Patients who present with ketoacidosis, elevated liver tests (alanine aminotransferase more than three times the upper limit of normal) on two consecutive occasions, or patients who become pregnant will be discontinued from study medication but will be followed until the end of the study.

Statistical considerations
The sample size calculation is based on the event rates in patients with diabetes, as published in major clinical trials. In the

Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT), ~32% of the diabetic population died from coronary heart disease or had a nonfatal MI or confirmed stroke over the 5.1-year follow-up (52), i.e., a rate of 7.3% per year. In a post hoc subgroup analysis of the Scandinavian Simvastatin Survival Study (4S), patients with diabetes were found to have an annual rate of death or major event from coronary heart disease of ~6% (53). Based on the assumption of an annual rate of 6% for macrovascular events in the placebo group and an average follow-up of 3 years, a minimum of 5,000 patients (2,500 per treatment group) are necessary in order to observe a minimum of 760 first events. This provides 91% power to detect a reduction of at least 20% in the primary end point event rate (by log-rank test).

Two interim analyses will be conducted by an Independent Statistical Center when ~50 and 75% of the target number of end point events are reached and then reported to the Data and Safety Monitoring Committee. This provides the opportunity to stop the study early if the benefits of pioglitazone are unambiguous. Each interim analysis will consider a one-sided log-rank test for the superiority of pioglitazone. All study outcomes will be analyzed on an intention-to-treat basis, defined as a patient having received at least one dose of study medication.

Study organization
An International Steering Committee is responsible for the overall design and conduct of the study. It comprises the National Principal Investigators and the Executive Committee for the daily management of the study. A Data and Safety Monitoring Committee reviews the outcome and safety data at regular intervals during the study, while end points are confirmed by an Endpoint Adjudication Panel and Committee.

The study protocol has been approved by local/national ethics committees and regulatory bodies, as appropriate. The study is carried out in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines.

RESULTS

Baseline characteristics
Demography. By the end of April 2002, a total of 5,238 patients were recruited in

Table 1—*Baseline characteristics of the PROactive study population and other clinical history (dependent on medical opinion of investigator)*

n	5,238
Demographic data	
Age (years)	61.8 ± 7.7
Male	3,463 (66.1)
Caucasian	5,162 (98.5)
Duration of type 2 diabetes (years)	9.5 ± 7.0
Physical examination measurements	
Weight (kg)	88.0 ± 15.6
BMI (kg/m^2)	30.9 ± 4.8
Waist circumference (cm)	105.3 ± 11.9
Systolic blood pressure (mmHg)	143.4 ± 17.8
Diastolic blood pressure (mmHg)	83.0 ± 9.7
Laboratory data	
Triglycerides (mmol/l)	2.24 ± 1.81
HDL cholesterol (mmol/l)	1.16 ± 0.31
LDL cholesterol (mmol/l)	2.96 ± 0.95
Creatinine (μmol/l)	82.55 ± 23.2
HbA$_{1c}$ (%)	8.08 ± 1.41
Other clinical history	
Angina	3,010 (57.5)
Claudication	1,239 (23.7)
Amputation	72 (1.4)
Transient ischemic attack	299 (5.7)
Retinopathy	1,214 (23.2)
Photocoagulation therapy*	345 (28.4)
Nephropathy	41 (14.2)
Neuropathy	1,340 (25.6)
Hypertension	3,952 (75.4)
Current/past smoking	722 (13.8)/ 2,358 (45.0)

Data are means ± SD and *n* (%). *Expressed as a percentage of patients with retinopathy.

321 centers from 19 European countries; enrollment was then closed. The majority of the patients enrolled in the study are male (66.1%). The mean age at the time of entry is 61.8 years, and the mean time since diagnosis of type 2 diabetes is 9.5 years (Table 1).

Entry criteria. All patients have a history of macrovascular complications: MI >6 months (46.7%), coronary artery revascularization (30.8%), acute coronary syndrome >3 months (13.7%), other objective evidence of coronary artery disease (48.1%), symptomatic peripheral arterial obstructive disease (19.9%), or stroke >6 months (18.8%). One-quarter (23.4%) of patients have two and another quarter (25.1%) has three or more of these risk factors (Table 2).

Other patient history. Based on the actual reading of blood pressure at baseline

Table 2—Entry criteria and proportion of patients at high risk as determined by IDF risk assessment guidelines

Entry criteria	
MI	2,445 (46.7)
Acute coronary syndrome	715 (13.7)
Other evidence of CAD	2,521 (48.1)
Percutaneous coronary intervention/coronary artery bypass graft	1,613 (30.8)
Peripheral arterial obstructive disease	1,041 (19.9)
Stroke	985 (18.8)
Patients meeting one entry criterion	2,654 (51.5)
Patients meeting two entry criteria	1,204 (23.4)
Patients meeting more than three entry criteria	1,296 (25.1)
Proportion of patients at high risk	
Triglycerides	1,858 (36.0)
HDL cholesterol	1,679 (32.6)
LDL cholesterol	714 (13.9)
Combined blood pressure*	3,727 (71.2)
Systolic blood pressure	3,405 (65.0)
Diastolic blood pressure	2,279 (43.5)

Data are n (%). *Combined blood pressure "high risk" is defined as systolic blood pressure at "high risk" (≥140 mmHg) and/or diastolic blood pressure at "high risk" (≥85 mmHg).

and the IDF definition of risk assessments (systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥85 mmHg) (49), 71.2% are at high vascular risk, despite an extensive use of antihypertensive drugs (Table 1 and Table 2). In addition, 14.2% of patients have a history of nephropathy.

Physical examination and laboratory data. The mean HbA_{1c} is high (8.1%), although nearly all patients are taking glucose-lowering drugs (95.9%), most frequently a sulfonylurea and/or metformin (Table 3). Insulin is combined with oral glucose-lowering medications in 33.6% of the cases, with a mean daily dose of 46.6 units, 2.3 injections per day. Only 4.1% of patients were managed with diet alone at entry into the study.

The mean BMI is 30.9 kg/m², and the majority of patients present with central obesity, as shown by a mean waist circumference of 107 cm in men and 103 cm in women. Almost half (44.5%) of the patients presented with albuminuria (positive Micral test [≥20 mg/l]), and 13.8% are smokers.

One-third of the patients are at high vascular risk based on HDL cholesterol levels (32.6%) or based on triglycerides (36.0%) (defined using IDF Europe criteria) (51) (Table 2). Two-thirds of patients are at risk based on raised systolic and/or raised diastolic pressure.

Concomitant medication. Half of the patients are taking lipid-lowering medication (51.6%), with the majority on statins (42.9% of all patients). Nearly all patients (95.0%) are taking cardiovascular medications, with ACE inhibitors (62.7%), β-blockers (54.6%), nitrates (39.3%), and calcium channel blockers (35.4%) as the most common. Eighty-three percent of patients are receiving antiplatelet medications, most commonly acetylsalicylic acid (Table 3).

CONCLUSIONS — Macrovascular mortality and morbidity are the biggest risks for patients with diabetes, and type 2 diabetes is associated with a two- to fourfold increased risk of coronary heart disease. Other cardiovascular risk factors, such as dyslipidemia and hypertension, are also often present in patients with type 2 diabetes. Type 2 diabetes itself is now considered as an independent coronary heart disease risk factor (54).

The Multiple Risk Factor Intervention Trial (MRFIT) provided evidence that tight control of hypertension, cholesterol, and smoking reduced cardiovascular mortality in patients with type 2 diabetes (55). In the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study, the benefit of intervention with antiplatelet medication was greater in patients with peripheral vascular disease than in those with coronary or cerebral disease (56). Previous studies examining the impact of the management of dyslipidemia and hypertension have shown beneficial effects on the reduction of cardiovascular events in patients with type 2 diabetes (52,53,57–61). The UKPDS demonstrated that intensive glycemic control of type 2 diabetes aids in reducing all microvascular complications—for every 1% decrease in HbA_{1c} there was an associated 37% reduction in microvascular complications (9). However, to date there is no conclusive evidence that intervention with conventional glucose-lowering agents is successful in modifying macrovascular disease.

Pioglitazone is known to improve glycemic control and also to possess additional properties that may have an impact on clinical vascular outcomes. It is conceivable that these characteristics are related to its ability to reduce insulin resistance and the associated disorders. Studies of nonhypoglycemic effects of pioglitazone have shown improvements in several cardiovascular risk factors, including modification of lipids and independent predictors of coronary heart disease (e.g., microalbuminuria and plasminogen activator inhibitor-1) and reductions in carotid intima-media thickness that could result in decreased morbidity for macrovascular disease (22–28,37,38).

PROactive is designed to investigate whether the addition of pioglitazone to patients' usual medications for glycemic, lipidemic, and hypertensive management will reduce total mortality and macrovascular morbidity in high-risk patients. In addition, it assesses treatment effects on individual risk factors for vascular complications in type 2 diabetes. Optimization of the management of lipids, glycemia, and blood pressure is highly recommended to give patients the best possible available management.

Baseline data presented here show

Table 3—Concomitant medications

Blood glucose–lowering medications	
Any medication	5,024 (95.9)
Sulfonylurea alone	1,000 (19.1)
Metformin alone	515 (9.9)
Metformin plus sulfonylurea	1,294 (24.7)
Insulin (in combination with oral agents)	1,760 (33.6)
Other antidiabetic agents (alone or in combination)	611 (11.7)
Lipid-lowering medications	2,703 (51.6)
Statins alone	2,135 (40.8)
Fibrates alone	448 (8.6)
Statins plus fibrates	110 (2.1)
Cardiovascular medications	4,974 (95.0)
ACE inhibitors	3,286 (62.7)
β-Blockers	2,859 (54.6)
Calcium channel blockers	1,855 (35.4)
Nitrates	2,058 (39.3)
Angiotensin II antagonists	356 (6.8)
α-Blockers	310 (5.9)
Thiazide diuretics	830 (15.8)
Potassium-sparing diuretics	336 (6.4)
Loop diuretics	748 (14.3)
Cardiac glycosides	255 (4.9)
Antiarrhythmics	112 (2.1)
Antiplatelet medications	4,394 (83.9)
Acetylsalicylic acid	3,829 (73.1)
Ticlopidine/clopidogrel	240 (4.6)
Oral anticoagulants	362 (6.9)

Data are n (%).

that the cohort enrolled in PROactive is at high risk of macrovascular events. Risk assessment of lipids, HbA$_{1c}$, and blood pressure confirms that PROactive has enrolled the planned target high-risk population. Investigators are encouraged to give an appropriate recommended treatment for these high-risk patients. Looking at concomitant therapy at baseline, 43% of patients are also taking statins, 84% are on antiplatelet therapies, and almost all patients are receiving cardiovascular medications. Changes in lipid-lowering agent use will be analyzed.

The results of PROactive and additional information from the CHICAGO and PERISCOPE studies on the effects of pioglitazone on atherosclerosis should provide important information to help to clarify pioglitazone's ability to reduce macrovascular mortality and morbidity in this high-risk patient population and could provide the first data on the modification of macrovascular disease in type 2 diabetes by a glucose-lowering agent.

APPENDIX

The PROactive Study Group

Study committees
Executive Committee. J. Dormandy, Chairman (U.K.); B. Charbonnel (France); D. Eckland (U.K.); E. Erdmann (Germany); M. Massi-Benedetti (Italy); I. Moules (U.K.); A. Skene (U.K.); and M. Tan (U.S.).
Data and Safety Monitoring Committee. P. Lefèbvre, Chairman (Belgium); G. Murray (U.K.); E. Standl (Germany); R. Wilcox (U.K.); and L. Wilhelmsen (Sweden).
Endpoint Adjudication Committee M.G. Brousser (France), P. Brunetti (Italy), L. Norgren (Sweden), and D. Thomas (France).
International Steering Committee. J. Betteridge (U.K.), K. Birkeland (Norway), B. Charbonnel (France), A. Golay (Switzerland), R.J. Heine (Netherlands), L. Koranyi (Hungary), M. Laakso (Finland), M. Massi-Benedetti (Italy), M. Mokán (Slovakia), A. Norkus (Lithuania), V. Pirags (Latvia), T. Podar (Estonia), A.

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Operations Committee. G. Belcher (U.K.), L. Bennett (U.K.), J. Dormandy (U.K.), A. Kempton (U.K.), J. Kinley (U.K.), E. Löschel (U.K.), I. Moules (U.K.), H. Thomas (U.K.), and R. Urquhart (U.K.).

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