Effects on the incidence of cardiovascular events of the addition of pioglitazone versus sulfonylureas in patients with type 2 diabetes inadequately controlled with metformin (TOSCA.IT): a randomised, multicentre trial

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Summary

Background The best treatment option for patients with type 2 diabetes in whom treatment with metformin alone fails to achieve adequate glycaemic control is debated. We aimed to compare the long-term effects of pioglitazone versus sulfonylureas, given in addition to metformin, on cardiovascular events in patients with type 2 diabetes.

Methods TOSCA.IT was a multicentre, randomised, pragmatic clinical trial, in which patients aged 50–75 years with type 2 diabetes inadequately controlled with metformin monotherapy (2–3 g per day) were recruited from 57 diabetes clinics in Italy. Patients were randomly assigned (1:1), by permuted blocks randomisation (block size 10), stratified by site and previous cardiovascular events, to add-on pioglitazone (15–45 mg) or a sulfonylurea (5–15 mg glibenclamide, 2–6 mg glimepiride, or 30–120 mg gliclazide, in accordance with local practice). The trial was unblinded, but event adjudicators were unaware of treatment assignment. The primary outcome, assessed with a Cox proportional-hazards model, was a composite of first occurrence of all-cause death, non-fatal myocardial infarction, non-fatal stroke, or urgent coronary revascularisation, assessed in the modified intention-to-treat population (all randomly assigned participants with baseline data available and without any protocol violations in relation to inclusion or exclusion criteria). This study is registered with ClinicalTrials.gov, number NCT00700856.

Findings Between Sept 18, 2008, and Jan 15, 2014, 3028 patients were randomly assigned and included in the analyses. 1535 were assigned to pioglitazone and 1493 to sulfonylureas (glibenclamide 24 [2%], glimepiride 723 [48%], gliclazide 745 [50%]). At baseline, 335 (11%) participants had a previous cardiovascular event. The study was stopped early on the basis of a futility analysis after a median follow-up of 57·3 months. The primary outcome occurred in 105 patients (1·5 per 100 person-years) who were given pioglitazone and 108 (1·5 per 100 person-years) who were given sulfonylureas (hazard ratio 0·96, 95% CI 0·74–1·26, p=0·79). Fewer patients had hypoglycaemias in the pioglitazone group than in the sulfonylureas group (148 [10%] *vs* 508 [34%], p<0·0001). Moderate weight gain (less than 2 kg, on average) occurred in both groups. Rates of heart failure, bladder cancer, and fractures were not significantly different between treatment groups.

Interpretation In this long-term, pragmatic trial, incidence of cardiovascular events was similar with sulfonylureas (mostly glimepiride and gliclazide) and pioglitazone as add-on treatments to metformin. Both of these widely available and affordable treatments are suitable options with respect to efficacy and adverse events, although pioglitazone was associated with fewer hypoglycaemia events.

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Introduction

Cardiovascular disease is the most common cause of morbidity and mortality in patients with diabetes.[1] Findings from the UK Prospective Diabetes Study (UKPDS) have shown that good glycaemic control established at the time of diagnosis can reduce the incidence of cardiovascular events and microvascular complications in patients with type 2 diabetes.[2,3] However, maintaining appropriate glucose control over time is difficult. In UKPDS, only 50% of patients had attained satisfactory glucose control with monotherapy (metformin, sulfonylurea, or insulin) 3 years after

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Research in context

Evidence before this study

We searched PubMed, ScienceDirect, and the Cochrane Library for articles published in English between Jan 1, 1997, and Dec 31, 2007, with search terms "type 2 diabetes", "metformin", "pioglitazone", "sulfonylureas", and "cardiovascular events", or "cardiovascular disease" or "cardiovascular mortality", or "glycated haemoglobin", or "treatment failure" or "heart failure". In patients with type 2 diabetes, metformin is the recommended first-line drug treatment, but there is considerable uncertainty as to the best add-on treatment in patients whose glycaemia is inadequately controlled with metformin alone. Sulfonylureas are the most widely used choice, but their cardiovascular safety is uncertain. Pioglitazone could represent a suitable alternative, in view of the evidence supporting its protective effect on ischaemic cardiovascular disease, although concerns remain about possible clinically relevant side-effects. The cardiovascular effects, glycaemic effects, and safety of these therapeutic approaches have not previously been compared in a long-term, head-to-head trial.

Added value of this study

The TOSCA.IT trial provides a direct comparison of two widely available and affordable second-line treatment regimens for patients with type 2 diabetes. The patients enrolled represent an almost primary prevention population that is usually neglected in trials done to investigate the cardiovascular effects of glucose-lowering drugs. The results showed that, if used appropriately, in terms of patient selection and dose, both pioglitazone and a sulfonylurea (glimepiride or gliclazide) as add-on to metformin are associated with similarly low rates of cardiovascular events and few clinically relevant side-effects. Our findings also suggest that pioglitazone could be advantageous compared with sulfonylureas in terms of durability of glycaemic control and frequency of hypoglycaemia.

Implications of all the available evidence

Our results lend support to current treatment guidelines for type 2 diabetes, particularly in relation to patients with a low cardiovascular risk, by suggesting that both pioglitazone and sulfonylureas (glimepiride or gliclazide) are suitable alternatives as add-on treatment when metformin alone fails to provide adequate glycaemic control.

diagnosis, the proportion decreasing to 25% after 9 years.[4]

The progressive nature of type 2 diabetes requires a stepwise therapeutic approach combining different antihyperglycaemic drugs. Currently, metformin is the recommended first-line drug, but there is considerable uncertainty about the best therapeutic option in patients whose glycaemia is inadequately controlled with metformin alone.[5,6] Sulfonylureas are very effective glucose-lowering drugs, which are still largely used in combination with metformin,[7] despite their well-documented side-effects, particularly hypoglycaemia and weight gain. Because the cardiovascular safety of sulfonylureas has been questioned,[8,9] assessment of the cardiovascular effects of this drug class (as well as its long-term effect on glucose control and general safety) compared with other treatment strategies is needed.

Thiazolidinediones (glitazones) are glucose-lowering drugs that are associated with a minimal risk of hypoglycaemia and can ameliorate insulin resistance and cardiovascular risk factors; therefore, they have great potential for cardiovascular protection. Although rosiglitazone has been dismissed because of a purported increase in cardiovascular risk, pioglitazone has been shown to reduce ischaemic cardiovascular events in placebo-controlled studies of individuals with and without diabetes,[10,11] although concerns remain about its potential side-effects.[12–15]

We undertook a pragmatic trial to compare, in usual clinical practice conditions, the long-term effects of a sulfonylurea or pioglitazone as add-on therapy to metformin in the treatment of patients with type 2 diabetes inadequately controlled with metformin monotherapy. The aim of the study was to compare the long-term effect of these two therapeutic options with respect to incidence of cardiovascular events, as well as their effects on glucose control and safety.

Methods

Study design and participants

The Thiazolidinediones Or Sulfonylureas Cardiovascular Accidents Intervention Trial (TOSCA.IT) was a pragmatic, multicentre, randomised, parallel-group, clinical trial done at 57 diabetes clinics in Italy. We used a multicentre prospective, randomised, open label, blinded endpoint (PROBE) study design. The ethics committees of the coordinating centre (Federico II University of Naples, Italy) and of each trial site approved the study protocol and all participants provided written informed consent before entering the study.

Details of the study design have been reported previously.[16] Briefly, eligible participants were men and women (aged 50–75 years) who had type 2 diabetes of at least 2 years' duration and were on stable treatment with full-dose metformin (2–3 g per day), had an HbA_{1c} of 7·0–9·0% (53–75 mmol/mol), and a BMI of 20–45 kg/m². Key exclusion criteria were acute cardiovascular events in the previous 6 months, chronic heart failure (New York Heart Association class 1 or higher), and a serum creatinine concentration greater than 132 µmol/L (a

contraindication for the use of metformin at full dose). A full list of inclusion and exclusion criteria is provided in the appendix.

Randomisation and masking

Participants were randomly assigned (1:1) to either pioglitazone or a sulfonylurea as add-on to metformin. In accordance with local practice, glibenclamide, gliclazide, or glimepiride could be prescribed in the sulfonylurea group. Permuted blocks randomisation (block size 10) was done centrally via an interactive telephone system and was stratified by site and history of cardiovascular events. Participants and investigators were aware of treatment assignment. The components of the primary outcome and some selected adverse events of particular interest with respect to the study drugs (heart failure, pathological fractures, macular oedema, and neoplasms) were adjudicated by an independent endpoint committee unaware of treatment-group assignment. The prespecified criteria for event adjudication are listed in the appendix.

An independent data and safety monitoring board provided surveillance of the study and had access to the unblinded data.

Procedures

Follow-up visits were scheduled at 1, 3, and 6 months after randomisation and every 6 months thereafter until study end. More frequent visits could be scheduled if deemed appropriate, based on clinical conditions or glucose-control status. Drug compliance, efficacy, and safety were assessed at each visit; doses of the drugs taken, temporary or permanent discontinuation of the study drugs, and the reasons for discontinuation were reported in the study records on the basis of a patient's interview. Metformin dose remained unchanged throughout the study whereas the study add-on drugs could be titrated at the investigators' discretion, on the basis of home glucose monitoring and occurrence of hypoglycaemia. Doses of 15–45 mg for pioglitazone, 5–15 mg for glibenclamide, 30–120 mg for gliclazide, and 2–6 mg for glimepiride were used, as deemed appropriate by the treating physician. All drugs were given orally. Home glucose monitoring was done in accordance with local practice. For the specific purposes of the study, patients were required to provide glucose measurements at fasting and 2 h after lunch and dinner on one day per week in the 4 weeks preceding each follow-up visit.

We measured HbA_{1c} every 6 months; for values of 8% (64 mmol/mol) or higher, an extra visit was scheduled 3 months apart. We defined treatment failure of the assigned treatment as an HbA_{1c} of 8% (64 mmol/mol) or higher on two consecutive visits 3 months apart. If treatment failure occurred, basal insulin glargine and, subsequently, prandial short-acting insulin analogues were added, in a stepwise manner, to the previous treatment, which continued at the same doses. We assessed fasting plasma lipids, C-reactive protein, microalbuminuria, and electrocardiograms (ECG) annually. Investigators were encouraged to treat cardiovascular risk factors in accordance with current American Diabetes Association and Italian guidelines.[6,17]

Due to safety concerns regarding the risk of bladder cancer with pioglitazone,[18] the study protocol was amended in 2012 to include assessment of haematuria at each study visit. Biochemical analyses and ECG reading were done centrally. We collected information on symptoms and events possibly related to the study outcomes at each visit with specific questionnaires. Patients who prematurely discontinued the study drugs were followed up for ascertainment of cardiovascular outcomes and information on vital status was obtained from the national health registry using the patient's fiscal code as identifier for patients lost to follow-up.

Outcomes

The primary outcome was a composite of first occurrence of all-cause death, non-fatal myocardial infarction (including silent myocardial infarction), non-fatal stroke, or urgent coronary revascularisation. Because the study was designed as a pragmatic trial, the selection of all-cause death as part of the primary composite outcome was clearly of relevance because this is the most robustly ascertained endpoint, and arguably of the greatest clinical significance.

The key secondary outcome was a composite of ischaemic cardiovascular disease, which included first occurrence of sudden death, fatal and non-fatal myocardial infarction (including silent myocardial infarction), fatal and non-fatal stroke, leg amputation above the ankle, and any revascularisation of the coronary, leg, or carotid arteries.

An expanded composite cardiovascular outcome was among the remaining secondary outcomes—this included the primary outcome plus heart failure; any revascularisation of the coronary, leg, or carotid arteries; angina confirmed by new ECG abnormalities; and intermittent claudication with an ankle-brachial index less than 0·90. At the suggestion of the data and safety monitoring board, heart failure, initially listed only among the components of the expanded secondary cardiovascular outcome, was also made a stand-alone secondary outcome to be adjudicated by the endpoint committee (approved protocol amendment, July, 2010). The other secondary outcomes were new or worsening nephropathy (ie, new-onset macroalbuminuria, twice the baseline levels of serum creatinine, creatinine clearance reduction of ≥20 mL/min per 1·73m², plasma creatinine >290 µmol/L, or need for permanent dialysis), time to failure of hypoglycaemic treatment (defined as HbA_{1c} ≥8% [≥64 mmol/mol] on two consecutive visits 3 months apart), and changes in HbA_{1c} and major cardiovascular risk factors (BMI, waist circumference, plasma lipids, blood pressure, microalbuminuria,

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See Online for appendix

C-reactive protein, estimated glomerular filtration rate [eGFR], and heart rate) over time.

Adverse events were reported in the electronic case report form using ad-hoc forms, in which the investigators also explained whether in their judgement the event was causally related to the study drugs. For all reported cases of cancer, heart failure, bone fractures, and macular oedema, the investigators were required to provide documentation and these events were reviewed and adjudicated by the event committee. Adverse events of special interest were hypoglycaemic episodes defined as a documented glucose value of less than 3·3 mmol/L and graded as moderate (not requiring help for treatment) or severe (requiring assistance for treatment).

The study was designed to be event driven. The initial sample size calculation was based on an estimated primary endpoint rate of 3·5% per year, with the study intended to have 80% power to detect a reduction of 20% in the primary outcome in either group versus the other, based on the results of the PROACTIVE trial.[10] On the basis of these assumptions, 652 events were needed for the primary efficacy analysis. Therefore, 4396 patients had to be enrolled and followed up for at least 4 years; assuming a trial discontinuation rate of 15%, 5172 patients needed to be recruited and randomly assigned (2586 in each treatment group).

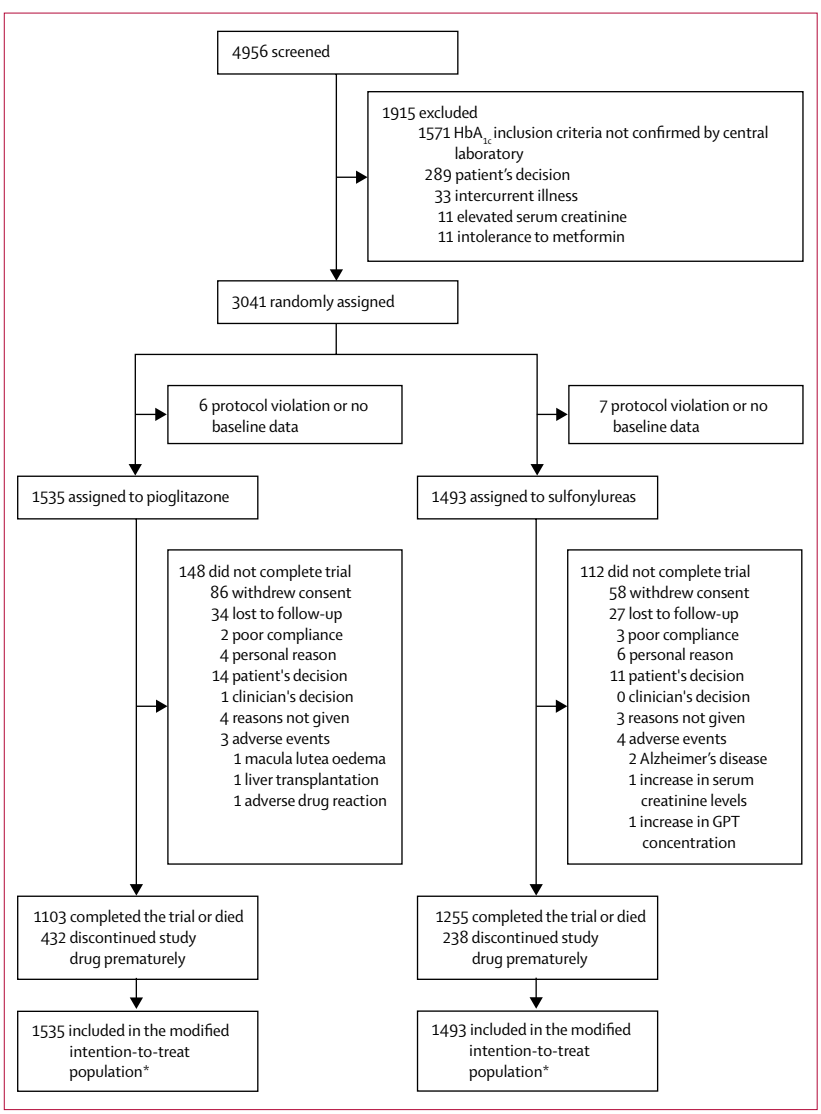


Figure 1: **Trial profile**
GPT=glutamic pyruvic transaminase. *Same number included in the safety analysis population and the post-hoc on-treatment analysis population.

However, because of the lower than expected rate of recruitment and because the number of participants discontinuing the study was lower than initially foreseen, an approved protocol amendment (January, 2012) subsequently reduced the sample size requirement. Accordingly, 3371 patients should have been enrolled to expect the 498 endpoint events needed to detect a 20% reduction in the incidence of events with a statistical power of 80% (hazard ratio [HR] 0·80, p=0·05 [one-sided log-rank test]), assuming an estimated occurrence rate of the primary endpoint of 3·5% per year and a 5% loss to follow-up. Nonetheless, nearly 9 years after the beginning of the study, the number of events needed was still not reached, and a futility analysis was done as recommended by the data and safety monitoring board.

3028 patients were recruited between Sept 18, 2008, and Jan 15, 2014, given the difficulties in further prolonging the enrolment phase (organisational problems related to investigators' retirements and reorganisation of the national health-care system whereby small hospitals or medical centres were consolidated). The observed event rate during follow-up was lower than expected, with 213 adjudicated primary endpoint events in total. Following the data and safety monitoring board's recommendation, a futility analysis for the primary endpoint using a frequentist approach[19] was done in March 31, 2017. The results of this analysis showed that, if the future data distribution followed the current trend (the most plausible hypothesis), the probability of observing a significant positive result (ie, an HR of 0·80, two-sided log-rank test) at the planned end of follow-up would be as low as 5%. On the basis of the futility analysis, the study was discontinued on May 23, 2017.

The trial efficacy analysis was done in the modified intention-to-treat population, which included all randomly assigned participants with baseline data available and without any protocol violations in relation to inclusion or exclusion criteria. Data from the patients who completed or discontinued the trial without having an outcome were censored from the day of their last visit; events occurring after that visit were not included. We also did a post-hoc on-treatment analysis for the primary and secondary composite cardiovascular outcomes and components of the primary outcome, which included only data from follow-up trial periods during which patients were taking the assigned study drug; patients were censored at the time of permanent study drug

discontinuation (with data included in the analysis for an additional 30 days after study drug discontinuation). The safety analysis set includes only participants exposed to the trial medications. Participants were regarded as exposed to the trial medications as long as they had taken at least one dose of pioglitazone or sulfonylurea.

We assessed incidence rates using cumulative incidence curves that were compared (metformin plus pioglitazone *vs* metformin plus sulfonylurea) using log-rank analysis. The analysis of the time-dependent primary endpoint and secondary endpoints was based on a two-sided Cox proportional-hazards model. We compared incidence and severity of hypoglycaemic events between groups using a Poisson regression model with correction for overdispersion. We did prespecified subgroup analyses for the primary outcome by sex (between treatments in men and women), age (<60 years or ≥60 years), BMI (≤30 kg/m² or >30 kg/m²), duration of diabetes (≤8 years or >8 years), HbA_{1c} (≤8·0% [64mmol/mol] or >8·0% [64 mmol/mol]), and eGFR (<60 mL/min per 1·73 m² or ≥60 mL/min per 1·73 m²).

We compared proportions in the two treatment groups using the continuity adjusted χ^2 test, or two-sided Fisher's exact test, as appropriate. We estimated the mean differences between the trial groups for HbA_{1c}, BMI, bodyweight, waist circumference, lipid profile, blood pressure, eGFR, heart rate, C-reactive protein, and urinary albumin-to-creatinine ratio using a mixed model for repeated measurements.[20]

All statistical analyses were done with SAS (version 9.4). Data are expressed as mean (SD), mean (SE), or n (%), as appropriate. All reported p values are two-sided and are not adjusted for multiple comparisons.

This study is registered with ClinicalTrials.gov, number NCT00700856.

	Metformin plus pioglitazone (n=1535)	Metformin plus sulfonylurea (n=1493)	Overall (n=3028)
Age (years)	62·4 (6·4)	62·2 (6·5)	62·3 (6·5)
Sex			
Men	909 (59%)	865 (58%)	1774 (59%)
Women	626 (41%)	628 (42%)	1254 (41%)
BMI (kg/m²)	30·2 (4·4)	30·4 (4·5)	30·3 (4·5)
Cardiovascular risk factors			
Smokers	281 (18%)	252 (17%)	533 (18%)
LDL cholesterol (mmol/L)	2·67 (0·81)	2·66 (0·82)	2·67 (0·81)
HDL cholesterol (mmol/L)	1·20 (0·34)	1·20 (0·33)	1·20 (0·34)
Triglycerides (mmol/L)	1·72 (1·04)	1·73 (0·93)	1·73 (1·00)
Systolic blood pressure (mm Hg)	134·3 (15·1)	133·7 (14·2)	134·0 (14·7)
Diastolic blood pressure (mm Hg)	79·6 (8·7)	79·6 (8·1)	79·6 (8·4)
Microalbuminuria	321 (21%)	312 (21%)	633 (21%)
Diabetes characteristics			
Duration of diabetes (years)	8·4 (5·6)	8·5 (5·8)	8·5 (5·7)
HbA_{1c} (%)	7·67 (0·50)	7·69 (0·51)	7·68 (0·50)
HbA_{1c} (mmol/mol)	60·3 (5·4)	60·5 (5·6)	60·4 (5·5)
Previous cardiovascular history			
Previous cardiovascular disease*	187 (12%)	148 (10%)	335 (11%)
Previous acute myocardial infarction	109 (7%)	86 (6%)	195 (6%)
Previous stroke	28 (2%)	13 (1%)	41 (1%)
Previous acute coronary syndrome	39 (3%)	40 (3%)	79 (3%)
Carotid artery revascularisation	14 (1%)	12 (1%)	26 (1%)
Coronary artery revascularisation	105 (7%)	101 (7%)	206 (7%)
Use of cardiovascular drugs			
Antihypertensive drugs	1072 (70%)	1049 (70%)	2121 (70%)
Lipid-lowering drugs	888 (58%)	847 (57%)	1735 (57%)
Antiplatelet drugs	644 (42%)	574 (38%)	1218 (40%)

Data are mean (SD) or n (%). *Some patients had more than one condition.

Table 1: **Baseline characteristics**

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Sept 18, 2008, and Jan 15, 2014, 4956 patients were screened and 3041 were randomly assigned to a treatment group although 13 of these patients were excluded because of protocol violation or because they had no baseline data. Therefore, 3028 patients were included in the intention-to-treat analysis (figure 1), with 1535 patients in the metformin plus pioglitazone group and 1493 in the metformin plus sulfonylureas group. In the metformin plus sulfonylureas group, 24 (2%) patients were given glibenclamide, 723 (48%) were given glimepiride, and 745 (50%) were given gliclazide. On the basis of a futility analysis, the study was stopped when the median follow-up was 57·3 months (IQR 42·2–60·2); follow-up time was similar in the two treatment groups (appendix). Overall, 1387 (90%) patients in the pioglitazone group and 1381 (92%) in the sulfonylureas group attended a final visit or had died by the end of the study (figure 1, appendix). The study groups were well balanced with respect to baseline demographic characteristics, diabetes duration, HbA_{1c}, and major cardiovascular risk factors (table 1). At randomisation, patients were started at the lowest recommended dose of the study drugs. The mean dose of pioglitazone used was 23·0 mg (SD 8·6), and for the sulfonylureas the mean doses were 7·6 mg (4·0) for glibenclamide, 42·0 mg (18·6) for gliclazide, and 2·5 mg (0·9) for glimepiride. Premature permanent discontinuation of the study medications was significantly more frequent in the metformin plus pioglitazone group than in the metformin plus sulfonylureas group (432 [28%] *vs* 238 [16%], p<0·0001; appendix).

The primary cardiovascular composite outcome occurred in 105 patients (7%, 1·5 per 100 person-years) who were

given pioglitazone and 108 patients (7%, 1·5 per 100 person-years) who were given sulfonylureas. There were no significant between-group differences in the composite primary outcome (HR 0·96, 95% CI 0·74–1·26, p=0·79) or in its components (figure 2, table 2). The key secondary outcome occurred in 74 patients (5%, 1·1 per 100 person-years) in the pioglitazone group and in 83 patients (6%, 1·2 per 100 person-years) in the sulfonylureas group (HR 0·88, 0·65–1·21, p=0·44). Details on the individual components of the key secondary outcome are provided in the appendix. The proportion of patients who had the expanded cardiovascular outcome was also similar in the two study groups (HR 1·03, 0·82–1·28, p=0·81; table 2). Analysis of the primary endpoint by prespecified baseline categories of sex, age, BMI, diabetes duration, HbA_{1c}, and eGFR did not show significant between-group differences or significant interactions (appendix). A post-hoc comparison of the incidence of the primary outcome between the two study groups after exclusion of patients with a previous cardiovascular event also did not show any significant difference between the treatment groups (HR 0·99, 0·73–1·34, p=0·94; appendix). Heart failure occurred in 19 (1%) patients in the pioglitazone group and 12 (1%) patients in the sulfonylureas group (HR 1·57, 0·76–3·24, p=0·22).

We also did a post-hoc on-treatment analysis of the primary and secondary composite cardiovascular outcomes and of the components of the primary outcome. Only events occurring in patients while they were taking study drugs, or after 30 days from discontinuation, were included in this analysis. In this data subset, the incidence of the primary outcome was

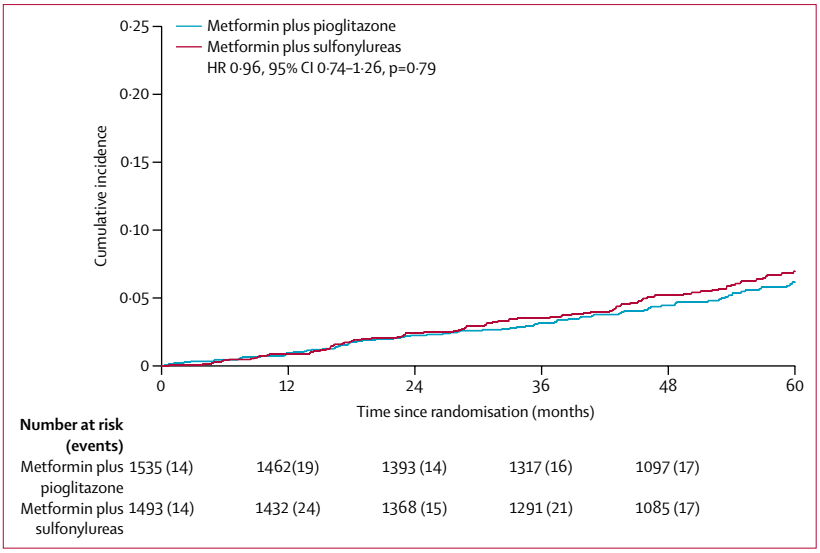


Figure 2: **Cumulative incidence of the composite primary outcome**
The primary composite outcome was the first occurrence of all-cause death, non-fatal myocardial infarction (including silent myocardial infarction), non-fatal stroke, or urgent coronary revascularisation. HR=hazard ratio.

	Metformin plus pioglitazone (n=1535)		Metformin plus sulfonylurea (n=1493)		Hazard ratio (95% CI)	p value
	n (%)	n per 100 patient-years	n (%)	n per 100 patient-years		
Intention-to-treat analysis						
Primary composite outcome*	105 (7%)	1·5	108 (7%)	1·5	0·96 (0·74–1·26)	0·79
All-cause death	55 (4%)	0·8	50 (3%)	0·7	1·10 (0·75–1·61)	0·63
Non-fatal myocardial infarction (including silent myocardial infarction)	21 (1%)	0·3	24 (2%)	0·3	0·87 (0·48–1·55)	0·63
Non-fatal stroke	16 (1%)	0·2	20 (1%)	0·3	0·79 (0·41–1·53)	0·49
Urgent coronary revascularisation	31 (2%)	0·4	34 (2%)	0·5	0·91 (0·56–1·48)	0·70
Key secondary outcome†	74 (5%)	1·1	83 (6%)	1·2	0·88 (0·65–1·21)	0·44
Expanded composite outcome‡	163 (11%)	2·3	157 (11%)	2·3	1·03 (0·82–1·28)	0·81
On-treatment analysis (post hoc)						
Primary composite outcome*	73 (5%)	1·2	99 (7%)	1·5	0·82 (0·60–1·10)	0·19
All-cause death	43 (3%)	0·7	45 (3%)	0·7	1·08 (0·71–1·65)	0·70
Non-fatal myocardial infarction (including silent myocardial infarction)	13 (1%)	0·2	23 (2%)	0·4	0·63 (0·32–1·24)	0·18
Non-fatal stroke	11 (1%)	0·2	18 (1%)	0·3	0·67 (0·32–1·42)	0·30
Urgent coronary revascularisation	18 (1%)	0·3	32 (2%)	0·5	0·62 (0·35–1·11)	0·11
Key secondary outcome†	48 (3%)	0·8	79 (5%)	1·2	0·67 (0·47–0·96)	0·03
Expanded composite outcome‡	122 (8%)	2·1	147 (10%)	2·3	0·90 (0·71–1·15)	0·41

*The primary composite outcome was the first occurrence of all-cause death, non-fatal myocardial infarction (including silent myocardial infarction), non-fatal stroke, or urgent coronary revascularisation. †The key secondary outcome includes the first occurrence of sudden death, fatal and non-fatal myocardial infarction (including silent myocardial infarction), fatal and non-fatal stroke, major leg amputation (above the ankle), and any revascularisation of the coronary, carotid, or leg arteries. ‡The expanded composite outcome includes first occurrence of all-cause death, non-fatal myocardial infarction (including silent myocardial infarction), non-fatal stroke, heart failure, any revascularisation of the coronary, carotid, or leg arteries, angina confirmed by electrocardiogram changes, and intermittent claudication with an ankle brachial index of less than 0·90.

Table 2: **Primary and secondary cardiovascular outcomes**

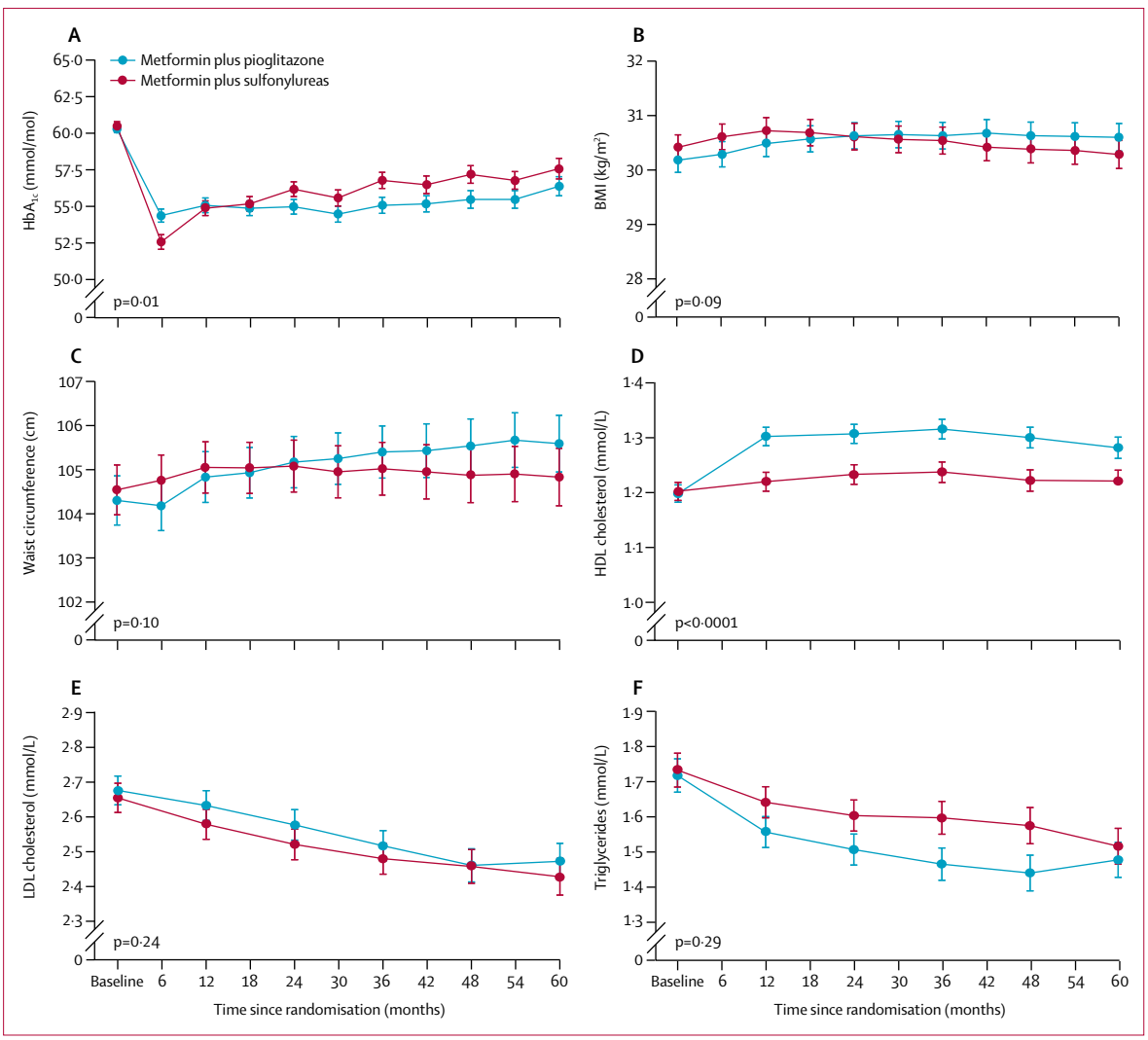


Figure 3: **Cardiovascular risk factors over time**

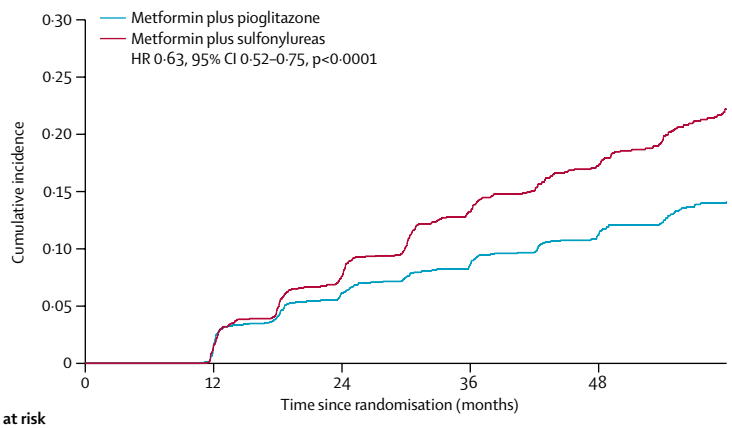
Data are mean values for HbA_{1c} (A), BMI (B), waist circumference (C), HDL cholesterol (D), LDL cholesterol (E), and triglycerides (F) during the trial period. Error bars show SEs. Data were estimated on the basis of measurements taken at scheduled visits. The analyses are based on a mixed model for repeated measurements, taking into account within-participant correlation. p values were calculated with a mixed model for repeated measurements.

1·2 per 100 person-years in the pioglitazone group and 1·5 per 100 person-years in the sulfonylureas group (HR 0·82, 95% CI 0·60–1·10, p=0·19; table 2); none of the components of the primary outcome was significantly different between the study groups. However, the key secondary outcome, a composite of ischaemic cardiovascular events, was significantly reduced in the pioglitazone group compared with the sulfonylureas group in the post-hoc on-treatment analysis (HR 0·67, 95% CI 0·47–0·96, p=0·03; table 2). The expanded composite cardiovascular outcome did not differ between the groups in this post-hoc analysis (table 2).

New or worsening nephropathy occurred in 282 (23%) patients in the pioglitazone group and 270 (23%) patients in the sulfonylureas group, in the intention-to-treat analysis (HR 1·03, 95% CI 0·89–1·19, p=0·37). In both groups, HbA_{1c} decreased significantly after starting treatment with the study drugs and remained significantly lower than at baseline throughout the study (figure 3, appendix) with 39% of study participants who had good glucose control (HbA_{1c} ≤7%, 53 mmol/mol) over a median observation period of almost 5 years with both treatment regimens. Mean HbA_{1c} over time was slightly lower for patients in the pioglitazone group than for patients in the sulfonylureas group (7·24% [SD 0·20] *vs* 7·30% [SD 0·21], p=0·01; 55 mm/mol *vs* 56 mmol/mol). Fewer patients had treatment failure with pioglitazone than with sulfonylureas (193 patients [13%] *vs* 295 [20%]; HR 0·63, 95% CI 0·52–0·75, p<0·0001; figure 4). Accordingly, fewer patients in the pioglitazone group were prescribed rescue insulin therapy during the study (164 [11%] *vs* 233 [16%], p<0·0001).

In both groups, BMI changed slightly during the first 2 years after starting treatment with the study drugs (corresponding to a weight gain of less than 2 kg, on average, in both groups), and then levelled off until the end of the study (figure 3). No significant between-group differences were recorded during the study for BMI, waist circumference, LDL cholesterol, and triglycerides, whereas HDL-cholesterol concentrations were significantly higher in the pioglitazone group (figure 3, appendix). As for other cardiovascular risk factors, blood pressure, albumin-to-creatinine ratio, eGFR, and C-reactive protein were similar in the two treatment groups during the study period.

The overall incidence of serious adverse events was similar in the pioglitazone and sulfonylureas groups (table 3, appendix). The occurrence of confirmed malignant neoplasms, including bladder cancer, was also similar. Pathological bone fractures and macular oedema occurred in a small proportion of patients, with no significant differences between treatment groups. Further details on all adverse events are reported in the appendix. Severe hypoglycaemic events were fairly uncommon, but were more frequent with sulfonylureas (table 4).



Number at risk (events)					
Metformin plus pioglitazone	1535 (19)	1449(70)	1321 (33)	1223 (33)	990 (29)
Metformin plus sulfonylureas	1493 (18)	1418 (90)	1287 (77)	1145 (49)	928 (48)

Figure 4: **Cumulative incidence of treatment failure**
Failure of hypoglycaemic treatment was defined as HbA_{1c} of 8% (64 mmol/mol) or above on two consecutive visits 3 months apart. HR=hazard ratio.

	Metformin plus pioglitazone (n=1535)	Metformin plus sulfonylurea (n=1493)	p value
Serious adverse events*	208 (14%)	195 (13%)	0·73
Malignant neoplasms†	78 (5%)	71 (5%)	0·74
Lung	9 (1%)	3 (<1%)	0·15
Colorectal	12 (1%)	9 (1%)	0·66
Breast	3 (<1%)	4 (<1%)	0·72
Bladder	8 (1%)	8 (1%)	1·00
Pancreatic	2 (<1%)	6 (<1%)	0·17
Other	44 (3%)	41 (3%)	0·91
Pathological fractures†	6 (<1%)	4 (<1%)	0·75
Men	3/909 (<1%)	1/865 (<1%)	0·62
Women	3/626 (<1%)	3/628 (<1%)	1·00
Macular oedema†	7 (<1%)	3 (<1%)	0·34
Respiratory, thoracic, and mediastinal disorders	16 (1%)	5 (<1%)	0·03

Data are n (%), unless otherwise specified. Proportion of participants experiencing adverse events was compared using the continuity-adjusted χ^2 test, or two-sided Fisher's exact test, as appropriate. Data are for patients who had one or more events among those who received at least one dose of assigned study drug. Adverse events were selected on the basis of the most relevant side-effects of the study drugs. All adverse events occurring at significantly different rates between the two study groups are also reported. Data are based on investigator-reported adverse events, unless otherwise specified. A complete list of serious adverse events according to system organ class is provided in the appendix. Adverse event categories were defined in accordance with the system organ class in the Medical Dictionary of Regulatory Activities. *A serious adverse event was defined as death, a life-threatening episode, hospital admission or prolongation of existing hospital admission, or a persistent or substantial disability. †Neoplasms, pathological fractures, and macular oedema were adjudicated.

Table 3: **Selected adverse events**

Discussion

In this long-term pragmatic trial, the incidence of cardiovascular events was similar with sulfonylureas (mostly glimepiride and gliclazide) or pioglitazone as add-on to metformin in patients with type 2 diabetes inadequately controlled with metformin alone. Both treatments were effective overall and were not associated with high risk of clinically relevant side-effects; however, patients given pioglitazone had better durability of glycaemia control, less frequent hypoglycaemia, and higher HDL-cholesterol concentrations than patients given sulfonylureas.

We detected no difference between the treatment groups in the incidence of any of the prespecified cardiovascular outcomes, including fatal and non-fatal myocardial infarction or stroke, or all-cause death, during the study. Findings of previous cardiovascular outcome trials with pioglitazone in people with (PROACTIVE[10]) or without (IRIS[11]) diabetes support its beneficial effects on ischaemic cardiovascular outcomes, although total cardiovascular events and all-cause deaths were not significantly reduced in these studies. The reasons for the discrepancy between TOSCA.IT and previous findings might relate not only to the outcomes assessed, but also to features of the study population and the choice of comparator. In both PROACTIVE and IRIS, patients had previous cardiovascular events, whereas in our study population the prevalence of baseline cardiovascular diseases was low (11%) and the annual rate of events was among the lowest reported in the scientific literature for patients with type 2 diabetes of similar age.[21] In this low-risk population, the beneficial effects of pioglitazone on cardiovascular diseases might be too small to be detected in absolute terms; however, results of the post-hoc on-treatment analysis of the key secondary endpoint, a composite outcome of ischaemic cardiovascular events, are in agreement with findings from previous studies.[10,11]

The use of an active comparator, rather than placebo, might have further affected the study outcomes. The hypothesis that the comparator drugs might have had a beneficial effect on cardiovascular events cannot be dismissed, because the cardiovascular effects of sulfonylureas are far from clearly established. In the UKPDS, the combination of sulfonylureas and metformin was associated with higher diabetes-related mortality than sulfonylureas alone;[22] conversely, in other intervention trials, treatment with sulfonylureas was associated with similar or lower risk of cardiovascular events compared with other therapeutic strategies.[23,24] The potentially increased cardiovascular risk associated with sulfonylureas has been largely attributed to glibenclamide.[25] In our study, only 2% of patients were given glibenclamide, with the remaining participants receiving glimepiride or gliclazide.

The results of TOSCA.IT, which was done in the context of usual clinical practice, show that both treatment regimens are effective in maintaining satisfactory blood glucose control for a median observation period of almost 5 years in most patients, with a relatively low rate of clinically relevant side-effects associated with the study drugs. Specifically, bodyweight increased slightly during the study period in both treatment groups, with no significant difference between groups. A more substantial increase in bodyweight was reported in previous studies with pioglitazone;[10,11] the discrepancy might be partly explained by the exclusion of patients with heart failure or reduced renal function from our study, since such patients are predisposed to fluid retention, a relevant cause of weight gain with use of pioglitazone. Compared with sulfonylureas, pioglitazone as add-on to metformin achieved marginally lower HbA_{1c} values, a lower risk of hypoglycaemias (partly because of the higher proportion of patients on insulin in the sulfonylureas group due to a higher rate of treatment failure), and improved HDL-cholesterol concentrations, in agreement with previous data.[26,27] Patients in the pioglitazone group achieved a significantly better durability of glycaemic control, as reported in a previous study with rosiglitazone.[28]

As to the long-term safety of the study drugs, heart failure, although numerically more frequent with pioglitazone, occurred in fairly few patients overall and did not differ significantly between the treatment groups. This finding could be partly ascribed to the selection criteria of the study, which excluded patients with heart failure in New York Heart class 1 or higher, and is in agreement with the results of the IRIS trial,[11] in which the (non-diabetes) study population was at low risk for heart failure. This result might also be related to the dose of pioglitazone used in TOSCA.IT, which on average was about half the maximum recommended dose. The occurrence of bladder cancer was also low and not significantly different between the two study groups, and the same was true for pathological fractures and macular oedema. Nevertheless, the present study had too few of these events to allow any definitive conclusions to be drawn. Altogether, the results of TOSCA.IT suggest that, if used appropriately (in terms of patient selection and dose), pioglitazone is generally not associated with a high risk of clinically relevant side-effects. However, as many as 28% of the participants assigned to pioglitazone discontinued the study drug prematurely; in many cases, this discontinuation was due to the safety concerns raised in 2012, when the drug was withdrawn from the market in France and Germany. A similarly high rate of drug discontinuation with pioglitazone was also reported in the IRIS study.[11]

	Metformin plus pioglitazone (n=1535)		Metformin plus sulfonylurea (n=1493)		Incidence rate ratio (95% CI)	p value
	Patients	Events	Patients	Events		
Severe hypoglycaemic events	1 (<1%)	2	24 (2%)	33	0·06 (0·01–0·25)	<0·0001
Moderate hypoglycaemic events	147 (10%)	515	484 (32%)	1868	0·27 (0·24–0·30)	<0·0001

Data are n (%) or n, unless otherwise specified. Hypoglycaemic events were defined as a glucose value lower than 3·3 mmol/L and graded as moderate (not requiring help for treatment) or severe (requiring assistance for treatment). Data are shown for patients who received at least one dose of assigned study drugs.

Table 4: **Hypoglycaemic events**

Major strengths of this study are the head-to-head comparison, within an usual care setting, of two therapeutic strategies suitable as second-line treatment for type 2 diabetes, as well as the long follow-up period. Furthermore, the study drugs are among the least expensive glucose-lowering drugs available. All recent cardiovascular outcome trials with newer antidiabetes drugs are placebo-controlled and do not provide comparative efficacy and a risk–benefit balance of different drug combinations.[29] The only ongoing cardiovascular outcome trial with an active comparator is CAROLINA,[30] in which the dipeptidyl peptidase-4 inhibitor linagliptin is being compared with the sulfonylurea glimepiride. Moreover, most of the cardiovascular outcome trials reported so far have had a much shorter duration than did TOSCA.IT. The vascular effects of antidiabetes drugs took about 5 years to be detected in both the UKPDS and the Diabetes Control and Complications Trial, and possible effects on cancer and fractures will probably take a similar time to become apparent.[2,3] Therefore, trials such as TOSCA.IT, which have a sufficiently long follow-up, are needed to effectively address the crucial question of the comparative balance of risks and benefits in relation to relevant treatment strategies for type 2 diabetes. A further strength of our study is that the patients enrolled were mostly free of previous cardiovascular events. To date, information about the effect of different types of glucose-lowering drugs in this group of low-risk patients is scarce. Unfortunately, because patients with a previous

cardiovascular event in our study population were so few, it was not possible to do a meaningful subanalysis in this group.

This study also has limitations. First, the incidence of the primary endpoint was lower than anticipated, leading to a lower statistical power than planned. The low incidence of cardiovascular events might be related to the characteristics of the patients enrolled and to the intensive treatment of cardiovascular risk factors. A further limitation is the rate of discontinuation of the study drugs, which, although in line with the IRIS trial,[11] was unbalanced between the study groups (ie, significantly higher in patients treated with pioglitazone). This difference in discontinuation might dilute differences between the study groups, as suggested by the results of the post-hoc on-treatment analysis. Additionally, the study is based on a PROBE design; therefore, although the components of the primary outcome and some selected adverse events (ie, heart failure, fractures, macular oedema, and neoplasms) were adjudicated by an independent committee unaware of treatment group assignment, both patients and study physicians were not masked to treatment assignment.

In conclusion, the results from this pragmatic trial show that, within an usual clinical setting and over a median observation period of almost 5 years, both sulfonylureas (mostly glimepiride and gliclazide) or pioglitazone have a similar effect as add-on to metformin on the incidence of total cardiovascular events. This finding suggests that in patients with type 2 diabetes without cardiovascular diseases and with reasonable glucose control, the choice of the treatment strategy when metformin monotherapy fails might not have a major effect on cardiovascular complications. Additionally, the two treatment strategies effectively controlled blood glucose in the long term, with few clinically relevant side-effects. Altogether, our study suggests that both pioglitazone or a sulfonylurea are suitable alternatives as add-on treatment to metformin, although the combination of metformin and pioglitazone was advantageous in terms of durability of glycaemic control and frequency of hypoglycaemia. These results are relevant for public health in view of the affordability and wide availability of the study drugs. Further studies are needed to assess whether similar results could be obtained in head-to-head comparisons of these commonly used drugs with newer glucose-lowering drugs.

Contributors

OV, MM, AN, AAR, EB, SDP, APM, SSq, CBG, GS, PM, and GR contributed to the design of the study, and the analysis and interpretation of data. OV, MM, and GR wrote the first draft of the report. AN, AAR, EB, SDP, APM, SSq, CBG, GS, and PM provided relevant intellectual contribution to the development of the report. AN, GL, and MS did the statistical analysis. SSi and FC were responsible for the central laboratory (running of the laboratory and laboratory results). All authors provided substantial contribution to the acquisition of data, critically revised the report, and gave final approval of the version to be submitted for publication.

Declaration of interests

OV has received speaker's fees from Novartis and Sanofi-Aventis; research grants to the her institution from Guidotti; and travel support from Sigma Tau. MM has received honoraria for consulting activity from AstraZeneca, Eli Lilly, and Johnson & Johnson; and travel support from Sanofi-Aventis, Eli Lilly, and Sigma Tau. AN has received speaking fees or research funding from Novo Nordisk, AstraZeneca, Medtronic, Sanofi-Aventis, Sigma Tau, and Eli Lilly. EB has received consultancy fees from Abbott, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Bruno Farmaceutici, Janssen, Johnson & Johnson, Eli Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Roche, Sanofi, Servier, and Takeda; has worked on clinical trials funded by Amgen, Janssen, Eli Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, and Sanofi; and has received research support from AstraZeneca, Genzyme, Menarini Diagnostics, Novo Nordisk, Roche, and Takeda. SDP has received fees for participation on advisory panels for AstraZeneca, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Intarcia, Janssen, Merck, Novartis, Novo Nordisk, Sanofi, Servier, and Takeda; and has received research support from AstraZeneca, Boehringer Ingelheim, Merck, and Novartis. APM has received personal fees from Novartis, Bayer, Cardiorentis, Fresenius, and Sanofi for the participation in trial committees. AAR has received speaker's fees from Sanofi-Aventis and Eli Lilly; has received travel support from Sanofi-Aventis; has worked on clinical trials funded by Sanofi-Aventis and GlaxoSmithKline; and has participated in a research project with Medtronic. GS has received honoraria for consulting activity or speaking engagements from Servier, Intarcia Therapeutics, Novo Nordisk, Janssen, Boehringer Ingelheim, Eli Lilly, AstraZeneca, Merck Sharp & Dohme, Sanofi, Abbott, and Pfizer. ACBa has received travel support from Eli Lilly, Sanofi-Aventis, Bayer, and Novo Nordisk. GC reports personal fees from Bayer, Medtronic, Novartis, and Eli Lilly. RI has received speaker's fees from Sanofi, Sigma Tau, and Guidotti. CS has received personal fees from AstraZeneca, Eli Lilly, and Sanofi-Aventis. MB has received speaker's fees from Sanofi, Eli Lilly, Novo Nordisk, Boehringer Ingelheim, Merck Sharp & Dohme, Sigma Tau, Novartis, and AstraZeneca; and has received fees for participation in advisory boards from Sanofi, Eli Lilly, and Janssen. LT has received personal fees from Sanofi, Artsana, Roche, and Novo Nordisk. GPu has received personal fees from AbbVie, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Shire, and Takeda. DL has received personal fees from Boehringer Ingelheim/Eli Lilly, AbbVie, Merck, Sanofi, and Novo Nordisk. ACBo has received consultancy fees, received advisory board fees, or received lecture fees for Eli Lilly, Novo Nordisk, Sanofi, Johnson & Johnson, Boehringer Ingelheim, Takeda, Bayer, and Artsana. FD has received personal fees from Novo Nordisk, Eli Lilly, AstraZeneca, and Merck Sharp & Dohme. DA has received speaker's fees from Sanofi and Novo Nordisk; and travel support from Bruno. FG has received fees for participation on advisory boards for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Roche Diagnostics, and Takeda; has received consultancy fees from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Lifescan, Merck Sharp & Dohme, Novo Nordisk, and Sanofi; and has received research support from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Lifescan, Sanofi, and Takeda. CS has received personal fees from Boehringer Ingelheim, Eli Lilly, Novartis, Novo Nordisk, and Sanofi-Aventis. PDB has received personal fees from Eli Lilly, Novo Nordisk, Abbot Diagnostics, AstraZeneca, Sanofi, Boehringer, Janssen, MD, and Novartis. PF has received speaker's fees from Takeda, Merck Sharp & Dohme, and Eli Lilly. GR has worked on clinical trials funded by Boehringer Ingelheim, Merck Sharp & Dohme, and Sanofi; has received travel support from Takeda; has received research grants to his institution from Guidotti; and has received speaker's fees from Eli Lilly and Sanofi. All other authors declare no competing interests.

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