Cardiovascular Outcome Trials in Type 2 Diabetes: What Do They Mean for Clinical Practice?

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IN BRIEF Cardiovascular disease is the leading cause of morbidity and mortality in people with diabetes, and deaths from heart disease are two to four times higher among adults with type 2 diabetes. Trials such as the U.K. Prospective Diabetes Study, ACCORD (Action to Control Cardiovascular Risk in Diabetes), ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation), and VADT (Veteran's Affairs Diabetes Trial) produced mixed findings regarding whether intensive glycemic control results in improved cardiovascular (CV) outcomes for patients with diabetes. In response to concerns, including the CV safety of the thiazolidinedione rosiglitazone, the U.S. Food and Drug Administration and subsequently the European Medicines Agency issued guidance that trials should be conducted to prove that antihyperglycemic agents have acceptable CV risk profiles. In this article, the authors review the study designs and results of CV outcomes trials conducted with sodium–glucose cotransporter 2 inhibitors and glucagon-like peptide 1 receptor agonists and discuss how these may affect clinical practice.

Cardiovascular disease (CVD) is the leading cause of death and morbidity in people with diabetes. In 2017, the total cost of diagnosed diabetes in the United States was $327 billion (1), and CVD is the largest contributor to the direct and indirect costs of diabetes (2,3). Diabetes is a well-established risk factor for CVD; in a retrospective study of nearly 1.4 million individuals with type 2 diabetes in the Quintiles Electronic Medical Record database, 21.6% of eligible individuals had CVD (4). Deaths from heart disease are two to four times higher among adults with type 2 diabetes compared with those without (5). The American College of Cardiology guidelines include the presence of type 2 diabetes as a risk factor for CVD (6). Although preventing and managing CVD in patients with type 2 diabetes involves assessing for and addressing risk factors such as hypertension and dyslipidemia (3), glycemic control is also important, as demonstrated in several studies, which will be discussed.

In type 2 diabetes, the U.K. Prospective Diabetes Study (UKPDS) demonstrated that improved glycemic control with intensive therapy with either sulfonylureas or insulin was associated with a significant reduction in the risk of microvascular, but not macrovascular, complications (7). Data from a 10-year follow-up of the UKPDS, however, suggested that improved glycemic control also resulted in significant cardiovascular (CV) benefits (8). Interestingly, after the randomized phase of the study ended, glycemic control no longer differed between the intensive and standard groups. The fact that a macrovascular benefit emerged over the long term, despite a relatively short period of better glycemic control, suggests in the case of the newly diagnosed individuals with type 2 diabetes

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who were enrolled in the UKPDS that early aggressive control of glucose is important after diagnosis.

Three later, shorter-term studies in patients with longstanding diabetes included middle-aged and older individuals with established type 2 diabetes who were at a high risk of CV events: ACCORD (Action to Control Cardiovascular Risk in Diabetes) (9), ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) (10), and VADT (Veterans Affairs Diabetes Trial) (11). All of these studies failed to demonstrate any statistically significant reduction in composite CV endpoints with intensive glucose control (targeted to A1C <6.0 or 6.5%).

A meta-analysis of these trials did show a reduction in the risk of major CV events, particularly myocardial infarction (MI), with more intensive glucose control (12). It should be noted, however, that composite endpoints may not be the best indicator in these types of studies because they can often be driven by just one of the components, which may be of lesser importance. Furthermore, the study populations varied widely among studies.

A Brief History of CV Outcome Trials

In 2008, in the wake of concerns about the CV safety of the thiazolidinedione rosiglitazone in patients with type 2 diabetes (13), the U.S. Food and Drug Administration (FDA) issued guidance that CV safety trials should be conducted to prove that antihyperglycemic agents have acceptable CV risk profiles (14). These recommendations include: *1*) an upper bound of the 95% CI <1.3 for the risk ratio of important CV events to be used as a key criterion for excluding unacceptable CV risk for new antihyperglycemic agents; *2*) a requirement that studies must include individuals with relatively advanced disease, elderly patients, and patients with some degree of renal impairment; *3*) a requirement that a minimum of 2 years' CV safety data be provided; *4*) a requirement that all phase 2 and phase 3 studies should include a prospective independent adjudication of CV events and that adjudicated events should include CV mortality, MI, and stroke (i.e., major adverse CV events [MACE]) and can include hospitalization for acute coronary syndrome (ACS), urgent revascularization procedures, and possibly other endpoints; and *5*) to satisfy the new statistical guidelines, the analysis of CV events may include a meta-analysis of all placebo-controlled trials, add-on trials (i.e., drug vs. placebo, each added to standard therapy), and active-controlled trials, and/or an additional single, large safety trial may be conducted that alone or added to other trials would be able to satisfy an upper bound of 1.8 for the risk ratio before a new drug application/biologics license application is approved. Post-marketing studies should then be conducted to demonstrate an upper bound ≤1.3, unless the estimated risk ratio was already shown to be <1.3 (14,15). Similar requirements have also been set out by the European Medicines Agency (EMA) (16).

Since 2008, 13 CV outcome trials (CVOTs) have been performed and their results published, with many others ongoing (17). Early CVOTs with the dipeptidyl peptidase 4 (DPP-4) inhibitors alogliptin (18), sitagliptin (19), and saxagliptin (20) showed no increase in risk of MACE in patients with CVD compared to placebo, but there was an increase in hospitalization for heart failure (HF) with saxagliptin (20). In the CARMELINA (Cardiovascular and Renal Microvascular Outcome Study with Linagliptin in Patients with Type 2 Diabetes Mellitus) trial, linagliptin demonstrated CV safety with no increase in risk of HF but not superiority versus placebo (21). More recently, other CVOTs have studied the CV safety of the injectable glucagon-like peptide 1 (GLP-1) receptor agonists lixisenatide in the ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome) trial (22), liraglutide in the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial (23), semaglutide in SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes) (24), extended-release exenatide in the EXSCEL (Exenatide Study of Cardiovascular Event Lowering) trial (25), albiglutide in the Harmony Outcomes (A Long Term, Randomised, Double Blind, Placebo-Controlled Study to Determine the Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Patients With Type 2 Diabetes Mellitus) trial (26), and dulaglutide in the REWIND (Researching cardiovascular Events with a Weekly INcretin in Diabetes) trial (27–29). Similarly, CV safety in the treatment of type 2 diabetes has been demonstrated for the sodium–glucose cotransporter 2 (SGLT2) inhibitors empagliflozin in EMPA-REG OUTCOME (BI 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) (30,31), canagliflozin in the CANVAS (Canagliflozin Cardiovascular Assessment Study) Program (32), and dapagliflozin in the DECLARE–TIMI 58 (Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58) trial (33,34).

All CVOTs conducted to date with injectable GLP-1 receptor agonists (ELIXA [22], LEADER [23], SUSTAIN-6 [24], EXSCEL [25], Harmony Outcomes [26], and REWIND [28]) or SGLT2 inhibitors (EMPA-REG OUTCOME [30,31], the CANVAS Program [32], and DECLARE–TIMI 58 [34]) have successfully demonstrated CV safety. Some have also indicated a potential CV benefit for these agents, such as a significantly lower risk of MACE with liraglutide in LEADER (23), with albiglutide in Harmony Outcomes (26), and with semaglu-

tide in SUSTAIN-6 (24); reduction in CV outcomes with dulaglutide in REWIND (28); reductions in MACE, CV mortality, and total mortality versus placebo with empagliflozin in EMPA-REG OUTCOME (30); reduction in MACE with canagliflozin in the CANVAS Program (32); and reduction in CV death or hospitalization for HF with dapagliflozin in DECLARE–TIMI 58 (34).

Although the four completed DPP-4 inhibitor trials demonstrated CV safety (18–21,32), there was no indication of superiority and an unexpected increase in hospitalization for HF with saxagliptin (20). This article will therefore focus on recent CVOTs conducted using GLP-1 receptor agonists and SGLT2 inhibitors.

Comparing CVOTs

Although regulatory authorities have provided guidance on CVOTs, they have not specified the exact protocol these trials should follow. The result of this lack of specification is that CVOTs performed to date differ markedly in terms of factors that could affect outcomes such as patient characteristics, duration of type 2 diabetes, severity of CVD history, and study duration. Because of this disparity in trial design, comparisons of CVOT outcomes need to be carefully considered in the context of all patient population and design differences. The potential impact of some of the differences in study design and patient characteristics on outcomes and the comparison of findings between studies are discussed hereafter.

GLP-1 Receptor Agonist CVOTs

Study Designs

There were a number of differences in the study designs and characteristics of enrolled patients among the six injectable GLP-1 receptor agonist CVOTs (3). The dulaglutide trial differed from previous CVOTs, which were designed to show noninferiority to placebo with respect to CV events, by testing the hypothesis that dulaglutide was superior to placebo (27,28). Whereas the lixisenatide, liraglutide, semaglutide, albiglutide, and dulaglutide trials were standard randomized, placebo-controlled trials, the EXSCEL exenatide study was a pragmatic trial, the only such CVOT to date.

Pragmatic trials are designed to more closely reflect the routine care situation but are less controlled than conventional randomized controlled trials (RCTs). The EXSCEL trial included integration with usual care, and patients were managed by their usual care physicians but had study visits at least twice yearly (6-month visits after year 1), supported by telephone contact (35). The EXSCEL trial had a broad range of eligibility criteria so its results could be more generalizable to daily clinical practice; 73% of enrolled patients had prior CV events, and 27% did not. Prior CV events were defined as a history of major clinical manifestation of coronary artery disease, ischemic cerebrovascular disease, or atherosclerotic peripheral vascular disease (25).

Furthermore, the level of exposure to the study drug during the course of the trials may have affected the results. Exposure, as defined by the mean percentage of time that a participant received the trial regimen, was lower in the EXSCEL trial compared with other RCTs of GLP-1 receptor agonists and similar to that in the ELIXA trial (36). Different factors may lead to differences in drug exposures. For example, a shorter trial duration in the lixisenatide study and longer duration in the dulaglutide REWIND trial (median follow-up 5.4 years), a high rate of dropouts and lower adherence to the study drug perhaps due to an inconvenient pen device in the exenatide study, and a higher discontinuation rate among the U.S. population in the liraglutide trial (27 vs. 13% in the non-U.S. population) all could have affected drug exposures (22,23,25,28).

Primary Endpoints

The primary endpoint for all six GLP-1 receptor agonist trials was first occurrence of a composite of MACE; the liraglutide, semaglutide, exenatide, albiglutide, and dulaglutide trials used a three-point MACE composite (CV death, nonfatal MI, or nonfatal stroke), and the lixisenatide study used a four-point MACE composite, which also included hospitalization for unstable angina (UA) (Table 1). Data from CVOTs suggest that hospitalization for UA is difficult to influence with glucose-lowering agents, which may dilute any treatment effect for the composite endpoint. Effectively, the addition of hospitalization for UA may make it more likely that noninferiority is demonstrated but may also mask potential CV benefits or harm (37).

Glycemic Control

The definition of "routine care" varied among studies, particularly with regard to glycemic control. In the lixisenatide trial, decisions regarding glycemic control and intensification of therapy were at the discretion of the investigators according to local guidelines. Although no A1C targets were specified, this treatment approach was expected to produce similar glycemic control in both study arms. In the semaglutide trial, investigators were encouraged to treat all patients according to local guidelines to achieve the most effective glycemic control. In the liraglutide trial, the recommended target for glycemic control was A1C ≤7.0% (or individualized target at the investigator's discretion), with intensification of therapy if not at target. In the exenatide trial, investigators were encouraged to promote glycemic equipoise between the two trial groups, although this was not a requirement, and to help patients reach clinically appropriate A1C targets. In the albiglutide trial, glycemic goals (based on local guidelines) were determined by the investigators and intensification of therapy was also at their discretion. In the dulaglutide trial, investigators were encouraged to manage patients' glucose levels with any medication except a GLP-1 receptor agonist according to their best judgment, as

TABLE 1. GLP-1 Receptor Agonist CVOT Study Designs

	ELIXA (22) (Lixisenatide) (*n* = 6,068)	LEADER (23) (Liraglutide) (*n* = 9,340)	SUSTAIN-6 (24) (Semaglutide) (*n* = 3,297)	EXSCEL (25) (Exenatide) (*n* = 14,752)	Harmony Outcomes (26) (Albiglutide) (*n* = 9,463)	REWIND (27,28) (Dulaglutide) (*n* = 9,901)
Primary endpoint	CVD death, nonfatal MI, nonfatal stroke, or HUA	CVD death, nonfatal MI, or nonfatal stroke	CVD death, nonfatal MI, or nonfatal stroke	CVD death, nonfatal MI, or nonfatal stroke	CVD death, nonfatal MI, or nonfatal stroke	CVD death, nonfatal MI, or nonfatal stroke
Run-in period	1 week	2 weeks	2 weeks	None	None	3 weeks
Key inclusion criteria	A1C 5.5–11%; age ≥30 years; an acute coronary event within 180 days before screening	A1C ≥7.0%; age ≥50 years with at least one CV coexisting condition (CHD, cerebrovascular disease, peripheral vascular disease, CKD of stage 3 or greater) or CHF (NYHA class II or III) or age ≥60 years with at least one CV risk factor	A1C ≥7.0%; age ≥50 years with established CVD (previous CV, cerebrovascular, or peripheral vascular disease), CHF (NYHA class II or III), or CKD of stage 3 or greater, or age ≥60 years with at least one CV risk factor	A1C 6.5–10.0%; 70% of patients with a previous CV event (coronary artery disease, ischemic cerebrovascular disease, or atherosclerotic peripheral arterial disease); 30% with no previous CV event	A1C >7.0%; age ≥40 years; established disease of the coronary (MI, ≥50% stenosis in at least one coronary artery, or previous coronary revascularization), cerebrovascular (ischemic stroke, ≥50% carotid artery stenosis, or a previous carotid vascular procedure), or peripheral arterial (intermittent claudication and an ankle-brachial index <0.9, nontraumatic amputation, or a previous peripheral vascular procedure) circulation	A1C ≤9.5%; age ≥50 years; on 0–2 classes of oral glucose-lowering drugs, with or without basal insulin; patients aged 50–54 years had to have previous CVD, those aged 55–59 years had to have either previous CVD or evidence of other vascular or renal disease, and those aged ≥60 years had to have previous CVD, other vascular or renal disease, or at least two other CV risk factors
Cardiovascular exclusion criteria	CABG surgery following the qualifying acute coronary event; PCI within 15 days prior to screening; planned revascularization procedure or coronary angiogram	Acute coronary or cerebrovascular event within past 14 days; planned revascularization procedure; CHF NYHA class IV	Acute coronary or cerebrovascular event within past 90 days; planned revascularization procedure; CHF NYHA class IV	Planned or anticipated revascularization procedure	None specified	Coronary or cerebrovascular event in preceding 2 months or plans to revascularize
Intervention	Lixisenatide 20 µg versus usual care (no incretin-based drugs)	Liraglutide 1.8 mg versus usual care (no incretin-based drugs)	Semaglutide 0.5 or 1.0 mg versus usual care (no incretin-based drugs)	Exenatide extended release 2 mg versus usual care (no GLP-1 receptor agonists)	Albiglutide 30–50 mg (based on glycemic response and tolerability) versus placebo, in addition to usual care (no GLP-1 receptor agonists)	Dulaglutide 1.5 mg once weekly versus placebo, in addition to usual care (no GLP-1 receptor agonists)

TABLE CONTINUED ON P. 320 →

TABLE 1. GLP-1 Receptor Agonist CVOT Study Designs, *continued from p. 319*

	ELIXA (22) (Lixisenatide) (*n* = 6,068)	LEADER (23) (Liraglutide) (*n* = 9,340)	SUSTAIN-6 (24) (Semaglutide) (*n* = 3,297)	EXSCEL (25) (Exenatide) (*n* = 14,752)	Harmony Outcomes (26) (Albiglutide) (*n* = 9,463)	REWIND (27,28) (Dulaglutide) (*n* = 9,901)
Usual care	Glycemic control managed by investigators in accordance with local clinical practice guidelines by the adjustment of concomitant glucose-lowering agents or the addition of new antihyperglycemic agents (with the exception of other incretins)	If A1C ≤7% (or individualized target at investigator's discretion) after randomization, addition of any antihyperglycemic agents (except for GLP-1 receptor agonists, DPP-4 inhibitors, or pramlintide) was permitted	All investigators were encouraged to treat all the patients according to local guidelines to achieve the most effective glycemic control (A1C ≤7.0%, individualized depending on patient); recommendation to intensify treatment with additional noninvestigational antihyperglycemic medication (non–incretin-based therapy) if not at goal after 3 months	Use of open-label glucose-lowering agents (including DPP-4 inhibitors but not GLP-1 receptor agonists) was encouraged to promote glycemic equipoise between the two trial groups and to help patients reach clinically appropriate A1C targets	If glycemic goal (based on local guidelines), as determined by the investigator, was not met after an increase in the dose of the study medication to 50 mg, other glucose-lowering medications could be adjusted or added (except for GLP-1 receptor agonists)	Investigators were encouraged to manage patients' glucose levels with any medication except for GLP-1 receptor agonists according to their best judgment as informed by local clinical practice guidelines for the management of diabetes
Median follow-up, years	2.1	3.8	2.1	3.2	1.6	5.4

CABG, coronary artery bypass surgery; CHD, coronary heart disease; CHF, chronic heart failure; HUA, hospitalization for UA; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

informed by local clinical practice guidelines. Although the impact of more intensive glycemic control on CVD is debated, differences in the level of glycemic control should be considered when making comparisons of the study findings.

Inclusion and Exclusion Criteria

Inclusion and exclusion criteria differed among the trials, most markedly in the lixisenatide trial, in which only patients with a recent history of acute coronary events within 180 days of screening were enrolled, while the occurrence of an acute coronary event in the previous 14 days or 90 days was an exclusion criterion for the liraglutide and semaglutide trials, respectively. Patients in the liraglutide trial who were ≥50 years of age were required to have at least one CVD coexisting condition, whereas those aged ≥60 years were required to have at least one CVD risk factor. In the semaglutide trial, those aged ≥50 years were required to have established CVD, chronic HF, or chronic kidney disease (CKD), whereas those aged ≥60 years were required to have at least one CVD risk factor. The exenatide trial had wide-ranging inclusion criteria, with no upper age limit and any degree of CV risk. In the albiglutide trial, patients were required to have established disease of the coronary (MI, ≥50% stenosis in at least one coronary artery, or previous coronary revascularization), cerebrovascular (ischemic stroke, ≥50% carotid artery stenosis, or a previous carotid vascular procedure), or peripheral arterial (intermittent claudication and an ankle-brachial index <0.9, nontraumatic amputation, or a previous peripheral vascular procedure) circulation. In the dulaglutide trial, patients aged 50–54 years had to have previous CVD, those aged 55–59 years had to have either previous CVD or evidence of other vascular or renal disease, and those aged ≥60 years had to have previous CVD, other vascular or renal disease, or at least two other CV risk factors.

Baseline Characteristics

The lixisenatide, liraglutide, semaglutide, exenatide, albiglutide, and dulaglutide studies included 6,068, 9,340, 3,297, 14,752, 9,463, and 9,901 patients, respectively. Overall, patients enrolled in the lixisenatide trial were somewhat younger, with a shorter diabetes duration and lower BMI compared with the liraglutide, semaglutide (which had similar trial design), and exenatide trials (Table 2). Patients in the albiglutide trial had the longest duration of diabetes. The dulaglutide trial had the lowest baseline A1C (7.3%) and a high proportion of women (46%). The proportion of patients with CVD at baseline (according to the individual study definitions) was 100% in the lixisenatide and albiglutide trials, 81% in the liraglutide trial, 83% in the semaglutide trial, 73% in the exenatide trial, and 31% in the dulaglutide trial. There were also differences among the studies in participants' ethnic origins and geographical locations, which have been reported to influence response to glycemic therapy (38).

Outcomes

Primary Endpoints

All six trials achieved their primary objective of demonstrating noninferiority to placebo in terms of their primary endpoint (Figures 1 and 2). However, significant reductions in MACE were reported with liraglutide (13.0 vs. 14.9%, hazard ratio [HR] 0.87, 95% CI 0.78–0.97, P <0.001 for noninferiority, P = 0.01 for superiority) (23), semaglutide (6.6 vs. 8.9%, HR 0.74, 95% CI 0.58–0.95, P <0.001 for noninferiority, P = 0.02 [nominal] for superiority) (24), albiglutide (7 vs. 9%, HR 0.78, 95% CI 0.68–0.90, P <0.0001 for noninferiority, P = 0.0006 for superiority) (26), and dulaglutide (12.0 vs. 13.4%, HR 0.88, 95% CI 0.79–0.99, P = 0.026 for superiority) (28). With liraglutide, this was driven by a reduction in the incidence of CV mortality (4.7 vs. 6.0%, P = 0.007) and MI (1.6 vs. 1.9%, P = 0.046) (23), while with

TABLE 2. Baseline Characteristics for GLP-1 Receptor Agonist CVOTs

	ELIXA (22) (Lixisenatide) (n = 6,068)	LEADER (23) (Liraglutide) (n = 9,340)	SUSTAIN-6 (24) (Semaglutide) (n = 3,297)	EXSCEL (25) (Exenatide) (n = 14,752)	Harmony Outcomes (26) (Albiglutide) (n = 9,463)†	REWIND (27) (Dulaglutide) (n = 9,901)
Age, years	60	64	65	62	64	66
Race, %						
White	75.4	77.5	83.0	75.8	70.0	75.7
Asian	12.8	10.0	8.3	9.8	5.0	—
Black	3.6	8.3	6.7	6.0	2.0	—
Hispanic	—	—	—	—	21.0	—
Other	8.2	4.2	2.0	8.4	2.0	—
Geographical location, %						
Europe	38.2	35.3	19.2	46.0	—	—
Western	—	—	—	—	36.0	—
Eastern and Central	—	—	—	—	22.0	—
North America	13.3	30.5	34.5	25.1	20.0	20.9
Latin America	—	—	—	—	18.0	30.5
Asia	11.6	7.6	—	10.4	4.0	1.5
Rest of the world	36.9	26.6	46.3	18.6	—	47.1‡
Duration of diabetes, years	9.3	12.9	13.9	12.0	14.1	10.0
Baseline A1C, %	7.7	8.7	8.7	8.0	8.8	7.3

TABLE CONTINUED ON P. 322 →

TABLE 2. Baseline Characteristics for GLP-1 Receptor Agonist CVOTs, *continued from p. 321*

	ELIXA (22) (Lixisenatide) (*n* = 6,068)	LEADER (23) (Liraglutide) (*n* = 9,340)	SUSTAIN-6 (24) (Semaglutide) (*n* = 3,297)	EXSCEL (25) (Exenatide) (*n* = 14,752)	Harmony Outcomes (26) (Albiglutide) (*n* = 9,463)†	REWIND (27) (Dulaglutide) (*n* = 9,901)
BMI, kg/m^2	30	32.5	32.8	31.7	32.3	32.3
CV history, %						
CVD	100	81.3	83	73	100	31.4
MI	22.1*	30.7	32.5	—	47.0	16.2
HF	22.4	17.8	23.6	16.2	20.0	8.6
Stroke/TIA	5.5	16.1	14.9	—	17.0	5.3
Hypertension	76.3		92.8	—	86.0	93.2
eGFR <60 mL/min/m^2, %	23.2	23.1	28.5	21.6	—	22.2

**Prior to index acute coronary event. †Data presented are for the albiglutide treatment group (n = 4,731). ‡Includes Europe. TIA, transient ischemic attack.*

semaglutide, this was largely driven by a reduced incidence of nonfatal stroke (1.6 vs. 2.7%; $P = 0.04$) (24) and with albiglutide by a significant reduction in fatal or nonfatal MI (4 vs. 5%; $P = 0.003$) (26). The liraglutide trial also demonstrated an important reduction in all-cause mortality (HR 0.85, 95% CI 0.74–0.97, $P = 0.02$ [nominal]), which was not seen with lixisenatide, semaglutide, exenatide, albiglutide, or dulaglutide.

Differences in inclusion criteria for the trials are reflected in the rate per patient-year of primary events, which was markedly higher in ELIXA (6.3 in the lixisenatide arm, 6.4 in the placebo arm) compared with LEADER (3.4 in the liraglutide arm, 3.9 in the placebo arm), SUSTAIN-6 (3.2 in the semaglutide arm, 4.4 in the placebo arm), and REWIND (2.4 in the dulaglutide arm, 2.7 in the placebo arm). This finding indicates that, because the lixisenatide trial only enrolled patients who had experienced a recent acute coronary event, patients were less stable or at a particularly high CV risk compared with those enrolled in the liraglutide and semaglutide trials, in which recent CV events were exclusion criteria. Although the lixisenatide trial was the only study to require patients to have experienced a recent acute coronary event, it should be noted that a proportion of patients in the liraglutide trial had also experienced a recent event, with patients only being excluded if the event occurred within 14 days of randomization. The inclusion and exclusion criteria of the albiglutide trial permitted a high incidence rate of CV events (4.57 events per 100 person-years in the albiglutide arm vs. 5.87 events per 100 person-years in the placebo arm).

Renal Outcomes

In the REWIND trial, in which 35% of patients had albuminuria at baseline, secondary outcomes included a composite clinical microvascular outcome comprising diabetic retinopathy (photocoagulation, antivascular endothelial growth factor therapy, or

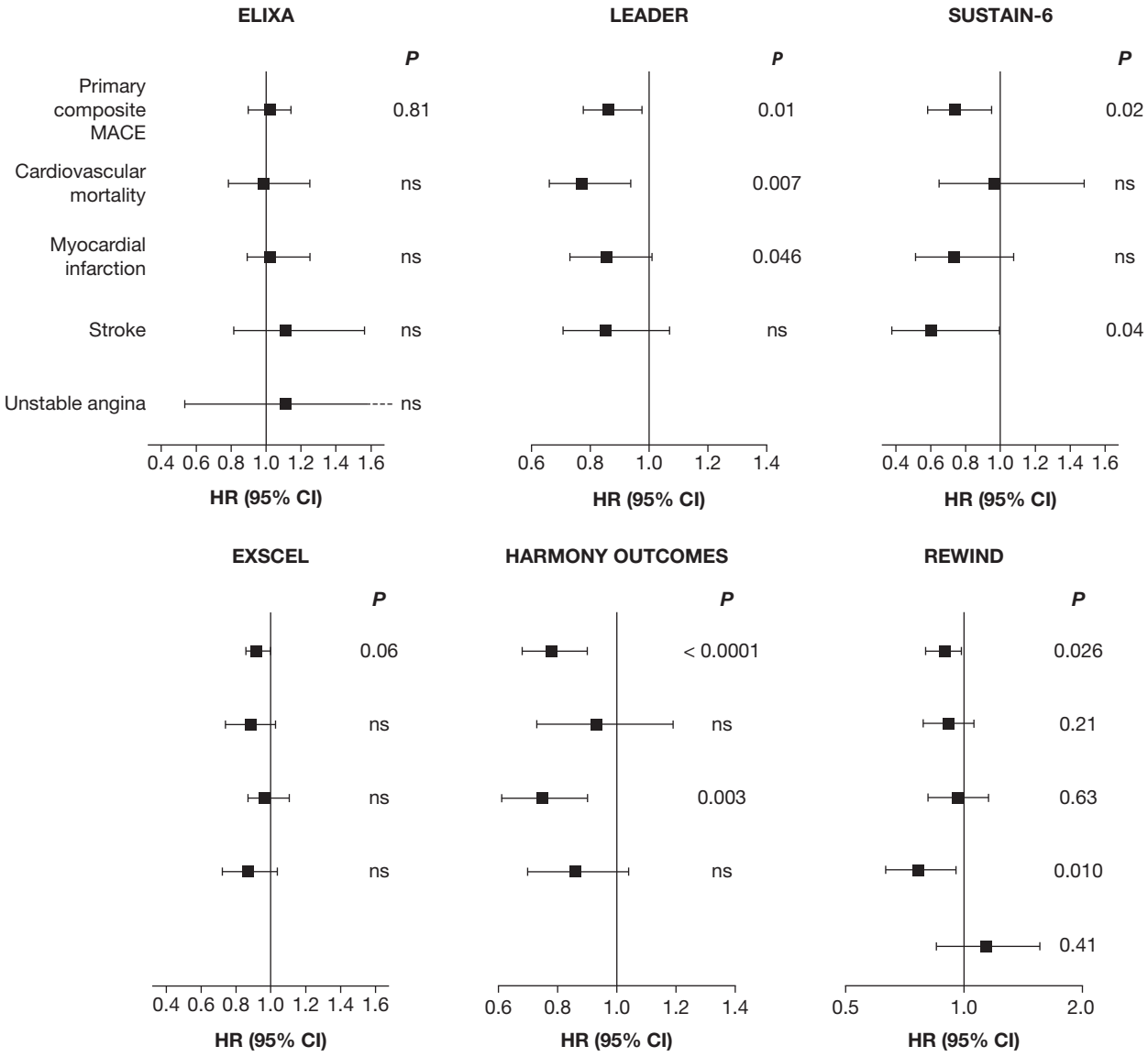


FIGURE 1. Primary endpoints and components in the ELIXA (lixisenatide), LEADER (liraglutide), SUSTAIN-6 (semaglutide), EXSCEL (exenatide), Harmony Outcomes (albiglutide), and REWIND (dulaglutide) trials (22–26,28). ns, not significant.

vitrectomy) or renal disease (development of new macroalbuminuria, defined as urinary albumin-to-creatinine ratio [UACR] >33.9 mg/mmol in those with a lower baseline concentration, a sustained ≥30% decline in estimated glomerular filtration rate [eGFR], or chronic renal replacement therapy) (28). The incidence of the composite microvascular outcome was lower in the dulaglutide group than in the placebo group (3.8 vs. 4.3 per 100 person-years, HR 0.87, 95% CI 0.79–0.95, P = 0.0020), with the difference mainly being due to fewer renal outcomes in the dulaglutide group than in the placebo group. In an exploratory analysis of dulaglutide's effects on renal outcomes, the greatest effect was on the macroalbuminuria component (29). A renal outcome developed in 848 patients (17.1%) in the dulaglutide group (incidence rate 3.5 per 100 person-years) compared with 970 patients (19.6%) in the placebo group (incidence rate 4.1 per 100 person-years) (HR 0.85, 95% CI 0.77–0.93, P = 0·0004), with the greatest effect being on new macroalbuminuria (HR 0.77, 95% CI 0.68–0.87, P <0·0001).

Selected Safety Information

Heart Rate

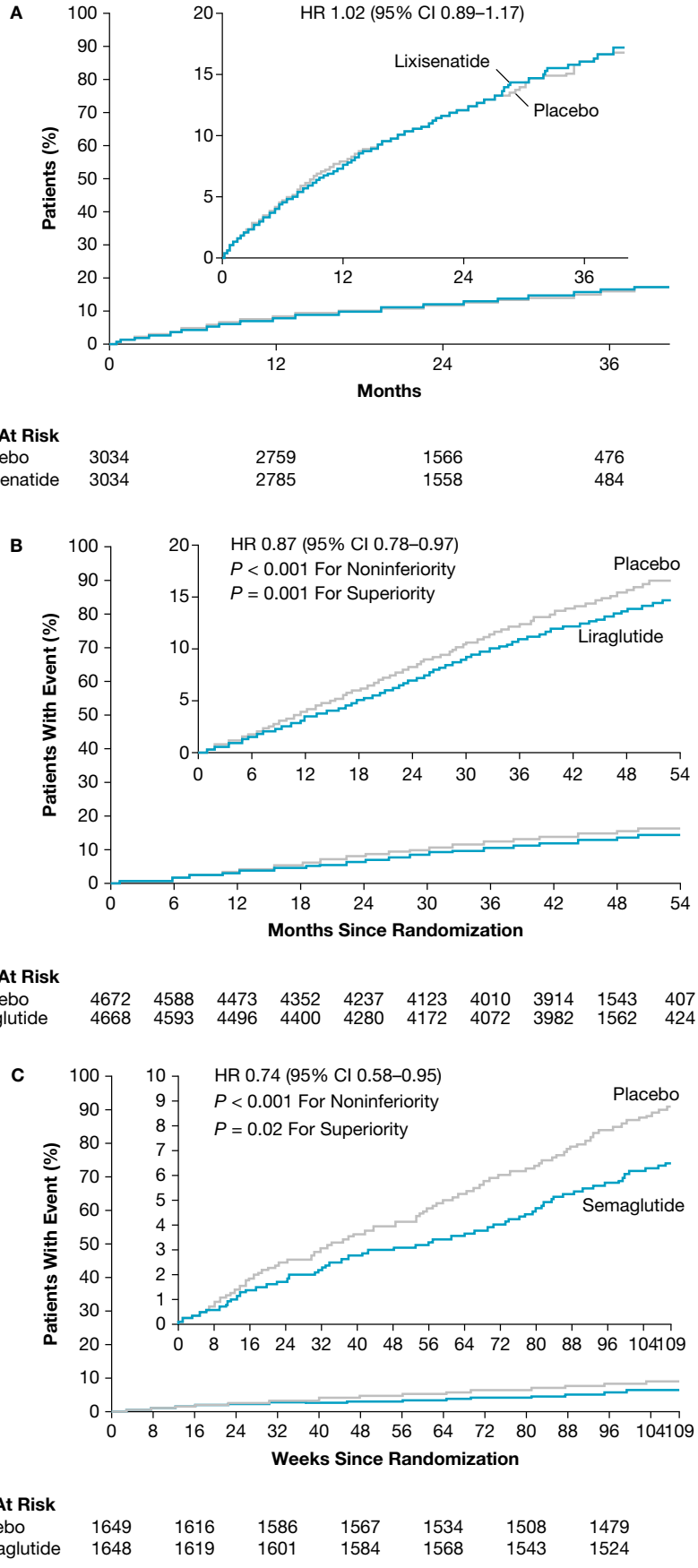
Increase in heart rate is a known effect of GLP-1 receptor agonist treatment (39). The lowest increase in heart rate was seen in the lixisenatide trial, with a small but noteworthy average difference of 0.4 more beats per minute (bpm) versus placebo across all visits, predominantly related to an increase

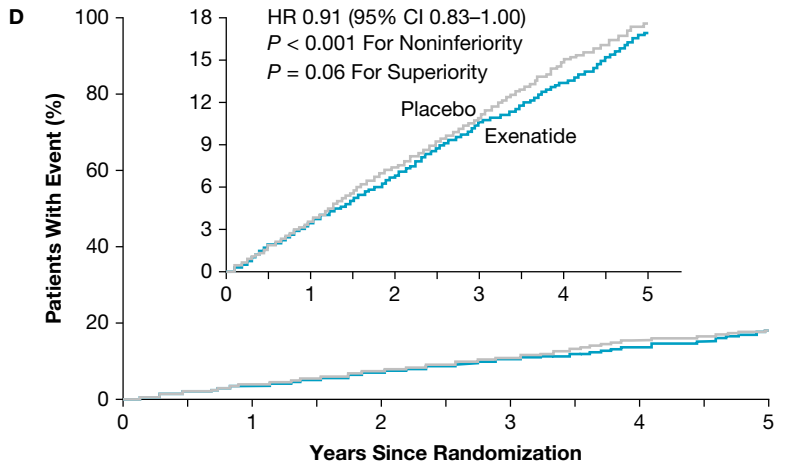
of 1 bpm at weeks 2 and 6 that was not detected at later time points (22). In the albiglutide trial, the heart rate of patients in the albiglutide group increased by 1.4 bpm (26). Increases in heart rate versus placebo were highest in the liraglutide trial (3 bpm) (23) and similar in the semaglutide (2.1–2.4 bpm) (24) and exenatide (2.51 bpm) trials (25).

Although studies demonstrate a GLP-1 receptor agonist–induced increase in heart rate, this increase does not appear to increase CV risk in patients with type 2 diabetes (39). The underlying mechanism for the GLP-1 receptor agonist–induced increase in heart rate is unknown, but it could be related to a direct effect at the sinus node related to the duration of action of the GLP-1 receptor agonist (39). An increase in heart rate may also be associated with adverse clinical outcomes in those with advanced HF (39).

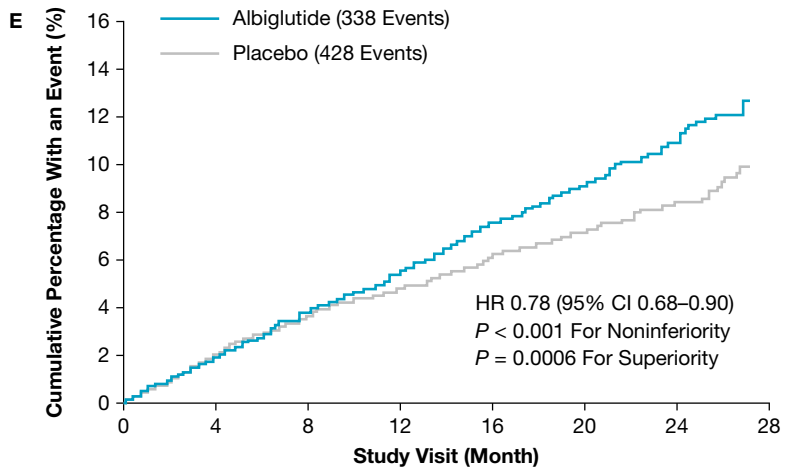
Acute Pancreatitis and Pancreatic Cancer

There was no increase in occurrence of acute pancreatitis in the GLP-1 receptor agonist–treated groups in the lixisenatide, exenatide, liraglutide, semaglutide, albiglutide, and dulaglutide trials. There was an increase in the incidence of pancreatic cancer with liraglutide in LEADER compared with placebo (13 vs. 5 cases, HR 2.60, 95% CI 0.93–7.28), although this observation was not supported by data from a large international retrospective cohort study or the majority of observational studies (40). Furthermore, there were four deaths due to pancreatic cancer in the placebo group and none in the liraglutide group of LEADER. Increases in the incidence of pancreatic cancer were not seen in ELIXA (three cases in the lixisenatide group compared with nine cases in the placebo group) (22), SUSTAIN-6 (one patient receiving 1.0 mg semaglutide and four patients receiving placebo) (24), EXSCEL (15 cases in the exenatide group vs. 16 in the placebo group) (25), or Harmony Outcomes (six cases in the albiglutide group vs.

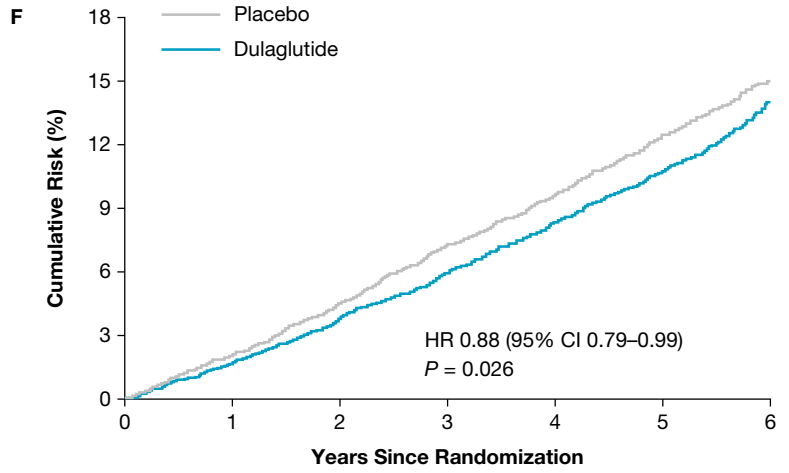




No. At Risk											
Placebo	7396	7120	6897	6565	5908	4468	3565	2961	2209	1366	687
Exenatide	7356	7101	6893	6580	5912	4475	3595	3053	2281	1417	727



No. At Risk								
Placebo	4732	4603	4460	4208	3074	2077	1030	-
Albiglutide	4731	4613	4503	4239	3148	2142	1064	-



No. At Risk							
Placebo	4952	4791	4625	4437	4275	3575	742
Dulaglutide	4949	4815	4670	4521	4369	3686	741

FIGURE 2. Kaplan–Meier plot of the primary outcome* for *A*) ELIXA (lixisenatide), *B*) LEADER (liraglutide), *C*) SUSTAIN-6 (semaglutide), *D*) EXSCEL (exenatide), *E*) Harmony Outcomes (albiglutide), and *F*) REWIND (dulaglutide) (22–26,28). Insets show the same data on an expanded *y*-axis. *Death from CV causes, nonfatal MI, nonfatal stroke, or hospitalization for UA for ELIXA; death from CV causes, nonfatal MI, or nonfatal stroke for LEADER, SUSTAIN-6, EXSCEL, Harmony Outcomes, and REWIND. Reproduced from refs. 22–25. ©2015, 2016, and 2017. Massachusetts Medical Society. All rights reserved. Reproduced from ref. 26. ©2018 Elsevier Ltd. All rights reserved. Reproduced from ref. 28. ©2019 Elsevier Ltd. All rights reserved.

five in the placebo group) (26). In a meta-analysis of the lixisenatide, liraglutide, semaglutide, and exenatide trials, there was no noteworthy difference in the incidence of pancreatitis or pancreatic cancer between the GLP-1 receptor agonist and placebo groups (41).

Retinopathy

Rates of retinopathy complications (vitreous hemorrhage, blindness, or conditions requiring treatment with an intravitreal agent or photocoagulation) were higher with semaglutide versus placebo in SUSTAIN-6 (HR 1.76, 95% CI 1.11–2.78). The treatment difference between the two groups was first seen very early in the trial. The HR for retinopathy events in LEADER was 1.15 (95% CI 0.87–1.52). In SUSTAIN-6, initial semaglutide treatment was associated with a relatively rapid and profound decrease in A1C levels. Indeed, a recent analysis of SUSTAIN-6 concluded that observed effects of semaglutide on diabetic retinopathy appeared to be primarily attributable to large A1C reductions in patients with a history of retinopathy (42). There was no increase in the risk of diabetic retinopathy complications in patients with no history of retinopathy.

Nephropathy

In the lixisenatide trial, there was a low incidence of serious renal or urinary events, which was the same (1.6%) in both the lixisenatide and placebo groups. Although there was a difference between the groups in favor of lixisenatide in UACR from baseline to week 108 (P = 0.004), the median values at baseline and follow-up were clinically similar. In an exploratory analysis, lixisenatide was shown to reduce the progression of albuminuria in macroalbuminuric patients and to be associated with a lower risk of new-onset macroalbuminuria after adjustment for A1C and other renal risk factors (43). In the liraglutide trial, there was a lower rate of nephropathy events with liraglutide versus placebo (1.5 vs. 1.9 events per 100 patient-years of observation, P = 0.003) (23). This finding was driven by lower rates of new-onset persistent macroalbuminuria, which occurred in 161 liraglutide-treated patients and 215 placebo-treated patients (HR 0.74, 95% CI 0.60–0.91, P = 0.004) (44). Rates of new or worsening nephropathy were lower with semaglutide (3.8%) than placebo (6.1%; P = 0.005, SUSTAIN-6 study), similar to liraglutide, due to a reduction in albuminuria. In the exenatide trial, rates of microalbuminuria and macroalbuminuria were similar in the exenatide (7.2 and 2.2%, respectively) and placebo groups (7.5 and 2.8%, respectively). Urinary albumin excretion was not measured in the albiglutide trial, but there was no difference in renal function between albiglutide and placebo. Thus, current CVOTs indicate that, although there is generally no beneficial effect on eGFR with GLP- 1 receptor agonists, there is some evidence of benefit in the REWIND dulaglutide trial.

Potential Impact of Differences in Patient Populations

There were considerable differences in patient populations among these trials, leading to varying degrees of results that do not allow for direct comparison among the trials. The majority of current CVOTs with GLP-1 receptor agonists were performed in relatively high-risk patients with established atherosclerotic CVD (ASCVD), and some, but not all, reported a reduction in MACE. Although all trials enrolled individuals with established CV events, the prevalence ranged from 31 to 100% (Table 2) (22–25,27). Furthermore, although having had a prior established CV event was an inclusion criterion in most CVOTs, information on the timing of these events before enrollment was only available in the lixisenatide trial (22). Patients with ACS are at a considerably higher risk of further MACE events in the following few years (45).

The lixisenatide trial enrolled patients at a considerably higher risk of CV events; 100% of its patients had had an acute coronary event within 180 days before screening (median 52 days post-ACS) (22). Despite a relatively shorter follow-up time in the lixisenatide trial, the incidence of MACE was up to twofold higher compared with other CVOTs (22). This high event rate over only 2 years perhaps minimized the treatment effect, as with lixisenatide, this was most probably due to the inherent risk of the study population. In line with the lixisenatide trial, a subgroup post-hoc analysis of the liraglutide trial reported a sevenfold greater risk of CV death or hospitalization for HF (HR 7.0, 95% CI 5.8–8.4) in a total of 631 patients (292 on liraglutide and 339 on placebo) who experienced an MI during the trial compared with those who did not. Liraglutide was not associated with a reduced risk of CV death or hospitalization for HF after an MI versus placebo (HR 0.91, 95% CI 0.66–1.26) during the study (46). The dulaglutide trial included a high proportion of women (46%), and patients had a low mean A1C of 7.3% at baseline (27,28). These and other differences in the patient populations could have led to the differences in outcomes.

Potential Impact of Differences in Molecular Properties and Mechanisms of Action

Although differences in outcome may be related to study design and execution and patient population differences, they may also relate to differences between individual GLP-1 receptor agonists. Liraglutide and semaglutide are synthetic forms of human GLP-1, with >90% structural homology to the native protein and modifications developed to extend their duration of action (47). Albiglutide is generated through genetic fusion of two tandem copies of human GLP-1 (with 97% sequence homology to the endogenous protein) to human albumin (48,49). Dulaglutide is a recombinant fusion protein consisting of two GLP-1 peptides covalently linked to a human IgG4-Fc heavy-chain variant (48,49). In contrast, lixisenatide and exenatide are synthetic forms of exendin-4, a peptide extracted from Gila monster venom (47,50). Although lixisenatide and exenatide share only about a 53% sequence identity with human GLP-1, many of the conserved amino acids face the interaction site of the receptor. Despite this, GLP-1 receptor agonists show varying levels of affinity for the GLP-1 receptor, and it has been shown that biased agonism (i.e., the ability of different ligands acting at the same receptor to promote different responses) occurs at the GLP-1 receptor and is related to distinct elements on the binding site that activate individual pathways in a ligand-dependent manner (51). However, the applicability of this to the GLP-1 receptor agonists studied in these trials is unknown. GLP-1 receptor agonists derived from exendin-4 (exenatide and lixisenatide) are more frequently associated with anti-drug antibody production than those modified from human GLP-1; however, no relevant differences have been reported in terms of safety and efficacy between antibody-positive and antibody-negative patients in exenatide and lixisenatide studies (52). Thus, it is unlikely that the differences in

CVOT results are due to the structure of, or antibodies produced in relation to, GLP-1 receptor agonists.

A recent retrospective real-world analysis of >105,000 patients in an electronic health record system with type 2 diabetes with and without established CVD treated over 9 years showed a reduction in the risk of CVD events and overall mortality associated with the use of GLP-1 receptor agonists (exenatide, exenatide extended release, and liraglutide) (53). The study found lower rates of acute MI (HR 0.80, 95% CI 0.65–0.99, P = 0.045), cerebrovascular accident (HR 0.82, 95% CI 0.74–0.91, P <0.001), overall mortality (HR 0.48, 95% CI 0.41–0.57, P <0.001), and the composite of all three outcomes (HR 0.82, 95% CI 0.74–0.91, P <0.002) during treatment with GLP-1 receptor agonists. Importantly, benefits of treatment with GLP-1 receptor agonists were similar between patients with and without a history of CVD. The 57% reduction in mortality rate in patients without prior CVD reported in this study suggests that initiation of GLP-1 receptor agonist therapy would be beneficial in patients who have a low CVD risk, a population largely missing from CVOTs and unlikely to be studied because of the cost of carrying out such event-driven studies in a lower-risk population. However, one caveat is that real-world studies cannot compensate for patient population differences, although the reported use of statistical models could have partly resolved this.

Similarly, a recent meta-analysis assessed CV mortality, nonfatal MI, and nonfatal stroke in adults with type 2 diabetes treated with GLP-1 receptor agonists (41). A total of 12 articles were analyzed, and the four GLP-1 receptor agonist CVOT trials then completed (lixisenatide, liraglutide, semaglutide, and exenatide) were captured. The authors concluded that GLP-1 receptor agonists demonstrated CV safety across all CVOTs and showed a 10% relative risk reduction in the three-point MACE primary outcome (CV mortality, nonfatal MI, or nonfatal stroke; HR 0.90, 95% CI 0.82–0.99, P = 0.033), a 13% relative risk reduction in CV mortality (HR 0.87, 95% CI 0.79–0.96, P = 0.007), and a 12% relative risk reduction in all-cause mortality (HR 0.88, 95% CI 0.81–0.95, P = 0.002), all with low to moderate evidence of between-trial statistical heterogeneity. GLP-1 receptor agonists had no noteworthy effect on fatal or nonfatal MI, fatal or nonfatal stroke, hospitalization for UA, or hospitalization for HF. Therefore, studies consistently demonstrate CV safety across the GLP-1 receptor agonist class.

SGLT2 Inhibitor CVOTs

To date, three CVOTs have reported data for SGLT2 inhibitors: EMPA-REG OUTCOME with empagliflozin (30,31), integrated CANVAS Program (CANVAS and CANVAS-R [CANVAS Renal]) data analysis of canagliflozin (32), and DECLARE–TIMI 58 with dapagliflozin (34). The CANVAS trial was initiated before the FDA approved canagliflozin with the initial goal of showing CV safety. Due to the inclusion of unmasked interim CV outcome data in the regulatory filing, a planned expansion of the sample size to enable a test of CV protection was not undertaken. Instead, CANVAS-R was designed as a second CANVAS-like trial to be analyzed jointly with CANVAS, to meet a post-approval CV safety commitment. The integrated analysis of CANVAS and CANVAS-R was undertaken to maximize statistical power.

Study Designs and Patient Characteristics

The empagliflozin (30), canagliflozin (32), and dapagliflozin (33) trials had a number of differences in design, perhaps most importantly the fact that patients aged ≥50 years enrolled in the canagliflozin trial were not required to have established CVD, whereas in the empagliflozin trial, CVD was the key inclusion criteria, and in the dapagliflozin trial, patients either had established CVD or multiple risk factors for CVD (Table 3). As a result, while almost all patients in the empagliflozin trial had CVD, 66% of patients in the canagliflozin trial and 41% of patients in the dapagliflozin trial had CVD (30,32,34) (Table 4). Because the dapagliflozin trial evaluated a larger number of patients with type 2 diabetes without prior CV events than the empagliflozin and canagliflozin trials, it has been suggested that this may allow for a broader generalizability of its findings to patients seen in primary care (54).

Outcomes

Primary Endpoints

The empagliflozin, canagliflozin, and dapagliflozin trials all met their primary objective of demonstrating noninferiority to placebo, with empagliflozin and canagliflozin also demonstrating significant reductions in the primary MACE endpoint (empagliflozin HR 0.86, 95.02% CI 0.74–0.99, P <0.001 for noninferiority and P = 0.04 for superiority; canagliflozin HR 0.86, 95% CI 0.75–0.97, P <0.001 for noninferiority and P = 0.02 for superiority; dapagliflozin HR 0.93, 95% CI 0.84–1.03, P <0.001 for noninferiority) (Figures 3 and 4). Empagliflozin reduced the incidence of death from CV causes compared with placebo; however, there were no noteworthy differences between the two in the risk of MI, which showed a slight decline, or stroke, which showed a correspondingly small increase (30) (Figure 3). In a separate analysis of cerebrovascular events, there was no noteworthy difference in risk between empagliflozin and placebo (31). There was no noteworthy difference in the rates of individual MACE components in the canagliflozin research program, although these studies were not powered to test this (Figure 3). The lack of noteworthy differences described here may reflect differences in the study populations, as discussed previously, but the underlying reason is unknown.

A further analysis of HF outcomes found that empagliflozin reduced hos-

TABLE 3. SGLT2 Inhibitor CVOT Study Designs

	EMPA-REG OUTCOME (Empagliflozin) (27) (*n* = 7,020)	CANVAS Program (Canagliflozin) (29) (*n* = 10,142)	DECLARE–TIMI 58 (Dapagliflozin) (30,31) (*n* = 17,160)
Primary endpoint	CVD death, nonfatal MI, or nonfatal stroke	CVD death, nonfatal MI, or nonfatal stroke	MACE, CVD death, or hospitalization for HF
Run-in period	2 weeks	2 weeks	4–8 weeks
Key inclusion criteria	Established CVD; A1C ≥7.0 and ≤9.0% and no glucose-lowering agents for at least 12 weeks before randomization, or A1C ≥7.0 and ≤10.0% on stable glucose-lowering therapy for at least 12 weeks before randomization	A1C ≥7.0 and ≤10.5%; age ≥30 years with a history of symptomatic ASCVD or ≥50 years of age with two or more CV risk factors (duration of diabetes ≥10 years, systolic blood pressure >140 mmHg while receiving one or more antihypertensive agents, current smoking, microalbuminuria or macroalbuminuria, or HDL cholesterol <1 mmol/L [38.7 mg/dL])	A1C ≥6.5 and ≤12.0%, creatinine clearance ≥60 mL/min; age ≥40 years with multiple risk factors for ASCVD or had established ASCVD (defined as clinically evident ischemic heart disease, ischemic cerebrovascular disease, or peripheral artery disease)
Cardiovascular exclusion criteria	ACS, stroke, or TIA within 2 months before informed consent; planned cardiac surgery or angioplasty within 3 months	MI, UA, revascularization procedure, or cerebrovascular accident within 3 months before screening, a planned revascularization procedure, or history of NYHA class IV CVD	Acute CV event (e.g., ACS, TIA, stroke, any revascularization, decompensated HF, or sustained tachycardia) <8 weeks before randomization
Intervention	Empagliflozin 10 or 25 mg versus standard of care	Canagliflozin 100 or 300 mg versus standard of care	Dapagliflozin 10 mg versus placebo
Usual care	Background glucose-lowering therapy was to remain unchanged for the first 12 weeks after randomization, although intensification was permitted if the patient had a confirmed fasting glucose level >240 mg/dL (>13.3 mmol/L). After week 12, investigators were encouraged to adjust glucose-lowering therapy at their discretion to achieve glycemic control according to local guidelines	Use of other background therapy for glycemic management and other control of risk factors guided by best practice instituted in line with local guidelines	Use of other glucose-lowering agents (other than an open-label SGLT2 inhibitor, pioglitazone, or rosiglitazone) was at the discretion of the investigator
Median follow-up, years	3.1	2.4	4.2

TIA, transient ischemic attack.

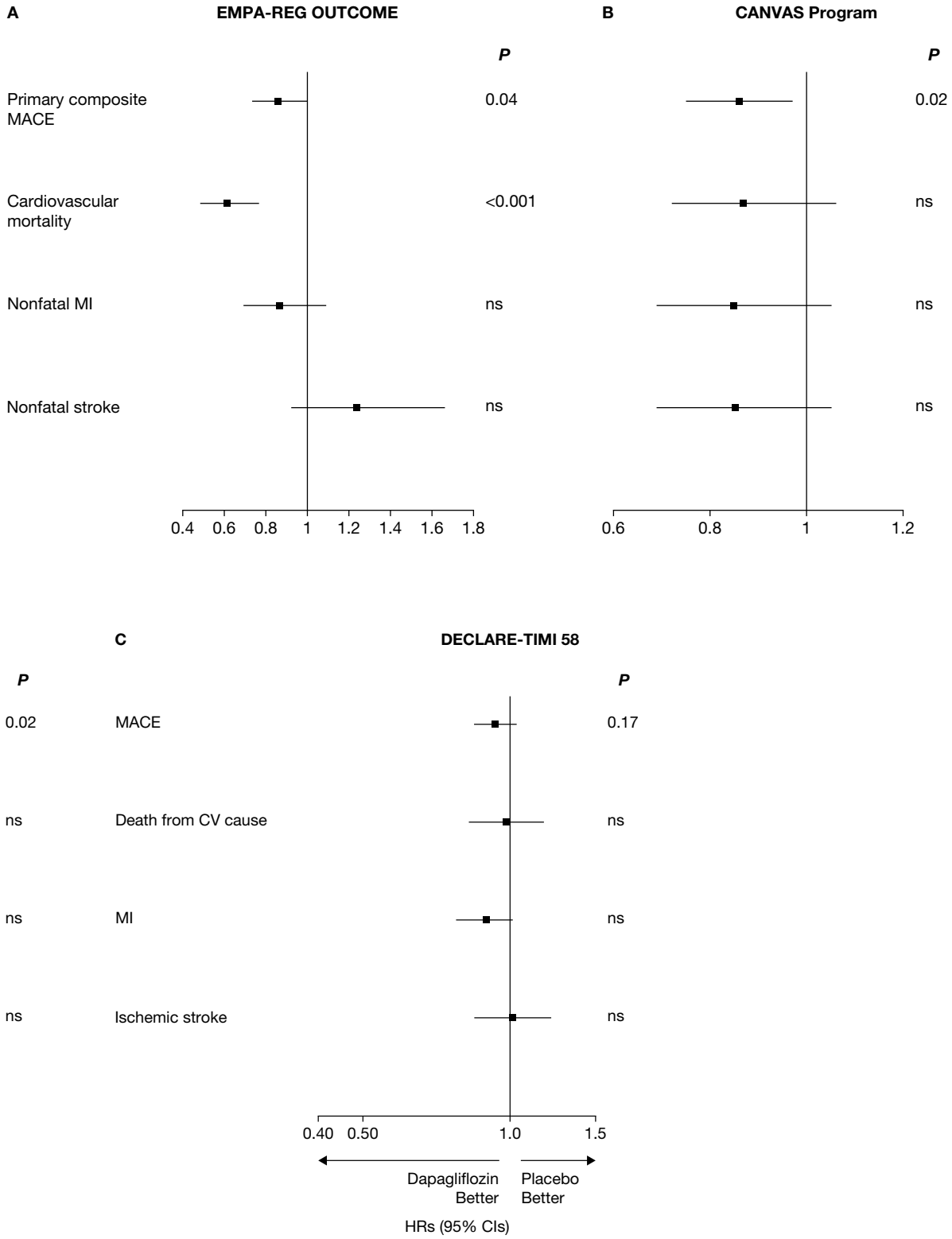


FIGURE 3. Primary endpoints and components in *A*) EMPA-REG OUTCOME (empagliflozin), *B*) CANVAS Program (canagliflozin), and *C*) DECLARE–TIMI 58 (dapagliflozin) (30,32,33). Reproduced from ref. 33. ©2019 Massachusetts Medical Society. All rights reserved.

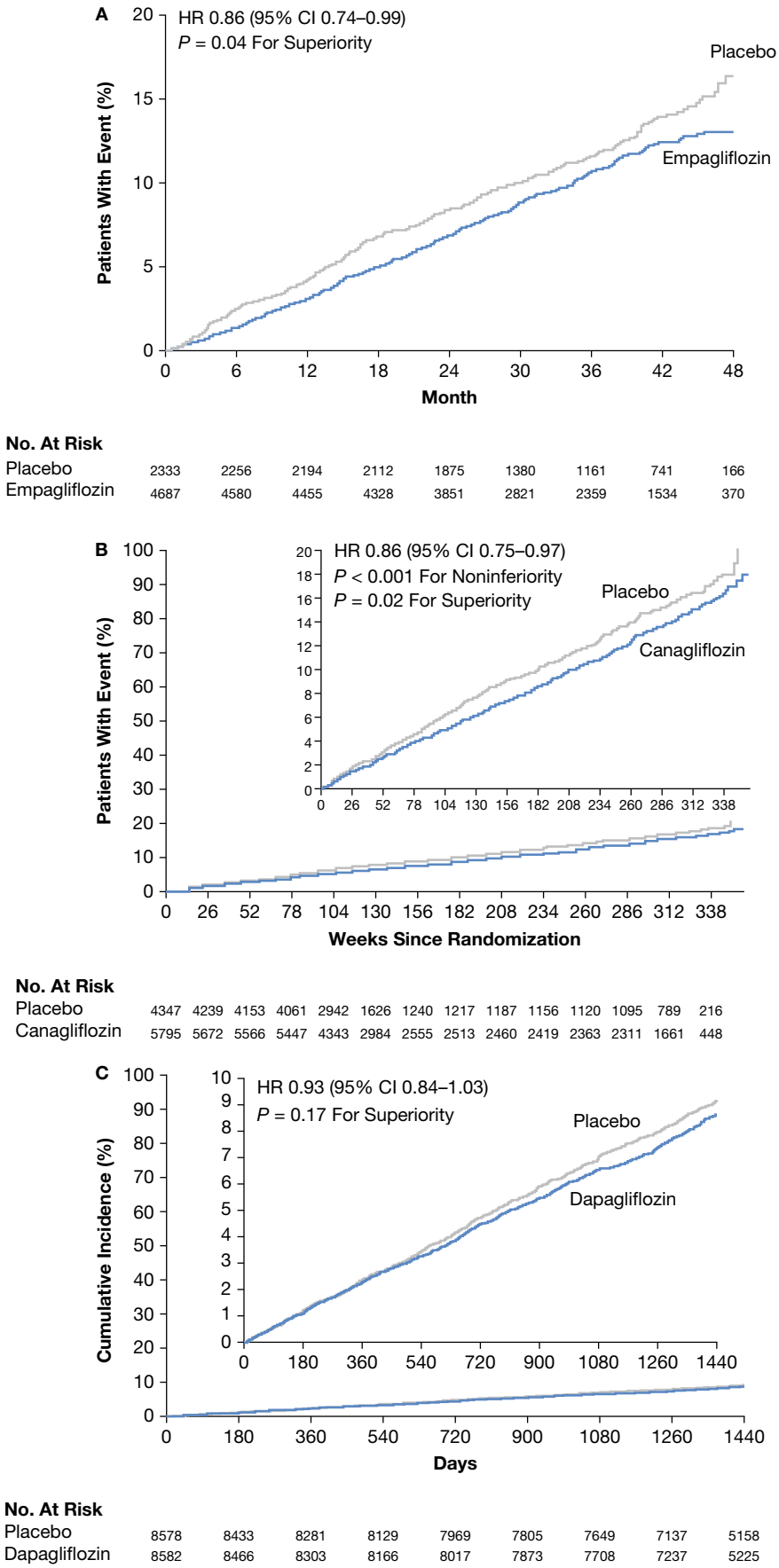


FIGURE 4. Kaplan–Meier plot of the primary outcome* for *A*) EMPA-REG OUTCOME (empagliflozin), *B*) CANVAS Program (canagliflozin), and *C*) DECLARE–TIMI 58 (dapagliflozin) (30,32,33). Inset shows the same data on an expanded *y*-axis. *Death from CV causes, nonfatal MI, or nonfatal stroke. Reproduced from refs. 30, 32, and 33. ©2015, 2017, and 2019 Massachusetts Medical Society. All rights reserved.

pitalization due to HF and CV-related death in patients at high CV risk irrespective of whether they had baseline HF (55). This is the first analysis to show improvements in HF outcomes with glucose-lowering drugs in patients with type 2 diabetes who are at high CV risk. Canagliflozin was also shown to be associated with a lower risk of hospitalization for HF in the CANVAS Program (HR 0.67, 95% CI 0.52–0.87), although based on the prespecified testing sequence, this was considered to be only nominally significant (32). Hospitalization for HF was also reduced in the primary prevention cohort (individuals ≥50 years of age with two or more risk factors for CV events but with no prior CV event: HR 0.64, 95% CI 0.35–1.15, log-rank $P = 0.13$) and the secondary prevention cohort (individuals ≥30 years of age with a prior CV event: HR 0.68, 95% CI 0.51–0.90, log-rank $P = 0.007$) (56). Dapagliflozin also resulted in a lower rate of CV death or hospitalization for HF compared with placebo (4.9 vs. 5.8%, HR 0.83, 95% CI 0.73–0.95, $P = 0.005$), with a similar benefit seen in patients with and without a history of CVD. The dapagliflozin trial was the only study to have CV death or hospitalization for HF as a dual primary endpoint. The precise mechanisms by which SGLT2 inhibitors decrease the risk of HF are unknown; however, multiple potential biological explanations exist (57). Regardless of the reasons, there is little doubt regarding the benefit that SGLT2 inhibitors offer to patients with type 2 diabetes.

TABLE 4. Baseline Characteristics for SGLT2 Inhibitor CVOTs

	EMPA-REG OUTCOME (Empagliflozin) (27) (*n* = 7,020)	CANVAS Program (Canagliflozin) (29) (*n* = 10,142)	DECLARE–TIMI 58 (Dapagliflozin) (31) (*n* = 17,160)
Age, years	63	63	64
Race, %			
White	72.4	78.3	79.6
Asian	21.6	12.7	13.5
Black	5.1	3.3	3.5
Other	0.9	5.7	3.5
Geographical location, %			
Europe	41.1	—	44.5
North America	19.9	—	31.9
Asia	19.2	—	12.7
Rest of the world	19.8	—	11.0
Duration of diabetes, years	>10 (in 57%)	13.5	10.5
Baseline A1C, %	8.1	8.2	8.3
BMI, kg/m^2	30.6	32.0	32.1
CV history, %			
CVD	99	65.6	40.7
MI	46.6	—	—
HF	10.1	14.4	10.1
Stroke/TIA	23.3	—	7.6
Hypertension	—	90.0	—
eGFR <60 mL/min/m^2, %	25.9	—	—

TIA, transient ischemic attack.

In contrast to the GLP-1 receptor agonist trials, all three SGLT2 inhibitor trials showed reductions in prespecified renal composite outcomes. Importantly, they also showed renal benefits, even if one excludes proteinuria (58). The renal benefits of SGLT2 inhibitors include both a reduction in albuminuria and a reduction in the rate of decline in eGFR. Similar results were reported by the recent CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial, which assessed the effects of canagliflozin on renal outcomes in patients with type 2 diabetes and albuminuric CKD (59). In addition, the beneficial effects of canagliflozin in the CREDENCE trial, as determined by the primary composite outcome of end-stage kidney disease, a doubling of the serum creatinine level, or death from renal or CV causes, were seen in the three patient subgroups according to eGFR at screening (30 to <45, 45 to <60, and 60 to <90 mL/min/1.73 m^2) (59).

Safety

Treatment with canagliflozin increased the risk of bone fractures (HR 1.26, 95% CI 1.04–1.52) and doubled the risk of lower-limb amputation, primarily of the toe or metatarsal (6.3 vs. 3.4 cases per 1,000 patient-years, HR 1.97, 95% CI 1.41–2.75); amputations of the leg (below and above the knee) also occurred (32). The absolute risk of amputation was highest in patients with a history of amputation or peripheral vascular disease, but the relative risk of amputation with canagliflozin versus placebo was similar across these subgroups (32). This increased risk of amputation in the CANVAS Program led to the requirement of a boxed warning for canagliflozin in the United States (60). However, in the recent CREDENCE trial, there were no significant differences between canagliflozin and placebo in the rates of fracture or lower-limb amputation (59). In addition, there was a low rate of diabetic ketoacidosis (DKA), although this risk was higher with canagliflozin than with placebo (2.2 vs. 0.2 per 1,000 patient-years) (59). No increase in the risk of lower-limb amputation was observed with empagliflozin in the EMPA-REG OUTCOME trial (61). In the DECLARE–TIMI 58 trial, the rates of amputation and fracture were similar in the dapagliflozin and placebo groups (33). These findings indicate that the amputation risk seen in the CANVAS Program

does not appear to be a class effect of SGLT2 inhibitors. Nevertheless, the EMA issued a recommendation for warnings to be added to the E.U. prescribing information for canagliflozin, dapagliflozin, and empagliflozin of the risk of lower-limb amputation, which occurred in 0.1–1.0% of patients treated with canagliflozin (62). However, in a recent real-world meta-analysis using data from four large U.S. administrative claims databases, there was no increased risk of below-the-knee amputation with canagliflozin or other SGLT2 inhibitors versus non-SGLT2 inhibitor drugs (63).

In all three SGLT2 inhibitor trials, there was an increased risk of genital infection with the SGLT inhibitor compared with placebo (30,32,33). In the empagliflozin trial, the proportion of patients with DKA was low (≤0.1%) and similar in the empagliflozin and placebo groups (30). In the canagliflozin trials, the event rate for DKA was higher with canagliflozin than with placebo (32). In the dapagliflozin trial, DKA was more common with dapagliflozin than with placebo (P = 0.02), although the method of ascertainment of DKA varied across the trials (34).

Potential Impact of Differences in Patient Populations

As with the GLP-1 receptor agonist trials, differences in patient populations could have had an impact on outcomes. In particular, patients in the canagliflozin trials were not required to have established CVD (Table 3) (54).

Potential Impact of Differences in Molecular Properties and Mechanisms of Action

Empagliflozin, dapagliflozin, and canagliflozin share the same mechanism of action and have similar antihyperglycemic, antihypertensive, and weight loss class effects (64). However, there are differences among these agents in their selectivity for the glucose transporter SGLT2 versus other SGLTs, but it is not known whether these differences have any clinical implications (64). For example, empagliflozin has the greatest selectivity (>2,500-fold) for SGLT2 versus SGLT1 compared with dapagliflozin (>1,200-fold) and canagliflozin (>250-fold). The precise mechanism through which they decrease the risk of new-onset HF is unknown; however, possible explanations include hemodynamic benefits, reductions in sympathetic tone, an anti-aldosterone effect, reduction in oxidative stress, and reduction in myocardial oxygen demand (64). Regardless, multiple studies have shown their benefit in HF prevention in patients with diabetes.

Driving Changes in Clinical Practice

CVOTs and the Real World

Overall, current prospective CVOTs have confirmed CV safety but have yielded mixed results in terms of various CV benefits and safety findings, which may be related to differences in the included populations of high-risk CVD patients and in trial designs, in addition to any intrinsic within- and between-class differences. In a recent systematic review and meta-analysis, both GLP-1 receptor agonists and SGLT2 inhibitors were significantly associated with lower CV mortality than control therapy (65). In addition, SGLT2 inhibitors were significantly associated with lower rates of HF and MI than control therapy (65). In a real-world setting, liraglutide was shown to be safe but, unlike in the liraglutide trial, did not demonstrate CV risk reduction in patients with type 2 diabetes over 3 years (66). Real-world studies with exenatide have demonstrated a CV risk reduction, which contrasts with the exenatide trial (53,67,68). In addition, studies that do not specify the type of GLP-1 receptor agonist prescribed have shown varying degrees of results, from safety to a reduced risk of CV outcomes (69,70). In line with the results from RCTs, the existing studies with real-world data confirm the CV safety of GLP-1 receptor agonists but yield mixed results in terms of CV event reduction.

Importantly, trials predominantly included populations of patients at high CVD risk with defined (and varying) characteristics and generally with longstanding diabetes; therefore, it is not clear how generalizable their results are to the overall population of patients with type 2 diabetes, although the dapagliflozin trial had more "primary prevention" patients and so has been suggested to be more generalizable (54,71,72). For example, in the empagliflozin trial, the proportion of patients with type 2 diabetes in a representative English national population that had the same CV risk as those in the trial was 15.7% (73). The inclusion of patients at high CVD risk in event-driven CVOTs is necessary to demonstrate safety in these patients, as well as to ensure that a sufficient number of events are accrued in a reasonably short timeframe. However, these patients form a relatively small number of individuals with type 2 diabetes treated in routine practice; CV safety concerns equally apply to the great many patients without established CVD who face many years of treatment with new antihyperglycemic agents. Studies from routine practice settings are important to confirm findings from highly controlled CVOTs in the more challenging and varied real-world practice.

U.S. Indications

The data from all CVOTs discussed fulfill the FDA criteria of establishing CV safety for lixisenatide, liraglutide, semaglutide, exenatide extended release, albiglutide, dulaglutide, empagliflozin, canagliflozin, and dapagliflozin in patients with type 2 diabetes at high CV risk. In the United States, empagliflozin is now indicated to reduce the risk of CVD-related death in adult patients with type 2 diabetes and established CVD (74), and the indication for liraglutide has also recently been expanded to reduce the risk of MACE in the same population (75); to date, neither drug has such an in-

dication in the European Union. The results of these CVOTs have been included in recent treatment guideline updates from the American Diabetes Association (ADA) (76,77), Diabetes Canada (78), and the recent consensus report on the management of hyperglycemia in type 2 diabetes from the ADA and the European Association for the Study of Diabetes (EASD) (79).

Treatment Guidelines

The ADA's *Standards of Medical Care in Diabetes—2019* recommend that a patient-centered approach should be used to guide treatment choice, with comorbidities such as ASCVD, HF, and CKD; hypoglycemia risk; impact on weight, cost; risk of side effects; and patient preference taken into consideration (76). The 2019 Standards of Care also recommend that, among patients with type 2 diabetes who have established ASCVD, an SGLT2 inhibitor or GLP-1 receptor agonist with demonstrated CVD benefit should be part of the antihyperglycemic regimen (76). Among patients with ASCVD at high risk of HF or for whom HF coexists, SGLT2 inhibitors are preferred. For patients with type 2 diabetes and CKD, an SGLT2 inhibitor or GLP-1 receptor agonist that reduces the risk of CKD progression, CV events, or both should be considered (76). Similarly, in its 2018 update, Diabetes Canada used data from the empagliflozin, liraglutide, and canagliflozin trials to recommend that adults with type 2 diabetes and clinical CVD who are not meeting glycemic targets should have an "antihyperglycemic agent with demonstrated CV outcome benefit" added to reduce the risk of major CVD events, with Grade A, Level 1A recommendations for empagliflozin and liraglutide and a Grade C, Level 2 recommendation for canagliflozin (78). The recent ADA/EASD consensus report recommends that clinicians consider whether a patient has a history of CVD early in the treatment selection process. GLP-1 receptor agonists with a proven CV benefit or SGLT2 inhibitors (if eGFR is adequate) are recommended for patients with type 2 diabetes and existing ASCVD. In addition, SGLT2 inhibitors with a proven benefit of reducing HF and/or CKD progression are recommended for patients with HF and/or CKD and adequate eGFR among patients with ASCVD in whom HF or CKD is a concern (or, if SGLT2 inhibitors are contraindicated or not tolerated or eGFR not adequate, a GLP-1 receptor agonist with a proven CVD benefit) (79).

Clearly, the level of evidence from large CVOTs supporting the CV benefits of newer therapies is markedly more robust in modern CVOTs, which randomized thousands of patients with type 2 diabetes (80), than in earlier trials. Cost is likely to be a factor in the earlier use of newer (and more expensive) drugs, and certain guidelines (e.g., the U.S. Veterans Affairs and National Institute for Health and Care Excellence guidelines) factor cost of treatment into their algorithms more than others. Cost-effectiveness analyses are also beginning to emerge; for example, based on the results of the empagliflozin trial, taking the expected reductions in CVD deaths, hospitalizations for HF, and the need for dialysis or transplantation into account, treating patients with type 2 diabetes at high CVD risk with empagliflozin added to standard of care was found to be very cost-effective in a Canadian study (81).

Treatment Algorithms

The ADA/EASD consensus report created separate algorithms for patients with and without CVD to help guide individualization of therapy (79), and future guidelines may also need to take this approach. There could also be a need to look at supplementing A1C with CVD risk factors in future algorithms (80). Glycemic control assessed by A1C has been the cornerstone of type 2 diabetes management to reduce the risk of microvascular and macrovascular complications, largely based on results from the UKPDS. In recent CVOTs, however, CV benefits were seen with the investigational drugs compared with placebo despite statistically significant but relatively small differences in A1C levels, with a reduction in the number of CV events occurring at all levels of A1C. Thus, rather than A1C level being the basis for choosing either a GLP-1 receptor agonist or an SGLT2 inhibitor, the selection of these agents should be based on the need for CV protection in patients at high risk of CVD. Furthermore, a recent meta-analysis of 46 studies concluded that A1C is a reliable risk factor for all-cause and CV mortality (82). Regardless, based on these trials, the specific agent used to achieve glycemic control appears to drive CV benefit.

Individualizing Therapy

Guidelines recommend individualization of therapy, and the aforementioned CVOTs had broad inclusion criteria for A1C levels. It may be preferable to target specific complications and inherent risks, rather than glucose levels alone. Thus, it is key to include appropriate cardioprotective antihyperglycemic agents in the regimen of a patient with a history of CVD or who is at a very high risk.

For practicing clinicians, individualization of therapy remains the cornerstone for selection of hyperglycemic agents in type 2 diabetes. Although the latitude of choice given by treatment guidelines can be a positive in this respect, it can also be a negative for busy clinicians faced with an ever-increasing number of options. In addition to their efficacy in reducing A1C and their CV benefits, GLP-1 receptor agonists and SGLT2 inhibitors are also attractive from patients' and clinicians' perspectives given that they pose no increased risk of hypoglycemia (provided they are not used with agents that cause hypoglycemia, such as sulfonylureas and insulin) and provide the benefit of weight loss. In addition, the SGLT2 inhibitors canagliflozin, empagliflozin, and dapagliflozin have a beneficial effect

on the progression of CKD and prevention of HF.

GLP-1 receptor agonists have beneficial effects on a number of CV risk factors such as weight, blood pressure, lipid profile, UACR, and inflammatory markers, among others. Lixisenatide reduced the progression of albuminuria in patients with macroalbuminuria and was also associated with a reduced risk of developing new-onset macroalbuminuria, consistent with the results of the liraglutide and semaglutide trials (22,24,43,58).

Clinical Trial Design

As more data from CVOTs emerge, more focused guidance on trial design should be given to reach agreement on a standard trial design, including such factors as standard inclusion/exclusion criteria, comparators, and length of study. For example, it may be possible to stratify patients into benefit groups, analogous to blood cholesterol guidelines, with recommendations matching level of therapy to the level of CVD risk. Guidelines may need to become more focused based on patient characteristics and risk factors or level of risk.

One consideration for future CVOTs in patients with type 2 diabetes with high CVD risk would be to include an active control therapy that has proven superiority to placebo, but this would need an appropriate criterion to address noninferiority to avoid prohibitively large sample sizes. An alternative criterion for an active control therapy trial could involve an indirect comparison to placebo through an integrated analysis of future and previous CVOTs for comparison of active control therapy and placebo and could use a model that includes predictive baseline variables for CV outcomes for the active control therapy and placebo in previous trials. This paradigm could be expanded for future trials to address comparisons to two or more active control therapies with proven superiority to placebo. For CVOTs in patients with type 2 diabetes and low CVD risk, one consideration is to produce CIs that exclude excess CVD risk. Well-designed, prospective, observational studies could be used to address the required sample sizes and follow-up duration.

Given that multiple trials have demonstrated a benefit to CVD risk, it is important to question whether it is ethical to conduct placebo-controlled trials (83). Placebo-controlled trials would still be possible in specific at-risk populations that represent an unmet need (e.g., HF or CKD) (83). In active-comparator trials, it may also be possible to define different noninferiority criteria. Because diabetes is a progressive disease that requires intensification of therapy with multiple agents, it may also be clinically relevant to compare therapeutic approaches rather than comparing one agent against another. One question that would be of interest is whether metformin should remain the first agent of choice to manage type 2 diabetes. The evidence of the beneficial effect of metformin to reduce CVD events in the UKPDS was limited to a relatively small number of events. On the other hand, the evidence from CVOTs conducted with GLP-1 receptor agonists and SGLT2 inhibitors relates mostly to secondary prevention. Thus, for a newly diagnosed person with type 2 diabetes and no CV risk factors, there are no randomized data to support a newer agent instead of metformin. One potential trial in patients treated with metformin could be to compare sequential therapy addition with early combination therapy using a GLP-1 receptor agonist and an SGLT2 inhibitor. However, a trial comparing metformin to one of the newer agents showing CV benefit has yet to be undertaken.

Clinical Trial Endpoints

Consideration needs to be given to the selection of suitable endpoints in future trials (37). Because of their different mechanisms of action, individual glucose-lowering drugs may have very different impacts on various CVD outcomes; therefore, no particular endpoint can be considered a gold standard for all CVOTs. A three-point MACE is likely to remain the primary endpoint for CVOTs; it best captures clinically relevant CV outcomes, has individual components that are reasonably straightforward to adjudicate, is relatively easy to implement, and is favored by regulatory authorities. However, other endpoints have also been considered and may be appropriate for some drug classes.

There has been debate around including hospitalization for UA in the MACE definition (four-point MACE). Although UA, like MI, is part of the spectrum of ACS and is thus clinically relevant, its diagnosis is subjective, and central adjudication is challenging. Data from CVOTs also suggest that UA is difficult to influence with glucose-lowering agents, which may dilute any treatment effect for this composite endpoint. The addition of hospitalization for UA to the MACE definition may make it more likely that noninferiority is demonstrated but may also mask potential CVD benefit or harm.

Comparing CVOTs

For GLP-1 receptor agonists, given possible differences in binding, signaling, and pharmacokinetics, and a range of differences in study designs, endpoints, and patient characteristics in CVOTs, it is difficult to directly compare individual agents. However, a meta-analysis of the large CVOTs (41) and the results of a recent retrospective real-world analysis (53) suggest that there may be a class effect for GLP-1 receptor agonists in terms of CV safety and the reduction in risk of CV events.

The CV safety and potential CV benefits of SGLT2 inhibitors may also be a class effect (84). As for SGLT2 inhibitors overall, as discussed previously, comparisons between the outcomes of recent CVOTs are complicated by a number of factors, including differences in patient pop-

ulations (e.g., selection and exclusion criteria, race, and definition of CVD risk), sample sizes, trial durations, and endpoints used (71). Discontinuation rates and rates of rescue medication initiation in these studies were high, which may also affect the interpretation of these results. Therefore, it is not possible to directly compare outcomes between drugs within or between classes.

For both GLP-1 receptor agonists and SGLT2 inhibitors, only well-planned, head-to-head CVOTs can fully address whether any CVD benefits or safety concerns are indeed class effects or whether one agent is superior to another. In such trials, a third arm of patients receiving combination therapy would be of great interest.

Summary and Conclusion

Subsequent to the FDA guidance on the design of CVOTs issued in 2008, CVOTs have shown CV safety with DPP-4 inhibitors. More recently, the CV safety of injectable GLP-1 receptor agonists and SGLT2 inhibitors has been demonstrated in CVOTs, as well as their CV benefits, which may be class effects. The results of the recent REWIND trial suggest that dulaglutide may have both primary and secondary CV benefits, adding to the body of evidence on the CV effects of injectable GLP-1 receptor agonists. Further studies are needed to determine the mechanisms of action of both these drug classes that are responsible for the beneficial CV effects. In addition to their CV benefits, the fact that both GLP-1 receptor agonists and SGLT2 inhibitors induce weight loss and do not cause hypoglycemia makes them attractive clinical tools. The importance of GLP-1 receptor agonists and SGLT2 inhibitors in clinical care has been highlighted in the 2019 ADA Standards of Care (77), where they are now recommended as second-line options (before insulin therapy) for the following patient groups failing to achieve target A1C with metformin and lifestyle modifications: *1*) those with established ASCVD, *2*) those with a compelling need to minimize hypoglycemia, and *3*) those with a compelling need to minimize weight gain or promote weight loss.

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Author Contributions

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