AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS | AMERICAN COLLEGE OF ENDOCRINOLOGY

Cardiovascular Outcomes Trials in Type 2 Diabetes

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Introduction

- What are the main objectives of the cardiovascular outcomes trials (CVOT) for type 2 diabetes (T2D) therapeutics?
- Over the past 7 years, what have the outcomes of major CVOTs for T2D therapeutics shown?
- Which drug classes have demonstrated the greatest cardiovascular benefits?
- How have diabetes guidelines changed in response to results of CVOT trials?

2008 FDA CV Safety of T2D Drugs

- Primarily in response to findings of possible increased CV risk with rosiglitazone[1]
- FDA recommendation:
  - *"To establish safety of a new antidiabetic therapy to treat T2D, sponsors should demonstrate that the therapy will not result in an unacceptable increase in CV risk."*[2]
- CV outcomes trials (CVOTs) are characterized by:[1]
  - Inclusion of high-risk patients
  - Non-inferiority design (show no harm compared to placebo)
  - If non-inferiority threshold is met, trials can also assess for superiority

CV, cardiovascular; CVOT, cardiovascular outcomes trials; FDA, Food and Drug Administration; T2D, type 2 diabetes.

1. Kaul S. *Diabetes Care*. 2017;40:821-831.
2. U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research Guidance for Industry. *Diabetes Mellitus—Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes* (2008):1-5 (FDA Maryland).

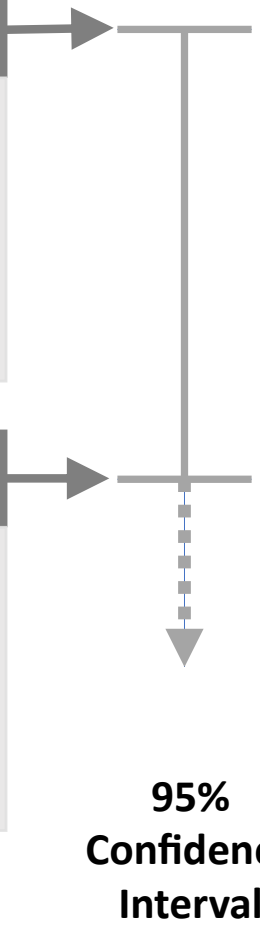
Noninferiority and Superiority Criteria in CVOTs

Noninferiority[1]

- Upper bound of the confidence interval for primary endpoint is less than a prespecified threshold (often 1.3, but criteria vary with study design)
- **Means study drug performed no worse than comparator and is safe**

Superiority[1]

- Upper bound of confidence interval for primary endpoint is typically <1 (criteria may vary with study design)
- Tested after noninferiority criteria are met
- **Means study drug reduced CV outcomes relative to comparator**



Agents shown to have CV safety:
All anti-hyperglycemic agents evaluated in CVOTs to date

Agents shown to reduce CV outcomes:
canagliflozin
empagliflozin
liraglutide
semaglutide

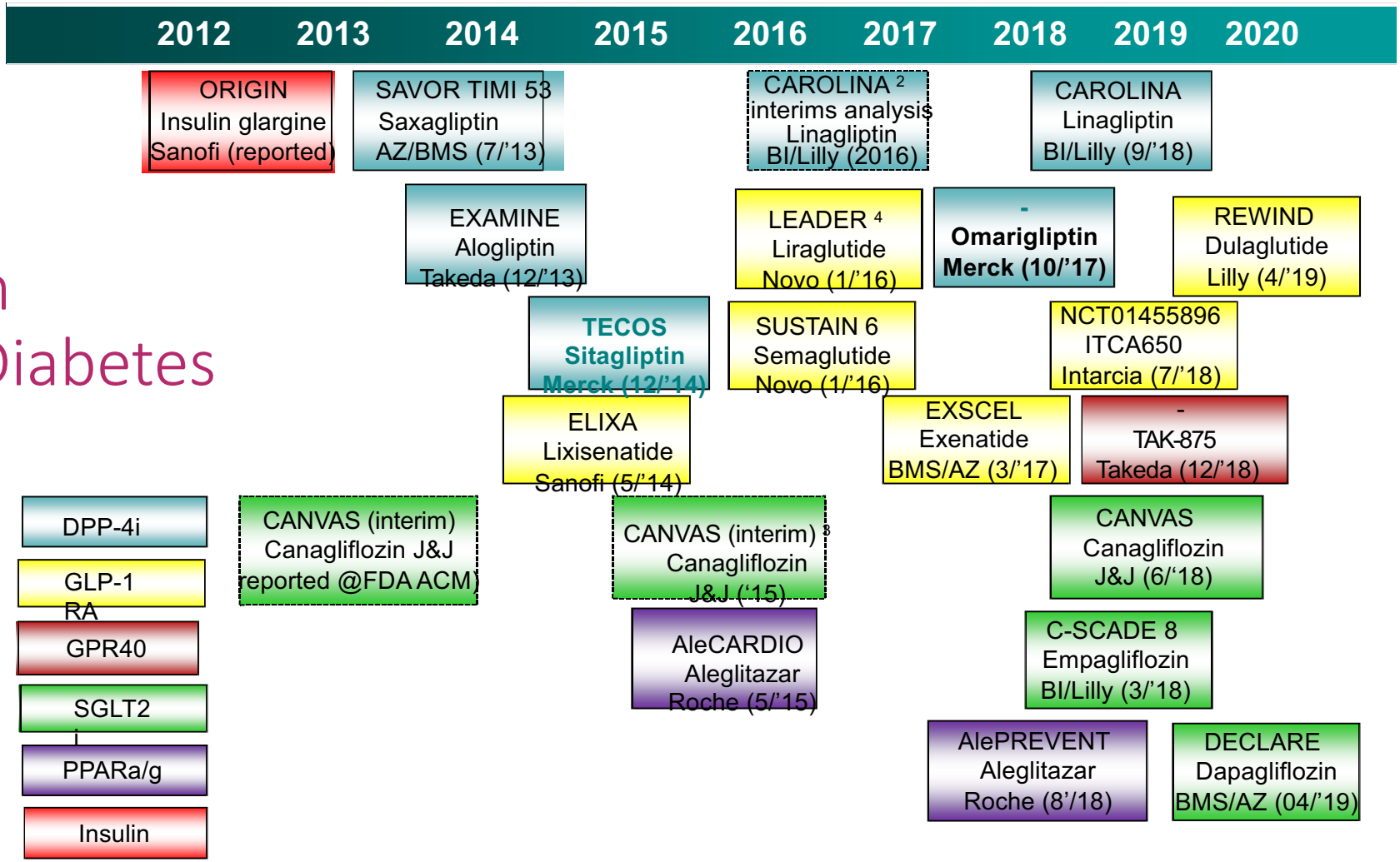
Evaluating a composite of major adverse CV events (MACE)

1. CV death
2. Nonfatal MI
3. Nonfatal stroke

CV, cardiovascular; CVOT, cardiovascular outcomes trials; MACE, major adverse cardiovascular events; MI, myocardial infarction.

1. U.S. Food and Drug Administration. Guidance for Industry, Evaluating Cardiovascular Risk. December 2008.

CVOTs in Type 2 Diabetes



DPP-4i, dipeptidyl peptidase-4 inhibitor; CANVAS, Canagliflozin Cardiovascular Assessment Study; CAROLINA, Cardiovascular Outcomes Study of Linagliptin Versus Glimepiride in Patients with Type 2 Diabetes; C-SCADE 8, trial of empagliflozin; CVOT, cardiovascular outcomes trials; DECLARE, Dapagliflozin Effect on Cardiovascular Events; Exenatide Study of Cardiovascular Event Lowering; EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; GLP-1 RA, glucagon-like peptide-1 receptor;GPR40, G-protein-coupled receptor; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; ORIGIN, Outcome Reduction with Initial Glargine Intervention; PPARa/g, peroxisome proliferator-activated receptors; REWIND, Researching cardiovascular Events with a Weekly Incretin in Diabetes; SAVOR-TIMI, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SUSTAIN-6, Semaglutide in Subjects with Type 2 Diabetes.

Cardiovascular Outcomes Trials in Diabetes

GLP-1 Receptor Agonists

GLP-1 Receptor Agonists

Benefits	Risks	FDA-Approved Agents
• Improved satiety • Promote weight loss • Improved cardiovascular outcomes (liraglutide and semaglutide)	• Common side effects of nausea, vomiting and diarrhea • Increase hypoglycemic effect of insulin and sulfonylureas • Increased risk gallbladder events • Increased retinopathy complications in patients with baseline retinopathy and rapid improvement in glycemic control (semaglutide)	• albiglutide* • dulaglutide • exenatide • exenatide ER • liraglutide • semaglutide • lixisenatide

*As of July 31, 2018, a business decision was made to discontinue manufacturing of albiglutide

ER, extended release; FDA, Food and Drug Administration; GLP-1, glucagon-like peptide-1.

Davies, MJ, et al. *Diabetes Care* 2018;doi:10.2337/dci18-0033. (Epub ahead of print)

GLP-1 Receptor Agonists: LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of CV Outcomes Results)

LEADER Study Design and Objectives

Eligibility criteria:

- T2D with A1C ≥7.0%
- Age ≥50 years with ≥1 coexisting CV condition[a] or
- Age ≥60 years with ≥1 CV risk factor[b]

R 1:1

liraglutide (0.6-1.8 mg)[c] + standard care n=4668

P lacebo + standard care n=4672

Primary outcome:
Composite of CV death, nonfatal MI, or nonfatal stroke

Key secondary outcome:
Composite of CV death, nonfatal MI, nonfatal stroke, revascularization, hospitalization for unstable angina, or HF

- **Study design:** Phase 3B**,** multi-center, international, randomized, double-blind, placebo-controlled clinical trial with long-term follow-up at 410 sites in 32 countries.
- **Primary objective:** To assess the effect of treatment with liraglutide compared to placebo (for at least 3.5 years and up to 5 years) on the incidence of CV events

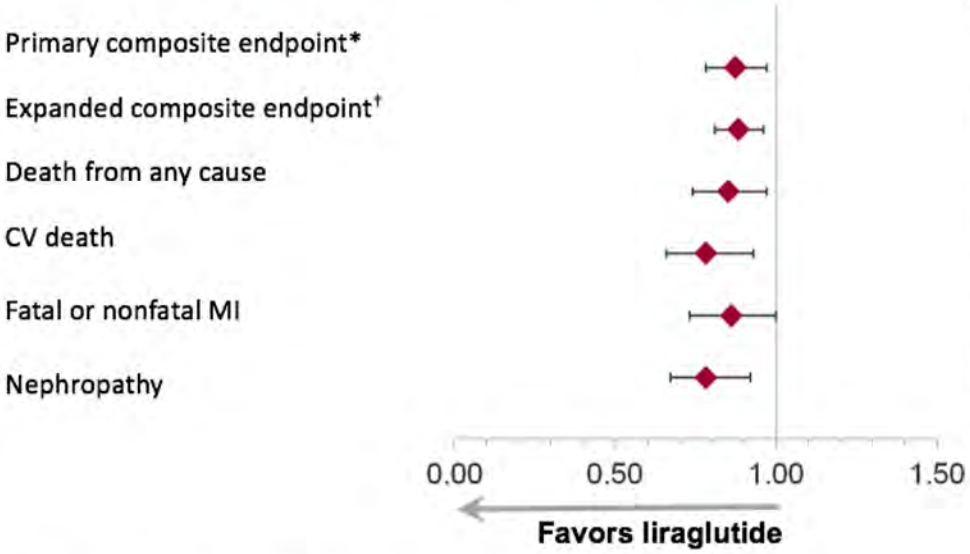
[a]Coronary heart disease, cerebrovascular disease, peripheral vascular disease, CKD stage ≥3, chronic heart failure NYHA class II/III.
[b]Microalbumiuria or proteinuria, hypertension and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction, or an ankle-brachial index (the ratio of the systolic BP at the ankle to the systolic BP in the arm) of <0.9.
[c]Liraglutide was administered at 0.6 mg daily for 1 week, 1.2 mg/day for an additional week, and a potential maximum dosage of 1.8 mg/day thereafter.

A1C, glycated hemoglobin; CV, cardiovascular; GLP-1, glucagon-like peptide-1; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcomes Results trial; MI, myocardial infarction; T2D, type 2 diabetes.

Marso SP, et al. *Am Heart J.* 2013;166:823-30.e5; Marso SP, et al. *N Engl J Med.* 2016;375(4):311-322.

GLP-1 Receptor Agonists: LEADER (Liraglutide) Results

Median follow-up: 3.8 years



	Hazard ratio (95% CI)	*P*-value
Primary composite endpoint*	0.87 (0.78-0.97)	0.01
Expanded composite endpoint†	0.88 (0.81-0.96)	0.005
Death from any cause	0.85 (0.74-0.97)	0.02
CV death	0.78 (0.66-0.93)	0.007
Fatal or nonfatal MI	0.86 (0.73-1.00)	0.046
Nephropathy	0.78 (0.67-0.92)	0.003

Conclusion:
In time-to-event analysis, rate of first occurrence of death from CV causes, nonfatal MI, or nonfatal stroke among patients with T2D was lower with liraglutide than with placebo

- 13% RRR CV Events, NNT=66
- 22% RRR CV Death, NNT= 98

*CV death, nonfatal MI (including silent MI), or nonfatal stroke.
†CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, and hospitalization for unstable angina or HF.

CI, confidence interval; CV, cardiovascular; GLP-1 RA, glucagon-like peptide-1 receptor agonists; HF, heart failure; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcomes Results trial; MI, myocardial infarction; NNT, number needed to treat; RRR, relative risk reduction; T2D, type 2 diabetes. Marso, SP, et al. *N Engl J Med.* 2016;375(4):311-322.

GLP-1 Receptor Agonists: Liraglutide

FDA Approval of New Indication with LEADER Data

US Food and Drug Administration has approved Victoza® (liraglutide) injection 1.2 mg or 1.8 mg to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease.

August 25, 2017

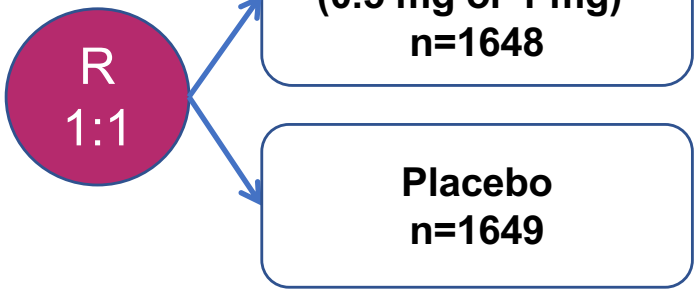
GLP-1, glucagon-like peptide; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcomes Results trial.

GLP-1 Receptor Agonists: SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes)

SUSTAIN-6 Study Design and Objectives

Eligibility criteria:

- Age ≥50 with T2D and CVD, CHF, CKD or,
- Age ≥60 with ≥1 CV risk factor



- **Study design:** Randomized, double-blind, placebo-controlled, parallel-group trial at 230 sites in 20 countries; noninferiority margin of 1.8 for upper boundary of 95% confidence interval of hazard ratio
- **Primary objective:** To assess the noninferiority of semaglutide vs placebo in terms of CV safety in patients with T2D

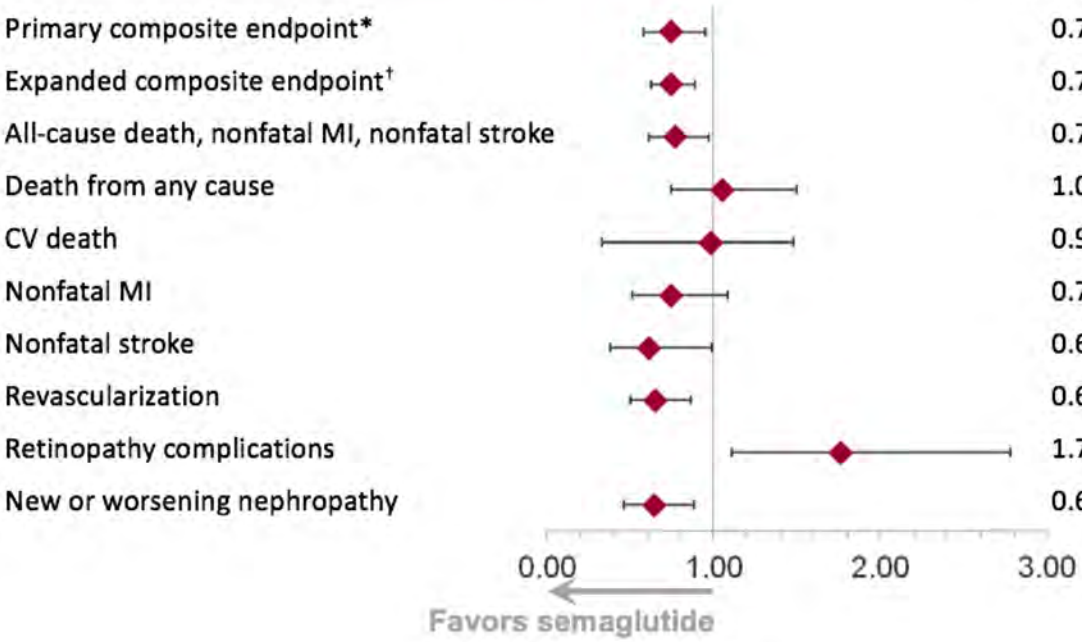
Primary outcome:
Composite of CV death, nonfatal MI (including silent MI), or nonfatal stroke

Key secondary outcomes:
- Composite of CV death, nonfatal MI, nonfatal stroke, coronary or peripheral revascularization, and hospitalization for unstable angina or HF
- Composite of all-cause death, nonfatal MI, nonfatal stroke
-Retinopathy complications
-New or worsening nephropathy

[a]0.5 mg or 1.0 mg of once-weekly subcutaneous semaglutide was administered.
CI, confidence interval; CHF, congestive heart failure; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; GLP-1, glucagon-like peptide-1; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; T2D, type 2 diabetes. Marso SP, et al. *N Engl J Med*. 2016:375:1834-1844.

GLP-1 Receptor Agonists: SUSTAIN-6

Median follow-up: 2.1 years



Conclusion: Primary hypothesis confirmed that semaglutide would be noninferior to placebo.

26% RRR, NNT = 45 (to prevent 1 primary outcome over 24 months)

*CV death, nonfatal MI (including silent MI), or nonfatal stroke; †CV death, nonfatal MI, nonfatal stroke, coronary or peripheral revascularization, and hospitalization for unstable angina or HF.

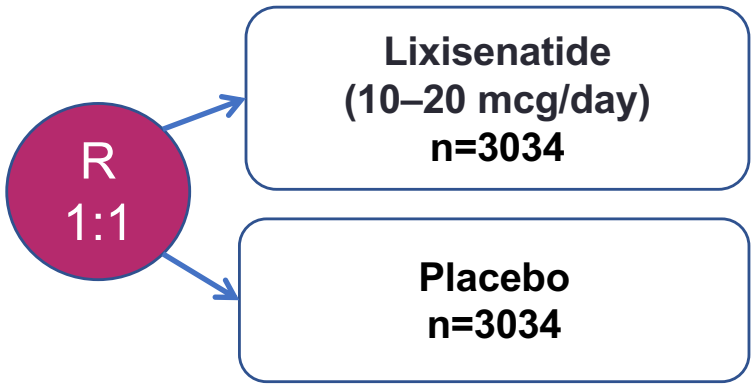
CI, confidence interval; CV, cardiovascular; GLP-1, glucagon-like peptide-1; HF, heart failure; MI, myocardial infarction; NNT, number needed to treat; NS, not significant; RRR, relative risk reduction; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes.

Marso SP, et al. *N Engl J Med*. 2016:375:1834-1844.

GLP-1 Receptor Agonists: ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome)

ELIXA Study Design and Objectives

Eligibility criteria:
N=6068 patients with T2D and MI or unstable angina within 180 days prior to enrollment



Primary outcome:
Composite of first occurrence of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina

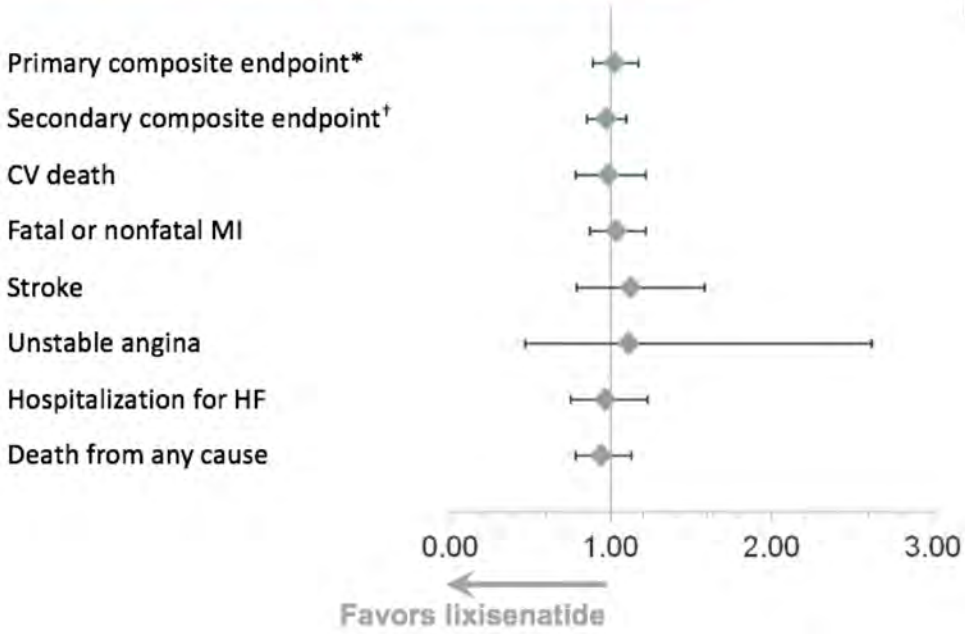
Key secondary outcome:
- Composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina or HF
- Composite of CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina or HF, or coronary revascularization

- **Study design:** Multicenter, randomized, double-blind, placebo-controlled trial of patients with T2D with recent ACS. Noninferiority criteria: upper bound of 95% CI of the HR for a primary endpoint <1.3
- **Primary objective:** to assess the effects of lixisenatide on CV morbidity and mortality

ACS, acute coronary syndrome; CI, confidence interval; CV, cardiovascular; ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome; GLP-1, glucagon-like peptide-1; HF, heart failure; HR, hazard ratio; MI, myocardial infarction, T2D, type 2 diabetes.
Pfeffer MA, et al. *N Engl J Med*. 2015;373:2247-2257.

GLP-1 Receptor Agonists: ELIXA (Lixisenatide) Results

Median follow-up: 25 months



	Hazard ratio (95% CI)	*P*-value
Primary composite endpoint*	1.02 (0.89-1.17)	0.81
Secondary composite endpoint†	0.97 (0.85-1.10)	0.63
CV death	0.98 (0.78-1.22)	0.85
Fatal or nonfatal MI	1.03 (0.87-1.22)	0.71
Stroke	1.12 (0.79-1.58)	0.54
Unstable angina	1.11 (0.47-2.62)	0.81
Hospitalization for HF	0.96 (0.75-1.23)	0.75
Death from any cause	0.94 (0.78-1.13)	0.50

Conclusion:
In patients with T2D and a recent acute coronary syndrome, treatment with lixisenatide, added to conventional therapy was not associated with a significant difference in rates of CV events vs conventional therapy plus placebo.

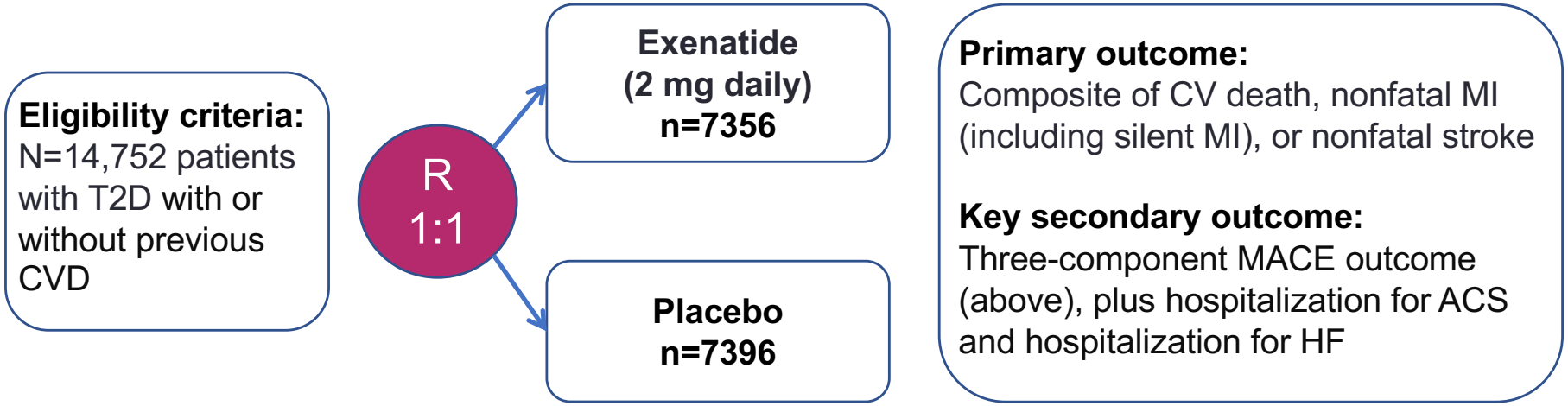
*CV death, nonfatal MI, or nonfatal stroke, and hospitalization for unstable angina; †CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina, hospitalization for HF, and coronary revascularization.

CI, confidence interval; CV, cardiovascular; GLP-1, glucagon-like peptide-1; ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; T2D, type 2 diabetes.

Pfeffer MA, et al. *N Engl J Med*. 2015;373:2247-2257.

GLP-1 Receptor Agonists: EXSCEL (Exenatide Study of Cardiovascular Event Lowering)

EXSCEL Study Design and Objectives

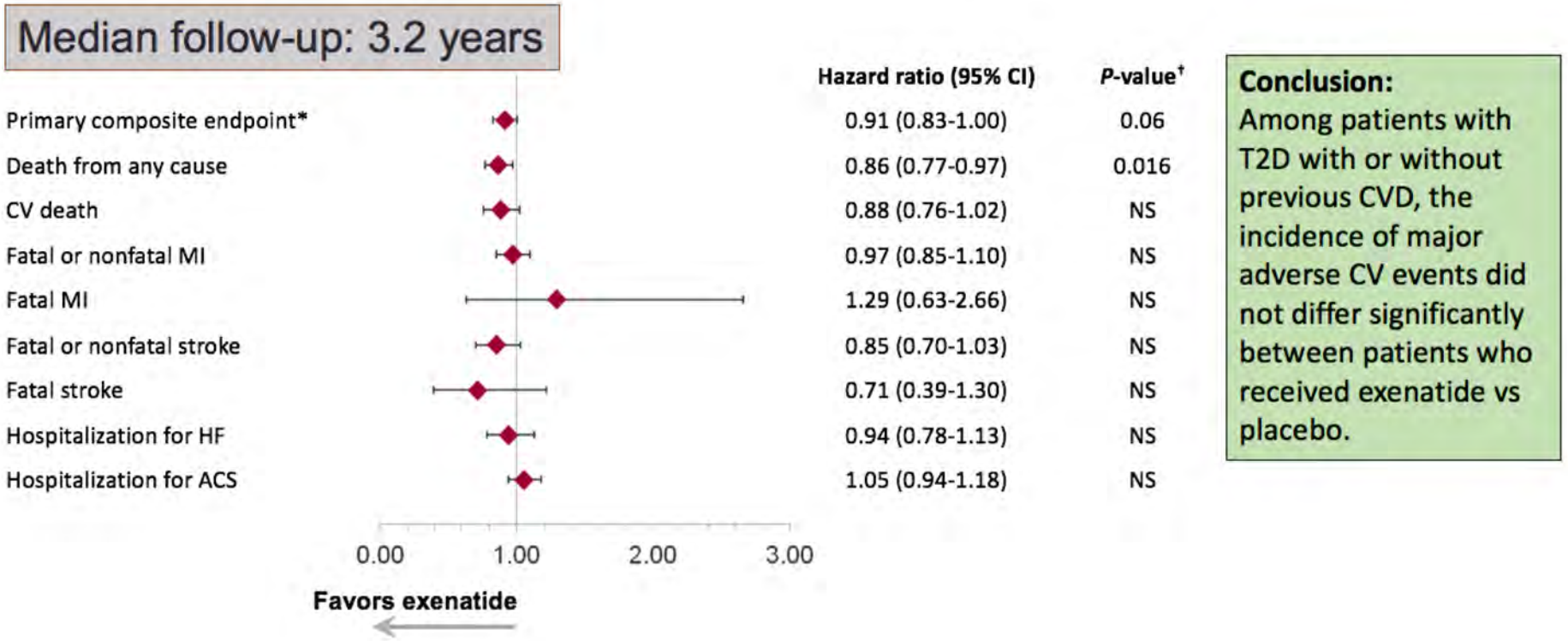


- **Study design:** Randomized, double- blind, placebo-controlled, event-driven trial at 687 sites in 35 countries.
- **Primary objective:** To assess long-term CV safety and efficacy of once-weekly exenatide in patients with T2D with a wide range of CV risk

ACS, acute coronary syndrome; CV, cardiovascular; CVD, cardiovascular disease; GLP-1, glucagon-like peptide-1; HF, heart failure; MACE, major adverse cardiac event; MI, myocardial infarction, T2D, type 2 diabetes.

Holman RR, et al. *N Engl J Med*. 2017;377(13):1228-1239.

GLP-1 Receptor Agonists: EXSCEL (Exenatide) Results

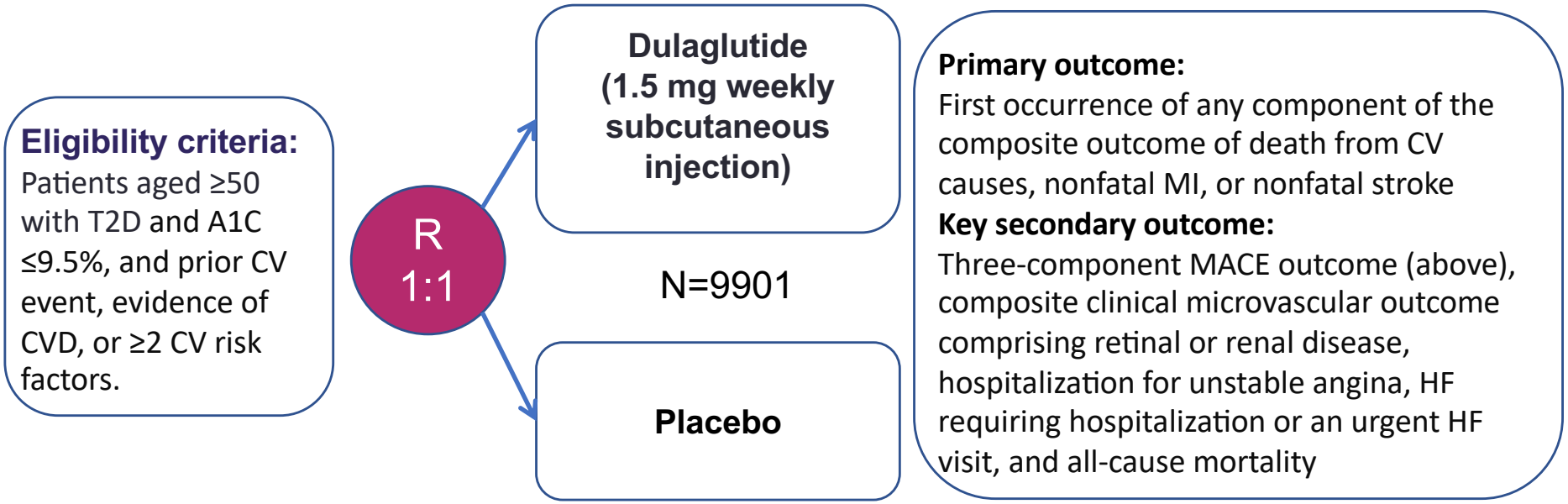


*CV death, nonfatal MI, or nonfatal stroke.
†For superiority.

ACS, acute coronary syndrome; CI, confidence interval; CV, cardiovascular; EXSCEL, Exenatide Study of Cardiovascular Event Lowering; HF, heart failure; MI, myocardial infarction; NS, not statistically significant based on hierarchical testing plan.
Holman RR, et al. *N Engl J Med*. 2017:377(13):1228-1239.

GLP-1 Receptor Agonists: REWIND (Researching Cardiovascular Events with a Weekly Incretin in Diabetes)

REWIND Outcomes Study Design and Objectives



- **Study design:** Multi-center, randomized, double-blind, placebo-controlled trial at 370 sites in 24 countries
- **Primary objective:** To determine whether people allocated to dulaglutide have a lower hazard of CV events than those allocated to placebo, and to assess potential side effects of dulaglutide and its effect on all-cause mortality, renal disease, HF hospitalizations, cancer, and pancreatitis; focus on "typical" middle-aged patient

CV, cardiovascular; CVD, cardiovascular disease; GLP-1, glucagon-like peptide-1; HF, heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction;T2D, type 2 diabetes.

Gerstein HC, et al. *Diabetes Obes Metab.* 2018;20(1):42-49; Ferdinand KC, Mahata, I. *Ann Transl Med.* 2017;5(23)476.

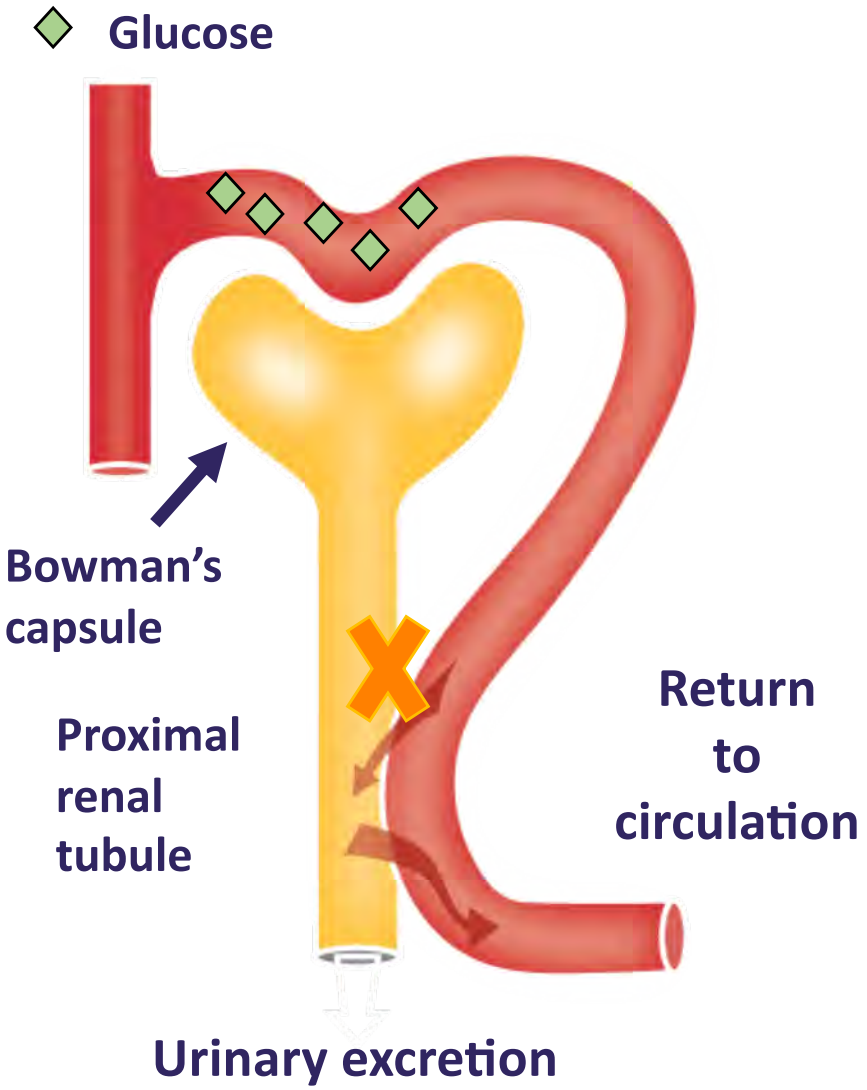
GLP-1 Receptor Agonists, REWIND Trial: Preliminary Results

- Dulaglutide once-weekly reduced MACE in adults with T2D with and without established CVD
- The first T2D agent to be evaluated in a broad T2D population (mean baseline A1C 7.3%; only 31% had established CVD)
- Median follow-up 5 years
- Consistent safety profile with other GLP-1 receptor agonists
- Full findings will be presented at the American Diabetes Association 2019 Scientific Sessions

A1C, glycated hemoglobin; CVD, cardiovascular disease; GLP-1, glucagon-like peptide-1, MACE, major adverse cardiovascular event; T2D, type 2 diabetes. Garber, AJ. (2018, November 5) *REWIND: Dulaglutide reduces CV risk in type 2 diabetes without CVD. [Online article]* Retrieved from http://www.healio.com. Lilly. (2018, November 6). *Trulicity® (dulaglutide) demonstrates superiority in reduction of cardiovascular events for broad range of people with type 2 diabetes.* [Press release] Retrieved from https://investor.lilly.com/news-releases/news-release-details/trulicityr-dulaglutide-demonstrates-superiority-reduction.

Cardiovascular Outcomes Trials in Diabetes
SGLT2 Inhibitors

SGLT2 (Sodium-glucose Cotransporter-2) Inhibitors



- SGLT2 inhibitors are oral medications that reduce plasma glucose by enhancing urinary excretion of glucose, decreasing return of glucose to circulation and decreasing blood glucose levels[1,2]
- SGLT2 mediates most (≈90%) glucose reabsorption from the proximal renal tubular lumen back into circulation[1]

FDA-approved agents:

- canagliflozin
- dapagliflozin
- empagliflozin

SGLT2, sodium-glucose cotransporter-2.

1. Chao E, Henry R. *Nature Rev Drug Discov*. 2010;9:551-559.
2. Davies MJ, et al. *Diabetes Care*. 2018 September; [Epub ahead of print] dci180033.

SGLT2 Inhibitors: Risks and Benefits

Benefits

- Low hypoglycemia rates[1]
- Small reduction in TGs[1]
- Insulin-independent glucose lowering effect (irrespective of T2D duration)[2]
- Decreased uric acid[2]
- Decreased albuminuria[2]
- Reduction in BP[3]
- Weight loss[3]
- Cardiac and renal benefits in patients with established or high risk for ASCVD (empagliflozin and canagliflozin)[3]

Risks

- Small increase in hemoglobin/hematocrit[1]
- Urinary tract infections[2]
- Polyuria / dehydration[2]
- Small increase in LDL-C[2]
- Diabetic ketoacidosis[3]
- Genital mycotic infections[3]
- Acute kidney injury[3]
- Dehydration[3]
- Orthostatic hypotension[3]
- Lower limb amputation (canagliflozin)[3]
- Fractures (canagliflozin)[3]

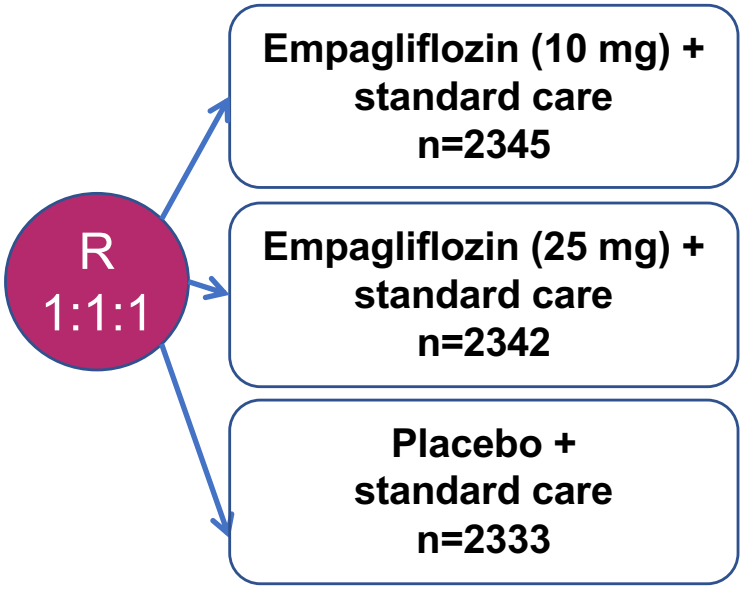
ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; LDL-C, low-density lipoprotein cholesterol; SGLT2, sodium-glucose cotransporter-2; T2D, type 2 diabetes; TG, triglycerides.

1. Kim Y, et al. *Diabetes Metab Syndr Obes.* 2012;5:313-327.
2. Inzucchi SE, et al. *Diabetes Care* 2015;38:140-159.
3. Davies, MJ, et al. *Diabetes Care* 2018;doi:10.2337/dci18-0033. (Epub ahead of print)

SGLT2 Inhibitors: EMPA-REG Study

EMPA-REG Study Design and Objectives

Eligibility criteria:
- T2D with A1C 7.0%-10.0%[a]
- Age ≥18 years
- BMI ≤45 kg/m
- GFR ≥30 mL/min/ 1.73 m
- Established CVD



Primary outcome:
Composite of CV death, nonfatal MI, or nonfatal stroke

Key secondary outcome:
Composite of CV death, nonfatal MI, nonfatal stroke, and hospitalization for unstable angina

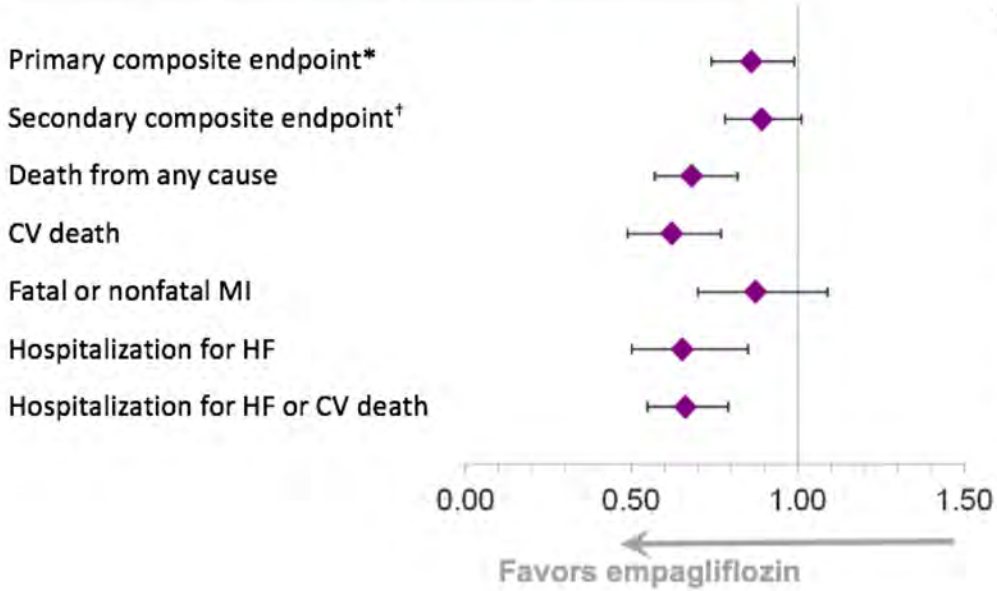
- **Study design:** Multicenter, randomized, double-blind, placebo-controlled study at 590 sites in 42 countries
- **Primary objective:** To assess the effects of empagliflozin (pooled group) vs. placebo on CV morbidity and mortality in patients with T2D at high risk for CV events and receiving standard care

A1C, glycated hemoglobin; BMI, body mass index; CV, cardiovascular; CVD, cardiovascular disease; EMPA-REG; Empagliflozin, Cardiovascular Outcomes; and Mortality in Type 2 Diabetes trial; GFR, glomerular filtration rate; MI, myocardial infarction; SGLT2, sodium-glucose cotransporter-2. [a]A1C 7.0%-9.0% in patients who did not receive any glucose lowering agents ≥12 weeks prior to randomization 1. Zinman B, et al. *N Engl J Med.* 2015;373:2117-28.

SGLT2 Inhibitors: EMPA-REG (Empagliflozin) Results

EMPA-REG OUTCOME Pooled Analysis (N=7020)

Median follow-up: 3.1 years



	Hazard ratio (95% CI)	*P*-value
Primary composite endpoint*	0.86 (0.74-0.99)	0.04
Secondary composite endpoint†	0.89 (0.78-1.01)	0.08
Death from any cause	0.68 (0.57-0.82)	<0.001
CV death	0.62 (0.49-0.77)	<0.001
Fatal or nonfatal MI	0.87 (0.70-1.09)	0.23
Hospitalization for HF	0.65 (0.50-0.85)	0.002
Hospitalization for HF or CV death	0.66 (0.55-0.79)	<0.001

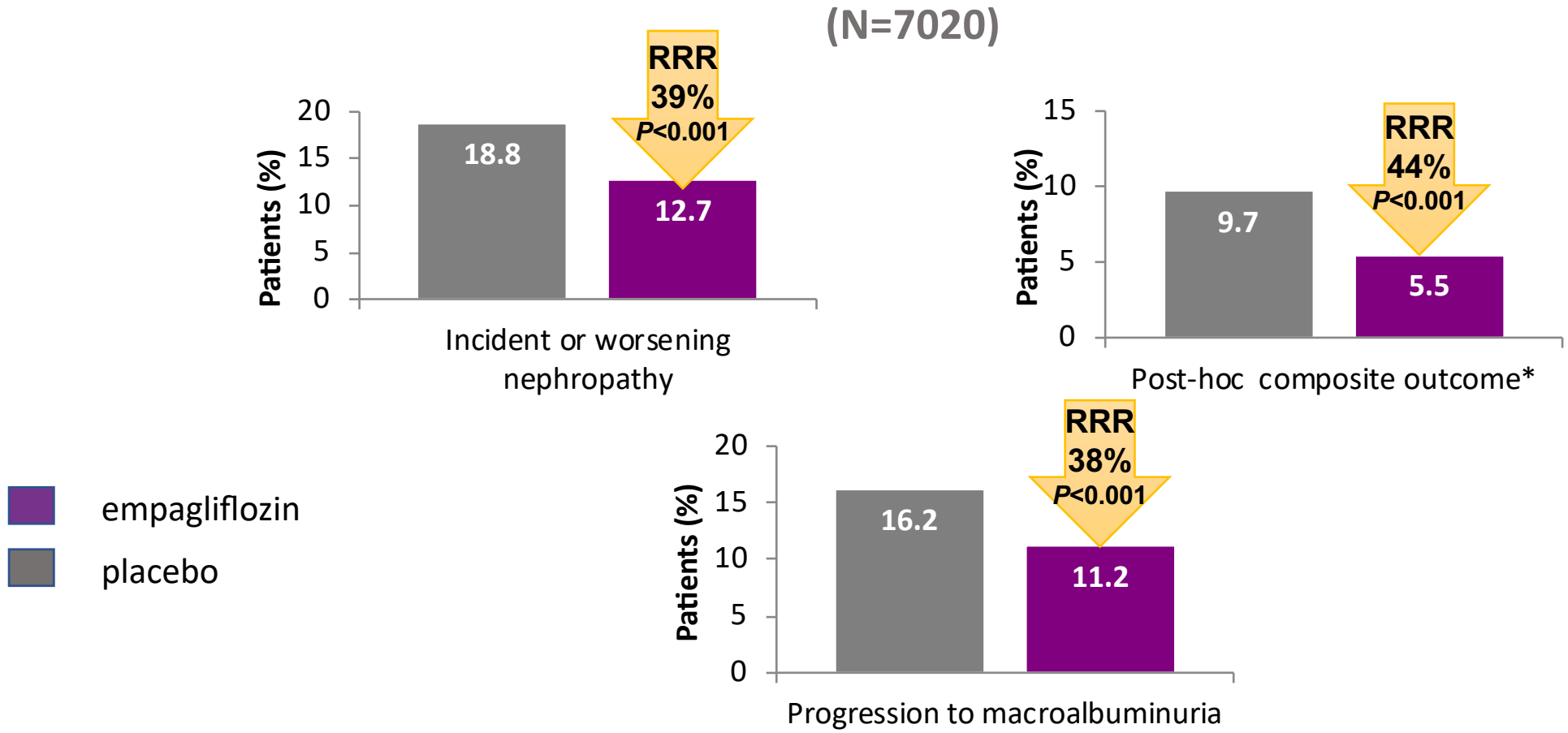
Conclusion: Patients with T2D at high risk for CV events who received empagliflozin vs placebo added to standard care, had a lower rate of the primary composite CV outcome and of death from any cause.

- 14% RRR, primary outcome
- 32% RRR, all-cause mortality
- 38% RRR, CV death

*CV death, nonfatal MI (excluding silent MI), or nonfatal stroke; †CV death, nonfatal MI (excluding silent MI), nonfatal stroke, and hospitalization for unstable angina.

CI, confidence interval; CV, cardiovascular; EMPA-REG OUTCOME; Empagliflozin, Cardiovascular Outcomes; and Mortality in Type 2 Diabetes trial; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; RRR, relative risk reduction; T2D, type 2 diabetes.
Zinman B, et al. *N Engl J Med*. 2015;373:2117-2128.

SGLT2 Inhibitors, EMPA-REG Renal: Renal Outcomes with Empagliflozin Over 3.2 Years



*Doubling of SCr + eGFR ≤45 mL/min/1.73 m^2, initiation of renal replacement therapy, or death from renal disease.

CI, confidence interval; eGFR, estimated glomerular filtration rate; ; EMPA-REG; Empagliflozin, Cardiovascular Outcomes; and Mortality in Type 2 Diabetes trial; SCr, serum creatinine; SGLT2, sodium-glucose cotransporter-2.

Wanner C, et al. *N Engl J Med*. 2016;375:323-334.

SGLT2 Inhibitors: Empagliflozin

FDA approves empagliflozin to reduce cardiovascular death in adults with type 2 diabetes

The U.S. Food and Drug Administration today approved a new indication for Jardiance (empagliflozin) to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and cardiovascular disease.

December 2, 2016

U.S. Food and Drug Administration. (2016, December). *FDA approves Jardiance to reduce cardiovascular death in adults with type 2 diabetes [FDA News release]* Retrieved from https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm531517.htm.

SGLT2 Inhibitors: CANVAS (Canagliflozin Cardiovascular Assessment Study) Program

- Two studies: CANVAS and CANVAS-R[1]
- Canagliflozin was the first FDA-approved SGLT-2 inhibitor[2]
- CANVAS studies began in December 2009; FDA approval in March 2013 based on interim data from CANVAS[1]
- CANVAS-R, a separate trial (2014), added assessment for albuminuria[1]
- Integrated analysis for CV, kidney, and safety outcomes to maximize statistical power[1]
- 10,142 participants with T2D and high CV in the combined studies[1]

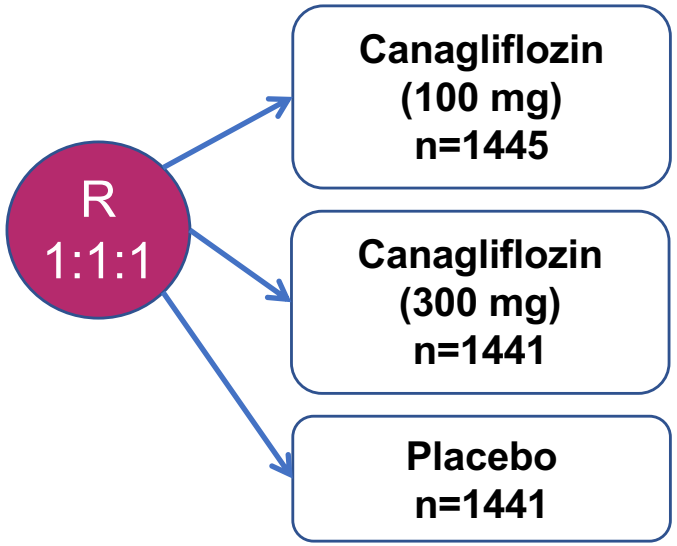
CANVAS, Canagliflozin Cardiovascular Assessment study; CANVAS-R, Canagliflozin Cardiovascular Assessment Study–Renal; CV, cardiovascular; FDA, US Food and Drug Administration; SGLT2, sodium-glucose cotransporter-2; T2D, type 2 diabetes.

1. Neal B, et al. *N Engl J Med*. 2017;377(7):644-657.
2. Dietrich E, Powell J, Taylor JR. *Drug Des Devel Ther.* 2013;7:1399-1408.

SGLT2 Inhibitors: CANVAS (Canagliflozin)

CANVAS Study Design and Objectives

Eligibility criteria:
- T2D with A1C 7.0%-10.5%
- Elevated risk for CVD[a]



Primary outcome:
Composite of CV death, nonfatal MI, or nonfatal stroke

Key secondary outcome:
Composite of CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina

- **Study design:** Multicenter, randomized, double-blind, placebo-controlled, parallel group study
- **Primary objective:** To determine the effects of canagliflozin vs placebo (against a background of standard care) on the risk of CVD and to provide data on safety and tolerability

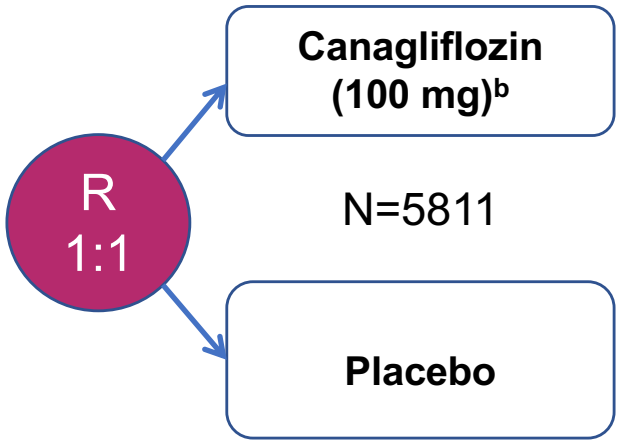
[a] Increased CV risk defined as: Age ≥30 years with history of CV disease or age ≥50 years with ≥2 CV risk factors (≥10 years diabetes duration, systolic BP >140 mm Hg while receiving antihypertensive agent(s), current smoking, microalbuminuria or macroalbuminuria, or HDL-C <1 mmol/L [<38.7 mg/dL])

A1C, glycated hemoglobin; CANVAS, Canagliflozin Cardiovascular Assessment study; CV, cardiovascular; MI, myocardial infarction; SGLT2, sodium-glucose cotransporter-2.
Neal B, et al. *Am Heart J.* 2013;166(2):217-223.e11

SGLT2 Inhibitors: CANVAS (Canagliflozin)- Renal

CANVAS-Renal Study Design and Objectives

Eligibility criteria:[2]
Men and women with inadequately controlled T2D (A1C ≥7.0% and ≤10.5%) and a history of or elevated risk of CV disease



Primary outcome:
Composite of CV death, nonfatal MI, or nonfatal stroke

Key secondary outcome:
Composite of death from any cause, death from CV causes, progression of albuminuria, and composite of death from CV causes and hospitalization for HF[1]

- **Study design:** Multicenter, randomized, double-blind, placebo-controlled, parallel group study in 24 countries[2]
- **Primary objective:** To assess the effect of canagliflozin vs placebo on progression of albuminuria in patients with T2D receiving standard care but with inadequate glycemic control and at elevated risk of CV events[1]

[a]Increased CV risk defined as: Age ≥30 years with history of CV disease or age ≥50 years with ≥2 CV risk factors (≥10 years diabetes duration, systolic BP >140 mm Hg while receiving antihypertensive agent(s), current smoking, microalbuminuria or macroalbuminuria, or HDL-C <1 mmol/L [<38.7 mg/dL]).[2] [b]Dose may be increased to 300 mg once daily after first 13 weeks of treatment. CANVAS-R, Canagliflozin Cardiovascular Assessment study–Renal; CV, cardiovascular; HF, heart failure; SGLT2, sodium-glucose cotransporter-2; T2D, type 2 diabetes.

1. Neal B, et al. *N Engl J Med.* 2017;377(7):644-657.
2. Neal B, et al. *Diabetes. Obes Metab.* 2017;19(3):387-393 (Epub:doi:10.1111/dom.12829.

SGLT2 Inhibitors: Canagliflozin

FDA approves canagliflozin to reduce cardiovascular death in adults with type 2 diabetes

The U.S. Food and Drug Administration today approved a new indication for Invokana (canagliflozin) to reduce the risk of heart attack, stroke, or cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease.

October 30, 2018

FDA, U.S. Food and Drug Administration; SGLT2, sodium-glucose cotransporters 2.

Janssen. (2018, October 30). *U.S. FDA Approves Invokana® (canagliflozin) to Reduce the Risk of Heart Attack, Stroke or Cardiovascular Death in Adults with Type 2 Diabetes and Established Cardiovascular Disease* [Press release] Retrieved from: https://www.janssen.com/us-fda-approves-invokanar-canagliflozin-reduce-risk-heart-attack-stroke-or-cardiovascular-death.

SGLT2 Inhibitors: Canagliflozin

FDA issues black box warning on canagliflozin amputation risk

In patients with T2D who have established CVD or are at risk for CVD, canagliflozin has been associated with lower limb amputations, most frequently of the toe and mid-foot, as well as the leg. Before initiating treatment, consider factors that may increase amputation risk. Monitor patients receiving canagliflozin for infections or ulcers of the lower limbs, and discontinue if these occur.[1,2]

May 16, 2017

CVD, cardiovascular disease; FDA, U.S. Food and Drug Administration, SGLT2, sodium-glucose cotransporters 2; T2D, type 2 diabetes.

1. Tucker M. (2017, May 16); *FDA Adds Boxed Warning to Canagliflozin for Amputation Risk*. [News alert] Retrieved from https://www.medscape.com/viewarticle/880059.
2. Invokana (canagliflozin) [Prescribing information]. 2013, Titusville, NJ: Janssen Pharmaceuticals, Inc.

SGLT2 Inhibitors: CVD-REAL STUDY

Real-world evidence from an international study of >300,000 patients with T2D

- Multinational, retrospective, observational cohort study in patients with T2D initiating treatment with a SGLT-2 inhibitor or another glucose-lowering drug.
- CVD-REAL is a comparative effectiveness study that aimed to compare new users of SGLT-2 inhibitors vs new users of other glucose-lowering drugs with regard to hospitalization for HF and all-cause mortality.
- The study analysis is based on data from at least 6 countries: United States, United Kingdom, Germany, Sweden, Denmark and Norway.

CVD-REAL, Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors; HF, heart failure; SGLT-2, sodium-glucose cotransporter-2; T2D, type 2 diabetes.

Kosiborod M, et al. *Circulation*. 2017;136(3):249-259. (Epub 2017, May 18) doi:10.1161/CIRCULATIONAHA.117.029190.

SGLT2 Inhibitors: CVD-REAL Results

Compared with new users of other glucose-lowering drugs, new SGLT-2i users had:

- A 46% reduction for the composite endpoint of hospitalization for HF and death from any cause ($P<0.001$).
- Reduced rate of hospitalization for HF (39%; $P<0.001$)
- Reduction in death from any cause (51%; $P<0.001$) vs other T2D medicines

- Treatment with SGLT-2i vs other glucose-lowering drugs was associated with a lower risk of hospitalization for HF and death, suggesting that the benefits seen with empagliflozin in a randomized trial may be a class effect applicable to a broad population of patients with T2D in real-world practice.

CVD-REAL, Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors; ; HF, heart failure; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; T2D, type 2 diabetes.

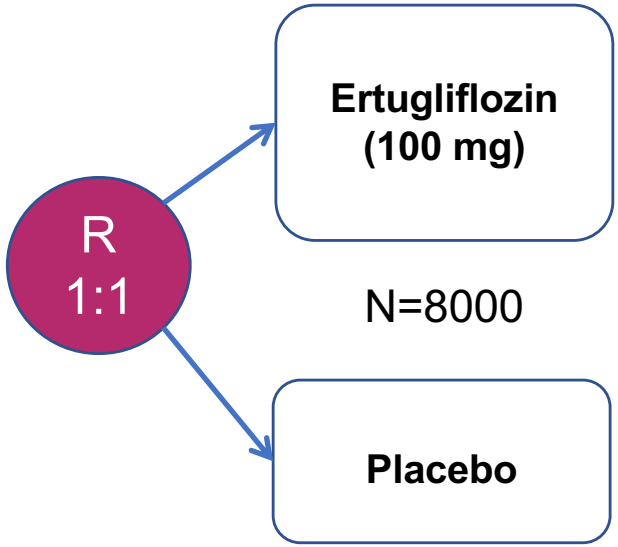
Kosiborod M, et al. *Circulation*. 2017;136(3):249-259. (Epub 2017, May 18) doi:10.1161/CIRCULATIONAHA.117.029190.

SGLT2 Inhibitors: Study to Assess CV Outcomes Following Treatment With Ertugliflozin in Patients with T2D and Established Vascular Disease (VERTIS CV)

VERTIS CV Study Design and Objectives

Eligibility criteria:
Patients with T2D and established vascular disease, receiving background therapy of:

- Insulin with/without metformin
- Metformin with sulfonylurea
- Sulfonylurea monotherapy



Primary outcome:
Time to first event of MACE (composite of CV death, nonfatal MI, or nonfatal stroke)

Key secondary outcome:
Time to first CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina

- **Study design:** Randomized, double-blind, placebo-controlled, parallel-group study in men and women ≥40 years of age
- **Primary objective:** To assess the CV safety of ertugliflozin in patients with T2D and established vascular disease

CV, cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction; SGLT2, sodium-glucose cotransporter-2; T2D, type 2 diabetes. Merck Sharp & Dohme Corp. (2013, November 19). *Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease, The VERTIS CV Study (MK08835-004.* Study record detail: Retrieved from https://clinicaltrials.gov/ct2/show/NCT01986881.

SGLT2 Inhibitors: FDA Warning

FDA issues warning on SGLT2 inhibitors for diabetes

Cases of a rare but serious infection of the genitals and area around the genitals have been reported with the class of T2D medicines called SGLT2 inhibitors. This serious rare infection, called necrotizing fasciitis of the perineum, is also referred to as Fournier's gangrene.

August 29, 2018

FDA, U.S. Food and Drug Administration; SGLT2, sodium-glucose cotransport-2, T2D, type 2 diabetes.

U.S. FDA. (2018, August 29). *SGLT2(sodium-glucose cotransporter-2) Inhibitors for Diabetes: Drug Safety Communication—Regarding Rare Occurrences of a Serious Infection of the Genital Area.* Safety alert: Retrieved from https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm618908.htm.

Cardiovascular Outcomes Trials in Diabetes
DPP-4 Inhibitors

DPP-4 Inhibitors

Benefits

- Neutral effect on weight[1]
- Minimal risk of hypoglycemia*[1]
- Demonstrated cardiovascular safety but no benefit[1]

Risks

- Rare but increased rates of pancreatitis[1]
- Musculoskeletal side effects[1]

Key Features[2]:

- Oral administration
- Inhibit actions of DPP-4
- Increase endogenous GLP-1 and GIP levels
- Increase glucose-dependent insulin secretion
- Suppress glucagon production

*Hypoglycemia risk increases by 50% when combines with sulfonylureas.

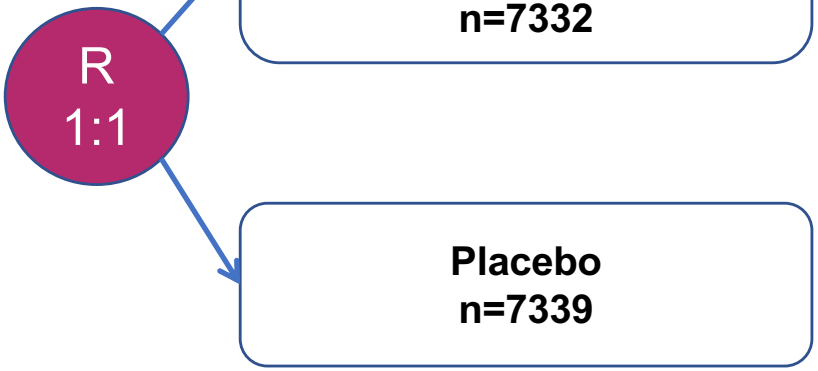
DPP-4, dipeptidyl peptidase 4; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1.

1. Davies, MJ, et al. *Diabetes Care* 2018;doi:10.2337/dci18-0033. (Epub ahead of print)
2. Garber AJ, et al. *Endocr Pract*. 2018;24(1):91-120.

DPP-4 Inhibitors: TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin)

TECOS Study Design and Objectives

Eligibility criteria: Patients with T2D and established CVD, ≥50 years of age with an A1C 6.5% to 8.0% when treated with stable doses of 1 or 2 oral antihyperglycemic agents.



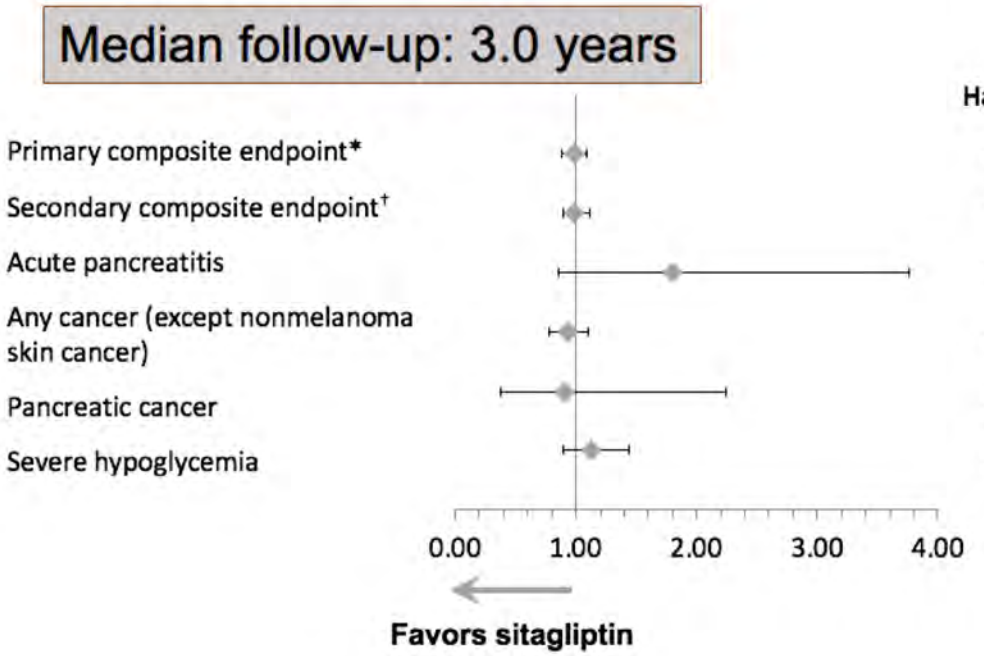
Primary outcome: Composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina

Key secondary outcome: CV death, nonfatal MI, or nonfatal stroke

- **Study design:** Randomized, double-blind, placebo-controlled, event-driven trial at 673 sites in 38 countries
- **Primary objective:** Assess the long-term CV safety of adding sitagliptin to usual care, as compared with usual care alone, in patients with T2D and established CVD

A1C, glycated hemoglobin; CV, cardiovascular; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase 4, MI, myocardial infarction; T2D, type 2 diabetes. Green JB, et al. *N Engl J Med*. 2015;373:232-242.

DPP-4 Inhibitors: TECOS (Sitagliptin) Results



	Hazard ratio (95% CI)	*P*-value
Primary composite endpoint*	0.98 (0.88-1.09)	<0.001 (NF)
Secondary composite endpoint†	0.99 (0.89-1.11)	<0.001 (NF)
Acute pancreatitis	1.80 (0.86-3.76)	0.12
Any cancer (except nonmelanoma skin cancer)	0.93 (0.78-1.10)	0.38
Pancreatic cancer	0.91 (0.37-2.25)	0.85
Severe hypoglycemia	1.13 (0.89-1.44)	0.31

Conclusions:
Among patients with T2D and established CVD, adding sitagliptin to usual care did not increase the risk of major adverse CV events, hospitalization for HF, or other adverse events.

Concern was raised about adverse pancreatic effects, although results were not statistically significant.

*CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina.
†Secondary composite: CV death, nonfatal MI, or nonfatal stroke.

CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase 4; HF, heart failure; MI, myocardial infarction; NF, noninferiority; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin; T2D, type 2 diabetes.
Green JB, et al. N Engl J Med. 2015;373:232-242.

DPP-4 Inhibitors: EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin vs Standard of Care)

EXAMINE Study Design and Objectives

Eligibility criteria:[a] Patients with T2D receiving antidiabetic therapy (other than a DPP-4 inhibitor or GLP-1 RA), with an ACS 15 to 90 days before randomization

R
1:1

Alogliptin (25 mg daily or 12.5 mg daily if impaired renal function) n=2701

Placebo n=2679

Primary outcome:
Composite of death from CV causes, nonfatal MI, or nonfatal stroke

Key secondary outcome:
Primary composite endpoint with the addition of urgent revascularization due to unstable angina within 24 hours after hospital admission

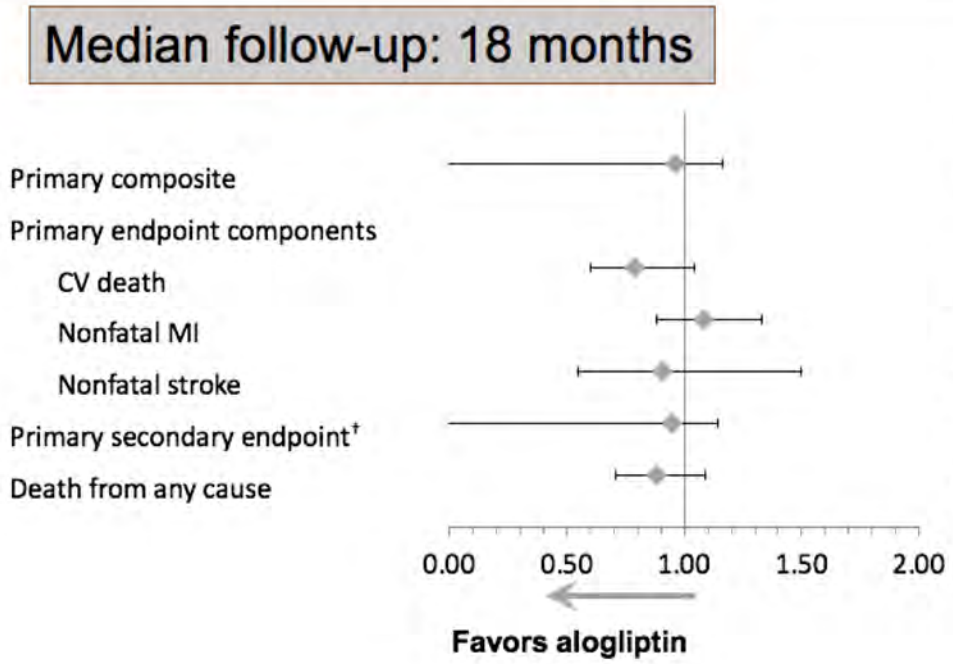
- **Study design:** Multicenter, randomized, double-blind trial
- **Primary objective:** To determine whether alogliptin is noninferior to placebo with respect to major CV events in patients with T2D at very high CV risk (recent acute coronary syndrome)

[a]Further criteria for the diagnosis of type 2 diabetes included a glycated hemoglobin level of 6.5 to 11.0% at screening, or if the antidiabetic regimen included insulin, a glycated hemoglobin level of 7.0 to 11.0%.

ACS, acute coronary syndrome; CV, cardiovascular; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase 4; GLP-1 RA, glucagon-like peptide-1 receptor agonists; MI, myocardial infarction; T2D, type 2 diabetes.

White W, et al. *N Engl J Med*. 2013;369:1327-1335.

DPP-4 Inhibitors: EXAMINE (Alogliptin) Results



Conclusions: Among patients with T2D and a recent acute coronary syndrome, treatment with alogliptin resulted in similar rates of death from CV causes, nonfatal MI, and nonfatal stroke vs placebo.

*Upper boundary of 1-sided repeated CI, alpha level 0.01.
†CV death, nonfatal MI, nonfatal stroke, urgent revascularization for unstable angina.

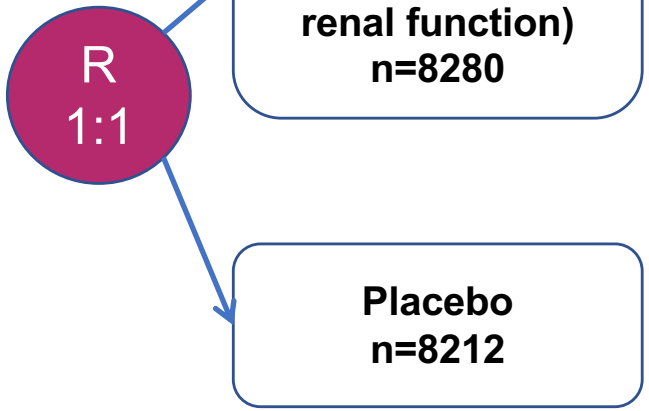
CI, confidence interval; CV, cardiovascular; DPP-4, dipeptidyl peptidase 4; EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; MI, myocardial infarction; T2D, type 2 diabetes.
White W, et al. *N Engl J Med*. 2013;369:1327-1335.

DPP-4 Inhibitors: SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction)

SAVOR-TIMI 53 Study Design and Objectives

Eligibility Criteria:

- Patients ≥40 years, with history of atherosclerotic clinical event involving coronary, cerebrovascular or peripheral vascular system
- Documented T2D and either a history of established CVD or multiple risk factors for vascular disease



Primary Outcome:
Composite of CV death, nonfatal MI, or nonfatal ischemic stroke

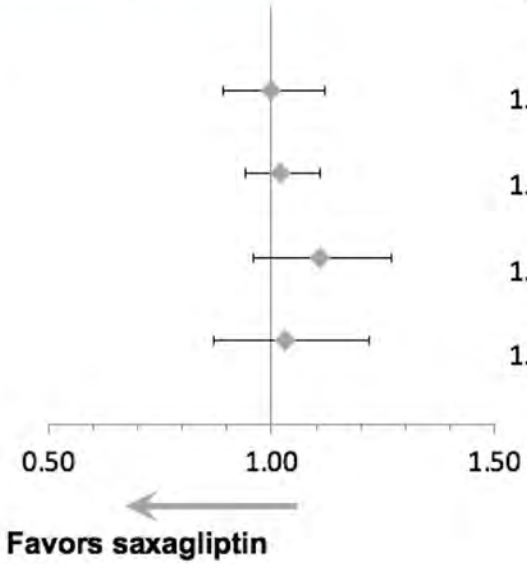
Key Secondary Outcome:
Primary composite endpoint plus hospitalization for HF, coronary revascularization, or unstable angina

- **Study design:** Multicenter, randomized, double-blind, placebo-controlled, phase 4 trial at 788 sites in 26 countries
- **Primary objective:** To evaluate the safety and efficacy of saxagliptin with respect to CV outcomes in patients with T2D at risk for CV events

CV, cardiovascular; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase 4; HF, heart failure; MI, myocardial infarction; T2D, type 2 diabetes. Scirica BM, et al. *N Engl J Med*. 2013;369:1317-1326.

DPP-4 Inhibitors: SAVOR-TIMI 53 (Saxagliptin) Results

Median follow-up: 2.1 years



	Hazard ratio (95% CI)	*P*-value
Primary composite endpoint*	1.00 (0.89-1.12)	0.99
Secondary composite endpoint†	1.02 (0.94-1.11)	0.66
Death from any cause	1.11 (0.96-1.27)	0.15
CV death	1.03 (0.87-1.22)	0.72

Conclusions:
Saxagliptin neither reduced nor increased the risk of the primary composite endpoint of CV death, MI, or ischemic stroke when added to standard care in patients at high risk for CV events.

Thus, saxagliptin met the criterion for non-inferiority to placebo, but did not provide cardioprotective benefit. Saxagliptin increased the risk of hospitalization for HF and the risk of hypoglycemic events.

*CV death, nonfatal MI, or nonfatal ischemic stroke; †CV death, nonfatal MI, nonfatal ischemic stroke, hospitalization for HF, coronary revascularization, or unstable angina. CI, confidence interval; CV, cardiovascular; DPP-4, dipeptidyl peptidase 4; HF, heart failure; MI, myocardial infarction; SAVOR-TIMI, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction. Scirica BM, et al. *N Engl J Med*. 2013;369:1317-1326.

DPP-4 Inhibitors

FDA adds warnings about HF risks to T2D medicines containing saxagliptin, alogliptin, and sitagliptin

"A U.S. Food and Drug Administration (FDA) safety review has found that T2D medicines containing saxagliptin and alogliptin may increase the risk of HF, particularly in patients who already have heart or kidney disease."

The FDA analyzed results from SAVOR-TIMI 53 and EXAMINE and found:

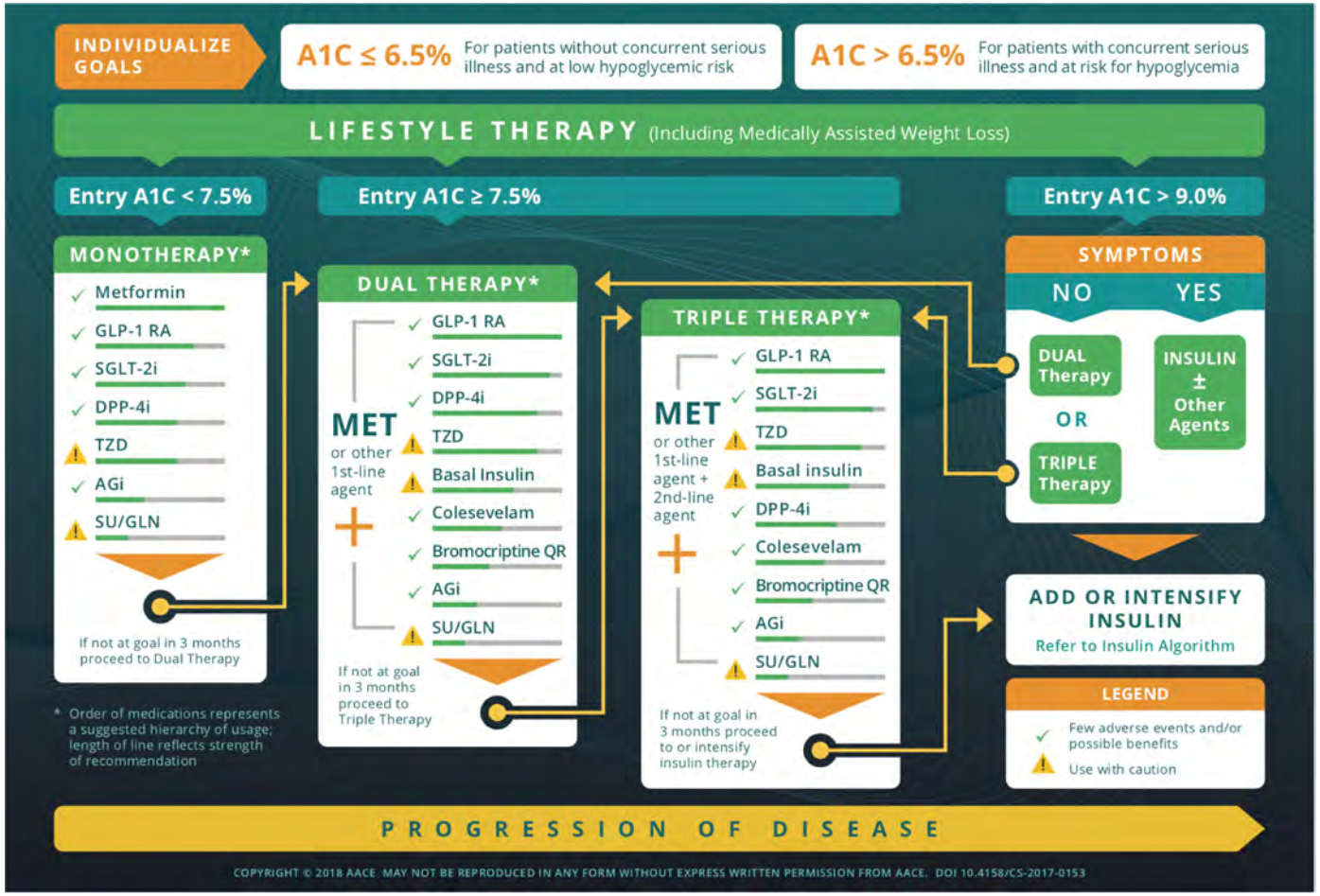
- SAVOR-TIMI 53: 3.5% patients hospitalized for HF vs 2.8% of patients receiving placebo
- EXAMINE: 3.9% patients on alogliptin hospitalized for HF at least once vs. 3.3% of patients receiving placebo

A related warning was also added to sitagliptin prescribing information:
"Heart failure has been observed with two other members of the DPP-4 inhibitor class. Consider risks and benefits of sitagliptin in patients who have known risk factors for heart failure. Monitor patients for signs and symptoms."

DPP-4, dipeptidyl peptidase-4; EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; SAVOR-TIMI, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction; T2D, type 2 diabetes. U.S. Food and Drug Administration. (2018, October 2) *FDA adds warnings about heart failure risk to labels of type 2 diabetes medicines containing saxagliptin and alogliptin.* FDA Drug Safety Communication. Retrieved from https://www.fda.gov/Drugs/DrugSafety/ucm486096.htm.

Summary of CVOT in T2DM and Impact on Guidelines

AACE/ACE 2018 Glycemic Control Algorithm



Metformin is typically first-line therapy.

Metformin, GLP1 RAs, SGLT2 inhibitors, DPP-4 inhibitors, and AG inhibitors are all acceptable first-line therapy.

AG, alpha-glucosidase; DPP-4, dipeptidyl peptidase-4; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2, sodium-glucose cotransporter 2; SU/GLN, sulphonylureas/glinides; TZD, thiazolidinediones.

Garber, AJ, et al. *Endocr Pract.* 2018;24(1):91-120.

AACE/ACE: Therapeutic and Cardiovascular Priorities For Selecting T2D Therapeutics

- **Metformin:** Low hypoglycemia risk, good antihyperglycemic efficacy, may promote modest weight loss, robust CV safety relative to sulfonylureas
- **GLP-1 RAs:** Robust A1C-lowering, usually associated with weight loss and BP reductions, low hypoglycemia risk, available in several formulations; reduced or neutral effect on CV events, dependent on formulation
- **SGLT-2 inhibitors:** Decreased A1C, weight, and systolic BP, low hypoglycemia risk; empagliflozin associated with significantly lower rates of all-cause and CV death and lower risk of hospitalization for HF
- **DPP-4 inhibitors**: Modest A1C-lowering properties, weight-neutral, low hypoglycemia risk; available in combination tablets with metformin, SGLT-2 inhibitor, or TZD

A1C, glycated hemoglobin; AACE, American Association of Clinical Endocrinologists; ACE, American College of Endocrinology; CV, cardiovascular; SGLT, sodium-glucose cotransporter 2; T2D, type 2 diabetes; TZD, thiazolidinediones.
Handelsman Y, et al. *Endocr Pract.* 2015;21(Suppl 1):1-87

ADA/EASD 2018 T2D Management Consensus Recommendations

- The major change from prior consensus reports is based on new evidence that specific SGLT2 inhibitors inhibitors or GLP-1 RAs improve CV outcomes, as well as secondary outcomes such as HF and renal disease progression, in patients with established CVD or CKD.
- SGLT2 inhibitors or GLP-1 RAs with proven CV benefit are recommended as part of glycemic management for patients with T2D and established ASCVD.
- SGLT2 inhibitors are recommended in patients with ASCVD in whom HF coexists or is of special concern.
- For patients with T2D and CKD, with or without CVD, consider the use of an SGLT2 inhibitor shown to reduce CKD progression or a GLP-1 RA shown to reduce CKD progression (if SGLT2 inhibitor contraindicated or not preferred).

ADA, American Diabetes Association; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease, CVD, cardiovascular disease; EASD, European Association for the Study of Diabetes; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; SGLT2i, sodium-glucose cotransporter 2 inhibitor;T2D, type 2 diabetes.

Davies, MJ, et al. *Diabetes Care* 2018;doi:10.2337/dci18-0033. (Epub ahead of print).

ESC Recommendations: T2D in Patients with Heart Failure

- DPP-4 inhibitors improve glycemic indices, but do not reduce and may increase the risk of CV events and worsening HF
- There are no data on the safety of DPP-4 inhibitors and GLP-1 RAs in patients with HF
- Recently, empagliflozin, an SGLT2 inhibitor, reduced HF hospitalization and mortality, but not MI or stroke, in patients with diabetes at high CV risk
- In the absence of other studies with drugs from this class, these empagliflozin results cannot be considered proof of a class effect

CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; ESC, European Society of Cardiology; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; MI, myocardial infarction; SGLT2, sodium-glucose cotransporter 2; T2D, type 2 diabetes.

Ponikowski P, et al. *Eur Heart J.* 2016;18(8):891-975. (Epub 2016, May 20)

Summary: Impact of CVOT on Contemporary T2D Care

- Treatment decisions should not be solely based on A1C or blood glucose levels—they should also take into account the patient's individual CV risk profile
- Typical first treatment options are metformin with GLP-1 RAs and/or SGLT2 inhibitors
- Select treatments based on safety/efficacy and positive effect on CV risk parameters, especially weight and blood pressure
- Monitor every 3 months and intensify/advance treatment as needed

A1C, glycated hemoglobin; CV, cardiovascular; CVOT, cardiovascular outcomes trials; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2, sodium-glucose cotransporter 2; T2D, type 2 diabetes.

FDA Advisors Narrowly Vote to Keep CVOTs, But Recognize Need To Simplify Process

- Since 2008, the U.S. FDA has required that glucose-lowering therapies for T2D demonstrate CV safety as part of the approval process
  - These data have been obtained via randomized, adjudicated CVOTs
- In October 2018, FDA advisors voted to continue requiring CVOTs (10 yes, 9 no):
  - Industry representatives argued that high cost of CVOTs ($200-$400 million each) stifles innovation
  - Broad consensus for a more simple, streamlined process to reduce cost/burden

CV=cardiovascular; CVOT=cardiovascular outcome trial; FDA=Food and Drug Administration; T2D=type 2 diabetes.
https://www.medpagetoday.com/cardiology/prevention/75938

CVOTs: Summary

- Agents that significantly decreased MACE in CVOTs
  - empagliflozin (EMPA-REG)
  - canagliflozin (CANVAS)
  - semaglutide (SUSTAIN-6)
  - liraglutide (LEADER)
- Secondary endpoint of all-cause death was significantly reduced in EMPA-REG, EXSCEL, and LEADER
- Hospitalization for HF was reduced only in EMPA-REG
- HF risk may be increased with alogliptin and saxagliptin
- Basal insulin, the preferred initial insulin formulation in patients with T2D, has a neutral effect on CV outcomes and cancer.

CV, cardiovascular; CANVAS, Canagliflozin Cardiovascular Assessment study; CVOT, cardiovascular outcomes trials; EMPA-REG; Empagliflozin, Cardiovascular Outcomes; and Mortality in Type 2 Diabetes trial; HF, heart failure; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcomes Results trial; MACE, major adverse cardiovascular event; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; T2D, type 2 diabetes.