Design and Baseline Characteristics of Participants in the Researching cardiovascular Events with a Weekly INcretin in Diabetes (REWIND) Trial of Dulaglutide's Cardiovascular Effects

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Abstract

Background: Dulaglutide, a synthetic once-weekly, injectable human glucagon-like peptide 1 (GLP1) analogue lowers blood glucose, body weight, appetite, and blood pressure. Its effect on cardiovascular outcomes is unknown.

Methods: People with type 2 diabetes, aged 50 or older, a HbA1c ≤9.5%, and either a previous cardiovascular (CV) event, evidence of CV disease or ≥ 2 CV risk factors were randomly allocated to a weekly subcutaneous injection of either dulaglutide (1.5 mg) or placebo and followed within the 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 MI or nonfatal 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.

Results: Recruitment of 9901 participants (mean age 66, 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.

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

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 dysglycemia[2], obesity, dyslipidemia, hypertension, and endothelial damage or dysfunction[3,4]. Such abnormalities have provided the basis for an array of randomized, controlled trials of 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 the 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 due to an effect on ischemic 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 DPP4 inhibitors[20-22] have a neutral effect on cardiovascular outcomes; and one SGLT2 inhibitor, empagliflozin, reduces cardiovascular and total mortality as well as heart failure hospitalization[23].

Glucagon-like Peptide 1 (GLP1) receptor agonists are analogues of natural GLP1, 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]. Biologic effects of this hormone on the circulatory system suggest that it may also have salutary cardiovascular effects. Because natural GLP1 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 hypoglycemia, modestly lower blood pressure, increase heart rate by 2-4 beats per minute, and promote modest weight loss[24].

The effects of some of these agents on cardiovascular outcomes have also been reported. Thus, once daily lixisenatide had a neutral effect on cardiovascular outcomes following a diagnosis of acute coronary syndrome in 6068 people of mean age 60 years whose mean baseline 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 of mean age 64 years whose mean baseline HbA1c was 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 of mean age 65 years whose mean baseline HbA1c was 8.7% and who were followed for a median of 2.1 years[28].

Dulaglutide is a synthetic analogue of human GLP1 that structurally comprises 2 GLP1 receptor agonist molecules that are covalently linked to 1 IgG4 heavy chain by a small peptide linker. It has pharmacologic half-life of 5 days, which allows it to be administered as a weekly subcutaneous injection[29]. 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[30]. A meta-analysis of randomized controlled trials comprising 6010 individuals with diabetes followed for a median of approximately one year reported a neutral effect on the first occurrence of nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, or cardiovascular death[31]. When

given alone the drug does not cause hypoglycemia. However, like other GLP1 receptor agonists, it can cause nausea and diarrhea in up to 10% of individuals. Dulaglutide's effects on glucose, blood pressure, and weight[29], together with evidence that GLP1 receptors are expressed in the heart and that GLP1 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.

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 approximately 2% per year. Briefly, men and women with previous or newly detected diabetes whose HbA1c was ≤9.5%, and who were on 0-2 classes of oral glucose lowering drugs, with or without basal insulin, were recruited. People aged 50-54 years old had to have previous cardiovascular disease, those aged 55-59 had to have either previous cardiovascular disease or evidence of other vascular or renal disease, and those aged 60 and over were eligible if they had previous cardiovascular disease, other vascular or renal disease, or at least two other cardiovascular risk factors. Candidates with an estimated glomerular filtration rate (eGFR) <15 ml/min/1.73m^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 3-6 months for the occurrence of cardiovascular and other serious health outcomes. At the time of run-in any participant taking a GLP1 receptor agonist or DPP4 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 GLP1 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[4,32,33].

The primary cardiovascular outcome for the REWIND trial is the first occurrence of the composite of either cardiovascular death or non-fatal MI or nonfatal 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 hypoglycemia, 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 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.

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 1 error of 5%. These assumptions indicated that recruitment of 9,600 patients would result in a total of 1,200 participants with at least 1 primary cardiovascular outcome over a maximum follow-up period of 8 years, and will provide 90% power to detect a hazard ratio of 0.82 for cardiovascular events. Follow-up will end after 1,200 participants have had a primary cardiovascular outcome confirmed by adjudication.

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 analyzed using

Cox proportional hazards models with the only independent variable being allocation to dulaglutide versus 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 analyzed in a predetermined order defined by a graphical approach to control the overall type I error[34-36]. If the null hypothesis of no effect is rejected for the primary outcome, the graphical testing approach allocates the alpha parsimoniously for each secondary outcome. A detailed description of the graphical approaches is provided in the Appendix.

All sub-group analyses will be considered exploratory and will be conducted only for outcomes where the event number is at least 50. Sub-groups to be examined include gender; age below versus at or above the median; duration of diabetes <5 years, 5-9.9 years and 10 years or more; body mass index below versus at or above the median; HbA1c below versus 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 sub-group analyses, an interaction P-value of <0.1 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 (IDMC) 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 approximately 61% of the primary, adjudication-confirmed composite endpoints have occurred. This analysis was done using an O'Brien-Fleming alpha spending function to control the overall 5% alpha. Nobody other than the members of the IDMC and its 2 unblinded statisticians have access to any accruing data according to allocated group.

Results

Of 12137 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 a personal decision (25%). The first participant was randomized in August 2011 and recruitment ended one 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 body mass index was 32 kg/m^2 and 31% had a history of cardiovascular disease (defined as a history of myocardial infarction, ischemic stroke, revascularization, hospitalization for unstable angina with concordant new ischemic 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% were taking insulin, 81% were taking metformin, 57% were on a sulfonylurea, and the mean baseline HbA1c was 7.3%. An ACE inhibitor or angiotensin receptor blocker was used by 81%, 45% were taking a beta 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.

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 programs throughout the world. Its focus on the "typical" middle aged patient with type 2 diabetes distinguishes it from the other GLP1 receptor agonist cardiovascular outcomes trials reported to date[26-28] that are summarized in Table 5, which have focused on high-risk patients either following an acute coronary syndrome 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 1,200 first primary outcomes during a fairly long follow-up period of 7-8 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.

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Dualities of Interest

HCG 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. HMC has received research support and honoraria for advice and speaking from Sanofi Aventis, Regeneron, Eli Lilly, Novartis, Roche, Pfizer, Boehringer Ingelheim and AstraZeneca; and she is a shareholder of Roche Pharmaceuticals and Bayer. RD 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. PP's institution receives fees for some of his research from AstraZeneca, and DX's institution receives fees for some of his research from Duke Clinical Research Institute. MCR 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. LR 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. ML and CMA are employees of Eli Lilly and Company and own stock in the company. AA has received research grant support from Pfizer, Merck; honoraria for speaking from Boehringer Ingelheim, and Pfizer; and consulting fees from Pfizer and Boehringer Ingelheim. JB 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. IC has received honoraria for lectures and consulting fees from Medtronic, Bayer, GlaxoSmithKline, Eli Lilly, Novo Nordisk, Sanofi-Aventis, Novartis and MSD. WC has received research grant support from Lilly and has conducted uncompensated consulting with Takeda. EF has received honoraria for speaking from Sanofi, MSD, Merck, Novo Nordisk, Eli Lilly, Boehringer lingelheim, Bioton and AstraZeneca, and consulting fees from Astra Zeneca, Boehringer Ingelheim, Novo-Nordisk, and MSD. NH has received honoraria for speaking from Sanofi, Lilly, Novo Nordisk, AstraZeneca, MSD, Servier, and Mylan; and consulting fees from Sanofi and Lilly. MH has received honoraria for lectures from Sanofi, Amgen Novartis, Lilly, Bayer, and Abbot and grants from Sanofi and Novartis. LAL 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.PL-J has received honoraria for speaking from Sanofi, Boehringer Ingelheim and Astra Zeneca. EM has received honoraria for speaking from Sanofi and Novo Nordisk. VP has received consulting fees from Merck, Novo Nordisk, and Boehringer Ingelheim. PJR has received honoraria and consulting fees from Roche and Medscheme. JS 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. WS 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. GRD, JP, NC, SH, PJ, MK, FL, NP, and TT-K have no competing interests.

Table 1: Selection Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Previous/new type 2 diabetes with HbA1c ≤ 9.5% • Stable dose of 0, 1 or 2 oral glucose lowering drugs +/- basal insulin for ≥ 3 months • Body mass index ≥ 23 kg/m^2 • If age ≥ 50, at least 1 of: prior MI; prior ischemic stroke; coronary revascularization ≥ 2 years earlier; carotid, or peripheral revascularization ≥ 2 months earlier; unstable angina hospitalization; image proven myocardial ischemia; or percutaneous coronary intervention • If age ≥ 55, any of the above or at least 1 of: documented myocardial ischemia by stress test or imaging; >50% coronary, carotid, or lower extremity artery stenosis; ankle-brachial index <0.9; eGFR persistently <60 mL/minute/1.73m^2; hypertension with LV hypertrophy; or persistent albuminuria • If age ≥ 60, any of the above or at least 2 of: any tobacco use; use of lipid modifying therapy or a documented untreated LDL ≥3.4 mmol/L (130 mg/dL) within the past 6 months; HDL-C <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 SBP ≥140 mm Hg or DBP ≥95 mmHg; or waist-to-hip ratio >1.0 (men) and >0.8 (women) • Run-in adherence to study drug = 100%	• Uncontrolled diabetes • Severe hypoglycemia in prior year • Coronary or cerebrovascular event in prior 2 months or plans to revascularize • eGFR <15 ml/min/1.73 m^2 or on dialysis • Gastric bypass or emptying abnormality • Prior pancreatitis/concordant symptoms • Liver disease or ALT ≥3.0 X normal • 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 GLP1 RA or DPP4 inhibitor or weight loss drug • Cancer within prior 5 years • Pregnant or not using reliable birth control • Life expectancy < 1 year

eGFR – estimated glomerular filtration rate; MEN – multiple endocrine neoplasia

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/Hip Ratio	• Serious GI events
• Heart failure hospitalization or urgent visit	• Expanded Composite CV Outcome: nonfatal MI, nonfatal stroke, unstable angina, hospitalization or cardiovascular death	• Cancers: pancreatic, medullary thyroid, other thyroid, other (excluding non-melanoma skin cancers)
• Nonfatal MI	• Revascularization (coronary, carotid, or peripheral)	• Severe hypoglycemia
• Nonfatal stroke	• Any hospitalization	• Immune reactions
• CV death	• Any fracture	• Serious hepatic events
• Death	• Cholelithiasis	• Serious renal events
	• Erectile dysfunction (men)	• Supraventricular arrhythmias and CV conduction disorders
	• Cognitive decline	• Drug discontinuation

The primary outcome for REWIND is the first occurrence of either a nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. VEGF - vascular endothelial growth factor; eGFR-estimated glomerular filtration rate; MI -Myocardial infarction; GI – gastrointestinal; CV - cardiovascular

Table 3: Baseline Clinical Characteristics of 9901 Randomized Participants	
Characteristic	**All Participants**
Age (years) – mean (SD)	66.2 (6.5)
Females – N (%)	4589 (46.3)
Geography	
USA and Canada – N (%)	2071 (20.9)
Mexico and South America – N (%)	3021 (30.5)
Europe, Russia and South Africa – N (%)	4339 (43.8)
Asia: Taiwan and Korea – N (%)	148 (1.5)
Pacific: Australia and New Zealand – N (%)	322 (3.3)
Prior cardiovascular disease ($\geq$ 1 of the following 6) – N (%)	3111 (31.4)
Prior myocardial infarction – N (%)	1600 (16.2)
Prior ischemic stroke – N (%)	526 (5.3)
Prior unstable angina – N (%)	587 (5.9)
Prior revascularization[a]	1787 (18.1)
Prior hospitalization for ischemia-related events[b] – N (%)	1193 (12.1)
Prior documented myocardial ischemia – N (%)	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 (SD)	10.0 (7.2)
Weight (kg) – mean (SD)	88.7 (18.5)
Body Mass Index (kg/m^2) – mean (SD)	32.3 (5.7)
Blood pressure (mm Hg) – mean (SD)	137.2 (16.8)/78.5 (9.8)
Pulse (beats/min) – mean (SD)	71.5 (10.9)
Male Waist/Hip – mean (SD)	110.6 (13.1)/108.4 (11.2)
Female Waist/Hip – mean (SD)	106.7 (13.1)/113.3 (13.7)
HbA1c (%)– mean (SD)	7.3 (1.1)
Cholesterol (mmol/L) – mean (SD)	4.52 (1.16)
LDL cholesterol (mmol/L) – mean (SD)	2.56 (0.98)
HDL cholesterol (mmol/L) – mean (SD)	1.18 (0.34)
Triglycerides (mmol/L) – median (IQR)	1.60 (1.17, 2.22)
eGFR ($ml/min/1.73m^2$)[c] – mean (SD)	77.6 (24.1)
eGFR <60 – N (%)	2199 (22.2)
Albumin/creatinine (mg/mmol) – median (IQR)	1.94 (0.75, 8.02)
Macro or microalbuminuria[d] – N (%)	3491 (35.3)

SD – standard deviation; IQR – interquartile range; [a] coronary, carotid or peripheral; [b]unstable angina or myocardial ischemia on imaging, or need for percutaneous coronary intervention; [c]estimated glomerular filtration rate; [d]albumin/creatinine $\geq$ 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[a]	4909 (49.6)
Only 1 oral agent	4926 (49.8)	ARB[b]	3366 (34.0)
Only 2 oral agents	3894 (39.3)	ACE-inhibitor or ARB	8054 (81.4)
Any insulin	2398 (24.2)	Aldosterone[c] 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)	Beta blocker	4502 (45.5)
DPP4[c] 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)	PPI[d]	1673 (16.9)

Values shown in the cells represent counts and percentage of all randomized; [a]angiotensin converting enzyme; [b]angiotensin receptor blocker; [c]dipeptidyl peptidase 4;[d]proton pump inhibitor

Table 5: Key Characteristics of Completed Trials and REWIND

	ELIXA	LEADER	SUSTAIN 6	REWIND
Drug tested	Lisixenatide	Liraglutide	Semaglutide	Dulaglutide
Dose	20 ug/day	1.8 mg/day	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 or unstable angina	MACE	MACE	MACE

MACE –Nonfatal myocardial infarction, nonfatal stroke or cardiovascular death; CVD – cardiovascular disease; BMI – body mass index

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