Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial

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Summary

Background We aimed to assess efficacy and safety, with a special focus on cardiovascular safety, of the novel dual GIP and GLP-1 receptor agonist tirzepatide versus insulin glargine in adults with type 2 diabetes and high cardiovascular risk inadequately controlled on oral glucose-lowering medications.

Methods This open-label, parallel-group, phase 3 study was done in 187 sites in 14 countries on five continents. Eligible participants, aged 18 years or older, had type 2 diabetes treated with any combination of metformin, sulfonylurea, or sodium-glucose co-transporter-2 inhibitor, a baseline glycated haemoglobin (HbA_{1c}) of 7·5–10·5% (58–91 mmol/mol), body-mass index of 25 kg/m² or greater, and established cardiovascular disease or a high risk of cardiovascular events. Participants were randomly assigned (1:1:1:3) via an interactive web-response system to subcutaneous injection of either once-per-week tirzepatide (5 mg, 10 mg, or 15 mg) or glargine (100 U/mL), titrated to reach fasting blood glucose of less than 100 mg/dL. The primary endpoint was non-inferiority (0·3% non-inferiority boundary) of tirzepatide 10 mg or 15 mg, or both, versus glargine in HbA_{1c} change from baseline to 52 weeks. All participants were treated for at least 52 weeks, with treatment continued for a maximum of 104 weeks or until study completion to collect and adjudicate major adverse cardiovascular events (MACE). Safety measures were assessed over the full study period. This study was registered with ClinicalTrials.gov, NCT03730662.

Findings Patients were recruited between Nov 20, 2018, and Dec 30, 2019. 3045 participants were screened, with 2002 participants randomly assigned to tirzepatide or glargine. 1995 received at least one dose of tirzepatide 5 mg (n=329, 17%), 10 mg (n=328, 16%), or 15 mg (n=338, 17%), or glargine (n=1000, 50%), and were included in the modified intention-to-treat population. At 52 weeks, mean HbA_{1c} changes with tirzepatide were –2·43% (SD 0·05) with 10 mg and –2·58% (0·05) with 15 mg, versus –1·44% (0·03) with glargine. The estimated treatment difference versus glargine was –0·99% (multiplicity adjusted 97·5% CI –1·13 to –0·86) for tirzepatide 10 mg and –1·14% (–1·28 to –1·00) for 15 mg, and the non-inferiority margin of 0·3% was met for both doses. Nausea (12–23%), diarrhoea (13–22%), decreased appetite (9–11%), and vomiting (5–9%) were more frequent with tirzepatide than glargine (nausea 2%, diarrhoea 4%, decreased appetite <1%, and vomiting 2%, respectively); most cases were mild to moderate and occurred during the dose-escalation phase. The percentage of participants with hypoglycaemia (glucose <54 mg/dL or severe) was lower with tirzepatide (6–9%) versus glargine (19%), particularly in participants not on sulfonylureas (tirzepatide 1–3% *vs* glargine 16%). Adjudicated MACE-4 events (cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina) occurred in 109 participants and were not increased on tirzepatide compared with glargine (hazard ratio 0·74, 95% CI 0·51–1·08). 60 deaths (n=25 [3%] tirzepatide; n=35 [4%] glargine) occurred during the study.

Interpretation In people with type 2 diabetes and elevated cardiovascular risk, tirzepatide, compared with glargine, demonstrated greater and clinically meaningful HbA_{1c} reduction with a lower incidence of hypoglycaemia at week 52. Tirzepatide treatment was not associated with excess cardiovascular risk.

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Introduction

Current guidelines recommend GLP-1 receptor agonists as the first injectable therapy in people with type 2 diabetes.[1] Treatment with GLP-1 receptor agonists achieves similar or better glycaemic control than basal insulins with weight loss and lower risk of hypoglycaemia,[2–5] but is associated with frequent gastrointestinal side-effects.[6]

Combined GIP and GLP-1 receptor activation has been established as a promising therapeutic concept for the treatment of type 2 diabetes.[7] Tirzepatide (Eli Lilly and Company, Indianapolis, IN, USA), a novel dual GIP and GLP-1 receptor agonist, is under development for the treatment of type 2 diabetes. When compared with a GLP-1 receptor agonist, tirzepatide further improves glycaemic control by actions on pancreatic β cells to

Research in context

Evidence before this study

We searched PubMed on Aug 5, 2021, with no restrictions other than English language, using the terms "albiglutide", "dulaglutide", "exenatide", "liraglutide", "lixisenatide", "semaglutide", "tirzepatide", "glucagon-like peptide-1 (GLP-1) receptor agonist", "glucose-dependent insulinotropic polypeptide (GIP)", "basal insulin", "insulin degludec", "insulin glargine", and "type 2 diabetes". Basal insulin or GLP-1 receptor agonists are currently recommended as the first injectable therapies for the treatment of type 2 diabetes. Tirzepatide is a novel once-per-week dual GIP and GLP-1 receptor agonist representing a first-in-class medication for the treatment of type 2 diabetes. It has shown clinically meaningful improvements in glycated haemoglobin (HbA_{1c}) and bodyweight in various background therapies when compared with placebo, dulaglutide, semaglutide, and insulin degludec in studies of 26–52 weeks duration. Its non-cardiovascular safety profile is similar to that of GLP-1 receptor agonists. These previous results were obtained in individuals with type 2 diabetes and overall low cardiovascular risk.

Added value of this study

To our knowledge, this was the first study to compare the efficacy and safety of a dual GIP and GLP-1 receptor agonist with a basal insulin in patients with type 2 diabetes and high risk for cardiovascular events. The study duration was longer than other studies in the SURPASS programme, providing the first evidence of the sustained effects of tirzepatide. In addition, conducting the study in this high risk population provided an initial assessment of cardiovascular safety of tirzepatide. As a first injectable treatment, after 52 weeks of treatment, tirzepatide 5 mg, 10 mg, and 15 mg demonstrated clinically meaningful HbA_{1c} reductions and bodyweight loss compared with titrated glargine in people with long duration type 2 diabetes and high cardiovascular risk. Greater proportions of tirzepatide-treated participants achieved HbA_{1c} treatment goals, with a lower incidence of hypoglycaemia (glucose <54 mg/dL or severe). HbA_{1c} and bodyweight reductions were sustained for up to 104 weeks. Tirzepatide also decreased systolic and diastolic blood pressure, triglycerides, and non-HDL cholesterol. The hazard ratio for major adverse cardiovascular events (109 participants with first event of cardiovascular death, myocardial infarction, stroke, or hospitalisation for unstable angina) for pooled tirzepatide groups versus glargine was 0·74 (95% CI 0·51–1·08), indicating no increased cardiovascular risk with tirzepatide treatment compared with glargine.

Implications of all the available evidence

Once-per-week tirzepatide provides long-term meaningful improvement of glycaemic control with low risk of clinically relevant hypoglycaemia in participants with various durations of type 2 diabetes, with or without cardiovascular disease, treated with diverse glucose-lowering medications, including sulfonylureas. Additional benefits of tirzepatide included bodyweight and blood pressure reductions and improvements in the lipid profile. Importantly, no increased cardiovascular risk was observed versus glargine in people with type 2 diabetes and elevated risk for cardiovascular disease. Further clinical research is ongoing to evaluate potential cardiovascular benefits of tirzepatide.

enhance insulin secretion, by reducing glucose adjusted glucagon secretion, and by insulin-sensitising effects beyond the level explained by weight loss.[8] In addition, tirzepatide treatment is associated with improvements in adipose tissue and lipoprotein metabolism, blood pressure, and other surrogate markers of cardiovascular protection.[9,10] It also has a marked anorexigenic effect, probably by integrating the activation signals of both GLP-1 and GIP receptor pathways in the brain.[10,11] When compared with placebo,[12] semaglutide 1 mg per week,[13] or insulin degludec,[14] tirzepatide was more effective in achieving glycaemic control and weight reduction in people with type 2 diabetes over 40–52-week treatment periods.

Although tirzepatide has been shown to be superior to other glucose-lowering agents for glycaemic and weight effects, and has shown favourable effects on cardiovascular risk factors, its long-term efficacy and safety have not been evaluated. In particular, cardiovascular safety remains to be addressed in individuals with type 2 diabetes and high cardiovascular risk, especially in those with a history of cardiovascular disease or chronic kidney disease. Tirzepatide has been evaluated against the basal insulin degludec,[14] but not against glargine, one of the most frequently prescribed basal insulins used for blood glucose management in type 2 diabetes. Therefore, the objective of SURPASS-4 was to compare the efficacy and safety of three doses of tirzepatide (5 mg, 10 mg, and 15 mg) versus glargine titrated to a fasting glucose of less than 100 mg/dL in people with type 2 diabetes and high cardiovascular risk inadequately controlled on oral glucose-lowering medications.

Methods

Study design

This randomised, open-label, active-controlled, parallel-group, phase 3 study was conducted at 187 sites in 14 countries (Argentina, Australia, Brazil, Canada, Greece, Israel, Mexico, Poland, Romania, Russia, Slovakia, Spain, Taiwan, and the USA) on five continents. The protocol was approved by institutional review boards for each site and the trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol for this study is available in the appendix (p 36).

Participants

Key inclusion criteria were adults (aged ≥18 years) with type 2 diabetes inadequately controlled (glycated haemoglobin [HbA_{1c}] 7·5–10·5% [58–91 mmol/mol]), with any of three oral glucose-lowering medications (ie, metformin, sulfonylurea, or sodium-glucose co-transporter-2 [SGLT-2] inhibitor) either alone or in any combination, body-mass index (BMI) of 25 kg/m² or more, and stable weight (≤5% fluctuation in either direction) during the previous 3 months. Eligible participants were at increased risk of cardiovascular events, defined as known coronary, peripheral arterial, or cerebrovascular disease, or aged 50 years or older with either history of chronic kidney disease and an estimated glomerular filtration rate (eGFR) of less than 60 mL/min per 1·73 m² or history of congestive heart failure (New York Heart Association Class II or III). Key exclusion criteria included type 1 diabetes and history of pancreatitis. Full eligibility criteria and recruitment information are given in the appendix (pp 7, 10). All participants provided written informed consent before entering the study.

Randomisation and masking

Participants were randomly assigned (1:1:1:3), by the Eli Lilly and Company computer-generated random sequence using an interactive web-response system to receive tirzepatide or glargine. The interactive web-response system was externally validated and compliant with the Code of Federal Regulations 21 part 11. The randomisation system was overseen by a dedicated group at Eli Lilly and Company independent from the study team, according to their standard operating procedures; access to the randomisation system was documented in the blinding and unblinding plan. Participants were stratified at randomisation based on country, baseline HbA_{1c} of 8·5% or less or more than 8·5% (69 mmol/mol), and baseline SGLT-2 inhibitor use. This study was open-label due to the differences in dosing schedule, titration, and devices between once-per-week tirzepatide and once-per-day insulin glargine.

Procedures

Tirzepatide was administered as a once-per-week subcutaneous injection (5 mg, 10 mg, or 15 mg) with a prefilled syringe. Tirzepatide treatment was initiated at 2·5 mg once per week, and increased by 2·5 mg every 4 weeks until the randomised dose was achieved and maintained for the study duration (appendix p 23). If intolerable gastrointestinal symptoms or events occurred during tirzepatide dose escalation, the dose could be de-escalated to a lower, tolerated maintenance dose (5 mg or 10 mg) of tirzepatide. Participants remained on the lower dose for the remainder of the study. Dose de-escalation was only allowed once during the dose escalation period.

Insulin glargine (Basaglar, Eli Lilly and Company, Indianapolis, IN, USA) was administered once per day via subcutaneous injection with a prefilled pen containing 3 mL (U100/mL), typically before bedtime. Insulin glargine treatment was initiated at 10 U/day and titrated to a fasting blood glucose of less than 100 mg/dL; dose adjustments were made based on the median value of the last three self-monitored fasting blood glucose values (appendix p 16).[15]

Participants remained on their background glucose-lowering medications throughout the study. These medications could be reduced or discontinued due to the occurrence of hypoglycaemia. Additional glucose-lowering medications could be used as rescue therapy for persistent hyperglycaemia based on prespecified criteria (appendix p 11), or after early discontinuation of study medication, or both. GLP-1 receptor agonists, DPP-4 inhibitors, and pramlintide were not allowed throughout the study.

Following a 1-week screening and 2-week lead-in period, participants were treated for 52 weeks, with the primary efficacy endpoint assessed at this timepoint (appendix p 23). For the study to collect additional cardiovascular outcome data in these high-risk individuals, after 52 weeks there was a variable treatment period of up to, but not longer than, an additional 52 weeks. The key criteria for timing of study conclusion were all participants reaching 52 weeks, 300 or more tirzepatide-treated participants reaching 78 weeks, and approximately 110 participants having at least one positively adjudicated component of the composite cardiovascular endpoint. This variable treatment period facilitated collection of long-term efficacy and safety data. The study concluded with a 4-week safety follow-up period.

See Online for appendix

The protocol was amended due to the COVID-19 pandemic. This amendment allowed mobile (in-home) health-care visits to be performed and samples to be collected by qualified personnel at participants' homes, when they could not travel to the clinical site due to extenuating circumstances. Also, the primary endpoint visit window was widened from 52 weeks (within 7 days either side of this timeframe) to between 50 weeks and 60 weeks if needed to provide greater opportunity for participants to perform this visit.

Outcomes

The primary endpoint was change in HbA_{1c} from baseline to 52 weeks. Key secondary endpoints were bodyweight change from baseline to 52 weeks and achievement of HbA_{1c} target of less than 7·0% (<53 mmol/mol; appendix p 17). Other endpoints included the proportion of participants achieving HbA_{1c} of 6·5% or lower (≤48 mmol/mol) and less than 5·7% (<39 mmol/mol); weight loss of 5% or more, 10% or more, and 15% or more; mean change from baseline in fasting serum glucose (FSG); and daily mean seven-point self-monitored blood

glucose profiles, BMI, waist circumference, and serum lipids. These measures were also assessed during the variable treatment period. All biochemical analysis, except for self-monitored blood glucose, were done at a central laboratory.

A cardiovascular risk comparison between tirzepatide and glargine was a prespecified safety objective. This comparison was done relative to the four-component composite endpoint of cardiovascular death, myocardial infarction, stroke, and hospitalisation for unstable angina (major adverse cardiovascular events; MACE-4). MACE-4, transient ischaemic attacks, coronary revascularisations, hospitalisations for heart failure, and mortality were adjudicated by an independent clinical endpoint committee (Cleveland Clinic Coordinating Center for Clinical Research, Cleveland, OH, USA) blinded to treatment allocation. Participants with MACE were expected to stay in the study and on treatment. This committee also adjudicated potential cases of pancreatitis in a blinded manner.

Additional safety endpoints were treatment-emergent adverse events, study medication discontinuation due to adverse events, adjudicated pancreatic adverse events, serum calcitonin, incidence of hypersensitivity reactions, treatment-emergent anti-drug antibodies for tirzepatide, mean changes from baseline in pulse rate, systolic and diastolic blood pressure, need for initiation of rescue therapy for glucose lowering, and occurrence of clinically significant (glucose <54 mg/dL, documented either symptomatic, asymptomatic or unspecified) or severe hypoglycaemia (a severe event characterised by altered mental or physical status, or both, requiring assistance for treatment of hypoglycaemia).[16]

A data monitoring committee external to the study team supported by statisticians external to the study team reviewed the safety data every 6 months.

Statistical analysis

This study was designed to randomly assign participants (1:1:1:3) to tirzepatide 5 mg, 10 mg, and 15 mg, and glargine, respectively. The sample size calculation assumed at least a 0·3% (3 mmol/mol) superior HbA_{1c} reduction of tirzepatide 10 mg and 15 mg to glargine, a common SD of 1·1% (12 mmol/mol), and no more than 28% initiation of any rescue glucose-lowering medication or premature discontinuation of study medication by 52 weeks. A sample size of 1878 participants in a 1:1:1:3 ratio (313 in each tirzepatide group and 939 in the glargine group) would provide at least 90% power to demonstrate superiority of tirzepatide 10 mg and 15 mg to glargine each at a two-sided significance level of 0·025. Under the same assumptions, along with the 0·3% non-inferiority boundary, a sample size of 1878 participants also provided more than 99% power to achieve non-inferiority relative to the primary efficacy endpoint at a one-sided significance level of 0·0125.

The trial was designed to establish superiority of tirzepatide to glargine relative to the primary endpoint of HbA_{1c} change from baseline to 52 weeks with demonstrating non-inferiority of once-per-week administration of tirzepatide to daily administration of glargine, a clinically relevant outcome, as a fallback option, which was designated as the primary objective. Therefore, to control type I error rate non-inferiority of tirzepatide 10 mg or 15 mg, or both, to glargine (0·3% non-inferiority boundary)[17] was assessed before assessing superiority. Key secondary objectives, controlled for type I error, included non-inferiority and superiority of tirzepatide 5 mg compared with glargine relative to HbA_{1c}, and superiority of all doses of tirzepatide versus glargine relative to weight and the proportion of participants achieving HbA_{1c} of less than 7·0% (<53 mmol/mol).

Two estimands were used to assess treatment efficacy from different perspectives and accounted for intercurrent events differently. First, the efficacy estimand is the treatment effect between tirzepatide and glargine if participants who underwent randomisation continued to receive the study medication without rescue medication. Second, the treatment-regimen estimand is the treatment effect in treated participants regardless of premature study medication discontinuation and rescue medication use. Analyses aligned to the efficacy estimand were considered as primary for assessing primary and secondary endpoints. Analyses aligned to the treatment-regimen estimand were considered as sensitivity analyses. All randomly assigned participants who took at least one dose of study medication (modified intention-to-treat [mITT] population) were included in the analyses assessing both estimands. All reported results are for the efficacy estimand, with results aligned to the treatment-regimen estimand presented in the appendix (p 34). Participants who discontinued study medication due to inadvertent enrolment (six participants, one each in the tirzepatide 5 mg and 15 mg groups, two each in the tirzepatide 10 mg and glargine groups) were excluded from efficacy analyses. Details on estimands and analysis methods are provided in the appendix (p 12).

The analysis aligned to the efficacy estimand for change from baseline in HbA_{1c} was conducted using mixed model for repeated measures (MMRM). Restricted maximum likelihood was used to obtain model parameter estimates and Kenward-Roger option to estimate denominator degrees of freedom. The MMRM used treatment, visit, treatment by visit interaction, country, and SGLT2 inhibitor use at baseline as fixed effects, and baseline HbA_{1c} as a covariate. An unstructured covariance structure was used to model the within-participant errors. Missing data due to either use of rescue medication, treatment discontinuation, or not being measured, were implicitly handled by the MMRM under the assumption of missing at random.

The analysis aligned to treatment-regimen estimand for change from baseline in HbA_{1c} was conducted using

analysis of covariance (ANCOVA). The ANCOVA model used treatment, country, SGLT2 inhibitor use at baseline as fixed effects, and baseline HbA_{1c} as a covariate. The ANCOVA analysis was conducted with multiple imputation of missing HbA_{1c} values at the primary endpoint visit and statistical inference over multiple imputation of missing data, guided by Rubin.[18]

Because this trial was conducted in participants at high risk for MACE, the incidence of first MACE-4 endpoint was also investigated. The trial was not powered to evaluate differences in MACE-4 incidence between tirzepatide treatment groups and glargine. The study was designed to contribute the majority of the MACE-4 events to the meta-analysis requested by regulatory authorities to evaluate the cardiovascular safety of new glucose-lowering medications.

To control for type I error, non-inferiority of tirzepatide 10 mg and 15 mg to glargine was assessed in parallel, each at one-sided 0·0125 α level. Contingent on successfully demonstrating non-inferiority, superiority of tirzepatide 10 mg and 15 mg to glargine was assessed relative to weight and HbA_{1c} reduction, respectively, each at a two-sided 0·025 level in a hierarchical fashion. Contingent on successfully establishing superiority of either 10 mg or 15 mg, other key secondary endpoints were evaluated hierarchically, beginning with comparisons between 5 mg tirzepatide and glargine; comparisons were conducted at two-sided 0·05 level if both 10 mg and 15 mg were superior relative to HbA_{1c} reduction and at two-sided 0·025 level if only one dose was superior to glargine relative to HbA_{1c} reduction. Additional information regarding type I error rate-control for evaluation of other secondary objectives is provided in the appendix (pp 13–14).

Safety analyses were performed on the safety analysis set, the mITT population, with all data whether on or off study medication. These analyses included all data from the start of treatment to the end of safety follow-up, which included the variable treatment period. The primary measure of cardiovascular events was the time to first occurrence of a MACE-4 event. Time to first occurrence of MACE-4 was conducted using Cox proportional hazards model.

The proportion of patients with hypoglycaemia events with blood glucose level of no more than 70 mg/dL (3·9 mmol/L) and less than 54 mg/dL (3·0 mmol/L) were summarised by treatment and comparisons between tirzepatide and glargine were analysed using logistic regression. In addition, since recurrence of hypoglycaemia is not uncommon, the total number, as well as the rate, of hypoglycaemic episodes were determined by treatment with rates compared using negative binomial model. A summary of hypoglycaemic events was also calculated separately in participants on or not on stable dose of sulfonylureas. Statistical analysis was done using SAS, version 9.4.

The trial was registered with ClinicalTrials.gov, NCT03730662.

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, data interpretation and writing of the report through the assistance of medical writers employed by Eli Lilly and Company.

Results

The study was initiated on Nov 20, 2018, with participant recruitment continuing until Dec 30, 2019. The study was completed on April 22, 2021. 3045 participants were screened, with 2002 participants randomly assigned to tirzepatide or glargine. 1995 received at least one dose of tirzepatide 5 mg (n=329, 17%), 10 mg (n=328, 16%), or 15 mg (n=338, 17%), or glargine (n=1000, 50%). 1819 (91%) participants had the primary endpoint measured at 52 weeks while still on study medication and 1909 (95%) while in the study (figure 1). At study end, MACE-4 events had occurred in 109 participants. A summary of study duration, including the variable treatment period that occurred after week 52, is shown in the appendix (p 18). The median study duration was 85 weeks. Overall, 1801 (90%) of 1995 participants completed the study, with 1706 (85%) completing study treatment. Among the 1706 participants who completed study treatment, 132 (7%) completed treatment at the 104-week visit, and 1574 (79%) completed treatment at the final treatment visit. The most common reason for premature study medication discontinuation was gastrointestinal-related adverse events in the tirzepatide groups and withdrawal of consent in the insulin glargine group (appendix p 19).

Demographics and clinical characteristics were similar across groups (table 1). The overall mean duration of diabetes was 11·8 years (SD 7·5), with a mean HbA_{1c} of 8·52% (SD 0·88), and bodyweight of 90·3 kg (SD 18·7). 1738 (87%) participants had a history of cardiovascular disease and 342 (17%) an eGFR of less than 60 mL/min per 1·73 m² (table 1). Use of blood pressure lowering (n=1855, 93%), lipid lowering (n=1638, 82%), and anti-platelet (n=1389, 70%) medications was common (appendix p 20).

At 52 weeks, mean HbA_{1c} changes with tirzepatide were –2·24% (SE 0·05) at 5 mg, –2·43% (0·05) at 10 mg, and –2·58% (0·05) at 15 mg, versus –1·44% (0·03) with glargine (table 2; appendix p 24). The estimated treatment difference versus glargine was –0·99% (multiplicity adjusted 97·5% CI –1·13 to –0·86) for tirzepatide 10 mg and –1·14% (–1·28 to –1·00) for tirzepatide 15 mg. The primary objective of the study, non-inferiority of tirzepatide 10 mg or 15 mg, or both, versus glargine for the primary efficacy endpoint, was met, because the upper limits of the CIs were less than 0·3. Superiority of tirzepatide 10 mg and 15 mg versus glargine for HbA_{1c} change from baseline to week 52 was also achieved (p<0·0001 for both doses). Tirzepatide 5 mg was also superior to glargine, with an estimated treatment difference of –0·80% (multiplicity adjusted 95% CI

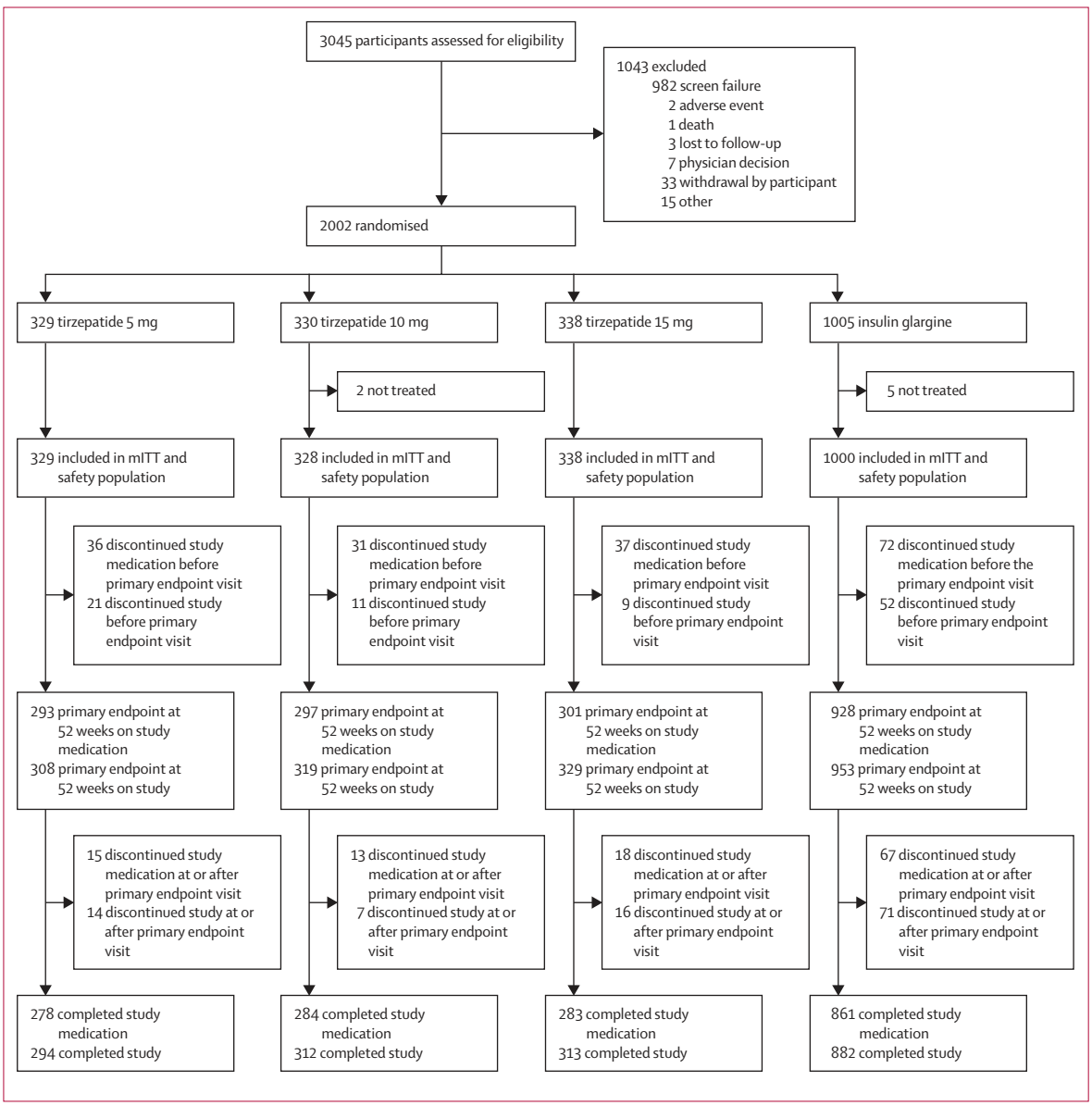

Figure 1: **Trial profile**
Six participants (one each on tirzepatide 5 mg and 15 mg, two each on tirzepatide 10 mg and glargine) discontinued study medication due to inadvertent enrolment and were excluded from efficacy analyses. The number of patients discontinuing study medication and discontinuing study overlap. mITT population=modified intention-to-treat.

–0·92 to –0·68; p<0·0001). The profile of HbA_{1c} level over time with tirzepatide treatment indicated a sustained reduction up to 104 weeks, with non-missing baseline HbA_{1c} and 78-week data for 1166 (58%) participants and 104-week data for 199 (10%) participants included in the MMRM analyses (appendix p 24). HbA_{1c} of less than 7·0% (<53 mmol/mol) was achieved in 81–91% of tirzepatide-treated participants versus 51% with glargine; a HbA_{1c} of 6·5% or lower (≤48 mmol/mol) was achieved in 66–81% of tirzepatide-treated participants versus 32% with glargine; and a HbA_{1c} of less than 5·7% (<39 mmol/mol) in 23–43% of tirzepatide-treated participants versus 3% with glargine (appendix p 24). The composite endpoint of HbA_{1c} of less than 7·0% without weight gain and clinically significant documented symptomatic or severe hypoglycaemia was achieved in 74–88% of tirzepatide-treated participants compared with 13% with glargine (appendix p 25). Changes in FSG were larger with tirzepatide 15 mg (–59·3 mg/dL [SE 2·0]) and not different for tirzepatide 5 mg (–50·4 mg/dL [2·1]) and 10 mg (–54·9 mg/dL [2·1]) versus glargine (–51·4 mg/dL [1·2]) at 52 weeks. The estimated treatment difference versus glargine for FSG at 52 weeks was 1·0 (–3·7, 5·7; p=0·6724) for 5 mg, –3·6 (–8·2 to 1·1;

	Tirzepatide 5 mg (n=329)	Tirzepatide 10 mg (n=328)	Tirzepatide 15 mg (n=338)	Insulin glargine (n=1000)	Overall population (N=1995)
Age, years	62·9 (8·6)	63·7 (8·7)	63·7 (8·6)	63·8 (8·5)	63·6 (8·6)
Sex					
Female	131 (40%)	119 (36%)	135 (40%)	364 (36%)	749 (38%)
Male	198 (60%)	209 (64%)	203 (60%)	636 (64%)	1246 (62%)
Race					
Asian	15 (5%)	16 (5%)	8 (2%)	31 (3%)	70 (4%)
Black or African American	13 (4%)	17 (5%)	11 (3%)	32 (3%)	73 (4%)
White	260 (79%)	259 (79%)	285 (85%)	825 (83%)	1629 (82%)
Duration of diabetes, years	9·8 (6·2–15·3)	10·6 (6·5–16·2)	10·4 (5·5–15·7)	10·7 (6·3–16·5)	10·5 (6·2–15·9)
HbA_{1c}, %; mmol/mol	8·52 (0·84); 69·6 (9·21)	8·59 (0·91); 70·4 (9·95)	8·52 (0·98); 69·6 (10·68)	8·50 (0·85); 69·4 (9·32)	8·52 (0·88); 69·7 (9·65)
Fasting serum glucose, mg/dL	172·3 (49·11)	175·5 (51·93)	174·1 (53·84)	168·4 (49·72)	171·2 (50·75)
Weight, kg	90·3 (20·32)	90·6 (18·21)	90·0 (16·34)	90·2 (19·00)	90·3 (18·66)
Body-mass index, kg/m^2	32·6 (6·06)	32·8 (5·51)	32·5 (5·02)	32·5 (5·55)	32·6 (5·54)
History of cardiovascular disease	275 (84%)	296 (90%)	293 (87%)	874 (87%)	1738 (87%)
Documented coronary artery disease	133 (40%)	146 (44%)	146 (43%)	455 (45%)	880 (44%)
Myocardial infarction	109 (33%)	87 (26%)	106 (31%)	344 (34%)	646 (32%)
Coronary revascularisation procedure	109 (33%)	104 (32%)	102 (30%)	329 (33%)	644 (32%)
Hospitalisation for unstable angina	21 (6%)	30 (9%)	22 (7%)	91 (9%)	164 (8%)
Hospitalisation for heart failure	22 (7%)	31 (9%)	19 (6%)	68 (7%)	140 (7%)
Stroke	37 (11%)	36 (11%)	43 (13%)	125 (12%)	241 (12%)
Transient ischaemic attack	16 (5%)	12 (4%)	17 (5%)	53 (5%)	98 (5%)
Peripheral artery disease	89 (27%)	109 (33%)	106 (31%)	302 (30%)	606 (30%)
eGFR, CKD-EPI mL/min per 1·73 m^2	80·3 (22·66)	81·4 (20·44)	81·6 (21·22)	81·5 (20·78)	81·3 (21·11)
eGFR <60, CKD-EPI mL/min per 1·73 m^2	62 (19%)	56 (17%)	58 (17%)	166 (17%)	342 (17%)
Macroalbuminuria (UACR >300 mg/g)	25 (8%)	33 (10%)	24 (7%)	79 (8%)	161 (8%)
Microalbuminuria (UACR 30–300 mg/g)	76 (24%)	97 (30%)	103 (31%)	270 (28%)	546 (28%)
Non-proliferative diabetic retinopathy	68 (21%)	63 (19%)	89 (26%)	187 (19%)	407 (20%)
Systolic blood pressure, mm Hg	133·3 (14·18)	135·1 (16·11)	134·3 (15·02)	134·6 (15·67)	134·4 (15·40)
Diastolic blood pressure, mm Hg	78·4 (8·75)	78·6 (9·50)	78·2 (9·16)	78·4 (9·62)	78·4 (9·38)
Pulse rate, beats per min	72·4 (10·82)	73·2 (10·61)	72·7 (10·53)	72·8 (10·34)	72·8 (10·49)
SGLT2 inhibitor use, yes	78 (24%)	81 (25%)	86 (25%)	256 (26%)	501 (25%)
Sulfonylurea use, yes	189 (57%)	181 (55%)	179 (53%)	537 (54%)	1086 (54%)
Metformin use, yes	306 (93%)	316 (96%)	317 (94%)	954 (95%)	1893 (95%)
Concomitant medications					
Blood pressure lowering	303 (92%)	307 (94%)	315 (93%)	930 (93%)	1855 (93%)
Lipid lowering	262 (80%)	274 (84%)	284 (84%)	818 (82%)	1638 (82%)
Anti-platelet	228 (69%)	218 (67%)	239 (71%)	704 (70%)	1389 (70%)
Lipids, geometric mean (coefficient of variation [%])*					
Serum triglycerides, mg/dL	167·7 (54·64)	161·7 (49·44)	161·2 (54·43)	158·4 (54·58)	160·9 (53·74)
Serum total cholesterol, mg/dL	158·5 (26·32)	152·0 (26·59)	155·1 (27·05)	154·7 (27·43)	154·9 (27·06)
Serum non-HDL cholesterol, mg/dL	114·4 (35·18)	109·7 (35·03)	111·8 (34·42)	111·2 (36·96)	111·6 (35·94)

Data are mean (SD), n (%), or median (IQR) unless otherwise indicated. CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration. eGFR=estimated glomerular filtration rate. HbA_{1c}=glycated haemoglobin. mITT=modified intention-to-treat. UACR=urinary albumin-to-creatinine ratio. SGLT2=sodium-glucose cotransporter-2. *Only participants with non-missing baseline value and at least one non-missing post-baseline value of the response variable were included in analysis.

Table 1: **Baseline demographics and clinical characteristics in the mITT population**

p=0·1340) for 10 mg, and –8·0 (–12·6, –3·4; p=0·0007) for 15 mg tirzepatide. 2 weeks after study medication initiation, the reduction in FSG was significantly larger in all tirzepatide groups (all participants assigned to 2·5 mg tirzepatide per week at that point of time) when compared with glargine: tirzepatide 5 mg (–31·4 mg/dL [SE 2·1]), 10 mg (–31·1 mg/dL [2·1]), and 15 mg (–33·9 mg/dL [2·1]), versus glargine (–25·9 mg/dL [1·2]). The estimated treatment difference versus glargine for FSG at 2 weeks was –5·5 (95% CI –10·3 to –0·7; p=0·0237) for 5 mg tirzepatide, –5·2 (–10·0 to –0·4; p=0·0343) for 10 mg tirzepatide, and –8·0 (–12·7 to –3·3;

	Tirzepatide 5 mg (n=326)	Tirzepatide 10 mg (n=321)	Tirzepatide 15 mg (n=334)	Insulin glargine (n=978)
HbA_{1c}, %				
Baseline	8·52 (0·049)	8·60 (0·049)	8·52 (0·048)	8·51 (0·028)
At week 52	6·29 (0·054)	6·09 (0·054)	5·95 (0·054)	7·09 (0·031)
Change from baseline at week 52*†	−2·24 (0·053)	−2·43 (0·053)	−2·58 (0·053)	−1·44 (0·030)
ETD *vs* insulin glargine	−0·80 (−0·92 to −0·68), p<0·0001‡	−0·99 (−1·11 to −0·87), p<0·0001‡	−1·14 (−1·26 to −1·02), p<0·0001‡	..
HbA_{1c}, mmol/mol				
Baseline	69·6 (0·54)	70·5 (0·54)	69·6 (0·53)	69·5 (0·31)
At week 52	45·3 (0·59)	43·1 (0·59)	41·5 (0·59)	54·0 (0·34)
Change from baseline at week 52*†	−24·5 (0·59)	−26·6 (0·59)	−28·2 (0·59)	−15·7 (0·34)
ETD *vs* insulin glargine	−8·8 (−10·1 to −7·4), p<0·0001‡	−10·9 (−12·3 to −9·6), p<0·0001‡	−12·5 (−13·8 to −11·2), p<0·0001‡	..
Bodyweight, kg				
Baseline	90·3 (1·03)	90·7 (1·04)	90·0 (1·02)	90·3 (0·60)
At week 52	83·4 (0·29)	81·1 (0·29)	78·9 (0·29)	92·4 (0·17)
Change from baseline at week 52†	−7·1 (0·34)	−9·5 (0·34)	−11·7 (0·33)	1·9 (0·19)
ETD *vs* insulin glargine	−9·0 (−9·8 to −8·3), p<0·0001	−11·4 (−12·1 to −10·6), p<0·0001	−13·5 (−14·3 to −12·8), p<0·0001	..
Participants achieving HbA_{1c} targets at week 52				
<7·0% (<53 mmol/mol)†	264 (81%)	283 (88%)	303 (91%)	496 (51%)
OR *vs* insulin glargine	4·78 (3·47 to 6·58), p<0·0001	9·23 (6·31 to 13·49), p<0·0001	11·87 (7·88 to 17·89), p<0·0001	..
≤6·5% (≤48 mmol/mol)	215 (66%)	244 (76%)	271 (81%)	310 (32%)
OR *vs* insulin glargine	4·86 (3·66 to 6·45), p<0·0001	8·93 (6·53 to 12·21), p<0·0001	11·84 (8·52 to 16·45), p<0·0001	..
<5·7% (<39 mmol/mol)	75 (23%)	105 (33%)	144 (43%)	33 (3%)
OR *vs* insulin glargine	9·57 (6·16 to 14·86), p<0·0001	17·11 (11·12 to 26·35), p<0·0001	26·53 (17·35 to 40·56), p<0·0001	..
FSG, mmol/L				
Baseline	9·57 (0·156)	9·75 (0·157)	9·67 (0·154)	9·37 (0·090)
At week 52	6·71 (0·116)	6·46 (0·116)	6·23 (0·115)	6·67 (0·066)
Change from baseline at week 52	−2·80 (0·116)	−3·06 (0·116)	−3·29 (0·115)	−2·84 (0·066)
ETD *vs* insulin glargine	0·04 (−0·22 to 0·30), p=0·7678	−0·21 (−0·48 to 0·05), p=0·1097	−0·44 (−0·71 to −0·18), p=0·0008	..
FSG, mg/dL				
Baseline	172·3 (2·81)	175·7 (2·84)	174·2 (2·78)	168·7 (1·62)
At week 52	121·0 (2·07)	116·4 (2·06)	112·0 (2·04)	120·0 (1·17)
Change from baseline at week 52	−50·4 (2·07)	−54·9 (2·06)	−59·3 (2·04)	−51·4 (1·17)
ETD *vs* insulin glargine	1·0 (−3·7 to 5·7), p=0·6724	−3·6 (−8·2 to 1·1), p=0·1340	−8·0 (−12·6 to −3·4), p=0·0007	..
Participants achieving bodyweight loss targets at week 52				
≥5% loss	205 (63%)	249 (78%)	285 (85%)	78 (8%)
OR vs insulin glargine	21·42 (15·35 to 29·89), p<0·0001	46·14 (32·05 to 66·42), p<0·0001	76·93 (51·76 to 114·35), p<0·0001	..
≥10% loss	117 (36%)	170 (53%)	219 (66%)	15 (2%)
OR vs insulin glargine	35·61 (20·61 to 61·55), p<0·0001	76·79 (44·42 to 132·75), p<0·0001	127·51 (73·52 to 221·14), p<0·0001	..
≥15% loss	45 (14%)	77 (24%)	122 (37%)	5 (<1%)
OR vs insulin glargine	28·58 (11·88 to 68·75), p<0·0001	59·14 (25·01 to 139·86), p<0·0001	105·74 (45·11 to 247·87), p<0·0001	..

Data are least squares mean (SE); n (%); ETD (95% CI), p value; or OR (95% CI), p value. ETD=estimated treatment difference. FSG=fasting serum glucose. HbA_{1c}=glycated haemoglobin. mITT=modified intention-to-treat. OR=odds ratio. *Tested for non-inferiority, controlled for type I error. †Tested for superiority, controlled for type I error. ‡p value applicable for both non-inferiority and superiority comparison.

Table 2: **Summary of primary and secondary endpoints in the mITT population, efficacy analysis set**

p=0·0009) for 15 mg tirzepatide. Over the entire duration of the study, the reductions were similar between tirzepatide and glargine (appendix p 24). All tirzepatide doses versus glargine showed greater reductions in daily, pre-meal, and post-meal mean self-monitored blood glucose levels from baseline (appendix p 26). The mean glargine dose was 43·5 U (SD 24·96) at week 52 and 47·0 U (22·69) at week 104 (appendix p 27). During the study, rescue therapy for persistent hyperglycaemia was initiated in 0·3–0·9% of tirzepatide-treated participants versus 0·5% of glargine-treated participants.

Tirzepatide dose-dependently reduced bodyweight. At 52 weeks, mean bodyweight changes with tirzepatide were –7·1 kg (SE 0·34), –8·1% (SE 0·37) at 5 mg; –9·5 kg (0·34), –10·7% (0·37) at 10 mg; and –11·7 kg (0·33), –13·0% (0·36) at 15 mg versus an increase of 1·9 kg

(0·19), 2·2% (0·21) with glargine (table 2; appendix p 28). All tirzepatide doses demonstrated superiority to glargine with estimated treatment differences of –9·0 kg (95% CI –9·8 to –8·3) at 5 mg, –11·4 kg (–12·1 to –10·6) with 10 mg, and –13·5 kg (–14·3 to –12·8) with 15 mg (all p<0·0001). The reductions from baseline in bodyweight for the three tirzepatide groups remained similar from 52 weeks to 104 weeks (appendix p 28). Bodyweight reductions of 5% or more were achieved in 63–85% of tirzepatide-treated participants versus 8% with glargine, 10% or more weight loss was achieved in 36–66% of tirzepatide-treated participants versus 2% with glargine, and 15% or more weight loss was achieved in 14–37% of tirzepatide-treated participants versus <1% with glargine (appendix p 28). Similarly, BMI and waist circumference decreased with tirzepatide, but not with glargine at 52 weeks and remained constant from 52 weeks through to 104 weeks (appendix p 29).

At 52 weeks, mean systolic (–2·8 to –4·8 mm Hg) and diastolic (–0·8 to –1·0 mm Hg) blood pressures decreased with tirzepatide and increased with insulin glargine (systolic 1·3 mm Hg increase and diastolic 0·7 mm Hg increase; table 3). The increase in mean pulse rate was 2·9 beats per min (bpm) to 4·1 bpm in tirzepatide-treated participants, compared with an increase of 1·2 bpm in glargine-treated participants.

	Tirzepatide 5 mg (n=329)	Tirzepatide 10 mg (n=328)	Tirzepatide 15 mg (n=338)	Insulin glargine (n=1000)
Participants with at least one treatment emergent adverse event	232 (71%)	241 (74%)	259 (77%)	679 (68%)
Serious adverse events	48 (15%)	54 (17%)	41 (12%)	193 (19%)
Deaths*	15 (5%)	2 (<1%)	8 (2%)	35 (4%)
Adverse events leading to study treatment discontinuation	37 (11%)	28 (9%)	36 (11%)	54 (5%)
Adverse events occurring in at least four participants across all treatment groups leading to study treatment discontinuation				
Diarrhoea	2 (<1%)	1 (<1%)	8 (2%)	0
Vomiting	1 (<1%)	4 (1%)	4 (1%)	0
COVID-19	2 (<1%)	1 (<1%)	0	6 (<1%)
Nausea	5 (2%)	2 (<1%)	1 (<1%)	0
Acute myocardial infarction	2 (<1%)	2 (<1%)	1 (<1%)	3 (<1%)
COVID-19 pneumonia	1 (<1%)	0	2 (<1%)	4 (<1%)
Decreased appetite	2 (<1%)	1 (<1%)	2 (<1%)	0
Cardiac failure	1 (<1%)	0	1 (<1%)	2 (<1%)
Dyspepsia	1 (<1%)	2 (<1%)	1 (<1%)	0
Respiratory failure	0	0	0	4 (<1%)
Treatment emergent adverse events with at least 5% frequency in any treatment group				
Diarrhoea	41 (13%)	65 (20%)	74 (22%)	44 (4%)
Nausea	39 (12%)	53 (16%)	76 (23%)	23 (2%)
COVID-19	15 (5%)	14 (4%)	19 (6%)	59 (6%)
Nasopharyngitis	10 (3%)	16 (5%)	16 (5%)	65 (7%)
Decreased appetite	29 (9%)	36 (11%)	35 (10%)	5 (<1%)
Vomiting	16 (5%)	27 (8%)	29 (9%)	16 (2%)
Dyspepsia	18 (6%)	27 (8%)	26 (8%)	13 (1%)
Lipase increased	10 (3%)	13 (4%)	21 (6%)	18 (2%)
Constipation	17 (5%)	14 (4%)	14 (4%)	5 (<1%)
Other treatment emergent adverse events of interest				
Injection site reaction	1 (<1%)	2 (<1%)	1 (<1%)	4 (<1%)
Cholelithiasis	3 (<1%)	1 (<1%)	1 (<1%)	4 (<1%)
Cholecystitis	0	2 (<1%)	0	6 (<1%)
Pancreatitis†	3 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)
Diabetic retinopathy complications	5 (2%)	5 (2%)	4 (1%)	15 (2%)
Vital signs				
Systolic blood pressure, mm Hg	–2·8 (0·77)	–3·7 (0·76)	–4·8 (0·74)	1·3 (0·44)
Diastolic blood pressure, mm Hg	–1·0 (0·45)	–0·8 (0·45)	–1·0 (0·44)	0·7 (0·26)
Pulse rate, beats per min	2·9 (0·50)	3·2 (0·50)	4·1 (0·48)	1·2 (0·29)

Data are n (%), or LSMean change from baseline at 52 weeks (SE). Participants may be counted in more than one category· bpm=beats per minute. LSMean=least squares mean. mITT=modified intention-to-treat. *Deaths are also included as serious adverse events and discontinuations due to adverse events. †Adjudication-confirmed.

Table 3: **Adverse events and safety parameters in the mITT population, safety analysis set**

Similar trends in blood pressure and pulse were observed over the remainder of the study (appendix p 30).

Dose-dependent reductions of serum triglyceride (up to –23%), LDL cholesterol (up to –8%) and non-HDL cholesterol (up to –12%) concentrations at 52 weeks were observed with tirzepatide compared with marginal changes with glargine (appendix pp 31–32). The estimated treatment difference versus glargine for percent change in triglycerides at 52 weeks was –10·6 (95% CI –15·2 to –5·7; p<0·0001) for 5 mg, –14·6 (–19·0 to –10·0; p<0·0001) for 10 mg, and –17·2 (–21·4 to –12·8; p<0·0001) for 15 mg tirzepatide. The estimated treatment difference versus glargine for percent change in LDL cholesterol at 52 weeks was –8·0 (–12·3 to –3·6; p=0·0005) for 5 mg, –9·5 (–13·7 to –5·2; p<0·0001) for 10 mg, and –9·2 (–13·3 to –4·8; p<0·0001) for 15 mg tirzepatide. The estimated treatment difference versus glargine for percent change in non-HDL cholesterol at 52 weeks was –9·0 (–12·4 to –5·5; p<0·0001) for 5 mg, –10·7 (–14·0 to –7·3; p<0·0001) for 10 mg, and –11·1 (–14·3 to –7·7; p<0·0001) for 15 mg tirzepatide. Changes in other lipoprotein concentrations at week 52 are given in the appendix (p 32). All these changes were observed at nearly constant use of lipid-lowering medications in all groups.

Over the duration of the entire study, 109 participants experienced at least one positively adjudicated component of the composite endpoint of MACE-4. 60 deaths occurred during the study (tirzepatide, n=25 [3%] and glargine, n=35 [4%]); none were considered by the investigator to be related to study medication. Six COVID-19-related deaths were recorded in participants treated with tirzepatide (<1%) and eight (<1%) on glargine. Six deaths (<1%) in participants receiving tirzepatide and nine (<1%) in participants receiving glargine were adjudicated as cardiovascular. Ten deaths (1%) on tirzepatide and 12 (1%) on glargine were adjudicated as undetermined, and thus considered cardiovascular deaths for MACE determination. There was no increased risk of MACE-4 events for pooled tirzepatide versus glargine, hazard ratio 0·74 (95% CI 0·51 to 1·08; table 4). Kaplan-Meier curves for time to first occurrence of MACE-4 events for the treatment groups are presented in figure 2.

Over the entire study, diarrhoea was reported in 13–22% of patients on tirzepatide versus 4% on glargine, nausea in 12–23% on tirzepatide versus 2% on glargine, decreased appetite in 9–11% on tirzepatide versus less than 1% on glargine, and vomiting in 5–9% on tirzepatide versus 2% on glargine (table 3). Most cases of nausea, vomiting, and diarrhoea were mild to moderate and were reported more frequently in all tirzepatide groups during the dose-escalation period (appendix p 21). After the initial 24-week dose escalation, a diminishing number of participants on tirzepatide reported treatment emergent gastrointestinal side-effects. In addition, events occurring in the later phase of the study were more commonly mild and less frequently severe when compared with the dose-escalation phase (data not shown). These changes are also reflected in the study medication discontinuation; 40 tirzepatide participants discontinued study medication due to gastrointestinal adverse event before the primary endpoint at week 52, with the majority occurring during the escalation phase. In contrast, only five participants on tirzepatide discontinued study medication due to gastrointestinal adverse events during the rest of the study.

Clinically significant (<54 mg/dL) or severe hypoglycaemia was reported in 76 (8%) participants in pooled tirzepatide groups (29 [9%] on 5 mg, 20 [6%] on

	Tirzepatide 5 mg (n=329)	Tirzepatide 10 mg (n=328)	Tirzepatide 15 mg (n=338)	All tirzepatide (n=995)	Insulin glargine (n=1000)	Hazard ratio (95% CI)
MACE-4	19 (6%)	17 (5%)	11 (3%)	47 (5%), 2·97	62 (6%), 3·99	0·74 (0·51–1·08)*
Cardiovascular death	10 (3%)	1 (<1%)	5 (2%)	16 (2%), 1·01	21 (2%), 1·35	..
Myocardial infarction	7 (2%)	9 (3%)	3 (<1%)	19 (2%), 1·20	26 (3%), 1·67	..
Hospitalisation for unstable angina	0	2 (<1%)	2 (<1%)	4 (<1%), 0·25	8 (<1%), 0·51	..
Stroke	5 (2%)	5 (2%)	1 (<1%)	11 (1%), 0·70	13 (1%), 0·84	..
Other MACE						
Coronary interventions†	10 (3%)	11 (3%)	8 (2%)	29 (3%), 1·83	37 (4%), 2·38	..
Transient ischaemic attack	0	2 (<1%)	1 (<1%)	3 (<1%), 0·19	0	..
Hospitalisation for heart failure	1 (<1%)	1 (<1%)	2 (<1%)	4 (<1%), 0·25	6 (<1%), 0·39	..
Death	15 (5%)	2 (<1%)	8 (2%)	25 (3%), 1·58	35 (4%), 2·25	0·70 (0·42–1·17)*
Cardiovascular	4 (1%)	0	2 (<1%)	6 (<1%), 0·38	9 (<1%), 0·58	..
Undetermined	6 (2%)	1 (<1%)	3 (<1%)	10 (1%), 0·63	12 (1%), 0·77	..
Non-cardiovascular	5 (2%)	1 (<1%)	3 (<1%)	9 (<1%), 0·57	14 (1%), 0·90	..

Data are n (%); n (%), n/100 person-years; unless otherwise specified. All events confirmed by the Clinical Endpoint Committee. MACE=major adverse cardiovascular events. mITT=modified intention to treat. *Point estimate and 95% CI of hazard ratio comparing pooled tirzepatide groups versus glargine obtained from time to first event analysis using Cox proportional hazards model. †Includes coronary artery bypass graft and percutaneous coronary intervention.

Table 4: **Summary of MACE and deaths during the study in the mITT population, safety analysis set**

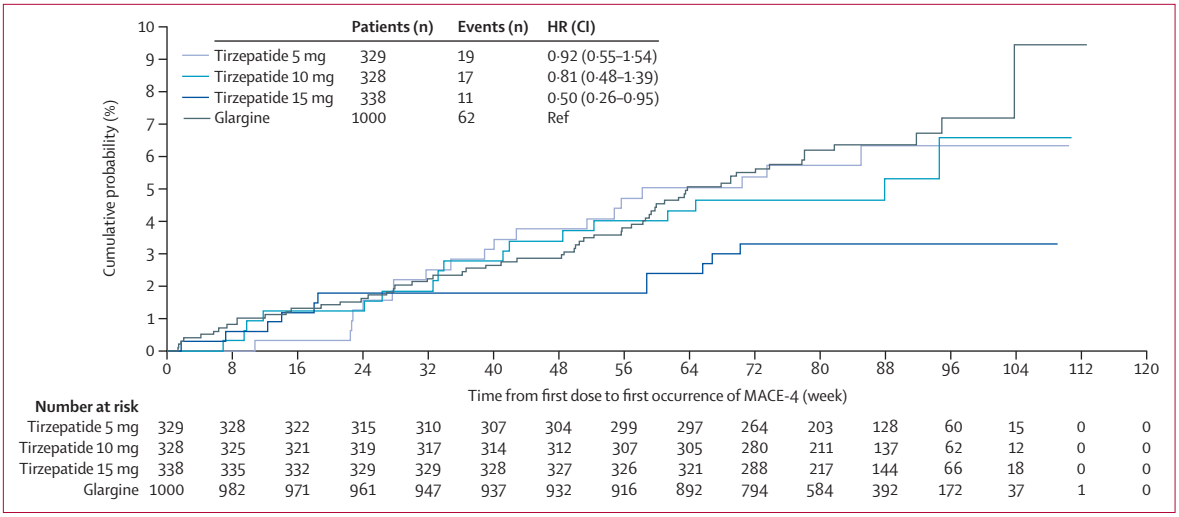

***Figure 2*: Time to first occurrence of MACE-4**

Kaplan-Meier plot of time to first occurrence of positively adjudicated MACE-4, mITT population (safety analysis set). Hazard ratios and 95% CIs unstratified are for comparison of tirzepatide treatment groups versus glargine (100 U/mL) from Cox proportional-hazards model. Deaths with an undetermined cause are included in death due to cardiovascular cause for analysis purposes. MACE-4 includes cardiovascular death, myocardial infarction, stroke, and hospitalisation for unstable angina. HR=hazard ratio. MACE-4=major adverse cardiovascular events. mITT=modified intention-to-treat.

10 mg, and 27 [8%] on 15 mg), and 191 (19%) on glargine; participants receiving tirzepatide had a total of 145 episodes and those receiving glargine had 492 episodes (appendix pp 22, 33). More hypoglycaemic events were reported in participants who also used sulfonylureas (appendix pp 22, 33). Hypoglycaemia of 70 mg/dL or less, or severe, occurred in 33–38% of tirzepatide-treated participants and 64% on glargine; 2112 episodes were reported with tirzepatide and 7882 with glargine (appendix p 22).

Adjudicated cases of pancreatitis occurred with tirzepatide (5 mg n=3 [<1%]; 10 mg n=2 [<1%]; and 15 mg n=1 [<1%]) and glargine (n=1 [<1%]; table 3). Five (<1%) cases of cholelithiasis were reported with tirzepatide and four (<1%) with glargine (table 3). No clinically relevant changes in mean calcitonin levels were observed and no cases of medullary thyroid hyperplasia or cancer were reported. Five cases of treatment-emergent diabetic retinopathy (tirzepatide 5 mg n=2 [<1%], 10 mg n=1 [<1%], 15 mg n=1 [<1%]; glargine n=1 [<1%]) were reported.

Hypersensitivity reactions (immediate and non-immediate) occurred in 35 (4%) and injection site reactions in 17 (2%) tirzepatide-treated participants, and in 23 (2%) and 16 (2%), respectively, of glargine-treated participants. In samples of tirzepatide participants with anti-drug antibodies, no difference was apparent in pharmacokinetics and glycaemic efficacy compared with participants with no detectable treatment-emergent anti-drug antibodies.

Similar results for HbA_{1c} and weight loss and the proportion of participants achieving HbA_{1c} and weight loss targets were reported with the treatment-regimen estimand (appendix p 34).

A post-hoc analysis was performed to evaluate the long-term glycaemic effect of tirzepatide at an earlier timepoint and with a larger sample size than available at 104 weeks. After 88 weeks of treatment (n=577), least squares mean HbA_{1c} change from baseline for tirzepatide was –2·31% (SE 0·10) for 5 mg, –2·42% (0·10) for 10 mg, and –2·49% (0·10) for 15 mg, and –1·39% (0·06) for insulin glargine.

Discussion

In this study of individuals with long-standing type 2 diabetes at high cardiovascular risk and inadequately controlled glycaemia with up to three oral glucose-lowering medications, including sulfonylureas, all three doses of the dual GIP and GLP-1 receptor agonist tirzepatide markedly improved glucose control, reduced bodyweight, and improved the cardiovascular risk profile. A higher proportion of participants reached the glycaemic targets with fewer clinically significant hypoglycaemic events when treated with tirzepatide versus glargine. The study also suggests, for the first time in a population with long-standing diabetes at elevated cardiovascular disease risk, that the glycaemic and weight benefits of tirzepatide can be sustained beyond 1 year. Importantly, these benefits were achieved with no increased risk for MACE-4.

The active comparator glargine (100 U/mL) has been used in treat-to-target studies[15,19–21] and shown to be safe from a cardiovascular standpoint.[22,23] In the present study, the doses of glargine used and the fasting glucose achieved suggest that the glargine titration algorithm was followed appropriately. Comparison of tirzepatide to titrated glargine demonstrated a dose-dependent superiority of all three tirzepatide doses on glucose control. Large proportions (81–91%) of participants receiving tirzepatide achieved the American Diabetes

Association–European Association for the Study of Diabetes glycaemic control target of a HbA_{1c} less than 7% compared with 51% receiving glargine, and 23–43% attained a HbA_{1c} of less than 5·7%, defined as the upper limit of normal by many organisations compared with 3% of those receiving glargine.[16]

The changes in glycaemia and weight after 52 weeks of tirzepatide treatment are similar in magnitude to those observed in other studies that compared tirzepatide with placebo,[12] injectable semaglutide,[13] and the long-acting insulin degludec.[14] However, these studies lasted 40–52 weeks and were conducted in cohorts with a shorter duration of diabetes and with a lower proportion of people with a history of cardiovascular disease compared with the current study. In addition, sulfonylureas were excluded as a concomitant medication in those studies.

The changes in fasting glucose were similar across all four study groups. Therefore, the better overall glycaemic control achieved with tirzepatide could be attributable to the more effective control of preprandial glycaemia and, to a larger extent, postprandial glycaemia, as shown by lower mean seven-point self-monitored blood glucose levels. The magnitude of HbA_{1c} reduction and proportions of people reaching glycaemic targets appear to be larger than in similar studies in which GLP-1 receptor agonists have been compared with glargine (100 U/mL).[2–5]

The reductions in HbA_{1c} observed for tirzepatide at 52 weeks were maintained after 78 weeks and 88 weeks of treatment. Data after 104 weeks of treatment were consistent, although the sample size was smaller. The current study provides initial support for glycaemic control being sustained for more than 1 year with tirzepatide treatment.

The main challenge in achieving target HbA_{1c} of less than 7% in vulnerable people with type 2 diabetes is hypoglycaemia. The greater improvement in glucose control with tirzepatide treatment was achieved with fewer participants experiencing clinically significant (<54 mg/dL) or severe hypoglycaemia. Furthermore, the total number of hypoglycaemic events was lower with tirzepatide compared with glargine, with nearly all events on tirzepatide occurring in participants using sulfonylureas at baseline. Additional research is needed to evaluate the potential role of GIP-related glucagonotropic effect of tirzepatide in the prevention of hypoglycaemia.[24] These data suggest that tirzepatide is an effective and safe glucose-lowering agent.

The long study duration also allowed examination of the bodyweight profile and other cardiovascular risk factors over time. In previous studies with tirzepatide, the profile of bodyweight reduction had not reached a plateau by 40–52 weeks.[12–14] Although progressively fewer individuals completed study visits in the variable treatment period, the observations suggest the maximal effect achieved after 1 year can be maintained for up to an additional 9–12 months with tirzepatide.

Favourable changes have been observed in blood pressure, irrespective of the wide use of diverse blood pressure-lowering medications in the study population. These changes are in line with findings in GLP-1 receptor agonist cardiovascular outcome trials and could contribute to the cardiovascular safety of tirzepatide.[25–30] In the present study, tirzepatide favourably impacted the lipoprotein profile, including reductions in triglyceride, non-HDL and LDL cholesterol, and these changes were maintained throughout the trial. It was previously demonstrated that tirzepatide dose-dependently decreased triglyceride, apolipoprotein (apo)B, and apoC-III levels and decreased the number of large triglyceride-rich lipoprotein particles and small LDL particles.[10] These favourable changes are larger than typically observed with GLP-1 receptor agonists. In a head-to-head study between tirzepatide 5 mg, 10 mg, and 15 mg and semaglutide 1 mg, tirzepatide reduced the concentrations of triglyceride and very low-density lipoprotein cholesterol to a greater extent than semaglutide.[13]

The inclusion of participants with high-risk cardiovascular profiles who were followed up for up to 104 weeks showed no difference in MACE-4 events with tirzepatide compared with glargine, the latter having been demonstrated to be safe from a cardiovascular perspective.[22] These results suggest that there is no excess cardiovascular risk with tirzepatide, and are consistent with the beneficial changes in numerous surrogate markers of cardiovascular health, including weight reduction, glycaemic control with less hypoglycaemia, blood pressure reduction, and improvements in the lipoprotein profile. The definitive impact of tirzepatide on cardiovascular disease will be addressed in an ongoing study comparing tirzepatide with the long-acting GLP-1 receptor agonist dulaglutide (SURPASS-CVOT, NCT04255433). SURPASS-CVOT is unique, in that it compares the dual incretin agonist with a GLP-1 receptor agonist that has been shown to be cardioprotective in people with type 2 diabetes and high risk for MACE.[27] Furthermore, given the ability of tirzepatide to near normalise and even normalise glucose as shown in the current study, as well as attain better glucose control than the GLP-1 receptor agonist semaglutide,[13] SURPASS-CVOT might also provide additional insight into the impact of markedly lowering glucose levels with less hypoglycaemia on cardiovascular events.[31–33]

The adverse event profile of tirzepatide was similar to selective GLP-1 receptor agonists and adverse events were mainly gastrointestinal in nature (nausea, vomiting, and diarrhoea).[34] These side-effects, however, were generally mild to moderate and occurred in diminishing frequency after dose escalation. In a head-to-head study in which the doses of tirzepatide were blinded, there were no meaningful differences in the occurrence of nausea, diarrhoea or vomiting between tirzepatide 5–15 mg and semaglutide 1 mg.[13] Similar to this study, gastrointestinal side-effects and medication

discontinuation due to these events were more frequent in all GLP1-RA medications when compared with glargine (100 U/mL).[2–5]

The current study has certain limitations. First, the interventions were not blinded because of differences in devices and dose-escalation schemes. Second, since the variable treatment period beyond 52 weeks was designed to collect longer-term safety data and achieve a predefined number of MACE-4, not all participants were treated for 104 weeks. The strengths of this study are the large sample size, the selection of glargine, a commonly used insulin with proven cardiovascular safety, a successful treat-to-target titration of glargine, and a duration that goes beyond any previous experience with tirzepatide.

In conclusion, in people with long-standing type 2 diabetes and high cardiovascular risk, tirzepatide demonstrated superiority and sustainability in overall glycaemic control and weight reduction compared with glargine. Given the progressive nature of type 2 diabetes,[35] evaluating the durability of glycaemic and weight effects of dual incretin receptor agonists like tirzepatide is important to determine the expected therapeutic benefits. The improvement in cardiovascular risk profile and distribution of cardiovascular events between treatment groups suggests that tirzepatide is safe from a cardiovascular perspective; further definitive studies are required to assess cardiovascular safety, as well as potential cardiovascular protection.

Contributors

IP, GJW, ZY, JSR, and RJW contributed to the study design, and RJW, JSR, and IP provided medical oversight during the trial. GJW and ZY were responsible for the statistical analyses. IP, GJW, ZY, RJH, and RJW are the guarantors of this work and, as such, take responsibility for the integrity of the data and the accuracy of the data analysis. SDP and SEK were involved in the tirzepatide development programme and drafted the Article. All authors participated in interpretation of the data and critical review of the Article, had full access to the data and approved submission of the final version of the Article.

Declaration of interests

SDP declares grants from AstraZeneca and Boehringer Ingelheim; consulting fees from Applied Therapeutics, AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Merck Sharpe and Dohme, Novartis Pharmaceuticals, Novo Nordisk, Sanofi; and honoraria for lectures from AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Merck Sharpe and Dohme, Novartis Pharmaceuticals, Novo Nordisk, and Sanofi. SEK declares consulting fees from Casma Therapeutics, Eli Lilly and Company, Intarcia, Merck, Novo Nordisk, Pfizer and Third Rock Ventures; and honoraria for lectures from Boehringer Ingelheim. IP, GJW, ZY, RJH, JSR and RJW are employees and shareholders of Eli Lilly and Company. JD declares grants from Eli Lilly and Company; honoraria as a speaker from Sanofi Aventis, Eli Lilly and Company, AstraZeneca, Novo Nordisk; support for attending meetings from Eli Lilly and Company, Novo Nordisk and Sanofi Aventis; and has served on advisory boards and other boards for Eli Lilly and Company, Novo Nordisk, Hellenic Diabetes Association, National Health Service and Hellenic Ministry of Health. DA and AGW report no competing interests.

Data sharing

Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymisation, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the USA and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at https://www.vivli.org.

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References

1 Buse JB, Wexler DJ, Tsapas A, et al. 2019 update to: management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 2020; **63:** 221–28.

2 Aroda VR, Bain SC, Cariou B, et al. Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. *Lancet Diabetes Endocrinol* 2017; **5:** 355–66.

3 Giorgino F, Benroubi M, Sun JH, Zimmermann AG, Pechtner V. Efficacy and safety of once-weekly dulaglutide versus insulin glargine in patients with type 2 diabetes on metformin and glimepiride (AWARD-2). *Diabetes Care* 2015; **38:** 2241–49.

4 Russell-Jones D, Vaag A, Schmitz O, et al. Liraglutide *vs* insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. *Diabetologia* 2009; **52:** 2046–55.

5 Weissman PN, Carr MC, Ye J, et al. HARMONY 4: randomised clinical trial comparing once-weekly albiglutide and insulin glargine in patients with type 2 diabetes inadequately controlled with metformin with or without sulfonylurea. *Diabetologia* 2014; **57:** 2475–84.

6 Nauck M. Incretin therapies: highlighting common features and differences in the modes of action of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. *Diabetes Obes Metab* 2016; **18:** 203–16.

7 Holst JJ, Rosenkilde MM. GIP as a therapeutic target in diabetes and obesity: insight from incretin co-agonists. *J Clin Endocrinol Metab* 2020; **105:** e2710–16.

8 Thomas MK, Nikooienejad A, Bray R, et al. Dual GIP and GLP-1 receptor agonist tirzepatide improves beta-cell function and insulin sensitivity in type 2 diabetes. *J Clin Endocrinol Metab* 2021; **106:** 388–96.

9 Wilson JM, Nikooienejad A, Robins DA, et al. The dual glucose-dependent insulinotropic peptide and glucagon-like peptide-1 receptor agonist, tirzepatide, improves lipoprotein biomarkers associated with insulin resistance and cardiovascular risk in patients with type 2 diabetes. *Diabetes Obes Metab* 2020; **22:** 2451–59.

10 Frias JP, Nauck MA, Van J, et al. Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial. *Lancet* 2018; **392:** 2180–93.

11 Coskun T, Sloop KW, Loghin C, et al. LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: from discovery to clinical proof of concept. *Mol Metab* 2018; **18:** 3–14.

12 Rosenstock J, Wysham C, Frías JP, et al. Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial. *Lancet* 2021; **398:** 143–55.

13 Frías JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. *N Engl J Med* 2021; **385:** 503–15.

14 Ludvik B, Giorgino F, Jódar E, et al. Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without sodium-glucose co-transporter-2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial. *Lancet* 2021; **398:** 583–98.

15 Riddle MC, Rosenstock J, Gerich J. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care* 2003; **26:** 3080–86.

16 American Diabetes Association. 6. Glycemic targets: standards of medical care in diabetes—2021. *Diabetes Care* 2021; **44** (suppl 1)**:** S73–84.

17 European Medicines Agency. Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus. 2018. https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-clinical-investigation-medicinal-products-treatment-prevention-diabetes-mellitus_en.pdf (accessed Aug 16, 2021).

18 Rubin DB. Multiple imputation for nonresponse in surveys. New York, NY: John Wiley & Sons, 1987.

19 Wysham C, Bhargava A, Chaykin L, et al. Effect of insulin degludec *vs* insulin glargine U100 on hypoglycemia in patients with type 2 diabetes: the SWITCH 2 randomized clinical trial. *JAMA* 2017; **318:** 45–56.

20 Rosenstock J, Davies M, Home PD, Larsen J, Koenen C, Schernthaner G. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetologia* 2008; **51:** 408–16.

21 Marso SP, McGuire DK, Zinman B, et al. Efficacy and safety of degludec versus glargine in type 2 diabetes. *N Engl J Med* 2017; **377:** 723–32.

22 Gerstein HC, Bosch J, Dagenais GR, et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med* 2012; **367:** 319–28.

23 Li J, Tong Y, Zhang Y, et al. Effects on all-cause mortality and cardiovascular outcomes in patients with type 2 diabetes by comparing insulin with oral hypoglycemic agent therapy: a meta-analysis of randomized controlled trials. *Clin Ther* 2016; **38:** 372–386.

24 Christensen M, Vedtofte L, Holst JJ, Vilsbøll T, Knop FK. Glucose-dependent insulinotropic polypeptide: a bifunctional glucose-dependent regulator of glucagon and insulin secretion in humans. *Diabetes* 2011; **60:** 3103–09.

25 Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016; **375:** 1834–44.

26 Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016; **375:** 311–22.

27 Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet* 2019; **394:** 121–30.

28 Hernandez AF, Green JB, Janmohamed S, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet* 2018; **392:** 1519–29.

29 Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2019; **381:** 841–51.

30 Holman RR, Bethel MA, Mentz RJ, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2017; **377:** 1228–39.

31 Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; **358:** 2545–59.

32 Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009; **360:** 129–39.

33 Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008; **358:** 2560–72.

34 Bettge K, Kahle M, Abd El Aziz MS, Meier JJ, Nauck MA. Occurrence of nausea, vomiting and diarrhoea reported as adverse events in clinical trials studying glucagon-like peptide-1 receptor agonists: a systematic analysis of published clinical trials. *Diabetes Obes Metab* 2017; **19:** 336–47.

35 Kahn SE, Cooper ME, Del Prato S. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. *Lancet* 2014; **383:** 1068–83.