Received: 19 April 2017 | Revised: 12 May 2017 | Accepted: 24 May 2017

DOI: 10.1111/dom.13028

WILEY

CLINICAL TRIAL DESIGN

Design and baseline characteristics of participants in the Researching cardiovascular Events with a Weekly INcretin in Diabetes (REWIND) trial on the cardiovascular effects of dulaglutide

Hertzel C. Gerstein MD, MSc[1] | Helen M. Colhoun MD, MSc[2] | Gilles R. Dagenais MD[3] | Rafael Diaz MD[4] | Mark Lakshmanan MD[5] | Prem Pais MD[6] | Jeffrey Probstfield MD[7] | Matthew C. Riddle MD[8] | Lars Rydén MD[9] | Denis Xavier MD[6] | Charles M. Atisso PhD[5] | Alvaro Avezum MD[10] | Jan Basile MD[11] | Namsik Chung MD[12] | Ignacio Conget MD[13] | William C. Cushman MD[14] | Edward Franek MD[15] | Nicolae Hancu MD[16] | Markolf Hanefeld MD, DHC, PhD[17] | Shaun Holt MBChB (hons)[18] | Petr Jansky MD[19] | Matyas Keltai MD[20] | Fernando Lanas MD, PhD[21] | Lawrence A. Leiter MD[22] | Patricio Lopez-Jaramillo MD, PhD[23] | Ernesto G. Cardona-Munoz MD[24] | Valdis Pirags MD[25] | Nana Pogosova MD[26] | Peter J. Raubenheimer MBBCh[27] | Jonathan Shaw MD[28] | Wayne H-H. Sheu MD[29] | Theodora Temelkova-Kurktschiev MD[30] | on behalf of the REWIND Trial Investigators

A video related to the article is available on the journal's YouTube site: https://www.youtube.com/watch?v=vg_XhSPKxww&feature=youtu.be

[1]Department of Medicine and Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, Canada

[2]University of Edinburgh, Edinburgh, UK

[3]Universite Laval, Quebec City, Canada

[4]ECLA Academic Research Organization and ICR Instituto Cardiovascular de Rosario, Rosario, Argentina

[5]Eli Lilly and Company, Indianapolis, Indiana

[6]St. John's Research Institute, Bangalore, India

[7]Department of Medicine, University of Washington, Seattle, Washington

[8]Department of Medicine, Oregon Health & Science University Portland, Portland, Oregon

[9]Karolinska Institute, Stockholm, Sweden

[10]Instituto Dante Pazzanese de Cardiologia and University Santos Amaro, São Paulo, Brazil

[11]Medical University of South Carolina, Charleston, South Carolina

[12]Yonsei University Health System, Seoul, South Korea

The aim was to determine the effects of dulaglutide, a synthetic once-weekly, injectable human glucagon-like peptide 1 analogue that lowers blood glucose, body weight, appetite and blood pressure, on cardiovascular outcomes. People with type 2 diabetes, aged ≥50 years, with glycated haemoglobin (HbA1c) ≤9.5%, and either a previous cardiovascular event, evidence of cardiovascular disease or ≥2 cardiovascular risk factors were randomly allocated to a weekly subcutaneous injection of either dulaglutide (1.5 mg) or placebo and followed within the ongoing Researching cardiovascular Events with a Weekly INcretin in Diabetes (REWIND) trial every 3 to 6 months. The primary cardiovascular outcome is the first occurrence of the composite of cardiovascular death or non-fatal myocardial infarction or non-fatal stroke. Secondary outcomes include each component of the primary composite cardiovascular outcome, a composite clinical microvascular outcome comprising retinal or renal disease, hospitalization for unstable angina, heart failure requiring hospitalization or an urgent heart failure visit, and all-cause mortality. Follow-up will continue until the accrual of 1200 confirmed primary outcomes. Recruitment of 9901 participants (mean age 66 years, 46% women) occurred in 370 sites located in 24 countries over a period of 2 years. The mean duration of diabetes was 10 years, mean baseline HbA1c was 7.3%, and 31% had prior cardiovascular disease. The REWIND trial's international scope, high proportion of women, high proportion of people without prior cardiovascular disease and inclusion of participants whose mean baseline HbA1c was 7.3% suggests that its cardiovascular and safety findings will be

*clinicaltrials.gov: NCT01394952

[13]Endocrinology and Nutrition Department, Hospital Clínic i Universitari, Barcelona, Spain

[14]Memphis Veterans Affairs Medical Center, Memphis, Tennessee

[15]Mossakowski Medical Research Centre, Polish Academy of Sciences and Central Clinical Hospital MSW, Warsaw, Poland

[16]Iuliu Hatieganu University of Medicine and Pharmacy, Cluj Napoca, Romania

[17]Dresden Technical University, Dresden, Germany

[18]Victoria University of Wellington, Wellington, New Zealand

[19]University Hospital Motol, Prague, Czech Republic

[20]Hungarian Institute of Cardiology, Semmelweis University, Budapest, Hungary

[21]Universidad de La Frontera, Temuco, Chile

[22]Keenan Research Centre in the Li Ka Shing Knowledge Institute of St. Michael's Hospital, University of Toronto, Toronto, Canada

[23]Research Institute, FOSCAL and Medical School, Universidad d Santander UDES, Bucaramanga, Colombia

[24]Universidad de Guadalajara Centro Universitario de Ciencias de la Salud, Guadalajara, Mexico

[25]Latvijas Universitate, Riga, Latvia

[26]National Research Center for Preventive Medicine, Moscow, Russia

[27]University of Cape Town, Cape Town, South Africa

[28]Baker Heart and Diabetes Institute, Melbourne, Australia

[29]Taichung Veterans General Hospital, Taichung, Taiwan

[30]Robert Koch Medical Center, Sofia, Bulgaria

Correspondence
Hertzel C. Gerstein MD MSc, Department of Medicine, McMaster University HSC 3V38, 1280 Main Street West, Hamilton, Ontario, Canada, L8S 4K1.
Email: gerstein@mcmaster.ca

Funding information
The REWIND trial is funded by Eli Lilly and Company

directly relevant to the typical middle-aged patient seen in general practice throughout the world.

KEYWORDS

antidiabetic drug, cardiovascular disease, clinical trial, diabetes complications, GLP-1 receptor agonist

1 | INTRODUCTION

The incidence of cardiovascular events in people with type 2 diabetes is about twice as high as it is in similar individuals without type 2 diabetes.[1] This higher incidence is caused by a number of risk factors related to the causes and consequences of dysglycaemia,[2] obesity, dyslipidaemia, hypertension and endothelial damage or dysfunction.[3,4] Such abnormalities have provided the basis for an array of randomized controlled trials on the effect of both glucometabolic and non-glucometabolic interventions on cardiovascular events in people with diabetes. To date, trials with non-glucometabolic therapies have shown that statins,[5] renin angiotensin system modulators,[6,7] other blood pressure-lowering agents,[8,9] and a Mediterranean diet[10] can reduce cardiovascular events, whereas lifestyle interventions focused on weight reduction have, to date, had a neutral effect.[11] Trials of glucometabolic therapies in people with diabetes have shown that intensive glucose-lowering modestly reduces cardiovascular outcomes, mainly because of an effect on ischaemic heart disease,[12–15] and has an uncertain effect on mortality.[16] Other studies that focused on drug effects rather than glucose-lowering effects have shown that insulin-sensitizing approaches have the same effect on cardiovascular outcomes as insulin-providing approaches,[17] pioglitazone has a mixed effect on cardiovascular outcomes,[18] basal insulin[19] and dipeptidyl peptidase-4 (DPP-4) inhibitors[20–22] have a neutral

effect on cardiovascular outcomes, and one sodium-glucose co-transporter-2 (SGLT2) inhibitor, empagliflozin, reduces cardiovascular and total mortality as well as hospitalization for heart failure.[23]

Glucagon-like peptide-1 (GLP-1) receptor agonists are analogues of natural GLP-1, a gastrointestinal hormone which is secreted in response to food intake and increases insulin secretion in response to glucose, reduces glucagon secretion, reduces appetite, and slows gastric emptying.[24] The biological effects of this hormone on the circulatory system suggest that it may also have salutary cardiovascular effects. Because natural GLP-1 has a very short half-life, analogues that resist degradation and that are given once (liraglutide, lixisenatide) or twice (exenatide) daily, weekly (long-acting exenatide, dulaglutide, semaglutide, albiglutide) or less frequently (implanted subcutaneous exenatide pump) have been developed.[25] Clinical trials of these analogues have shown that these drugs lower glucose levels without promoting hypoglycaemia, modestly lower blood pressure, increase heart rate by 2 to 4 beats/min, and promote modest weight loss.[24]

The effects of some of these agents on cardiovascular outcomes have also been reported: once-daily lixisenatide had a neutral effect on cardiovascular outcomes after a diagnosis of acute coronary syndrome in 6068 people with a mean age of 60 years, whose mean baseline glycated haemoglobin (HbA1c) was 7.7% and who were treated for a median of 2.1 years[26]; once-daily liraglutide reduced cardiovascular events as well as cardiovascular deaths in 9340 people with a mean age of 64 years and a mean baseline HbA1c of 8.7% and who were followed for a median of 3.8 years[27]; and once-weekly semaglutide reduced cardiovascular events and stroke in 3297 people with a mean age of 65 years and a mean baseline HbA1c of 8.7% and who were followed for a median of 2.1 years.[27]

Dulaglutide is a synthetic analogue of human GLP-1 that structurally comprises 2 GLP-1 receptor agonist molecules that are covalently linked to 1 IgG4 heavy chain by a small peptide linker. It has pharmacological half-life of 5 days, which allows it to be administered as a weekly subcutaneous injection.[28] Clinical trials have shown that doses of 0.75 to 1.5 mg weekly reduce HbA1c as well as body weight, appetite and blood pressure.[29] A meta-analysis of randomized controlled trials comprising 6010 individuals with diabetes followed for a median of ~1 year reported a neutral effect on the first occurrence of non-fatal myocardial infarction (MI), non-fatal stroke, hospitalization for unstable angina, or death from cardiovascular causes.[30] When given alone the drug does not cause hypoglycaemia; however, like other GLP-1 receptor agonists, it can cause nausea and diarrhoea in up to 10% of individuals. Dulaglutide's effects on glucose, blood pressure and weight,[28] together with evidence that GLP-1 receptors are expressed in the heart and that GLP-1 has anti-atherosclerotic and anti-inflammatory effects in animal studies, all suggest its potential for cardiovascular benefits, and support its assessment in a long-term cardiovascular outcomes trial.

2 | METHODS

The Researching cardiovascular Events with a Weekly INcretin in Diabetes (REWIND) trial is designed to determine whether the addition of a once-weekly dulaglutide injection to the diabetes medication regimen of middle-aged and older people with type 2 diabetes safely reduces the incidence of cardiovascular outcomes. The selection criteria (Table 1) were designed to include participants who were similar to patients seen within a typical diabetes practice, who had varying cardiovascular risk factors, and who collectively would have an estimated cardiovascular outcome incidence rate of ~2% per year. Briefly, men and women with previous or newly detected diabetes whose HbA1c was ≤9.5%, and who were on 0 to 2 classes of oral glucose-lowering drugs, with or without basal insulin, were recruited. People aged 50 to 54 years had to have previous cardiovascular disease, those aged 55 to 59 years had to have either previous cardiovascular disease or evidence of other vascular or renal disease, and those aged ≥60 years were eligible if they had previous cardiovascular disease, other vascular or renal disease, or at least 2 other cardiovascular risk factors. Candidates with an estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2, a gastric emptying abnormality, previous pancreatitis, liver disease or medullary carcinoma of the thyroid gland as well as a number of other criteria were excluded (Table 1).

Ethics review boards responsible for each participating institution approved the protocol. After providing written, informed consent, participants were stratified by site and randomly allocated using blocks of 4 to either a weekly subcutaneous injection of dulaglutide (1.5 mg) or matching placebo and assessed every 3 to 6 months for the occurrence of cardiovascular and other serious health outcomes. At the time of run-in, any participant taking a GLP-1 receptor agonist or DPP-4 inhibitor had this medication stopped. HbA1c levels were measured and reported to investigators at least every 6 months and investigators were encouraged to manage participants' glucose levels with any medication except for a GLP-1 receptor agonist according to their best judgement as informed by local clinical practice guidelines for the management of diabetes. Investigators were similarly advised and periodically reminded to optimize use of cardioprotective measures including treatment of lipids and blood pressure, use of anti-platelet agents, and promotion of healthy lifestyles according to applicable guidelines.[4,31,32]

The primary cardiovascular outcome for the REWIND trial is the first occurrence of the composite of either cardiovascular death or non-fatal MI or non-fatal stroke. Secondary outcomes include each component of the primary composite cardiovascular outcome, a composite clinical microvascular outcome comprising retinal or renal disease, hospitalization for unstable angina, heart failure requiring hospitalization or an urgent heart failure visit, and all-cause mortality. These and other prespecified clinical and biochemical outcomes are noted in Table 2. Safety outcomes include acute pancreatitis, serious and severe gastrointestinal pain, pancreatic, thyroid or other cancers, severe hypoglycaemia, hypersensitivity reactions, and other liver, renal or cardiovascular events as well as drug discontinuation.

All deaths and cardiovascular, pancreatic and thyroid events (i.e. both efficacy and safety outcomes) are adjudicated by an external adjudication committee, which is blinded to treatment allocation. Participants will continue to be followed until the trial is completed regardless of whether or not they have had a study outcome or whether or not they continue to take study medication. Unless

TABLE 1 Selection criteria

Key inclusion criteria	Key exclusion criteria
Previous/new type 2 diabetes with HbA1c ≤9.5%	Uncontrolled diabetes
Stable dose of 0, 1 or 2 oral glucose-lowering drugs ± basal insulin for ≥3 months	Severe hypoglycaemia in preceding year
BMI ≥ 23 kg/m^2	Coronary or cerebrovascular event in preceding 2 months or plans to revascularize
If age ≥50 years, at least 1 of: prior MI; prior ischaemic stroke; coronary revascularization ≥2 years earlier; carotid or peripheral revascularization ≥2 months earlier; unstable angina hospitalization; image proven myocardial ischaemia; or percutaneous coronary intervention	eGFR <15 mL/min/1.73 m^2 or on dialysis
If age ≥55 years, any of the above or at least 1 of: documented myocardial ischaemia by stress test or imaging; >50% coronary, carotid or lower extremity artery stenosis; ankle–brachial index <0.9; eGFR persistently <60 mL/min/1.73 m^2; hypertension with left ventricular hypertrophy; or persistent albuminuria	Gastric bypass or emptying abnormality
If age ≥ 60 years, any of the above or at least 2 of: any tobacco use; use of lipid-modifying therapy or a documented untreated LDL cholesterol ≥3.4 mmol/L (130 mg/dL) within the past 6 months; HDL cholesterol <1.0 mmol/L (40 mg/dL) for men and <1.3 mmol/L (50 mg/dL) for women or triglycerides ≥2.3 mmol/L (200 mg/dL) within the past 6 months; use of ≥1 blood pressure drug or untreated systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 95 mm Hg; or waist-to-hip ratio >1.0 (men) and >0.8 (women)	Prior pancreatitis/concordant symptoms
Run-in adherence to study drug = 100%	Liver disease or ALT ≥3.0 × normal
Signed informed consent	Family history of/or C-cell hyperplasia or medullary thyroid cancer or MEN 2A or 2B or calcitonin value ≥20 pg/mL
	Unwilling to stop GLP-1 receptor agonist or DPP-4 inhibitor or weight loss drug
	Cancer within prior 5 years
	Pregnant or not using reliable birth control
	Life expectancy <1 year

Abbreviation: MEN, multiple endocrine neoplasia.

permission is explicitly revoked, vital status at the end of the trial will be obtained on all randomized participants whenever possible.

The REWIND trial is sponsored by Eli Lilly, site management and data collection are conducted by ICON Clinical Research, scientific leadership is provided by an international steering committee coordinated by the Population Health Research Institute in Hamilton, Canada, and data analysis will be conducted by the Population Health Research Institute.

2.1 | Sample size

Sample size calculations were based on a 3-year recruitment period, an anticipated primary outcome event rate of 2% per year in the control group, annual dropout rate of 0.15%, and a 2-sided type I error of 5%. These assumptions indicated that recruitment of 9600 patients would result in a total of 1200 participants with at least 1 primary cardiovascular outcome over a maximum follow-up period of

TABLE 2 Secondary and other outcomes

Secondary outcomes	Other outcomes	Safety outcomes
Composite microvascular outcome: diabetic retinopathy needing laser, anti-VEGF therapy, or vitrectomy; or clinical proteinuria; or a 30% decline in eGFR; or chronic renal replacement therapy	HbA1c	Acute pancreatitis
Unstable angina hospitalization	Weight, and waist-to-hip ratio	Serious gastrointestinal events
Heart failure hospitalization or urgent visit	Expanded composite cardiovascular outcome: non-fatal MI; non-fatal stroke; unstable angina; hospitalization; or cardiovascular death	Cancers: pancreatic, medullary thyroid, other thyroid, other (excluding non-melanoma skin cancers)
Non-fatal MI	Revascularization (coronary, carotid or peripheral)	Severe hypoglycaemia
Non-fatal stroke	Any hospitalization	Immune reactions
Cardiovascular death	Any fracture	Serious hepatic events
Death	Cholelithiasis	Serious renal events
	Erectile dysfunction (men)	Supraventricular arrhythmias and cardiovascular conduction disorders
	Cognitive decline	Drug discontinuation

Abbreviation: VEGF, vascular endothelial growth factor. The primary outcome for REWIND is the first occurrence of either a non-fatal MI, non-fatal stroke, or cardiovascular death.

8 years, and would provide 90% power to detect a hazard ratio of 0.82 for cardiovascular events. Follow-up will end after 1200 participants have had a primary cardiovascular outcome confirmed by adjudication.

2.2 | Statistical analysis

All efficacy and safety analyses will be conducted using an intention-to-treat approach that includes all randomized participants regardless of adherence. Baseline continuous variables will be summarized as either means or medians with their standard deviations or interquartile ranges, and categorical variables will be summarized as the number and percentage. The effect of the intervention on the time to the first occurrence of the primary outcome will be analysed using Cox proportional hazards models with the only independent variable being allocation to dulaglutide vs placebo. The proportional hazard assumption will be assessed graphically. Kaplan–Meier curves will also be generated along with log-rank *P* values. The incidence rate per 100 person-years will be calculated for each treatment group for all key outcomes.

All secondary outcomes will be analysed in a predetermined order defined by a graphical approach to control the overall type I error.[33–35] If the null hypothesis of no effect is rejected for the primary outcome, the graphical testing approach allocates the α parsimoniously for each secondary outcome. A detailed description of the graphical approaches is provided in the online supporting information.

All subgroup analyses will be considered exploratory and will be conducted only for outcomes where the event number is at least 50. Subgroups to be examined include: gender; age below vs at or above the median; duration of diabetes <5 years, 5 to 9.9 years and ≥10 years; body mass index (BMI) below vs at or above the median; HbA1c below vs at or above the median; geographical region (North America, South America and Mexico, Europe and South Africa, and Asia Pacific); or a prior cardiovascular event. For all subgroup analyses, an interaction *P* value of <.1 will be considered suggestive of an interaction. No adjustments for multiplicity will be performed. Other exploratory analyses will include the effect of the intervention on recurrent primary or secondary outcomes, other clinical outcomes, anthropometric and biochemical measures, cognitive function and erectile function.

An Independent Data Monitoring Committee meets every 6 months to review accruing and unblinded data within the trial and determine whether any change in the conduct of the trial is warranted. In addition to regular review of the findings, this committee also conducted a formal interim analysis of the accruing data after ~61% of the primary, adjudication-confirmed composite endpoints have occurred. This analysis was carried out using an O'Brien–Fleming α spending function to control the overall 5% α value. Nobody other than the members of the Independent Data Monitoring Committee and its 2 unblinded statisticians have access to any accruing data according to allocated group.

3 | RESULTS

Of 12 137 individuals who were screened, 9901 in 370 sites located in 24 countries were randomly allocated to either dulaglutide or placebo. The main reasons for not being randomized included not meeting eligibility criteria (68%) or personal decision (25%). The first participant was randomized in August 2011 and recruitment ended 1 year ahead of schedule in August 2013. As noted in Tables 3 and 4, the mean age of participants (46% women) was 66 years, the mean BMI was 32 kg/m^2 and 31% had a history of cardiovascular disease

TABLE 3 Baseline clinical characteristics of 9901 randomized participants

Characteristic	All participants
Age, years: mean (s.d.)	66.2 (6.5)
Females, n (%)	4589 (46.3)
Geography, n (%)	
USA and Canada	2071 (20.9)
Mexico and South America	3021 (30.5)
Europe, Russia and South Africa	4339 (43.8)
Asia: Taiwan and Korea	148 (1.5)
Pacific: Australia and New Zealand	322 (3.3)
Prior cardiovascular disease (≥1 of the following 6), n (%)	3111 (31.4)
Prior MI	1600 (16.2)
Prior ischemic stroke	526 (5.3)
Prior unstable angina	587 (5.9)
Prior revascularization[a]	1787 (18.1)
Prior hospitalization for ischaemia-related events[b]	1193 (12.1)
Prior documented myocardial ischaemia	922 (9.3)
Prior hypertension, n (%)	9223 (93.2)
Prior heart failure, n (%)	852 (8.6)
Prior diabetic retinopathy, n (%)	891 (9.0)
Prior fracture, n (%)	1510 (15.3)
Prior cholecystectomy, n (%)	1465 (14.8)
Current tobacco use, n (%)	1407 (14.2)
Diabetes duration, years: mean (s.d.)	10.0 (7.2)
Weight, kg: mean (s.d.)	88.7 (18.5)
BMI, kg/m^2: mean (s.d.)	32.3 (5.7)
Blood pressure, mm Hg: mean (s.d.)	137.2 (16.8)/78.5 (9.8)
Pulse, beats/min: mean (s.d.)	71.5 (10.9)
Male waist-to-hip ratio: mean (s.d.)	110.6 (13.1)/108.4 (11.2)
Female waist-to-hip ratio: mean (s.d.)	106.7 (13.1)/113.3 (13.7)
HbA1c, %: mean (s.d.)	7.3 (1.1)
Cholesterol, mmol/L: mean (s.d.)	4.52 (1.16)
LDL cholesterol, mmol/L: mean (s.d.)	2.56 (0.98)
HDL cholesterol, mmol/L: mean (s.d.)	1.18 (0.34)
Triglycerides, mmol/L: median (IQR)	1.60 (1.17, 2.22)
eGFR, mL/min/1.73 m^2: mean (s.d.)	77.6 (24.1)
eGFR <60 mL/min/1.73 m^2, n (%)	2199 (22.2)
Albumin/creatinine, mg/mmol: median (IQR)	1.94 (0.75, 8.02)
Macro or microalbuminuria[c], n (%)	3491 (35.3)

Abbreviations: IQR, interquartile range; s.d., standard deviation.

[a] Coronary, carotid or peripheral.

[b] Unstable angina or myocardial ischaemia on imaging, or need for percutaneous coronary intervention.

[c] Albumin/creatinine ≥3.39 mg/mmol.

TABLE 4 Baseline use of drug classes in 9901 randomized participants

Diabetes-specific drugs classes		Other drug classes	
None	600 (6.1)	ACE inhibitor	4909 (49.6)
Only 1 oral agent	4926 (49.8)	ARB	3366 (34.0)
Only 2 oral agents	3894 (39.3)	ACE inhibitor or ARB	8054 (81.4)
Any insulin	2398 (24.2)	Aldosterone antagonist	464 (4.7)
Metformin	8016 (81.0)	All diuretic	4592 (46.4)
Glibenclamide/ glyburide	1271 (12.8)	Thiazides	652 (6,6)
Other sulfonylureas	4373 (44.2)	β blocker	4502 (45.5)
DPP-4 inhibitors	88 (0.9)	Ca channel blocker	3385 (34.2)
SGLT2 inhibitors	12 (0.1)	Acetylsalicylic acid	5001 (50.5)
Meglitinides	64 (0.7)	Other antiplatelet	820 (8.3)
α-Glucosidase inhibitors	118 (1.2)	Statin	6537 (66.0)
Thiazolidinediones	168 (1.7)	Fibrate	892 (9.0)
Dopamine agonist	47 (0.5)	Other lipid drug	112 (1.1)
Other	84 (0.9)	Proton pump inhibitor	1673 (16.9)

Values shown in the cells represent counts and percentage of all randomized.

(defined as a history of MI, ischaemic stroke, revascularization, hospitalization for unstable angina with concordant new ischaemic ECG changes, or a positive stress test with concordant imaging). In addition, 93% had a history of hypertension, 9% had a history of prior heart failure, and the mean blood pressure was 137/78 mmHg. The mean reported duration of diabetes was 10 years, 24% of participants were taking insulin, 81% were taking metformin, 57% were on a sulphonylurea, and the mean baseline HbA1c was 7.3%. An angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) was used by 81% of participants, 45% were taking a β-blocker, 66% were taking a statin at baseline, 51% were on acetylsalicylic acid, 8% were on other antiplatelet agents, and the mean baseline LDL cholesterol was 2.56 nmol/L.

TABLE 5 Key characteristics of completed trials and REWIND

	ELIXA	LEADER	SUSTAIN 6	REWIND
Drug tested	Lisixenatide	Liraglutide	Semaglutide	Dulaglutide
Dose	20 μg/d	1.8 mg/d	0.5 or 1 mg/wk	1.5 mg/wk
N	6068	9340	3297	9901
Mean age, years	60	64	65	66
Percent women	31	36	39	46
Percent prior CVD	100	81	59	31
Mean BMI, kg/m^2	30	33	31	32
Mean HbA1c, %	7.7	8.7	8.7	7.3
Primary outcome	MACE[a] or unstable angina	MACE[a]	MACE[a]	MACE[a]

Abbreviations: CVD, cardiovascular disease; MACE, major adverse cardiac events.

[a] Non-fatal MI, non-fatal stroke or cardiovascular death.

4 | DISCUSSION

REWIND is a randomized placebo-controlled trial measuring the cardiovascular effects of once-weekly dulaglutide in patients with type 2 diabetes. This trial's international scope, high proportion of women, high proportion of people without prior cardiovascular disease, and inclusion of participants whose mean baseline HbA1c was 7.3% means that its results will be directly relevant to the average middle-aged patient with diabetes seen in many programmes throughout the world. Its focus on the "typical" middle-aged patient with type 2 diabetes distinguishes it from the other GLP-1 receptor agonist cardiovascular outcomes trials reported to date[26,27,36] that are summarized in Table 5, which have focused on high-risk patients either after an acute coronary syndrome event or with a very high prevalence of prior cardiovascular disease, and with higher levels of HbA1c at baseline.

The REWIND trial is designed to determine whether people allocated to dulaglutide have a lower hazard of cardiovascular events than those allocated to placebo, and the planned accrual of 1200 first primary outcomes during a fairly long follow-up period of 7 to 8 years will provide high power to detect a clinically relevant 18% reduction. This high number of outcomes also ensures that there will be narrow confidence intervals around the estimated effect size.

REWIND is also explicitly assessing potential side effects of dulaglutide and its effect on a large variety of clinically important outcomes including all-cause mortality, renal disease, hospitalizations for heart failure or angina, cancer (including thyroid cancer), and pancreatitis. Moreover, its predefined graphical testing strategy will optimize the ability to identify those components of the primary and secondary outcomes that are most affected by dulaglutide. These considerations suggest that REWIND will provide a comprehensive assessment of the clinical effects of the drug and will clearly facilitate clinicians' ability to practice evidence-based care of patients with type 2 diabetes who are typical of those seen on a day-to-day basis.

ACKNOWLEDGEMENTS

The REWIND trial is funded by Eli Lilly and Company.

Conflict of interest

H. C. G. has received research grant support from Sanofi, Lilly, AstraZeneca and Merck, honoraria for speaking from Sanofi, Novo Nordisk, Boehringer Ingelheim and AstraZeneca, and consulting fees from Sanofi, Lilly, AstraZeneca, Merck, Novo Nordisk, Abbot, Amgen and Boehringer Ingelheim. H. M. C. has received research support and honoraria for advice and speaking from Sanofi Aventis, Regeneron, Eli Lilly, Novartis, Roche, Pfizer, Boehringer Ingelheim and AstraZeneca, and is a shareholder of Roche Pharmaceuticals and Bayer. R. D. has received research grant support from Sanofi and DALCOR, honoraria for speaking from Sanofi, and Boehringer Ingelheim, and consulting fees from Sanofi, AMGEN, Lilly and DALCOR. P. P.'s institution receives fees for some of his research from AstraZeneca, and D. X.'s institution receives fees for some of his research from Duke Clinical Research Institute. M. C. R. has received research grant

support from AstraZeneca, Eli Lilly and NovoNordisk, honoraria for speaking from Sanofi, and consulting fees from AstraZeneca, Elcelyx, Eli Lilly, GlaxoSmithKline, Sanofi, Theracos and Valeritas. L. R. reports research support from Amgen, Bayer, Boehringer Ingelheim, MSD and Novo Nordisk, and consulting fees from Bayer, Boehringer Ingelheim, Lexington, Novo Nordisk and Sanofi-Aventis. M. L. and C. M. A. are employees of Eli Lilly and Company and own stock in the company. A. A. has received research grant support from Pfizer and Merck, honoraria for speaking from Boehringer Ingelheim and Pfizer, and consulting fees from Pfizer and Boehringer Ingelheim. J. B. has received research grant support from Lilly, honoraria for speaking from Amgen, Arbor Labs and Janssen, and consulting fees from Up-to-Date, Novartis and Medtronic. I. C. has received honoraria for lectures and consulting fees from Medtronic, Bayer GlaxoSmithKline, Eli Lilly, Novo Nordisk, Sanofi-Aventis, Novartis and MSD. W. C. has received research grant support from Lilly and has conducted uncompensated consulting with Takeda. E. F. has received honoraria for speaking from Sanofi, MSD, Merck, Novo Nordisk, Eli Lilly, Boehringer Ingelheim, Bioton and AstraZeneca, and consulting fees from Astra Zeneca, Boehringer Ingelheim, Novo-Nordisk and MSD. N. H. has received honoraria for speaking from Sanofi, Lilly, Novo Nordisk, AstraZeneca, MSD, Servier and Mylan, and consulting fees from Sanofi and Lilly. M. H. has received honoraria for lectures from Sanofi, Amgen Novartis, Lilly, Bayer and Abbot, and grants from Sanofi and Novartis. L. A. L. has received research grant support from Astra Zeneca, Boehringer Ingelheim, Eli Lilly, GSK, Janssen, Merck, Novo Nordisk and Sanofi, honoraria for speaking from Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk and Sanofi, and consulting fees from Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, Sanofi, Servier and Takeda. P. L.-J. has received honoraria for speaking from Sanofi, Boehringer Ingelheim and Astra Zeneca. E. M. has received honoraria for speaking from Sanofi and Novo Nordisk. V. P. has received consulting fees from Merck, Novo Nordisk and Boehringer Ingelheim. P. J. R. has received honoraria and consulting fees from Roche and Medscheme. J. S. has received research support from Boehringer Ingelheim, Novartis and Mylan Pharmaceuticals and has received speaker and consulting fees from Astra Zeneca, MSD, Novo Nordisk, Sanofi, Mylan, Eli Lilly and Sigma Pharmaceuticals. W. S. has received honoraria for speaking from Sanofi, Novo Nordisk, Boehringer Ingelheim and AstraZeneca, and consulting fees from MSD, Sanofi, Lilly, Novo Nordisk and Boehringer Ingelheim. G. R. D., J. P., N. C., S. H., P. J., M. K., F. L., N. P. and T. T.-K. have no competing interests.

REFERENCES

1. Sarwar N, Gao P, Seshasai SR, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet*. 2010;375:2215–2222.
2. Gerstein HC. Diabetes: dysglycaemia as a cause of cardiovascular outcomes. *Nat Rev Endocrinol*. 2015;11:508–510.
3. Gerstein HC, Werstuck GH. Dysglycaemia, vasculopenia, and the chronic consequences of diabetes. *Lancet Diabetes Endocrinol*. 2013;1:71–78.
4. American Diabetes Association. 9. Cardiovascular disease and risk management. *Diabetes Care*. 2017;40:S75–S87.
5. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet*. 2004;364:685–696.
6. Heart Outcome Prevention Evaluation (HOPE) Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO HOPE substudy. *Lancet*. 2000;255:253–259.
7. Yusuf S, Teo KK, Pogue J, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008;358:1547–1559.
8. Patel A, Macmahon S, Chalmers J, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet*. 2007;370:829–840.
9. Holman RR, Paul SK, Bethel MA, Neil HA, Matthews DR. Long-term follow-up after tight control of blood pressure in type 2 diabetes. *N Engl J Med*. 2008;359:1565–1576.
10. Estruch R, Ros E, Salas-Salvado J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med*. 2013;368:1279–1290.
11. Wing RR, Bolin P, Brancati FL, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med*. 2013;369:145–154.
12. Turnbull FM, Abraira C, Anderson RJ, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia*. 2009;52:2288–2298.
13. Gerstein HC, Miller ME, Ismail-Beigi F, et al. Effects of intensive glycaemic control on ischaemic heart disease: analysis of data from the randomised, controlled ACCORD trial. *Lancet*. 2014;384:1936–1941.
14. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008;359:1577–1589.
15. Hayward RA, Reaven PD, Wiitala WL, et al. Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2015;372:2197–2206.
16. Group AS. Nine-year effects of 3.7 years of intensive glycemic control on cardiovascular outcomes. *Diabetes Care*. 2016;39:701–708.
17. Frye RL, August P, Brooks MM, et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med*. 2009;360:2503–2515.
18. Dormandy J, Charbonnel B, Eckland DJA, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet*. 2005;366:1279–1289.
19. Gerstein HC, Bosch J, Dagenais GR, et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med*. 2012;367:319–328.
20. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med*. 2013;369:1317–1326.
21. White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med*. 2013;369:1327–1335.
22. Green JB, Bethel MA, Armstrong PW, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2015;373:232–242.
23. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117–2128.
24. Ussher JR, Drucker DJ. Cardiovascular biology of the incretin system. *Endocr Rev*. 2012;33:187–215.
25. Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. *Nat Rev Endocrinol*. 2012;8:728–742.
26. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med*. 2015;373:2247–2257.
27. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375(19):1834–1844.
28. Sanford M. Dulaglutide: first global approval. *Drugs*. 2014;74:2097–2103.

29. Jendle J, Grunberger G, Blevins T, Giorgino F, Hietpas RT, Botros FT. Efficacy and safety of dulaglutide in the treatment of type 2 diabetes: a comprehensive review of the dulaglutide clinical data focusing on the AWARD phase 3 clinical trial program. *Diabetes Metab Res Rev*. 2016;32:776–790.
30. Ferdinand KC, Botros FT, Atisso CM, Sager PT. Cardiovascular safety for once-weekly dulaglutide in type 2 diabetes: a pre-specified meta-analysis of prospectively adjudicated cardiovascular events. *Cardiovasc Diabetol*. 2016;15:38.
31. Task Force on Diabetes, Pre-diabetes, and Cardiovascular Diseases of the European Society of Cardiology (ESC), European Association for the Study of Diabetes (EASD), Rydén L, et al. ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD – summary. *Diab Vasc Dis Res*. 2014;11:133–173.
32. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, Stone JA, Fitchett D, Grover S, Lewanczuk R, Lin P. Vascular protection in people with diabetes. *Can J Diabetes*. 2013;37-(suppl 1):S100–S104.
33. Bretz F, Posch M, Glimm E, Klinglmueller F, Maurer W, Rohmeyer K. Graphical approaches for multiple comparison procedures using weighted Bonferroni, Simes, or parametric tests. *Biom J*. 2011;53:894–913.
34. Bretz F, Maurer W, Brannath W, Posch M. A graphical approach to sequentially rejective multiple test procedures. *Stat Med*. 2009;28:586–604.
35. Alosh M, Bretz F, Huque M. Advanced multiplicity adjustment methods in clinical trials. *Stat Med*. 2014;33:693–713.
36. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375:311–322.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Gerstein HC, Colhoun HM, Dagenais GR, et al. Design and baseline characteristics of participants in the Researching cardiovascular Events with a Weekly INcretin in Diabetes (REWIND) trial on the cardiovascular effects of dulaglutide. *Diabetes Obes Metab*. 2018;20:42–49. https://doi.org/10.1111/dom.13028