Peer reviewed article

Cost-effectiveness of pioglitazone in patients with type 2 diabetes and a history of macrovascular disease in a Swiss setting

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Summary

Objectives: To evaluate the cost-effectiveness of pioglitazone versus placebo, given in addition to existing treatment regimens, in patients with type 2 diabetes and evidence of macrovascular disease in Switzerland.

Methods: Event rates corresponding to macrovascular outcomes from the PROactive (Prospective Pioglitazone Clinical Trial in Macrovascular Events) trial of pioglitazone were used to project long-term clinical outcomes as part of a modified version of the previously validated CORE Diabetes Model. Direct medical costs associated with treatment regimens, complications and patient management were accounted in 2005 values based on Swiss-specific unit costs. Time horizon was set to lifetime (35 years). Future costs and clinical benefits were discounted at 2.5% annually in line with Swiss recommendations. One-way sensitivity analyses were performed.

Results: Addition of pioglitazone was associated with a reduced incidence of most diabetes-related complications, improved life expectancy (0.258 years) and improved quality-adjusted life expectancy (0.180 QALYs) compared with placebo. Pioglitazone treatment increased direct costs by CHF 10,914 per patient over a lifetime horizon. The incremental cost-effectiveness ratio (ICER) of pioglitazone versus placebo was CHF 42,274 per life-year gained and CHF 60,596 per QALY gained. ICERs were sensitive to variation in time horizon and duration of pioglitazone treatment effects. With a willingness to pay of CHF 80,000 per QALY in the Swiss setting, there was a 62.5% chance that pioglitazone would be cost-effective.

Conclusions: Addition of pioglitazone to existing therapy was projected to reduce the long-term cumulative incidence of most diabetes complications and improve quality-adjusted life expectancy. Evaluation of incremental direct medical costs associated with these clinical benefits indicated that pioglitazone is likely to be a cost-effective treatment option in the Swiss setting over patient lifetimes.

Key words: type 2 diabetes; pioglitazone; PRO active; Switzerland; cost-effectiveness; macrovascular events

Introduction

The central aim of diabetes treatment is the prevention or delay of onset and/or progression of microvascular and macrovascular complications. It is well established that in patients with type 2 diabetes improved glycaemic control was associated with significant reductions in diabetes-related complications [1]. Based on these findings, most diabetes organisations, including those in Switzerland, currently recommend a target HbA1c of 7.0% or less for patients with type 2 diabetes [2–5].

Although the benefits of tight glycaemic control in terms of reducing microvascular complications are well established, the impact of good glycaemic control on macrovascular endpoints initially appeared less marked [1]. However, more recent data from the UKPDS (UKPDS 80) has now demonstrated a significant reduction in myocardial infarction events in patients receiving tight glycaemic control compared to those receiving standard care [6]. Multi-factorial therapeutic strategies that include improving lipid and blood

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pressure levels in addition to glycaemic control have a greater impact on macrovascular events than concentrating solely on normoglycaemia [7–9].

The PROspective pioglitAzone Clinical Trial in macroVascular Events (PROactive) was one of the few large scale outcomes studies to investigate prospectively the effect of an oral glucose-lowering drug (pioglitazone) on macrovascular outcomes [10]. Pioglitazone is a member of the thiazolidinedione class of antidiabetic medications and has blood glucose lowering properties. In addition to positive effects on glycaemic control, pioglitazone also has the potential to improve lipid abnormalities [11]. The PROactive study enrolled 5,238 patients with type 2 diabetes and evidence of macrovascular disease [12, 13]. Patients were randomly allocated to receive either pioglitazone or placebo in addition to their usual treatment regimen in line with the International Diabetes Federation (IDF) European region 1999 guidelines for diabetes care [14]. By the end of PROactive (36 months of follow-up), HbA1c was reduced by –0.9% (versus –0.3% with placebo), HDL-cholesterol increased by 0.54 mmol/l (versus 0.3 mmol/l) and triglycerides decreased by –0.064 mmol/l (versus an increase by 0.076 mmol/l for placebo) with pioglitazone treatment. There was a non-significant 10% relative risk reduction (RRR) with pioglitazone in the primary endpoint (P = 0.09), which was a composite of all cause mortality, non-fatal myocardial infarction (NFMI) (including silent MI), stroke, acute coronary syndrome (ACS), endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle. Pioglitazone was also associated with a significant RRR of 16% (P = 0.02) in the principal secondary endpoint of time to first event of death from any cause, MI (excluding silent MI) and stroke. Pioglitazone also reduced the number of patients progressing to long-term insulin therapy by approximately 50%. Taken together these findings demonstrate that improved glycaemic and lipid control associated with pioglitazone treatment lead to a reduced incidence of macrovascular events.

An estimated 250,000 individuals in Switzerland have diagnosed type 2 diabetes [15]. Recent surveys indicate that many of these patients are inadequately controlled with respect to glycaemia and lipid levels, and estimate that approximately 25% of patients have at least one macrovascular complication [15, 16]. In the Swiss setting the annual cost per patient with at least one macrovascular complication was reportedly three times more than that corresponding to patients without complications (CHF 5050 versus CHF 1723 per year) [15]. Therefore, in the Swiss setting the addition of pioglitazone to current treatment regimens may be beneficial in clinical terms and subsequently in economic terms, due to the avoidance of future costly macrovascular events and improved quality of life. To investigate this hypothesis, a published and validated model of type 2 diabetes was adapted to incorporate clinical data from PROactive to estimate the impact of treatment on life expectancy, quality-adjusted life expectancy and incidence of macrovascular events, and to account for direct medical costs over patient lifetimes in a Swiss setting.

Methods

PROactive

The PROactive study was a prospective, randomised, double-blind, placebo-controlled trial conducted in 19 European countries (321 centres) [10]. Designed to test the hypothesis that pioglitazone used as an 'add on' therapy would lower the incidence of macrovascular events in patients with type 2 diabetes and a history of macrovascular events, PROactive was the first adequately powered study to look at the secondary prevention of macrovascular events. In total 5238 patients were enrolled and the average length of follow-up was 36 months.

At study end there was a non-significant 10% relative risk reduction (RRR) with pioglitazone in a composite of all cause mortality, non-fatal MI (including silent MI), stroke, ACS, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle. Pioglitazone was also associated with a significant RRR of 16% in time to first event of death from any cause, MI (excluding silent MI) and stroke.

Model description and statistical approach

The important short-term clinical effects of the pioglitazone and placebo treatment regimens from PROactive were used to project long-term outcomes using a modified version of the validated and peer-reviewed CORE Diabetes Model (CDM) [17, 18]. The CORE Diabetes Model is a computer simulation model developed to determine the long-term health outcomes and economic consequences of interventions in type 1 and type 2 diabetes. Disease progression is based on 15 interdependent semi-Markov sub-models that simulate progression of disease-related complications (angina, MI, congestive heart failure, stroke, peripheral vascular disease, diabetic retinopathy, macula oedema, cataract, hypoglycaemia, ketoacidosis, lactic acidosis, nephropathy and end-stage renal disease, neuropathy, foot ulcer, amputation and non-specific mortality). Each sub-model uses time, state and diabetes type-dependent probabilities derived from published sources. The reliability of simulated outcomes has been tested, with results extensively validated in 66 separate analyses against outcomes reported by clinical trials and epidemiological studies [18]. In addition to this the CDM was presented at the Fourth Mt. Hood challenge where it compared favourably with a number of currently available diabetes simulation models [19].

Data from PROactive was used as a basis for long-term projections using the CORE Diabetes Model adapted to include clinical data from PROactive [20]. Whilst a brief overview of the modified model used in the current analysis is provided here and in the accompanying

appendix (see Appendix, fig. 3), we recommend that the interested reader refer to the detailed account of the model provided in the publication of Valentine et al. [20]. In short, a total of 15 complication-related sub-models were included in the final PROactive long-term simulation model.

For the sub-models of acute coronary syndrome, myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, bypass surgery/revascularization of the leg, hospital admission for heart failure, non-serious heart failure, oedema, transient ischaemic attack, stroke, photocoagulation and severe vision loss, event rates were taken directly from PROactive. Event rates in the placebo arm were calculated directly from the annual hazard rates observed over months 0–36 of PROactive assuming constant risk (see Appendix, table 6) [20]. Hazard ratios were then applied to the event rates from the placebo arm in line with the relative risk observed for each event during PROactive to calculate event rates in the pioglitazone treatment arm. The remaining sub-models of cataract, nephropathy and end-stage renal disease, neuropathy, peripheral vascular disease, diabetic foot and amputation, were as presented in the original CDM and therefore based on transition probabilities drawn from published studies including UKPDS to simulate complication progression.

All-cause and cardiovascular mortality rates were derived from PROactive for years 1–3, with rates subsequently doubling every 10 years [21]. Event rates for following years were calculated by applying relative risk adjustments [22–26] for each additional life-year gained (*i.e.* as the patient gets older, his/her risk of experiencing an event increases). In all sub-models, the occurrence of events resulted in the accrual of event costs and, where applicable, subsequent state costs as well as assignment of the appropriate disutility values.

For the base case simulation, the clinical effects associated with the pioglitazone and placebo treatment regimens were applied as observed during PROactive for acute coronary syndrome, myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, bypass surgery/revascularisation of the leg, hospital admission for heart failure, non-serious heart failure, oedema, transient ischaemic attack, stroke, photocoagulation and severe vision loss. In those sub-models it was assumed that the treatment-related changes in HbA1c, lipids and blood pressure were reflected in the observed event rates. For those complication sub-models not based on PROactive it was necessary to apply the treatment associated effects on HbA1c, lipids and blood pressure to simulate the impact of this on future events. Treatment effects on HbA1c were applied separately in simulation years 1, 2 and 3, and in subsequent years, based on the findings from PROactive, the UKPDS and Framingham (for long-term projection). Changes in HbA1c and other parameters for pioglitazone and placebo regimens were applied as summarised in table 1. The long-term progression of all of these clinical parameters subsequently followed the patterns previously described by Palmer *et al.* in their description of the CORE Diabetes Model [17].

The health economic analysis was performed using a non-parametric bootstrapping approach in which the progression of diabetes was simulated in 1000 patients through the model 1000 times to calculate the mean and standard deviation of costs, life expectancy and quality-adjusted life expectancy using second order Monte Carlo simulation [27]. The model estimated the impact of treatment on life expectancy, quality-adjusted life expectancy (based on CODE-2 utilities, and assuming a baseline utility score of 0.814 for diabetes without complications), diabetes-related complications (cumulative event rates), direct medical costs and cost-effectiveness ratios over patient lifetimes, in line with specifications for health economic evaluations [28]. Mean results from each of the 1000 iterations were used to create a scatter plot, comparing the differences in costs and effects for pioglitazone and placebo treatment regimens. These values were in turn used to generate a cost-effectiveness acceptability curve over a range of willingness to pay values in the Swiss setting.

Table 1

Summary of base case intervention effects.

Effect	Mean change from baseline	
	Pioglitazone	Placebo
Change in HbA1c in year 1 (%-points)	–0.9	–0.3
Change in HbA1c in year 2 (%-points)	+0.1	+0.1
Change in HbA1c in year 3 (%-points)	+0.3	+0.2
Change in subsequent years (% points)	+0.15	+0.15
Total cholesterol (mmol/l)	+0.90	+0.57
HDL-C (mmol/l)	+0.54	+0.30
LDL-C (mmol/l)	+0.35	+0.22
Triglycerides (mmol/l)	–0.064	+0.076
Systolic blood pressure (mmHg)	–3.8	–2.4
BMI ($kg.m^{-2}$)	+1.1	–0.1
Hypoglycemic event rate (per 100 patient years)	+9.29	+6.68

HDL-C = high density lipoprotein cholesterol;
LDL-C = low density lipoprotein cholesterol;
BMI = body mass index. Long-term progression (beyond 4 years) follows patterns described in Scuffham and Chaplin [42]

Simulation cohorts

A cohort of patients was defined with baseline demographics, complications, and important concomitant medications representative of the two treatment arms from PROactive. Long-term outcomes were calculated 1000 times in the model using a simulated population of 1000 patients to capture the effects of random variation between individual simulated patients. At baseline 66.1% of the cohort was male with a mean age of 61.8 years, duration of diabetes 10 years, and a mean HbA1c level of 8.1% (see Appendix, table 7 for more detail). For the purposes of this analysis patients were assumed to remain on the same treatment regimen for the duration of the simulation (35 years or death).

The proportion of patients receiving angiotensin converting enzyme inhibitors (ACE inhibitors) in the simulation cohort was set to 62.8% based on data from PROactive. This has an important influence on renal outcomes and it is relevant to note here that a survey of Swiss patients reported a similar rate of ACE inhibitor use, with 59% of patients reporting treatment with this class of antihypertensive agent [16]. Also in line with data from PROactive 42.9% of the simulation cohort were assigned to use of statins and 73.1% use of aspirin at baseline. Risk adjustment for the use of aspirin or statins was disabled in the analysis as the influence of these agents was already taken into account, along with the impact of ACE inhibitors, in the cardiovascular event rates taken from PROactive. Other settings for patient management parameters (e.g. screening for renal disease and foot ulcer prevention programs) were set in line with the standard of care patients in the PROactive study were receiving, with all patients receiving regular screening and foot checkups.

Costs

Direct medical costs were expressed in 2005 Swiss Francs (CHF). Swiss unit costs were retrieved from published sources (table 2) and those not expressed in 2005 CHF were inflated using indices from the Swiss Statistical Yearbook 2006, published by the Swiss Federal Statistical Office. Where Swiss costs could not be identified no costs were accounted (table 2). Direct medical costs were calculated as the sum of drug acquisition costs (based on data from PROactive), patient management costs and the cost of complications. The annual costs of study medication were accounted based on a mean annual cost of CHF 1153.03 per patient for pioglitazone (taken directly from PROactive data and corresponding to daily costs of CHF 2.35, 3.12 and 3.71 for treatment with 15 mg, 30 mg and 45 mg per day) and zero for placebo.

Discounting, time horizon and perspective

A lifetime horizon of 35 years was used in the analysis to capture all relevant long-term complications, their associated costs and impact on life expectancy. Discounting was applied to costs, life expectancy and quality-adjusted life expectancy at an annual rate of 2.5% in line with current recommendations for the Swiss setting [29]. The analysis was conducted from a healthcare payer perspective in Switzerland.

Sensitivity analyses

One-way sensitivity analyses were performed to investigate the impact of varying key parameters on the base case incremental cost-effectiveness ratio (ICER). The impact of time horizon was investigated by reporting ICERs at 5, 10 and 20 years. Similarly the impact of discounting was assessed by using alternative discount rates between zero and 5%. To investigate the potential impact of pioglitazone-associated improvement in beta-cell function, a sensitivity analysis was performed where the HbA1c creep of 0.15% annually in years 4+ of the simulation was reduced to 0.1%. The influence of risk adjustment for age on the event rates taken from PROactive was investigated by performing an analysis where no risk adjustment for age was applied during the simulation (risk adjustment factors all set to 1).

In the base case it was assumed that the pioglitazone related treatment effects were maintained over patient lifetimes. The validity of this assumption was investigated by limiting treatment effect to a period of only five years, and thereafter both treatment arms followed the clinical progression based on event rates from the placebo arm of PROactive. For the base case analysis input parameters were based on the corresponding mean reported from the RCT. To investigate the impact of uncertainty surrounding input parameters probabilistic sensitivity analy-

Table 2

Cost per event or state used in the analysis, expressed in 2005 Swiss Francs (CHF).

	Event cost (CHF)	Follow up cost (CHF)	Reference(s)
Death (all causes)	4,029.38	0.00	(43)
CVD death	4,029.38	0.00	Assumed to be the same as all-cause mortality (43)
MI (excluding silent MI)	14,174.93	2,424.70	(44)
Silent MI	0.00	0.00	Assumed
Acute coronary syndrome (ACS)	9,780.03	2,424.70	(44)
CABG only	16,618.13	2,424.70	(44)
PCI only	7,442.74	2,424.70	(44)
Stroke	33,154.01	2,424.70	(44)
Leg amputation (major, above ankle)	33,502.66	0.00	(45)
Bypass surgery/revascularization of leg	9,484.91	2,424.70	(44)
Transient ischemic attack (TIA)	6,240.98	0.00	(46, 47)
Retinal photocoagulation	564.24	0.00	(48) No follow up costs found so assumed to be zero
Severe vision loss (SVL)	0.00	0.00	No published data available*
Hospitalization for CHF	21,436.68	2,424.70	(44)
Non-serious heart failure	35.95	0.00	Assumed cost of physician visit. Calculated as TARMED 00.051 assumed 10 min + 00.1550 assumed 15 min (48)
Edema	35.95	0.00	Assumed cost of physician visit. Calculated as TARMED 00.051 assumed 10 min + 00.1550 assumed 15 min (48)
Peripheral vascular disease (onset)	0.00	0.00	No published data available*
Hemodialysis	81,226.65	81,226.65	(49)
Peritoneal dialysis	42,195.66	42,195.66	(49)
Kidney transplant	97,768.11	25,728.45	Personal communication: flat rates include hospitalization, transplantation and re-hospitalization <7 days (50)
Cataract extraction	1,228.02	0.00	(48)
Neuropathy, onset	0.00	0.00	No published data available*
Uninfected ulcer	2,013.78	182.50	(45)
Infected ulcer	5,211.38	182.50	(45)
Gangrene	6,114.33	0.00	(45)
Major hypoglycemic event	645.03	0.00	(51)

* Where Swiss costs could not be identified no costs were accounted

sis was performed, outcomes were projected with sampling from the distributions defined by the mean and standard deviation of patient age, HbA1c, duration of diabetes, SBP, BMI, individual lipid fractions and treatment effects observed in the RCT from which data was taken for the base case analysis.

In the base case scenario, quality-adjusted life expectancy was calculated using a published formula and utility scores from the CODE-2 study [30]. Whilst this approach ensures a robust estimation of QALYs in the base case analysis (through preservation of the integrity of the CODE-2 formula), a potential limitation of this approach is that it fails to take into account utilities associated with a number of the endpoints reported in PROactive and captured in the present modelling analysis (e.g. heart failure, oedema and myocardial infarction). To investigate the influence of including quality of life disutilities that were not included in the CODE-2 formula, a number of sensitivity analyses were run to include additional quality of life disutilities. In brief, this involved repeating the base case analysis using the CORE default method of quality-adjusted life expectancy estimation [17], applying an event disutility of –0.01 for oedema and a follow up disutility of 0 (as the condition is typically short-lived), applying an event disutility to hospitalisation for heart failure of –0.121 and a follow-up disutility of –0.181, based on the UKPDS [31], or applying an event disutility of –0.0605 for non-serious heart failure and a follow-up disutility of 0. Utility values for oedema and non-hospitalised heart failure were based on assumptions.

Results

Clinical outcomes

Based on clinical findings for PROactive, long-term projections with a modified version of the CORE Diabetes Model indicated that treatment with pioglitazone was associated with improvements in life expectancy and quality-adjusted life expectancy (expressed in quality-adjusted life years, QALYs) compared to placebo. Mean life expectancy increased by 0.258 years with pioglitazone and after adjustment for quality of life an improvement of 0.180 QALYs was projected versus placebo (table 3). When the discount rate was set to zero (no discounting), mean life expectancy in the pioglitazone treatment arm was 0.406 years longer than in the placebo arm.

Estimation of long-term complication rates demonstrated that, over patient lifetimes, the pioglitazone treatment regimen was associated with a reduced number of events versus placebo for most diabetes-related outcomes, including MI, TIA, stroke, PCI, ACS and CABG. Exceptions to this were projected for heart failure, oedema and leg revascularisation where pioglitazone was associated with increased cumulative events versus placebo.

Lifetime costs and cost-effectiveness

Over patient lifetimes, treatment with pioglitazone was associated with higher direct medical costs than the placebo regimen (table 3). Direct costs increased by CHF 10 914 with pioglitazone compared to placebo. This increase was largely due to increased drug acquisition costs (CHF 63 813 versus CHF 55 633). Complication-related costs were slightly higher in the pioglitazone arm (difference CHF 2734) due mainly to the increase in hospitalisation for heart failure (difference CHF 5680) and longer life expectancy (resulting in patients being exposed to the risk of complications for a longer period). Treatment with pioglitazone was associated with a reduced cost for stroke events by CHF 2953 per patient, for MI events (CHF 901), ACS (CHF 956) and PCI and CABG (CHF 1226) compared to placebo.

Estimation of incremental cost-effectiveness ratios (ICER) for pioglitazone versus placebo treatment produced values of CHF 42 274 per life year gained and, taking quality of life into account, CHF 60 596 per QALY gained (table 3). The values from the 1000 means (each from 1000 patients) of incremental costs and incremental effectiveness (in terms of quality-adjusted life ex-

Table 3

Summary of base case results for pioglitazone versus placebo.

Outcome	Pioglitazone	Placebo	Difference (PIO – PLA)
Clinical outcomes			
Life expectancy (years)	12.592 (0.200)	12.333 (0.196)	0.258
Quality-adjusted life expectancy (QALYs)	9.329 (0.142)	9.149 (0.141)	0.180
Cost outcomes			
Total direct costs (CHF)	229,308 (6,295)	218,394 (5,956)	10,914
Incremental cost-effectiveness based on life expectancy		CHF 42,274 per life year gained	
Incremental cost-effectiveness based on quality-adjusted life expectancy		CHF 60,596 per QALY gained	

Values shown are means with standard deviation in parentheses; QALY = quality-adjusted life-years; ICER = incremental cost-effectiveness ratio. Incremental values are given as the pioglitazone value minus the placebo value.

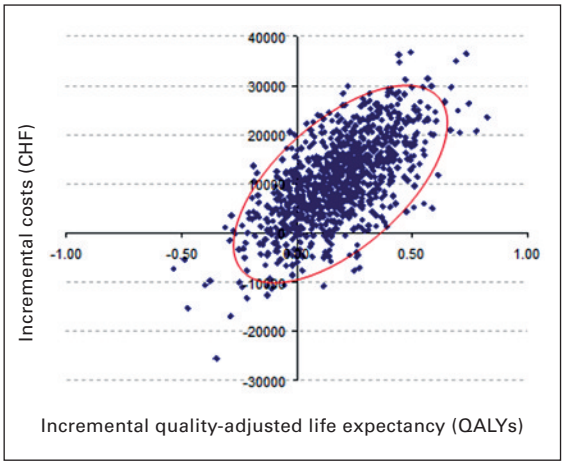

Figure 1

Scatter plot of incremental costs and incremental effectiveness for pioglitazone versus placebo.

The red ellipse indicates a 95% confidence interval.

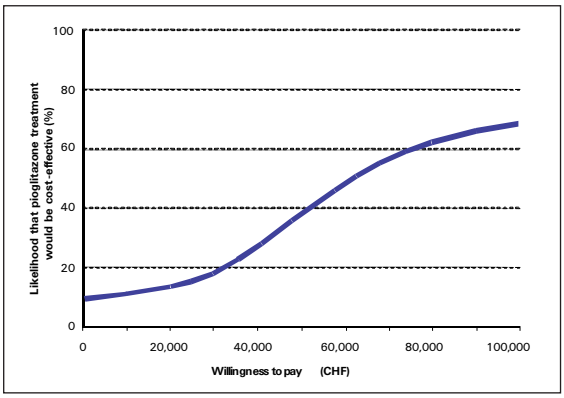

Figure 2

Cost-effectiveness acceptability curve for pioglitazone versus placebo.

pectancy) were used to generate a scatter plot on the cost-effectiveness plane (fig. 1). This analysis shows that the majority of points were in the upper right quadrant of the plane, indicating increased effectiveness and increased costs associated with pioglitazone treatment over placebo. These values were then used to create a cost-effectiveness acceptability curve, by assessing what proportion of values fell below set willingness to pay values (fig. 2). The analysis demonstrated that, with a willingness to pay of CHF 80 000 per QALY in the Swiss setting, there was a 62.5% chance that pioglitazone would be cost-effective. Assuming a willingness to pay of CHF 61,000 (€ 40 000) per QALY, in line with the threshold applied in a recently published analysis of drug-eluting stents in the Swiss setting (2004 costs), there was a 54% chance that pioglitazone would be cost-effective.

Sensitivity analyses

Sensitivity analysis demonstrated the results were most sensitive to variation in the time horizon and assumptions on the duration of the benefits of pioglitazone treatment seen in the trial (table 4). Shorter time horizons were associated with increased ICERs compared to the base case because development of many long-term complications was not captured. Many of the clinical and subsequent economic benefits, such as reduced rates and costs of nephropathy and macrovascular complications, associated with improved HbA1c levels in patients on pioglitazone, are more likely to occur at later stages beyond the 10-year time horizon.

Where the effect of pioglitazone treatment on CVD risk was applied for the first five years of the simulation only, life expectancy and quality-adjusted life expectancy were reduced for pioglitazone treatment in the sensitivity analysis compared to the base case. Total costs were largely unchanged which produced an ICER of CHF 439 313 per QALY gained for pioglitazone versus placebo. Addition of various disutility values not included in the base case analysis and probabilistic sensitivity analysis to investigate the impact of uncertainty surrounding patient- and treatment effect-related input variables had little effect on the overall findings of the analysis.

Reducing the annual HbA1c creep from 0.15% to a value of 0.1% to simulate a pioglitazone associated delay in β-cell deterioration improved projected QALE and reduced direct costs resulting in an ICER of CHF 33 845 per QALY gained compared to the base case value of CHF 60 596 per QALY gained.

Discussion

In Switzerland it is estimated that approximately 25% of patients with type 2 diabetes have a history of macrovascular events, and therefore in common with patients from PROactive these patients are at an increased risk for future cardiovascular events compared to most Swiss patients with diabetes. The findings of this long-term analysis of the cost-effectiveness of pioglitazone versus placebo treatment arms from PROactive indicate that the pioglitazone regimen would be associated with an ICER of approximately CHF 42 274 per life year gained and CHF 60 596 per QALY gained over patients' lifetimes for those with a history of macrovascular events. In the base case analysis, treatment with pioglitazone was associated with improvements in life expectancy of 0.258 years and quality-adjusted life expectancy of 0.180 QALYs, and higher direct medical costs (CHF 10 914) over patient lifetimes. Cost-effectiveness acceptability curve analysis indicated that there would be a 62.5% likelihood that pioglitazone would be cost-effective with a willingness to pay threshold of CHF 80 000 per QALY gained. In line with a recent Swiss based analysis of the cost-effectiveness of drug-eluting stents, a willingness to pay threshold of CHF 61 000 (€ 40 000) per QALY was also examined, and under this assumption the likelihood that pioglitazone would be cost-effective was approximately 54%. Whilst we acknowledge that these represent arbitrary willingness to pay thresholds, to our knowledge a defined threshold has not been an-

nounced for the Swiss setting. Indeed, in many countries the definition of willingness-to-pay thresholds has become a controversial issue, with some rejecting or limiting the use of this in decision-making, whilst in others such as the UK there has been a call for both increases and decreases of the currently defined threshold by different sectors of the health care industry [33].

Recently a similar analysis of pioglitazone in the UK setting was published where the ICER of pioglitazone versus placebo was £ 5396 (approximately CHF 13 274) per QALY gained [20]. The difference in results between these settings was largely due to differences in cost structure, for example the daily cost of treatment with 30 mg pioglitazone was CHF 3.12 in the Swiss setting versus CHF 2.85 (£ 1.19) in the UK, whilst the cost of hospitalisation for MI was CHF 14 174.93 versus CHF 15 027.85 (£ 6219.03) and for haemodialysis CHF 81 226.65 versus CHF 63 003.60 (£ 26 073) in the Swiss and UK settings respectively. These differences in costs and projected outcomes emphasise the importance of conducting country-specific health economic evaluations that take these differences into consideration [34–36].

There have been two major cost-effectiveness analyses in the treatment of patients with type 2 diabetes published in recent years. In 2008, Gaede et al. published a long-term cost-effectiveness of intensive multifactorial intervention versus conventional therapy based on data from the STENO Diabetes Centre in Denmark [37]. In this population with inadequate glycaemic control and microalbuminuria at baseline, long-term projections with a bespoke, trial-based model indicated that intensive therapy was associated with a an ICER of € 2538 per QALY gained from a Danish healthcare payer perspective. In 2001, the UKPDS group reported an analysis designed to estimate the cost-effectiveness of intensive blood-glucose control with metformin compared with conventional therapy (primarily diet) in newly-diagnosed overweight patients with type 2 diabetes [38]. This analysis showed that the metformin intervention was dominant to conventional therapy

Table 4

Summary of sensitivity analysis results for pioglitazone versus placebo.

Sensitivity analysis	Quality-adjusted life expectancy (QALYs)			Lifetime direct costs (CHF)			ICER (CHF per QALY gained)
	Pioglitazone	Placebo	Difference	Pioglitazone	Placebo	Difference	
Base case	9.329 (0.142)	9.149 (0.141)	0.180	229,308 (6,295)	218,394 (5,956)	10,914	60,596
5 year time horizon	3.446 (0.027)	3.442 (0.027)	0.004	48,946 (953)	46,156 (931)	2,791	734,031
10 year time horizon	5.908 (0.061)	5.878 (0.059)	0.030	97,705 (2,033)	93,044 (1,846)	4,661	154,246
20 year time horizon	8.517 (0.113)	8.420 (0.114)	0.097	180,132 (4,238)	172,493 (3,967)	7,639	78,562
Delay of β-cell detoriation	9.310 (0.143)	9.149 (0.141)	0.161	223,843 (6,241)	218,394 (5956)	5,449	33,845
No risk adjustment for age	9.381 (0.149)	9.206 (0.138)	0.176	206,229 (5,752)	194,406 (5,314)	11,823	67,333
PIO effects last only 5 years	9.165 (0.134)	9.149 (0.141)	0.016	225,569 (6,192)	218,394 (5,956)	7,175	439,313
0% discount rates	11.947 (0.209)	11.666 (0.205)	0.281	324,819 (10,140)	308,833 (9,554)	15,986	56,850
5% discount rates	7.543 (0.102)	7.422 (0.102)	0.120	169,772 (4,169)	161,826 (3,967)	7,946	66,065
Sampling over base case	9.332 (0.295)	9.151 (0.294)	0.181	230,409 (12,707)	219,444 (12,404)	10,964	60,599
CORE QoL estimation method, using CODE-2 CVD disutilities	8.079 (0.127)	7.908 (0.127)	0.172	229,308 (6,295)	218,394 (5,956)	10,914	63,531
Edema disutility included	8.067 (0.127)	7.900 (0.127)	0.167	229,308 (6,295)	218,394 (5,956)	10,914	65,261
Non-serious heart failure disutility	8.046 (0.126)	7.886 (0.126)	0.160	229,308 (6,295)	218,394 (5,956)	10,914	68,165
Hospitalization for heart failure disutility	7.919 (0.124)	7.796 (0.125)	0.123	229,308 (6,295)	218,394 (5,956)	10,914	88,538
"Worst case" disutilities included	7.890	7.775 (0.123)	0.115 (0.124)	229,308	218,394 (6,295)	10,914 (5,956)	94,654
"All" CVD disutilities included	7.706 (0.120)	7.570 (0.120)	0.135	229,308 (6,295)	218,394 (5,956)	10,914	80,612

Values shown are means with standard deviation in parentheses. ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life years.

(improved life expectancy and reduced costs due to complications avoided). Whilst it is difficult to make any form of comparison between cost-effectiveness studies in different populations of diabetes patients in different cost settings, these data serve to suggest that there is potential to have highly cost-effective or even cost-saving interventions in the right target population.

Even comparisons between studies conducted in the same country-specific setting can be difficult due to differences in the approach taken and reporting of health economic outcomes according to different measures such as cost per quality adjusted life year gained versus per life year saved and cost per event avoided. Nevertheless a review of the published literature identified a number of studies conducted in the Swiss setting that serve to place the results presented here into a context relevant to the healthcare payer (table 5). It should be noted here that some of the listed cost-effectiveness studies report outcomes in terms of life years gained, and accordingly these should only be compared directly to the current study ICER of CHF 42 274 per life year gained. In contrast, the remaining studies listed in table 5, report ICERs ranging between CHF 10 700 and CHF 61 550 (€ 40 467) per QALY gained which can be compared to the cost-effectiveness of pioglitazone reported here at CHF 60 596 per QALY gained over patients' lifetimes.

A potential weakness of this analysis was the conservative approach taken to the estimation of quality-adjusted life expectancy using only data from CODE-2. This estimation did not capture changes in quality of life associated with several macrovascular endpoints (MI, ACS, PCI, CABG, TIA, stroke, oedema or revascularisation of the leg). It is possible that this methodology may underestimate the improvements in quality-adjusted life expectancy as the formula does not capture some of the benefits of pioglitazone treatment (reduced rates of MI ACS, PCI and CABG, stroke) or certain disadvantages such as oedema (although this was partially captured by the inclusion of BMI disutility data), hospitalisation for heart failure and revascularisation of the leg. This was addressed in the sensitivity analysis by including quality of life disutilities related to these endpoints and resulted in ICERs that were higher than projected in the base case because of a reduced between-treatment group difference in quality-adjusted life expectancy (ICER range CHF 63 531-94 654 per QALY gained versus base case CHF 60 596 per QALY gained). Of particular note, when disutilities for all CVD events captured by the model were included the difference in QALE, was 0.135 QALYs versus 0.180 QALYs in the base case, and the corresponding ICER was CHF 80 612 per QALY gained.

A second potential criticism of the current study was the simulation of a pan European cohort as opposed to a Swiss cohort. The reason for this was that we were unable to identify sufficiently detailed and published reports of Swiss diabetes patients with a history of macrovascular events. Given that such patients comprise only approximately 25% of the Swiss diabetes population, it was considered inappropriate to use the profile of "typical" Swiss patients. However, PROactive was conducted exclusively in European countries and 0.8% of the 5238 patients were recruited from Swiss centres. Therefore, until suitable cohort data specific for Switzerland is published, we believe that this approach was the most appropriate for the current analysis. We also acknowledge that given the association of pioglitazone with both benefits (improved HbA1c and lipids) and side effects (increased HF and oedema) the provision of information regarding the lowest numbers needed to treat and the highest number needed to harm would be of value to health care providers. Unfortunately this is not currently possible with the PROactive model but would be an important consideration for future development.

Table 5

Comparison of health economic results reported for the Swiss setting.

Study	Cost year	Intervention	Currency	ICER
Current analysis	2005	pioglitazone for patients with a history of macrovascular events	CHF	60,596/ QALY gained
Ess et al. (52)	2000	Pneumococcal conjugate vaccine	CHF	28,900/ QALY gained
Ara et al. (53)	2002	Sibutramine in obese patients	CHF (€)	15,664 (10,700)*/ QALY gained
Brunner-La Rocca et al. (32)	2004	Drug-eluting stents	CHF (€)	62,283 (40,467)*/ QALY gained
Current analysis	2005	pioglitazone for patients with a history of macrovascular events	CHF	42,274 / LYG
Zurn et al. (54)	1996	Hepatitis B vaccination	CHF	60,060 /LYG
Diel et al. (55)	2005	T-SPOT® TB assay for latent tuberculosis screening	CHF (€)	36,606 (23,692)*/ LYG
Neeser et al. (56)	2005	Routine mammography screening	CHF	73,018/LYG
Sendi et al. (57)	1997	Highly active antiretroviral therapy	CHF	14,000/LYG
Szucs et al. (58)	2005	Eplerenone after myocardial infarction	CHF	10,145/LYG

ICER = Incremental cost-effectiveness ratio; QALY = Quality-adjusted life years; LYG = Life years gained *based on exchange rates corresponding to the year of study as supplied by www.xe.com

Given that declining β-cell function is a major contributor to deterioration in glucose tolerance, it is reasoned that the potential for pioglitazone-related beta-cell preservation, as suggested by studies such as the COM06, might serve to delay the progression of type 2 diabetes [39]. The association between TZDs and stabilisation of β-cell function has not been reported with other oral antidiabetic agents such as metformin and sulfonylureas, and clearly warrants further investigation. Sensitivity analysis that accounted for pioglitazone-associated stabilisation of β-cell function showed improvement in the projected QALE and reduced complication costs leading to an ICER of CHF 33 845 per life year gained. As new information becomes available regarding the longer-term impact of TZDs on pancreatic islet function it will be of interest to investigate the potential impact on health and economic outcomes.

The PROactive cohort was recruited based on a diagnosis of type 2 diabetes and evidence of macrovascular events, with approximately 19% and 46% of patients reporting a history of stroke or AMI respectively. The positive impact of pioglitazone on outcomes observed in PROactive is likely to be a consequence of both improved glycaemic control and improved lipid levels. Surveys of Swiss type 2 diabetes patients indicate that approximately 50% of patients have dyslipidemia, 60% are hypertensive and approximately 25% of patients have at least one macrovascular complication [15, 16, 40, 41]. Hence the predominately European cohort included in PROactive and the outcomes reported from PROactive are highly relevant to at least 25% of type 2 diabetes patients currently cared for in the Swiss setting. Based on outcomes from PROactive, the health-economic analysis presented here has shown that for type 2 diabetes patients with a history of macrovascular complications the addition of pioglitazone to current treatment regimens would represent an acceptable treatment option both in clinical and economic terms in the Swiss setting.

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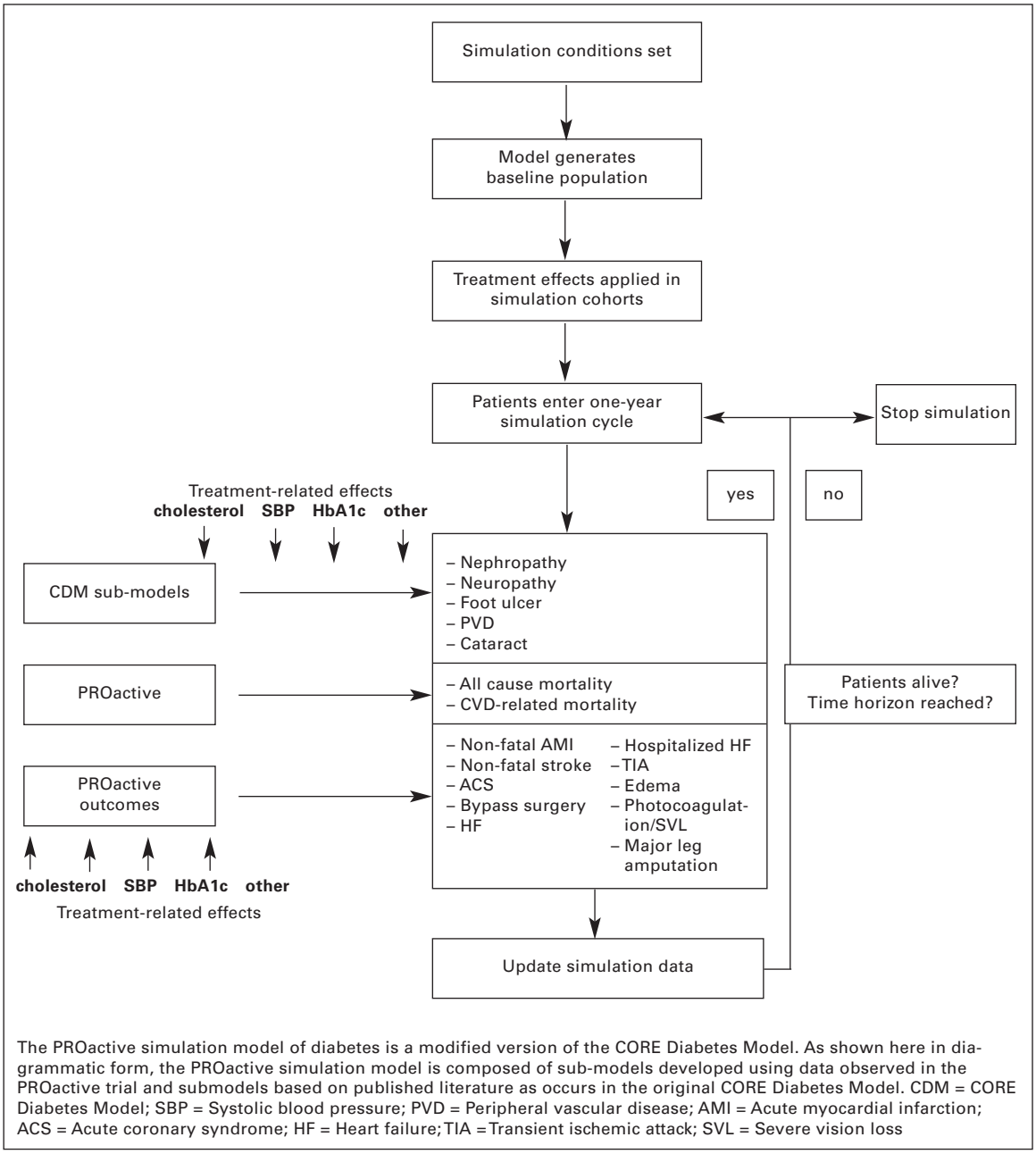
Appendix

Figure 3

Overview of the PROactive simulation model.



The PROactive simulation model of diabetes is a modified version of the CORE Diabetes Model. As shown here in diagrammatic form, the PROactive simulation model is composed of sub-models developed using data observed in the PROactive trial and submodels based on published literature as occurs in the original CORE Diabetes Model. CDM = CORE Diabetes Model; SBP = Systolic blood pressure; PVD = Peripheral vascular disease; AMI = Acute myocardial infarction; ACS = Acute coronary syndrome; HF = Heart failure; TIA = Transient ischemic attack; SVL = Severe vision loss

Table 6

Summary of events, event rates and hazard rates from PROactive Study.

	Annual hazard rate			Hazard ratio				Lognormal distribution	
Event	**Months**	**PIO**	**PLA**	**Months**	**Estimate**	**Lower**	**Upper**	**μ**	**σ**
Death (all causes)	0–36+	2.40%	2.58%	0–36+	0.96	0.78	1.18	–0.0435	0.1050
CV death	0–36+	1.77%	1.89%	0–36+	0.94	0.74	1.20	–0.0618	0.1234
MI (excluding silent MI)	0–36	1.49%	1.81%	0–36+	0.81	0.62	1.06	–0.2108	0.1372
Silent MI	0–36	0.34%	0.36%	0–36+	0.90	0.52	1.55	–0.1101	0.2805
ACS	0–36	0.90%	1.09%	0–36+	0.78	0.55	1.11	–0.2456	0.1782
CABG	0–36	0.93%	1.11%	0–36+	0.83	0.60	1.15	–0.1840	0.1663
PCI	0–36	1.73%	2.13%	0–36+	0.90	0.69	1.17	–0.1037	0.1350
Stroke	0–36	1.30%	1.65%	0–36+	0.81	0.61	1.07	–0.2138	0.1448
Major leg amputation	0–36	0.39%	0.38%	0–36+	1.01	0.58	1.73	0.0062	0.2774
Bypass surgery/ revascularization of leg		1.625%	1.29%	0–36+	1.25	0.90	1.73	0.2196	0.1670
TIA	0–36	0.54%	0.60%	0–36+	0.86	0.54	1.35	–0.1563	0.2333
Retinal photocoagulation	0–36	3.79%	3.78%	0–36+	1.01	0.82	1.25	0.0098	0.1072
Non-serious heart failure	0–36	2.92%	2.04%	0–36+	1.50	1.18	1.91	0.4068	0.1213

Table 6
Continued.

	Annual hazard rate			Hazard ratio				Lognormal distribution	
Event	**Months**	**PIO**	**PLA**	**Months**	**Estimate**	**Lower**	**Upper**	**μ**	**σ**
Hospital admission for heart failure	0–36	2.92%	2.09%	0–36+	1.40	1.10	1.80	0.3397	0.1264
Edema	0–12	25.38%	11.91%	0–12	2.09	1.80	2.42	0.7356	0.0757
	12–36	9.52%	5.79%	12–36+	1.46	1.18	1.80	0.3778	0.1075
Hospital admissions	0–36	31.98%	35.56%	0–36+	0.93	0.86	1.01	–0.0676	0.0412
ICU admissions (subgroup of hospital admissions)	0–36	6.31%	6.66%	0–36+	0.88	0.76	1.01	–0.1332	0.0749

ACS = acute coronary syndrome; CABG = coronary artery bypass graft; CV = cardiovascular; ICU = intensive care unit; MI = myocardial infarction; PCI = percutaneous transluminal angioplasty; PIO=pioglitazone; PLA = placebo; TIA = transient ischaemic attack. Lognormal distributions were defined by the terms μ and σ where m and s correspond to the geometric mean [exp(μ)] and the geometric standard deviation [exp(σ)]

Table 7
Baseline characteristics of the simulation cohort.

Characteristic	**Value**	**SD**	**Data Source**
Demographics			
Proportion male (%)	66.1	–	PROactive
Mean age (years)	61.8	7.7	PROactive
Duration of diabetes (years)	10	7	PROactive
Ethnic Group			
Proportion White (%)	98.6	–	PROactive
Proportion Black (%)	1.4	–	PROactive
Proportion Hispanic (%)	0.0	–	PROactive
Proportion Other (%)	0.0	–	PROactive
Baseline risk factors			
HbA1c (%-points)	8.1	1.4	PROactive
Systolic blood pressure (mm Hg)	143.4	17.8	PROactive
BMI ($kg.m^{-2}$)	30.9	4.8	PROactive
HDL-C (mmol/l)	1.2	0.3	PROactive
LDL-C (mmol/l)	3.0	1.0	PROactive
Total cholesterol (mmol/l)	5.2	2.1	PROactive
Triglycerides (mmol/l)	2.2	1.8	PROactive
Proportion smokers (%)	13.8	–	PROactive
Alcohol consumption (ml per week)	0.0	–	No data available
Baseline complications			
ACS (%)	13.65	–	PROactive
CABG / PCI (%)	30.75	–	PROactive
Major leg amputation (%)	0.0	–-	No data available
Bypass surgery / revascularization of the leg (%)	0.0	–-	No data available
TIA (%)	0.0	–	No data available
Photocoagulation (%)	0.0	–	No data available
SVL (%)	0.0	–	No data available
Hospitalization for heart failure (%)	0.0	–	No data available
Edema (%)	0.0	–	No data available
PVD (%)	24.3	–	PROactive
MI (%)	47.0	–	PROactive
Stroke (%)	19.0	–	PROactive
Microalbuminuria (%)	14.3	–	PROactive
Gross proteinuria (%)	0.0	–	No data available
End-stage renal disease (%)	0.0	–	No data available
Cataract (%)	0.0	–	No data available
Neuropathy (%)	25.6	–	PROactive