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DIABETES AND CARDIOVASCULAR DISEASE (ND WONG, SECTION EDITOR)

Glucagon-Like Peptide-1 Receptor Agonists and Cardiovascular Risk Reduction in Type 2 Diabetes Mellitus: Is It a Class Effect?

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Abstract

Purpose of Review Mimetics and analogs that extend the half-life of native glucagon-like peptide-1 (GLP-1), i.e., glucagon-like peptide-1 receptor agonists (GLP-1 RAs), at therapeutic doses, are indicated as adjuncts to diet and exercise, to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). In patients with T2DM, GLP-1 RAs not only affect improvements in impaired beta cell and alpha cell function, suppress appetite, and induce weight loss but also possess multiple cardiovascular protective properties that potentially have a beneficial impact on atherosclerotic cardiovascular disease (ASCVD) morbidity and mortality.

Recent Findings Required to demonstrate CV safety, compared to standard-of-care antidiabetic therapies, GLP-1 RAs have revealed statistically significant non-inferiority ($p < 0.001$), among CV outcome trials (CVOTs) thus far completed. Once-daily liraglutide and once-weekly semaglutide demonstrated significant superiority ($p = 0.01$ and $p = 0.02$, respectively), reducing 3-point composite major adverse cardiovascular events (MACE) in extreme risk secondary prevention adults with T2DM. Once-weekly exenatide demonstrated only a non-significant ($p = 0.06$) favorable trend for CV superiority, possibly due to in-trial mishaps, including placebo drop-ins with other CV protective medications. The short half-life lixisenatide was neutral ($p = 0.81$) in reducing MACE, most likely due to ineffective once-daily dosing. Structural differences among GLP-1 mimetics and analogs may explain potency differences in both A1C reduction and weight loss that may parallel important cardiovascular protective properties of the GLP-1 RA class.

Summary Significant superiority in reducing 3-point composite MACE in adults with T2DM with GLP-1 RAs has been limited to liraglutide and semaglutide. Careful attention to within-trial drop-in of cardioprotective antidiabetic agents assuring equipoise between placebo and investigational product groups might demonstrate significant MACE risk reduction with once-weekly exenatide. Maintenance of 24-h circulating levels, by an alternative administration method, may resurrect lixisenatide as a cardioprotective agent. Before a GLP-1 RA bioequivalence "class effect" claim for composite MACE risk reduction superiority can be fully discussed, we are obliged to wait for the pending results of CVOTs with other GLP-1 RAs, particularly albiglutide and dulaglutide, where steric hindrance may potentially inhibit full mimicry of pharmacologic GLP-1.

Keywords Type 2 diabetes mellitus (T2DM) · Cardiovascular disease · Glucagon-like peptide-1 · Receptor agonists (GLP-1 RAs) · LEADER · SUSTAIN-6 · EXSCEL · ELIXIR · HARMONY · REWIND

Abbreviations

ARR	Absolute risk reduction
BMI	Body mass index
CKD	Chronic kidney disease
CVD	Cardiovascular disease
CVOTs	CV (safety) outcome trials

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DPP-4	Dipeptidyl peptidase-4
FDA	Food and Drug Administration
GLP-1 RAs	Glucagon-like peptide-1 receptor agonists
HR	Hazard ratio
MACE	Major adverse cardiovascular events
NF-MI	Non-fatal myocardial infarction
NNH	Number needed to harm
NNT	Number needed to treat
PEP	Primary endpoint
RCTs	Randomized clinical trials
RRR	Relative risk reduction
T2DM	Type 2 diabetes mellitus
UA	Unstable angina

Acronyms

ELIXA	Evaluation of Lixisenatide in Acute Coronary Syndrome
EXSCEL	Effect of Once Weekly Exenatide On Cardiovascular Outcome in Type 2 Diabetes'
FREEDOM-CVO	Cardiovascular outcome safety study of ITCA 650, an injection-free exenatide osmotic mini-pump delivery system
HARMONY	Trial of the effect of albiglutide on major adverse cardiovascular (CV) events in patients with T2DM and established CV disease
LEADER	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results
REWIND	Researching cardiovascular Events with a Weekly Incretin in Diabetes
SUSTAIN-6	Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes

Introduction

In patients with type 2 diabetes mellitus (T2DM), atherosclerotic cardiovascular (CV) disease (ASCVD), the most common of diabetes-related complications, is caused by multiple risk factors, requiring decades to develop, even before a dysglycemia diagnosis, and is the leading cause of morbidity, multimorbidity, and mortality [1]. Standard-of-care therapeutic approaches are directed at causal factors, and the earlier in life these risks are recognized, and managed, the more likely success in primary prevention of complications is realized. Clinical observations and randomized clinical trials (RCTs) have demonstrated that once complications have occurred, secondary prevention requires vigilance to even more aggressive therapies and even when known risk factors appear optimized, considerable residual risk for progression to multimorbidity and mortality exists [2, 3].

The causal association of hyperglycemia with microvascular and neuropathic complications (i.e., retinopathy, nephropathy (CKD), neuropathy) as well as RCTs has demonstrated that reducing hyperglycemia reduces their onset and progression [4, 5]. An association of hyperglycemia with ASCVD events has been demonstrated in multiple epidemiological studies and a multifactorial role of hyperglycemia in unfavorably modifying the atherosclerotic environment has been recognized for decades [6–8]. However, historically, there has been a failure within RCTs ≤ 10-year duration, to demonstrate that glycemic control reduces ASCVD events significantly, possibly due to an ethically driven narrow between-group A1c difference (≤ 1.8%) of these previous trial designs. Fortunately, however, post hoc analysis across a 6 to 10% A1C range does support a linear 14% reduction of ASCVD events for each 1% reduction of A1C [9] and, furthermore, legacy or memory effects have been noted [10], suggesting early treatment can have long-term positive effects. Glycemic control in the face of progressive deterioration of beta cell function in T2DM is one of several important challenges of clinical management in preventive cardiodiabetology and requires an understanding of the multiple pathophysiological mechanisms and contributors to the hyperglycemic state [11].

To establish their safety, as well as efficacy, the US Food and Drug Administration in 2008 issued new industry guidelines mandating RCTs to assess potential major adverse cardiovascular event (MACE) risk among new therapies to treat hyperglycemia in T2DM [12]. Such RCTs permit assessment of a drug's potential benefits or harms and assist in the avoidance of dubious claims or conclusions from unrandomized CV studies and analyses. A 3-point MACE composite of CV death, non-fatal myocardial infarction (NF-MI), and NF-stroke has been the primary endpoint of these randomized cardiovascular outcome trials (CVOTs); some primary endpoints include additional components. Although designed as non-inferiority studies, some study designs prespecify a test for superiority if non-inferiority criteria are met. Recognized limitations of these recent requirements include the utilization of event-driven "composite" endpoints to shorten these expensive RCTs, in large populations at "extreme risk," i.e., patients with T2DM and prior recognized cardiovascular disease (CVD) that are already ethically standard-of-care-managed aggressively to reduce secondary ASCVD events.

The Role of Glucagon-Like Peptide-1 Receptor Agonists in the Management of Hyperglycemia and Potential Cardiovascular Protection

A significant advance in diabetes management appeared with discoveries related to the incretin system for glucose homeostasis, a defective pathway in T2DM described as incretin resistance [13•, 14•]. Glucagon-like peptide-1 (GLP-1), the

pluripotent incretin, is induced postprandially and secreted from both the neurons in the caudal regions of the nucleus of the solitary tract (NTS) and mostly the enteroendocrine (intestinal epithelial) L-cells located in the distal jejunum, ileum, and colon. The NTS releases GLP-1 into the hypothalamus to control food intake [15]. GLP-1 secreted by L-cells is rapidly inactivated by the ubiquitous enzyme dipeptidyl peptidase-4 (DPP-4). The primary actions of native GLP-1 on beta cell stimulation of insulin synthesis and secretion and alpha cell suppression of glucagon are glucose-dependent, with secondary actions including insulin-stimulated peripheral glucose utilization and reduction of glucagon-stimulated hepatic glucose production [16]. The benefits of continuous administration of pharmacologic doses of native GLP-1 intravenously or subcutaneously have been elucidated [13•, 14•]. Long-term utilization of pharmacological GLP-1 may also preserve the morphology and biochemical pathways of beta cells, including reduced apoptotic cell death [17]. Additional actions of GLP-1 on the hypothalamic appetite center and gastric emptying reduce postprandial glucose excursions and result in weight loss [13•, 14•, 15].

Synthesized to resist DPP-4 inactivation and considerably extend the GLP-1 half-life, several GLP-1 mimetics and analogs, as GLP-1 receptor agonists (GLP-1 RAs), when administered subcutaneously, mimic the primary and secondary actions of continuously delivered native GLP-1 [16] including its extremely important glucose-dependent actions. Thus, while pharmacologic GLP-1 RAs reduce A1c, hypoglycemic risk can be avoided when utilized as monotherapy or in combination with other "antihyperglycemic" agents, i.e., agents without hypoglycemic risk, but if utilized with "hypoglycemic" agents, i.e., insulin or sulfonylureas, careful attention to hypoglycemic risk is still required.

Cardiovascular GLP-1 Effects Beyond Glucose

In addition to weight loss, other non-glucose-lowering GLP-1 effects on the cardiovascular system include small increases in natriuresis, small reductions in blood pressure, reduced inflammation, reduced ischemic injury, increased LV function and heart rate, improved endothelial function, increased vasodilatation, increased plaque stability, increased blood flow, decreased smooth muscle proliferation, and reduced platelet aggregation [13•, 14•]. GLP-1 RA has also been demonstrated to significantly reduce postprandial hyperlipidemia (i.e., hypertriglyceridemia) [18, 19], chylomicrons, liver fat, VLDL, remnant particle cholesterol, and apo CIII [20]. Hypertriglyceridemia and triglyceride-rich lipoprotein cholesterol is recognized as an independent causal risk factor for atherosclerotic cardiovascular disease (ASCVD) [21] and are particularly prevalent in states of insulin resistance, i.e., T2DM [18–21]. Thus, GLP-1 RA may have cumulative long-term effects on the reduction of ASCVD.

Approved GLP-1 RAs

Six GLP-1 RAs have been studied as subcutaneous injection therapy, administered twice daily (exenatide), once daily (liraglutide, lixisenatide), and once weekly (exenatide extended-release, albiglutide, dulaglutide, semaglutide) formulations. At therapeutic doses, the GLP-1 RAs are Food and Drug Administration (FDA) indicated for treatment of hyperglycemia in type 2 diabetes. A once-daily oral formulation of semaglutide is currently investigational. All GLP-1 RAs, at their therapeutic glycemia-lowering indicated doses, have been shown to cause significant weight loss of varying degrees but are not FDA-approved for weight loss. Only at a relatively higher dose, liraglutide, under a different brand name, has been FDA-approved for the treatment of obesity. A once-weekly high-dose semaglutide injection is investigational for a weight loss indication. The most common adverse effects of GLP-1 RAs are varying degrees of gastrointestinal disturbances, i.e., nausea and rarely vomiting.

Effects of GLP-1 RA in CV Outcome Trials Assessing CV Safety

Four of the six marketed GLP-1 RAs, to date, have completed CVOTs among extreme risk secondary prevention patients with T2DM and demonstrated the minimum non-inferiority ($p = 0.001$), relative to standard care, with respect to CV safety mandated by the FDA [12]. Only two of the four completed large CVOTs (Table 1) demonstrated CV efficacy superiority, suggesting a lack of bioequivalence among all GLP-1 RAs.

LEADER

The GLP-1 RA, liraglutide, has FDA-approved indications as an adjunct to diet and exercise to improve glycemic control in adults with T2DM and to reduce the risk of MACE in adults with T2DM and established CVD (https://www.novo-pi.com/victoza.pdf). This latter indication was based on the results of the 3.8-year duration "Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results" (LEADER) multi-national, multicenter, placebo-controlled, double-blind clinical trial in which 9340 patients with inadequately controlled T2DM and atherosclerotic CVD (81%) were randomized to liraglutide 1.8 mg or placebo used concomitantly with background standard of care treatments for T2DM [22•]. The primary outcome was the time to first occurrence of a 3-point MACE composite (death from CV causes, non-fatal myocardial infarction (MI), or non-fatal stroke). The primary outcome occurred in 13% of the liraglutide group compared to 14.9% of the placebo group for a 13% relative risk reduction (RRR) or hazard ratio (HR) of 0.87 and 95% confidence interval (CI) 0.78 to 0.97. The p value for non-inferiority was < 0.001 and for superiority was

Table 1 Selected prespecified outcomes and data from completed and published cardiovascular outcome trials (CVOTs) with glucagon-like peptide-1 receptor agonists (GLP-1 RAs) among patients with type 2 diabetes, the majority of whom had history of prior CVD

Trial and study drug characteristics				
Trial Name	LEADER	SUSTAIN-6	EXSCEL	ELIXA
Study drug	Liraglutide Once-daily	Semaglutide Once-weekly	Exenatide extended-release Once-weekly	Lixisenatide Once-daily
Half-life	12 h	1 week	Continuous	2–4 h
Baseline trial characteristics				
No. of patients randomized	9,340	3,297	14,572	6,068
Age	64.3	64	62	60
Duration of diabetes	12.7	13.9	12	9.3
Baseline CVD events history	81% and stable	83% and stable	73% and stable	100%, ACS
Baseline HbA1C (%)	8.7	8.7	8.0	7.7
Baseline BMI (kg/m^2)	32.5	32.8	30.9	30.1
Trial completion				
Median follow-up time (years)	3.8	2.1	3.2	2.1
Median treatment exposure duration (years)	3.5	2.1	2.4	1.89
Patients completed the study (%)	97	99.2	96.2	96.3
Composite primary endpoint cardiovascular event results				
Primary composite outcome (stroke, MI, or CV death) (ELIXA add UA)	Placebo 14.9% vs. liraglutide 13.0%	Placebo 8.9% vs. semaglutide 6.6%	Placebo 12.2% vs. exenatide 11.4%	Placebo 13.2% vs. lixisenatide 13.4%
Placebo vs. Tx (no. events/100 patient-years)	3.9 vs. 3.4	4.44 vs. 3.24	4.0 vs. 3.7	6.3 vs. 6.4
Primary endpoint (PEP) outcome—MACE change [RRR, HR; p for non-inferiority; p for superiority	− 13%; HR 0.87 (0.78–0.97); $p < 0.001$ for non-inferiority; $p = 0.01$ for superiority	− 16%; HR 0.74 (0.58–0.95) $p < 0.001$ for non-inferiority; $p = 0.02$ for superiority	− 9%; HR 0.91 (0.83–1.00); $p < 0.001$ for non-inferiority; $p = 0.06$ for superiority	+ 2%; HR 1.02 (0.89–1.17); $p < 0.001$ for non-inferiority; $p = 0.81$ for inferiority
PEP: ARR; NNT	1.9%; 53	2.3%; 43	0.8%; 125	0.2%; NNH 500
Cardiovascular event results of components of composites				
RRR: death from CV cause component	22%; HR 0.78; (0.66 to 0.93) $p = 0.007$ 4.7% vs. 6.0%; ARR 1.3%; NNT 77	2%, HR 0.98 (0.65–1.48) $p = 0.92$ (NS)	12%; HR 0.88 (0.76–1.02) Not significant	2%; HR 0.98 (0.78–1.22) $p = 0.85$
RRR: component non-fatal MI	12%, HR 0.88 (0.75 to 1.03 $p = 0.11$ (NS); 6.0% vs. 6.8%	16%, HR 0.74 (0.51–1.08) $p = 0.12$ (NS)	NR 0%	− 3%, HR 1.03 (0.87–1.22) $p = 0.71$
RRR: component non-fatal stroke	11%, HR 0.89 (0.72 to 1.11) $p = 0.30$ (NS) 3.4 vs. 3.8%	39% HR 0.61 (0.38–0.99) $p = 0.044$	Reduction not significant	− 12%, HR 1.12 (0.79–1.58) $p = 0.54$
Fatal or non-fatal myocardial infarction	NR	26%; HR 0.74 (0.51–1.08)	3%; HR 0.97 (0.85–1.10)	NR
Death from any cause	15% RRR, $p = 0.02$	+ 5% HR 1.05 (0.74–1.50) $p = 0.79$	14%; HR 0.86 (0.77–0.97) 13%	6%, HR 0.94 (0.78–1.13) $p = 0.05$

Table 1 (continued)

In-trial changes in cardiovascular risks					
Weight change by study end, kg	− 2.3	− 2.9 for 0.5 mg − 4.3 for 1.0 mg	− 1.27	− 0.7	
A1C change	− 0.4%	− 0.7% for 0.5 mg − 1.0% for 1.0 mg	− 0.7%	− 0.4%	
BP-systolic change, mmHg	− 1.2	− 1.3 for 0.5 mg − 2.6 for 1.0 mg	− 1.57	− 0.8	
BP-diastolic change, mmHg	+0.6	+ 0.04 for 0.5 mg + 0.14 for 1.0 mg	+ 0.25	NR	
Heart rate, BPM	+3	2.0 for 0.5 mg 2.5 for 1.0 mg	+ 2.51	+ 0.4	
Triglyceride change, mg/dL	NR	− 4.9 for 0.5 mg − 11 for 1.0 mg	− 1.8	NR	

BP blood pressure, *NA* not applicable, *NR* not reported, *NS* not significant, *RRR* relative risk reduction

0.01. The 3.8-year absolute risk reduction (ARR) was 1.9% and the number needed to treat (NNT) to prevent the composite primary endpoint was 53. The component of death from CV causes occurred in 4.7% in the liraglutide group compared to 6.0% in the placebo group for a 22% RRR or HR of 0.78 (CI 0.66 to 0.93, $p = 0.007$). The 3.8-year ARR was 1.3% and NNT to prevent CV death was 77.

The rates of the non-fatal MI and non-fatal stroke components of the 3-point MACE were not significantly lower in the liraglutide group than in the placebo group; however, there was a 12% RRR trend for non-fatal MI in the liraglutide group (6%) compared to the placebo group (6.8%; $p = 0.11$) and there was an 11% RRR trend for non-fatal stroke in the liraglutide group (3.4%) compared to the placebo group (3.8%; $p = 0.30$). There was a 15% RRR [1.4% ARR, NNT 71] for death from any cause (CV and non-CV) for the liraglutide group (8.2%) compared to the placebo group (9.6%; $p = 0.02$) and a non-significant ($p = 0.66$; 5%) RRR trend for non-CV death. There was a non-significant ($p = 0.14$; 13%) RRR for hospitalization for heart failure (218; 4.7%) patients in the liraglutide group compared to the placebo group (248; 5.3%). Nephropathy (defined as the new onset of macroalbuminuria or a doubling of the serum creatinine level and an eGFR of ≤ 45 ml/min//1.73 m^2, the need for continuous renal replacement therapy, or death from renal disease) was significantly reduced by 22% ($p = 0.003$). There were minor but significant improvements in A1C (− 0.4%, $p < 0.001$), weight (− 2.3 kg; $p < 0.001$), and SBP (− 1.2 mmHg, $p < 0.001$), and HR was 3 beats per minute.

SUSTAIN-6

Semaglutide has FDA-approved indications as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. The pre-approval "Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes" (SUSTAIN-6) [23•] was prespecified/designed to assess non-inferiority, but not prespecified to assess superiority, of semaglutide as compared with placebo in terms of cardiovascular safety in patients with T2DM. SUSTAIN-6 was a relatively short 2.1-year duration trial, with 3,297 participants, 83% of whom had a history of cardiovascular disease. The primary outcome rate of composite of 3-point MACE occurred in 6.6% of the semaglutide group and 8.9% of the placebo group, for a RRR of 26%, not only demonstrating its prespecified designed, noninferiority safety ($p < 0.001$), but also its superiority ($p = 0.02$) relative to placebo. The non-fatal stroke component showed a significant 39% RRR ($p = 0.04$). The 2.1-year ARR was 2.3% or NNT was 43. Furthermore, the expanded composite outcome that included first occurrence of death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, revascularization (coronary or peripheral), and hospitalization

for unstable angina or heart failure showed a 26% RRR ($p = 0.002$). A composite of all-cause death, non-fatal myocardial infarction, or non-fatal stroke showed a 23% RRR ($p = 0.03$) or ARR 2.2% and NNT = 45. Also new or worsening nephropathy defined by persistent macroalbuminuria, persistent doubling of the serum creatinine level, and a creatinine clearance of less than 45 ml/min/1.73 m^2 body surface area or the need for continuous renal replacement therapy showed a 36% RRR ($p = 0.005$) or ARR 2.3% and NNT 43. Although promising, SUSTAIN-6 was relatively small ($n = 3297$), powered as a non-inferiority study to exclude a pre-approval safety margin of 1.8 set by the FDA and not prespecified to convincingly conclude superiority to warrant seeking a 3-point MACE risk reduction indication. In addition, there was no difference in CV death (− 2%; $p = 0.92$) or death from any cause (+ 5%; $p = 0.79$). Non-fatal MI showed a non-significant 26% RRR trend ($p = 0.12$). Retinopathy complications defined as vitreous hemorrhage, onset of diabetes-related blindness, and the need for treatment with an intravitreal agent or retinal photocoagulation had a relative 76% increase (3.0% for semaglutide vs. 1.8% for placebo, $p = 0.02$) in incidence or number needed to harm (NNH) of 83. There were minor between-group changes favoring the two doses of semaglutide: in weight (kg) [− 2.9 ($p < 0.0001$) for 0.5 mg, − 4.3 ($p < 0.0001$) for 1.0 mg)]; for A1C [− 0.7% ($p < 0.0001$) for 0.5 mg, − 1.0% ($p < 0.0001$) for 1.0 mg)]; for systolic blood pressure in mmHg [(− 1.3 (NS) for 0.5 mg, − 2.6 ($p < 0.001$) for 1.0 mg]; and for triglycerides [(− 3% (NS) for 0.5 mg and − 7% ($p < 0.001$) for 1 mg], respectively.

EXSCEL

In the "Effect of Once Weekly Exenatide On Cardiovascular Outcome in Type 2 Diabetes" (EXSCEL) trial, once-weekly exenatide extended-release in biodegradable polymeric microspheres, was evaluated vs. matching placebo among 14,752 patients with T2D with CVD (10,782, 73%) [24•]. At a median follow-up of 3.2 years, EXSCEL was event-driven requiring 1591 primary composite outcome events defined as the time to the first occurrence of the 3-point MACE (CV death, non-fatal MI, and non-fatal stroke). There were 1744 primary outcome events; the primary outcome percent for the placebo group was 12.2%, while for the exenatide extended-release group 11.4%, for a modest 9% relative risk reduction trend, not statistically significant, with upper end of the narrow confidence interval just touching the line of unity [HR 0.91 (0.83 to 1.00; $p < 0.001$ for non-inferiority and $p = 0.061$ for superiority)]. Although the primary outcome was statistically negative, all-cause mortality occurred in 7.9% of patients in the placebo group and 6.9% in the once-weekly exenatide group for significant 14% RRR (HR 0.86 (0.77–0.97), $p = 0.016$). There were minor but significant improvements in A1C (− 0.53%; $p < 0.001$), weight (− 1.3 kg; $p < 0.001$), and SBP (− 1.6 mmHg; $p < 0.001$), favoring exenatide-extended release.

ELIXA

The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) was a multicenter, randomized, double-blind, placebo-controlled trial designed with adequate statistical power to assess whether once-daily lixisenatide 20 micrograms, in patients ($n = 6068$) with T2DM who had had a recent acute coronary event or who had been hospitalized for unstable angina within the previous 180 days, was not only non-inferior but also superior to placebo, for the primary composite endpoint (CV death, MI, stroke, or hospitalization for unstable angina).

Followed for a median of 2.1 years (25 months) post-ACS [25•], the primary endpoint event occurred in 13.4% of the lixisenatide group and in 13.2% of the placebo group demonstrating non-inferiority of lixisenatide to placebo ($p < 0.001$) but, clearly, not superiority ($p = 0.81$). There was a non-significant 4% RRR in the rate of hospitalization for heart failure and a non-significant 6% RRR in the rate of all-cause death. Lixisenatide was also neutral on CV endpoints in the individual components of the primary composite endpoint. There were minor but significant between-group improvements in A1C (− 0.4%; $p < 0.001$), weight (− 0.7 kg; $p < 0.001$), and systolic BP (− 0.8 mmHg; $p = 0.001$) favoring lixisenatide.

GLP-1 RA CVOTS Pending Publication

FREEDOM-CVO

FREEDOM-CVO Safety Study (NCT01455896) [26] is a global, placebo-controlled, small, pre-approval CV outcomes trial examining the safety of ITCA 650, exenatide, delivered continuously once or twice yearly through a matchstick-sized, miniature osmotic pump that is placed sub-dermally to provide continuous and consistent drug (exenatide) therapy, and the company's proprietary formulation technology, which maintains stability of therapeutic peptides above human body temperature for extended periods of time injection-free GLP-1 therapy that can deliver up to a full year of treatment from a single placement of the osmotic mini-pump at 60 mcg/day vs. placebo in approximately 4000 patients, > 40 years of age, A1c > 6.5%, and history of coronary, cerebrovascular, or peripheral artery disease, on a variety of approved standard of care antidiabetes therapies. The mean treatment duration was very short in duration (1.2 years) and the small target number of 160 (4.0%) event-driven CV events was reached in the fourth quarter of 2015. The study has been completed and met its primary and secondary endpoints by demonstrating FDA-required non-inferiority for pre-approval CV safety.

Since there has been no mention of CV superiority, a larger CVOT of ITCA would be appropriate continuous maintenance delivery is achieved with described technology. Final data has yet to be published.

HARMONY

A preliminary evaluation of the CV safety of albiglutide was afforded by the published meta-analysis of the nine HARMONY program's studies required by the regulatory agencies approval process [27]. In these eight phase 3 studies and one phase 2b study, patients were randomly assigned to albiglutide, or placebo, or active comparators (glimepiride, insulin glargine, insulin lispro, liraglutide, pioglitazone, or sitagliptin). The duration of these studies differed: five lasted up to 3 years, two lasted 1 year, one lasted 32 weeks, and the phase 2b study only 16 weeks. This CV safety population included 5107 patients, of whom 2524 took albiglutide (4870 person-years) and 2583 took comparators (5213 person-years). Low percentages of participants in the clinical development programs had a history of CVD; approximately 5% with prior MI, 1% with unstable angina, 3% with stable angina, 1.8% with stroke, 4.4% with PAD, and the incidence of the primary endpoints for each group were low. The primary endpoint, defined as a composite of first occurrence of composite 4-point MACE (i.e., 3-point MACE (CV death, non-fatal MI, or non-fatal stroke) or hospital admission for unstable angina), occurred in 2.3% patients on albiglutide and 2.2% patients on comparators. Secondary endpoints were components of the composites, as MACE alone, all-cause mortality, silent MI, hospital admission for HF, chest pain, other angina, and subdural or extradural hemorrhage. No significant differences were noted in any of the primary or secondary outcome endpoints. That most of these patients were at the primary prevention level accounts for low MACE incidence rates. In this meta-analysis, the upper bound of the 95% CI for the primary outcome was greater than 1.3, exceeding the key criterion for excluding unacceptable risk and therefore, a dedicated HARMONY Outcomes trial of predominantly secondary CV prevention patients was undertaken to more rigorously assess CV safety.

Harmony Outcomes [28•] is a randomized, double-blind, placebo-controlled, event-driven trial of the effect of once-weekly albiglutide 30 mg, or up to 50 mg, vs. placebo, in patients ($n = 9463$), with baseline mean age 64.1 and 13.8-year duration of T2DM with established CV disease. The percentage of patients with prior coronary artery disease was 70.5%; peripheral arterial disease, 25.0%; stroke, 17.7%; heart failure, 20.2%; and chronic kidney disease, 22.6%. The primary outcome is 3-point MACE (CV death, myocardial infarction, or stroke). Harmony Outcomes (ClinicalTrials.gov number NCT02465515) was recently completed and will provide information critical to our understanding of the GLP-1 RA "class effect" and its results and publication are pending.

REWIND

The Researching cardiovascular Events with a Weekly INcretin in Diabetes (REWIND) [29•] is a global (24 countries) trial to evaluate CV safety and efficacy, of once-weekly dulaglutide. The studied population at baseline were aged ≥ 50 years (mean 66 years old) ($n = 9900$), with mean duration of T2DM of 10 years, mean A1C 7.3%, of whom only 31% had established CVD; thus, a high proportion of patients without CVD, and, therefore, an expected fairly long follow-up period of 7 to 8 years to provide high power to detect a clinically relevant 18% CV event risk reduction. The study started in 2011, and follow-up was prespecified as event-driven based on a 12% accrual primary outcome events, defined as the first occurrence of the 3-point MACE composite (CV death or non-fatal MI or non-fatal stroke), for an expected completion in 2018. In REWIND, once-weekly dulaglutide was added to other antidiabetic agents, mostly metformin (81%), sulfonylureas (57%), and insulin (24%). At least at baseline, use of other drugs with potential CV protective properties was rare; i.e., alpha glucosidase inhibitors (1.2%), TZDs (1.7%), dopamine agonist (0.5%), and SGLT2 inhibitors (0.1%). While most of the study participants (69%) are at the primary prevention level, a relatively high proportion of participants are on background standard-of-care CV preventative pharmacology including ACE inhibitors or ARBs (81%), Beta blockade (46%), statins (66%), and aspirin (51%). 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. Thus, REWIND will add to the growing body of CVOTs evaluating potential ASCVD risk reduction benefits.

Discussion

Can We Generalize an ASCVD Risk Reduction "Class Effect" in Type 2 Diabetes Mellitus for GLP-1 Receptor Antagonists?

CVOTs designed to prove CV safety, among newly developed antidiabetes drugs, have been event-driven, utilizing study populations usually in the very highest risk category, i.e., secondary prevention, to generate sufficient events in a short duration and perhaps limit expenses. Indeed, recent CVOTs of patients with T2DM have been enriched with recruited participants with prior established CVD. Extreme (> 30% 10-year MACE) risk [30] participant estimates from the

GLP-1 RA trials (10-year risk) in the placebo groups were in LEADER (39%), SEMAGLUTIDE (42%), ELIXA (63%), EXSCEL (38%), and FREEDOM-CVO (33%). Two of four CV safety trials with subcutaneous GLP-1 analogues, once-daily liraglutide (LEADER) at 3.8-year duration and once-weekly semaglutide (SUSTAIN-6) at 2.1-year duration, have demonstrated statistically significant improvement in primary 3-point MACE outcomes [22•, 23•]. Two of four RCTs (EXSCEL and ELIXA) were negative in terms of their MACE composites [24•, 25•]. This raises the possibility that as a class, the four GLP-1 RAs evaluated to date may not all be bioequivalent. The results of large CVOTs with two other GLP-1 RAs, albiglutide (HARMONY Outcomes) [28•] and dulaglutide (REWIND) [29•], are pending.

Chemical and Structure Differences Among GLP-1 RAs

Native GLP-1 is a 30-amino acid long peptide hormone derived from post-translational processing of the proglucagon peptide, produced and secreted by intestinal enteroendocrine L-cells and certain neurons within the nucleus of the solitary tract in the brainstem at the time of food consumption. The initial product GLP-1 (1–37) is susceptible to amidation and proteolytic cleavage which gives rise to the two truncated and equipotent biologically active forms, GLP-1 (7–36) amide and GLP-1 (7–37). Native endogenous GLP-1 is rapidly degraded primarily by ubiquitous enzymes, dipeptidyl peptidase-4 (DPP4), and neutral endopeptidases (NEP) and renal clearance, resulting in a half-life of approximately 2 min [31].

Liraglutide is very similar in chemical structure to native GLP-1, with 97% homology to native GLP-1, acylated with palmitic acid attached to human GLP-1-(7–37), and this lipophilic acylated product reversibly binds to albumin that protects liraglutide from immediate degradation and elimination and causes GLP-1 to be released from albumin in a slow and consistent manner. Therefore, unlike endogenous GLP-1, liraglutide is stable against metabolic degradation by peptidases, with a plasma half-life of 13 h [32].

Semaglutide has a 94% similarity in chemical structure to native GLP-1; where two amino acid at positions 8 and 34, 2-aminoisobutyric acid and arginine are substituted. In addition, lysine at position 26 is in its derivative form (acylated with stearic diacid). Semaglutide has a high affinity for albumin binding and is stable against peptidase with a half-life of 1 week [33].

Albiglutide is a GLP-1 receptor agonist, a recombinant fusion protein comprised of two tandem copies of modified human GLP-1 genetically fused in tandem to human albumin. The human GLP-1 fragment sequence 7–36 has been modified with a glycine substituted for the naturally occurring alanine at position 8 to confer resistance to DPP-IV-mediated proteolysis. The human albumin moiety of the recombinant fusion protein, together with the DPP-IV resistance, extends the half-life allowing once-weekly dosing half-life of albiglutide is ~ 5 days [34].

Dulaglutide is a synthetic analog of human GLP-1 that structurally comprises two GLP-1 receptor agonist molecules covalently linked to one 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 [35].

Exenatide, the first marketed GLP-1 mimetic, as a 39-amino acid peptide synthetic version of Extendin-4, a hormone found in the saliva of the Gila monster that has a 53% amino acid homology to native GLP-1 and it has a longer half-life in vivo, 2.4 h vs. 2 min, respectively [36].

Lixisenatide is a once-daily GLP-1 RA derivative of exenatide derived from the first 39 amino acids in the sequence of the peptide Exendin-4, with 53% homology to native GLP-1, omitting proline at position 38 and adding six lysine residues for total of 44 amino acids; these alterations result in $t½$ in plasma of 2–3 h [37].

These chemical and structural differences and half-lives may be important predictors of biological activities, including glycemic control, appetite suppression, and weight loss and potentially beneficial cardiovascular effects, therefore, GLP-1 RA bioequivalence.

EXSCEL Was Statistically Negative but on the Favorable Side of the Line of Unity

While the between-group difference in the primary outcome composite was not significant, the numerical benefits of the once-weekly exenatide extended-release GLP-1 mimetic in EXSCEL (9% RRR) were in the favorable direction and similar relative to once-daily liraglutide in LEADER (13% RRR) and once-weekly semaglutide in SUSTAIN-6 (26% RRR). Furthermore, while EXSCEL, with 14,752 patients enrolled, had the largest study so far, its entire population at baseline was at a somewhat lower established secondary CV risk (73%), relative to LEADER (81%) and SUSTAIN 6 (83%). Therefore, the pharmacological CV effect of medication could be less prominent, requiring a greater than 2.4-year median treatment exposure. A similar effect may explain differences in CV death benefit observed when empagliflozin in EMPA-REG (99% at CV risk) [38] and canagliflozin in CANVAS program (65% at risk) [39] were compared. The median follow-up time in EXSCEL was somewhat shorter than that in the LEADER trial (3.2 vs. 3.8 years), as was the duration of exposure to the trial regimen (2.4 vs. 3.5 years); thus, if once-weekly exenatide has cardioprotective effect, it could be that an advantage had not shown itself. On the other hand, SUSTAIN 6 trial duration was even shorter at 2.1 years.

There are other factors that could affect the magnitude of effectiveness of once-weekly exenatide. Baseline A1C was lower in EXSCEL (mean A1C = 8.0) than that in LEADER (A1C = 8.7) or in SUSTAIN-6 (A1C = 8.7). Exenatide and its

derivatives share approximately 50% amino acid sequence identity with mammalian GLP-1. Antibodies against exenatide have been detected in 40–60% of patients treated with the drug. In patients with high antibody titers, the exenatide-induced reduction in HbA1c level was significantly smaller than in patients with low titers of antibodies [40]. Rates of discontinuation in EXSCEL were remarkably high (~ 44%) for a clinical trial. Although the exclusion criteria of EXSCEL prevented participation of patients that had ever been treated with an approved or investigational GLP-1 receptor agonist, there was a documented disproportionate placebo group drop-in of GLP-1 receptor agonists, 782 or 3.6% vs. 549 or 2.5%. Furthermore, other diabetes therapies known to reduce cardiovascular risk, such as SGLT-2 inhibitors, $n = 401$ or 9.4% vs. 274 or 6.5%, and may have preferentially resulted in lower event rates in the placebo group. In-trial placebo drop-in by mishaps have explained other negative trial results with statins [41–43], fibrates [44], and per pre-trial design with niacin [45, 46]; the latter niacin trials designed to test the HDL-C raising hypothesis, intentionally minimized between-group LDL-C differences, that negatively affected conclusions related to niacin benefits.

Glucose-Lowering and Weight Loss Potency Could Parallel Other More Important Cardiovascular-Reducing Protective Mechanisms

While short-term RCTs have not indicated that glycemic control per se effectively reduces CV events, the differences in glycemic efficacy between different agents in the GLP-1 RA class could reflect differences in other potential special properties beyond glucose control (i.e., cardiovascular properties). In the head-to-head LEAD-6 study [47], liraglutide reduced mean A1C by − 1.12% and weight (0.9 kg) compared to exenatide twice daily where mean A1C was reduced by − 0.79%. In DURATION-5 [48], once-weekly exenatide 2.0 mg resulted in greater improvements in glycemic control compared with exenatide twice daily (− 1.6 vs. − 0.9%, $p < 0.0001$), fasting BG (− 35 vs. − 12 mg/dL, $p = 0.0008$), and weight (− 2.3 vs. − 1.4 kg) in patients with T2DM. Thus, exenatide with a half-life of 2.4 h, although given twice daily, was inferior to once-weekly exenatide in blood glucose control potency.

The ELIXA trial not only utilized ACS patients but also included admissions for unstable angina and as such the placebo events were greatest; the estimated 10-year risk of 4-point MACE events was 63% relative to more stable CVD and primary endpoint limited to 3-point MACE in LEADER, SUSTAIN-6, and EXSCEL. Unfortunately, in ELIXA, lixisenatide, with a similar half-life of 2–3 h compared to exenatide 2.4 h, was only administered once-daily. Thus, lixisenatide may have failed simply related to a major design error, i.e., inadequate dosing, and weaker CV protective properties paralleling its inability to sustain a lower A1C throughout a 24-h period. But, even twice daily administration might have been of inadequate potency compared to liraglutide, as in LEAD-6 [47] and DURATION-5 [48] described above. In the DURATION-6 study, liraglutide reduced A1C by − 1.48% and once-weekly exenatide reduced A1C by − 1.28% [49]. The results of ELIXA appear related not due to a failed drug but rather a failed trial design.

In the head-to-head Efficacy and Safety of Semaglutide Once-weekly vs. Exenatide ER 2.0 mg Once-weekly as add-on to 1–2 Oral Antidiabetic Drugs (OADs) in Subjects with Type 2 Diabetes (SUSTAIN 3) [50], semaglutide reduced A1c by 1.5%, while once-weekly exenatide reduced A1c by 0.9%. Thus, relative to the longer half-lives (12 h +) of once-daily liraglutide and (1 week) of once-weekly semaglutide, the relatively shorter-acting GLP-1 RA mimetics, exenatide and lixisenatide, with half-lives of 2–5 h, may have less potent 24-h effects.

In the head-to-head AWARD-6 [51], there was no significant difference in A1C lowering between once-daily liraglutide (− 1.36%) and once-weekly dulaglutide (− 1.42%) [between-group difference − 0.06% (95% CI − 0.19 to 0.07), with body weight changes somewhat greater for liraglutide (− 3.61 kg) compared to dulaglutide (− 2.90 kg, $p = 0.011$). The effect of albiglutide on reduction of A1C and body weight is less than once-daily liraglutide at low and high doses, exenatide once-weekly, and dulaglutide [52]. Animal studies suggested less potent anorectic effects compared to exenatide or liraglutide, possibly due to steric hindrance from the enlarged (albumin) molecule and impaired permeability of the blood-brain barrier [53], that may also explain the weight differences observed in AWARD-6. In SUSTAIN 7, at 40 weeks of exposure, at low and high doses, semaglutide was superior to dulaglutide in improving glycemic control (at low doses, A1C, − 1.5 vs. − 1.1%; at high doses, A1C, − 1.8 vs. − 1.4%, respectively) and reducing bodyweight (at low doses, body weight − 4.6 vs. − 2.3 kg; at high doses − 6.5 vs. − 3.0 kg, respectively) [54]. The Swedish Institute for Health Economics cohort model for T2D was used to compare liraglutide and lixisenatide (both added to basal insulin), with a societal perspective and with comparative treatment effects derived by indirect treatment comparison (ITC). From the ITC, decreases in HbA1c were − 1.32 and − 0.43% with liraglutide and lixisenatide, respectively; decreases in BMI were − 1.29 and − 0.65 kg/m^2, respectively [55].

The results of other GLP-1 RA cardiovascular safety trials (albiglutide: HARMONY OUTCOMES (NCT02465515) and dulaglutide: REWIND (NCT01394952)), expected to be reported in 2018, should add additional light as to safety and CV efficacy of GLP-1 RA.

One meta-analysis of all four published CVOT trials demonstrated significant 10% RRR in 3-point MACE, 13% RRR in CV mortality, 12% RRR in all-cause mortality, but only a

non-significant 6% RRR trend for fatal and non-fatal MI and 13% RRR in fatal and non-fatal stroke [56]. The inability to significantly reduce the components of the composite endpoints (fatal and non-fatal MI and fatal and non-fatal stroke) may have been due to the short duration of the trials or relatively small numbers of trial participants. Importantly, there were no significant differences seen between GLP-1 RA-treated and placebo-treated patients for the incidence of severe hypoglycemia, pancreatitis, pancreatic cancer, or medullary thyroid cancer. Another meta-analysis [57] showed a significant 11% reduction in all-cause mortality (RR = 0.89; 95% CI = 0.82 to 0.96) and 12% reduction in cardiovascular mortality (RR = 0.88; 95% CI = 0.80 to 0.97) favoring GLP-1R agonists over placebo. There were no significant differences in MACE, non-fatal MI, non-fatal stroke, hospitalization for heart failure, and coronary revascularization between GLP-1 RA and placebo. However, in subgroup analysis of only the long-acting GLP-1 RAs, i.e., liraglutide, semaglutide, and exenatide ER, there was a significant 12% RR for the 3-point MACE and a 13% RRR for non-fatal stroke.

Conclusion

A variety of factors could hinder realization of a beneficial GLP-1 RA-induced cardiovascular risk reduction "class effect." Current GLP-1 RAs possess different chemical structures that potentially affect multiple properties including absorption, ability to pass the blood-brain barrier and suppress appetite, gastric emptying, injection site reactions, antibody formation, efficacy, interactions with GLP-1 receptors, peak effects, toxic side effects (i.e., nausea) and tolerance, half-life, pharmacokinetics, A1C potency, weight loss potency, and their degradation or clearance.

Given that lixisenatide has a relatively half-life (2–3 h), similar to exenatide (2.4 h) that is therapeutically administered twice daily, a new lixisenatide CVOT design, in which lixisenatide is administered either two to three times daily or continuously, is needed to fairly assess its potential for CV protection.

A new once-weekly exenatide CVOT to assess potential CV protection properties is needed with more careful attention to placebo drop-in drugs with demonstrated CV protection; equipoise of in-trial drop-in to the investigational product group and placebo group in all new CVOTS would reduce confounding results. In-trial mishaps particularly investigational drug-group drop-outs or placebo group drop-ins can sabotage an otherwise well-designed trial that narrows the between-group differences.

If most participants in one trial are at the secondary prevention risk level and in a second trial are at the primary prevention risk level, the same GLP-1 RA could yield conflicting results if limited to a short-term duration RCT given different study populations. Assuring secondary prevention in near 100% of participants for short-duration trials is also critical for appropriate comparisons.

If event-driven, demonstrating benefit may require a longer-duration RCT, when its participants' global risks are well-treated and exquisitely controlled with background standard-of-care LDL-lowering, BP-lowering, and antiplatelet pharmacologic agents.

Standardizing the primary outcome among all trials; i.e., all 3-point MACE or all 4-point MACE, avoids comparative confusion. Lengthening trial duration may permit better evaluations and conclusions of the ischemic components of chosen primary outcome composites.

To date, marketed GLP-1 RAs are subcutaneous injections, either twice daily, once-daily, or once weekly. Oral administered semaglutide is under investigation. All GLP-1 RAs are indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM, i.e., reduce fasting and post prandial blood glucose and A1c, with evidence for differences in potencies.

While not indicated for weight loss at the therapeutic doses utilized for glycemic control, all are associated with weight loss, to varying degrees. Once-daily liraglutide, under a different proprietary name, and at a higher dose (3 mg), is indicated for weight loss and once-weekly semaglutide, at a higher dose (2.4 mg), is currently being investigated for a weight loss indication (NCT03611582). If the potency of weight loss parallels the potency of reduction in multifactorial causal risk factors' contributing to CVD risk reduction, testing these two "higher-dosed" GLP-1 RAs in CV outcome studies may be of significance.

That only two of four analogs have demonstrated CV benefit may possibly be due to differences in drug structure (mimetic vs. analog), half-lives, differences in trial design or duration, or combinations. Relative to the GLP-1 RA analogs, albiglutide and duraglutide and the GLP-1 mimetics (exendin derivatives), both liraglutide and semaglutide, possess the closest resemblance structurally to native GLP-1 RA and both have demonstrated statistically significant reductions in the primary composite (3-point MACE) outcomes (CV death, NF-MI, and NF-stroke). Although, in general, statistically significant reductions were not demonstrated in all the ischemic components of the composites, favorable trends were noted that may have become significant simply with a larger populations or longer-duration trials. These CV safety "approval" trials, therefore, may simply have been too short to demonstrate beneficial superiority effect; underestimating the time required to realize between-group separation.

Anticipation of the results of HARMONY Outcomes and REWIND with albiglutide and dulaglutide are of interest. These two GLP-1 analogs possess structural differences from liraglutide or semaglutide, imposing considerable macromolecular steric hindrance that could inhibit blood-brain barrier

passage and have reduced effects on incretin resistance at the level of the neurons within the nucleus of the solitary tract in the brainstem at the time of food consumption, ultimately affecting food consumption, A1C levels, and weight loss.

In summary, the favorable CV results with liraglutide (1.8 mg) and semaglutide (1 mg) may be related to their duration of action and relative superiority in potency of A1c and weight reductions, although not directly causal in terms of the observed CV risk reduction but rather as markers that parallel other favorable GLP-1 RA mechanisms of actions on CVD.

While the GLP-RA CVOTs, to date, have demonstrated CV safety, bioequivalence for significant CV superiority has been limited to two of the four major CVOTs. There is evidence to suggest one trial was poorly designed, with a once daily short-acting GLP-1 mimetic inadequate for 24-h duration and a second trial utilizing an extended release GLP-1 mimetic was plagued by in-trial mishaps. Before bioequivalence issues can be fully discussed, we are obliged to wait for the pending results of CVOTs of GLP-1 RAs, albiglutide and dulaglutide, where steric hindrance may potentially inhibit full mimicry of pharmacologic GLP-1 and may shed additional light. Therefore, it is too early to make the CVD risk reduction benefit "class effect" claim.

Compliance with Ethical Standards

Conflict of Interest Yixing Li declares that he has no conflicts of interest.

Paul D. Rosenblit reports the following: Clinical Research Trial site for Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers-Squib, Glaxo SmithKline, Ionis, Lexicon, Novo Nordisk, and Sanofi; Speaking/Teaching Honoraria from Akcea, Amgen, Janssen, Novo Nordisk, and Merck; and Advisory Board Honoraria from Akcea, Amarin, Amgen, Novo Nordisk, and Sanofi-Regeneron.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance

1. Kannel W, McGee DL. Diabetes and cardiovascular disease: the Framingham study. JAMA. 1979;241(19):2035–8.
2. Fruchart JC, Sacks F, Hermans MP, Assmann G, Brown WV, Ceska R, et al. The residual risk reduction initiative: a call to action to reduce residual vascular risk in patients with dyslipidemia. Am J Cardiol. 2008;102(10 Suppl):1K–34K.
3. Lin F-J, Tseng W-K, Yin W-H, Yeh H-I, Chen J-W, Wu C-C. Residual risk factors to predict major adverse cardiovascular events in atherosclerotic cardiovascular disease patients with and without diabetes mellitus. Sci Rep. 2017;7:9179. 1–9
4. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352(9131):837–53.
5. Reichard P, Nilsson BY, Rosenqvist U. The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. N Engl J Med. 1993;329(5):304–9.
6. Aronson D. Hyperglycemia and the pathobiology of diabetic complications. Adv Cardiol. 2008;45:1–16.
7. Stefano GB, Challenger S, Kream RM. Hyperglycemia-associated alterations in cellular signaling and dysregulated mitochondrial bioenergetics in human metabolic disorders. Eur J Nutr. 2016;55(8):2339–45.
8. Shah MS, Brownlee M. Molecular and cellular mechanisms of cardiovascular disorders in diabetes. Circ Res. 2016;118(11):1808–29.
9. Stratton IM, Adler AI, Neil HAW, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000;321:405–12.
10. 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;359:1577–89.
11. DeFronzo RA. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes. 2009;58:773–95.
12. US Department of Human and Health Services Food and Drug Administration (2008) Guidance for industry: diabetes mellitus—evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. https://www.fda.gov/downloads/Drugs/Guidances/ucm071627.pdf
13. • Nauck MA, Meier JJ, Cavender MA, Abd El Aziz M, Drucker D. Cardiovascular actions and clinical outcomes with glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. Circulation 2017;136(9):849–870. **A recent extensive review of the potential cardiovascular benefits of DPP-4 inhibitors and pharmacological GLP-1 and its receptor agonists**.
14. • Drucker DJ. The cardiovascular biology of glucagon-like peptide-1. Cell Metab. 2016;24(1):15–30. **A recent extensive review of the potential cardiovascular benefits of pharmacological GLP-1 and its receptor agonists**
15. Alhadeff AL, Rupprecht LE, Hayes MR. GLP-1 neurons in the nucleus of the solitary tract project directly to the ventral tegmental area and nucleus accumbens to control for food intake. Endocrinology. 2012;153(2):647–58.
16. Chang AM, Jakobsen G, Sturis J, Smith MJ, Bloem CJ, An B, et al. The GLP-1 derivative NN2211 restores beta-cell sensitivity to glucose in type 2 diabetic patients after a single dose. Diabetes. 2003;52(7):1786–91.
17. Farilla L, Bulotta A, Hirshberg B, Li Calzi S, Khoury N, Noushmehr H, et al. Glucagon-like peptide 1 inhibits cell apoptosis and improves glucose responsiveness of freshly isolated human islets. Endocrinol. 2003;144:5149–51.
18. Hyson D, Rutledge JC, Berglund L. Postprandial lipemia and cardiovascular disease. Curr Atheroscler Rep. 2003;5:437–44.
19. Meier JJ, Gethmann A, Götze O, Gallwitz B, Holst JJ, Schmidt WE, et al. Glucagon-like peptide 1 abolishes the postprandial rise in triglyceride concentrations and lowers levels of non-esterified fatty acids in humans. Diabetologia. 2006;49:452–8.
20. Matikainen N, Söderlund S, Björnson E, Pietiläinen K, Hakkarainen A, Lundbom N, et al. Liraglutide treatment improves postprandial lipid metabolism and cardiometabolic risk factors in humans with adequately controlled type 2 diabetes: a single-centre randomised controlled study. Diabetes Obes Metab. 2018; https://doi.org/10.1111/dom.13487.

21. Nordestgaard BG. Triglyceride-rich lipoproteins and atherosclerotic cardiovascular disease: new insights from epidemiology, genetics, and biology. Circ Res. 2016;118(4):547–63.
22.• Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JFE, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375:311–22. **The liraglutide LEADER CVOT results**
23.• Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;37(5):1834–44. **The semaglutide SUSTAIN-6 CVOT results**
24.• Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2017;377:1228–39. **The once-weekly exenatide EXSCEL CVOT results**
25.• Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Køber LV, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med. 2015;373:2247–57. **The lixisenatide ELIXA CVOT results**
26. A study to evaluate cardiovascular outcomes in patients with type 2 diabetes treated with ITCA 650. ClinicalTrials.gov website. clinicaltrials.gov/ct2/show/NCT01455896.
27. Fisher M, Petrie MC, Ambery PD, Donaldson J, Ye J, McMurray JJV. Cardiovascular safety of albiglutide in the Harmony programme: a meta-analysis. Lancet Diabetes Endocrinol. 2015;3(9):697–703.
28.• Green JB, Hernandez AF, D'Agostino RB, Granger CB, Janmohamed S, Jones NP, et al. Harmony outcomes: a randomized, double-blind, placebo-controlled trial of the effect of albiglutide on major cardiovascular events in patients with type 2 diabetes mellitus—rationale, design, and baseline characteristics. Am Heart J. 2018;12(203):30–8. **The rationale and design of the albiglutide HARMONY CVOT**
29.• Gerstein HC, Colhoun H, Dagenais GR, Diaz R, Lakshmanan M, Pais P, 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(1):42–9. **The rationale and design of the dulaglutide REWIND CVOT**
30. Jellinger PS, Handelsman Y, Rosenblit PD, Bloomgarden ZT, Fonseca VA, Garber AJ, et al. AACE/ACE guidelines: American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. Endocr Pract. 2017;23(Supplement 2):1–87.
31. Baggio LL, Huang Q, Brown TJ, Drucker DJ. A recombinant human glucagon-like peptide (GLP)-1-albumin protein (albugon) mimics peptidergic activation of GLP-1 receptor-dependent pathways coupled with satiety, gastrointestinal motility, and glucose homeostasis. Diabetes. 2004;53(9):2492–500.
32. Jacobsen LV, Flint A, Olsen AK, Ingwersen SH. Liraglutide in type 2 diabetes mellitus: clinical pharmacokinetics and pharmacodynamics. Clin Pharmacokinet. 2016;55:657–72.
33. Lau J, Bloch P, Schäffer L, Pettersson I, Spetzler J, Kofoed J, et al. Discovery of the once-weekly glucagon-like peptide-1 (GLP-1) analogue semaglutide. J Med Chem. 2015;58(18):7370–80.
34. Blair HA, Keating GM. Albiglutide: a review of its use in patients with type 2 diabetes mellitus. Drugs. 2015;75:651–63.
35. Jimenez-Solem E, Rasmussen MH, Christensen M, Knop FK. Dulaglutide, a long-acting GLP-1 analog fused with an Fc antibody fragment for the potential treatment of type 2 diabetes. Curr Opin Mol Ther. 2010;12(6):790–7.
36. Koole C, Reynolds CA, Mobarec JC, Hick C, Sexton PM, Sakmar TP. Genetically-encoded photocrosslinkers determine the biological binding site of Exendin-4 in the N-terminal domain of the intact human glucagon-like peptide-1 receptor (GLP-1R). J Biol Chem. 2017;292:7131–44.
37. Werner U, Haschke G, Herling AW, Kramer W. Pharmacological profile of lixisenatide: a new GLP-1 receptor agonist for the treatment of type 2 diabetes. Regul Pept. 2010;164:58–64.
38. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373:2117–28.
39. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377:644–57.
40. Buse JB, Garber A, Rosenstock J, Schmidt WE, Brett JH, Videbæk N, et al. Liraglutide treatment is associated with a low frequency and magnitude of antibody formation with no apparent impact on glycemic response or increased frequency of adverse events: results from the Liraglutide Effect and Action in Diabetes (LEAD) trials. J Clin Endocrinol Metab. 2011;96:1695–702.
41. Knopp RH, D'Emden M, Smilde JG, for the ASPEN Study Group, et al. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the atorvastatin study for prevention of coronary heart disease endpoints in non-insulin-dependent diabetes mellitus (ASPEN). Diabetes Care. 2006;29:1478–85.
42. Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomized controlled trial. Lancet. 2003;361(9364):1149–58.
43. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA. 2002;288:2998–3007.
44. Keech A, Simes RJ, Barter P, for The FIELD study investigators, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomized controlled trial. Lancet. 2005;366(9500):1849–61.
45. The AIM-HIGH Investigators, Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med. 2011;365:2255–67.
46. HPS2-THRIVE Collaborative Group. Effects of extended-release niacin with laropiprant in high-risk patients. NEJM. 2014;371(3):203–12.
47. Buse JB, Sesti G, Schmidt WE, Montanya E, Chang CT, Xu Y, et al. Switching to once-daily liraglutide from twice-daily exenatide further improves glycemic control in patients with type 2 diabetes using oral agents. Diabetes Care. 2010;33(6):1300–3.
48. Blevins T, Pullman J, Malloy J, Yan P, Taylor K, Schulteis C, et al. DURATION-5: exenatide once weekly resulted in greater improvements in glycemic control compared with exenatide twice daily in patients with type 2 diabetes. J Clin Endocrinol Metab. 2011;96(5):1301–10.
49. Buse JB, Nauck M, Forst T, Sheu WH, Shenouda SK, Heilmann CR, et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. Lancet. 2013;381(9861):117–24.
50. Ahmann AJ, Capehorn M, Charpentier G, Dotta F, Henkel E, Lingvay I, et al. Efficacy and safety of once-weekly semaglutide versus exenatide ER in subjects with type 2 diabetes (SUSTAIN 3): a 56-week, open-label, randomized clinical trial. Diabetes Care. 2018;41(2):258–66.

51. Dungan KM, Povedano ST, Forst T, González JG, Atisso C, Sealls W, et al. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. Lancet. 2014;384(9951):1349–57.
52. Kayaniyil S, Lozano-Ortega G, Bennett HA, Johnsson K, Shaunik A, Grandy S, et al. A network meta-analysis comparing exenatide once weekly with other GLP-1 receptor agonists for the treatment of type 2 diabetes mellitus. Diabetes Ther. 2016;7:27–43.
53. Baggio LL, Huang Q, Cao X, Drucker DJ. An albumin-exendin-4 conjugate engages central and peripheral circuits regulating murine energy and glucose homeostasis. Gastroenterology. 2008;134: 1137–47.
54. Pratley RE, Aroda VR, Lingvay I, Lüdemann J, Andreassen C, Navarria A, et al. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. Lancet Diabetes Endocrinol. 2018;6(4):275–86.
55. Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. Nat Rev Endocrinol. 2012;8:728–42.
56. Jia X, Alam M, Ye Y, Bajaj M, Birnbaum Y. GLP-1 receptor agonists and cardiovascular disease: a meta-analysis of recent cardiac outcome trials. Cardiovasc Drugs Ther. 2018;32:65–72.
57. Bethel MA, Patel RA, Merrill P, Lokhnygina Y, Buse JB, Mentz RJ, et al. Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a meta-analysis. Lancet Diabetes Endocrinol. 2018;6:105–13.