Effect of lorcaserin on prevention and remission of type 2 diabetes in overweight and obese patients (CAMELLIA-TIMI 61): a randomised, placebo-controlled trial

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Summary

Background There is a direct relationship between bodyweight and risk of diabetes. Lorcaserin, a selective serotonin 2C receptor agonist that suppresses appetite, has been shown to facilitate sustained weight loss in obese or overweight patients. We aimed to evaluate the long-term effects of lorcaserin on diabetes prevention and remission.

Methods In this randomised, double-blind, placebo-controlled trial done in eight countries, we recruited overweight or obese patients (body-mass index ≥27 kg/m²) with or at high risk for atherosclerotic vascular disease. Eligible patients were aged 40 years or older; patients at high risk for atherosclerotic vascular disease had to be aged 50 years or older with diabetes and at least one other risk factor. Patients were randomly assigned to receive either lorcaserin (10 mg twice daily) or matching placebo. Additionally, all patients had access to a standardised weight management programme based on lifestyle modification. The prespecified primary metabolic efficacy endpoint of time to incident diabetes was assessed in patients with prediabetes at baseline. The prespecified secondary outcomes for efficacy were incident diabetes in all patients without diabetes, achievement of normoglycaemia in patients with prediabetes, and change in glycated haemoglobin (HbA_{1c}) in patients with diabetes. Hypoglycaemia was a prespecified safety outcome. Analysis was by intention to treat, using Cox proportional hazard models for time-to-event analyses. This trial is registered with ClinicalTrials.gov, number NCT02019264.

Findings Between Feb 7, 2014, and Nov 20, 2015, 12 000 patients were randomly assigned to lorcaserin or placebo (6000 patients in each group) and followed up for a median of 3·3 years (IQR 3·0–3·5). At baseline, 6816 patients (56·8%) had diabetes, 3991 (33·3%) prediabetes, and 1193 (9·9%) normoglycaemia. At 1 year, patients treated with lorcaserin had a net weight loss beyond placebo of 2·6 kg (95% CI 2·3–2·9) for those with diabetes, 2·8 kg (2·5–3·2) for those with prediabetes, and 3·3 kg (2·6–4·0) for those with normoglycaemia (p<0·0001 for all analyses). Lorcaserin reduced the risk of incident diabetes by 19% in patients with prediabetes (172 [8·5%] of 2015 *vs* 204 [10·3%] of 1976; hazard ratio 0·81, 95% CI 0·66–0·99; p=0·038) and by 23% in patients without diabetes (174 [6·7%] of 2615 *vs* 215 [8·4%] of 2569; 0·77, 0·63–0·94; p=0·012). Lorcaserin resulted in a non-significant increase in the rate of achievement of normoglycaemia in patients with prediabetes (185 [9·2%] *vs* 151 [7·6%]; 1·20, 0·97–1·49; p=0·093). In patients with diabetes, lorcaserin resulted in a reduction of 0·33% (95% CI 0·29–0·38; p<0·0001) in HbA_{1c} compared with placebo at 1 year from a mean baseline of 53 mmol/mol (7·0%). In patients with diabetes at baseline, severe hypoglycaemia with serious complications was rare, but more common with lorcaserin (12 [0·4%] *vs* four [0·1%] events; p=0·054).

Interpretation Lorcaserin decreases risk for incident diabetes, induces remission of hyperglycaemia, and reduces the risk of microvascular complications in obese and overweight patients, supporting the role of lorcaserin as an adjunct to lifestyle modification for chronic management of weight and metabolic health.

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Introduction

The global prevalence of obesity has nearly tripled over the past 40 years; in 2016, 13% of adults were obese (defined as body mass index [BMI] ≥30 kg/m²) and another 39% were overweight (BMI 25–29 kg/m²).[1] Obesity is associated with the development and progression of impaired glucose tolerance and type 2 diabetes in patients without diabetes and worsening glycaemic control among patients with diabetes.[2] Dysglycaemia, a well described risk factor for both microvascular and macrovascular disease, further compounds the risk in obese patients for comorbid complications, such as chronic kidney disease, neuropathy, coronary artery disease, stroke, and death.[2–5]

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See Online for appendix

For the **study protocol** see https://www.nejm.org/doi/suppl/10.1056/NEJMoa1808721/suppl_file/nejmoa1808721_protocol.pdf

Research in context

Evidence before this study

We searched MEDLINE from inception until Aug 1, 2018, for the terms "weight loss", "diabetes", "glycaemic control", "microvascular", "bariatric", and "lorcaserin" to identify previous publications in English describing the association between weight loss and metabolic outcomes in contemporary studies of weight loss strategies, including lifestyle, pharmacological agents, and bariatric surgery. Pharmacological weight loss agents are guideline-recommended adjuncts to lifestyle modification for long-term weight management and for the prevention of prediabetes and diabetes. The cardiovascular and metabolic effects of lorcaserin in overweight and obese patients—thrombolysis in myocardial infarction 61 (CAMELLIA-TIMI 61) trial was designed to investigate the long-term cardiovascular and metabolic safety and efficacy of lorcaserin, a selective agonist of the 5-hydroxytryptamine 2C serotonin receptor that regulates appetite, in obese or overweight patients with or at high risk for diabetes and adverse cardiovascular events. On a background of lifestyle interventions, lorcaserin improved long-term weight loss without any increase in the risk of major adverse cardiovascular events.

Added value of this study

Here, we report prespecified metabolic efficacy and safety outcomes with lorcaserin in overweight and obese patients. When added to lifestyle interventions, lorcaserin significantly reduced the incidence of diabetes, non-significantly increased the proportion of patients with prediabetes achieving normoglycaemia, significantly increased the proportion of patients with diabetes achieving remission of hyperglycaemia, and significantly reduced the risk of diabetic microvascular complications.

Implications of all the available evidence

Taken together, these findings reinforce the notion that modest, durable weight loss can improve cardiometabolic health and supports the role of lorcaserin as an adjunctive therapy in chronic weight management and metabolic health.

Pharmacological weight loss agents are guideline-recommended adjuncts to lifestyle modification for long-term weight management and for the prevention of prediabetes and diabetes.[3,6] Predominantly short-term studies (typically 1 year in length) of pharmacological weight loss agents have shown improvements in glycaemic parameters, but few long-term data from large randomised trials are available.[3]

Lorcaserin is a selective agonist of the 5-hydroxytryptamine 2C serotonin receptor (5-HT2C) that regulates appetite through hypothalamic activation of the anorexigenic pro-opiomelanocortin pathway.[7] Lorcaserin was approved by the US Food and Drug Administration as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management.[8–10] The cardiovascular and metabolic effects of lorcaserin in overweight and obese patients—thrombolysis in myocardial infarction 61 (CAMELLIA-TIMI 61) trial was designed to investigate the long-term cardiovascular and metabolic safety and efficacy of lorcaserin in obese or overweight patients with or at high risk for diabetes and adverse cardiovascular events.[11] On a background of lifestyle interventions, lorcaserin improved long-term weight loss without any increase in the risk of major adverse cardiovascular events.[12] Here, we report prespecified metabolic efficacy and safety outcomes with lorcaserin in overweight and obese patients.

Methods

Study design and participants

CAMELLIA-TIMI 61 was a randomised, double-blind, placebo-controlled, multinational clinical trial done at 473 sites in eight countries (see appendix for details). The study was designed by the TIMI Study Group in conjunction with the executive committee and the trial sponsor, Eisai.[11,12] The protocol and amendments were approved by the relevant ethics committees for all participating sites.

Eligible patients were obese or overweight (BMI ≥27 kg/m²) with either established atherosclerotic cardiovascular disease or multiple cardiovascular risk factors. To qualify for established atherosclerotic cardiovascular disease, patients had to be at least 40 years old with a history of coronary, cerebrovascular, or peripheral artery disease. To qualify for the multiple risk factor criteria, patients had to be at least 50 years of age (men) or 55 years of age (women) with diabetes and at least one of the following cardiovascular risk factors: dyslipidaemia, hypertension, estimated glomerular filtration rate (eGFR) 30–60 mL/min per 1·73 m², high-sensitivity C-reactive protein greater than 3 mg/L, or microalbuminuria or macroalbuminuria. To qualify for diabetes, patients had to have glycated haemoglobin A_{1c} (HbA_{1c}) lower than 86 mmol/mol (10%) at screening and a stable clinical and treatment course of diabetes in the preceeding 3 months with no hospitalisations for hypoglycaemia or hyperglycaemia. Key exclusion criteria included moderate to severe pulmonary hypertension, heart failure, or hepatic dysfunction, severe valvular disease or renal dysfunction, planned bariatric surgery, or use of pharmacological weight loss therapy. Full eligibility criteria have been reported previously.[11,12] In the absence of prevalent diabetes, prediabetes was defined as a HbA_{1c} of at least 39 mmol/mol (5·7%) but lower than 48 mmol/mol (6·5%) or a fasting plasma glucose of 5·6–6·9 mmol/L (100–125 mg/dL). Written informed consent was obtained from all patients.

Randomisation and masking

Eligible patients were randomly assigned (1:1) in a double-blind fashion to receive either lorcaserin or matched placebo. Both lorcaserin and placebo tablets were produced by the study sponsor. Randomisation was based on a computer-generated randomisation scheme and was stratified according to cardiovascular disease status (established cardiovascular disease or multiple cardiovascular risk factors only).

Procedures

Patients were given either lorcaserin (10 mg twice daily) or matched placebo until the end of the follow-up period. All patients were provided with access to and encouraged to participate in a standardised weight management programme consisting of intensive multicomponent behavioural therapy that included dietary and exercise information and unlimited telephonic access to a registered dietician. Visits were conducted every 3 months for the first 2 years following randomisation and every 4 months thereafter. Additional study procedures have been previously described.[11,12] After randomisation, medications for the treatment of diabetes could be started, discontinued, or adjusted during the study according to local standards of care (additional details in the appendix). Concomitant use of other pharmacological weight loss agents was prohibited.

Outcomes

The cardiovascular outcomes have been previously reported.[12] The primary metabolic efficacy outcome was the time to incident type 2 diabetes among patients with prediabetes at baseline. Based on the American Diabetes Association guidelines,[13] the primary definition for incident diabetes required either a single occurrence of a random plasma glucose of at least 11·1 mmol/L (200 mg/dL) with symptoms of hyperglycaemia or another abnormal glycaemic parameter (ie, HbA_{1c} ≥48 mmol/mol [6·5%], fasting plasma glucose ≥7·0 mmol/L [126 mg/dL], or a 2-h plasma glucose of ≥11·1 mmol/L [200 mg/dL] during an oral glucose tolerance test) that was confirmed on simultaneous or consecutive testing or with initiation of glucose-lowering medications (appendix).

Prespecified secondary metabolic efficacy endpoints were incident type 2 diabetes in the full non-diabetic population, achievement of normoglycaemia (in the absence of any glucose-lowering medications) in patients with prediabetes at baseline, and change in HbA_{1c} in patients with diabetes. In patients with diabetes, prespecified exploratory metabolic endpoints included achievement of normoglycaemia (in the absence of any glucose-lowering medications) and remission of hyperglycaemia (ie, shift to prediabetes or normoglycaemia in the absence of glucose-lowering medications). Hypoglycaemia was a prespecified safety outcome (see appendix). Microvascular complications associated with diabetes, comprising retinopathy, neuropathy, and albuminuria, were prespecified exploratory outcomes. Occurences of incident diabetic retinopathy and neuropathy were investigator reported on a dedicated electronic case report form. Incident persistent albuminuria was based on centrally measured spot urinary albumin-to-creatinine ratio (ACR; definitions outlined in the appendix). Other prespecified renal outcomes will be reported elsewhere.

A central clinical events adjudication committee, whose members were unaware of treatment assignment, adjudicated events of incident diabetes using the primary trial definition (appendix).[13] Events using sensitivity definitions for diabetes and all definitions for remission of prediabetes or diabetes were identified programmatically on the basis of the criteria outlined in the appendix.

Statistical analysis

CAMELLIA-TIMI 61 employed a two-step analysis procedure in which the primary assessment was for cardiovascular safety, followed by an assessment of cardiovascular and metabolic efficacy, as previously described.[11] In the original protocol, study closure was dependent on accrual of a prespecified number of both cardiovascular (n=1401) and incident diabetes events (n=808) to provide 85% power to detect a 15% risk reduction in cardiovascular events at a two-sided α of 0·045 and 90% power to detect a 25% risk reduction in incident diabetes at a two-sided α of 0·005. To provide an adequate sample size to power the efficacy endpoint of incident diabetes, enrolment was targeted to achieve approximately 50% of patients without diabetes at baseline.

To maintain trial timelines due to a sponsor-mandated change in the primary analytic population for incident diabetes from all patients without diabetes to only those with prediabetes at baseline, and a slower than anticipated accrual of incident diabetes events, the sponsor amended the protocol prior to the interim data monitoring committee review to remove the criterion for at least 808 patients developing incident diabetes. Prior to study closure, the academic leadership elected to maintain cardiovascular and incident diabetes as coprimary efficacy endpoints, each tested at a two-sided α of 0·05, estimating more than 450 events of conversion to diabetes would provide more than 85% power to detect a 25% risk reduction.

Definitions for glycaemic subgroups, including patients with diabetes, prediabetes, normoglycaemia, and no diabetes (ie, prediabetes or normoglycaemia) are detailed in the appendix. The primary analysis for time to incident diabetes was in patients with prediabetes at baseline with a secondary analysis in all patients without diabetes at baseline. Hazard ratios (HRs), 95% CIs, and p values for time-to-event analyses were generated with the use of Cox proportional-hazards model. Efficacy analyses, including incident diabetes, were done by intention to treat, with on-treatment sensitivity analyses including events that occurred prior to permanent discontinuation of study drug. Safety analyses (ie, hypoglycaemic events) were done

	Diabetes		Prediabetes		Normoglycaemia	
	Lorcaserin (n=3385)	Placebo (n=3431)	Lorcaserin (n=2015)	Placebo (n=1976)	Lorcaserin (n=600)	Placebo (n=593)
Demographics						
Age, years	64 (59–69)	64 (59–70)	64 (58–70)	64 (58–70)	62 (55–68)	63 (56–68)
Sex						
Female	1349 (39·9%)	1398 (40·7%)	541 (26·8%)	585 (29·6%)	222 (37·0%)	203 (34·2%)
Male	2036 (60·1%)	2033 (59·3%)	1474 (73·2%)	1391 (70·4%)	378 (63·0%)	390 (65·8%)
Race						
White	2864 (84·6%)	2936 (85·6%)	1881 (93·3%)	1837 (93·0%)	564 (94·0%)	558 (94·1%)
Other	521 (15·4%)	495 (14·4%)	134 (6·7%)	139 (7·0%)	36 (6·0%)	35 (5·9%)
Weight, kg	105 (92–120)	105 (93–120)	100 (89–113)*	99 (88–111)*	97 (86–109)	95 (86–105)
BMI, kg/m²	36 (32–41)	36 (33–41)	34 (31–37)	34 (31–37)	33 (30–37)	33 (30–36)
Comorbidities						
Hypertension	3151 (93·1%)*	3238 (94·4%)*	1772 (87·9%)	1705 (86·3%)	491 (81·8%)	491 (82·8%)
Hyperlipidemia	3191 (94·3%)	3237 (94·3%)	1882 (93·4%)	1840 (93·1%)	543 (90·5%)	536 (90·4%)
eGFR <60	756 (22·3%)	809 (23·6%)	305 (15·1%)	309 (15·6%)	88 (14·7%)	90 (15·2%)
ACR ≤30 mg/dL	836 (24·7%)	849 (24·7%)	228 (11·3%)	262 (13·3%)	39 (6·5%)*	64 (10·8%)*
Median HbA_{1c}, mmol/mol (95% CI)	51 (51–52)	51 (50–51)	40 (39–40)	39 (39–40)	36 (34–36)	36 (34–36)
Median HbA_{1c}, % (95% CI)	6·8% (6·8–6·9)	6·8% (6·7–6·8)	5·8% (5·7–5·8)	5·7% (5·7–5·8)	5·4% (5·3–5·4)	5·4% (5·3–5·4)
Duration of diabetes, years	9 (4–15)	9 (4–15)	..	..	..	..
Cardiovascular strata						
Multiple cardiovascular risk factors	1511 (44·6%)	1528 (44·5%)	1 (<0·1%)	1 (0·1%)	0	1 (0·2%)
Established cardiovascular disease	1874 (55·4%)	1903 (55·5%)	2014 (>99·9%)	1975 (99·9%)	600 (100%)	592 (99·8%)
Coronary artery disease	1713 (50·6%)	1722 (50·2%)	1860 (92·3%)	1806 (91·4%)	523 (87·2%)	529 (89·2%)
Peripheral arterial disease	176 (5·2%)	151 (4·4%)	119 (5·9%)	123 (6·2%)	44 (7·3%)	44 (7·4%)
Cerebrovascular disease	280 (8·3%)	306 (8·9%)	198 (9·8%)	217 (11·0%)	69 (11·5%)	60 (10·1%)
Baseline medications						
Any diabetes medication	2815 (83·2%)	2855 (83·2%)	..	..	..	..
Insulin	981 (29·0%)	979 (28·5%)	..	..	..	..
GLP-1 receptor agonist	314 (9·3%)	293 (8·5%)	..	..	..	..
SGLT-2 inhibitor	103 (3·0%)	124 (3·6%)	..	..	..	..
Metformin	2024 (59·8%)	2091 (60·9%)	..	..	..	..
DPP4 inhibitor	332 (9·8%)	330 (9·6%)	..	..	..	..
Sulfonylurea	871 (25·7%)	860 (25·1%)	..	..	..	..
Thiazolidinediones	157 (4·6%)	158 (4·6%)	..	..	..	..
Aspirin	2276 (67·2%)	2308 (67·3%)	1740 (86·4%)	1708 (86·4%)	513 (85·5%)	502 (84·7%)
Statin	2794 (82·5%)	2863 (83·4%)	1824 (90·5%)	1763 (89·2%)	505 (84·2%)	503 (84·8%)
ACEi/ARB	2706 (79·9%)	2756 (80·3%)	1411 (70·0%)	1383 (70·0%)	360 (60·0%)*	390 (65·8%)*

Data are n (%) or median (IQR) unless otherwise specified. p value for trend <0·0001 for all variables pooled by randomised treatment across glycaemic subgroups. BMI=body-mass index. eGFR= estimated glomerular filtration rate per the Chronic Kidney Disease Epidemiology Collaboration equation (mL/min per 1·73 m²). ACR=albumin-creatinine ratio. HbA_{1c}=glycated haemoglobin. GLP-1=glucagon-like peptide-1. SGLT-2=sodium-glucose cotransporter-2. DPP4=dipeptidyl peptidase 4. ACEi=angiotensin converting enzyme inhibitors. ARB=angiotensin II receptor blockers. *p value <0·05.

Table 1: **Baseline characteristics by glycaemic status**

in the safety population, defined as patients who underwent randomisation, received at least one dose of study drug, and had at least one post-dose safety assessment, and included events during the on-treatment period. The stratification factor was included as a covariate in analyses of the full population. Additional statistical procedures are described in the appendix.

This trial is registered with ClinicalTrials.gov, number NCT02019264.

Role of the funding source

The sponsor was involved in trial design and study conduct, including site and database management and data collection. Representatives from the sponsor (TP, BF, WM, SD, CP) reviewed the manuscript. Authors from the TIMI Study Group (EAB, BMS, EK, SAM, MSS, and SDW) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

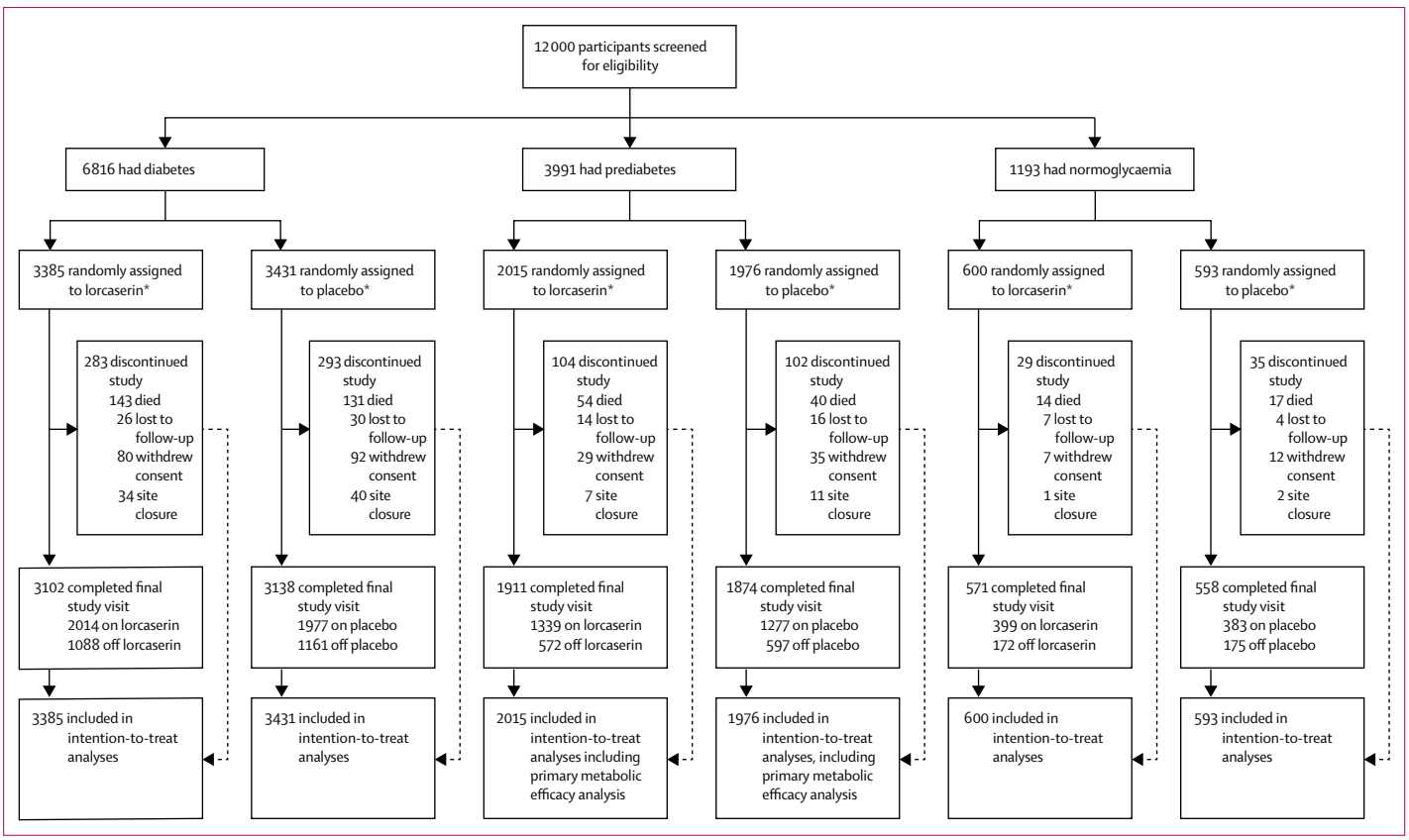

Figure 1: **Trial profile**

*Diabetes: one patient in the lorcaserin group and three patients in the placebo group did not receive allocated treatment. Prediabetes: one patient in the lorcaserin group and two patients in the placebo group did not receive allocated treatment. Normoglycaemia: two patients in the lorcaserin group and one patient in the placebo group did not receive allocated treatment.

Results

Between Feb 7, 2014, and Nov 20, 2015, 12 000 patients were randomly assigned to lorcaserin or placebo (6000 patients in each group). Patients were followed up for a median of 3·3 years (IQR 3·0–3·5). Overall, the median age was 64 years (58–69), 7702 (64·2%) patients were men and 4298 (35·8%) were women, and the median BMI was 35 kg/m² (32–39). At baseline, 6816 patients (56·8%) had diabetes, 3991 (33·3%) prediabetes, and 1193 (9·9%) normoglycaemia (table 1; figure 1). Almost all patients in the latter two cohorts had established cardiovascular disease: 4718 (91·0%) had coronary artery disease, 544 (10·5%) cerebrovascular disease, and 330 (6·4%) peripheral artery disease. Within the cohort with diabetes at baseline, 3777 (55·4%) had established cardiovascular disease. Compared with patients without diabetes, patients with diabetes were more often female, with a higher baseline weight and BMI (table 1). Baseline medications in patients with diabetes are shown in table 1. Patient follow-up was similar between treatment arms (figure 1).

Lorcaserin reduced the risk of incident diabetes by 19% in patients with prediabetes at baseline (HR 0·81, 95% CI 0·66–0·99; p=0·038), corresponding to a number needed to treat of 56 to prevent one event of diabetes over 3 years (figure 2, 3). Similar results were observed in all patients without diabetes at baseline with a 23% reduction (figure 3). When analysed while patients were on study drug, lorcaserin reduced the incidence of diabetes in patients with prediabetes by 25% and in all patients without diabetes by 28% (figure 3). Results for patients with prediabetes were similar in sensitivity analyses using alternative definitions of incident diabetes, including where confirmation of abnormal glycaemic parameters was not required to be consecutive (247 [12·3%] *vs* 324 [16·4%]; HR 0·72, 95% CI 0·61–0·85; p<0·0001) or not required (398 [19·8%] *vs* 508 [25·7%]; 0·73, 0·64–0·83; p<0·0001; appendix). Effects of lorcaserin on incident diabetes were largely consistent across subgroups (appendix).

The mean weight at baseline was 107·6 kg (SD 21·3) in patients with diabetes, 101·8 kg (19·2) in patients with prediabetes, and 97·8 kg (17·0) in patients with normoglycaemia. At 1 year, the net weight loss was significantly greater with lorcaserin compared with placebo for each of the three subgroups: diabetes (least-squares mean treatment difference at 1 year –2·6 kg,

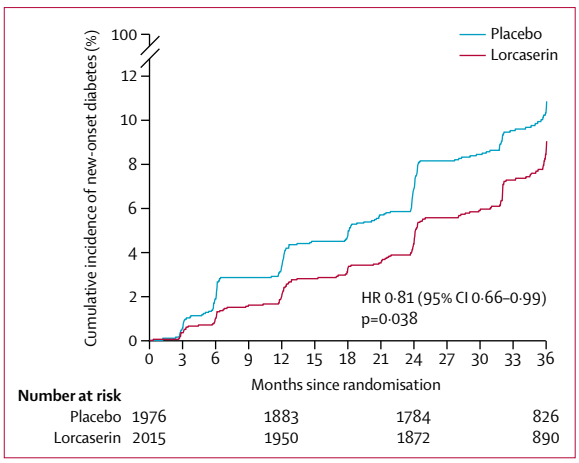

Figure 2: **Cumulative incidence of incident diabetes**
Incidence is assessed in patients with prediabetes at baseline according to the intention-to-treat method. HR=hazard ratio.

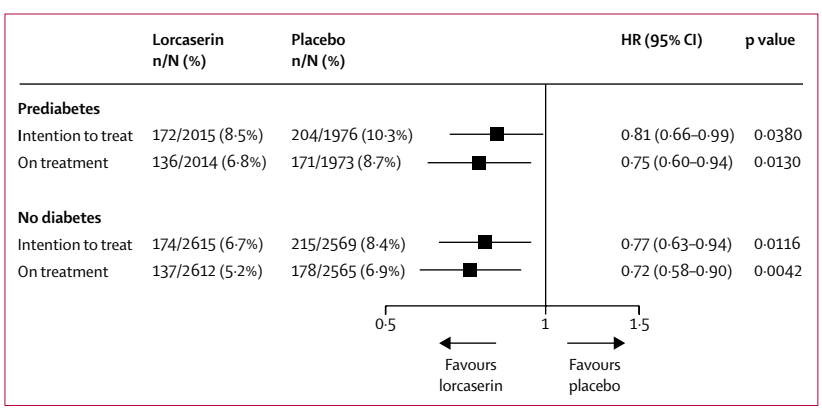

Figure 3: **Incident diabetes by randomised treatment in patients with prediabetes and normoglycaemia**
Analysis using the primary definition of incident diabetes, based on the American Diabetes Association definition, which requires an elevated random plasma glucose with symptoms of hyperglycaemia or an abnormal parameter (eg, HbA_{1c}, fasting plasma glucose, or oral glucose tolerance test) with confirmation on simultaneous or consecutive testing (as defined in the appendix). Analysis was in patients with prediabetes and patients without diabetes (ie, with prediabetes or normoglycaemia) at baseline, including events during complete follow-up (intention to treat) or only during the on-treatment window. HbA_{1c}=glycated haemoglobin.

95% CI –2·9 to –2·3; p<0·0001), prediabetes (–2·8 kg, –3·2 to –2·5; p<0·0001), and normoglycaemia (–3·3 kg, –4·0 to –2·6; p<0·0001; figure 4; appendix). At 1 year, significantly more patients in the lorcaserin group lost at least 5% of their bodyweight when compared with placebo in each subgroup: diabetes (1078 [37·4%] of 2881 patients *vs* 495 [17·0%] of 2910 patients; p<0·0001), prediabetes (691 [39·7%] of 1741 *vs* 305 [18·2%] of 1676]; p<0·0001), and normoglycaemia (217 [42·3%] of 513 *vs* 83 [16·7%] of 497; p<0·0001; appendix). The between-treatment group weight loss remained significant within each glycaemic subgroup over the duration of the trial (figure 4). In patients with diabetes, weight loss was similar regardless of whether patients were taking glucose-lowering medications that tend to promote weight gain (ie, insulin, sulfonylurea, or thiazolidinedione) or glucose-lowering medications that tend to promote weight loss (ie, glucagon-like peptide-1 [GLP-1] agonist or sodium-glucose cotransporter-2 inhibitor; appendix) at baseline.

At 1 year, patients in the lorcaserin group also had a greater reduction in BMI, waist circumference, and waist-to-hip ratio than did patients in the placebo group for each of the glycaemic subgroups (appendix).

At 1 year, locarserin reduced HbA_{1c} in patients with diabetes (least-squares mean treatment difference at 1 year –0·33%, 95% CI –0·38 to –0·29; p<0·0001) from a mean baseline of 53 mmol/mol (7·0%), with more modest effects in patients with prediabetes (–0·09%, –0·11 to –0·08; p<0·0001) and normoglycaemia (–0·08%, –0·11 to –0·04; p<0·0001; figure 4; appendix). The between-treatment differences in HbA_{1c} remained significant through at least 36 months follow-up in all groups, despite all groups showing upward trends in HbA_{1c} over time (figure 4). In the 1166 patients with diabetes with a baseline HbA_{1c} greater than 64 mmol/mol (8·0%), the mean reduction in HbA_{1c} at 1 year was substantially larger at 0·87% (95% CI 0·76–0·97) with lorcaserin compared with 0·35% (0·23–0·46) for placebo, translating into a net reduction of 0·52% (0·37–0·68; p<0·0001; appendix). Fasting plasma glucose and the homoeostatic model assessment of insulin resistance were significantly improved with lorcaserin compared with placebo in patients with diabetes or prediabetes, with the largest between-treatment differences noted in patients with diabetes at baseline (figure 4; appendix).

Glucose-lowering medication utilisation was lower in patients in the lorcaserin group than in the placebo group (appendix). The proportion of patients with diabetes with initiation of a new glucose-lowering medication was lower with lorcaserin than with placebo at 1 year (13·1% [n=444] *vs* 20·1% [n=690]; p<0·0001), with a lower proportion of patients with new insulin initiation (39 [1·6%] of 2404 patients *vs* 96 [3·9%] of 2452 patients]; p<0·0001) and new initiation of a non-insulin glucose-lowering medications (12·3% [n=415] *vs* 18·1% [n=622]; p<0·0001). Among patients with diabetes, there was a higher proportion of patients with discontinuation of glucose lowering medications at 1 year with lorcaserin compared with placebo (277 [10·1%] of 2749 patients *vs* 220 [7·9%] of 2789 patients; p=0·0045).

There was a numerically but not statistically significant greater proportion of patients with prediabetes who achieved normoglycaemia with lorcaserin versus placebo (ie, normalisation of glycaemic parameters in the absence of any glucose-lowering medication utilisation; figure 5) using persistent criteria (ie, requiring confirmation and maintainance throughout the duration of follow-up). The magnitude of effect was consistent and achieved statistical significance in sensitivity analyses using sustained achievement (ie, confirmation on at least two consecutive assessments separated in time) and any achievement (ie, criteria met on at least one occasion) (figure 5). Similar results were seen for lorcaserin facilitating achievement of normoglycaemia in patients with diabetes and in

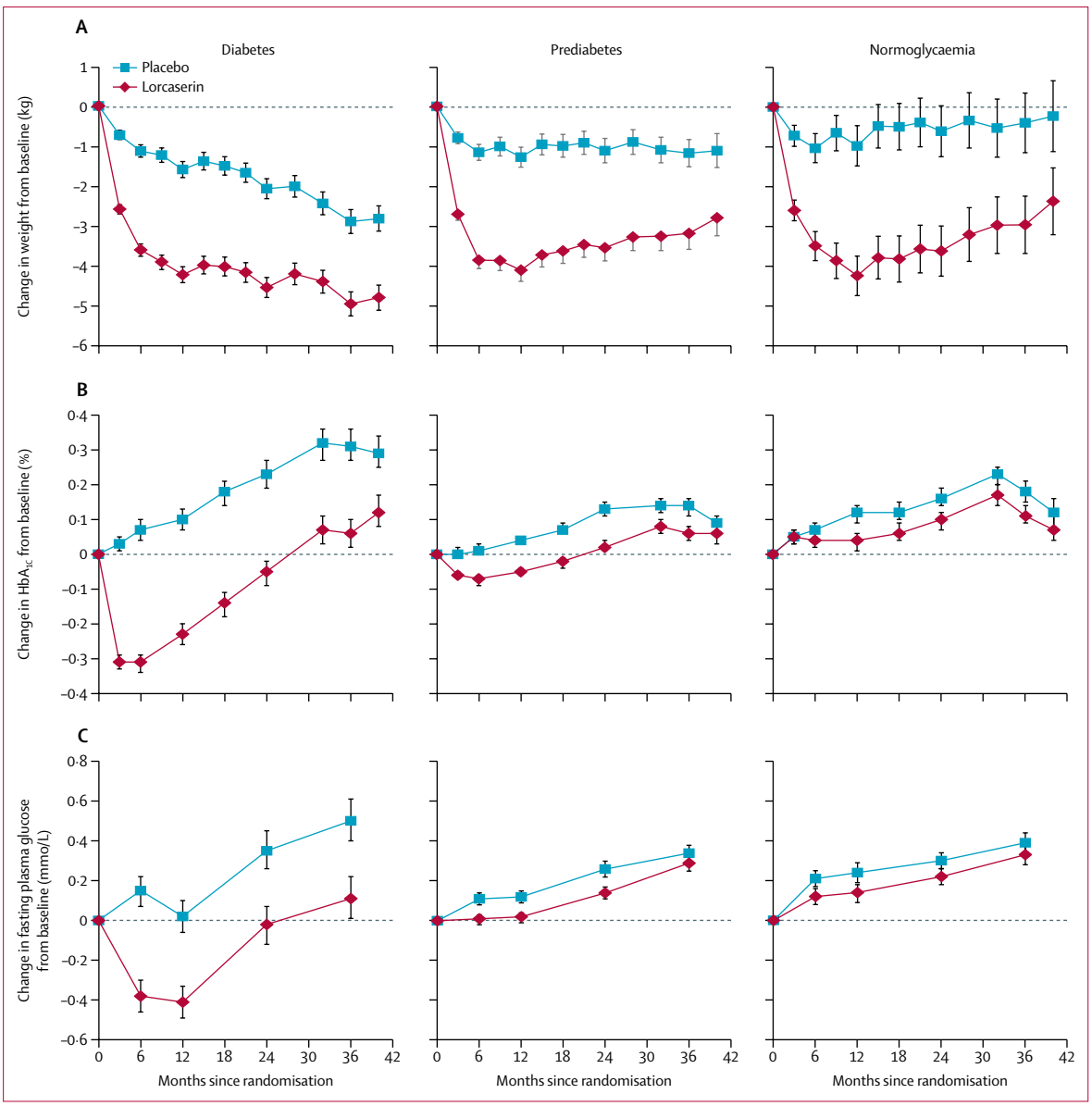

Figure 4: **Change in weight, HbA_{1c}, and fasting plasma glucose by baseline glycaemic subgroup**
All analyses were done in the intention-to-treat population. Change from baseline shown as least-squared mean (95% CI) based on linear mixed effect model with repeated measures including model terms with treatment, visit, visit by treatment interaction, baseline value, and randomisation strata. HbA_{1c}=glycated haemoglobin.

patients with either diabetes or prediabetes, both using the intention-to-treat method and while patients were on study drug (figure 5; appendix).

Lorcaserin resulted in more patients with diabetes experiencing remission of their hyperglycaemia (ie, shift to prediabetes or normoglycaemia) in the absence of any glucose-lowering medication using persistent, sustained, and any criteria (figure 5), with similar findings observed using an on-treatment analysis (appendix).

In patients with diabetes at baseline, the rates of remission of hyperglycaemia and achievement of normoglycaemia were numerically lower in those patients with a longer duration of diabetes, less pancreatic reserve, or use of one or more glucose-lowering agents at baseline, including insulin or a sulfonylurea; however, the relative benefits with lorcaserin compared with placebo were consistent across subgroups (appendix).

Lorcaserin reduced the risk of diabetic microvascular complications—a composite of incident persistent microalbuminuria, diabetic retinopathy or diabetic neuropathy—by 21% in patients with diabetes at baseline (table 2). There was directional consistency for each of the individual components, the most frequent of which was persistent microalbuminuria (table 2).

Hypoglycaemia was reported in 223 (6·6%) patients with diabetes in the lorcaserin group compared with

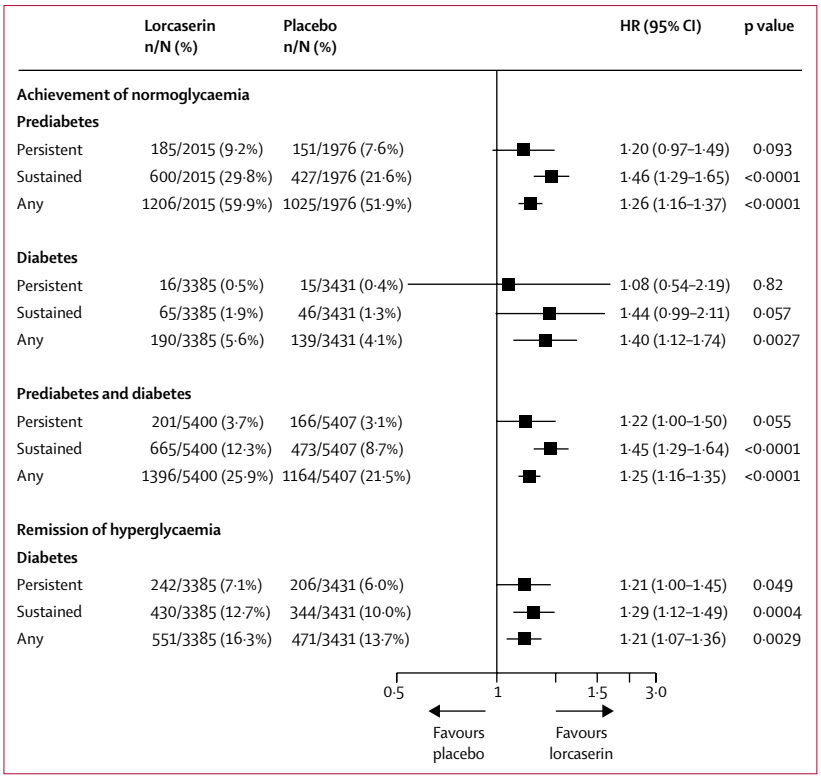

Figure 5: **Remission of diabetes or prediabetes**
Analyses are by intention to treat. Remission of hyperglycaemia is defined as HbA_{1c} of <48 mmol/mol (6·5%) and fasting plasma glucose <126 mg/dL (<7·0 mmol/L) in the absence of anti-hyperglycaemia medication in patients with diabetes at baseline. Achievement of normoglycaemia is defined as HbA_{1c} of ≤38 mmol/mol (5·6%) and fasting plasma glucose <100 mg/dL (<5·5 mmol/L) in the absence of anti-hyperglycaemia medication in patients with diabetes or prediabetes at baseline. Both criteria (HbA_{1c} and fasting plasma glucose) are required only if both tests are available. "Persistent" requires criteria to be achieved, confirmed, and maintained through the duration of the study. "Sustained" requires criteria to be achieved, confirmed, and maintained for two consecutive measurements separated by 30 days or more. "Any" is defined by achievement of at least one criteria at one or more timepoints during the study. HbA_{1c}=glycated haemoglobin.

	Lorcaserin (n=3385)	Placebo (n=3431)	Hazard ratio (95% CI)	p value
Microvascular composite*	341 (10·1%)	427 (12·4%)	0·79 (0·69–0·92)	0·0015
Persistent microalbuminuria	265 (7·8%)	343 (10·0%)	0·77 (0·66–0·90)	0·0015
Diabetic retinopathy	25 (0·7%)	30 (0·9%)	0·84 (0·50–1·43)	0·53
Diabetic neuropathy	64 (1·9%)	69 (2·0%)	0·94 (0·67–1·32)	0·71

Event rate (%) represents n/N in the total population using the intention-to-treat method. *Microvascular composite of new microalbuminuria, retinopathy, or neuropathy.

Table 2: **Incident microvascular complications of diabetes in patients with diabetes at baseline**

199 (5·8%) in the placebo group (p=0·18), with most (>85%) events occurring in patients on either insulin or a sulfonylurea at baseline (196 *vs* 171 events of hypoglycaemia; p=0·18; appendix). We observed a numerical imbalance in severe hypoglycaemia with serious complications, requiring either hospitalisation or considered life threatening or disabling (12 [0·4%] with lorcaserin *vs* four [0·1%] with placebo; p=0·054). There were no fatal events of hypoglycaemia. Hypoglycaemia was rare in patients who did not meet criteria for diabetes at baseline (nine events [0·3%] in 2612 patients *vs* three events [0·1%] in 2565 patients; p=0·10).

Discussion

Lorcaserin, a 5-HT2C receptor agonist, is effective for weight loss and, unlike many other obesity medications to date, has proven safety for major adverse cardiovascular events, including cardiovascular death, myocardial infarction, or stroke.[12] In addition to proven persistent weight loss efficacy with extended duration use, we report that when added to lifestyle interventions, lorcaserin significantly reduced the incidence of diabetes, showed a non-significant improvement in the proportion of patients with prediabetes achieving normoglycaemia, showed a significant improvement in the proportion of patients with diabetes achieving remission of hyperglycaemia, and significantly reduced the risk of a composite outcome for diabetic microvascular complications. Taken together, these findings reinforce the notion that modest, durable weight loss can improve cardiometabolic health and supports the role of lorcaserin as an adjunctive therapy in chronic management of weight and metabolic health.

A large body of literature supports the glycaemic benefit of weight loss via lifestyle, pharmacological, or surgical means. In the Diabetes Prevention Program randomised trial,[14] lifestyle interventions resulted in an average net weight loss of 5·5 kg and reduced the incidence of diabetes by 58%. Similarly, intensive lifestyle modification in the LOOK AHEAD randomised trial[15] resulted in durable reduction in HbA_{1c} compared with standard of care, where greater weight loss was associated with more robust improvements in glycaemic and other parameters. A cluster-randomised trial[16] in patients with type 2 diabetes and obesity had a 20-times increased odds of diabetes remission with a structured weight management programme compared with standard of care. Based on these and other studies, the National Heart, Lung and Blood Institute concluded that 2–5% weight loss by lifestyle interventions can lead to a 0·2–0·3% reduction in HbA_{1c} and weight losses of 5–10% can increase this to a 0·6–1·0% reduction in HbA_{1c}.[3] Another weight loss drug, orlistat, reduced weight by nearly 3 kg after 4 years and reduced the risk of incident diabetes by 37% in obese patients with prediabetes at baseline.[17] Unsurprisingly, dedicated glucose-lowering medications such as metformin and thiazolidinediones also reduce the incidence of diabetes in patients with prediabetes.[18,19] Moreover, the GLP-1 receptor agonist class of glucose-lowering medications also cause weight loss. Use of weight management dosing of liraglutide resulted in a 4·3% net weight loss and a 79% reduction in incident diabetes at 3 years in obese patients with pre-diabetes.[20] Bariatric surgery, which can result in more robust, sustained weight loss than other strategies (typically around 15–60%), results in profound improvements in

glycaemic parameters in the range of 1·5–3·0% decrease in HbA_{1c}, a 60–80% reduction in incident diabetes, and 30–95% rate of remision in patients with diabetes.[21–24] The observed reduction in incident diabetes observed in CAMELLIA-TIMI 61 is consistent with this prior literature, in that lorcaserin reduced weight by a net of 2·8–3·3 kg and the risk of incident diabetes by 19% in patients with prediabetes and by 23% in all patients without diabetes. Unsurprisingly, the benefit was more pronounced when analysed in patients who remained on study drug, showing a 25–28% relative reduction in risk of incident diabetes in patients with prediabetes or no diabetes at baseline.

In CAMELLIA-TIMI 61, patients with diabetes were well controlled at baseline with a mean HbA_{1c} of 53 mmol/mol (7·0%). Despite this relatively low baseline HbA_{1c}, the net decrease in HbA_{1c} of 0·33% at 1 year in patients with diabetes compares favourably to the other targeted weight loss agents and with the HbA_{1c} reductions observed in similarly designed outcome trials with glucose-lowering agents.[25,26] Notably, this reduction was observed in the setting of open titration of background glucose-lowering medications, potentially attenuating the difference in HbA_{1c} between treatment arms. Furthermore, in patients with a baseline HbA_{1c} greater than 64 mmol/mol (8·0%), lorcaserin resulted in a net reduction in HbA_{1c} of 0·52%. Moreover, lorcaserin resulted in fewer new initiations of insulin and other glucose-lowering medications and more discontinuations of glucose-lowering medications in patients with diabetes. Lastly, lorcaserin showed a non-significant increase in the proportion of patients with prediabetes achieving normoglycaemia and a significant increase in the proportion of patients with diabetes achieving remission of hyperglycaemia. Consistent point estimates were observed across several definitions for glycaemic outcomes, including ones more stringent than are typically used in clinical practice.

Hypoglycaemia was previously observed to be more frequent in patients with diabetes receiving lorcaserin compared with placebo.[10] In the current study, severe hypoglycaemia with serious complications was numerically increased with all but one event occurring in patients with diabetes receiving insulin or sulfonylurea. This finding highlights the importance of careful titration of agents known to cause hypoglycaemia in the setting of major physiological changes, such as weight loss.

Given the previously discussed observations regarding the dose–response relationship between the magnitude of weight loss and improvements in glycaemic parameters, it is presumed that much of the glycaemic benefit is weight dependent. Of note, at 1 year, lorcaserin resulted in a modest but sustained weight loss in all glycaemic subgroups. As has been observed with lorcaserin previously and with other agents and weight loss strategies (eg, lifestyle interventions), the proportionate weight loss tended to be less in patients with dysglycaemia.[2,8–10] Specifically, at 1 year, patients with diabetes had a net weight loss of 2·6% compared with 2·8% in those with prediabetes and 3·3% in those with normoglycaemia. The reason for this somewhat lesser degree of weight loss in patients with diabetes has not been definitely elucidated. Moreover, it is interesting to note that in the CAMELLIA-TIMI 61 study, reductions in glycaemic parameters were maximal as soon as 3 months, well in advance of the nadir in weight, which tended to occur at 12 months. Similar observations were made in BLOOM-DM,[27] where fasting plasma glucose decreased with lorcaserin compared with placebo as early as 2 weeks after initiation of therapy, prior to any significant weight loss. Preclinical data suggest that central and neurohormonal signalling pathways downstream of the 5-HT2C receptor can suppress hepatic gluconeogenesis.[28] It is not known whether the early glycaemic changes are due to decreased caloric intake or an alternative mechanism, such as suppression of hepatic gluconeogenesis.

Although it is well described that glycaemic control reduces microvascular complications in patients with diabetes, few data are available that link weight loss to a benefit in microvascular complications of diabetes.[13] Lifestyle intervention in the Diabetes Prevention Program trial[29] did not significantly reduce the rate of microvascular complications after 15 years of follow-up, despite the lower rates of incident diabetes compared with standard of care. The only randomised assessment for microvascular outcomes after bariatric surgery comes from the STAMPEDE trial,[21] which found numerically small but significant reductions in urinary ACR in the normal range at 5 years with bariatic surgery compared with medical therapy in patients with diabetes.[21] There was no difference in the proprotion of participants who remained free of albuminuria or retinopathy. Long-term observational data from the Swedish Obese Study[24] found that bariatric surgery was associated with a 56% lower incidence of microvascular complications at 20 years of follow-up. Liraglutide, when studied at the lower dose approved for diabetes (1·8 mg daily), resulted in a reduction in nephropathy.[30] In the CAMELLIA-TIMI 61 study, lorcaserin significantly reduced the incidence of microvascular complications of diabetes, approximately 80% of which were incident persistent microalbuminuria.

There are limitations of this study. Although urinary ACR was measured centrally, the other microvascular events of neuropathy and retinopathy were investigator reported. In the absence of protocol-specified screening procedures (eg, retinal exam), there was a possibility of undetected abnormalities at baseline as well as probable underdetection and under-reporting during follow-up; nevertheless, the comparisons between treatment arms would remain unbiased. Further, the benefits shown on microvascular events were driven numerically by effects on microalbuminuria with far fewer retinopathy and neuropathy events reported. Even larger studies than

ours would be needed to confirm the trends in the latter outcomes. The specific mechanisms of benefit for improvements in glycaemic and microvascular outcomes cannot be determined from this study. Although the protocol offered guidelines for titration of glucose-lowering medications in the setting of weight loss and improvements in glycaemia, it is likely that there was a range of approaches used with varied outcomes. For example, we observed more discontinuation of glucose-lowering medications with lorcaserin than placebo. We also observed numerically more events of serious hypoglycaemia in patients on lorcaserin and agents known to precipitate hypoglycaemia (ie, insulin and sulfonylureas), which might reflect reduced caloric intake or greater weight loss with insufficient down-titration of those agents. Although several weight parameters were captured, including weight, BMI, waist circumference, and waist-to-hip ratio, measures of body composition or fat distribution were not collected. Lastly, there was no adjustment for multiplicity, where the coprimary efficacy endpoints of cardiovascular events and incident diabetes were each tested at a nominal α of 0·05. This approach was felt to be reasonable because of (1) the distinct hypotheses for the effect of lorcaserin on cardiovascular events versus incident diabetes; (2) the fact that the hypothesis testing for incident diabetes was done primarily in patients with prediabetes, a sub-population distinct from the analytic set used for cardiovascular outcomes; and (3) the well validated association of weight loss and prevention of incident diabetes with other modalities.[3]

On the background of lifestyle modification, lorcaserin resulted in modest, but durable, weight loss in overweight and obese patients with and without diabetes and to overall improvements in glycaemic control, with lower rates of incident diabetes, higher rates of remission of hyperglycaemia, favourable trends for achievement of normoglycaemia, and a lower risk of diabetic microvascular complications.

Contributors

All authors contributed to study oversight, data interpretation, manuscript writing and revisions. EAB, BMS, MSS, SDW, SEI, DKM, ACK, SRS, LAL, JPD, TP, WM, CP, BF, EK, SAM, and SD contributed to study design, study conduct, and data analysis. MPB and CTR contributed to study conduct. EAB wrote the initial draft of the manuscript. All coauthors participated in subsequent manuscript revisions. The authors from the TIMI Study Group assume responsibility for the accuracy and completeness of the data and all the analyses.

Declaration of interests

EAB reports grants from Eisai, during the conduct of the study; and personal fees from Servier, Merck, National Institutes of Health, Lexicon, Medscape, Academic CME, MD Conference Express, Paradigm, and Novartis and grants from Amgen, AstraZeneca, and Merck, outside of the submitted work. MPB reports grants from BWH/TIMI Study Group, during the conduct of the study; and grants and other support from Amgen, Aralez, and AstraZeneca; other support from Bayer and Janssen; grants from MedImmune and Pfizer; grants, personal fees, and other support from Merck; and other support from Sanofi, outside of the submitted work. RC and JPD report personal fees from Eisai, during the conduct of the study. SEI reports personal fees from Eisai, during the conduct of the study; and personal fees from Merck, Janssen, AstraZeneca, Novo Nordisk, Sanofi/Lexicon, Intarcia, Daiichi Sankyo, Alere, and VTV Therapeutics; and personal fees and non-financial support from Boehringer Ingelheim, outside of the submitted work. EK reports grants from Abbott Laboratories, Amgen, AstraZeneca, Critical Diagnostics, Daiichi-Sankyo, Eisai, GlaxoSmithKline, Intarcia, Merck, Roche Diagnostics, Takeda, Gilead, Poxel, Novartis, MedImmune, Janssen Research Development, and Genzyme, outside of the submitted work. ACK reports other support from Eisai, during the conduct of the study; and grants and personal fees from Abbott and Mylan; personal fees from Amgen, Pfizer, Bayer, and AstraZeneca; and grants from Sanofi and Novartis, outside of the submitted work. LAL reports personal fees from Eisai, during the conduct of the study; and grants and personal fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, and Sanofi; personal fees from Servier; and grants from GlaxoSmithKline, outside of the submitted work. DKM reports personal fees from Eisai, during the conduct of the study; and personal fees from Boehringer Ingelheim, Janssen Research and Development, Sanofi US, Merck Sharp & Dohme, Eli Lilly, Novo Nordisk, GlaxoSmithKline, AstraZeneca, Lexicon, Eisai, Esperion, Metavant, and Pfizer, outside of the submitted work. SAM reports grants from Abbott Laboratories, Amgen, AstraZeneca, Critical Diagnostics, Daiichi-Sankyo, Eisai, GlaxoSmithKline, Intarcia, Roche Diagnostics, Takeda, Gilead, Poxel, Novartis, MedImmune, Janssen Research Development, and Genzyme; and grants and honorarium from Merck, outside of the submitted work. JCN reports personal fees from Amgen and Servier; grants from AstraZeneca, Bayer, BMS, CLS Behring, Novartis, and Dalcor; and grants and personal fees from Sanofi, Vifor, and Pfizer, outside of the submitted work. TP, WM, and CP report employment for Eisai. KKR reports personal fees from AbbVie; grants and personal fees from Amgen, Sanofi, Regeron, Merck Sharp & Dohme, Pfizer, AstraZeneca, MedCo, Resverlogix, Akcea, Boehringer Ingelheim, Novo Nordisk, Takeda, Kowa, Cerenis, Cipla, Algorithm, and Esperion, outside of the submitted work. CTR reports grants from Eisai, during the conduct of the study; and grants and personal fees from Boehringer-Ingelheim, Bayer, Janssen, Portola, and Daiichi Sankyo, outside of the submitted work. MSS reports grants from Eisai, during the conduct of the study; and grants and personal fees from Amgen, Intarcia, Janssen, Medicines Company, Medimmune, Merck, Novartis, AstraZeneca, Intarcia, Janssen Research and Development, Medicines Company, Medimmune, Merck, and Novartis; grants from Daiichi-Sankyo, Eisai, GlaxoSmithKline, Pfizer, Poxel, Takeda, Abbott Laboratories, Critical Diagnostics, Genzyme, Gilead, and Roche Diagnostics; and personal fees from Bristol-Myers Squibb, CVS Caremark, Dyrnamix, Esperion, Alnylam, Ionis, and MyoKardia, outside of the submitted work. BMS reports grants from Eisai, during the conduct of the study; and grants from AstraZenaca, Novartis, and Merck; personal fees from AstraZeneca, Biogen Idec, Boehringer Ingelheim, Covance, Dr Reddy's Laboratory, Eisai, Elsevier Practice Update Cardiology, GlaxoSmithKline, Merck, NovoNordisk, Sanofi, and St Jude's Medical; and other support from Health [at] Scale, outside of the submitted work. SRS reports personal fees from Eisai, outside of the submitted work. SDW reports grants from Eisai, during the conduct of the study; and grants from Amgen and Sanofi-Aventis; grants and personal fees from Arena, AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, Eisai, Eli Lilly, and Janssen; grants, personal fees, and other support from Merck; and personal fees from Aegerion, Allergan, Angelmed, Boehringer Ingelheim, Boston Clinical Research Institute, Icon Clinical, Lexicon, St Jude Medical, and Xoma, outside of the submitted work. All remaining authors declare no competing interests.

Data sharing

No additional data are available for this Article. We encourage parties interested in collaboration and data sharing to contact the corresponding author directly.

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