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Cardiovascular Outcome Trials for Type 2 Diabetes

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Methods

These bulletins are not systematic reviews and do not involve critical appraisal or include a detailed summary of study findings. Rather, they present an overview of the technology and available evidence. They are not intended to provide recommendations for or against a particular technology.

Guideline and Trial Identification

The identification of literature followed a pragmatic approach given that there was an awareness of several targeted CVOTs via work CADTH was doing on diabetes at the time that this project was initiated.

Published guidelines were identified by searching North American and European diabetes associations websites. The main search concepts were pharmacological therapies and diabetes in adults. Published trials were identified by reviewing the table summaries of clinical outcome trials and text mention of trials in the recommendations and the bibliography of the guidelines. The main search concepts were again the pharmacological therapies, diabetes, and CV outcomes. A summary of all identified trials is presented in Table 1. Retrieved guidelines were mainly used to identify CVOTs. In addition, a focused Internet search was conducted to clarify the status of selected publications.

Literature Search Strategy

A limited literature search was conducted using the following bibliographic databases: MEDLINE, Embase, PubMed, and ClinicalTrials.gov. The search strategy comprised both controlled vocabulary and keywords. The main search concepts were CV outcomes and all drugs in the following classes: DPP-4 inhibitors, SGLT-2 inhibitors, GLP-1 receptor agonists.

Methodological filters were applied to limit retrieval to randomized controlled trials. The retrieval was limited to English language documents published between January 1, 2017 and December 10, 2018 because this time period reflected the time gap during which CVOTs were not retrieved from recent guidelines. A supplementary search was conducted for conference abstracts for trials where no published literature was available.

Study Selection

One author screened the literature search results and reviewed the full text of all potentially relevant studies. Studies were considered for inclusion if the patient population was adults with T2DM; intervention was a DPP-4 inhibitor, SGLT-2 inhibitor, or GLP-1 receptor agonist; and outcomes included CV outcomes (e.g., CV death). A full-text article was ordered based on examination of the title and abstract of the article. The full-text article was also ordered for more information in cases of insufficient information from the abstract. The reviewers selected the final articles for inclusion based on the examination of full-text publications. Conference abstracts and grey literature were included when they provided additional information to unpublished studies for completed CVOTs.

Synthesis of the Evidence

This report provides a summary description of key elements and CV findings of each CVOT retrieved (Table 1). The study design, objective, PICO (Population, Intervention, Comparator, Outcomes) elements and key results for each published CVOT are summarized in tables and described in the text. Key results described are limited to CV outcomes, only, and do not include any other outcomes (e.g., renal outcomes). However, if there were significant adverse effects, these were reported. Critical appraisal of each CVOT was beyond the scope of this report.

Peer Review

A draft version of this bulletin was reviewed by one clinical expert.

Summary

- Dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, and glucagon-like peptide-1 (GLP-1) receptor agonists are classes of medications used in diabetes mellitus (DM) to improve glycemic control in people with type 2 diabetes mellitus (T2DM).
- Evidence from cardiovascular outcome trials (CVOT) is available for a number of medications; CVOTs are still in progress or have yet to be published for some others. The trials examined the addition of the medication in question to standard of care compared with placebo in patients with T2DM and established cardiovascular disease (CVD) or patients who are at high risk of cardiovascular (CV) events.The outcome measured is typically major adverse cardiovascular events (MACE) including CV mortality, myocardial infarction (MI), and stroke; they may or may not include hospitalization for acute coronary syndrome (ACS), urgent revascularization procedures, or other CV end points.
- Overall, CVOTs with published results mostly showed that the investigated drugs are cardio-neutral; i.e., are not associated with harms related to their CV effect. However, thus far, a number of CVOTs done for SGLT-2 inhibitors and GLP-1 receptor agonists reported a reduction in MACE. Recent guidelines have identified three drugs pertaining to these classes that may be preferred over other drugs for patients with CVD; i.e., canagliflozin, empagliflozin, and liraglutide.

Background

Diabetes mellitus, or diabetes, is a lifelong condition in which the body cannot transform sugar from food into energy, resulting in high blood sugar levels.[1] Two broad types of diabetes prevail. In type 1 diabetes (T1DM), the body makes an insufficient amount of insulin, whereas in T2DM, the body cannot use the insulin it produces. Within those with diabetes, 90% have T2DM. In 2015, the estimated prevalence of diabetes in Canada was 3.4 million (9.3%), with an estimated 44% increase by 2025.[1,2] Over time, high blood sugar levels can lead to complications including blindness, heart disease, kidney disease, and nerve damage.[2,3] Diabetes can be managed by appropriate pharmacotherapy to reduce blood sugar levels, and healthy behaviours to reduce risk factors. These risk factors include obesity, high blood pressure, and high cholesterol.[1,3]

Of interest, recent evidence indicates that a weight management program in the primary care setting can achieve a remission of T2DM in patients who are relatively early in the course of their condition.[4]

According to current Canadian guidelines, metformin monotherapy is used as initial therapy in patients with T2DM.[5] Other options are considered when metformin is contraindicated or tolerated, or when treatment goals are not achieved despite receiving the maximum tolerated dose after three months.[5] Other therapies include orlistat, alpha glucosidase inhibitors, meglitinides, sulfonylureas, thiazolidinediones (TZDs), DPP-4 inhibitors, SGLT-2 inhibitors, GLP-1 receptor agonists, or insulin.[5] The selection of these add-on drugs is based on characteristics of the person with diabetes and those of the drugs; cost may also be a consideration.[5]

Recently, the evidence basis for selecting pharmacotherapy for patients with T2DM expanded beyond glycemic control to include CV outcomes, as well as heart failure and renal outcomes.[5] Consideration for these outcomes come from CVOTs. The development of CVOTs was the result of a guidance document released in 2008 by the Food and Drug Administration (FDA) recommending that new drugs for T2DM indicating that they do not increase the risk of CV events.[6] The guidance was created after the T2DM drug class of TZDs, including rosiglitazone (Avandia), demonstrated possible increased CV mortality and MI.[7] As diabetes is associated with an increased risk of CVD, the latter being the leading cause of morbidity and mortality in this patient population, avoiding the undesired CV effect of T2DM drugs was deemed to be important.[8] Guidance for these CVOTs recommends enrolling in trials patients who are at a higher risk of CV events — such as those with relatively advanced disease, elderly patients, and patients with some degree of renal impairment.[8] CVOTs are to measure outcomes including CV mortality, MI, and stroke, as well as others such as hospitalization for ACS, urgent revascularization procedures, and possibly other CV end points.[8]

As a number of CVOTs have now been completed and their results published (Table 1), there is emerging evidence supporting the use of these drugs as second-line therapy in certain clinical situations such as in patients with a history of CVD; this is reflected in recent Canadian and international guidelines.[5,9] It has been suggested that, in future, as CVOTs mature, the way they are designed may be changed due to their cost and limitations to certain populations (e.g., only high-risk CV patients).[7]

In May 2017, the Canadian Expert Drug Committee (CDEC) recommended that adults with T2DM and established CVD should consider therapy; this was based on the CDEC recommendations for individual T2DM drugs that have been reviewed by the CADTH Common Drug Review (CDR) specifically for the CV indication.[10] Of note, empagliflozin is currently the only drug for T2DM that has been reviewed by CDR and recommended by CDEC for reimbursement in patients with T2DM at high risk of CV events.[10,11] Manufacturers of other drugs with CV data have not yet submitted to CDR for such an indication.

Table 1: Summary of Cardiovascular Outcome Trials

Drug Class	Drug	Trial Name	ClinicalTrials.Gov Number[12]	Date of Trial Completion and Publication[12]	Mentioned in Guidelines	
					Diabetes Canada (April 2018)[5]	ADA/EASD (October 2018)[9]
DPP-4 Inhibitors	alogliptin	EXAMINE	NCT00968708	• Completed June 2013 • Published October 2013	Yes	Yes
	linagliptin	CARMELINA	NCT01897532	• Completed January 2018 • Published November 2018	Yes	No
	linagliptin	CAROLINA	NCT01243424	• Completed August 2018 • Not yet published	Yes	No
	saxagliptin	SAVOR-TIMI 53	NCT01107886	• Completed May 2013 • Published October 2013	Yes	Yes
	sitagliptin	TECOS	NCT00790205	• Completed March 2015 • Published August 2015	Yes	Yes
SGLT-2 Inhibitors	canagliflozin	CANVAS	NCT01032629	• Completed February 2017 • Published January 2018	Yes	Yes
	canagliflozin	CANVAS-R	NCT01989754	• Completed February 2017 • Published August 2017	Yes	Yes
	dapagliflozin	DECLARE-TIMI58	NCT01730534	• Completed September 2018 • Published November 2018	Yes	No
	empagliflozin	EMPA-REG OUTCOME	NCT01131676	• Completed April 2015 • Published November 2015	Yes	Yes
	ertugliflozin	VERTIS CV	NCT01986881	• To be completed December 30, 2019	Yes	No

Drug Class	Drug	Trial Name	ClinicalTrials.Gov Number[12]	Date of Trial Completion and Publication[12]	Mentioned in Guidelines	
					Diabetes Canada (April 2018)[5]	ADA/EASD (October 2018)[9]
GLP-1 Receptor Agonists	dulaglutide	REWIND	NCT01394952	• Completed August 2018 • Not yet published	Yes	No
	exenatide	EXSCEL	NCT01144338	• Completed April 2017 • Published September 2017	Yes	Yes
	exenatide	FREEDOM-CVO[a]	NCT01455896	• Completed March 2016 • Not yet published	Yes	No
	liraglutide	LEADER	NCT01179048	• Completed December 2015 • Published November 2016	Yes	Yes
	lixisenatide	ELIXA	NCT01147250	• Completed February 2015 • Published December 2015	Yes	Yes
	semaglutide	PIONEER-6[a]	NCT02692716	• Completed September 2018 • Not yet published	Yes	No
	semaglutide	SUSTAIN-6	NCT01720446	• Completed March 2016 • Published November 2016	Yes	Yes

ADA = American Diabetes Association; EASD = European Association for the Study of Diabetes; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SGLT-2 = sodium-glucose cotransporter-2.

[a] The active ingredient is available in Canada, but the dosage form studied in this trial is not. See the Concurrent Developments section of this bulletin for more information.

The Technology

A number of DPP-4 inhibitors, SGLT-2 inhibitors, and GLP-1 receptor agonists have been approved and marketed in Canada (Table 2).

DPP-4 inhibitors work by enhancing incretin hormones including GLP-1 and glucose-dependent insulinotropic polypeptide (GIP).[13] The intestine releases these hormones throughout the day, increasing their levels in response to meals.[13] GLP-1 and GIP increase the synthesis and release of insulin from pancreatic beta cells using intracellular signalling pathways.[13] Higher insulin levels increase glucose uptake and thus lower blood glucose levels.[13] Additionally, GLP-1 lowers glucagon (the hormone that increases blood glucose levels) secretion from pancreatic alpha cells, which further contributes to decreasing glucose in the blood.[13] GLP-1 and GIP are converted into inactive products by the DPP-4 enzyme.[13] Thus, DPP-4 inhibitors prevent the hydrolysis of incretin hormones by the DPP-4 enzyme, resulting in an increased amount of active GLP-1 and GIP in the plasma.[13] This triggers a sequence of increasing insulin and lowering glucagon levels, resulting in lower blood glucose levels.[13]

GLP-1 receptor agonists are analogues to the incretin hormone GLP-1 previously mentioned.[14] By binding to the GLP-1 receptor, the secretion of glucose-dependent insulin from the pancreatic beta cells and the lowering of glucagon secretion occurs.[14] Thus, when blood glucose levels are elevated, a GLP-1 receptor agonist will aid in secreting more insulin and less glucagon, resulting in a decrease of blood glucose levels.[14] Additionally, the mechanism of blood glucose lowering involves a delay in gastric emptying.[14]

SGLT-2 inhibitors work in a different pathway by inhibiting the SGLT-2 transporter, which is predominantly responsible for glucose reabsorption from the kidney back into the bloodstream.[15] Thus, through the inhibition of this transporter, SGLT-2 inhibitors reduce both the glucose reabsorption and the glucose threshold in the kidney, increasing urinary glucose excretion and ultimately resulting in lower blood glucose.[15]

Regulatory Status

Over the last 11 years, four DPP-4 inhibitors, four SGLT-2 inhibitors, and five GLP-1 receptor agonists have been approved and marketed in Canada (Table 3). All were approved for glycemic control in adult patients with T2DM. Among these, three drugs, recently gained an additional indication as add-on combination therapy to reduce the incidence of some CV outcomes: canagliflozin for major adverse CV events (MACE) (CV death, non-fatal MI, and non-fatal stroke); empagliflozin for CV death; and liraglutide in patients with T2DM and established CVD.[16,15,14]

Table 2: DPP-4 Inhibitors, SGLT-2 Inhibitors, and GLP-1 Receptor Agonists in Canada

Drug Class	Drug	Brand Name	Manufacturer
Single Drug Products (ORAL)			
DPP-4 Inhibitors	alogliptin	Nesina	Takeda Canada Inc.
	linagliptin	Trajenta	Boehringer Ingelheim (Canada) Ltd.
	saxagliptin	Onglyza	AstraZeneca Canada
	sitagliptin	Januvia	Merck Canada Inc.
SGLT-2 Inhibitors	canagliflozin	Invokana	Janssen Inc.
	dapagliflozin	Forxiga	AstraZeneca Canada Inc.
	empagliflozin	Jardiance	Boehringer Ingelheim Canada Ltd.
	ertugliflozin	Steglatro	Merck Canada
Single Drug Products (INJECTABLE)			
GLP-1 Receptor Agonists	dulaglutide	Trulicity	Eli Lilly Canada
	exenatide, exenatide ER	Byetta, Bydureon	AstraZeneca Canada
	liraglutide	Victoza	Novo Nordisk Canada Inc.
	lixisenatide	Adlyxine	Sanofi Canada
	semaglutide	Ozempic	Novo Nordisk Canada Inc.

DPP-4 = dipeptidyl peptidase-4; ER = extended release; GLP-1 = glucagon-like peptide-1; SGLT-2 = sodium-glucose cotransporter-2.

Table 3: DPP-4 Inhibitors, SGLT-2 Inhibitors, and GLP-1 Receptor Agonists Marketed in Canada

Drug Class	Drug	Brand Name	Date Marketed [17a]
Single Drug Products (ORAL)			
DPP-4 Inhibitors	alogliptin	Nesina	April 2014
	linagliptin	Trajenta	September 2011
	saxagliptin	Onglyza	Original: October 2009 Current: December 2014
	sitagliptin	Januvia	January 2008
SGLT-2 Inhibitors	canagliflozin	Invokana	May 2014
	dapagliflozin	Forxiga	January 2015
	empagliflozin	Jardiance	August 2015
	ertugliflozin	Steglatro	May 2018
Single Drug Products (INJECTABLE)			
GLP-1 Receptor Agonists	dulaglutide	Trulicity	November 2015[b]
	exenatide, exenatide ER	Byetta	Original: May 2011 Current: July 2014
		Bydureon	February 2016[c]
	liraglutide	Victoza	May 2010
	lixisenatide	Adlyxine	September 2017
	semaglutide	Ozempic	February 2018

DPP-4 = dipeptidyl peptidase-4; ER = extended release; GLP-1 = glucagon-like peptide-1; SGLT-2 = sodium-glucose cotransporter-2

[a] Date marketed refers to the marketed date in Canada of the first available dosage strength as listed in the Health Canada Drug Product Database; i.e., not the approval date (i.e.,when the Notice of Compliance, or NOC, was granted).

[b] This date represents the marketed date for the Trulicity single-use pen and not the pre-filled syringe, which was approved November 2015 but is not currently marketed.

[c] This date represents Bydureon single-dose, dual-chamber pens and not Bydureon BCise single-use autoinjector, which was approved November 2018 but is not currently marketed.

Cost and Administration

Each class of medication varies in price (Table 4). There is also variation between different drugs within a class: the unit price of DPP-4 inhibitors ranges from $2.25 to $2.95, resulting in an annual cost of $821 to $1,078.[18] The SGLT-2 inhibitors cost approximately $2.62 per dosage unit resulting in an annual cost of $956.[15,16] The most expensive drug class is the GLP-1 receptor agonists, which have a cost range of $3.99 to $6.85 daily, resulting in an annual cost of $1,456 to $2,500.[19] All DPP-4 inhibitors and SGLT-2 inhibitors are taken once daily orally, whereas GLP-1 receptor agonists currently available in Canada are all injectable products given subcutaneously either once or twice daily, or once weekly.[20]

Target Population

As previously stated, most of these drugs are indicated to improve glycemic control in the target population of adult patients with T2DM.[15] This population ranges from patients using diet and exercise to improve glycemic control and for whom metformin is either insufficient to control their glycemia or is contraindicated or not well-tolerated to patients who are on other medications such as sulfonylureas or insulin and require optimization of their glycemic control.[15] A more recent target population for some of these newer drugs — more specifically at this time canagliflozin, empagliflozin, and liraglutide — is adults with T2DM and established CVD.[14-16]

Table 4: Cost and Administration of DPP-4 Inhibitors, SGLT-2 Inhibitors, and GLP-1 Receptor Agonists in Canada

Drug Class	Drug	Brand Name	Daily Cost	Annual Cost	Dosage Regimen / Route of Administration[20]
Single Drug Products (ORAL)					
DPP-4 Inhibitors[18]	alogliptin	Nesina	$2.62	$956	25 mg once daily PO
	linagliptin	Trajenta	$2.25 to $2.55	$821 to $931	5 mg once daily PO
	saxagliptin	Onglyza	$2.84	$1,037	5 mg once daily PO
	sitagliptin	Januvia	$2.95	$1,078	100 mg once daily PO
SGLT-2 Inhibitors[11]	canagliflozin	Invokana	$2.62	$956	100 mg to 300 mg once daily PO
	dapagliflozin	Forxiga	N/A	N/A	5 mg to 10 mg once daily PO
	empagliflozin	Jardiance	$2.62	$956	10 mg to 25 mg once daily PO
	ertugliflozin	Steglatro	N/A	N/A	5 mg to 15 mg once daily PO
Single Drug Products (INJECTABLE)					
GLP-1 Receptor Agonists[19,21]	dulaglutide	Trulicity	$6.85	$2,500	Initial: 0.75 mg weekly SC; typically increased to 1.5 mg weekly SC thereafter
	exenatide, exenatide ER	Byetta, Bydureon	$3.99 to $6.85	$1,456 to $2,500	Solution: 5 mcg b.i.d. SC; increased to 10 mcg b.i.d. SC after 1 month, if required Suspension: 2 mg weekly SC
	liraglutide	Victoza	$4.57 to $6.85	$1,668 to 2,500	Initial: 0.6 mg once daily SC; increased to 1.2 mg to 1.8 mg once daily SC
	lixisenatide	Adlyxine	$4.07	$1,486	Initial: 0.1 mg once daily SC for 14 days; increased to 0.2 mg once daily SC on day 15
	semaglutide	Ozempic	N/A	N/A	Initial: 0.25 mg weekly SC for 4 weeks; increased to 0.5 mg weekly SC from week 5 onward May increase to 1 mg weekly SC after a further 4 weeks

b.i.d. = twice daily; DPP-4 = dipeptidyl peptidase-4; ER = extended release; GLP-1 = glucagon-like peptide-1; N/A = not available; p.o. = orally; SC = subcutaneously; SGLT-2 = sodium-glucose cotransporter-2.

Current Practice

The current Canadian guidelines comprehensively review the diagnostic and therapeutic approaches used for diabetes. Risk factors are annually assessed to determine who to screen for diabetes.[5] Risk factors include family history, socioeconomic status and ethnicity, CV risk factors and conditions, or medications associated with diabetes.[5] Those who have risk factors undergo screening, along with those who are 40 years of age or older. Screening entails obtaining a fasting plasma glucose (FPG) reading or getting a glycated hemoglobin level (A1C).[5] Diabetes is defined as an FPG of ≥ 7.0 mmol/L and A1C ≥ 6.5%.[5] When the patient is asymptomatic, diagnosis is confirmed when both tests are done and results are in the diabetes range.[5] If the patient is symptomatic (e.g., increased thirst, frequent urination), only one test is necessary to diagnose diabetes.[1,5]

To treat patients with T2DM, healthy behaviour interventions (nutritional therapy, weight management, physical activity) should be initiated first.[5] Metformin is used as initial drug therapy when the treatment goal is not achieved with diet and lifestyle changes; i.e., typically achieving an A1C of ≤ 7%, as this has been shown to reduce long-term microvascular complications in newly diagnosed persons with T2DM.[5] Other options should be considered when metformin cannot be used or is not tolerated, or when treatment goals are not achieved despite receiving the maximum tolerated dose for three months.[5] These include orlistat, alpha glucosidase inhibitors, meglitinides, sulfonylureas, TZDs, DPP-4 inhibitors, SGLT-2 inhibitors, GLP-1 receptor agonists, and insulin.[5] Of note, the Canadian guidelines state that, for patients with clinical CVD, a diabetes medication with demonstrated CV benefit (i.e., canagliflizin, empagliflozin, and liraglutide) should be considered. These guidelines also state that in people without clinical CVD in whom an A1C target is not achieved with current therapy and there are concerns about hypoglycemia and weight gain, incretin agents (i.e., DPP-4 inhibitors or GLP-1 receptor agonists) and/or SGLT2 inhibitors may be preferred over other agents, as they improve glycemic control with a low risk of hypoglycemia and weight gain.[5]

Summary of the Evidence

The following section provides a summary of every CVOT mentioned in Table 1 of this report. As per this table, a CVOT has either been recently published or is currently ongoing for all drugs pertaining to DDP-4 inhibitors, SGLT-2 inhibitors, and GLP-1 receptor agonists available in Canada.

DPP-4 Inhibitors

Alogliptin

The EXamination of cArdiovascular outcoMes with alogliptIN versus standard of carE (EXAMINE) trial was completed in June 2013. Its aim was to assess CV outcomes associated with the use of alogliptin as compared with placebo in patients with T2DM who had had a recent (15 to 90 days before randomization) ACS.[22] The study was multi-centre, randomized, double-blinded, and placebo-controlled.[22] The EXAMINE trial studied patients diagnosed with T2DM receiving antihyperglycemic therapy (other than a DPP-4 inhibitor or GLP-1 receptor agonist) and who had ACS (acute MI and unstable angina requiring hospitalization). Patients entered in the trial received daily doses of alogliptin (25 mg, 12.5 mg, 6.25 mg, with the dose based on renal function) compared with placebo, in addition to standard-of-care treatment for T2DM.[22] The primary end point measured included a composite end point of death from CV causes, non-fatal MI, or non-fatal stroke.[22] The principal secondary end point included the primary composite end point with the addition of urgent revascularization due to unstable angina within 24 hours after hospital admission (Table 5).[22]

The results indicate that the primary end point incidence was similar in both groups; i.e., 11.3% of patients assigned to alogliptin had a primary end point compared to 11.8% of patients on placebo (HR 0.96; upper boundary of the one-sided repeated CI 1.16; $P < 0.001$ for noninferiority; $P = 0.32$ for superiority).[22] For the principal secondary end point, the events occurred in 12.7% of patients assigned to alogliptin compared to 13.4% assigned to placebo (HR 0.95; upper boundary of the one-sided repeated CI 1.14).[22] Based on the study results, the authors concluded that patients with T2DM with recent ACS did not have increased rates of major CV events with alogliptin compared with placebo.[22]

Linagliptin

The Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults with Type 2 Diabetes and High Cardiovascular and Renal Risk (CARMELINA) trial was completed in January 2018. The study was multi-centre, randomized, double-blinded, and placebo-controlled, and evaluated the effect of linagliptin on CV outcomes and renal outcomes in patients with T2DM at high risk of CV and renal events.[23] More specifically, patients enrolled in the CARMELINA trial were adults with T2DM (defined as A1C 6.5% to 10.0%) and high CV risk (i.e., history of coronary artery disease, stroke, or peripheral vascular disease, and microalbuminuria or macroalbuminuria — urine albumin-to-creatinine ratio [UACR] > 30 mg/g and renal risk (i.e., estimated glomerular filtration

Table 5: Key Elements of and Results of EXAMINE[22]

Study	Objective	PICO	Key Results
EXAMINE Design: Multi-centre, randomized, double-blind, placebo-controlled. N = 5,380 Duration: Up to 40 months (median, 18 months)	To assess CV outcomes with alogliptin as compared with placebo in patients with T2DM who had had a recent ACS	Population: Patients diagnosed with T2DM receiving antidiabetic therapy (other than a DPP-4 inhibitor or GLP-1 analogue) and had had ACS (defined as an acute MI or unstable angina requiring hospitalization) within 15 to 90 days before randomization Intervention: Daily doses of alogliptin (25 mg, 12.5 mg, 6.25 mg) based on renal function at the time of randomization and during the post-randomization period Comparator: Placebo in addition to standard of care for T2DM. Outcomes: • Primary: composite of death from CV causes, non-fatal MI, or non-fatal stroke • Secondary: primary composite end point with the addition of urgent revascularization due to unstable angina within 24 hours after hospital admission	• Primary end point: alogliptin = 11.3% vs. placebo = 11.8% (HR 0.96; upper boundary of the one-sided repeated CI 1.16) • Secondary end point: alogliptin = 12.7% vs. placebo = 13.4% (HR 0.95; upper boundary of the one-sided repeated CI 1.14)

ACS = acute coronary syndrome; CV = cardiovascular; CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; EXAMINE = EXamination of cArdiovascular outcoMes with alogliptIN versus standard of carE trial; GLP-1 = glucagon-like protein-1; HR = hazard ratio; CI = confidence interval; MI = myocardial infarction; PICO = Population, Intervention, Comparator, Outcomes; T2DM = type 2 diabetes; vs. = versus.

rate [eGFR] 45 mL/min/1.73m^2 to 75 mL/min/1.73m^2 and UACR >200 mg/g or eGFR 15 mL/min/1.73m^2 to 45 mL/min/1.73m^2 regardless of UACR). Patients received daily doses of linagliptin (5 mg) compared with placebo.[23] The primary end point measured was a 3-point MACE including time to first occurrence of CV death, non-fatal MI, or non-fatal stroke.[23] Safety end points included CV events (including hospitalization for heart failure [hHF]) and deaths by any cause (Table 6).[23]

The results indicate that the primary end point (i.e., 3-point MACE) incidence was similar in both groups, where 12.4% of patients assigned to linagliptin compared to 12.1% of patients on placebo, for an absolute incidence rate difference of 0.13 per 100 person-years (hazard ratio [HR] 1.02; 95% confidence interval [CI], 0.89 to 1.17; $P < 0.001$ for noninferiority; $P = 0.74$ for superiority).[23] With respect to safety end points, there was no significant difference in the incidence of death due to any cause with linagliptin (10.5%; 4.69 per 100 person-years) and placebo (10.7%; 4.80 per 100 person-years) for an absolute incidence rate difference of −0.11 (HR 0.98; 95% CI 0.84 to 1.13; $P = 0.74$).[23] The four-point MACE outcome (i.e., three-point MACE plus hospitalization for unstable angina) occurred in 13.3% of patients in the linagliptin group versus 13.2% in the placebo group, for an absolute incidence rate difference of −0.02 (HR 1.00; 95% CI 0.88 to 1.13; $P = 0.96$).[23] Lastly, hHF occurred in 6.0% (2.77 per 100 person-years) of those on linagliptin and 6.5% (3.04 per 100 person-years) of those on placebo, for an absolute incidence difference of −0.27 (HR 0.90; 95% CI 0.74 to 1.08; P = 0.26).23 Concerning safety, the proportion of pancreatitis was 0.3% (n = 11) in the linaglipitin group and 0.1% (n = 4) in the placebo group. Authors of the study concluded that patients with T2DM with a high CV and renal risk using linagliptin combined with usual care over a median period of 2.2 years did not have an increased risk of composite CV events compared to patients using placebo.[23]

Saxagliptin

The Saxaglipitin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)-Thrombolysis in Myocardial Infarction (TIMI) 53 trial was completed in May 2013 with the aim of evaluating the safety and efficacy of saxagliptin with respect to CV outcomes in patients with T2DM who are at risk for CV events.[24] The study was multi-centre, randomized,

Table 6: Key Elements of and Results of CARMELINA[23]

Study	Purpose	PICO	Key Results
CARMELINA Design: Multi-centre, randomized, double-blind, placebo-controlled. N = 6,979 Duration: median of 2.2 years	To evaluate the effect of linagliptin on CV outcomes and renal outcomes in patients with T2DM at high risk of CV and renal events	Population: adults with T2DM (A1C values of 6.5% to 10.0%) and high CV and renal risk Intervention: Daily doses of linagliptin (5 mg) Comparator: Placebo Outcomes: • Efficacy: time to first occurrence of CV death, non-fatal MI or non-fatal stroke (3-point adverse CV event [MACE]) • Safety: CV events (including hHF), deaths, secondary kidney outcomes, and pancreatitis	• Primary end point event (3-point MACE): placebo = 12.1% vs. linagliptin = 12.4% (HR 1.02; 95% CI, 0.89 to 1.17) • Death due to any cause: linagliptin = 10.5% vs. placebo = 10.7% (HR 0.98; 95% CI 0.84 to 1.13) • 4-point MACE: linagliptin = 13.3% vs. placebo = 13.2% (HR 1.00; 95% CI 0.88 to 1.13) • hHF: linagliptin = 6.0% vs. placebo = 6.5% (HR 0.90; 95% CI 0.74 to 1.08) • Pancreatitis: linagliptin = 0.3% (n = 11) vs. placebo = 0.1% (n = 4)

A1C = glycated hemoglobin; CARMELINA = Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults with Type 2 Diabetes and High Cardiovascular and Renal Risk trial; CI = confidence interval; CV = cardiovascular; hHF = hospitalization for heart failure; HR = hazard ratio; CI = confidence interval; MACE = major adverse cardiovascular event; MI = myocardial infarction; PICO = Population, Intervention, Comparator, Outcomes; T2DM = type 2 diabetes; vs. = versus.

double-blinded, and placebo-controlled.[24] More specifically, the SAVOR-TIMI 53 trial evaluated the effect of daily doses of saxagliptin (5 mg or 2.5 mg in patients with eGFR ≤ 50mL/min), compared with placebo, in patients with a history of documented T2DM, A1C of 6.5% to 12.0%, and either a history of established CVD or multiple risk factors for vascular disease.[24] The primary efficacy and safety end point was defined as a composite of CV death, non-fatal MI, or non-fatal ischemic stroke.[24] The secondary efficacy end point consisted of the primary composite end point plus hHF, coronary revascularization, or unstable angina (Table 7).[24]

The results indicate that the primary end point incidence was similar in both groups; 7.3% of patients assigned to saxaglipitin had a CV death, non-fatal MI, or non-fatal ischemic stroke compared to 7.2% of patients on placebo (HR 1.00; 95% CI, 0.89 to 1.12; $P < 0.001$ for noninferiority; $P = 0.99$ for superiority).[24] In the secondary end point, the events occurred in 12.8% of patients assigned to saxagliptin compared to 12.4% assigned to placebo (HR 1.02; 95% CI, 0.94 to 1.11; $P < 0.001$ for noninferiority; $P = 0.66$ for superiority). Of note, subgroup analyses suggested an increase risk of hHF associated with saxagliptin (HR 1.27 [1.07 to 1.51]).[24] Based on the study results, authors concluded that saxagliptin did not increase or decrease the rate of ischemic events, but the rate of hHF was increased.[24] Consequently, saxagliptin is not recommended in persons with a history of heart failure, especially in people who also have renal impairment and/or a history of MI.[5]

Sitagliptin

The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) was completed in March 2015. Its aim was to assess the long-term CV safety of adding sitagliptin to usual care, as compared with usual care alone, in patients with T2DM and established CVD.[25] The study was multi-centre, randomized, double-blinded, and placebo-controlled.[25] The TECOS trial evaluated the effect of daily doses of sitagliptin (100 mg or 50 mg in patients with eGFR 30mL/min to 50 mL/min) compared with placebo. Enrolled patients had T2DM with established CVD and were at least 50 years of age, with A1C of 6.5% to 9.0% when treated with stable doses of one or two oral antihyperglycemic agents (metformin, pioglitazone, or sulfonylurea) or insulin (with or without metformin).[25] The primary end point was a composite CV outcome defined as the first confirmed event of CV death, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina.[25] The secondary end point consisted of another composite CV outcome defined as the first event of CV death, non-fatal MI, or non-fatal stroke (Table 8).[25]

Table 7: Key Elements of and Results of SAVOR-TIMI 53[24]

Study	Purpose	PICO	Key Results
SAVOR-TIMI 53 Design: multi-centre, randomized, double-blind, placebo-controlled. N = 16,492 Duration: median of 2.1 years)	To evaluate the safety and efficacy of saxagliptin with respect to CV outcomes in patients with T2DM who are at risk for CV events	Population: patients with a history of documented T2DM, A1C of 6.5% to 12.0%, and either a history of established CVD or multiple risk factors for vascular disease. Intervention: daily doses of saxagliptin (5 mg or 2.5 mg in patients with eGFR ≤ 50mL/min) Comparator: placebo Outcomes: • Primary Efficacy and Safety: composite of CV death, non-fatal MI, or non-fatal ischemic stroke • Secondary efficacy: primary composite end point plus hHF, coronary revascularization, or unstable angina	• Primary end point event: saxagliptin = 7.3% vs. placebo = 7.2% (HR 1.00; 95% CI, 0.89 to 1.12) • Secondary end point: saxagliptin = 12.8% vs. placebo = 12.4% (HR 1.02; 95% CI, 0.94 to 1.11)

A1C = glycated hemoglobin; CI = confidence interval; CV = cardiovascular; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; hHF = hospitalization for heart failure; HR = hazard ratio; MI = myocardial infarction; PICO = Population, Intervention, Comparator, Outcomes; SAVOR-TIMI 53 = Saxaglipitin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53 trial; T2DM = type 2 diabetes; vs. = versus.

Table 8: Key Elements of and Results of TECOS[25]

Study	Purpose	PICO	Key Results
TECOS Design: multi-centre, randomized, double-blind, placebo-controlled N = 14,671 Duration: median of 3.0 years	To assess the long-term CV safety of adding sitagliptin to usual care, as compared with usual care alone, in patients with T2DM and established CVD	Population: patients with T2DM with established CVD who were at least 50 years of age, with A1C of 6.5% to 9.0% when treated with stable doses of one or two oral antihyperglycemic agents (metformin, pioglitazone, or sulfonylurea) or insulin (with or without metformin) Intervention: daily doses of sitagliptin (100 mg or 50 mg in patients with eGFR 30 mL/min to 50 mL/min) Comparator: placebo Outcomes: • Primary: composite CV outcome defined as the first confirmed event of CV death, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina • Secondary: composite CV outcome defined as the first event of CV death, non-fatal MI, or non-fatal stroke	• Primary end point: sitagliptin = 11.4% vs. placebo = 11.6% (per-protocol analysis: HR 0.98; 95% CI, 0.88 to 1.09) • Secondary end point: sitagliptin = 10.2% vs. placebo = 10.2% (per-protocol analysis: HR 0.99; 95% CI, 0.89 to 1.11)

A1C = glycated hemoglobin; CI = confidence interval; CV = cardiovascular; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; HR = hazard ratio; MI = myocardial infarction; PICO = Population, Intervention, Comparator, Outcomes; T2DM = type 2 diabetes; TECOS = Trial Evaluating Cardiovascular Outcomes with Sitagliptin; vs. = versus.

The results indicate that the primary end point incidence was similar in both groups, where 11.4% of patients assigned to sitagliptin experienced the composite end point compared to 11.6% of patients on placebo (per-protocol analysis: HR 0.98; 95% CI, 0.88 to 1.09; $P < 0.001$ for noninferiority; intention-to-treat analysis: HR 0.98; 95% CI, 0.89 to 1.08; $P = 0.65$ for superiority).[25] In the secondary end point, the composite end point occurred in 10.2% of patients assigned to sitagliptin compared to 10.2% assigned to placebo (per-protocol analysis: HR 0.99; 95% CI, 0.89 to 1.11; $P < 0.001$ for noninferiority; intention-to-treat analysis: HR 0.99; 95% CI, 0.89 to 1.10; $P = 0.84$ for superiority).[25] Authors of the study concluded that sitagliptin added to usual care does not appear to increase the risk of MACE, hHF, or other adverse events in patients with T2DM and established CVD.[25]

SGLT-2 Inhibitors

Canagliflozin

The Canagliflozin Cardiovascular Assessment Study (CANVAS) was completed in February 2017. Its aim was to assess the CV safety and efficacy of canagliflozin and to evaluate the balance between any potential benefits of the drug and the risks associated with it, such as genitourinary infection, diabetic ketoacidosis, and fracture.[26] The study was multi-centre, randomized, double-blinded, and placebo-controlled.[26] CANVAS consisted of both CANVAS and CANVAS-R — the renal component of the study. The trials enrolled men and women with T2DM (A1C 7% to 10.5%) who were either 30 years of age or older with a history of symptomatic atherosclerotic CVD, or 50 years of age or older with two or more risk factors for CVD.[26] The participants also had an eGFR > 30 mL/min at entry. The CANVAS trial evaluated canagliflozin used at a daily dose of 300 mg or 100 mg, compared with placebo, whereas in the CANVAS-R trial, patients received an initial dose of 100 mg daily with an optional increase to 300 mg daily starting from week 13.[26] The primary end point was a composite of death from CV causes, non-fatal MI, or non-fatal stroke.[26] The secondary end point consisted of death from any cause, death from CV causes, progression of albuminuria, and the composite of death from CV causes and hHF.[26] Additionally, there were exploratory CV outcomes pre-specified for evaluation including non-fatal MI, non-fatal stroke, and hHF (Table 9).[26]

Table 9: Key Elements of and Results of CANVAS[26]

Study	Purpose	PICO	Key Results
CANVAS Design: Multi-centre, randomized, double-blind, placebo-controlled N = 10,142 Duration: median of 188.2 weeks	To assess the CV safety and efficacy of canagliflozin and to evaluate the balance between any potential benefits of the drug and the risks associated with it, such as genitourinary infection, diabetic ketoacidosis, and fracture	Population: men and women with T2DM (A1C 7% to 10.5%) who were either 30 years of age or older with a history of symptomatic atherosclerotic CVD or 50 years of age or older with two or more risk factors for CVD; must also have had eGFR > 30 mL/min Intervention: CANVAS — canagliflozin at a daily dose of 300 mg or 100 mg CANVAS-R — initial dose of 100 mg daily, with an optional increase to 300 mg daily starting from week 13 Comparator: Placebo Outcomes: • Primary — composite of death from CV causes, non-fatal MI, or non-fatal stroke • Secondary — death from any cause, death from CV causes, progression of albuminuria, and the composite of death from CV causes and hHF • Exploratory CV outcomes pre-specified for evaluation were non-fatal MI, non-fatal stroke, and hHF	• Primary end point: canagliflozin = 26.9 events vs. placebo = 31.5 events per 1,000 patient-years(HR 0.86; 95% CI, 0.75 to 0.97)[a] • Secondary: death from any cause (HR 0.87; 95% CI, 0.74 to 1.01) • Death from CV causes (HR 0.87; 95% CI, 0.72 to 1.06) • Amputation of toes, feet, or legs: canagliflozin = 6.3 participants per 1,000 patient-years vs. placebo = 3.4 participants per 1,000 patient-years (HR 1.97; 95% CI, 1.31 to 2.75) • Fractures: canagliflozin = 15.4 participants per 1,000 patient-years vs. placebo = 11.9 participants per 1,000 patient-years (HR 1.26; 95% CI, 1.04 to1.52) • Trauma fracture events: canagliflozin = 11.6 participants per 1,000 patient-years vs. placebo = 9.2 participants per 1,000 patient-years (HR 1.23; 95% CI 0.99 to 1.52)

A1C = glycated hemoglobin; CANVAS = Canagliflozin Cardiovascular Assessment Study; CI = confidence interval; CV = cardiovascular; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; hHF = hospitalization for heart failure; HR = hazard ratio; MI = myocardial infarction; PICO = Population, Intervention, Comparator, Outcomes; R = renal component; T2DM = type 2 diabetes; vs. = versus.

[a] The effects were nearly the same when imputation or missing events was performed.

The results indicate that the primary end point incidence was favourable for canagliflozin; i.e., 26.9 of patients with an event per 1,000 patient-years assigned to canagliflozin experienced the composite end point compared to 31.5 of patients with an event per 1,000 patient-years in the placebo group (HR 0.86; 95% CI, 0.75 to 0.97; *P* < 0.001 for noninferiority; *P* = 0.02 for superiority).[26] In the secondary end point, the comparative incidence of death from any cause did not show superiority (*P* = 0.24) of canagliflozin, nor was it considered to be statistically significant (HR 0.87; 95% CI, 0.74 to 1.01). Similarly, death from CV causes was also not statistically significant (HR 0.87; 95% CI, 0.72 to 1.06).[26] With regards to safety, canagliflozin increased the risk of amputation of toes, feet, and legs where it occurred in 6.3 participants per 1,000 patient-years on this SGLT-2 inhibitor, compared with 3.4 participants per 1,000 patient-years on placebo (HR 1.97; 95% CI, 1.31 to 2.75).[26] Among these, 71% of the affected participants had their highest amputation at the level of the toe or metatarsal.[26] Generally, patients who had a history of amputation or peripheral vascular disease had the highest absolute risk of amputation, but the relative risk amputation with canagliflozin compared to placebo was similar across these subgroups.[26] Additionally, patients on canagliflozin had a higher rate of all fractures compared with those on placebo (15.4 versus 11.9 participants with fracture per 1,000 patient-years; HR 1.26; 95% CI, 1.04 to 1.52). Similar results were reported for low trauma fracture events (11.6 versus 9.2 participants with fracture per 1,000 patient-years; HR 1.23; 95% CI, 0.99 to 1.52).[26] Based on these results, the authors concluded that the use of canagliflozin resulted in a lower risk of CV events compared to placebo but also resulted in a greater risk of amputation, primarily at the level of the toe or metatarsal.[26]

Dapagliflozin

The Dapagliflozin Effect on Cardiovascular Events—Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial was completed in September 2018 with the aim of evaluating the effects of dapagliflozin on CV and renal outcomes in a broad population of patients who had or were at risk for atherosclerotic CVD.[27] The study was multi-centre, randomized, double-blinded, and placebo-controlled.[27] The DECLARE-TIMI 58 trial compared the use of daily doses of dapagliflozin (10 mg) with placebo in patients 40 years of age or older with T2D, an A1C of 6.5% to 12%, and a creatinine clearance > 60mL/min. Patients also had multiple risk factors for atherosclerotic CVD or had established CVD.[27] The primary safety end point was MACE (defined as CV death, MI, or ischemic stroke), while the primary efficacy end point was MACE and a composite of CV death or hHF.[27] The secondary efficacy end point consisted of a renal composite outcome including death from CV causes and death from any cause (Table 10).[27]

The results indicate that the primary safety end point of MACE was noninferior compared to placebo (upper boundary of the 95% CI, < 1.3; *P* < 0.001 for noninferiority).[27] The primary efficacy end point demonstrated that dapagliflozin resulted in a lower rate of CV death or hHF compared to placebo, consequently lowering the rate of the composite outcome (4.9% versus 5.8%; HR 0.83; 95% CI, 0.73 to 0.95; *P* = 0.005). In the subgroup of patients with established atherosclerotic CVD, the rate of CV death or hHF was similar in both groups. Patients on dapagliflozin did not have a lower rate of MACE compared to placebo (8.8% and 9.4% in the two groups, respectively; HR 0.93; 95% CI, 0.83 to 1.03; *P* = 0.17).[27] Among patients with established atherosclerotic CVD, the rate of MACE was 13.9% in the dapagliflozin group and 15.3% in the placebo group (HR 0.90; 95% CI, 0.79 to 1.02).[27] Although the use of dapagliflozin was associated with a statistically significant lower risk of serious adverse events (34.1% versus 36.2% in the placebo group; HR 0.91; 95% CI, 0.87 to 0.96, *P* < 0.001) and major hypoglycemic events (0.7% versus 1.0% in the placebo group; HR 0.68; 95% CI 0.49 to 0.95, *P* =0.02), it had increased rates of adverse events, leading to the discontinuation of the trial drug regimen (8.1% versus 6.9% in the placebo group; HR 1.15; 95% CI 1.03 to 1.23, *P* = 0.01). It also increased the risk of diabetic ketoacidosis compared to placebo (0.3% versus 0.1%; HR 2.81; 95% CI, 1.10 to 4.30, *P* = 0.02).[27] The authors therefore concluded that patients with T2DM with or at risk for atherosclerotic CVD using dapagliflozin do not have a higher or lower rate of MACE compared to using placebo. However, patients using dapagliflozin had a lower rate of CV death or hHF; the lower rate of the composite outcome was due to a lower rate of hHF.[27]

Empagliflozin

The (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) was completed in April 2015. It aimed to examine the effects of empagliflozin, used at daily doses of 10 mg or 25 mg compared with placebo, on CV morbidity and mortality in patients with T2DM at high risk for CV events who were receiving standard care.[28] The study was multi-centre, randomized, double-blinded, and placebo-controlled.[28] The EMPA-REG OUTCOME trial enrolled adults (≥ 18 years of age) with T2DM, with a body mass index of ≤ 45, an eGFR of > 30mL/min, and established CVD.[28] The primary end point was a composite of death from CV causes, non-fatal MI (excluding silent MI), or non-fatal stroke.[28] The secondary end point consisted of a composite of the primary end point plus hospitalization for unstable angina (Table 11).[28]

The results of this trial indicate that the primary end point incidence was lower with empagliflozin compared with placebo. More specifally, death from CV causes, non-fatal MI (excluding

Table 10: Key Elements of and Results of the DECLARE-TIMI 58 Trial[27]

Study	Purpose	PICO	Key Results
DECLARE-TIMI 58 Design: multi-centre, randomized, double-blind, placebo-controlled N = 17,160 Duration: median of 4.2 years	To evaluate the effects of dapagliflozin on CV and renal outcomes in a broad population of patients who had or were at risk for atherosclerotic CVD	Population: 40 years of age or older and had T2DM, an A1C of 6.5% to 12%, and CrCl of > 60mL/min; patients also had multiple risk factors for atherosclerotic CVD or had established atherosclerotic CVD; participants with multiple risk factors were men > 55 years old or women > 60 years old who had one or more traditional risk factors Intervention: 10 mg of dapagliflozin daily Comparator: Placebo Outcomes: • Primary safety: MACE (defined as CV death, MI, or ischemic stroke) • Primary efficacy outcomes: MACE and a composite of CV death or hHF • Secondary efficacy outcomes: renal composite outcome including death from CV causes and death from any cause	• CV death or hHF: dapagliflozin = 4.9% vs. placebo = 5.8% (HR 0.83; 95% CI, 0.73 to 0.95)[a] • MACE: dapagliflozin = 8.8% vs. placebo = 9.4% (HR 0.93; 95% CI, 0.83 to 1.03) • MACE among patients with established atherosclerotic CVD: dapagliflozin = 13.9% vs. placebo = 15.3% (HR 0.90; 95% CI 0.79 to 1.02) • Serious AE: dapagliflozin = 34.1% vs. placebo = 36.2% (HR 0.91; 95% CI 0.87 to 0.96) • AE leading to the discontinuation of trial: dapagliflozin = 8.1% vs. placebo = 6.9% (HR 1.15; 95% CI 1.03 to 1.23) • Major hypoglycemic event: dapagliflozin = 0.7% vs. placebo = 1.0% (HR 0.68; 95% CI 0.49 to 0.95) • DKA: dapagliflozin = 0.3% vs. placebo = 0.1% (HR 2.81; 95% CI 1.10 to 4.30)

A1C = glycated hemoglobin; AE = adverse event; CI = confidence interval; CrCl = creatinine clearance; CV = cardiovascular; CVD = cardiovascular disease; DECLARE-TIMI 58 = Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58; DKA = diabetic ketoacidosis; hHF = hospitalization for heart failure; HR = hazard ratio; MACE = major adverse cardiovascular event; MI = myocardial infarction; PICO = Population, Intervention, Comparator, Outcomes; T2DM = type 2 diabetes; vs. = versus.

[a] A lower rate of the composite outcome was due to a lower rate of hospitalization for heart failure.

Table 11: Key Elements of and Results of the EMPA-REG OUTCOME[28]

Study	Purpose	PICO	Key Results
EMPA-REG OUTCOME Design: multi-centre, randomized, double-blind, placebo-controlled. N = 7,072 Duration: median of 3.1 years	To examine the effects of empagliflozin, as compared with placebo, on CV morbidity and mortality in patients with T2DM at high risk for CV events who were receiving standard care	Population: adults (≥ 18 years of age) with T2DM, with a BMI of ≤ 45 and an eGFR of > 30mL/min. All patients had established CVD, had received no glucose-lowering drugs for at least 12 weeks before randomization, and had an A1C of 7% to 9% or had received stable glucose-lowering therapy for >12 weeks before randomization and had A1C of 7% to 10% Intervention: 10 mg or 25 mg of empagliflozin once daily Comparator: placebo Outcomes: • Primary: composite of death from CV causes, non-fatal MI (excluding silent MI), or non-fatal stroke • Secondary: composite of the primary outcome plus hospitalization for unstable angina	• Primary outcome: empagliflozin = 10.5% vs. placebo = 12.1% (HR 0.86; 95.02% CI, 0.74 to 0.99) • Secondary outcome: empagliflozin = 12.8% vs. placebo = 14.3% (HR: 0.89; 95% CI, 0.78 to 1.01) • Death from CV causes: empagliflozin 3.7% vs. placebo = 5.9% (HR 0.62; 95% CI, 0.49 to 0.77) • Death from any cause: empagliflozin = 5.7% vs. placebo = 8.3% (HR 0.68; 95% CI, 0.57 to 0.82) • hHF: empagliflozin = 2.7% vs. placebo = 4.1% (HR 0.65; 95% CI, 0.50 to 0.85) • Genital infection: empagliflozin = 6.4% vs. placebo = 1.8%

A1C = glycated hemoglobin; BMI = body mass index; CI = confidence interval; CV = cardiovascular; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; EMPA-REG OUTCOME = (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; hHF = hospitalization for heart failure; HR = hazard ratio; MI = myocardial infarction; PICO = Population, Intervention, Comparator, Outcomes; T2DM = type 2 diabetes, vs. = versus.

silent MI), or non-fatal stroke was reported in 10.5% of patients assigned to empagliflozin compared to 12.1% of patients on placebo (HR 0.86; 95.02% CI, 0.74 to 0.99; *P* < 0.001 for noninferiority and *P* = 0.04 for superiority).[28] For the secondary end point, events occurred in 12.8% of patients assigned to empagliflozin compared to 14.3% assigned to placebo (HR: 0.89; 95% CI, 0.78 to 1.01; *P* < 0.001 for noninferiority and *P* = 0.08 for superiority).[28] Subgroup analysis reported that the use of empagliflozin compared with placebo resulted in a significantly lower risk of death from CV causes (HR 0.62; 95% CI, 0.49 to 0.77; *P* < 0.001), death from any cause (HR 0.68; 95% CI, 0.57 to 0.82; *P* < 0.001), and hHF (HR 0.65; 95% CI, 0.50-0.85; *P* = 0.002).[28] Patients on empagliflozin experienced a higher incidence of genital infection; i.e., 6.4% of those in the pooled empagliflozin group compared to 1.8% in patients in the placebo group.[28] Authors of the study concluded that the addition of empagliflozin to standard care provided to patients with T2DM at high risk for CV events lowers the risk of primary composite CV outcome and of death from any cause compared with placebo.[28]

GLP-1 Receptor Agonists

Exenatide

The Exenatide Study of Cardiovascular Event Lowering (EXSCEL) was completed in April 2017 with the aim of assessing the long-term CV safety and efficacy of extended-release exenatide administered at subcutaneous doses of 2 mg once weekly in patients with T2DM.[29] The study was pragmatic, multi-centre, randomized, double-blinded, and placebo-controlled.[29] The EXSCEL trial enrolled adults with T2DM (A1C 6.5% to 10%). Of these, 70% would have had previous CV events.[29] The primary end point was first occurrence of any component of the composite outcome of death from CV causes, non-fatal MI, or non-fatal stroke (three-component MACE outcome), in a time-to-event analysis.[29] The secondary end point consisted of death from any cause; death from CV causes; and the first occurrence of non-fatal or fatal MI, non-fatal or fatal stroke, hospitalization for ACS, and hHF (Table 12).[29]

Table 12: Key Elements of and Results of the EXSCEL Trial[29]

Study	Purpose	PICO	Key Results
EXSCEL Design: multi-centre, randomized, double-blind, placebo-controlled Pragmatic trial N = 14,752 Duration: median of 3.2 years	To assess the long-term CV safety and efficacy of exenatide, administered once weekly, in patients with T2DM who had a wide range of CV risk	Population: adults with T2DM (A1C 6.5% to 10%); 70% of enrolled patients would have had previous CV events Intervention: S/C injections of extended-release exenatide at a dose of 2 mg once weekly Comparator: placebo Outcomes: • Primary: first occurrence of any component of the composite outcome of death from CV causes, non-fatal MI, or non-fatal stroke (3-component MACE outcome) in a time-to-event analysis • Secondary: death from any cause; death from CV causes; and the first occurrence of non-fatal or fatal MI, non-fatal or fatal stroke, hospitalization for ACS, and hHF	• Primary outcome: exenatide = 11.4% vs. placebo = 12.2% (HR 0.91; 95% CI, 0.83 to 1.00) • Death from any cause: exenatide = 6.9% vs. placebo = 7.9% (HR 0.86; 95% CI, 0.77 to 0.97) • CV or peripheral revascularization procedures: HR 0.94; 95% CI, 0.85 to 1.05: data not provided

ACS = acute coronary syndrome; A1C = glycated hemoglobin; CI = confidence interval; CV = cardiovascular; EXSCEL = Exenatide Study of Cardiovascular Event Lowering trial; hHF = hospitalization for heart failure; HR = hazard ratio; MI = myocardial infarction; PICO = Population, Intervention, Comparator, Outcomes; S/C = subcutaneous; T2DM = type 2 diabetes; vs. = versus.

The results indicate that the primary end point incidence was similar in both groups, where 11.4% of patients assigned to exenatide had an occurrence of any component of the composite outcome compared to 12.2% of patients on placebo (HR 0.91; 95% CI, 0.83 to 1.00; $P < 0.001$ for noninferiority and $P = 0.06$ for superiority).[29] When looking at the secondary end points, exenatide had a lower risk of death from any cause compared to placebo (6.9% versus 7.9%, respectively; HR 0.86; 95% CI, 0.77 to 0.97) and a similar rate of CV or peripheral revascularization procedures (HR 0.94; 95% CI, 0.85 to 1.05).[29] Based on the study results, the authors of the study concluded that, in patients with T2DM with or without previous CV disease, exenatide did not increase the incidence of MACE compared with placebo.[29]

Liraglutide

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial was completed in December 2015 with the aim of assessing the long-term effects of daily 1.8 mg doses of subcutaneous liraglutide on CV outcomes and other clinically important effects.[30] The study was pragmatic, multi-centre, randomized, double-blinded, and placebo-controlled.[30] The LEADER trial enrolled patients with T2DM (A1C of 7.0% or more), with CVD or CV risk factors varying by age.[30] The primary end point was the first occurrence of death from CV causes, non-fatal (including silent) MI, or non-fatal stroke.[30] Additional pre-specified exploratory CV outcomes included an expanded CV outcome (death from CV causes, non-fatal MI, non-fatal stroke, coronary revascularization, or hospitalization for unstable angina pectoris or heart failure) and death from any cause (Table 13).[30]

The results indicate that liraglutide was superior to placebo, where 13.0% of patients assigned to liraglutide experienced the first occurrence of death from CV causes, non-fatal (including silent) MI, or non-fatal stroke compared to 14.9% of patients on placebo (HR 0.87; 95% CI, 0.78 to 0.97; $P < 0.001$ for noninferiority and $P = 0.01$ for superiority).[30] In the exploratory outcomes, death from CV causes occurred in 4.7% in the liraglutide group compared to 6.0% in the placebo group (HR 0.78; 95% CI, 0.66 to 0.93; $P = 0.007$), rate of death from any cause occurred in 8.2% of the liraglutide group compared to 9.6% of the placebo group (HR 0.85; 95% CI, 0.74 to 0.97; $P = 0.02$), and the frequencies of non-fatal MI and non-fatal stroke were lower in the liraglutide group than in the placebo group, although the differences were

Table 13: Key Elements of and Results of the LEADER Trial[30]

Study	Purpose	PICO	Key Results
LEADER Design: multi-centre, randomized, double-blind, placebo-controlled Pragmatic trial N = 9,340 Duration: median of 3.8 years	To assess the long-term effects of liraglutide on CV outcomes and other clinically important effects	Population: patients with T2DM (A1C of 7.0% or more) were eligible if they either had not received drugs for this condition previously or had been treated with one or more oral antihyperglycemic agents or insulin, or a combination of these agents; age 50 or more with at least one CV coexisting condition or age 60 or more with at least one CV risk factor, as determined by the investigator Intervention: 1.8 mg S/C injection in addition to standard care Comparator: placebo Outcomes: • Primary: First occurrence of death from CV causes, non-fatal (including silent) MI, or non-fatal stroke • Pre-specified exploratory outcomes: expanded CV outcome (death from CV causes, non-fatal MI, non-fatal stroke, coronary revascularization, or hospitalization for unstable angina pectoris or HF) and death from any cause	• Primary outcome: liraglutide = 13.0% vs. placebo = 14.9% (HR 0.87; 95% CI, 0.78 to 0.97) • Secondary: ○ Death from CV causes: liraglutide = 4.7% vs. placebo = 6.0% (HR 0.78; 95% CI, 0.66 to 0.93) ○ Death from any cause: liraglutide = 8.2% vs. placebo = 9.6% (HR 0.85; 95% CI, 0.74 to 0.97; $P = 0.02$). • Benign neoplasms: liraglutide = 3.6% vs. placebo = 3.1% • Malignant neoplasms: liraglutide = 6.3% vs. placebo = 6.0% • Acute gallstone disease: liraglutide = 3.1% vs. placebo = 1.9%

A1C = glycated hemoglobin; CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; LEADER = Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results trial; MI = myocardial infarction; PICO = Population, Intervention, Comparator, Outcomes; S/C = subcutaneous; T2DM = type 2 diabetes; vs. = versus.

not statistically significant.[30] For adverse events, the overall rates of benign or malignant neoplasms were higher in the liraglutide group than in the placebo group, but the difference was not statistically significant. The incidence of different cancers varied in each group.[30] Additionally, acute gallstone disease was also more common in the liraglutide group compared with placebo.[30] Based on the study results, the authors of the study concluded that patients with T2DM using liraglutide had a lower rate of the first occurrence of death from CV causes, non-fatal MI, or non-fatal stroke compared with placebo.[30]

Lixisenatide

The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial was completed in February 2015. It aimed to assess the effects of daily subcutaneously administered lixisenatide (10 mcg the first two weeks and up to 20 mcg based on the investigator's discretion) on CV morbidity and mortality.[31] The study was multi-centre, randomized, double-blinded, and placebo-controlled.[31] The ELIXA trial enrolled patients with T2DM that had an acute coronary event within 180 days before screening.[31] The primary end point was a composite of the first occurrence of any of the following: death from CV causes, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina.[31] The secondary end point included a composite of primary end point or hHF and a composition of the primary end point, hHF, or coronary revascularization procedures.[31] All-cause mortality and the rates of the components of each of the composite end point were also examined (Table 14).[31]

The results showed that the incidence of the primary end point is similar in both groups, where 13.4% of patients assigned to lixisenatide had the first occurrence of death from CV causes,

Table 14: Key Elements of and Results of ELIXA[31]

Study	Purpose	PICO	Key Results
ELIXA Design: multi-centre, randomized, double-blind, placebo-controlled N = 6,068 Duration: median of 25 months	To assess the effects of lixisenatide on CV morbidity and mortality	Population: patients had T2DM and had had an acute coronary event within 180 days before screening. Intervention: starting dose of 10 mcg of lixisenatide per day during the 2 first weeks, then increased at the investigator's discretion to a maximum dose of 20 mcg of lixisenatide per day Comparator: placebo Outcomes: • Primary: composite of the first occurrence of any of the following — death from CV causes, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina • Secondary: composite of primary end point or hHF and a composition of the primary end point, hHF or coronary revascularization procedures; all-cause mortality and the rates of the components of each of the composite end point were also examined	• Primary outcome: lixisenatide = 13.4% vs. placebo = 13.2% (HR 1.02; 95% CI, 0.89 to 1.17) • hHF added to primary composite: lixisenatide = 15.0% vs. placebo = 15.5% (HR 0.97; 95% CI, 0.85 to 1.10) • Further addition of coronary revascularization procedure added to expanded composite: lixisenatide = 21.8% vs. placebo = 21.7% (HR 1.00; 95% CI, 0.90 to 1.11) • hHF: lixisenatide = 4.0% vs. placebo = 4.2% (HR 0.96; 95% CI, 0.75 to 1.23) • Death from any cause: lixisenatide = 7.0% vs. placebo = 7.4% (HR 0.94; 95% CI, 0.78 to 1.13) • AE that lead to the permanent discontinuation: lixisenatide = 11.4% vs. placebo = 7.2% • GI event: lixisenatide = 4.9% vs. placebo = 1.2

AE = adverse events; CI = confidence interval; CV = cardiovascular; ELIXA = Evaluation of Lixisenatide in Acute Coronary Syndrome trial; GI = gastrointestinal; hHF = hospitalization for heart failure; HR = hazard ratio; MI = myocardial infarction; PICO = Population, Intervention, Comparator, Outcomes; T2DM = type 2 diabetes; vs. = versus.

non-fatal MI, non-fatal stroke, or hospitalization for unstable angina compared to 13.2% of patients on placebo (HR 1.02; 95% CI, 0.89 to 1.17; *P* < 0.001 for noninferiority and *P* = 0.81 for superiority).[31] When looking at the separate CV components of each of the composite end points for the secondary end point, the frequency of each was similar in the two study groups.[31] However, patients in the lixisenatide group had more adverse events that led to the permanent treatment discontinuation (11.4%) compared to those in the placebo group (7.2%).[31] The most common adverse event was a gastrointestinal event (4.9% in lixisenatide versus 1.2% in placebo).[31] Within this category, nausea occurred in 3.0% in the lixisenatide group versus 0.4% in the placebo group and vomiting occurred in 1.1% in the lixisenatide group versus 0.2% in the placebo group (*P* < 0.001 for both comparisons).[31] Authors of the study concluded that patients with T2DM and a recent acute coronary event using lixisenatide did not have significantly different rates of major CV events or other serious adverse events compared with those using a placebo.[31]

Semaglutide

The Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) was completed in March 2016. It aimed to assess the noninferiority of weekly subcutaneously administered semaglutide (0.5 mg or 1.0 mg) for CV safety compared with placebo.[32] The study was multiecentre, randomized, double-blinded, and placebo-controlled.[32] The SUSTAIN-6 enrolled patients with T2DM who had not been treated with an antihyperglycemic drug or had been treated with no more than two oral antihyperglycemic agents, with or without basal or premixed insulin, along with CVD or risk factors.[32] The primary end point was a composite outcome of the first occurrence of death from CV causes, non-fatal MI, or non-fatal stroke.[32] The secondary end point included the first occurrence of an expanded composite CV outcome (death from CV causes, non-fatal MI, non-fatal stroke, revascularization, and hospitalization for unstable angina or HF), an additional composite outcome (death from all causes, non-fatal MI, or non-fatal stroke), and the individual components of the composite outcomes (Table 15).[32]

Table 15: Key Elements of and Results of SUSTAIN-6[32]

Study	Purpose	PICO	Key Results
SUSTAIN-6 Design: multi-centre, randomized, double-blind, placebo-controlled N = 3,297 Duration: median of 104 weeks	To assess the noninferiority of semaglutide as compared with placebo in terms of CV safety in patients with T2DM	Population: patients with T2DM (A1C of 7% or more) were eligible if they had not been treated with an antihyperglycemic drug or had been treated with no more than 2 oral antihyperglycemic agents, with or without basal or premixed insulin; were 50-years-old or more, with established CVD, chronic HF, or CKD of stage III or higher; or were aged 60 years or more, with at least one CV risk factor Intervention: 0.5 or 1.0 mg of once weekly S/C semaglutide Comparator: Placebo Outcomes: • Primary: composite outcome of the first occurrence of death from CV causes, non-fatal MI, or non-fatal stroke • Secondary: first occurrence of an expanded composite CV outcome (death from CV causes, non-fatal MI, non-fatal stroke, revascularization and hospitalization for unstable angina or HF), an additional composite outcome (death from all causes, non-fatal MI, or non-fatal stroke), and the individual components of the composite outcomes	• Primary outcome: semaglutide = 6.6% vs. placebo = 8.9% (HR 0.74; 95% CI, 0.58 to 0.95) • Non-fatal MI: semaglutide = 2.9% vs. placebo = 3.9% (HR 0.74; 95% CI, 0.51 to 1.08) • Non-fatal stroke: semaglutide = 1.6% vs. placebo = 2.7% (HR 0.61; 95% CI, 0.38 to 0.99) • CV death: semaglutide = 2.7% vs. placebo = 2.8% (HR 0.98; 95% CI, 0.65 to 1.48) • GI disorders: ○ 0.5 mg semaglutide = 50.7% vs. placebo = 35.7% ○ 1.0 mg semaglutide = 52.3% vs. placebo = 35.2%

A1C = glycated hemoglobin; CI = confidence interval; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; HF = heart failure; HR = hazard ratio; MI = myocardial infarction; PICO = Population, Intervention, Comparator, Outcomes; S/C = subcutaneous; SUSTAIN-6 = Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; T2DM = type 2 diabetes; vs. = versus.

The results indicate that the incidence of the primary end point was lower in the semaglutide group, where 6.6% of patients had the first occurrence of death from CV causes, non-fatal MI, or non-fatal stroke compared to 8.9% of patients on placebo (HR 0.74; 95% CI, 0.58 to 0.95; $P < 0.001$ for noninferiority and $P = 0.02$ for superiority).[32] For the secondary end point, only the incidence of non-fatal stroke was statistically significantly lower in the semaglutide group (1.6%) compared to the placebo group (2.7%), HR 0.61; 95% CI, 0.38 to 0.99; $P = 0.04$.[32] Rates of non-fatal MI and CV death were lower in the semaglutide group, but differences were not statistically significant compared with the placebo group.[32] Gastrointestinal disorders were more frequent in the semaglutide group than in the placebo group.[32] Authors of the study concluded that the rate of CV death, non-fatal MI, or non-fatal stroke was statistically significantly lower among high CV risk patients with T2DM receiving semaglutide compared to placebo.[32]

Topline Results

Dulaglutide

The Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) trial was completed in August 2018. It aimed to determine the effects on CV outcomes of dulaglutide — a synthetic, once weekly, injectable, human GLP-1 receptor agonist.[33] The study was multi-centre, randomized, double-blinded, and placebo-controlled.[33] The REWIND trial enrolled people with T2DM aged ≥ 50 years, with A1C of ≤ 9.5%; and either a previous CV event, evidence of CVD, or ≥ 2 CV risk factors.[33] The majority of patients (69%) did not have established CVD at baseline.[33] The REWIND trial evaluated the results of those receiving weekly doses of dulaglutide (1.5 mg) subcutaneously compared with placebo.[33] The primary end point was the first occurrence of MACE (the composite of CV death or non-fatal MI, or non-fatal stroke).[33] The secondary end point included each component of the primary composite CV outcome, a composite of clinical microvascular outcome comprising retinal or renal disease, hospitalization for unstable angina, HF requiring hospitalization, or an urgent HF visit and all-cause mortality (Table 16).[33]

Results from the REWIND study have not yet been published. However, the manufacturer released a press article on REWIND's topline results in 2018. The latter indicates that the primary end point incidence of MACE was significantty reduced in the dulaglutide group compared to placebo.[33] Based on the study results, the manufacturer stated that dulaglutide is the first drug to demonstrate superiority in the reduction of MACE in a T2DM clinical trial that included a majority of participants who did not have established CVD.[33] It would appear that the full results fo the

Table 16: Key Elements of and Topline Results of the REWIND Trial[33]

Study	Purpose	PICO	Key Results
REWIND Design: Multi-centre, randomized, double-blind, placebo-controlled N = 9,901 Duration: median of more than 5 years	To determine the effects of dulaglutide on CV outcomes	Population: people with T2DM aged ≥ 50 years, with A1C ≤ 9.5% and either a previous CV event, evidence of CVD, or ≥ 2 CV risk factors Note: majority of patients (69%) without established CVD at baseline Intervention: once weekly S/C dulaglutide 1.5 mg Comparator: placebo when added to standard of care Outcomes: • Primary: the first occurrence of MACE (the composite of CV death, or non-fatal MI or non-fatal stroke) • Secondary: each component of the primary composite CV outcome, a composite of clinical microvascular outcome comprising retinal or renal disease, hHF, or an urgent HF visit and all-cause mortality	MACE: dulaglutide = significant reduction versus placebo

A1C = glycated hemoglobin; CV = cardiovascular; hHF = hospitalization for heart failure; HF = heart failure; MACE = major adverse cardiovascular event; MI = myocardial infarction; PICO = Population, Intervention, Comparator, Outcomes; REWIND = Researching Cardiovascular Events with a Weekly Incretin in Diabetes; S/C = subcutaneously; T2DM = type 2 diabetes.

REWIND study will be presented on June 9, 2019 at the American Diabetes Association's 79th Scientific Sessions in San Francisco, California.[34]

Linagliptin

In February 2019, Boehringer Ingelheim and Eli Lilly and Company jointly announced the topline results of the CARdiovascular Outcome study of LINAgliptin versus glimepiride in patients with type 2 diabetes (CAROLINA). This trial compared linagliptin with sulfonylurea glimepiride and, as such, would appear to be the only active-controlled CVOT of a DPP-4 inhibitor. These treatments were respectively added to standard of care in 6,033 patients with T2DM and increased CV risk or established CVD; the mean follow-up period was more than six years. The manufacturers' statement indicates that CAROLINA met its primary end point of noninferiority for time to first occurrence of cardiovascular death, non-fatal MI, or non-fatal stroke. The overall safety profile of linagliptin in CAROLINA was consistent with previous data, with no new safety signals observed (Table 17).[35]

The results of CAROLINA have not been published yet, but the February 2019 manufacturers' statement indicated that the full results of CAROLINA will be presented on June 10, 2019 at the American Diabetes Association's 79th Scientific Sessions in San Francisco, California.[34,35]

Concurrent Developments

As T2DM incidence continues to increase, the number of drugs to treat this conditon also continues to increase. During the citation and study screening process, another DPP-4 inhibitor was identified: omarigliptin. This drug is currently marketed in Japan and was being investigated in a CVOT.[37] The trial was, however, terminated early because of the business decision of not marketing the drug in the US.[37] The results before termination indicated that omarigliptin does not increase the risk of MACE or hHF and is generally well-tolerated.[37]

Currently in the pipeline, two SGLT-2 inhibitors are in phase III clinical trials.[38] Bexagliflozin is currently testing the efficacy of lowering A1C in patients with T2DM, while sotagliflozin originally

Table 17: Key Elements of and Topline Results of CAROLINA[35,36]

Study	Purpose	PICO	Key Results
CAROLINA Design: multi-centre, international, randomized, parallel group, double-blind with active control N = 6,103 Note: results in 6,033) Duration: median of more than 6 years	**To investigate the long-term impact on CV morbidity and mortality, relevant efficacy parameters (e.g., glycemic parameters), and safety (e.g., weight and hypoglycemia) of linagliptin versus glimepiride**	Population: people with T2DM aged 40 to 85 years, with A1C between 6.5% and 8.5%, or 6.5% and 7.5% (depending on background therapy), pre-existing CVD or specified diabetes end-organ damage, or age ≥ 70 years or ≥ 2 specified CV risk factors, BMI ≤ 45 kg/m^2 Intervention: linagliptin 5 mg daily + glimepiride placebo Comparator: glimepiride 1mg to 4 mg daily + linagliptin placebo Outcomes: • Primary: time to first occurrence of any of the following adjudicated components of the primary composite end point: CV death (including fatal stroke and fatal MI), non-fatal MI (excluding silent MI), or non-fatal stroke • Secondary: time to first occurrence of any of the following adjudicated components of CV death (including fatal stroke and fatal MI), non-fatal MI (excluding silent MI), non-fatal stroke or hospitalization for unstable angina pectoris (Note: other measures such as glycemic parameters were also included as secondary outcomes)	Study met its primary end point of noninferiority in time to first occurrence of CV death, non-fatal MI, or non-fatal stroke; the overall safety profile of linagliptin in this study was consistent with previous data, with no new safety signals

A1C = glycated hemoglobin; BMI = body mass index; CAROLINA = CARdiovascular Outcome study of LINAgliptin versus glimepiride in patients with type 2 diabetes; CV = cardiovascular; CVD = cardiovascular disease; MI = myocardial infarction; PICO = Population, Intervention, Comparator, Outcomes; T2DM = type 2 diabetes.

assessed in T2DM is also being tested as an adjuvant to insulin in patients with T1DM.[39,40] Regarding the latter indication, on February 28, 2019, the European Medicines Agency's Committee for Medicinal Products for Human Use adopted a positive opinion for granting marketing authorization for sotagliflozin as an adjunct to insulin therapy to improve glycemic control in adults with T1DM with a body mass index of 27 kg/m^2 or more who have failed to achieve adequate glycemic control despite optimal insulin therapy.[41] This recommendation was associated with a list of conditions to minimize the risk of diabetic ketoacidosis.[42] The European Medicines Agency approved sotagliflozin for this indication on April 29, 2019; the trade name for this drug in Europe is Zynquista.[43] However, one month before — i.e., on March 22, 2019 — the FDA had issued a complete response letter regarding the New Drug Application for oral sotagliflozin for adults with T1DM. This letter indicated that the FDA could not approve the application in its present form.[44] Earlier, in January 2019, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee had a split vote (8-8) in recommending the approval of sotagliflozin for T1DM. The concern lay in the increased risk of diabetic ketoacidosis; members also requested that a risk evaluation and mitigation strategy be implemented if the drug was approved.[45]

Some ongoing phase III clinical trials of GLP-1 receptor agonists were also retrieved including two completed phase III clinical trials.[38] Of interest, ITCA 650 is an exenatide implant that can deliver 60 mcg of exenatide daily through a pump for six to 12 months, with the aim of improving patient adherence. The Study to Evaluate Cardiovascular Outcomes in Patients With Type 2 Diabetes Treated With ITCA 650 (FREEDOM-CVO) was completed in March 2016 with the aim of evaluating CV outcomes in patients with T2DM treated with ITCA 650 (Table 18).[46]

Results from the FREEDOM-CVO study have not yet been published. However, the manufacturer released a press release on the trial's topline results in 2016. These topline results indicate that exenatide was noninferior to placebo in the primary end point of time to first occurrence of any event included in the MACE end points previously outlined.[47] Additionally, the use of exenatide in this trial was consistent with the established safety profile observed in previous phase III clinical trials, as well as in other published literature for exenatide and other GLP-1 receptor agonist therapies.[47] The results led the manufacturer to submit a New Drug Application to the FDA.[48]

NN924 (an oral version of semaglutide) has recently completed its phase III clinical trial; it was also evaluated in a CVOT. The Researching cardiovascular Events with a Weekly INcretin in Diabetes (PIONEER 6) trial was completed in September 2018 with the aim of assessing the CV safety of once daily oral semaglutide (up to 14 mg) — the first tablet formulation of a GLP-1 receptor agonist (Table 19).[49,50]

Table 18: Key Elements of and Topline Results of FREEDOM-CVO[46]

Study	Purpose	PICO	Key Results
FREEDOM-CVO Design: multi-centre, randomized, placebo-controlled N = 4,156 Duration: median of 1.2 years	To evaluate CV outcomes in patients with T2DM treated with ITCA 650 (exenatide implant)	Population: patients (40 years or more) with T2DM (A1C > 6.5%) and a history of coronary, cerebrovascular, peripheral artery disease, or multiple CV risk factors Intervention: continous S/C delivery of exenatide at 60 mcg daily Comparator: placebo Outcomes: • Primary: time to first occurrence of any event included in the MACE composite end point (CV death, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina)	Primary outcome: exenatide = noninferior

A1C = glycated hemoglobin; CV = cardiovascular; FREEDOM-CVO = Study to Evaluate Cardiovascular Outcomes in Patients With Type 2 Diabetes Treated With ITCA 650; MACE = major adverse cardiovascular event; MI = myocardial infarction; PICO = Population, Intervention, Comparator, Outcomes; S/C = subcutaneous; T2DM = type 2 diabetes.

Table 19: Key Elements and Topline Results of the PIONEER 6 Trial[49,50]

Study	Purpose	PICO	Key Results
PIONEER-6 Design: multi-centre, randomized, double-blind, placebo-controlled N = 3,183 Duration: median of 16 months	To assess the CV safety of oral semaglutide	Population: patients with T2DM at high risk of CV events (defined as being aged ≥ 50 years and having established CVD or moderate [stage III] CKD, or being aged ≥ 60 years with ≥ 1 other CV risk factor) Intervention: once daily oral semaglutide (up to 14 mg) in addition to standard of care Comparator: placebo Outcomes: • Primary: MACE composite outcome of the first occurrence of CV death or non-fatal MI, or non-fatal stroke	• Primary outcome: semaglutide = 21% reduction vs. placebo (HR 0.79) • CV death: semaglutide = 51% reduction vs. placebo (HR 0.49) • Non-fatal MI: semaglutide similar rate vs. placebo (HR 1.18) • Non-fatal stroke: semaglutide similar rate vs. placebo (HR 0.74) • All-cause mortality: semaglutide = 49% reduction vs. placebo (HR 0.51)

CV = cardiovascular; CVD = cardiovascular disease; CKD = chronic kidney disease; HR = hazard ratio; MACE = major adverse cardiovascular event; MI = myocardial infarction; PICO = Population, Intervention, Comparator, Outcomes; PIONEER 6 = Researching cardiovascular Events with a Weekly INcretin in Diabetes; T2DM = type 2 diabetes, vs. = versus.

Results from the PIONEER 6 study have not yet been published. However, the manufacturer released a press release on the topline results of PIONEER 6 in 2018. These topline results indicate that the primary end point incidence of MACE was lower in the semaglutide group compared with placebo (HR 0.79); the 21% reduction in MACE in favour of oral semaglutide did not reach statistical significance.[49] The MACE results were driven by a statistically significant reduction in CV death of 51% (HR 0.49, *P* = 0.03), whereas non-fatal MI (HR 1.18, non-significant) or non-fatal stroke (HR 0.74, non-significant) were broadly similarly distributed between the two treatment arms.[49] There was also a statistically significant reduction in all-cause mortality of 49% (HR 0.51, *P* = 0.008).[49] In this trial, improvements in secondary end points including A1C, body weight and blood pressure were similar to results reported throughout the PIONEER clinical development program for oral semaglutide; the safety profile of oral semaglutide was also consistent with the established safety profile observed in previous PIONEER clinical trials.[49] In addition to these preliminary efficacy and safety data, results regarding the profile of study participants were recently released. Overall, 3,183 patients were enrolled (mean age 66.1 years, 31.6% females). These patients were recruited from 214 sites across 21 countries. At baseline, the mean duration of diabetes was 14.9 years and the mean A1C was 8.2%; 84.6% of patients had established CVD or moderate CKD.[50]

The GLP-1 receptor agonist efpeglenatide is currently in phase III clinical trials testing efficacy and safety in patients with T2DM.[38,51,52] Additionally, other GLP-1 receptor agonists are in phase I and phase II clinical development such as PB-119 and TTP273.[38] Also, although the release in Canada of the drug product was cancelled pre-marketing,[17] another GLP-1 receptor agonist (albiglutide) had been investigated in a CVOT (Harmony Outcomes) in March 2018.[53] The results showed that albiglutide was superior to placebo with respect to MACE.[53]

Some DPP-4 inhibitors, SGLT-2 inhibitors, and GLP-1 receptor agonists are also currently being investigated for indications other than T2DM. For example, the Dapa-CKD (ClinicalTrials.gov Identifier: NCT03036150)[54] and Dapa-HF (ClinicalTrials.gov Identifier: NCT03036124)[55] trials are investigating dapagliflozin in patients with CKD and chronic heart failure with reduced ejection fraction, respectively. Patients enrolled in these trials may or may not have T2DM. Additionally, the EMPEROR-Preserved (ClinicalTrials.gov Identifier: NCT03057951)[56] and EMPEROR-Reduced (ClinicalTrials.gov Identifier: NCT03057977)[57] trials investigate the use of empagliflozin in patients with heart failure with preserved and reduced ejection fraction, respectively. Patients enrolled in these trials may or may not not have T2DM. Commenting further on these trials is beyond the scope of this report, as it focuses on patients with T2DM specifically.

Implementation Issues

Many DPP-4 inhibitors, SGLT-2 inhibitors, and GLP-1 receptor agonists have already been marketed in Canada. Accordingly, they are currently used in practice to treat patients with T2DM, which implies some familiarity with these drugs on the part of precribers. In general, drug products pertaining to these classes are more costly than those from older drug classes (e.g., sulfonylureas); this may therefore impact their uptake.[5] Another factor that may influence the uptake of these drugs is their effect on CV outcomes. Thus far, a number of CVOTs conducted for SGLT-2 inhibitors and GLP-1 receptor agonists reported a reduction in MACE. The 2018 Diabetes Canada guidelines for the management of T2DM have identified three drugs pertaining to these classes that may be preferred over other drugs for patients with CVD — i.e., canagliflozin, empagliflozin, and liraglutide.[5]

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