Low-dose combination therapy with rosiglitazone and metformin to prevent type 2 diabetes mellitus (CANOE trial): a double-blind randomised controlled study

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Summary

Background The evolving epidemic of type 2 diabetes has challenged health-care providers to assess the safety and efficacy of various diabetes prevention strategies. The CANOE (CAnadian Normoglycemia Outcomes Evaluation) trial investigated whether low-dose combination therapy would affect development of type 2 diabetes.

Methods In this double-blind, randomised controlled trial undertaken in clinics in Canadian centres, 207 patients with impaired glucose tolerance were randomly assigned to receive combination rosiglitazone (2 mg) and metformin (500 mg) twice daily or matching placebo for a median of 3·9 years (IQR 3·0–4·6). Randomisation was computer-generated in blocks of four, with both participants and investigators masked to treatment allocation. The primary outcome was time to development of diabetes, measured by an oral glucose tolerance test or two fasting plasma glucose values of 7·0 mmol/L or greater. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00116932.

Findings 103 participants were assigned to rosiglitazone and metformin, and 104 to placebo; all were analysed. Vital status was obtained in 198 (96%) participants, and medication compliance (taking at least 80% of assigned medication) was 78% (n=77) in the metformin and rosiglitazone group and 81% (n=80) in the placebo group. Incident diabetes occurred in significantly fewer individuals in the active treatment group (n=14 [14%]) than in the placebo group (n=41 [39%]; p<0·0001). The relative risk reduction was 66% (95% CI 41–80) and the absolute risk reduction was 26% (14–37), yielding a number needed to treat of 4 (2·70–7·14). 70 (80%) patients in the treatment group regressed to normal glucose tolerance compared with 52 (53%) in the placebo group (p=0·0002). Insulin sensitivity decreased by study end in the placebo group (median −1·24, IQR −2·38 to −0·08) and remained unchanged with rosiglitazone and metformin treatment (−0·39, −1·30 to 0·84; p=0·0006 between groups). The change in β-cell function, as measured by the insulin secretion-sensitivity index-2, did not differ between groups (placebo −252·3, −382·2 to −58·0 *vs* rosiglitazone and metformin −221·8, −330·4 to −87·8; p=0·28). We recorded an increase in diarrhoea in participants in the active treatment group compared with the placebo group (16 [16%] *vs* 6 [6%]; p=0·0253).

Interpretation Low-dose combination therapy with rosiglitazone and metformin was highly effective in prevention of type 2 diabetes in patients with impaired glucose tolerance, with little effect on the clinically relevant adverse events of these two drugs.

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Introduction

Several studies have conclusively shown that lifestyle changes[1–4] and some pharmacological interventions[1,4–8] can substantially reduce the development of type 2 diabetes mellitus in individuals with impaired glucose tolerance (IGT; fasting glucose <7 mmol/L and postload glucose 7·8–11·0 mmol/L) or impaired fasting glucose (IFG; fasting glucose 6·1–6·9 mmol/L), or both. However, not all drug-based interventions are effective[9] and, most recently, the use of the β-cell secretagogue nateglinide did not show any beneficial effect on the development of type 2 diabetes.[10] Despite these largely positive findings, screening of at-risk populations with the implementation of either programmed lifestyle interventions or pharmacological therapies has not been widely embraced. Screening has not been adopted for many reasons, including unclear health economic benefits, difficulties in implementation of the lifestyle interventions in clinical practice, and the potential for adverse effects from the pharmacological interventions that have been shown to be effective.

The pathophysiology of type 2 diabetes is complex and involves at least two major abnormalities—namely, insulin resistance and impaired β-cell function.[11] In this context, interest has grown in use of combination therapies early in the management of diabetes to effectively target the underlying abnormalities that cause this common metabolic disorder. At the same time, the implementation of low-dose combination therapy in patients with type 2 diabetes could reduce the undesirable adverse effects associated with many oral antidiabetic agents.[12] These principles and considerations probably also apply to individuals who have not yet developed diabetes but have either IGT or

IFG. However, until now there have been no studies assessing low-dose combination therapies for the prevention of type 2 diabetes.

The thiazolidinedione rosiglitazone, studied in the DREAM trial,[6] effectively reduces the progression from IGT, IFG, or combined IGT and IFG to type 2 diabetes (60% relative risk reduction), and has durability (ADOPT study) in the context of monotherapy for recent onset (within 3 years) type 2 diabetes.[13] A post-hoc analysis from the DREAM trial has indicated that this effect of rosiglitazone is probably secondary to improvement of β-cell function.[14] However, at the recommended maximum doses, which were used in the DREAM and ADOPT studies, rosiglitazone was associated with an increased risk of undesirable outcomes—namely, weight gain, fluid retention, increased risk of heart failure, and bone fractures.[6,13] Metformin is a commonly used oral hypoglycaemic agent and is generally recommended as first-line therapy in most clinical practice guidelines for type 2 diabetes.[15] However, metformin is associated with significant gastrointestinal side-effects, particularly when it is used at maximum recommended doses. In the Diabetes Prevention Program (DPP), metformin at a dose of 850 mg twice daily was moderately effective in prevention of progression to type 2 diabetes (31% relative risk reduction compared with placebo) but was associated with an increased rate of gastrointestinal side-effects compared with placebo (77·8 *vs* 30·7 events per 100 person-years).[1] This rate of gastrointestinal side-effects with metformin seems to be higher than that which is generally recorded in clinical practice.

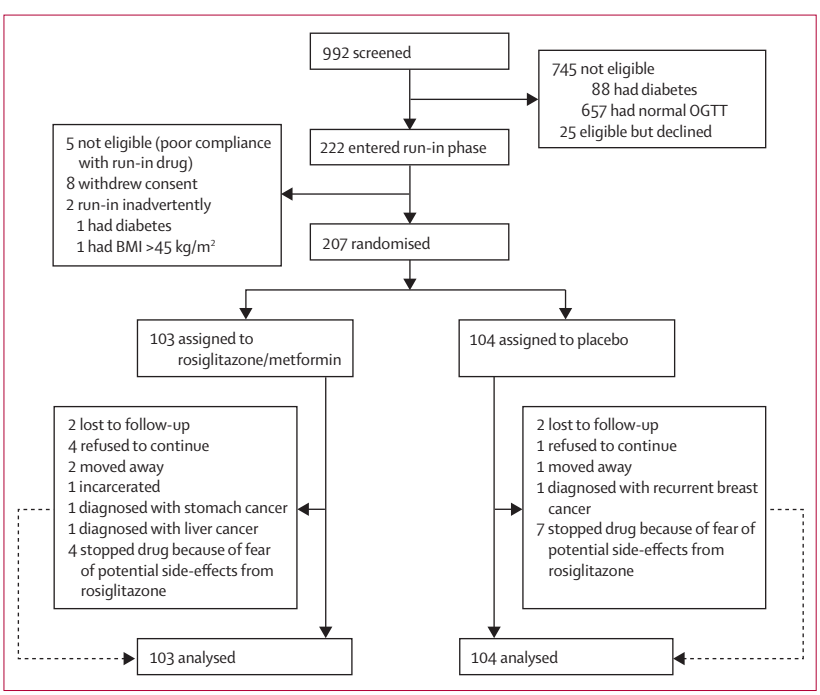

Figure 1: **Trial profile**
OGTT=oral glucose tolerance test. BMI=body-mass index.

Because thiazolidinediones and metformin have different mechanisms of action (increasing insulin sensitivity and reducing hepatic glucose production, respectively) and have both been shown to reduce the development of diabetes in patients with IGT, to establish whether this combination at half the maximum dose would provide a robust effect on diabetes prevention, while minimising undesirable side-effects, would be of interest. The CAnadian Normoglycemia Outcomes Evaluation (CANOE) trial assessed whether combination therapy with half the maximum dose of rosiglitazone and metformin on a background of a structured lifestyle intervention would prevent type 2 diabetes in individuals with IGT.

Methods

Study design and participants

A detailed description of the design and methods of the CANOE trial—a double-blind, randomised controlled study—has been previously published.[16] Study recruitment was undertaken between April 28, 2004, and Oct 30, 2006. In the active treatment group of the trial, patients received metformin 500 mg plus rosiglitazone 2 mg administered as a fixed-dose combination in one capsule twice daily. The response was compared with patients receiving a matched placebo. All patients received lifestyle intervention consisting of an active phase in the first year, made up of five one-on-one sessions lasting about 30 min each, followed by a passive phase for the remainder of the study when patients received additional educational materials either posted monthly on a website, or through newsletters with healthy lifestyle messaging.

Eligible patients were residents of the province of Ontario, Canada and were able to attend clinic visits in Toronto or London, Ontario. The study participants chosen to take part in this trial were aged 30–75 years inclusive for the general population, and 18–75 years for those of Canadian native ancestry (only three randomly assigned). To undergo a screening oral glucose tolerance test (OGTT) participants had to have at least one risk factor for type 2 diabetes: overweight (body-mass index [BMI] >25 kg/m² but not exceeding 45 kg/m²), family history of type 2 diabetes, self-reported high blood pressure (on medication or not), a history of gestational diabetes, or having given birth to a macrosomic infant. People were able to participate in the trial if they met the following criteria: diagnosis of IGT based on a fasting plasma glucose test result of less than 7·0 mmol/L and a plasma glucose value of 7·8 mmol/L or more and less than 11·1 mmol/L, 2 h after a 75 g oral glucose load. Potential participants were excluded if they had current use of metformin or rosiglitazone, previous use of a medication to treat diabetes with the exception of gestational diabetes, significant hepatic disease (transaminases >2·5 times the upper limit of normal), or renal dysfunction (serum

creatinine >136 μmol for men or >124 μmol for women). A 3-week (range 2–4) run-in period was scheduled with placebo only. Run-in must have taken place within 4 months of screening, and potential participants must have taken at least 80% of the pills to be eligible for randomisation. Height, weight, and waist and hip circumference were measured twice with standardised procedures, with the average used in the analysis. Waist circumference was measured at the natural waist, defined as the narrowest part of the torso, as viewed from behind, or the smallest circumference between the umbilicus and the xiphoid process as viewed from the front. Hip circumference was measured at the level of maximum extension of the buttocks as viewed from the side. Blood pressure was measured twice in the right arm with the participant seated after 5 min rest with an automatic sphygmomanometer.

CANOE was approved by the Institutional Review Boards of Mount Sinai Hospital (Toronto, ON, Canada) and the University of Western Ontario (London, ON, Canada). An independent data safety and monitoring board was established to review safety issues.

Randomisation and masking

Randomisation was done in blocks of four, and the study medication was distributed to the two sites. Compliance with the study medication was measured with pill count at every clinic visit. The randomisation code was generated in the GlaxoSmithKline Random System RandAll, a web server-based clinical trials randomisation system. The system uses SAS (version 8.2) to generate random codes and create a randomisation file. All study staff were masked to the group to which each participant was assigned, and active therapy and placebo were in identical capsules.

Outcomes

The primary outcome was the development of new onset type 2 diabetes diagnosed by either two fasting plasma glucose values of 7·0 mmol/L or more, or one positive OGTT with the 2-h plasma glucose value greater than 11·0 mmol/L. The date of diagnosis of diabetes was the date of the positive OGTT or the confirmatory plasma fasting glucose. Fasting plasma glucose was measured twice yearly and the OGTT every year. Secondary outcomes were changes in blood pressure, microalbuminuria, C-reactive protein (CRP), and lipid profile; and insulin sensitivity and β-cell function measures derived from the OGTT.

Procedures

Study participants received a telephone call 2 weeks (range 1–3) after randomisation to assess side-effects of the medication, and then made clinic visits every 2 months (1·5–2·5) thereafter for the first year. They were then seen every 6 months (5–7) for the duration of the study. At the midpoint of each 6-month interval, participants had a telephone visit to encourage compliance with taking study medications and to record information about side-effects and adverse events. At every clinic visit, data were collected for adverse events, compliance,

	Placebo (N=104)	Rosiglitazone and metformin (N=103)
Age (years)	55·0 (46·0–61·0)	50·0 (44·0–61·0)
Sex		
Female	71 (68·3%)	67 (65·0%)
Male	33 (31·7%)	36 (35·0%)
Ethnic origin		
White	77 (74·0%)	77 (74·8%)
South Asian	7 (6·8%)	8 (7·8%)
Latino	7 (6·7%)	7 (6·8%)
Others	13 (12·5%)	11 (10·7%)
Family history of diabetes	75 (72·8%)	73 (73·0%)
Smoking		
Never	63 (60·6%)	62 (60·2%)
Remote*	31 (29·8%)	35 (34·0%)
Current	10 (9·6%)	6 (5·8%)
History of hypertension	36 (34·6%)	41 (39·8%)
History of dyslipidaemia	31 (29·8%)	37 (35·9%)
Metabolic syndrome (AHA)	61 (59·2%)	66 (66·0%)
Metabolic syndrome (IDF)	68 (66·2%)	75 (75·0%)
History of CVD	3 (2·9%)	5 (4·9%)
Medications		
ACE or ARB	21 (20·2%)	27 (26·2%)
Other antihypertensives	29 (27·9%)	24 (23·3%)
Statin	15 (14·4%)	22 (21·4%)
Anthropometry		
Weight (kg)	86·3 (75·2–103·4)	89·9 (75·0–101·0)
BMI (kg/m²)	32·0 (28·3–36·8)	31·3 (27·1–35·7)
Waist circumference (cm)	103·0 (94·6–116·4)	104·3 (93·5–113·6)
Waist to hip ratio	0·90 (0·85–0·96)	0·90 (0·85–0·96)
Systolic blood pressure (mm Hg)	127·5 (118·0–140·8)	130·0 (115·5–139·0)
Diastolic blood pressure (mm Hg)	81·8 (75·3–87·5)	80·0 (74·5–87·5)
Liver/renal test		
ALT (U/L)	30·0 (22·0–38·0)	30·0 (21·0–42·0)
Serum creatinine (μmol/L)	71·0 (61·5–81·5)	70·0 (60·0 – 82·0)
Lipids		
Total cholesterol (mmol/L)	5·40 (4·80–6·10)	4·90 (4·20–5·60)
LDL cholesterol (mmol/L)	3·40 (2·90–4·00)	2·90 (2·30–3·60)
HDL cholesterol (mmol/L)	1·10 (1·00–1·40)	1·10 (0·90–1·30)
Triglycerides (mmol/L)	1·66 (1·16–2·22)	1·70 (1·17–2·21)
CRP (mg/L)	3·10 (1·40–5·00)	2·80 (1·65–6·10)
BNP (pmol/L)	3·60 (1·10–6·30)	3·40 (1·60–6·50)
Insulin sensitivity		
IS_{OGTT}	3·02 (2·24–5·46)	2·87 (1·91–4·53)
Insulin resistance		
HOMA-IR	2·9 (1·66–4·09)	3·31 (1·85–4·79)
β-cell function		
ISSI-2	490·2 (383·8–564·3)	499·4 (407·7–603·1)
HOMA-B	127·2 (82·2–191·0)	148·4 (90·6–244·8)

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	Placebo (N=104)	Rosiglitazone and metformin (N=103)
(Continued from previous page)		
Oral glucose tolerance test		
Fasting glucose (mmol/L)	5·4 (5·0–5·9)	5·4 (5·0–5·8)
30-min glucose (mmol/L)	9·8 (8·9–10·8)	9·2 (8·3–10·4)
2-h glucose (mmol/L)	8·8 (8·2–9·9)	8·9 (8·2–9·8)
Glucose tolerance status		
Isolated IGT	88 (84·6%)	92 (89·3%)
Combined IGT and IFG	16 (15·4%)	11 (10·7%)

Data are median (IQR) or number (%). AHA=American Heart Association. IDF=International Diabetes Federation. CVD=cardiovascular disease. ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blockers. BMI=body-mass index. ALT=alanine aminotransferase. CRP=C-reactive protein. BNP=pro-brain natriuretic peptide. IS=insulin sensitivity. OGTT=oral glucose tolerance test. HOMA-IR=homoeostasis model of assessment of insulin resistance. ISSI-2=insulin secretion-sensitivity index-2. HOMA-B=homoeostasis model of assessment of β-cell function. IGT=impaired glucose tolerance. IFG=impaired fasting glucose. *Defined as any history of past smoking but not currently smoking.

Table 1: **Demographic, clinical, and metabolic characteristics at baseline**

	Placebo (N=104)	Rosiglitazone/ metformin (N=103)	p value
Diabetes	41 (39·4%)	14 (13·6%)	<0·0001*
Regression to NGT	52 (53·1%)	70 (79·6%)	0·0002*
CVD events			
MI	1 (0·96%)	0	1·00
CHF	1 (0·96%)	0	1·00
Bone fracture	6 (5·8%)	4 (3·9%)	0·75
Large changes in weight			
Weight gain >2 kg	33 (32·4%)	28 (28·0%)	0·54
Weight gain >3 kg	22 (21·6%)	22 (22·0%)	1·00
Weight loss >2 kg	39 (38·2%)	27 (27·0%)	0·10
Weight loss >3 kg	31 (30·4%)	21 (21·0%)	0·15

Data are number (%), unless otherwise indicated. p values were obtained from χ^2 test or Fisher's exact test, when necessary. NGT=normal glucose tolerance. CVD=cardiovascular disease. MI=myocardial infarction. CHF=congestive heart failure. *p value for time to develop diabetes or time to regression to NGT were obtained from log-rank test.

Table 2: **Primary outcome and major clinical events of interest**

anthropometrics, blood pressure, and weight, and medication was dispensed. To monitor the safety of rosiglitazone, measurement of alanine transaminase (ALT) was made at every visit in the first year and every 6 months thereafter. Any values exceeding three times the upper limit of normal were repeated and if confirmed, the study drug was discontinued. Also done at every yearly visit were biochemistry, complete blood count, insulin, lipids, CRP, and pro-brain natriuretic peptide (NT-proBNP). Metabolic assessments during the study were done while on treatment, but participants did not take study medications in the morning on the days that they had an OGTT. Adverse events were reviewed by the principal investigators who were masked to assignment.

Insulin was measured with the ROCHE Elecsys 1010 immunoassay analyser and the electrochemiluminescence immunoassay kit (Roche Diagnostic, Basel, Switzerland). The assay shows 0·05% cross-reactivity with intact human pro-insulin in the primary split form (Des-31, 32). CRP concentration was measured with the Behring BN 100 and the N high-sensitivity CRP reagent (Dade Behring, Mississauga, ON, Canada). The concentration of proBNP was measured with an electrochemiluminescence immunoassay kit (Roche Diagnostic, Basel, Switzerland) with the Roche Elecsys 1010 immunoassay analyser.

Insulin sensitivity was calculated with the Matsuda index (IS_{OGTT}), a measure of whole-body insulin sensitivity that has been validated against the euglycaemic-hyperinsulinaemic clamp.[17] Insulin resistance was measured by the homoeostasis model of assessment of insulin resistance (HOMA-IR), as described by Matthews and colleagues.[18] β-cell function was assessed with the insulin secretion-sensitivity index-2 (ISSI-2). ISSI-2—defined as the ratio of the area under the insulin curve (AUC_{ins}) to the area under the glucose curve (AUC_{gluc}) multiplied by IS_{OGTT}—is an OGTT-derived measure of β-cell function that is analogous to the disposition index obtained from the frequently sampled intravenous glucose tolerance test and that shows stronger correlation with the disposition index than do other OGTT-based measures.[19,20] The homoeostasis model of assessment of β-cell function (HOMA-B) was calculated as a secondary measure of β-cell function.[18]

Statistical analysis

With the assumption that the median time to the development of diabetes was 6·25 years, a sample size of 100 participants per study group with a median of 3·2 years of follow-up would provide 80% power to detect a relative risk of 0·545, which is equivalent to a risk reduction of 45%, with a two-sided log-rank test at a significance level of 0·05.

The statistical analyses were based on the intention-to-treat population. Separate product-limit estimated cumulative incidence curves were calculated for the two treatment groups and compared with the log-rank test. Cox proportional hazards models were used to assess the effect of rosiglitazone and metformin on the hazard of the primary outcome and the time to regression to normal glucose tolerance. For the primary outcome, participants who prematurely discontinued follow-up were censored as of their last contact. Baseline characteristics of the two study groups were summarised with means and SDs for continuous variables, and frequencies and percentages for categorical variables. The Wilcoxon rank-sum test was used to assess differences between the two study groups for continuous variables, and χ^2 test (or Fisher's exact test when necessary) for categorical variables. Data for the primary outcome and major clinical events of interest are presented as frequencies and percentages for categorical variables. χ^2 test (or Fisher's exact test when necessary) was used to assess for differences between the two study groups for categorical variables, and log-rank test was

used for assessing time to develop diabetes or time to regression to normal glucose tolerance between the two study groups. The Wilcoxon rank-sum test was also used to measure for differences in BMI, waist, waist to hip ratio, total cholesterol, LDL, HDL, triglycerides, ALT, CRP, BNP, IS_{OGTT}, HOMA-IR, ISSI-2, and HOMA-B between the study groups at baseline and study end, and in their respective changes from baseline. All analyses were done with SAS (version 9.2). A p value less than 0·05 was regarded as statistically significant.

The study is registered with ClinicalTrials.gov, number NCT 00116932.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or in the 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

Figure 1 shows the trial profile. 207 eligible participants with either isolated IGT or combined IFG and IGT were randomly assigned to receive either placebo or rosiglitazone and metformin combination therapy (figure 1). Table 1 shows the baseline characteristics of the study participants. The only significant differences between the two groups at baseline were lower concentrations of total and LDL cholesterol in the treatment group (p=0·0002 and p=0·0003, respectively) compared with placebo.

Participants were followed up for a median of 3·9 years (IQR 3·0–4·6). During the course of the trial, 55 individuals developed diabetes as diagnosed on the basis of a study-related OGTT (n=44), fasting glucose of 7·0 mmol/L or more on two occasions (n=9), or physician diagnosis (n=2). Of the remaining 152 participants, 130 completed a final visit, 13 provided verbal report of their diabetes status, and nine did not respond to this inquiry. We thus had complete vital status for 198 of 207 (96%) participants. At their final study visit, of the 198 individuals in whom adherence could be assessed by pill count (99 in each group), the numbers taking at least 80% of their assigned study medication were 77 (78%) in the treatment group and 80 (81%) in the placebo group (p=0·60). The most common reason for stopping the study medication was concern about side-effects with rosiglitazone (figure 1).

The primary outcome of incident diabetes occurred in significantly fewer individuals in the active treatment group than in the placebo group (table 2). The relative risk reduction was 66% (95% CI 41–80) and the absolute risk reduction was 26% (14–37), yielding a number needed to treat of 4 (2·70–7·14) over a mean of 3·9 years. The event curves for the development of diabetes diverged by the time of the first study assessment at 1-year of follow-up, and the overall hazard ratio was 0·31 (95% CI 0·17–0·58, p=0·0002; figure 2). Furthermore, by study end, a significantly greater number of individuals had regressed to normal glucose tolerance in the treatment group than in the placebo group (table 2). Thus, at the final study assessment, although about 5% of participants in each group remained in the prediabetic range, the study groups otherwise differed substantially in glucose

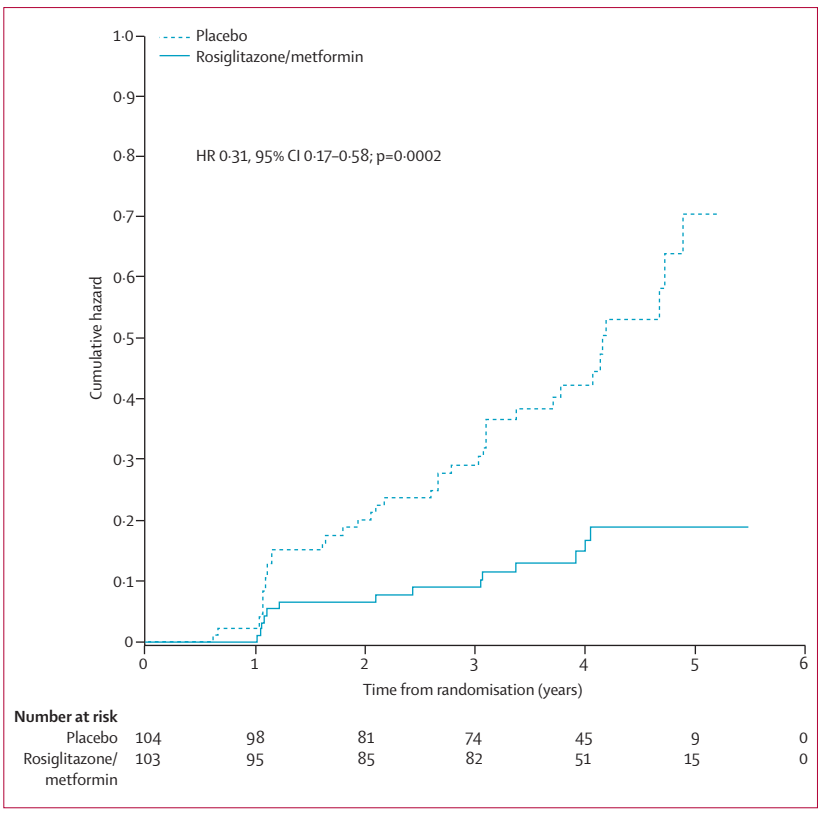

Figure 2: **Time to occurrence of the development of diabetes**
HR=hazard ratio.

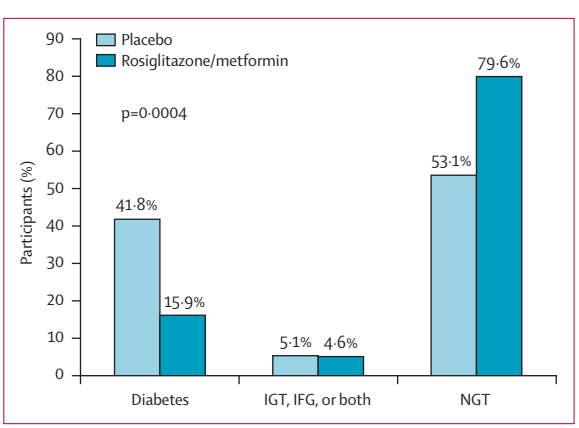

Figure 3: **Proportion of participants who developed diabetes, regressed to normal glucose tolerance (NGT), or had impaired glucose tolerance (IGT) or impaired fasting glucose (IFG), or both, at last study visit, by treatment group, as measured by the oral glucose tolerance test**
p value obtained from χ^2 test.

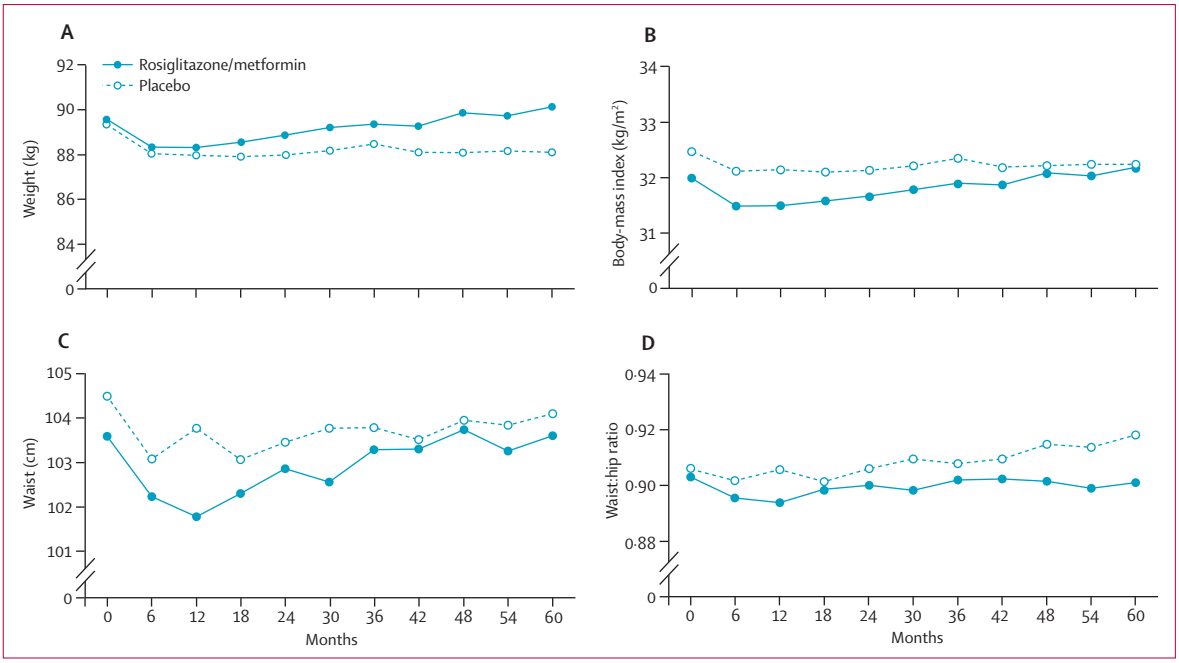

Figure 4: **The effects of rosiglitazone plus metformin and placebo on weight (A), body-mass index (B), waist circumference (C), and waist to hip ratio (D)**
Mean values for each measure are shown by group every 6 months. The change from baseline was not significant between the groups for all variables at each timepoint.

tolerance status, with almost 80% of the treatment group showing regression to normal glucose tolerance whereas nearly half of the placebo group had developed diabetes (overall p=0·0004; figure 3).

During the study, we recorded no cases of myocardial infarction or heart failure in the treatment group and one case of each in the placebo group (table 2). The occurrence of bone fractures was similar between the treatment and placebo groups (table 2). Furthermore, we noted no significant differences between the groups in either the gain or loss of at least 2 kg or 3 kg of weight (table 2). During the study, groups did not differ significantly with respect to changes in weight, BMI, waist circumference, and waist to hip ratio (figure 4).

At study end, the use of statin medication did not differ significantly between the groups (treatment group 29 [28%] *vs* placebo 38 [37%]; p=0·20). In view of questions about statins and incident diabetes,[21] we tested for interaction between statin use and treatment group and noted no significant interaction (p=0·68), indicating that statin use did not affect treatment effect for the primary outcome. Both total cholesterol and LDL cholesterol at study end remained lower in the treatment group (table 3), as they had been at baseline. Although the changes in anthropometric parameters were similar between the groups, we noted a significant difference in the change in CRP, which decreased to a greater extent in the rosiglitazone and metformin group (median change –0·70 mg/L, IQR –2·70 to 0·10) than in the placebo group (–0·25 mg/L, –1·00 to 0·50; p=0·0027 between groups). We also noted a greater decrease in ALT in the treatment group (–6·5 U/L, –16·0 to –1·0) than in the placebo group (–4·0 U/L, –11·0 to 4·0; p=0·0060 between groups). Furthermore, by study end, insulin sensitivity (IS_{OGTT}) had decreased to a greater extent in the placebo group (–1·24, –2·38 to –0·08) than in the rosiglitazone and metformin group (–0·39, –1·30 to 0·84; p=0·0006 between groups). We noted no significant difference between the groups in the change in β-cell function (ISSI-2) from baseline to study end (rosiglitazone and metformin: –221·8, –330·4 to –87·8; placebo: –252·3,

	Placebo	Rosiglitazone/metformin	p value
BMI (kg/m²)			
Baseline	32·0 (28·3 to 36·9)	31·2 (27·1 to 35·8)	0·58
End	32·0 (27·6 to 35·8)	31·6 (28·0 to 35·8)	0·62
Change from baseline	–0·1 (–1·2 to 1·2)	0·1 (–0·9 to 1·1)	0·47
Waist circumference (cm)			
Baseline	102·6 (94·6 to 116·3)	104·3 (93·4 to 113·7)	0·85
End	102·8 (94·8 to 113·8)	104·3 (94·1 to 112·6)	0·89
Change from baseline	0·1 (–4·50 to 3·40)	–0·0 (–4·3 to 3·9)	0·97
Waist to hip ratio			
Baseline	0·90 (0·85 to 0·96)	0·90 (0·85 to 0·96)	0·98
End	0·92 (0·87 to 0·97)	0·90 (0·85 to 0·96)	0·083
Change from baseline	0·01 (–0·02 to 0·03)	–0·00 (–0·02 to 0·03)	0·17
Total cholesterol (mmol/L)			
Baseline	5·45 (4·80 to 6·10)	4·90 (4·20 to 5·60)	0·0003
End	5·00 (4·40 to 5·80)	4·80 (4·30 to 5·60)	0·47
Change from baseline	–0·30 (–0·90 to 0·20)	0·00 (–0·30 to 0·40)	0·0009

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–382·2 to –58·0; p=0·28 between groups). We recorded a significant increase in diarrhoea in participants assigned to rosiglitazone and metformin, but no difference in other gastrointestinal symptoms, swollen ankles, fluid retention (based on BNP changes), or hypoglycaemia (table 4).

Discussion

Findings from the CANOE trial have shown that the combination of the thiazolidinedione rosiglitazone with metformin at half the maximum dose was highly effective in prevention of diabetes and in normalisation of glucose tolerance in individuals with IGT, with little effect on the well known clinically relevant adverse events of these two drugs. These results lend support to the notion of use of low-dose combination therapies as an effective means to manage complex metabolic disorders.

A comprehensive approach to the global epidemic of type 2 diabetes should include at least three strategies. First, a lifestyle intervention is needed, focusing on obesity and physical inactivity, with the option of pharmacological intervention for the primary prevention of diabetes. We can assume that if we prevent diabetes from occurring, diabetes-specific complications will be reduced. Second, more effective management of hyperglycaemia, lipid abnormalities, and blood pressure in individuals who already have diabetes has clearly been shown to reduce the risk of long-term complications.[22–25] Finally, for individuals with diabetes and end-organ complications, effective management of these complications (eg, laser therapy, renal replacement therapy, etc) significantly improves their quality of life and clinical outcomes.

Although primary prevention is a particularly attractive option, little progress has been made in implementation of an effective diabetes prevention programme despite favourable results from several long-term, well undertaken, randomised controlled trials showing the effectiveness of both lifestyle and pharmacological intervention strategies that have been systematically reviewed.[8] Traditional efforts at lifestyle interventions at a health-care professional level have been disappointing, and many have suggested that community-based or societal-based programmes similar to antismoking campaigns are needed. Pharmacologically, there seem to be equally effective interventions; however, concern with adverse effects and long-term safety might have resulted in slow adoption of these strategies. Thiazolidinediones, in particular, are very effective in reducing the development of type 2 diabetes in individuals with IGT or IFG, or both,[6,7,26] with an approximate 60% reduction in the relative risk of conversion to type 2 diabetes. In this regard metformin and acarbose were considerably less effective, with 31% and 25% reductions in relative risk, respectively.[1,5] However, in the DREAM study, the beneficial effect of thiazolidinediones on glucose tolerance was also associated with significant increased risks of congestive heart failure and weight gain. With metformin, there are substantial tolerability issues related to the gastrointestinal side-effects, even at the submaximum doses (1700 mg) used in the DPP.

	Placebo	Rosiglitazone/metformin	p value
(Continued from previous page)			
LDL cholesterol (mmol/L)			
Baseline	3·40 (2·90 to 4·00)	2·90 (2·30 to 3·60)	0·0003
End	3·00 (2·50 to 3·60)	2·70 (2·40 to 3·60)	0·38
Change from baseline	–0·40 (–0·70 to 0·10)	0·00 (–0·40 to 0·40)	0·0025
HDL cholesterol (mmol/L)			
Baseline	1·15 (1·00 to 1·40)	1·20 (1·00 to 1·35)	0·44
End	1·10 (1·00 to 1·50)	1·20 (1·00 to 1·50)	0·69
Change from baseline	0·00 (–0·10 to 0·10)	0·00 (0·00 to 0·20)	0·0283
Triglycerides (mmol/L)			
Baseline	1·63 (1·16 to 2·18)	1·68 (1·17 to 2·14)	0·91
End	1·48 (1·13 to 1·95)	1·52 (1·14 to 1·93)	0·99
Change from baseline	–0·07 (–0·40 to 0·34)	–0·10 (–0·44 to 0·35)	0·96
ALT (U/L)			
Baseline	30·0 (22·0 to 37·0)	29·5 (21·0 to 40·5)	0·88
End	25·0 (19·0 to 38·0)	21·0 (15·0 to 29·0)	0·0033
Change from baseline	–4·0 (–11·0 to 4·0)	–6·5 (–16·0 to –1·0)	0·0060
CRP (mg/L)			
Baseline	2·85 (1·30 to 4·60)	2·80 (1·50 to 5·90)	0·49
End	2·40 (1·00 to 5·20)	1·75 (0·90 to 3·90)	0·098
Change from baseline	–0·25 (–1·00 to 0·50)	–0·70 (–2·70 to 0·10)	0·0027
BNP (pmol/L)			
Baseline	3·70 (1·10 to 6·20)	3·40 (1·60 to 6·65)	0·60
End	3·90 (1·60 to 8·40)	5·10 (2·20 to 10·20)	0·14
Change from baseline	0·60 (–1·80 to 3·60)	0·75 (–1·50 to 3·60)	0·51
IS_{OGTT}			
Baseline	3·00 (2·24 to 5·46)	2·87 (1·91 to 4·57)	0·36
End	1·96 (1·28 to 3·02)	2·42 (1·52 to 4·57)	0·0450
Change from baseline	–1·24 (–2·38 to –0·08)	–0·39 (–1·30 to 0·84)	0·0006
HOMA-IR			
Baseline	2·90 (1·64 to 4·09)	3·31 (1·83 to 4·79)	0·19
End	7·77 (3·40 to 16·65)	7·81 (2·93 to 14·53)	0·29
Change from baseline	5·12 (0·55 to 13·23)	3·93 (0·59 to 9·19)	0·26
ISSI-2			
Baseline	486·9 (383·8 to 564·0)	498·3 (404·1 to 599·0)	0·45
End	201·4 (124·6 to 333·5)	213·7 (150·1 to 470·5)	0·088
Change from baseline	–252·3 (–382·2 to –58·0)	–221·8 (–330·4 to –87·8)	0·28
HOMA-B			
Baseline	126·9 (82·2 to 186·1)	148·2 (87·3 to 239·3)	0·077
End	294·1 (129·6 to 745·8)	337·3 (128·9 to 754·4)	0·75
Change from baseline	161·0 (–1·3 to 621·0)	220·8 (–2·8 to 510·3)	0·92

Data are median (IQR), unless otherwise stated. p values obtained by Wilcoxon rank-sum test. In some cases, the baseline values differ slightly from those in table 1, since this analysis includes only participants with at least 1 year of follow-up. BMI=body-mass index. ALT=alanine aminotransferase. CRP=C-reactive protein. BNP=pro-brain natriuretic peptide. IS=insulin sensitivity. OGTT=oral glucose tolerance test. HOMA-IR=homoeostasis model of assessment of insulin resistance. ISSI-2=insulin secretion-sensitivity index-2. HOMA-B=homoeostasis model of assessment of β-cell function.

Table 3: **Changes in cardiometabolic risk factors during between baseline and study end, by treatment group**

	Placebo (N=104)	Rosiglitazone/ metformin (N=103)	p value
Gastrointestinal events			
Diarrhoea	6 (6%)	16 (16%)	0.025
Nausea/vomiting	6 (6%)	6 (6%)	1·00
Abdominal pain	4 (4%)	9 (9%)	0.16
Constipation	1 (1%)	1 (1%)	1·00
Flatulence	1 (1%)	3 (3%)	0.37
Frequent, soft stools	1 (1%)	2 (2%)	0.62
Hypoglycaemia	1 (1%)	2 (2%)	0.62
Swollen ankles	4 (4%)	2 (2%)	0.68
Bloating/water retention	1 (1%)	2 (2%)	0.62
Allergic reaction	2 (2%)	0	0.50
Vertigo	1 (1%)	1 (1%)	1·00

Data are number (%), unless otherwise indicated. p values obtained from Fisher's exact test.

Table 4: **Number of participants with adverse events that were possibly or probably related to the study or study drug**

Thus the major study question for the CANOE trial was whether a diabetes prevention effect can be obtained commensurate with the previous studies at half the maximum dose, while keeping side-effects to a minimum and improving tolerability. In this context, the CANOE trial clearly showed that combining half the maximum dose of rosiglitazone with metformin results in a significant reduction in the progression to diabetes. The magnitude of this effect is equivalent to that of any of the published diabetes prevention strategies. Importantly, the CANOE participants had to show adequate medication compliance during the run-in period before randomisation, and these robust effects might not apply to the usual clinical setting. Although we recorded a beneficial effect of maintaining insulin sensitivity, we were unable to show a detectable difference in β-cell function, possibly as a result of the modest sample size and duration of follow-up. We did note a reduction in inflammation (as shown by a decrease in CRP), and improvement in hepatic function (as shown by a reduction in ALT) with this low-dose combination therapy. Furthermore, bodyweight did not change significantly with this pharmacological intervention, nor was there a change in BNP—a sensitive marker of fluid overload. Weight, BMI, waist circumference, and waist to hip ratio were essentially unchanged in the rosiglitazone and metformin group compared with the placebo group (figure 4), although there seemed to be a small decrease in BMI at 6 months in both groups. CANOE also incorporated a lifestyle intervention programme as part of the diabetes prevention strategy. During the active phase of this lifestyle intervention, there might have been a small positive effect on weight, BMI, and waist circumference in both treatment groups. Furthermore, bone fracture[27] occurred with the same frequency in the placebo group and the rosiglitazone and metformin group.

This study was powered to be able to establish whether a low-dose combination of rosiglitazone and metformin would have a robust effect on prevention of diabetes, while reducing the common clinical adverse effects. However, it was not designed nor powered to establish long-term effects on cardiovascular safety. CANOE cannot provide additional definitive data for the controversy relating to the specific cardiovascular safety of rosiglitazone,[28] but findings lend support to the notion that half the maximum dose of rosiglitazone could provide important therapeutic effect, with perhaps fewer adverse consequences. Larger long-term studies assessing low-dose combination with these agents will be needed to establish cardiovascular benefit and risk, and overall long-term safety, including fracture risk. Additionally, assessment of the pharmacoeconomic benefits of this intervention would be beneficial in the context of a high–risk, population-directed approach to diabetes prevention.

An important limitation of our study is that we cannot clearly differentiate whether the effect recorded represents true prevention of diabetes or early treatment of diabetes. This limitation applies to all pharmacological clinical trial interventions for diabetes prevention, and has been reviewed.[8] Further clarification of this question will need a longer follow-up after drug washout, with careful assessment of changes in the underlying pathophysiological events that bring about type 2 diabetes.

Contributors

The work presented here was undertaken in collaboration between all authors. BZ defined the research idea, designed the study's methodology, and wrote the report. BZ, SBH, JN, RRR, and AJGH contributed to research data collection, to the study design, and reviewed and edited the report. HCG, JR, and YQ contributed to the discussion and to the reviewing and the editing of the report. YQ and JR provided the statistical analysis. BZ and SBH are co-principal investigators of the CANOE trial. All authors have seen and approved the revised version of the report.

Conflicts of interest

BZ reports having received consulting fees, honoraria, and grant support from GlaxoSmithKline. SBH reports advisory board membership and having received consulting fees, travel and lecture fees, and grant support from GlaxoSmithKline. HCG reports having received consulting fees from Sanofi-Aventis, GlaxoSmithKline, Eli Lilly, Novo Nordisk, AstraZeneca, BMS, Roche, Medtronic, Merck, Bayer, Biovail, and Jansen Ortho; honoraria from Sanofi-Aventis, GlaxoSmithKline, Servier, Bayer, Eli Lilly, and Novo Nordisk; and grant support from Sanofi-Aventis, GlaxoSmithKline, Novo Nordisk, Merck, and Roche. JN, RRR, JR, YQ, and AJGH declare that they have no conflicts of interest.

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