Cardiovascular Outcomes with Once-Weekly GLP-1 RAs: Clinical and Economic Implications

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is associated with an increased risk of atherosclerotic cardiovascular (ASCVD) disease, which is the largest contributor to the economic burden of diabetes. Minimization of disease morbidity through comprehensive management of ASCVD risk factors, including but not limited to hyperglycemia, is a key goal of T2DM therapy. Emerging evidence with some glucagon-like peptide-1 receptor agonists (GLP-1 RAs) points to beneficial effects across a range of atherosclerotic risk factors and possible improvement of some cardiovascular outcomes independent of these effects. Given these benefits, there has been substantial interest in evaluating the cardiovascular safety of GLP-1 RAs as well as their potential to reduce the risk of major adverse cardiac events (MACE). Following the superior clinical outcome with the once-daily GLP-1 RA liraglutide (Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results [LEADER]), this review examines and summarizes the effects of once-weekly GLP-1 RAs, including exenatide extended release (ER), dulaglutide, and semaglutide, on reducing cardiovascular events in patients with T2DM. A phase 3 cardiovascular outcomes trial (EXSCEL) of exenatide ER found no significant difference between exenatide ER and placebo in reducing MACE in patients with T2DM. In a phase 3 premarketing trial in T2DM patients at high risk of cardiovascular disease (SUSTAIN-6), semaglutide significantly reduced the risks of MACE and non-fatal stroke compared with placebo. A phase 3 study (REWIND) is underway to evaluate the effects of dulaglutide on MACE. Considering the substantial costs of cardiovascular disease in patients with T2DM, it will be of interest to assess the impact of treatment with once-weekly GLP-1 RAs on cardiovascular disease-related costs among patients with T2DM.

Type 2 diabetes mellitus (T2DM) is associated with an increased risk of multiple comorbidities due to insulin resistance, hyperglycemia-induced abnormalities, oxidative stress, and inflammation throughout the vascular system.[1] Atherosclerotic cardiovascular disease (ASCVD) encompasses cardiac-related events such as acute coronary syndromes, stable or unstable angina, transient ischemic attack, history of myocardial infarction (MI), coronary or arterial revascularization, stroke, and peripheral arterial disease.[2] Both ASCVD and related risk factors are common among patients with diabetes.[1] There is a 2- to 4-fold increased risk of ASCVD development in people with T2DM.[1] In addition, ASCVD is the primary cause of death in patients with T2DM and has been established as the largest contributor to the direct and indirect costs of diabetes.[2]

Several studies have examined whether intensive blood glucose control (i.e., targeting glycated hemoglobin [A1c] levels as low as 6.0%-6.5%) can reduce CV risk, but collective findings have been inconclusive. The United Kingdom Prospective Diabetes Study (UKPDS) observed a trend toward reduced cardiovascular risk (MI) with intensive glycemic control over 10 years, but it was not statistically significant[3]; however, post-trial monitoring of the UKPDS for an additional 10 years demonstrated significant reductions in the risks of MI among patients with new-onset diabetes initially assigned to intensive glycemic control (15% reduction; $P = 0.01$) and all-cause mortality ($P = 0.007$).[4] Additional studies with median follow-up periods of 3.4-5.6 years, including the Action in Diabetes and Vascular Disease (ADVANCE) study,[5] the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study,[6] and the Veterans Affairs Diabetes Trial (VADT),[7] did not observe a significant benefit of intensive glycemic control on primary cardiovascular endpoints; further, the ACCORD study observed increased all-cause mortality in the intensive therapy arm. In the Steno-2 study (mean follow-up, 7.8 years), a significant reduction in cardiovascular risk in patients with T2DM and microalbuminuria was achieved with an intensive multifactorial strategy, but patients remain at risk.[8]

A meta-analysis of randomized rosiglitazone trials with more than 24 weeks of drug exposure suggested an increased risk of MI and death from ASCVD causes associated with rosiglitazone treatment.[9] Subsequently, based on the RECORD trial,[10] the U.S. Food and Drug Administration (FDA) recognized that rosiglitazone does not increase the risk of overall cardiovascular morbidity or mortality relative to other antidiabetic drugs. However, by that time, the FDA had implemented new antidiabetes drug cardiovascular safety guidelines. The FDA "Guidance for Industry" for new diabetes drugs, enacted in 2008, requires evidence of a lack of substantial increase in cardiovascular risk[11] either through meta-analysis of phase 2-3 trials or through clinical trials showing noninferiority versus placebo for cardiovascular outcomes. Given the mixed effect of glycemic control and residual ASCVD risk despite multifactorial therapy and data raising suggestions of increased ASCVD risk with certain antidiabetic agents,[9] long-term cardiovascular outcome trials for antidiabetes medications are essential to examine their effect on ASCVD risk. An ideal goal of T2DM therapy would be to improve a wide range of health outcomes and minimize disease morbidity through effective and cost-effective comprehensive management of blood glucose as well as all ASCVD risk factors.[2] As described below, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) exert beneficial effects across a range of ASCVD risk factors.

| TABLE 1 | Impact of Once-Weekly GLP-1 RAs on Cardiovascular Risk Factors: Change from Baseline (Ranges Reported in Clinical Studies) |

	Range of Mean Changes from Baseline Reported in Published Studies						
	A1c (Mean Absolute Change), %	Weight (kg)	Waist Circumference (cm)	Systolic Blood Pressure (mmHg)	LDL-C (mg/dL and/or % change)[a]	HDL-C (mg/dL and/or % change)[a,b]	Triglycerides (mg/dL and/or % change)[b]
Short-term studies (≤ 30 weeks)							
Exenatide ER[22-29]							
2.0 mg	-0.9 to -1.9	-2.0 to -3.7	-2.1 to -2.7	-1.3 to -4.7	+0.5 to -6.4	-0.4 to +0.4	-3.2/-4% to -15%
Dulaglutide[30-36]							
0.75 mg	-0.7 to -1.6	+0.2 to -1.4	NR	-0.4 to -2.6	-0.9 to -1.4/-3%	+0.4 to +0.5/+4%	-1.4 to -2.5/-2%
1.5 mg	-0.8 to -1.6	-0.9 to -2.9	NR	+0.1 to -3.4	-2.0 to -3.2/-7%	+0.2 to +1.1/+2%	-3.2 to -3.6/-2%
Semaglutide[37-39]							
0.5 mg	-1.2 to -1.5	-3.5 to -3.7	-3.2 to -3.7	-2.6 to -4.7	0% to -4%	-2% to +2%	-8% to -11%
1.0 mg	-1.5 to -1.8	-4.5 to -6.4	-4.1 to -4.5	-2.7 to -7.3	-5% to -8%	-1% to 0%	-8% to -13%
Long-term studies (≥ 52 weeks)							
Exenatide ER[40-45]							
2.0 mg	-1.0 to -2.0	-1.5 to -4.2	-2.0	+1.7 to -6.2	-3.1 to -9.1	-0.7 to +2.6	+18.4 to -8/ -12% to -15%
Dulaglutide[30-33,46,47]							
0.75 mg	-0.6 to -1.4	-1.3 to -2.6	NR	+1.6 to -2.7	+0.4 to -1.4/ -1% to -2%	-0.4 to +1.3/ +2% to +4%	+0.7 to -2.9/ +6% to -1%
1.5 mg	-0.7 to -1.5	-1.9 to -3.0	NR	+0.8 to -0.8	+1.1 to -1.1/-2%	0 to +0.9/ +2% to +5%	+0.9 to -4.7/ +3% to -4%
Semaglutide[48-50]							
0.5 mg	-1.3	-3.6 to -4.3	-4.3	-3.4 to -5.1	-3%	-1%	-7%
1.0 mg	-1.5 to -1.6	-4.9 to -6.1	-3.1 to -5.9	-4.6 to -5.6	-2% to -5%	+1% to +2%	-8% to -15%

[a]*Expressed as mg/dL if reported as mg/dL or mmol/L; expressed as % if reported only as a percentage change from baseline; if reported in some studies as mg/dL or mmol/L and in others as %, then expressed as mg/dL/%.*

[b]*Note that, unlike other outcomes, reported in order from negative to positive because an increase from baseline in HDL-C is desirable.*

ER = extended release; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; NR = not reported.

## ■ Glucagon-Like Peptide-1 Receptor Agonists

GLP-1 RAs activate the GLP-1 receptor on pancreatic beta cells to stimulate glucose-dependent insulin secretion. They also slow gastric emptying and increase satiety, which leads to reduced food intake.[2,12,13] Indirect effects on glucagon secretion have also been described, resulting in normalization of the abnormally elevated glucagon levels seen in T2DM.[2,12-14] The first approved GLP-1 RA was exenatide (Byetta; AstraZeneca Pharmaceuticals, Wilmington, DE),[15] which is administered twice daily via subcutaneous (SC) injection. Subsequently approved GLP-1 RAs with once-daily SC dosing include liraglutide (Victoza, Novo Nordisk, Plainsboro, NJ),[16] and, more recently, the short-acting lixisenatide (Adlyxin; Sanofi-Aventis U.S., Bridgewater, NJ).[17] Other agents have prolonged action and can be administered once weekly, including exenatide extended-release (ER; Bydureon; AstraZeneca Pharmaceuticals, Wilmington, DE),[18] dulaglutide (Trulicity; Eli Lilly and Company, Indianapolis, IN),[19] and semaglutide (Ozempic; Novo Nordisk, Plainsboro, NJ).[20]

To varying degrees, class advantages of GLP-1 RAs include effective lowering of A1c levels, weight loss, and a low risk of hypoglycemia.[2,21] As a class, the GLP-1 RAs are unique in that they have beneficial effects across a wide range of individual atherosclerotic risk factors, including hyperglycemia, overweight/central obesity, hypertension, and dyslipidemia. Table 1 describes the ranges of effects of once-weekly GLP-1 RAs on these factors as observed in phase 3 clinical studies. Although Table 1 indicates differences between individual once-weekly GLP-1 RAs with regard to their effects on various atherosclerotic risk factors, it should be considered that differences in patient selection criteria and background medication may have contributed to observed disparities.

Given the beneficial effects of GLP-1 RAs in several organ systems that affect cardiovascular health and the localization of GLP-1 receptors in cardiac and vascular tissues, researchers have suspected that GLP-1 RAs might have the potential to improve cardiovascular outcomes (Figure 1).[51] Accumulating evidence suggests that GLP-1 RAs may favorably affect cardiovascular risk through direct actions on the myocardium and blood vessels.[51-53] Animal studies have associated GLP-1 RAs with inflammatory response inhibition, increased coronary flow, and additional benefits for myocardial function.[54]

FIGURE 1 Potential Indirect Cardiovascular Effects of GLP-1 RAs[51]
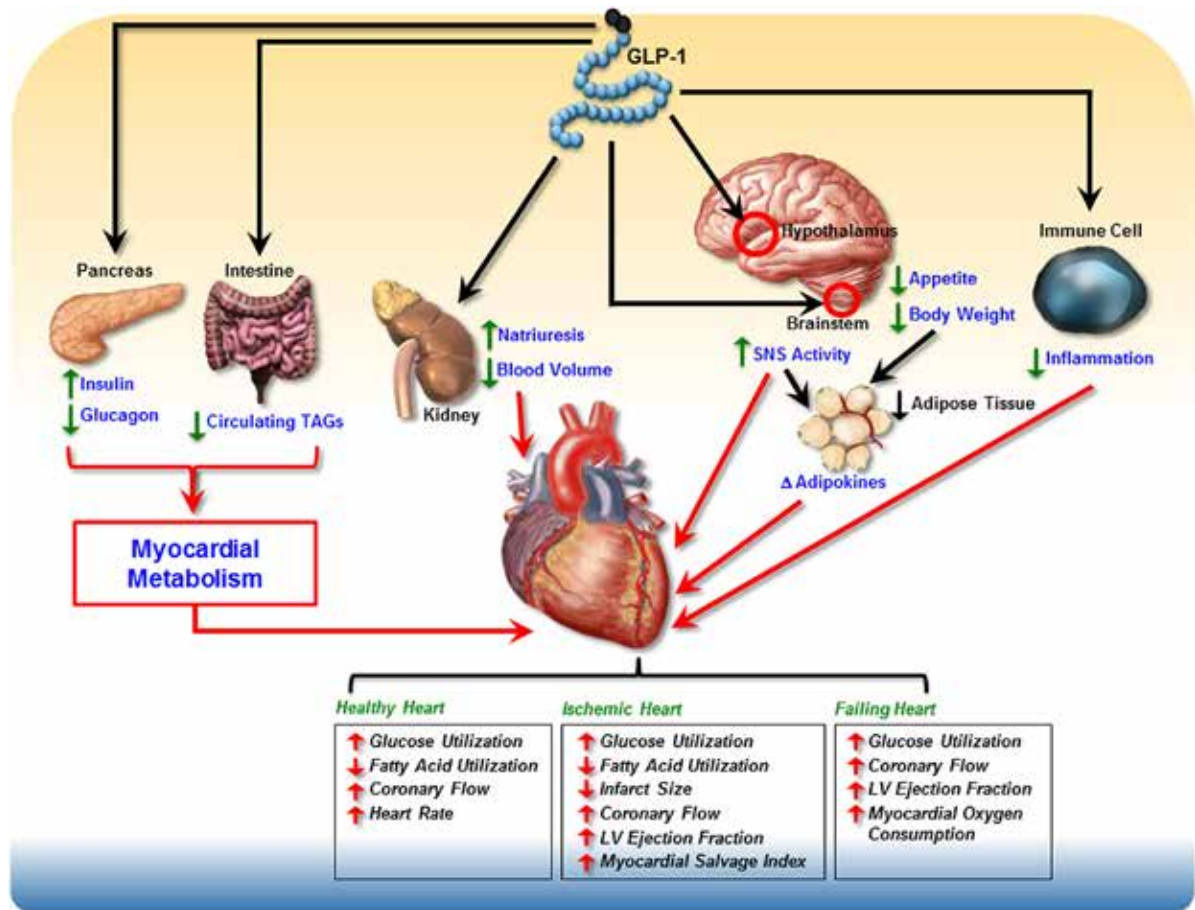
From Ussher JR, Drucker DJ. Cardiovascular actions of incretin-based therapies. Circ Res. 2014;114(11):1788-803 (https://www.ahajournals.org/doi/10.1161/CIRCRESAHA. 114.301958?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed). Copyright © 2014. Reprinted with permission.

Note: Direct actions of GLP-1 on islets result in elevated insulin and reduced glucagon levels, whereas GLP-1 action in the intestine has been associated with reductions in circulating lipids. These metabolic alterations decrease fatty acid delivery and enhance glucose uptake in the heart and may explain the increased glucose/decreased fatty acid utilization and enhanced LV function observed in the myocardium after systemic GLP-1 R activation. Direct actions on immune cells to decrease inflammation may also indirectly improve myocardial metabolism and subsequent contractile function. Furthermore, direct actions on the SNS may contribute to GLP-1-induced alterations in heart rate, whereas the reduction in appetite after hypothalamic GLP-1 R activation results in reductions in adiposity and body weight, which, combined with the direct and indirect effects on the kidney to decrease blood volume (through increased natriuresis), likely contribute to the overall improvement in LV function after systemic GLP-1 R activation.

GLP-1 = glucagon-like peptide-1 GLP-1 R = glucagon-like peptide-1 receptor; GLP-1 RA = glucagon-like peptide-1 receptor agonist; LV = left ventricular; SNS = sympathetic nervous system; TAG = triacylglycerol.

Relevant research in human populations requires large patient numbers and long-term studies, but such data are now starting to come to fruition, including some landmark trials with the once-daily GLP-1 RAs liraglutide and lixisenatide. The long-term cardiovascular benefits of liraglutide were illustrated in the Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER) study, an international, double-blind trial that randomized 9,340 patients with T2DM at high risk of cardiovascular disease to liraglutide or placebo.[52] This study showed that liraglutide significantly

(P = 0.01) reduced the risk of a composite major adverse cardiac event (MACE) outcome of death from cardiovascular causes, nonfatal MI, or nonfatal stroke compared with placebo (hazard ratio [HR] = 0.87; 95% confidence interval [CI] = 0.78-0.97) and also significantly reduced the rate of death from cardiovascular causes (HR = 0.78; 95% CI = 0.66-0.93; P = 0.007) and the rate of all-cause mortality (HR = 0.85; 95% CI = 0.74-0.97; P = 0.02).

The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial (N = 6,068) observed no significant differences between lixisenatide and placebo in the occurrence of MACE,

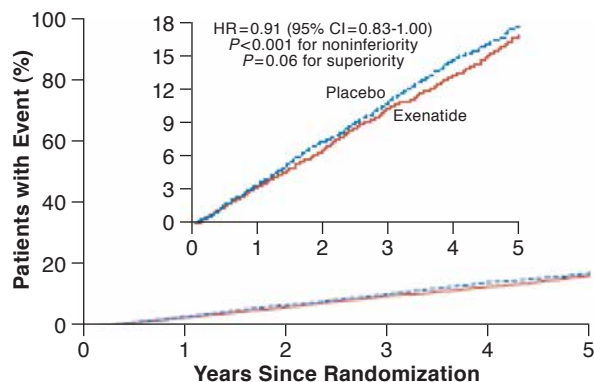| TABLE 2	Studies Evaluating MACE with Once-Weekly GLP-1 RAs
Exenatide QW: EXSCEL trial[61]	
Study population	Adults with T2DM, with or without previous CV disease; patients could receive ≤3 OADs or insulin+≤2 OADs (73.1% with prior CV disease)
Number/ observation period	Exenatide QW, n=7,356; placebo, n=7,396
	Median observation period=3.2 years
CV-related endpoints	*Primary:* Composite outcome: first occurrence of death from CV causes, nonfatal MI, or nonfatal stroke
	Secondary: Death from any cause, death from CV causes, and the first occurrence of nonfatal or fatal MI, nonfatal or fatal stroke, hospitalization for acute coronary syndrome, and hospitalization for heart failure in time-to-event analyses
Topline findings	*Primary:* 11.4% in the exenatide group (3.7 events per 100 person-years) vs. 12.2% in the placebo group (4.0 events per 100 person-years; HR=0.91; 95% CI=0.83-1.00)
	Secondary: The rates of the first fatal or nonfatal MI, fatal or nonfatal stroke, and other secondary outcomes were not significantly different between the 2 groups
Conclusions	The incidence of MACE was not significantly different between exenatide QW and placebo treatment
Dulaglutide: REWIND trial (ongoing)[62]	
Study population	Newly diagnosed T2DM patients with A1c≤9.5% treated with ≤2 classes of OADs, with or without basal insulin
	Additional eligibility requirements: 50-54 years of age: previous CV disease; 50-59 years of age: either previous CV disease or evidence of other vascular or renal disease; aged ≥60 years: previous CV disease, other vascular or renal disease, or ≥2 other CV risk factors
Number/ observation period	9,901 participants recruited
	Mean duration of follow-up: 6.5 years
CV-related endpoints	*Primary:* First occurrence of the composite of cardiovascular death or nonfatal MI or nonfatal stroke
	Secondary: Each component of the primary composite CV 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
Topline findings	TBD (expected completion July 2018)
Conclusions	TBD (expected completion July 2018)
Semaglutide: SUSTAIN-6 study[50]	
Study population	Patients ≥50 years of age with T2DM and A1c≥7% treated with ≤2 OADs±basal or premixed insulin
	Patients were at high CV risk
Number/ observation period	Semaglutide, n=1,648; placebo, n=1,649
	Median observation period=2.1 years
CV-related endpoints	*Primary:* Composite outcome: first occurrence of CV death, nonfatal MI, or nonfatal stroke
	Secondary: First occurrence of an expanded composite CV outcome (death from CV causes, nonfatal MI, nonfatal stroke, revascularization [coronary or peripheral], and hospitalization for unstable angina or heart failure), an additional composite outcome (death from all causes, nonfatal MI, or nonfatal stroke), or the individual components of the composite outcome
Topline findings	*Primary:* Semaglutide-treated patients had a significant 26% lower risk of the primary composite outcome; 6.6% in the semaglutide group vs. 8.9% in the placebo group (HR=0.74; 95% CI=0.58-0.95; *P*<0.001 for noninferiority)
	Secondary: Nonfatal MI occurred in 2.9% of patients receiving semaglutide vs. 3.9% of those receiving placebo (HR=0.74; 95% CI=0.51-1.08; *P*=0.12); nonfatal stroke occurred in 1.6% and 2.7%, respectively (HR=0.61; 95% CI=0.38-0.99; *P*=0.04); expanded composite CV outcome: 12.1% with semaglutide vs. 16.0% with placebo (HR=0.74; 95% CI=0.62-0.89); the following were not significantly different between groups (*P*≥0.05): death from any cause, death from CV cause, nonfatal MI, hospitalization for unstable angina, hospitalization for heart failure
Conclusions	The rate of MACE was significantly lower in patients receiving semaglutide compared with those receiving placebo and confirmed the noninferiority of semaglutide

A1c=glycated hemoglobin; CI=confidence interval; CV=cardiovascular; GLP-1 RA=glucagon-like peptide-1 receptor agonist; HR=hazard ratio; MACE=major adverse cardiovascular event; MI=myocardial infarction; OAD=oral antidiabetic drug; QW=once weekly; T2DM=type 2 diabetes mellitus; TBD=to be determined.

the rate of hospitalization for heart failure, or the rate of death among patients with T2DM who had experienced acute coronary syndrome within 180 days before screening.[55] In addition, recently published large meta-analyses of data from GLP-1 RA studies have identified potential benefits with regard to all-cause mortality, cardiovascular mortality, and MACE risk, although quality and conclusions of meta-analyses are not uniform, and there are likely differences between individual GLP-1 RAs.[56-60]

Once-weekly GLP-1 RAs are increasing in use as they provide an efficacious treatment, with lower rates of hypoglycemia and weight gain similar to the daily options but with the added benefit of a decreased injection burden. For this reason, the purpose of this article is to review published cardiovascular outcome data specific to once-weekly GLP-1 RAs, including exenatide ER, dulaglutide, and semaglutide.
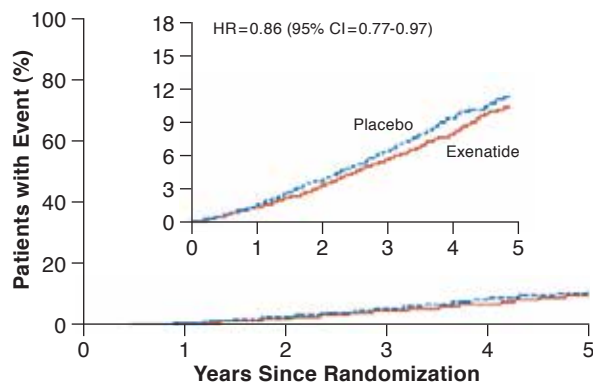
FIGURE 2 Cardiovascular Outcomes with Once-Weekly Exenatide Versus Placebo, EXSCEL Trial[61]
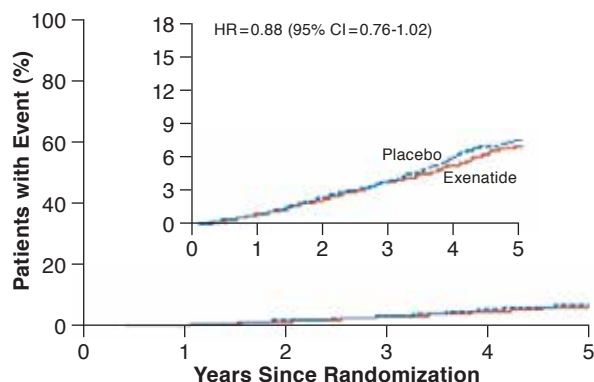

A. Primary Cardiovascular Outcome

HR=0.91 (95% CI=0.83-1.00)
P<0.001 for noninferiority
P=0.06 for superiority

At Risk, n											
Placebo	7,396	7,120	6,897	6,565	5,908	4,468	3,565	2,961	2,209	1,366	687
Exenatide	7,356	7,101	6,893	6,580	5,912	4,475	3,595	3,053	2,281	1,417	727

B. Death from Any Cause

HR=0.86 (95% CI=0.77-0.97)

At Risk, n											
Placebo	7,396	7,344	7,278	7,058	6,470	5,019	4,091	3,478	2,666	1,695	892
Exenatide	7,356	7,304	7,234	7,028	6,433	4,991	4,095	3,518	2,698	1,726	907

C. Death from Cardiovascular Causes

HR=0.88 (95% CI=0.76-1.02)

At Risk, n											
Placebo	7,396	7,344	7,278	7,058	6,470	5,019	4,091	3,478	2,666	1,695	907
Exenatide	7,356	7,304	7,234	7,028	6,433	4,991	4,095	3,518	2,698	1,726	892

D. Hospitalization for Heart Failure

HR=0.94 (95% CI=0.78-1.13)
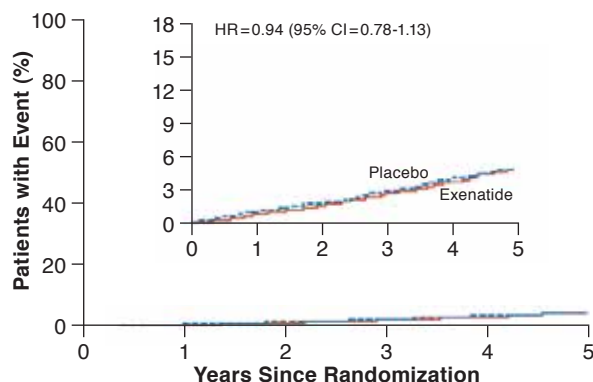
At Risk, n											
Placebo	7,396	7,183	7,019	6,743	6,112	4,678	3,756	3,156	2,375	1,464	735
Exenatide	7,356	7,174	7,023	6,756	6,108	4,669	3,790	3,234	2,430	1,517	776

From Holman RR, Bethel MA, Mentz RJ, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2017;377(13):1228-39. Copyright © 2017 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Note: This figure shows the rates of the primary cardiovascular outcome (a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke), death from any cause, death from cardiovascular causes, and hospitalization for heart failure in the exenatide and placebo groups. The inset in each panel shows the same data on an enlarged y-axis.
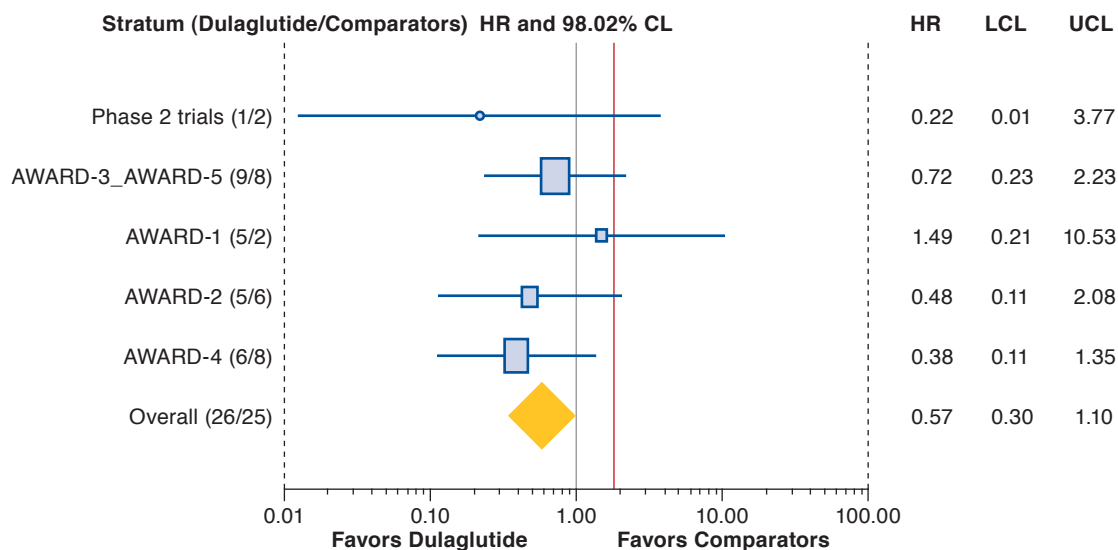
CI=confidence interval; HR=hazard ratio.

■ Prospective Cardiovascular Outcome Trials with Once-Weekly GLP-1 RAs

To date, there are 2 completed and published cardiovascular outcome trials that were designed to evaluate MACE with once-weekly GLP-1 RAs (EXenatide Study of Cardiovascular Event Lowering [EXSCEL],[61] SUSTAIN-6,[50] Table 2). An additional study, Researching cardiovascular Events with a Weekly INcretin in Diabetes (REWIND[62]), is ongoing.

EXSCEL was a phase 3, double-blind, randomized, placebo-controlled study that assessed the long-term cardiovascular safety and efficacy of once-weekly exenatide ER 2 mg in patients with T2DM who had a wide range of cardiovascular risk (Table 2).[50,61,62] Unlike SUSTAIN-6, this study was designed and powered to evaluate both noninferiority and superiority versus placebo, and therefore nonsignificant results cannot be attributed to insufficient power. Overall, 14,752 patients (of whom 10,782 [73.1%] had previous cardiovascular

FIGURE 3 Four-Component MACE Endpoints from Meta-Analysis of 9 Randomized Clinical Trials with Dulaglutide[63]

Stratum (Dulaglutide/Comparators) HR and 98.02% CL	HR	LCL	UCL
Phase 2 trials (1/2)	0.22	0.01	3.77
AWARD-3_AWARD-5 (9/8)	0.72	0.23	2.23
AWARD-1 (5/2)	1.49	0.21	10.53
AWARD-2 (5/6)	0.48	0.11	2.08
AWARD-4 (6/8)	0.38	0.11	1.35
Overall (26/25)	0.57	0.30	1.10

0.01   0.10   1.00   10.00   100.00
Favors Dulaglutide   Favors Comparators

From Ferdinand K, Botras K, Atisso C, Sager PT. Cardiovascular safety for once-weekly dulaglutide in type 2 diabetes: a pre-specified meta analysis of prospectively adjudicated cardiovascular events. Cardiovasc Diabetol. 2016;15:38. Reproduced without modification under the Creative Commons Attribution 4.0 International License (https://creativecommons.org/publicdomain/zero/1.0/).
Note: This figure illustrates the forest plot of the primary 4-component MACE endpoint by stratum. A comparison of the primary analysis results (HR, 98.02% CL) in each stratum (study or combinations of studies by which the primary analysis was stratified) with the overall result. Numbers of CV events per each treatment group (dulaglutide/comparators) are indicated by the parentheses in the y-axis under Stratum.
CL = confidence limit; CV = cardiovascular; HR = hazard ratio; LCL = lower confidence limit; MACE = major adverse cardiac event; UCL = upper confidence limit.

disease [CVD]) were followed for a median of 3.2 years. Based on the primary outcome of MACE (death from cardiovascular causes, nonfatal MI, or nonfatal stroke), which occurred in 11.4% of exenatide-treated patients and 12.2% of placebo-treated patients (HR = 0.91; 95% CI = 0.83-1.00), exenatide was noninferior to placebo with respect to safety ($P < 0.001$) but was not superior to placebo with respect to efficacy despite trending lower ($P = 0.06$; Figure 2). There were also no significant differences between exenatide ER and placebo with regard to risk of death from any cause (HR = 0.86; 95% CI = 0.77-0.97; nonsignificant on basis of the hierarchical testing plan), fatal or nonfatal MI (HR = 0.97; 95% CI = 0.85-1.10), fatal or nonfatal stroke (HR = 0.85; 95% CI = 0.70-1.03), hospitalization for heart failure (HR = 0.94; 95% CI = 0.78-1.13), and hospitalization for acute coronary syndrome (HR = 1.05; 95% CI = 0.94-1.18).

The REWIND trial is an ongoing (at the time of manuscript development) phase 3, double-blind, randomized, placebo-controlled study designed to assess the effects of once-weekly dulaglutide 1.5 mg on the incidence of cardiovascular outcomes.[62] The patient population consists of patients aged ≥ 50 years with T2DM, A1c ≤ 9.5%, and, depending on age category (≥ 50 years, ≥ 55 years, or ≥ 60 years), either a prior cardiovascular event, evidence of cardiovascular disorder, or at least 2

other cardiovascular risk factors, such as tobacco use, dyslipidemia, or hypertension. The primary cardiovascular outcome is the first occurrence of MACE. Secondary outcomes include cardiovascular death, nonfatal MI, nonfatal stroke, a composite outcome of retinal or renal disease, hospitalization for unstable angina, heart failure requiring hospitalization or an urgent heart failure visit, and all-cause mortality. Based on the ClinicalTrial.gov listing as of January 18, 2018, the study has enrolled an estimated 9,622 patients, with an average duration of follow-up of 6.5 years. The anticipated completion data for REWIND is July 2018.

Because the REWIND trial results are not yet available, the results of a meta-analysis of cardiovascular outcomes from safety and efficacy trials for dulaglutide are included in this review. The large (N = 6,010) meta-analysis examined the cardiovascular risk of dulaglutide from 9 randomized phase 2 and 3 clinical efficacy and safety trials ranging from 12 to 104 weeks in duration (mean treatment duration, 333 days).[63] Baseline cardiovascular risks were similar between dulaglutide and comparator groups. A composite MACE endpoint of death due to cardiovascular causes, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina occurred in 0.67% of patients in the dulaglutide group compared with 1.18% in the comparator
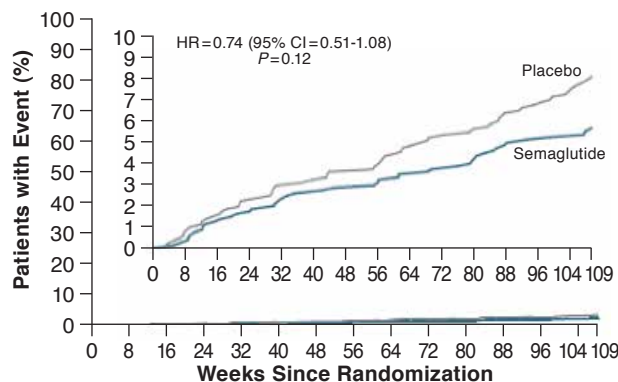
FIGURE 4 Cardiovascular Outcomes with Once-Weekly Semaglutide Versus Placebo, SUSTAIN-6 Trial[50]

A. Primary Outcome

HR=0.74 (95% CI=0.58-0.95)
P<0.001 for noninferiority
P=0.02 for superiority
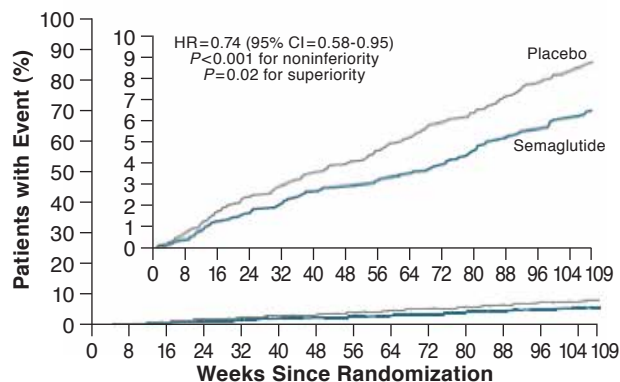
At Risk, n							
Placebo	1,649	1,616	1,586	1,567	1,534	1,508	1,479
Semaglutide	1,648	1,619	1,601	1,584	1,568	1,543	1,524

B. Nonfatal Myocardial Infarction

HR=0.74 (95% CI=0.51-1.08)
P=0.12

At Risk, n							
Placebo	1,649	1,624	1,598	1,587	1,562	1,542	1,516
Semaglutide	1,648	1,623	1,609	1,595	1,582	1,560	1,543

C. Nonfatal Stroke

HR=0.61 (95% CI=0.38-0.99)
P<0.004
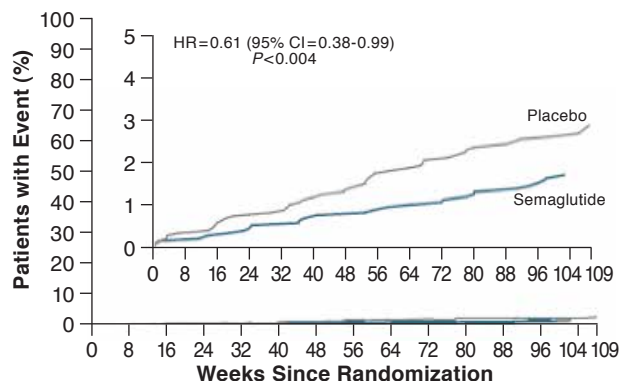
At Risk, n							
Placebo	1,649	1,629	1,611	1,597	1,571	1,548	1,528
Semaglutide	1,648	1,630	1,619	1,606	1,593	1,572	1,558

D. Death from Cardiovascular Causes

HR=0.98 (95% CI=0.65-1.48)
P=0.92
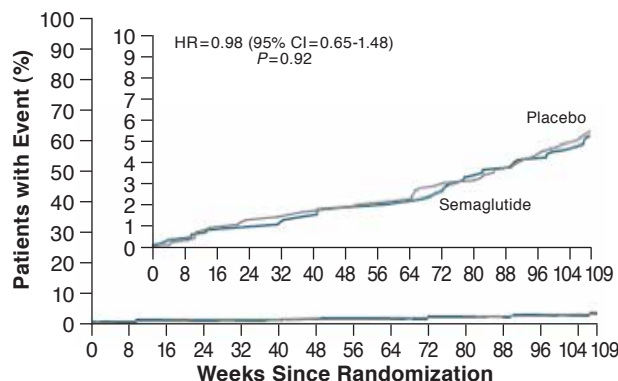
At Risk, n							
Placebo	1,649	1,637	1,623	1,617	1,600	1,584	1,566
Semaglutide	1,648	1,634	1,627	1,617	1,607	1,589	1,579

From Marso S, Bain S, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375(19):1834-44.
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Note: This figure shows the Kaplan-Meier plots of the primary outcome (a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke; Panel A), nonfatal myocardial infarction (Panel B), nonfatal stroke (Panel C), and death from cardiovascular causes (Panel D). The trial included a planned observation period of 109 weeks for all patients (a 104-week treatment period with a 5-week follow-up period). In Panel C, there were no events in the semaglutide group after week 104. Insets show the same data on an expanded y-axis.
CI=confidence interval; HR=hazard ratio.

group (active treatment or placebo). The estimated HR for dulaglutide versus comparators was 0.57, with an adjusted 98.02% confidence limit (CL) of 0.30-1.10 (*P*=0.046), indicating no significant difference between treatment groups (Figure 3). The relative risk of experiencing a nonfatal MI was significantly lower in the dulaglutide group versus the comparator group (estimated HR=0.35; adjusted 98.02% CL=0.13-0.95; *P*=0.014). There were no significant differences between dula-

glutide and comparator groups with regard to the risk of death due to cardiovascular causes, nonfatal stroke, or hospitalization for unstable angina. Thus, the authors concluded that dulaglutide does not increase the risk of MACE in patients with T2DM based on the meta-analysis findings.

SUSTAIN-6 was a 2-year, phase 3, premarketing, double-blind, randomized, placebo-controlled trial specifically designed to evaluate the cardiovascular safety of semaglutide

(0.5 mg and 1.0 mg) compared with placebo in accordance with regulatory guidelines (Table 2).[50] The study enrolled 3,297 patients aged 50 years and older with T2DM and established ASCVD, with an ASCVD risk equivalent (≥ stage 3 chronic kidney disease [CKD]) or at high risk of ASCVD (defined as having at least 1 of the following: persistent microalbuminuria or proteinuria; hypertension and left ventricular hypertrophy by electrocardiogram or imaging; left ventricular systolic or diastolic dysfunction by imaging; or ankle/brachial index less than 0.9); 83% of patients had established CVD, ≥ stage 3 CKD, or both. The composite primary outcome of MACE (death from cardiovascular causes, nonfatal MI, or nonfatal stroke) occurred in 6.6% of semaglutide-treatment patients versus 8.9% of those in the placebo group (HR = 0.74; 95% CI = 0.58-0.95; noninferiority achieved, $P < 0.001$; superiority achieved, $P = 0.02$; Figure 4). Compared with placebo, semaglutide was associated with a significant reduction in nonfatal stroke (1.6% vs. 2.7%, HR = 0.61; 95% CI = 0.38-0.99; $P = 0.04$) and no difference in nonfatal MI (2.9% vs. 3.9%, HR = 0.74; 95% CI = 0.51-1.08; $P = 0.12$). There were no significant differences between semaglutide and placebo for individual outcomes, including hospitalization for heart failure or death from any cause or cardiovascular causes. However, because this was a safety trial and the primary hypothesis was for noninferiority relative to placebo, the study was not statistically powered to demonstrate superiority.

■ Health Economic Implications

Cardiovascular-related disease and associated conditions and risk factors are the primary drivers of direct and indirect costs of diabetes.[2] While there are no data specifically evaluating cost implications relating to CV risks and events in patients treated with once-weekly GLP-1 RAs, several studies have quantified the impact of MACE on costs in patients with T2DM.[64-68] A retrospective claims database analysis using data representative of a large U.S. managed care population estimated that the mean cost of initial hospitalization (adjusted to 2018 dollars) for patients with T2DM was $28,689 for MI and $13,005 for stroke.[69] These costs were only slightly higher than corresponding costs estimated for patients without T2DM who had these events. However, patients with T2DM had significantly higher mean cumulative total direct costs per patient for cardiovascular events over 3 years of follow-up. Ward et al. (2014) used multiple sources (inpatient and emergency databases, national physician and laboratory fee schedules, published literature, and government reports) to estimate direct medical costs of diabetes complications, including acute event and follow-up care costs over 1 year, for U.S. health care payers.[64] Estimated acute event and follow-up care costs over 1 year were $60,937 per patient for MI and $45,471 per patient for ischemic stroke (adjusted to 2018 dollars).

Li et al. (2013) analyzed data from patient surveys, chart reviews, and health insurance claims from 7,109 patients with T2DM participating in the Translating Research Into Action for Diabetes (TRIAD) study between 1999 and 2002 to evaluate medical costs associated with T2DM complications and comorbidities.[65] Among patients with T2DM, estimated annualized medical costs were about 80% higher in the presence of coronary heart disease and about 35% higher in the presence of a cerebrovascular accident. These findings highlight the increased medical costs in patients with T2DM that are related to cardiovascular and cerebrovascular complications.

Cardiovascular events occurring in patients with T2DM contribute substantially to per-member health care costs in Medicare members with T2DM and in the overall Medicare population. A claims-based actuarial analysis of a randomly generated subset of 2013 and 2014 Medicare data found that annual rates for MI, stroke, unstable angina admission, and coronary revascularization in the T2DM population were 3.3, 2.4, 3.2, and 2.8 times higher, respectively, than in the non-T2DM population.[66] Although patients with T2DM accounted for only 22% of the Medicare sample, half of the cardiovascular event costs for the entire Medicare sample (i.e., patients with or without T2DM) were due to patients with T2DM. Additionally, 3.6% of the total per-member per-month (PMPM) cost for the overall Medicare sample was attributable to cardiovascular events occurring in patients with T2DM. After adjustments to account for underlying differences in demographics and morbidity between patients with and without cardiovascular events, costs associated with cardiovascular events occurring in the T2DM population were found to represent 18.1% of the total PMPM cost ($353 of $1,951, adjusted to 2018 dollars) for patients with T2DM and 6.9% of the PMPM cost ($78 of $1,132) in the overall Medicare sample.

Consideration of cardiovascular risk factors and the potential modifying effects of medications is important when evaluating the economic impact of MACE in patients with T2DM. A U.S. administrative claims data study evaluated cardiovascular event costs in commercially, Medicare Supplemental-, and Medicaid-insured patients with T2DM.[67] The sample included 1,415,598 patients with T2DM who were classified into 3 cardiovascular risk groups (highest, medium, and lowest) based on age and comorbidities. Patients were followed over a 1-year period (July 2010-June 2011), and those with MACE (death or nonfatal MI or nonfatal stroke) were additionally followed for up to 1 year after the initial event to determine longitudinal costs. Multivariable regression was used to compare costs between patients with and without MACE. Overall, 10,399 patients experienced MACE. The expected mean PMPM costs of MACE per 100 covered patients generally increased with CVD risk and varied by payer; costs (adjusted to 2018 dollars) ranged from $1,714 in the lowest-risk commercially insured patients to $20,636 in the highest-risk

Medicaid-insured patients. The mean longitudinal costs among patients with T2DM experiencing MACE ranged from $24,966 for the initial event and $2,742 PMPM for up to 1 year of follow-up care in Medicare Supplemental-insured patients with stroke to $45,736 for the initial event and $5,288 PMPM for up to 1 year of follow-up care among Medicaid-insured patients with MI.

Summary and Conclusions

The benefits of GLP-1 RAs appear to extend beyond reducing blood glucose and weight to positively affecting a range of atherosclerotic risk factors. Placebo-controlled studies to date that have looked specifically at the risk of MACE with once-weekly GLP-1 RAs found no increased risk with exenatide ER and a significant reduction of MACE events with semaglutide. Findings from the ongoing REWIND trial with dulaglutide are anticipated and may shed further light on the impact of once-weekly GLP-1 RAs on cardiovascular outcomes. When interpreting data from these clinical trials, it is important to consider differences in study populations and statistical design limitations. Choices of diabetes treatments have evolved to the point where broader health impacts beyond simple blood glucose regulation are relevant considerations and could reduce substantial costs of MACE in patients with T2DM. The potential for reducing cardiovascular events in patients with T2DM has obvious health benefits but, beyond that, may potentially translate into cost savings. Future studies are needed to assess the impact of long-term treatment with once-weekly GLP-1 RAs on CVD-related costs among patients with T2DM in the managed care setting.

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