Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial

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Summary

Background Glucagon-like peptide 1 receptor agonists differ in chemical structure, duration of action, and in their effects on clinical outcomes. The cardiovascular effects of once-weekly albiglutide in type 2 diabetes are unknown. We aimed to determine the safety and efficacy of albiglutide in preventing cardiovascular death, myocardial infarction, or stroke.

Methods We did a double-blind, randomised, placebo-controlled trial in 610 sites across 28 countries. We randomly assigned patients aged 40 years and older with type 2 diabetes and cardiovascular disease (at a 1:1 ratio) to groups that either received a subcutaneous injection of albiglutide (30–50 mg, based on glycaemic response and tolerability) or of a matched volume of placebo once a week, in addition to their standard care. Investigators used an interactive voice or web response system to obtain treatment assignment, and patients and all study investigators were masked to their treatment allocation. We hypothesised that albiglutide would be non-inferior to placebo for the primary outcome of the first occurrence of cardiovascular death, myocardial infarction, or stroke, which was assessed in the intention-to-treat population. If non-inferiority was confirmed by an upper limit of the 95% CI for a hazard ratio of less than 1·30, closed testing for superiority was prespecified. This study is registered with ClinicalTrials.gov, number NCT02465515.

Findings Patients were screened between July 1, 2015, and Nov 24, 2016. 10 793 patients were screened and 9463 participants were enrolled and randomly assigned to groups: 4731 patients were assigned to receive albiglutide and 4732 patients to receive placebo. On Nov 8, 2017, it was determined that 611 primary endpoints and a median follow-up of at least 1·5 years had accrued, and participants returned for a final visit and discontinuation from study treatment; the last patient visit was on March 12, 2018. These 9463 patients, the intention-to-treat population, were evaluated for a median duration of 1·6 years and were assessed for the primary outcome. The primary composite outcome occurred in 338 (7%) of 4731 patients at an incidence rate of 4·6 events per 100 person-years in the albiglutide group and in 428 (9%) of 4732 patients at an incidence rate of 5·9 events per 100 person-years in the placebo group (hazard ratio 0·78, 95% CI 0·68–0·90), which indicated that albiglutide was superior to placebo (p<0·0001 for non-inferiority; p=0·0006 for superiority). The incidence of acute pancreatitis (ten patients in the albiglutide group and seven patients in the placebo group), pancreatic cancer (six patients in the albiglutide group and five patients in the placebo group), medullary thyroid carcinoma (zero patients in both groups), and other serious adverse events did not differ between the two groups. There were three (<1%) deaths in the placebo group that were assessed by investigators, who were masked to study drug assignment, to be treatment-related and two (<1%) deaths in the albiglutide group.

Interpretation In patients with type 2 diabetes and cardiovascular disease, albiglutide was superior to placebo with respect to major adverse cardiovascular events. Evidence-based glucagon-like peptide 1 receptor agonists should therefore be considered as part of a comprehensive strategy to reduce the risk of cardiovascular events in patients with type 2 diabetes.

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*The Harmony Outcomes committee members and investigators are listed in appendix 1

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See Online for appendix 1

Introduction

The risk of fatal and non-fatal cardiovascular events is much higher in people with type 2 diabetes than in the general population.[1,2] Drugs in two classes of newer glucose-lowering therapies, the sodium-glucose co-transporter 2 (SGLT-2) inhibitors and the glucagon-like peptide 1 (GLP-1) receptor agonists, have been shown to reduce the risk of major adverse cardiovascular events, although findings regarding the GLP-1 receptor agonists have been inconsistent.[3–8] Specifically, not all tested GLP-1 receptor agonists have been shown to reduce cardiovascular events, and the effect of these treatments

Research in context

Evidence before this study

We searched PubMed for reports of randomised trials that assessed the effects of glucagon-like peptide 1 (GLP-1) receptor agonists on cardiovascular outcomes. We searched for studies that were published in English up to Aug 1, 2018, with the search terms "glucagon-like peptide 1 agonist OR analogue", "GLP-1 receptor agonist OR analogue", "exenatide", "lixisenatide", "semaglutide", "liraglutide", "exenatide", "dulaglutide", "taspoglutide", "albiglutide", "cardiovascular outcomes", and "diabetes". Four trials with cardiovascular outcomes were identified. The LEADER trial included 9340 patients with type 2 diabetes and cardiovascular disease or cardiovascular risk factors, who were followed up for a median duration of 3·8 years. Patients were randomly assigned to receive placebo or once-daily liraglutide, which is structurally homologous to native GLP-1, and this drug was added to standard care. Liraglutide reduced the frequency of the primary endpoint composite of major adverse cardiovascular events (MACE), which comprised cardiovascular death, myocardial infarction, and stroke, relative to the control group (hazard ratio 0·87, 95% CI 0·78–0·97; p<0·001 for non-inferiority; p=0·01 for superiority). Semaglutide, which is also structurally homologous to native GLP-1, was studied in 3297 similar participants in the SUSTAIN-6 trial, which showed, over a median duration of 2·1 years, that once-weekly semaglutide was non-inferior to placebo for MACE (0·74, 0·58–0·95; p<0·001 for non-inferiority). The ELIXA trial included 6068 patients with type 2 diabetes and a recent acute coronary syndrome, who were followed up for a median duration of 2·1 years. Patients were randomly assigned to receive placebo or once-daily lixisenatide, an exendin-4 based GLP-1 receptor agonist, which was added to standard care. Lixisenatide was non-inferior to placebo for the primary composite outcome of MACE plus unstable angina (1·02, 0·89–1·17; p<0·001 for non-inferiority). The EXSCEL trial included 14 752 patients with type 2 diabetes and cardiovascular disease or cardiovascular risk factors, who were followed up for a median duration of 3·2 years. Patients were randomly assigned to receive placebo or once-weekly exenatide, which is an exendin-4 based GLP-1 receptor agonist, which was added to standard care. Exenatide was non-inferior to placebo for the primary composite outcome of MACE (0·91, 0·83–1·00; p<0·001 for non-inferiority; p=0·06 for superiority). There seems to be variation in the results of previous trials with GLP-1 receptor agonists that, if correct, might reflect drug structure or duration of action, patients studied, duration of follow-up, or other factors.

Added value of this study

The results of the Harmony Outcomes trial showed that albiglutide, a GLP-1 receptor ligand that is structurally homologous with native GLP-1, when administered once-weekly over a median duration of 1·6 years, reduced the risk of MACE when added to standard care in patients with type 2 diabetes and cardiovascular disease. These data suggest that certain GLP-1 receptor agonists reduce the risk of atherothrombotic events in patients with type 2 diabetes and high cardiovascular risk.

Implications of all the available evidence

Evidence-based GLP-1 receptor agonists should therefore be considered as part of a comprehensive strategy to reduce the risk of cardiovascular events, the leading cause of death and disability in patients with type 2 diabetes.

on individual cardiovascular outcomes varied between the effective drugs.[5–8] Liraglutide and semaglutide, which have structural homology to native GLP-1, reduced cardiovascular events, whereas no benefit was associated with the exendin-4 based drugs lixisenatide and exenatide.[5–8] In addition to differences in chemical structure and potency, these treatments also differ markedly in duration of action and were studied in different patient populations and in trials of different design, size, and duration of follow-up.[5–8] Consequently, uncertainty remains about the cardiovascular effects of GLP-1 receptor agonists.

Albiglutide is a GLP-1 receptor agonist that is generated through genetic fusion of two tandem copies of modified human GLP-1 (with 97% aminoacid sequence homology to endogenous human GLP-1 fragment 7–36) to human albumin, and the resultant protein is sufficiently long-acting to be injected weekly.[9,10] In accordance with regulatory guidance, we aimed to assess the cardiovascular safety and efficacy of albiglutide in Harmony Outcomes, a trial that enrolled patients with type 2 diabetes and cardiovascular disease.[11]

Methods

Study design and participants

We did a double-blind, randomised, placebo-controlled, event-driven trial at 610 health-care sites in 28 countries across North and South America, Europe, Africa, and Asia.[11] Men and women aged 40 years or older with a diagnosis of type 2 diabetes and established disease of the coronary (myocardial infarction, at least 50% stenosis in one coronary artery or more, or previous coronary revascularisation), cerebrovascular (ischaemic stroke, at least 50% carotid artery stenosis, or a previous carotid vascular procedure), or peripheral arterial circulation (intermittent claudication and an ankle to brachial index <0·9, non-traumatic amputation, or a previous peripheral vascular procedure) who had a glycated haemoglobin concentration of more than 7·0% (53 mmol per mole) were eligible for participation in the trial.

Key exclusion criteria were an estimated glomerular filtration rate (eGFR) of less than 30 mL/min per 1·73 m², severe gastroparesis, previous pancreatitis or substantial risk factors for pancreatitis, a personal or family history of

medullary carcinoma of the thyroid or multiple endocrine neoplasia type 2, a history of pancreatic neuroendocrine tumours, or current use of a GLP-1 receptor agonist. A complete list of trial inclusion and exclusion criteria is provided in the protocol (appendix 2).

The protocol was approved by the ethics committee at each participating site and all patients provided written informed consent. An independent data and safety monitoring committee, with access to unblinded data, performed regular safety surveillance.

Randomisation and masking

Patients were assigned in a 1:1 ratio to receive subcutaneous injections of albiglutide or placebo (with matched administration device, diluent, and volume injected) once a week, according to a sequestered, fixed, computer-generated randomisation code that used balanced permuted blocks of treatment group allocations, without stratification. Investigators used an interactive voice or web response system to obtain treatment assignment. All investigators and patients involved in the trial were masked to treatment group.

Procedures

The starting dose of study medication was 30 mg in 0·5 mL once a week. If, after at least 5 weeks of study treatment, the investigator determined that a trial participant required intensification of glucose-lowering therapy, the dose of study treatment could be increased to 50 mg; the dose could be decreased back to 30 mg if 50 mg was not tolerated. If the glycaemic goal (which was based on local guidelines), as determined by the investigator, was not met after an increase in the dose of the study medication, other glucose-lowering medications could be adjusted or added (except for a GLP-1-receptor agonist). Protocol-specified reasons for discontinuation of trial medication included occurrence of pancreatitis, pancreatic cancer, medullary carcinoma of the thyroid or thyroid C-cell neoplasia, severe hypersensitivity reactions that were attributable to study medication, pregnancy, an eGFR of less than 15 mL/min per 1·73 m², kidney dialysis or transplantation, or liver chemistry abnormalities that exceeded protocol-specified thresholds.[11] Patients had study visits every 4 months, but endpoints were reported at the time of their occurrence. The number of visits was dependent on duration of involvement in the study; the assessments given at each visit are described in the protocol (appendix 2).

Outcomes

The primary outcome was the first occurrence of any component of the composite outcome, which comprised death from cardiovascular causes, myocardial infarction, and stroke, in an intention-to-treat population. Participants were assessed until their last study visit, withdrawal from the study, being lost to follow-up, or their death. The secondary cardiovascular outcomes were a four-component composite (the primary composite, with the addition of urgent revascularisation for unstable angina), the individual components of the primary endpoint, and the composite of cardiovascular death or hospital admission because of heart failure. The secondary metabolic outcomes were the time to initiation of chronic insulin therapy, the time to the first occurrence of an important microvascular event, changes in glycated haemoglobin and bodyweight, and the proportion of participants who attained glycaemic control without severe hypoglycaemia and who gained less than 5% of their bodyweight by the end of the study. The safety outcomes were the change in blood pressure and heart rate, change in eGFR, and adverse events of special interest, which included the development of prespecified malignancies (medullary thyroid cancer, pancreatic cancer, and haematological malignancies), pancreatitis, severe hypoglycaemia, injection site reactions, immunological reactions, diabetic retinopathy, worsening renal function, and death from any cause. A complete list of endpoints is included in the protocol (appendix 2). An independent clinical events classification committee, whose members were unaware of the trial group assignments, assessed all the components of the primary composite outcome, secondary cardiovascular outcomes, and death; these events are defined in the clinical event definitions (appendix 1). A separate expert committee evaluated suspected cases of pancreatitis.

See Online for appendix 2

Statistical analysis

We aimed to investigate the effect of albiglutide compared with placebo on the primary outcome; we first aimed to test for non-inferiority and, if the prespecified criterion for non-inferiority was met, then for superiority. We used a closed testing procedure and so no adjustment of the significance level was required for testing of superiority.[12] Consistent with regulatory guidance, non-inferiority would be declared if the upper limit of the two-sided 95% CI of the hazard ratio (HR) was less than 1·30, and superiority would be established if the upper limit was less than 1·00.[13,14]

Assuming a true hazard of 1·00, we estimated that 611 events would be needed to have 90% power for the test of non-inferiority. An event rate in the range of 2·0–3·0% per year was estimated for the primary endpoint, based on the results of previous trials,[2,3] meaning that the target of 611 events could be attained by assessing approximately 9400 patients for an average of 2·2–3·2 years. After the trial began, the masked aggregate event rate was observed to be higher than anticipated and, therefore, accrual of 611 events would occur over a much shorter period (potentially as short as a median duration of 1·1 years). To ensure adequate exposure for evaluation of safety, the protocol was revised on April 4, 2017, to require follow-up for a

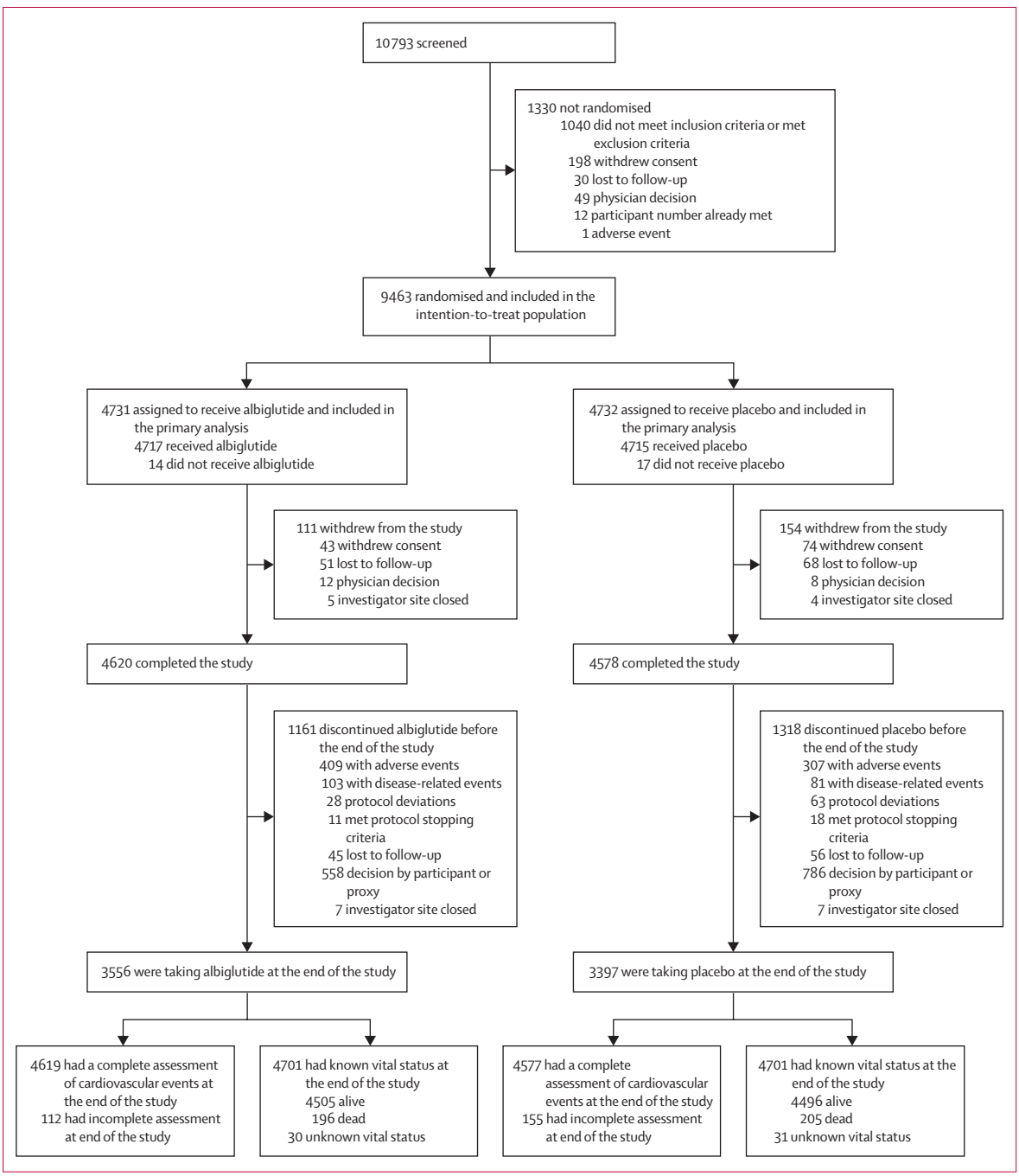

Figure 1: **Trial profile**
With regard to cardiovascular outcomes, 98·5% of the total possible follow-up time was attained in the albiglutide group, and 97·9% of the total possible follow-up time was attained in the placebo group. With regard to vital status endpoints, 99·8% of the total possible follow-up time was attained in both groups.

median duration of at least 1·5 years in addition to the occurrence of at least 611 primary events.

The time-to-event analyses of the primary and secondary cardiovascular outcomes were assessed in the intention-to-treat population by use of Cox proportional hazards regression, with treatment group as the only explanatory variable.[15] The Kaplan-Meier method was used to estimate event rates. These analyses included all patients who had been randomly assigned to study treatment, whether this treatment had been taken or not, until the study closure visit (or the final date that vital status could be ascertained). No adjustment for multiplicity was prespecified for the secondary and other endpoints and only 95% CIs and nominal p values are provided.[12]

	Albiglutide (n=4731)	Placebo (n=4732)
Age, years	64·1 (8·7)	64·2 (8·7)
Sex		
Female	1427 (30%)	1467 (31%)
Male	3304 (70%)	3265 (69%)
Race or ethnicity		
Non-Hispanic white	3295 (70%)	3288 (69%)
Asian	228 (5%)	242 (5%)
Non-Hispanic black or African-American	111 (2%)	114 (2%)
Hispanic	1005 (21%)	988 (21%)
Other	92 (2%)	100 (2%)
Geographic region		
Western Europe	1684 (36%)	1708 (36%)
Eastern and central Europe	1037 (22%)	1010 (21%)
North America	967 (20%)	978 (21%)
Latin America	858 (18%)	845 (18%)
Asia Pacific	185 (4%)	191 (4%)
Current smokers	737 (16%)	751 (16%)
Medical history		
Coronary artery disease*	3333 (70%)	3345 (71%)
Hypertension	4089 (86%)	4095 (87%)
Myocardial infarction	2223 (47%)	2236 (47%)
Coronary artery bypass surgery	890 (19%)	842 (18%)
Percutaneous coronary intervention	2050 (43%)	2113 (45%)
Stroke	827 (17%)	854 (18%)
Peripheral artery disease	1195 (25%)	1159 (24%)
Heart failure	954 (20%)	968 (20%)
Atrial fibrillation	394 (8%)	392 (8%)
Body-mass index, kg/m²	32·3 (5·9)	32·3 (5·9)
Blood pressure, mm Hg		
Systolic	134·8 (16·6)	134·7 (16·5)
Diastolic	76·8 (10·1)	76·8 (10·1)
Glycated haemoglobin, %	8·76 (1·5)	8·72 (1·5)
eGFR, mL/min per 1·73 m²	79·1 (25·6)	78·9 (25·4)

(Table 1 continues in next column)

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	Albiglutide (n=4731)	Placebo (n=4732)
Duration of diabetes, years	14·1 (8·6)	14·2 (8·9)
History of microvascular disease		
Diabetic eye disease	982 (21%)	955 (20%)
Nephropathy	898 (19%)	840 (18%)
Peripheral sensory neuropathy	1562 (33%)	1533 (32%)
Autonomic neuropathy	143 (3%)	107 (2%)
Cardiovascular medications		
Beta-blocker	3128 (66%)	3182 (67%)
Calcium channel blocker	1428 (30%)	1431 (30%)
Angiotensin-converting-enzyme inhibitor	2263 (48%)	2353 (50%)
Angiotensin receptor blocker	1599 (34%)	1511 (32%)
Thiazide diuretic	1089 (23%)	1037 (22%)
Loop diuretic	895 (19%)	899 (19%)
Statin	3967 (84%)	3988 (84%)
Aspirin	3652 (77%)	3639 (77%)
P2Y12 inhibitor	1224 (26%)	1251 (26%)
Glucose-lowering medications		
None or diet	42 (1%)	35 (1%)
Biguanide	3463 (73%)	3506 (74%)
Sulfonylurea	1346 (28%)	1379 (29%)
Insulin	2860 (60%)	2737 (58%)
Dipeptidyl peptidase 4 inhibitor	698 (15%)	739 (16%)
Sodium-glucose cotransporter 2 inhibitor	310 (7%)	265 (6%)
Thiazolidinedione	92 (2%)	102 (2%)
Glinide	66 (1%)	96 (2%)
α-glucosidase inhibitor	34 (1%)	37 (1%)

Data are mean (SD) or number (%). *Any of myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, or at least 50% stenosis of coronary artery on angiography. eGFR=estimated glomerular filtration rate.

Table 1: **Characteristics of the patients at baseline**

The primary composite outcome was analysed in prespecified subgroups that were defined by baseline characteristics, including age at randomisation; sex; race or ethnicity; geographic region; type of glucose-lowering therapy (insulin, metformin, and dipeptidyl peptidase-4 inhibitor); duration of diabetes; history or no history of coronary artery disease, cerebrovascular disease, or peripheral arterial disease, and combinations of these; history or no history of heart failure; use of statin or antiplatelet therapy; history of smoking; body-mass index; glycated haemoglobin concentration; and eGFR. The safety analyses were done in all patients who were randomly assigned to groups and who received at least one dose of albiglutide or placebo.

Baseline characteristics were summarised as means with SDs, medians with IQRs, or percentages. Longitudinal measures, such as glycated haemoglobin concentration and bodyweight, were analysed with a mixed model for repeated measurements, and the least-squares mean differences between treatment groups were estimated, together with 95% CIs. Analyses were done with SAS software, version 9.4 (SAS Institute).

Role of the funding source

The trial protocol was developed by the members of the Executive Committee in conjunction with Duke Clinical Research Institute and the sponsor, GlaxoSmithKline Research and Development. These parties were also responsible for oversight of the trial. The funder of the study was involved in data collection, data analysis, and data interpretation. The funder of the study was not involved in the writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between July 1, 2015, and Nov 24, 2016, 10 793 patients were screened. On or before Dec 7, 2016, 9463 patients

	Albiglutide (n=4731)		Placebo (n=4732)		Hazard ratio (95% CI)	p value*
	Number of patients (%)	Incidence rate (number of events per 100 person-years)	Number of patients (%)	Incidence rate (number of events per 100 person-years)		
Primary composite outcome†	338 (7%)	4·57	428 (9%)	5·87	0·78 (0·68–0·90)	<0·0001, 0·0006
Secondary outcomes						
Expanded composite outcome‡	373 (8%)	5·06	468 (10%)	6·45	0·78 (0·69–0·90)	0·0005
Death from cardiovascular causes	122 (3%)	1·61	130 (3%)	1·72	0·93 (0·73–1·19)	0·578
Fatal or non-fatal myocardial infarction	181 (4%)	2·43	240 (5%)	3·26	0·75 (0·61–0·90)	0·003
Fatal or non-fatal stroke	94 (2%)	1·25	108 (2%)	1·45	0·86 (0·66–1·14)	0·300
Composite of death from cardiovascular causes or hospital admission for heart failure	188 (4%)	2·49	218 (5%)	2·92	0·85 (0·70–1·04)	0·113
Death from any cause	196 (4%)	2·44	205 (4%)	2·56	0·95 (0·79–1·16)	0·644

Hazard ratios and p values were estimated with a Cox proportional hazards model with treatment as the sole explanatory variable. *Data for the primary outcome are the p value for non-inferiority, p value for superiority; all other p values are nominal p values for superiority. †Included death from cardiovascular causes (102 patients in the albiglutide group *vs* 109 patients in the placebo group), non-fatal myocardial infarction (160 patients *vs* 228 patients), or non-fatal stroke (76 patients *vs* 91 patients). ‡Included death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, or urgent coronary revascularisation for unstable angina.

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

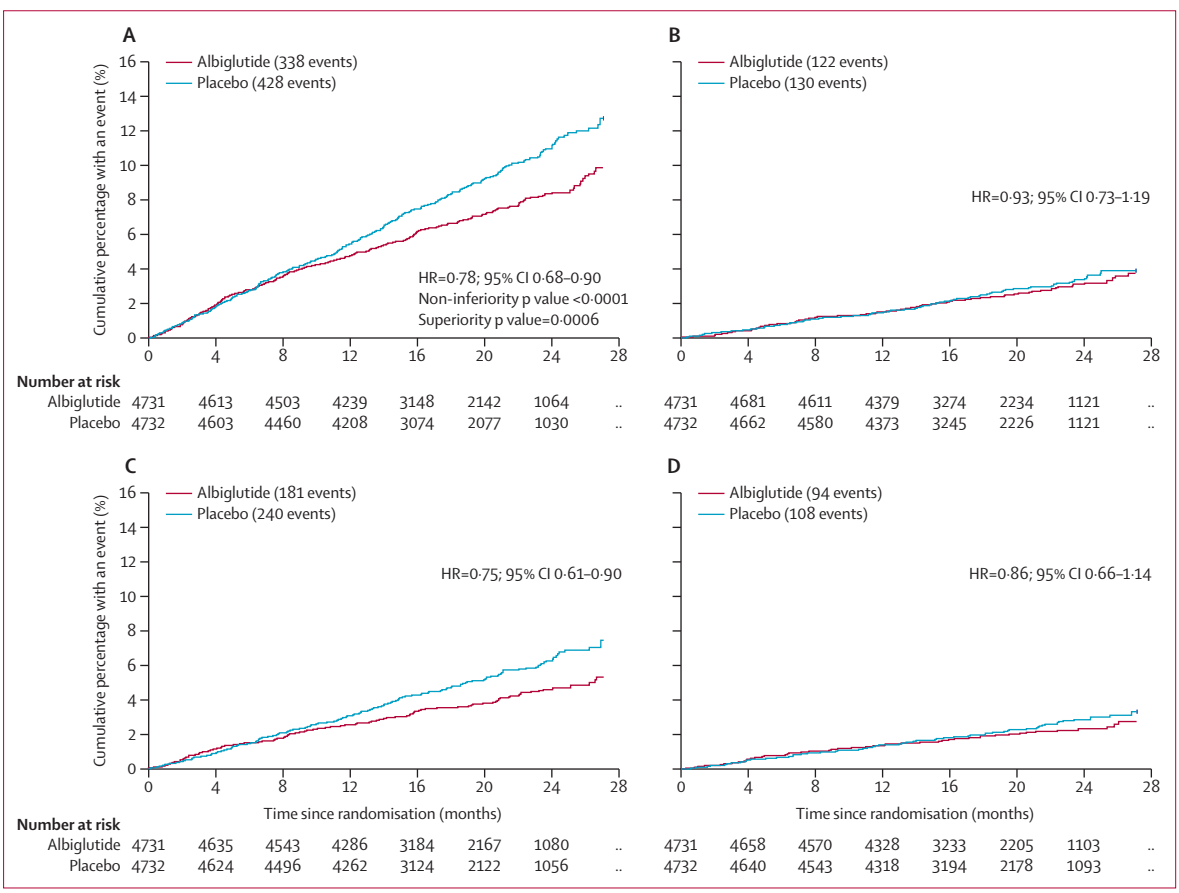

Figure 2: **Kaplan-Meier plot of time to first occurrence of major adverse cardiovascular events**
Data are (A) the primary outcome, which was a composite of death from cardiovascular causes, myocardial infarction, or stroke; and each of these components individually: (B) cardiovascular death, (C) myocardial infarction, and (D) stroke. Analyses are of all participants who were randomly assigned to groups. The graphs are truncated at the point at which less than 10% of patients remain at risk. HR=hazard ratio.

	Number of patients	Albiglutide Events/patients (%)	Placebo Events/patients (%)	Hazard ratio (95% CI)	$p_{interaction}$
Primary analysis	**9463**	**338/4731 (7·1%)**	**428/4732 (9·0%)**	**0·78 (0·68–0·90)**	
Sex					0·227
Female	2894	79/1427 (5·5%)	120/1467 (8·2%)	0·67 (0·50–0·89)	
Male	6569	259/3304 (7·8%)	308/3265 (9·4%)	0·82 (0·69–0·97)	
Race or ethnicity					0·065
Non-Hispanic white	6583	248/3295 (7·5%)	323/3288 (9·8%)	0·76 (0·64–0·89)	
Non-Hispanic black	225	19/111 (17·1%)	8/114 (7·0%)	2·60 (1·14–5·94)	
Hispanic	1993	51/1005 (5·1%)	65/988 (6·6%)	0·74 (0·52–1·07)	
Asian	470	13/228 (5·7%)	19/242 (7·9%)	0·73 (0·36–1·48)	
Other	192	7/92 (7·6%)	13/100 (13·0%)	0·56 (0·23–1·41)	
Age					0·037
<65 years	4714	134/2385 (5·6%)	193/2329 (8·3%)	0·66 (0·53–0·82)	
≥65 to <75 years	3609	154/1771 (8·7%)	166/1838 (9·0%)	0·97 (0·78–1·21)	
≥75 years	1140	50/575 (8·7%)	69/565 (12·2%)	0·69 (0·48–1·00)	
Region					0·691
North America	1945	107/967 (11·1%)	118/978 (12·1%)	0·92 (0·70–1·19)	
Latin America	1703	39/858 (4·5%)	49/845 (5·8%)	0·76 (0·50–1·16)	
Asia Pacific	376	8/185 (4·3%)	12/191 (6·3%)	0·69 (0·28–1·69)	
Eastern Europe	2047	64/1037 (6·2%)	89/1010 (8·8%)	0·68 (0·50–0·94)	
Western Europe	3392	120/1684 (7·1%)	160/1708 (9·4%)	0·76 (0·60–0·96)	
Coronary artery disease					0·066
Yes	6678	285/3333 (8·6%)	340/3345 (10·2%)	0·83 (0·71–0·97)	
No	2785	53/1398 (3·8%)	88/1387 (6·3%)	0·59 (0·42–0·82)	
Cerebrovascular disease					0·835
Yes	2342	100/1171 (8·5%)	124/1171 (10·6%)	0·80 (0·61–1·04)	
No	7121	238/3560 (6·7%)	304/3561 (8·5%)	0·77 (0·65–0·91)	
Peripheral arterial disease					0·077
Yes	2354	106/1195 (8·9%)	107/1159 (9·2%)	0·96 (0·73–1·25)	
No	7109	232/3536 (6·6%)	321/3573 (9·0%)	0·72 (0·61–0·85)	
Number of arterial beds involved					0·010
1	7702	209/3846 (5·4%)	301/3856 (7·8%)	0·68 (0·57–0·81)	
2 or 3	1742	129/877 (14·7%)	127/865 (14·7%)	1·02 (0·80–1·30)	
Heart failure history					0·278
Yes	1922	101/954 (10·6%)	146/968 (15·1%)	0·70 (0·54–0·90)	
No	7541	237/3777 (6·3%)	282/3764 (7·5%)	0·82 (0·69–0·98)	
Smoking history					0·038
Current	1488	72/737 (9·8%)	63/751 (8·4%)	1·16 (0·82–1·62)	
Former	4082	159/2083 (7·6%)	210/1999 (10·5%)	0·71 (0·58–0·88)	
Never	3891	107/1910 (5·6%)	155/1981 (7·8%)	0·71 (0·55–0·91)	
Baseline eGFR (mL/min per 1·73 m²)					0·186
<60	2222	116/1098 (10·6%)	128/1124 (11·4%)	0·93 (0·73–1·20)	
≥60 to <90	4417	144/2208 (6·5%)	206/2209 (9·3%)	0·69 (0·56–0·85)	
≥90	2824	78/1425 (5·5%)	94/1399 (6·7%)	0·79 (0·59–1·07)	
Baseline BMI (kg/m²)					0·435
<30	3613	116/1788 (6·5%)	164/1825 (9·0%)	0·72 (0·57–0·91)	
≥30	5800	219/2914 (7·5%)	262/2886 (9·1%)	0·81 (0·68–0·97)	
Duration of diabetes					0·308
< 10 years	3355	91/1660 (5·5%)	138/1695 (8·1%)	0·67 (0·51–0·87)	
≥10 years to <20 years	3925	146/1987 (7·3%)	178/1938 (9·2%)	0·78 (0·63–0·97)	
≥20 years	2167	98/1072 (9·1%)	112/1095 (10·2%)	0·90 (0·68–1·17)	
Baseline HbA_{1c}					0·187
<8·0%	3524	113/1749 (6·5%)	121/1775 (6·8%)	0·94 (0·73–1·22)	
≥8·0% to <9·0%	2691	88/1312 (6·7%)	133/1379 (9·6%)	0·68 (0·52–0·89)	
≥9·0%	3248	137/1670 (8·2%)	174/1578 (11·0%)	0·73 (0·58–0·91)	
Baseline insulin					0·053
Yes	5597	243/2860 (8·5%)	270/2737 (9·9%)	0·85 (0·72–1·01)	
No	3866	95/1871 (5·1%)	158/1995 (7·9%)	0·63 (0·49–0·81)	
Baseline metformin					0·928
Yes	6968	220/3462 (6·4%)	281/3506 (8·0%)	0·77 (0·65–0·92)	
No	2495	118/1269 (9·3%)	147/1226 (12·0%)	0·79 (0·62–1·00)	
Baseline dipeptidyl peptidase 4					0·100
Yes	1437	55/698 (7·9%)	57/739 (7·7%)	1·04 (0·72–1·50)	
No	8026	283/4033 (7·0%)	371/3993 (9·3%)	0·74 (0·63–0·86)	
Baseline statin					0·899
Yes	7955	283/3967 (7·1%)	362/3988 (9·1%)	0·78 (0·66–0·91)	
No	1503	55/760 (7·2%)	66/743 (8·9%)	0·80 (0·56–1·14)	
Baseline antiplatelet					0·852
Yes	7959	282/3971 (7·1%)	360/3988 (9·0%)	0·77 (0·66–0·90)	
No	1499	56/756 (7·4%)	68/743 (9·1%)	0·80 (0·56–1·14)	

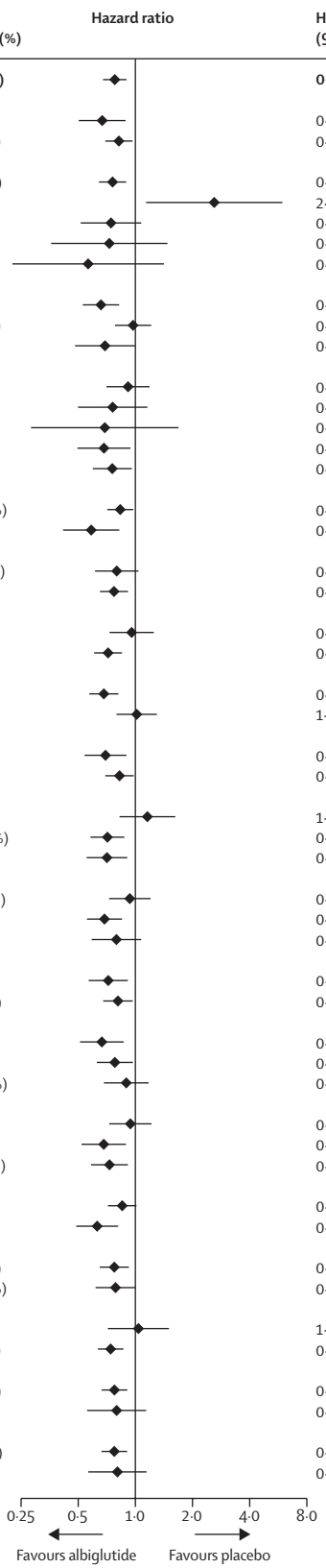

Figure 3: **Primary composite outcome in prespecified subgroups**
Patients self-reported their race or ethnicity. Cerebrovascular disease included any of stroke, at least 50% carotid artery stenosis, or a previous carotid arterial procedure. p values for homogeneity for between-group differences were obtained by fitting interaction terms, with no adjustment for multiple testing. eGFR=estimated glomerular filtration rate. BMI=body-mass index. HbA_{1c}=glycated haemoglobin.

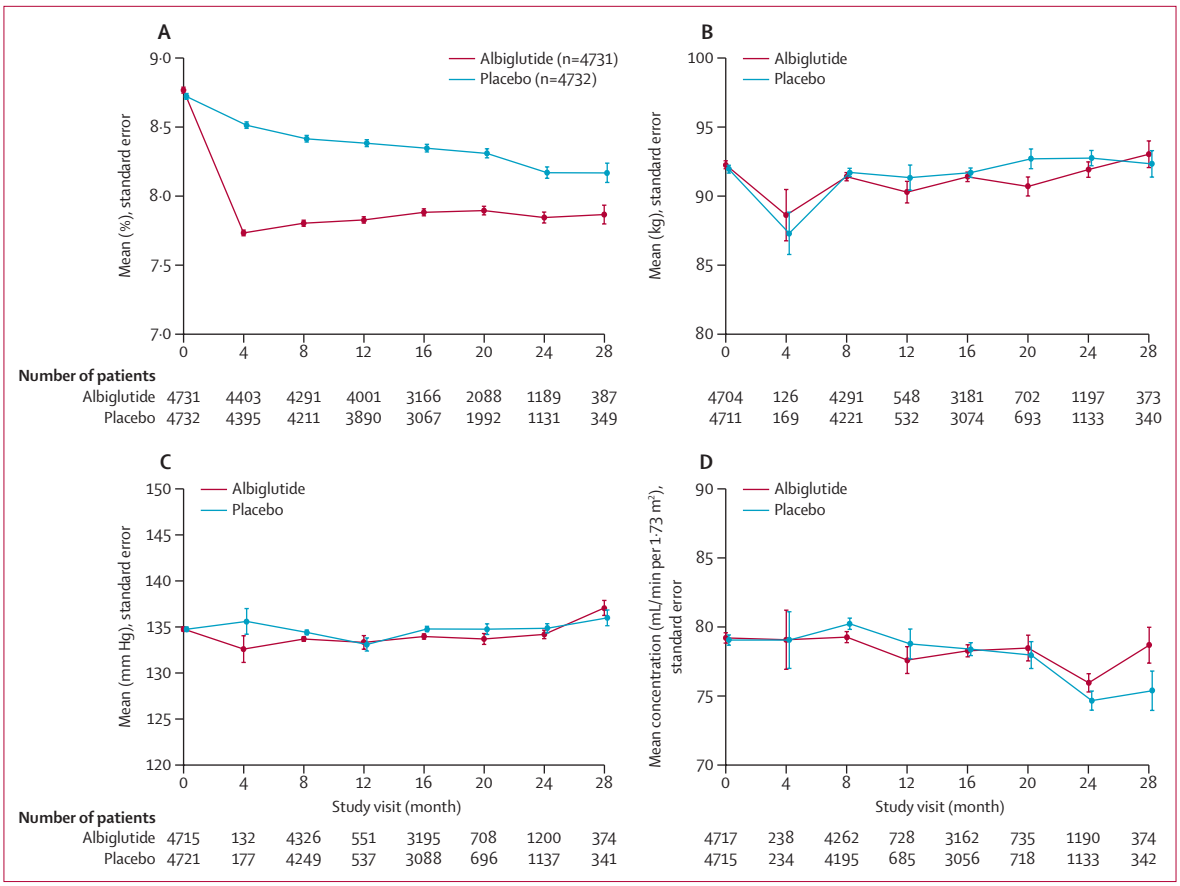

Figure 4: **Effects of once-weekly albiglutide**
Data are the effects of once-weekly administration of albiglutide on (A) glycated haemoglobin concentration, (B) bodyweight, (C) systolic blood pressure, and (D) estimated glomerular filtration rate.

were randomly assigned to groups (4731 patients in the albiglutide group and 4732 patients in the placebo group) and formed the intention-to-treat population who were included in the analysis of the primary outcome (figure 1). 1330 patients were excluded, of whom the majority (1040 [78%] patients) did not meet inclusion criteria or met exclusion criteria.

The demographic and clinical characteristics of the patients were similar between the two groups (table 1). The mean age of the participants was 64·1 years and 31% were women. The mean duration of diabetes was 14·1 years, the mean eGFR was 79 mL/min per 1·73 m², and the mean glycated haemoglobin concentration was 8·7% (SD 1·5). Among the participants, 6678 (71%) participants had a history of coronary artery disease, 2354 (25%) had peripheral artery disease, 2342 (25%) had cerebrovascular disease and 1922 (20%) had a history of heart failure. Patients received standard therapies for diabetes and cardiovascular disease.

From Nov 8, 2017, when it was projected that 611 primary endpoints and a median follow-up of at least 1·5 years had accrued, subjects returned for a final visit and discontinuation from study treatment, with the last patient study visit on March 12, 2018. The actual median duration of follow-up was 1·6 years (IQR 1·3–2·0; maximum 2·6) for the primary outcome. Vital status was not known for 61 (0·6%) of 9463 participants, which included 30 patients from the albiglutide group and 31 patients from the placebo group (figure 1). 1140 (24%) of 4731 patients assigned to receive albiglutide and 1297 (27%) of 4732 patients assigned to receive placebo discontinued study medication prematurely for reasons other than death. Study treatment was taken for 87% of the total follow-up time for cardiovascular outcomes in the albiglutide group and 85% of that time in the placebo group. Among patients who received at least one dose of albiglutide or placebo, 2371 (50%) of 4717 patients in the albiglutide group were taking the maximum dose of 50 mg at the time of their last recorded dose, and 2982 (63%) of 4715 patients in the placebo group were taking the volume-matched equivalent.

The primary composite endpoint occurred in 338 (7%) of 4731 patients at an event rate of 4·57 events per 100 person-years in the albiglutide group and in 428 (9%) of 4732 patients at an event rate of 5·87 events per 100 person-years in the placebo group (HR 0·78,

95% CI 0·68–0·90), indicating that albiglutide was both non-inferior to placebo for cardiovascular safety (p<0·0001 for non-inferiority) and superior to placebo for efficacy (p=0·0006 for superiority; table 2 and figure 2). The HRs for each of the components of the composite were 0·93 (95% CI 0·73–1·19) for death from cardiovascular causes, 0·75 (0·61–0·90) for myocardial infarction, and 0·86 (0·66–1·14) for stroke. Prespecified subgroup analyses are shown in figure 3. Three of 19 subgroups showed a nominally significant interaction between treatment and subgroup.

The effects of albiglutide on the other secondary cardiovascular outcomes were consistent with its effect on the primary outcome (table 2). The HR for death from any cause was 0·95 (95% CI 0·79–1·16). Mean glycated haemoglobin decreased more in patients in the albiglutide group than in those in the placebo group (difference from placebo at 8 months –0·63%, 95% CI –0·69 to –0·58; at 16 months –0·52%, –0·58 to –0·45, figure 4). Bodyweight decreased more in patients in the albiglutide group than the placebo group (difference from placebo at 8 months –0·66 kg, –0·83 to –0·49; at 16 months –0·83 kg, –1·06 to –0·60). New treatment with insulin (taken for more than 3 months) was started in 107 (6%) patients in the albiglutide group and 257 (13%) patients in the placebo group (HR 0·42, 95% CI 0·33–0·53; p<0·0001). Other glucose-lowering therapies were added more often in the placebo group than in the albiglutide group (appendix 1).

Prespecified safety outcomes of special interest are shown in table 3. The number of injection site reactions was greater in the albiglutide group than in the placebo group (86 patients *vs* 29 patients), although the number of patients with suspected hypersensitivity reactions was similar between the two groups (45 patients *vs* 48 patients). Severe hypoglycaemia was less common in the albiglutide group than in the placebo group (31 patients *vs* 55 patients). Other than for metabolism-related events, which were less common in the albiglutide group, there were no clinically meaningful differences in serious adverse events between treatment groups (appendix 1). One patient in the albiglutide group and two patients in the placebo group had lower-limb amputations. 409 (9%) patients who were given albiglutide and 307 (6%) patients who were given placebo discontinued the study medication prematurely because of an adverse event.

Mean systolic blood pressure decreased slightly more in patients in the albiglutide group than in those in the placebo group (difference at 8 months –0·65 mm Hg, 95% CI –1·27 to –0·03; difference at 16 months –0·67 mm Hg, –1·40 to 0·06; figure 4). Heart rate increased more in the patients in the albiglutide group than in those in the placebo group (1·3 beats per min, 0·9 to 1·6; 1·4 beats per min, 1·0 to 1·9; appendix 1). The difference in eGFR between patients in the albiglutide group and those in the placebo group was –1·11 mL/min per 1·73 m² (95% CI –1·84 to –0·39) at 8 months and –0·43 per 1·73 m² (–1·26 to 0·41) at 16 months. There were three (<1%) deaths in the placebo group that were assessed by investigators, who were masked to study drug assignment, to be treatment-related and two (<1%) deaths in the albiglutide group.

	Albiglutide (n=4717)	Placebo (n=4715)	Relative risk (95% CI)
Severe hypoglycaemia	31 (1%)	55 (1%)	0·56 (0·36–0·87)
Pancreatitis*	10 (<1%)	7 (<1%)	1·43 (0·54–3·75)
Injection site reactions	86 (2%)	29 (1%)	2·96 (1·95–4·51)
Thyroid cancer	0 (0)	0 (0)	..
Haematological neoplasia	9 (<1%)	5 (<1%)	1·80 (0·60–5·36)
Pancreatic cancer	6 (<1%)	5 (<1%)	1·20 (0·37–3·93)
Hypersensitivity syndrome or symptoms	45 (1%)	48 (1%)	0·94 (0·63–1·40)
Hepatobiliary disorders	51 (1%)	41 (1%)	1·24 (0·83–1·87)
Alanine aminotransferase of at least 3 times the ULN†	17 (<1%)	30 (1%)	0·57 (0·31–1·03)
Alanine aminotransferase of at least 5 times the ULN†	6 (<1%)	17 (<1%)	0·35 (0·14–0·89)
Bilirubin of at least twice the ULN†	12 (<1%)	7 (<1%)	1·71 (0·68–4·35)
Serious gastrointestinal events	92 (2%)	87 (2%)	1·06 (0·79–1·41)
Appendicitis	3 (<1%)	8 (<1%)	0·37 (0·10–1·41)
Atrial fibrillation or flutter	108 (2%)	131 (3%)	0·82 (0·64–1·06)
Pneumonia	131 (3%)	138 (3%)	0·95 (0·75–1·20)
Renal impairment‡	279 (6%)	319 (7%)	0·87 (0·75–1·02)
Diabetic retinopathy	78 (2%)	89 (2%)	0·88 (0·65–1·18)

Data are number of patients (%), in those who took at least one dose. Details of specified events are reported in the appendix. ULN=upper limit of normal. *Events prospectively adjudicated to be definite or possible pancreatitis by a treatment-blind adjudication committee. †Hepatic enzyme elevation was prespecified as an adverse event of special interest. There were four patients who had an alanine aminotransferase concentration of at least 3 times the ULN and a bilirubin concentration of at least twice the ULN: one patient in the albiglutide group, three patients in the placebo group. ‡Acute kidney injury was reported by investigators in 70 patients in the albiglutide group and 80 patients in the placebo group.

Table 3: **Prespecified adverse events of special interest**

Discussion

In patients with type 2 diabetes and cardiovascular disease who were receiving standard care, addition of once-weekly albiglutide reduced the risk of the primary composite outcome—death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke—by 22%, compared with the addition of placebo. 50 patients would need to be treated with albiglutide to prevent one event over a median duration of 1·6 years.

Of all three components of the primary outcome, which were prespecified secondary outcomes, only myocardial infarction showed a significant point estimate that indicated beneficial effect. Compared with trials[5–8] that evaluated other GLP-1-receptor agonists, the effects that we observed were consistent with the benefits of liraglutide and semaglutide, but they appear greater than those of lixisenatide and exenatide. Whether there are real differences among the findings of these trials is uncertain. Several factors, including the specific molecule and dose tested, differences in the patients randomised (such as in medical history and baseline characteristics), duration of

follow-up, and adherence to treatment, could account for the apparent variation in results. However, this question can only be properly resolved by direct comparisons between drugs;[5–8,16] a 2018 meta-analysis[17] showed only moderate heterogeneity between the previous trials that was not significant.

We did not observe a significant reduction in death from cardiovascular causes, which was noted in the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial.[5] However, we observed a delay between the initiation of treatment and the emergence of benefit, as was noted in previous trials[5–8] with GLP-1-receptor agonists, and the magnitude of the risk reduction for the primary outcome appeared to increase over time, both in our trial and the previous trials. The median duration of follow-up in our trial was considerably shorter than the 3·8 years in the LEADER trial, and it might be that an effect on death from cardiovascular causes requires additional time to accrue.

The effect of albiglutide was generally consistent across most subgroups analysed, although three of the 19 subgroups examined showed some heterogeneity in the effect of treatment. Given the absence of a biologically plausible explanation for this finding and of any similar interactions in other trials that used GLP-1-receptor agonists, we believe that our subgroup findings are probably due to chance and are related to the large number of subgroups analysed.

The point estimate for another secondary outcome—death from cardiovascular causes or hospital admission because of heart failure—did not significantly differ between the albiglutide and placebo groups. This finding is clinically relevant, given concerns about increased risk of heart failure with other glucose-lowering therapies.[18]

The benefit of albiglutide was evident in patients who were treated with other effective cardiovascular therapies. Despite no major difference between the treatment groups in blood pressure, bodyweight, or renal function over time, treatment with albiglutide reduced the risk of major cardiovascular events over a relatively short period of follow-up. The mean glycated haemoglobin concentration at baseline was 8·7% and was reduced by approximately 1% after 4 months in the albiglutide group compared with placebo and remained lower in the albiglutide group for the duration of the trial, despite a decrease in glycated haemoglobin over time in the placebo group. Other glucose-lowering therapies, including SGLT-2 inhibitors and insulin, were added more commonly to the treatment regimens of patients in the placebo group than those in the albiglutide group. The exact reasons why GLP-1 receptor agonists reduce the incidence of atherothrombotic events is unknown; however, putative, potentially beneficial, cardiovascular actions of these drugs have been described.[19]

The only prespecified adverse event of interest that was substantially more common in the albiglutide group was injection-site reactions, although this adverse event occurred in less than 2% of patients. Severe hypoglycaemia was uncommon overall and occurred less frequently in the albiglutide group than in the placebo group, probably due, in part, to the greater use of insulin and other glucose-lowering therapies in the placebo group. There was no excess of reported new or worsening retinopathy in the albiglutide group.[20,21] Only serious adverse events (excluding outcomes) were recorded in addition to the prespecified adverse events of interest, and these adverse events did not occur at any difference in frequency between the albiglutide and placebo groups for non-metabolism-related events. Overall, albiglutide treatment was discontinued slightly less frequently than placebo treatment, although it should be noted that, by design, our trial did not require forced up-titration of the dose of study drug.[11]

One strength of our trial was that, except for GLP-1-receptor agonists, investigators were free to use any other glucose-lowering therapy, including dipeptidyl peptidase 4 inhibitors and SGLT-2 inhibitors. The inclusion and exclusion criteria ensured a high rate of cardiovascular events. Our trial also has some limitations, including the short duration of follow-up, and absence of measurement of lipids and urinary albumin excretion. We also did not collect detailed information on microvascular complications. Although the short overall duration of follow-up might raise concerns about identification of longer-term safety problems, previous studies[10] on albiglutide collected information on safety and tolerability for up to 3 years. About a quarter of patients discontinued study treatment in our trial, which is concordant with discontinuation rates in other trials[3–8] that used GLP-1-receptor agonists, and study treatment was taken for approximately 86% of the total follow-up time for cardiovascular outcomes

In summary, when added to standard care in patients with type 2 diabetes and established cardiovascular disease, the long-acting GLP-1-receptor agonist albiglutide reduced the risk of major adverse cardiovascular events with acceptable tolerability and safety. These findings provide more evidence that certain GLP-1-receptor agonists can improve cardiovascular outcomes in patients with type 2 diabetes.[21–23]

Contributors

AFH, SJ, RBD'A, NPJ, LAL, AER, JJVM, and SDP contributed to the design of the study. KNS and MCS analysed the data. AFH, JBG, SJ, RBD'A, CBG, NPJ, LAL, KNS, MCS, KMT, JJVM, and SDP interpreted the data. JJVM drafted the report, which was critically revised by AFH, JBG, SJ, RBD'A, CBG, NPJ, LAL, KNS, MCS, KMT, JJVM, and SDP. All authors have read and approved the final version.

Declaration of interests

AFH reports grants to his institution from AstraZeneca, GlaxoSmithKline, Luitpold Pharmaceuticals, Novartis, Merck, Portola Pharmaceuticals, and Verily; and he has been a consultant for AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Novartis, and Merck. JBG reports grants to her institution from AstraZeneca, Boehringer Ingelheim, and GlaxoSmithKline; and she has been consultant for AstraZeneca, Boehringer Ingelheim, Novo Nordisk,

and Merck. SJ, NPJ, and KMT are GlaxoSmithKline employees and shareholders. RBD'A is a consultant for GlaxoSmithKline (for the Harmony Outcomes trial). CBG reports grants to his institution from Apple, Armetheon, Daiichi Sankyo, the US Food and Drug Administration, and AstraZeneca; and reports consultancy fees from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Janssen Pharmaceutica, Medtronic, the National Institutes of Health, Novartis, Pfizer, AbbVie, Boston Scientific, Gilead Sciences, Medscape, Merck, Novo Nordisk, Rho, Roche Diagnostics, Sirtex Medical, and Verseon. LAL reports grants to his institution from AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, GlaxoSmithKline, Janssen, Merck, Novo Nordisk, and Sanofi; he reports honoraria for presentation from AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Janssen Pharmaceutica, Merck, Novo Nordisk, Sanofi, and Servier; and he reports participation on advisory boards for AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Janssen, Merck, Novo Nordisk, Sanofi, and Servier. AER reports grants to her institution from GlaxoSmithKline. KNS reports grants to her institution from GlaxoSmithKline and CSL Behring. MCS is a former employee of and shareholder in GlaxoSmithKline and is an employee of PAREXEL International. JJVM reports grants to his institution from Boehringer Ingelheim and Bristol-Myers Squibb, consultancy fees to his institution from Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Cardurion Pharmaceuticals, DalCor Pharmaceuticals, GlaxoSmithKline, Johnson & Johnson, Merck, Novartis, and Theracos, and honoraria to his institution for presentations from AstraZeneca, Novartis, and Pfizer. SDP reports grants to his institution from AstraZeneca, Boehringer Ingelheim, Merck, and Novartis; he reports honoraria for presentations from AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Merck, Novartis, Novo Nordisk, and Takeda Pharmaceuticals; and he reports participation in advisory boards for Abbott Laboratories, AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, GlaxoSmithKline, Merck, Mundipharma, Novartis Pharmaceuticals, Novo Nordisk, Sanofi, Servier, and Takeda Pharmaceuticals.

Data sharing

Anonymised individual participant data and study documents can be requested for further research from Clinical Study Data Request after publication of this Article.

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