A CME satellite symposium held at the 2021 HFSA Annual Scientific Meeting of the Heart Failure Society of America

Expert Perspectives on SGLT2 INHIBITORS:

Reviewing Their Role in Type 2 Diabetes, Heart Failure, *and* Chronic Kidney Disease

SUNDAY, SEPTEMBER 12, 2021

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This satellite symposium is not part of the scientific program as planned by the Heart Failure Society of America ASM Program Committee.

Accredited Sponsor: Heart Failure Society of America

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Expert Perspectives on SGLT2 Inhibitors: Reviewing Their Role in Type 2 Diabetes, Heart Failure and Chronic Kidney Disease

FACULTY

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PROGRAM OVERVIEW

This live satellite symposium consists of a presentation from an expert faculty and 3D animation technology to discuss the role of SGLT2 in the management of patients with diabetes, heart failure, and/or chronic kidney disease, including an overview of key clinical trials.

TARGET AUDIENCE

This educational activity is intended for Endocrinologists, Cardiologists, Nephrologists, Primary Care Physicians, Hospitalists, Physician Assistants, Nurse Practitioners, Pharmacists, Certified Diabetes Educators, Managed Care HCPs, and other HCPs who care for patients with diabetes.

LEARNING OBJECTIVES

Upon the completion of this program, attendees should be able to:

- Identify patients with T2DM, heart failure or chronic kidney disease who would benefit from an SGLT2 inhibitor
- Apply guidelines and scientific evidence to the management of cardiovascular and/or renal risk in patients with T2DM
- Explain the mechanisms of action of SGLT-2 inhibitors in T2DM, heart failure, and chronic kidney disease
- Analyze clinical trial data on the use of SGLT2 inhibitors for managing cardiovascular and/or renal risk in patients with T2DM

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AGENDA

I. SGLT2 Inhibitors
   a. Mechanism of action
      i. Anti-hyperglycemic MOA
      ii. Extra-glycemic MOA
   b. Glycemic outcomes trials
   c. Results from CVOT
   d. Renal trials
   e. Heart failure trials
   f. Distinctions between agents in the class
      i. Indications
   g. Use in patients with/without diabetes
   h. Side effects/contraindications
   i. Recommendations/algorithms from clinical practice guidelines **(simulation challenge: selecting patients who would benefit from SGLT2 inhibitors)**
      i. ADA
      ii. ACC
      iii. Others
   j. Use in patients with COVID-19

II. Cross-specialty collaboration

III. Case studies

IV. Conclusions

V. Questions and Answers

SGLT2 Inhibitors: Reviewing Their Role in Type 2 Diabetes, Heart Failure, and Chronic Kidney Disease

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Disclosures

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Educational Objectives

1. Identify patients with T2DM, HF, or CKD who would benefit from an SGLT2 inhibitor
2. Apply guidelines and scientific evidence to the management of CV and/or renal risk in patients with T2DM
3. Explain the mechanisms of action of SGLT2 inhibitors in T2DM, HF, and CKD
4. Analyze clinical trial data on the use of SGLT2 inhibitors for managing CV and/or renal risk in patients with T2DM

CKD = chronic kidney disease; CV = cardiovascular; HF = heart failure; SGLT = sodium-glucose cotransporter; T2DM = type 2 diabetes mellitus.

Case 1: EP

- 74-year-old man with a 1-year history of T2DM who recently developed worsening DOE and pedal edema
- Past medical history
  - NSTEMI ≈1 year ago: DES x 2, Circ and LAD
  - Hypertension
  - Hypercholesterolemia
  - Prior smoker (quit 1 year ago)
- Medications
  - Atorvastatin 40 mg/d
  - Losartan 100 mg/d
  - Metoprolol XR 100 BID
  - Aspirin 81 mg/d
  - Ticagrelor 60 mg BID
  - Metformin 1,000 mg BID

BID = twice daily; Circ = circumflex; DES = drug-eluting stent; DOE = dyspnea on exertion; LAD = left anterior descending; NSTEMI = non–ST-segment–elevation myocardial infarction; XR = extended release.

Case 1: EP
(continued)

- Physical examination
  - BMI: 37.4 kg/m^2
  - BP: 144/88 mm Hg
  - Heart: normal S1, S2, no murmurs
  - Lungs: clear
  - Extremities: pulses diminished, 1-2+ edema bilaterally
- Laboratory results
  - Fasting plasma glucose: 154 mg/dL
  - HbA_{1c}: 7.4%
  - CMP, CBC normal
  - LDL-C: 101; HDL-C: 40; TG: 198
  - eGFR: 58 mL/min/1.73 m^2; UACR: 31 mg/g

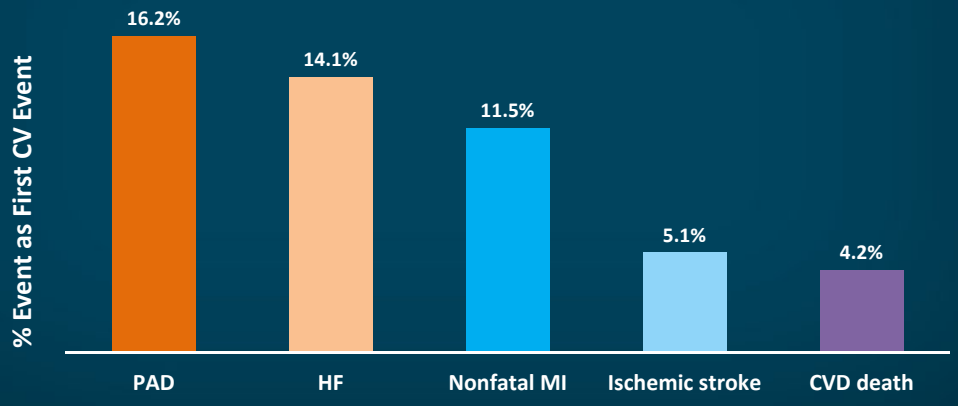
BMI = body mass index; BP = blood pressure; CBC = complete blood count; CMP = comprehensive metabolic panel; eGFR = estimated glomerular filtration rate; HbA_{1c} = hemoglobin A_{1c}; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglyceride; UACR = urine albumin-to-creatinine ratio.

Case 1: EP—Questions to Consider

- What is an optimal HbA_{1c} for this patient?
- Should his metformin be stopped or adjusted?
- Is this patient a candidate for an SGLT2 inhibitor?
- What clinical considerations would lead you to select an SGLT2 inhibitor?

HF Is One of the First Manifestations of T2D-Related CVD

Cohort study of UK patients (N≈1.9 million) with T2D and incidence of CVD



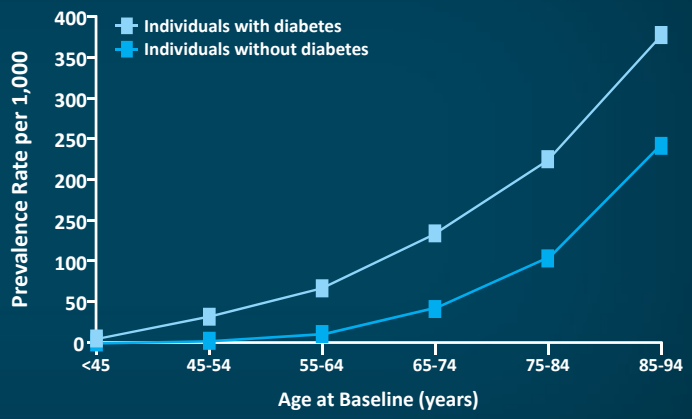
CVD = cardiovascular disease; MI = myocardial infarction; PAD = pulmonary arterial disease.
Shah AD, et al. *Lancet Diabetes Endocrinol*. 2015;3:105-113.

HF and Diabetes

Data from **The Framingham Study**[1] from 1974 suggest that

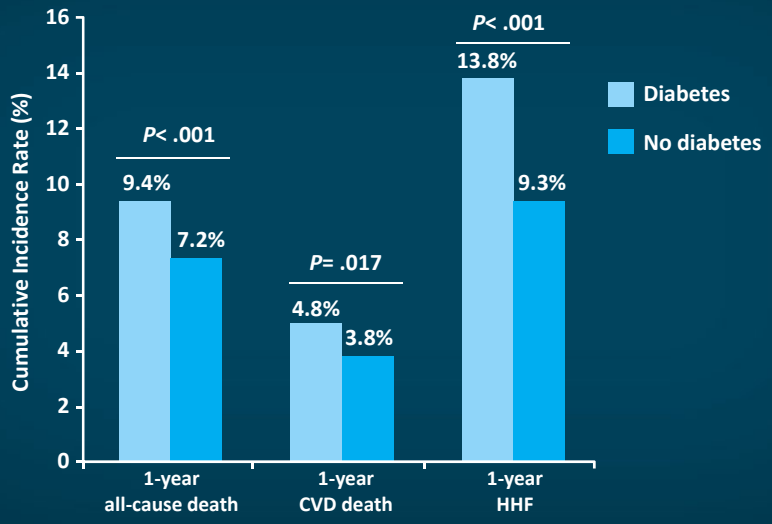
- "diabetes is another discrete cause of congestive heart failure and that some form of cardiomyopathy is associated with diabetes, as a result of either small vessel disease or metabolic disorders."

Age-associated prevalence of HF[2]



1. Kannel WB, et al. *Am J Cardiol.* 1974;34:29-34. 2. Gilbert RE, Krum H. *Lancet.* 2015;385:2107-2121. 3. Bauters C, et al. *Cardiovasc Diabetol.* 2003;2:1.

DM Is Associated With Increased HHF and Mortality



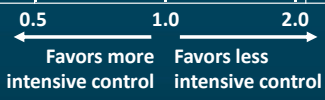
DM = diabetes mellitus; HHF = hospitalization for heart failure.

Dauriz M, et al. *Diabetes Care*. 2017;40:671-678.

Intensive Glucose Control Does Not Reduce HF Incidence

Admission to Hospital/Fatal Heart Failure

	Number of Events (Yearly Event Rate, %)		ΔHbA_{1c} (%)	HR (95% CI)
	More Intensive	Less Intensive		
ACCORD	152 (0.90)	124 (0.75)	-1.01	1.18 (0.93, 1.49)
ADVANCE	220 (0.83)	231 (0.88)	-0.72	0.95 (0.79, 1.14)
UKPDS	8 (0.06)	6 (0.11)	-0.66	0.55 (0.19, 1.60)
VADT	79 (1.80)	85 (1.94)	-1.16	0.92 (0.68, 1.25)
Overall	**459**	**446**	**-0.88**	**1.00 (0.86, 1.16)** (Q= 3.59, *P*= .31, I2= 16.4%)



HR = hazard ratio.

Turnbull FM, et al. *Diabetologia*. 2009;52:2288-2298.

THE LANCET Diabetes & Endocrinology 2014

Heart failure: a cardiovascular outcome in diabetes that can no longer be ignored

John J V McMurray, Hertzel C Gerstein, Rury R Holman, Marc A Pfeffer

In patients with type 1 or type 2 diabetes, glycaemic exposure assessed as HbA_{1c} correlates strongly with risk of future microvascular and macrovascular complications. Improved glucose control substantially reduces the risk of microvascular complications and, with extended follow-up, modestly reduces the risk of atherosclerotic events. The lowering of HbA_{1c} concentrations by newly developed glucose-lowering drugs (alone or when added to other glucose-

This omission is important because hospital admission for heart failure is a common and prognostically important cardiovascular complication of diabetes. Moreover, it is the one cardiovascular outcome for which the risk has been shown unequivocally to be increased by some glucose-lowering therapies. As such, we believe that heart failure should be systematically evaluated in cardiovascular outcome trials of all new glucose-lowering drugs.

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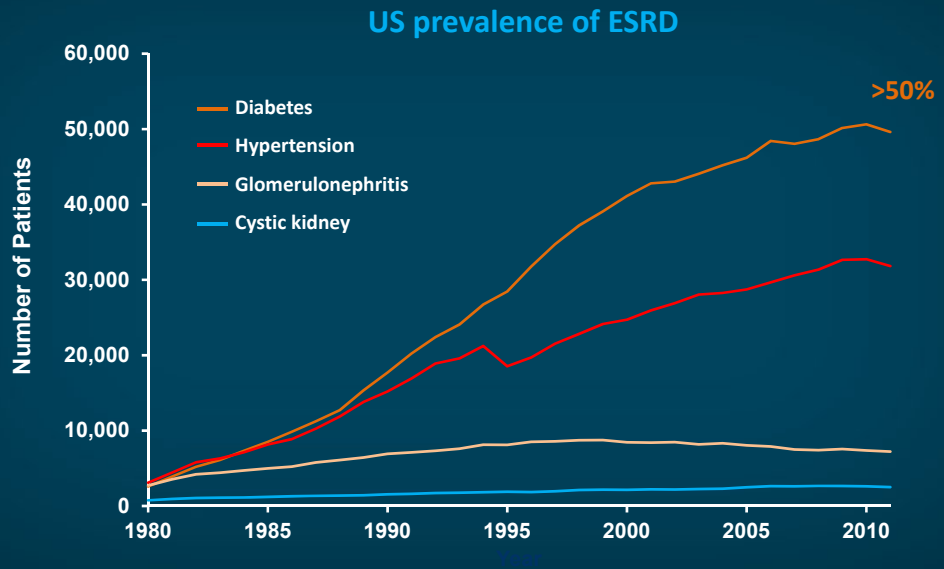
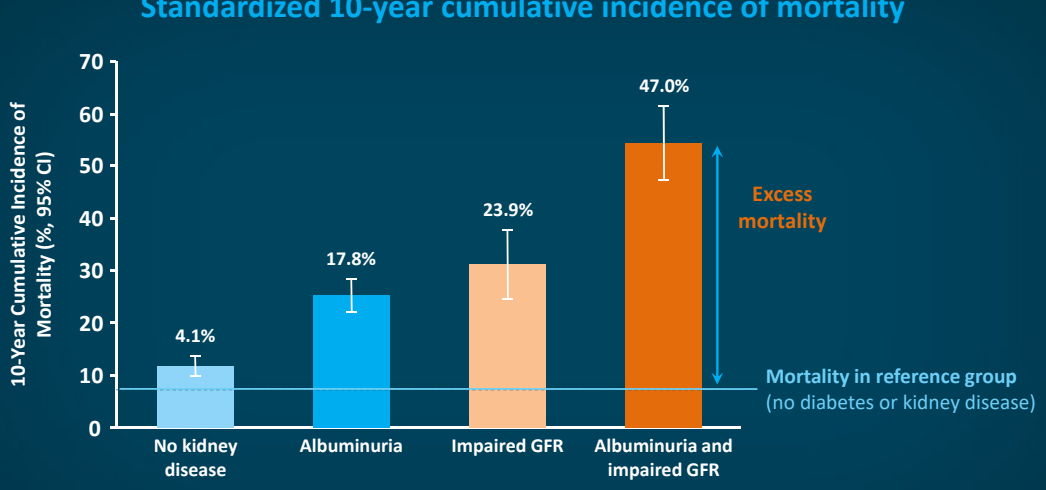
Diabetes Is the Leading Cause of ESRD



ESRD = end-stage renal disease.

United States Renal Data System. Annual data report. *Am J Kidney Dis.* 2014;63(1 suppl):e215-e228 (www.ajkd.org/article/S0272-6386(13)01411-X/pdf). Accessed 9/18/2020.

Mortality Is Increased in Patients With T2D and Kidney Disease

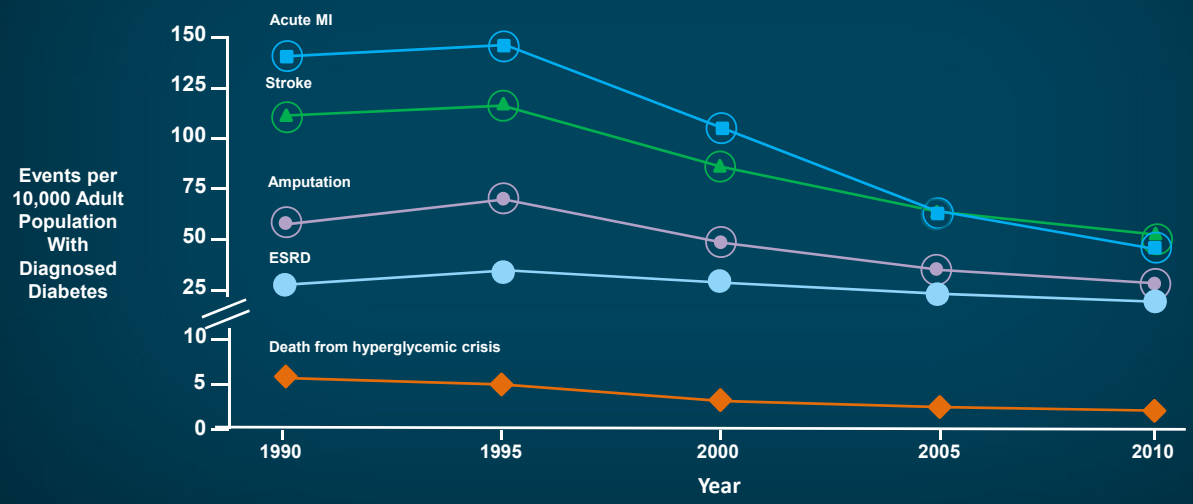


Percentages above bars indicate excess mortality **above** the reference group

GFR = glomerular filtration rate.

Afkarian M, et al. *J Am Soc Nephrol*. 2013;24:302-308.

Improvements in Rates of CVD but Not ESRD in Patients With Diabetes

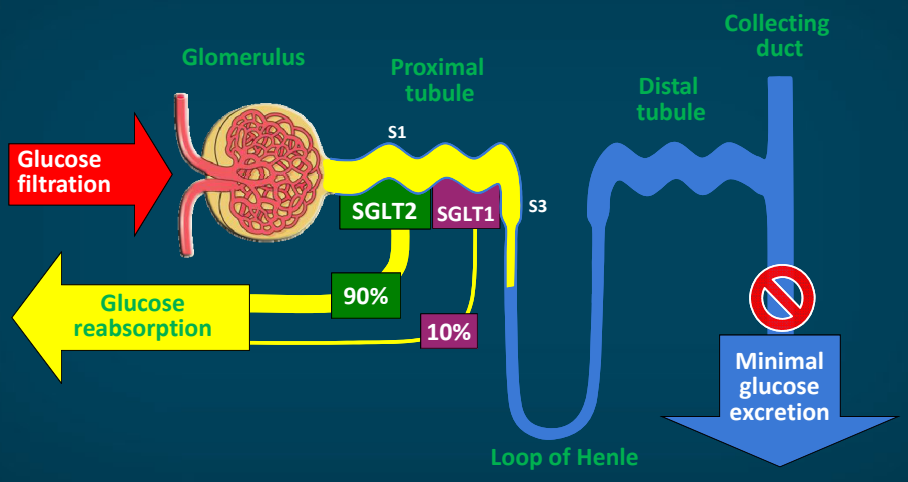


National Health Interview Survey Data 1990-2010.

Modified from Gregg EW, et al. *N Engl J Med*. 2014;370:1514-1523.

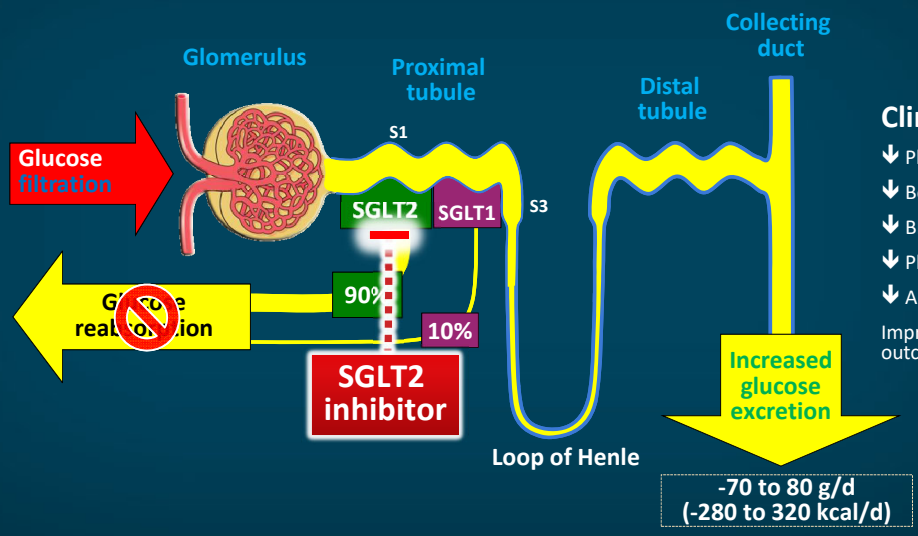
SGLT2 Inhibitors

Normal Physiology of Renal Glucose Homeostasis



Wright EM. *Am J Physiol Renal Physiol*. 2001;280:F10-F18. Lee YJ, et al. *Kidney Int Suppl*. 2007;106:S27-S35. Han S, et al. *Diabetes*. 2008;57:1723-1729.

SGLT2 Inhibition Reduces Renal Glucose Reabsorption



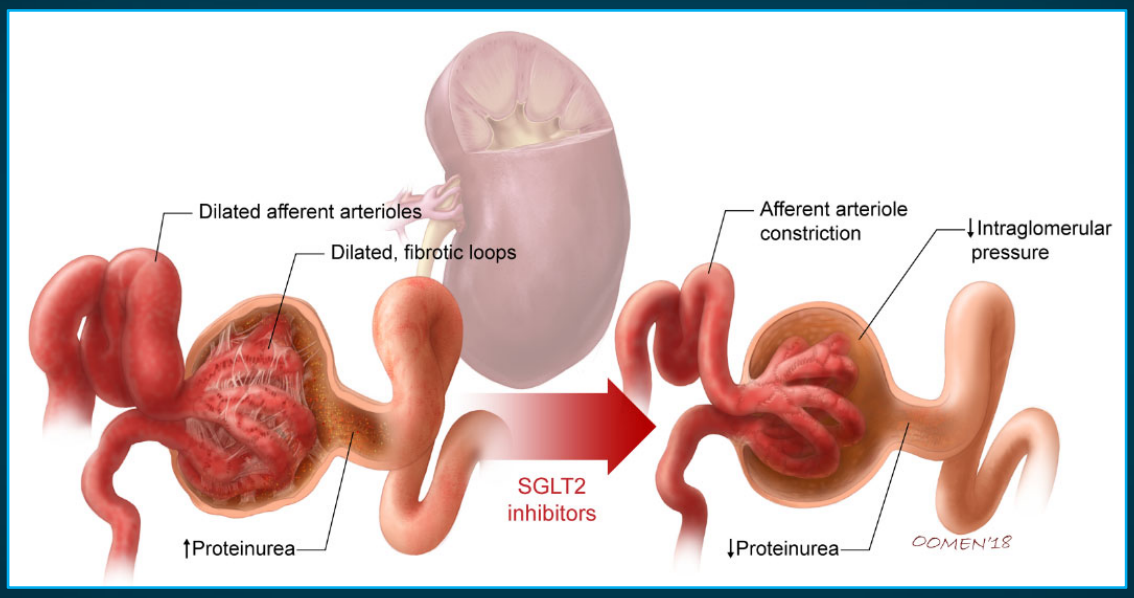
Clinical findings

- ↓ Plasma glucose
- ↓ Body weight
- ↓ Blood pressure
- ↓ Plasma uric acid
- ↓ Albumin excretion

Improved renal and CV outcomes

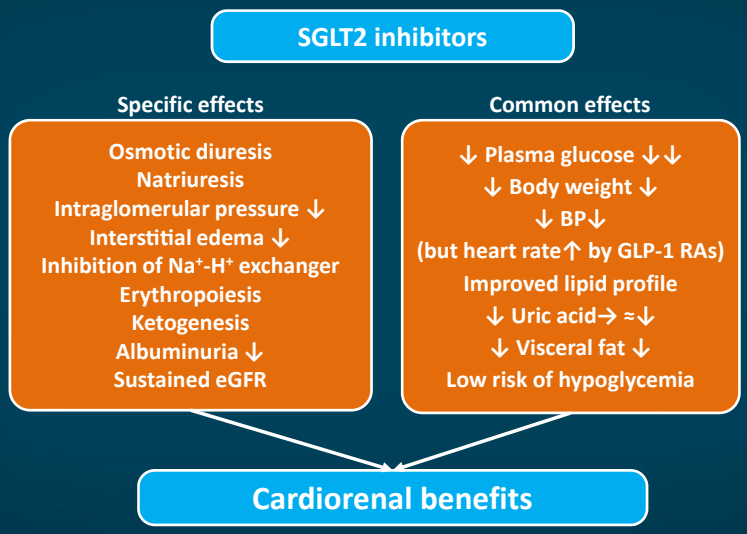
Wright EM. *Am J Physiol Renal Physiol*. 2001;280:F10-F18. Lee YJ, et al. *Kidney Int Suppl*. 2007;106:S27-S35. Han S, et al. *Diabetes*. 2008;57:1723-1729. Inzucchi SE, et al. *Diabetes Care*. 2015;38:140-149.

SGLT2 Inhibitors Improve Glomerular Loading Conditions



Verma S, McMurray JJV. *Diabetologia*. 2018;61:2108-2117. doi:10.1007/s00125-018-4670-7

SGLT2 Inhibitors: Potential Mechanisms for Cardiorenal Protection



eGFR = estimated GFR; GLP-1 RA = glucagon-like peptide-1 receptor agonist; H^+ = hydrogen (ion); Na^+ = sodium (ion).
Nagahisa T, Saisho Y. *Diabetes Ther*. 2019;10:1733-1752.

Overview of FDA-Approved SGLT2 Inhibitors

Drug Name	Dosage* (mg)	Reduction in HbA_{1c}†	SGLT2 IC50‡ (nmol/L)	Considerations for Patients	CV Outcomes	Future Potential
Canagliflozin	100, 300	-0.77 to -1.03	2.7	Strongest effect on reducing BP; increased risk of lower-limb amputations	CANVAS program Reduced risk of death from CV events, nonfatal MI, and nonfatal stroke	Uses in non-DM NAFLD SIADH Weight loss Alzheimer disease CAD Ischemic heart disease
Empagliflozin	10, 25	-0.66 to -0.78	3.1	Use in patients with previous stroke or MI	EMPA-REG OUTCOME Reduced HHF and death from CV causes	
Dapagliflozin	5, 10	-0.82 to -0.89	1.2	Positive effects on LDL-C and HDL-C	DECLARE-TIMI 58 Reduced HHF and CVD	
Ertugliflozin	5, 15	-0.99 to -1.16	0.9	Stricter eGFR restriction (<60 mL/min/1.73 m^2)	VERTIS-CV Reduced HHF	

*All dosages are once per day. †Percentage reduction from baseline 24-26 weeks. ‡Taken from reference.
CAD = coronary artery disease; FDA = US Food and Drug Administration; IC50 = half-maximal inhibitory concentration; NAFLD = non-alcoholic fatty liver disease; SIADH = syndrome of inappropriate (secretion of) antidiuretic hormone.
Adapted from Simes BC, MacGregor GG. *Diabetes Metab Syndr Obes*. 2019;12:2125-2136. Tehrani D, et al. *Latest Cardiol*. 2020 (www.acc.org/latest-in-cardiology/articles/2020/08/31/09/40/vertis-cv-trial). Accessed 9/21/2020.

SGLT2 Inhibitor Indications

SGLT2 Inhibitor	Diabetes	MACE/CVD	Heart Failure	Chronic Kidney Disease
Empagliflozin	• As an adjunct to diet and exercise to improve glycemic control in adults with T2DM	• To reduce the risk of CV death in adults with T2DM and established CVD	• To reduce the risk of CV death plus HHF in adults with heart failure with reduced ejection fraction,	
Ertugliflozin	• As an adjunct to diet and exercise to improve glycemic control in adults with T2DM			
Dapagliflozin	• As an adjunct to diet and exercise to improve glycemic control in adults with T2DM	• To reduce the risk of CV death and HHF in adults with HFrEF (NYHA class II-IV)	• To reduce the risk of HHF in adults with T2DM and established CVD or multiple CVD risk factors	• To reduce the risk of sustained eGFR decline, ESRD, ESKD, CV death, and HHF in adults with CKD at risk for progression
Canagliflozin	• As an adjunct to diet and exercise to improve glycemic control in adults with T2DM	• To reduce the risk of MACEs in adults with T2DM and established CVD		• To reduce the risk of ESRD, doubling of serum creatinine, CV death, and HHF in adults with T2DM and diabetic nephropathy with albuminuria

ESKD = end-stage kidney disease; HFrEF = heart failure with reduced ejection; MACE = major adverse CV event; NYHA = New York Heart Association.
Prescribing information for these agents.

Adverse Effects/Contraindications

- Not recommended in patients with T1DM given increased risk of diabetic ketoacidosis
- Not recommended for use to improve glycemic control in adults with T2DM with an eGFR <30 mL/min/1.73 m^2 or on dialysis (empagliflozin, dapagliflozin, canagliflozin)
- Not recommended in adults with T2DM with an eGFR <45 mL/min/1.73 m^2 (dapagliflozin, empagliflozin)
- Not recommended for CKD in patients with polycystic kidney disease or in those requiring or with a recent history of immunosuppressive therapy for the treatment of kidney disease (dapagliflozin)
- Most common side effects: female genital mycotic infections, increased urination, UTIs

T1DM = type 1 diabetes mellitus; UTI = urinary tract infection.
Prescribing information for these agents.

SGLT2 Inhibitors

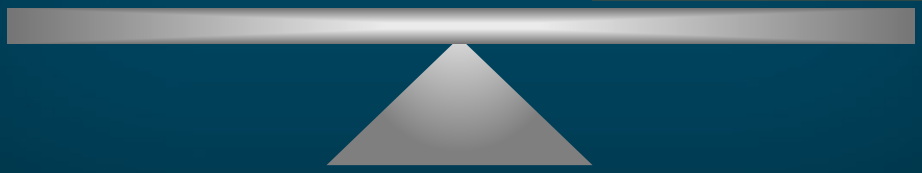
Risk-to-Benefit Ratio Prior to CV Outcome Trials

BENEFITS

- ↓ HbA_{1c} ≈0.6%-0.9%
- Low hypoglycemia risk
- Modest ↓ weight
- Modest ↓ BP
- ↓ Albuminuria
- Small ↓ TGs
- Small ↑ HDL-C

RISKS

- Polyuria/dehydration
- Genital mycotic infections
- ? UTIs
- Small ↓ GFR (reversible)
- Diabetic ketoacidosis
- Small ↑ LDL-C
- ? ↑ Fracture risk



Kim Y, Babu AR. *Diabetes Metab Syndr Obes.* 2012;5:313-327. Inzucchi SE, et al. *Diabetes Care.* 2015;38:140-149. Burke KR, et al. *Pharmacotherapy.* 2017;37:187-194.

SGLT2 Inhibitors and Glycemic Control

SGLT2 Inhibitor CVOTs: Baseline Characteristics

Characteristic	Empagliflozin		Canagliflozin		Dapagliflozin			Ertugliflozin
Study name	EMPA-REG[1]	EMPEROR-Reduced[2]	CANVAS, CANVAS-R[3]	CREDENCE[4]	DECLARE-TIMI[5]	DAPA-HF[6]	DAPA-CKD[7]	VERTIS-CV[8]
N	7020	3730	10,142	4401	17,160	4744	4304	8246
T2D, %	100	50	100	100	100	41.8	67	100
Established CVD, %	99	100	65.6	50.4	40.6	--	37	100
CKD, %	26	48	17.5	100 With albuminuria	7	40.6	100 With albuminuria	21.6
Mean baseline eGFR, L/min/1.73[2]	74	62	76.5	56.2	85	66	43.1	76.0
Baseline HF, %	10	100	14.4	14.8	10	100	11	23.1

CVOTs = cardiovascular outcome trials.

1. Zinman B, et al. *N Engl J Med*. 2015;373:2117-2128. 2. Packer M, et al. *N Engl J Med*. 2020;383:1413-1424. 3. Neal B, et al. *N Engl JMed*. 2017;377:644-657. 4. Perkovic V, et al. *N Engl J Med*. 2019;380:2295-2306. 5. Wiviott SD, et al. *N Engl J Med*. 2019;380:347-357. 6. McMurray JJV, et al. N Eng J Med. 2019;381:1995-2008. 7. Heerspink HJL, et al. *N Eng J Med*. 2020; 383:1436-1446. 8. Cannon CP, et al. *Am Heart J*. 2018;206:11-23.

SGLT2 in Cardiovascular Disease

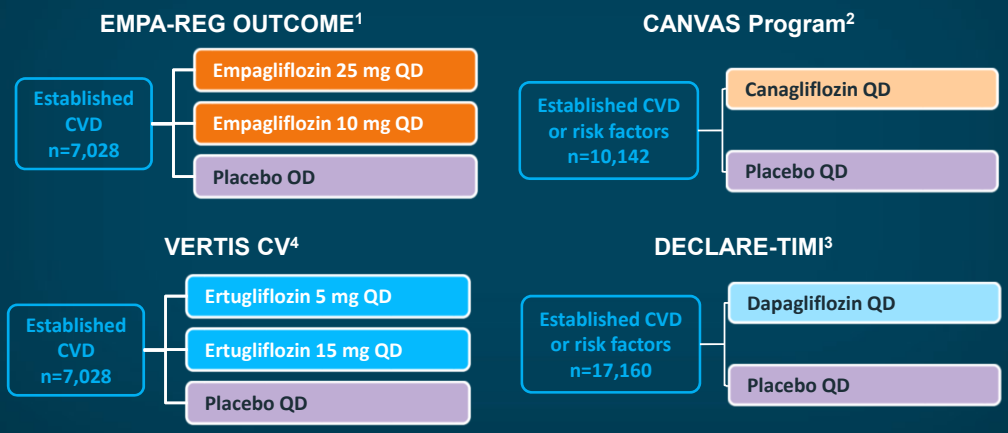
FDA-Mandated CV Outcomes Trials in T2DM SGLT2 Inhibitors

Study	EMPA-REG[1,2]	CANVAS[2,3]	CREDENCE[2,4]	DECLARE[2,5]	VERTIS CV[2,6]
SGLT2 inhibitor	Empagliflozin	Canagliflozin	Canagliflozin	Dapagliflozin	Ertugliflozin
Comparator	Placebo	Placebo	Placebo	Placebo	Placebo
N	7,020	4,330	4,401	17,190	8,246
Results	2015	2017	2018	2018	2020

1. NCT01131676 (EMPA-REG). 2. Tehrani D, et al. *Latest Cardiol.* 2020 (www.acc.org/latest-in-cardiology/articles/2020/08/31/09/40/vertis-cv-trial). Accessed 9/21/2020.
3. NCT01032629 (CANVAS). 4. NCT02065791 (CREDENCE). 5. NCT01730534 (DECLARE-TIMI 58). 6. NCT01986881 (VERTIS CV).

CV Outcome Trials With SGLT2 Inhibitors

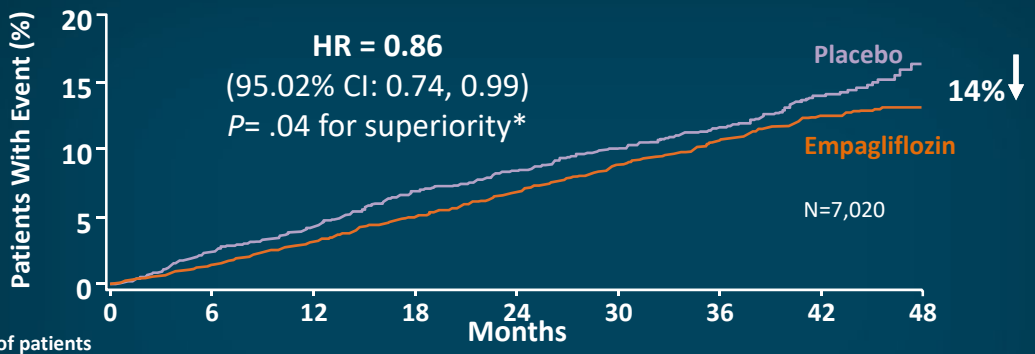
Trial designs



QD = once daily.
1. Zinman B, et al. *N Engl J Med.* 2015;373:2117-2128. 2. Neal B, et al. *N Engl J Med.* 2017;377:644-657. 3. Wiviott SD, et al. *New Engl J Med.* 2019380:347-357.
4. Cannon CP, et al. *N Engl J Med*. 2020;383:1425-1435.

EMPA-REG: Primary Outcome

Cumulative incidence of 3-point MACE (CV death, nonfatal MI, or nonfatal stroke)



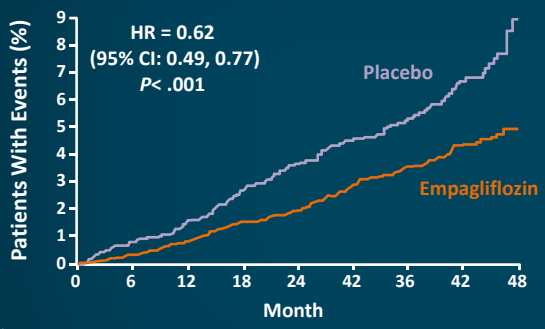
No. of patients									
Empagliflozin	4,687	4,580	4,455	4,328	3,851	2,821	2,359	1,534	370
Placebo	2,333	2,256	2,194	2,112	1,875	1,380	1,161	741	166

Primary outcome (composite of death from CV causes, nonfatal MI, or nonfatal stroke) occurred in a significantly lower percentage of patients in empagliflozin group (10.5%) vs placebo (12.1%).

Zinman B, et al. *N Engl J Med.* 2015;373:2117-2128.

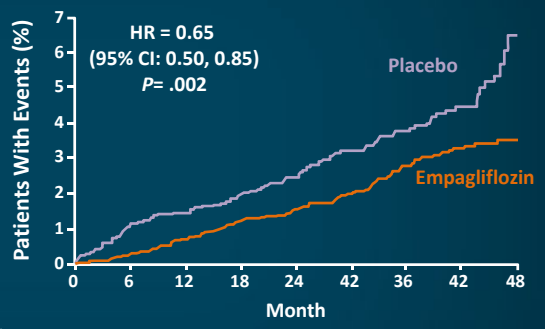
EMPA-REG: CV Death and Heart Failure Hospitalization

Death from CV causes



No. at risk									
Empagliflozin	4,687	4,651	4,608	4,556	4,128	3,079	2,617	1,772	414
Placebo	2,333	2,303	2,280	2,243	2,012	1,503	1,281	825	177

HHF



No. at risk									
Empagliflozin	4,687	4,614	4,523	4,427	3,988	2,950	2,487	1,634	395
Placebo	2,333	2,271	2,226	2,173	1,932	1,424	1,202	775	168

Zinman B, et al. *N Engl J Med.* 2015;373:2117-2128.

SGLT2 Inhibitor Trial Meta-analysis of CV Outcomes

Meta-analysis on MI, stroke, and CV death (MACE)*

	Patients		Events	Events/1,000 PY		Weight (%)	Hazard Ratio	HR (95% CI)
	Treatment	PBO		Treatment	PBO			
Patients with ASCVD								
EMPA-REG OUTCOME	4,687	2,333	772	37.4	43.9	29.4		0.86 (0.74, 0.99)
CANVAS Program	3,756	2,900	796	34.1	41.3	32.4		0.82 (0.72, 0.95)
DECLARE-TIMI 58	3,474	3,500	1,020	36.8	41.0	28.2		0.90 (0.79, 1.02)
Patients with ASCVD (*P*= .0002)								**0.86 (0.80, 0.93)**
Patients with multiple risk factors								
CANVAS Program	2,039	1,447	215	15.8	15.5	25.9		0.98 (0.74, 1.30)
DECLARE-TIMI 58	5,108	5,078	539	13.4	13.3	74.1		1.01 (0.86, 1.20)
Fixed-effects model for multiple risk factors (*P*= .98)								**1.00 (0.87, 1.16)**

0.35 0.50 1.0 2.50
Favors treatment Favors placebo

Meta-analysis on HHF and CV death*

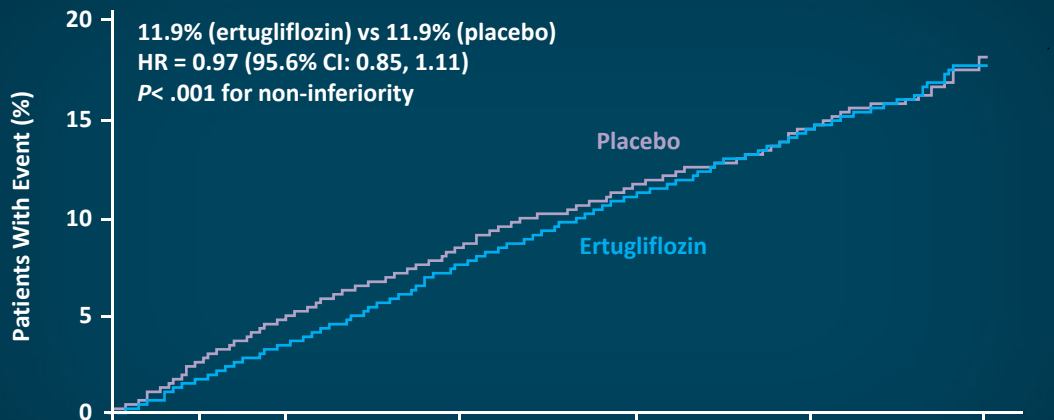
	Patients		Events	Events/1,000 PY		Weight (%)	Hazard Ratio	HR (95% CI)
	Treatment	PBO		Treatment	PBO			
Patients with ASCVD								
EMPA-REG OUTCOME	4,687	2,333	463	19.7	30.1	30.9		0.66 (0.55, 0.79)
CANVAS Program	3,756	2,900	524	21.0	27.4	32.8		0.77 (0.65, 0.92)
DECLARE-TIMI 58	3,474	3,500	597	19.9	23.9	36.4		0.83 (0.71, 0.98)
Patients with ASCVD (*P*< .0001)								**0.76 (0.69, 0.84)**
Patients with multiple risk factors								
CANVAS Program	2,039	1,447	128	8.9	9.8	30.2		0.83 (0.58, 1.19)
DECLARE-TIMI 58	5,108	5,078	316	7.0	8.4	69.8		0.84 (0.67, 1.04)
Fixed-effects model for multiple risk factors (*P*= .0634)								**0.84 (0.69, 1.01)**

0.35 0.50 1.0 2.50
Favors treatment Favors placebo

*Stratified by presence of established atherosclerotic disease.
ASCVD = atherosclerotic CVD; PBO = placebo; PY = patient-years.
Zelniker TA, et al. *Lancet*. 2019;393:31-39.

VERTIS CV: Ertugliflozin Effects on MACE

CV Death, Nonfatal MI, or Nonfatal Stroke



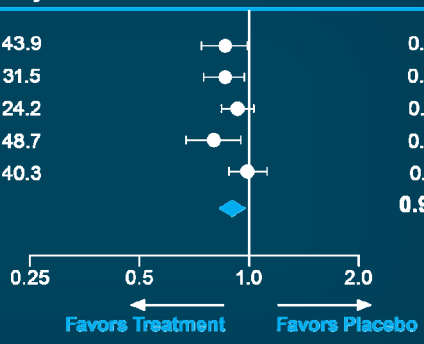
No. at risk							
Placebo	2,745	2,663	2,580	2,180	1,027	769	134
All ertugliflozin	5,493	5,346	5,203	4,448	2,216	1,690	272

*Full analysis set included all randomized patients who received ≥1 dose of study medication (n=5,493 for ertugliflozin; n=2,745 for placebo). Only confirmed MACEs occurring up to 365 days after the last confirmed dose of study medication were included in the primary analysis.
Cannon CP, et al. *N Engl J Med*. 2020;383:1425-1435.

VERTIS CV: Time to First MACE

MACE

	Treatment Rate/1000 patient-years	Placebo Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	37.4	43.9	0.86 (0.74-0.99)
CANVAS Program	26.9	31.5	0.86 (0.75-0.97)
DECLARE-TIMI 58	22.6	24.2	0.93 (0.84-1.03)
CREDENCE	38.7	48.7	0.80 (0.67-0.95)
VERTIS CV*	40.0	40.3	0.99 (0.88-1.12)
Pooled estimate			**0.90 (0.85-0.95)**
(Q statistic $P = 0.27$; $I^2 = 23.4\%$)			

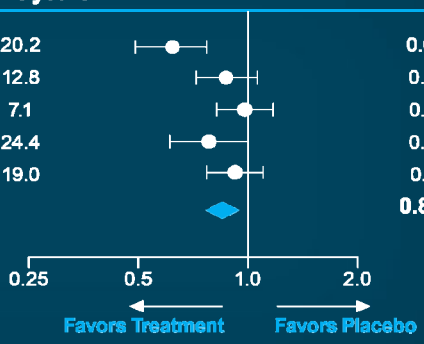


*Intent-to-treat population was used for consistency with other trials.
McGuire DK, et al. *JAMA Cardiol*. 2021;6:148-158.

VERTIS CV: Time to CV Death

CV DEATH

	Treatment Rate/1000 patient-years	Placebo Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	12.4	20.2	0.62 (0.49-0.77)
CANVAS Program	11.6	12.8	0.87 (0.72-1.06)
DECLARE-TIMI 58	7.0	7.1	0.98 (0.82-1.17)
CREDENCE	19.0	24.4	0.78 (0.61-1.00)
VERTIS CV	17.6	19.0	0.92 (0.77-1.10)
Pooled estimate			**0.85 (0.78-0.93)**
(Q statistic $P = 0.02$; $I^2 = 64.3\%$)			

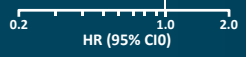


McGuire DK, et al. *JAMA Cardiol*. 2021;6:148-158.

Effects of SGLT2 Inhibitors on MACE

Overall MACEs

	Treatment No./ Total No	Treatment Rates 1000 patient-years	Placebo No./ Total No	Placebo Rates 1000 patient-years	Hazard ratio (95% CI0)	Weight, %
EMPA-REG OUTCOME	490/4687	37.4	282/2333	43.9	0.86 (0.74-0.99)	15.72
CANVAS program	NA/5795	26.9	NA/4347	31.5	0.86 (0.75-0.97)	20.12
OECLARE-TIMI 58	756/8582	22.6	803/8578	24.2	0,93 (0.84-1.03)	32.02
CREDENCE	217/2202	38.7	269/2199	48.7	0.80 (0.67-0.95)	10.92
VERTIS CV	735/5499	40.0	368/2747	40.3	0.99 (0.88-1.12)	21.23
Fixed-effects model (Q=5.22; *df* = 4; P = 0.27; I^2 = 23.4%)					**0.90 (0.85-0.95)**	



MACEs by ASCVD Status

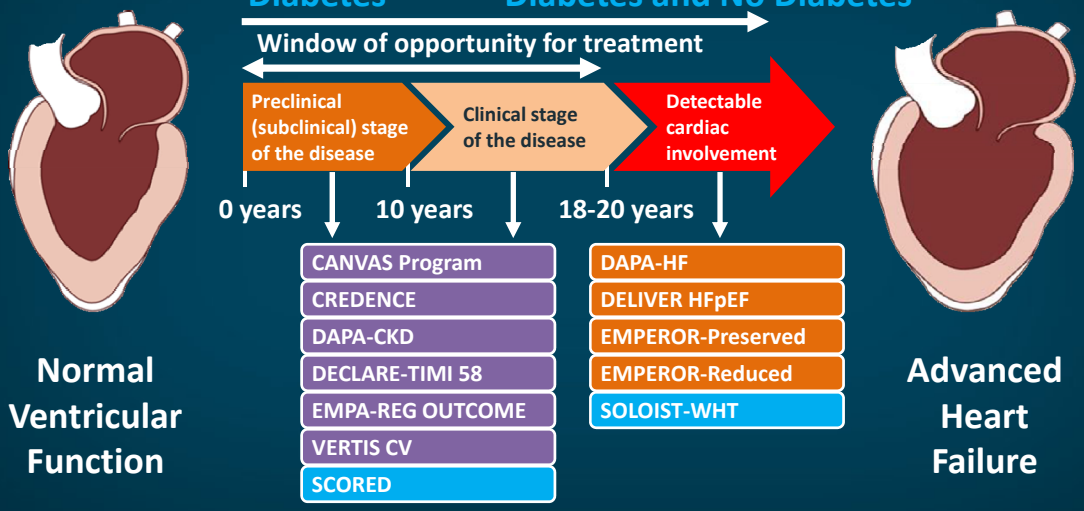
	Treatment No./ Total No.	Treatment Rates 1000 patient-years	Placebo No./ Total No.	Placebo Rates 1000 patient-years	Hazard ratio (95% CI0)	Weight, %
Patients with ASCVD						
EMPA-REG OUTCOME	490/4687	37.4	282/2333	43.9	0.86 (0.74-0.99)	19.19
CANVAS program	NA/3756	34.1	NA/290	41.3	0.82 (0.72-0.95)	21.16
OECLARE-TIMI 58	483/3474	36.8	537/3500	41.0	0.90 (0.79-1.02)	24.90
CREDENCE	155/1113	55.6	178/1107	65.0	0.85 (0.69-1.06)	8.82
VERTIS CV	735/5499	40.0	368/2747	40.3	0.99 (0.88-1.12)	25.93
Fixed-effects model (Q=4.53; *df* = 4; P = 0.34; I^2 = 11.8%)					0.89 (0.84-0.95)	
Patients without ASCVD						
CANVAS program	NA/2039	15.8	NA/1447	15.5	0.98 (0.74-1.30)	21.70
OECLARE-TIMI 58	273/5108	13.3	266/5078	13.3	1.01 (0.86-1.20)	62.07
CREDENCE	62/1089	22.0	91/1092	32.7	0.68 (0.49-0.94)	16.23
Fixed-effects model (Q=4.59; *df* = 4; P = 0.10; I^2 = 56.5%)					**0.94 (0.83-1.07)**	

MACE=composite of myocardial infarction, stroke, and CV death.

McGuire DK, et al. *JAMA Cardiol*. 2021;6(2):148-158.

SGLT2 Inhibitors in Heart Failure

The Evolution of SGLT2 Inhibitors in HF Management



Adapted from Bhatt DL, et al. *Cell Metab*. 2019;30:847-849.

Randomized Controlled Trials of SGLT2 Inhibitors in HF

	EMPEROR-Preserved[1]	EMPEROR-Reduced[2]	Dapa-HF[3,4]	DELIVER[5]
Intervention	**Empagliflozin**	**Empagliflozin**	**Dapagliflozin**	**Dapagliflozin**
Sample size	4,126*	3,730*	4,744*	Estimated 6,100 (recruiting)
HF criteria	**HFpEF (LVEF >40%)**	**HFrEF (LVEF ≤40%)**	**HFrEF (LVEF ≤40%)**	**HFpEF (LVEF >40%), structural heart disease, and NYHA II-IV**
Primary endpoint	Time to first event of adjudicated CV death or adjudicated HHF		Time to first occurrence of CV death, HHF, or urgent HF visit	Time to first occurrence of CV death, HHF, or urgent HF visit
Key secondary endpoints	• Individual components of primary endpoint • All-cause mortality • All-cause hospitalisation • Time to first occurrence of sustained reduction of eGFR • Change from baseline in KCCQ		• Total number of CV deaths or HHF • All-cause mortality • Composite of ≥50% sustained eGFR decline, ESRD, or renal death • Change from baseline in KCCQ	• Total number of CV death or HHF • All-cause mortality • Proportion of patients with worsened NYHA class • Change from baseline in KCCQ
Start date **Expected completion**	March 2017 June 2020 ✓	March 2017 June 2020 ✓	February 2017 **COMPLETED** ✓	August 2018 June 2021

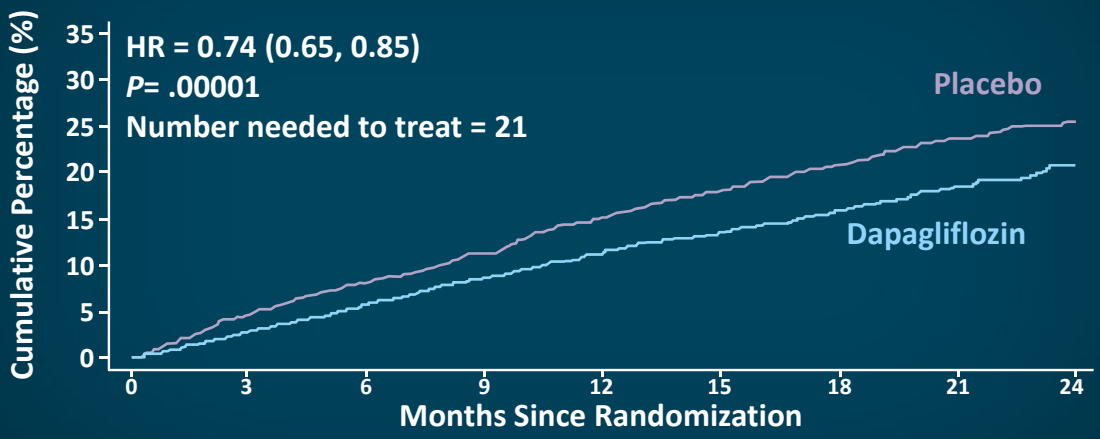
*NT-proBNP–based enrichment of population with patients at higher severity of HF.

ESRD = end-stage renal disease; HFpEF = HF with preserved ejection fraction; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal of prohormone brain natriuretic peptide.

1. NCT03057951 (EMPEROR-Preserved). 2. NCT03057977 (EMPEROR-Reduced). 3. NCT03036124 (DAPA-HF). 4. McMurray JJV, et al. *N Engl J Med*. 2019;381:1995-2008. 5. NCT03619213 (DELIVER).

DAPA-HF: Primary Outcome

CV death/HHF/urgent HF visit

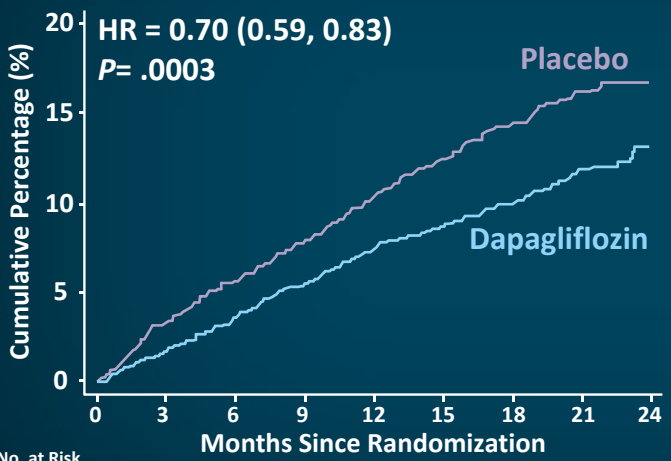


No. at Risk									
Dapagliflozin	2,373	2,305	2,221	2,147	2,002	1,560	1,146	612	210
Placebo	2,371	2,258	2,163	2,075	1,917	1,478	1,096	593	210

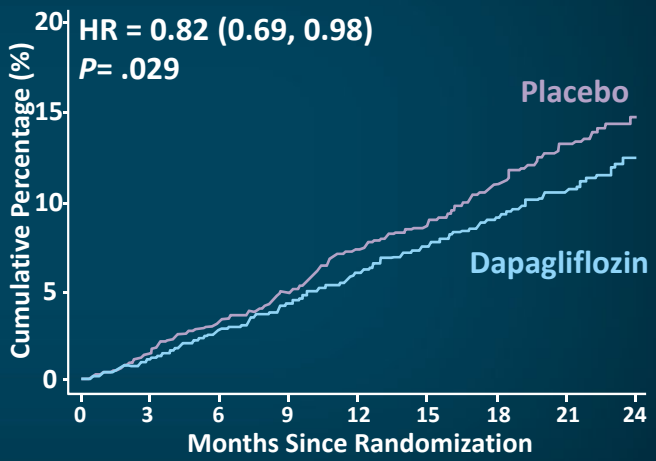
McMurray JJV, et al. ESC 2019. Hotline Session 1.

DAPA-HF: Components of Primary Outcome

WHF event



CV death



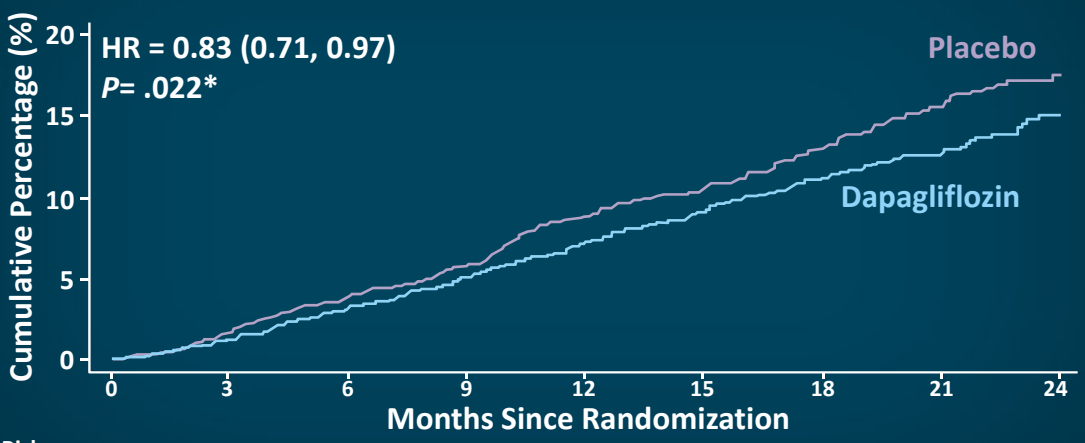
No. at Risk									
DAPA	2,373	2,305	2,221	2,147	2,002	1,560	1,146	612	210
Placebo	2,371	2,258	2,163	2,075	1,917	1,478	1,096	593	210

2,373	2,339	2,293	2,248	2,127	1,664	1,242	671	232
2,371	2,330	2,279	2,230	2,091	1,636	1,219	664	234

DAPA = dapagliflozin; WHF = worsening HF.

McMurray JJV, et al. ESC 2019. Hotline Session 1.

DAPA-HF: All-Cause Mortality



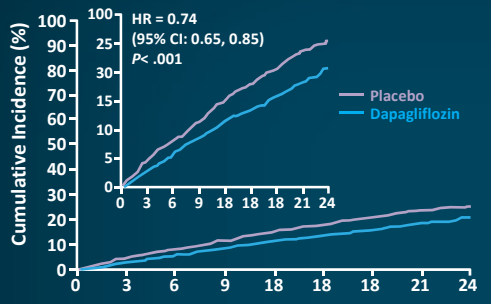
No. at Risk									
Dapagliflozin	2,373	2,342	2,296	2,251	2,130	1,666	1,243	672	233
Placebo	2,371	2,330	2,279	2,231	2,092	1,638	1,221	665	235

*Nominal *P* value.

McMurray JJV, et al. ESC 2019. Hotline Session 1.

DAPA-HF Primary Outcomes: DM vs Non-DM Subgroups

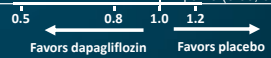
Primary outcome



No. at risk									
Dapagliflozin	2,371	2,258	2,163	2,075	1,917	1,478	1,096	593	210
Placebo	2,373	2,305	2,221	2,147	2,002	1,560	1,146	612	210

Primary outcome subgroup analysis

Subgroup	DAPA n=2,373	PBO n=2,371	HR (95% CI)
	Patients/total, no.		
HHF			
Yes	195/1,124	279/1,127	0.67 (0.56, 0.80)
No	191/1,249	223/1,244	0.84 (0.69, 1.01)
T2D at baseline			
Yes	215/1,075	271/1,064	0.75 (0.63, 0.90)
No	171/1,298	231/1,307	0.73 (0.60, 0.88)
AF or flutter on enrollment ECG			
Yes	109/569	126/559	0.82 (0.63, 1.06)
No	277/1,804	376/1,812	0.72 (0.61, 0.84)
Main cause of HF			
Ischemic	223/1,316	289/1,358	0.77 (0.65, 0.92)
Nonischemic or unknown	163/1,057	213/1,013	0.71 (0.58, 0.87)
BMI (kg/m^2)			
<30	259/1,537	320/1,533	0.78 (0.66, 0.92)
≥30	127/834	182/838	0.69 (0.55, 0.86)
Baseline eGFR (mL/min/1.73 m^2)			
<60	191/962	254/964	0.72 (0.59, 0.86)
≥60	195/1,410	248/1,406	0.76 (0.63, 0.92)



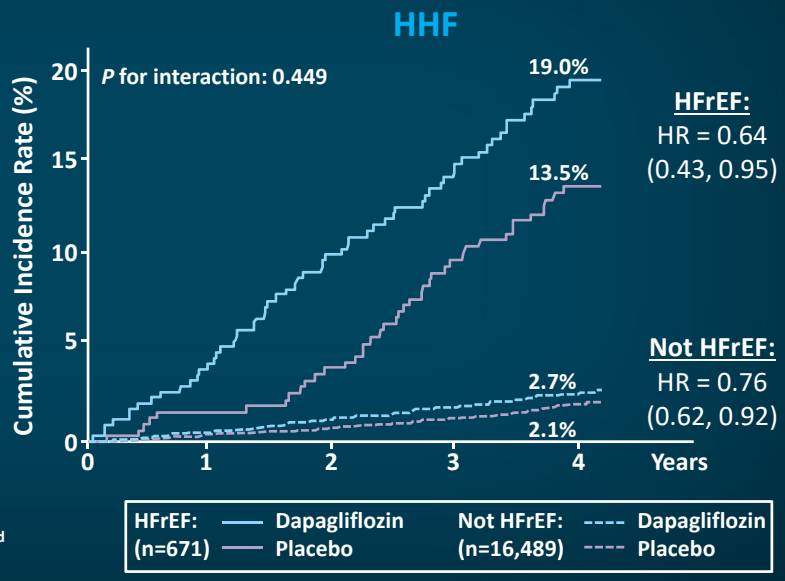
Primary outcome was composite of worsening HF (*HHF or urgent visit resulting in IV treatment for HF*) or CV death, which occurred in a significantly lower (*P*< .001) percentage of patients in dapagliflozin group (16.3%) vs placebo (21.2%).

AF = atrial fibrillation; ECG = electrocardiogram; IV = intravenous.

McMurray JJV, et al. *N Engl J Med.* 2019;381:1995-2008.

DECLARE-TIMI 58: Effects of Dapagliflozin on HHF by Baseline LVEF

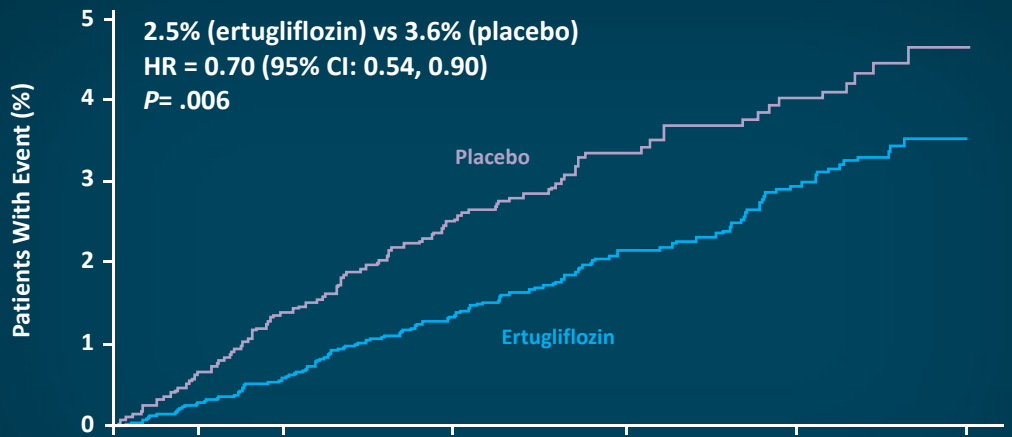
There was no modulation of the efficacy of dapagliflozin for reducing the risk of HHF in patients with HFrEF vs those without HFrEF



Not HFrEF defined as patients with HF without known reduced EF and patients without history of HF.

Kato ET, et al. *Circulation*. 2019;139:2528-2536.

VERTIS CV: Hospitalization for Heart Failure (HHF)



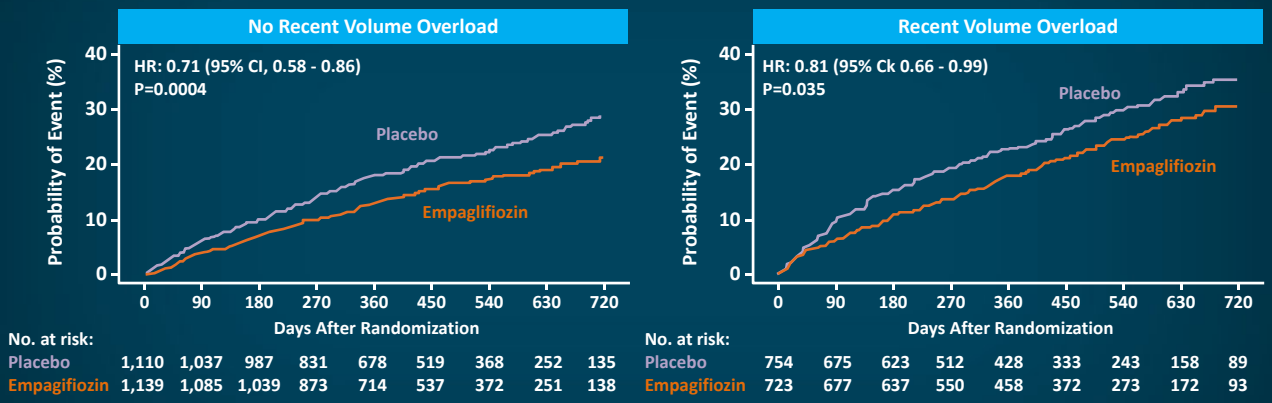
No. at risk							
Placebo	2,747	2,701	2,635	2,534	1,361	1,119	225
All ertugliflozin	5,499	5,396	5,297	5,119	2,766	2,286	416

*Intention-to-treat analysis set that included all randomized patients with no upper limit on the ascertainment window for the superiority outcomes (n=5,499 for ertugliflozin; n=2,747 for placebo).

Consentino F, et al. *Circulation*. 2020;142:2205-2215.

EMPEROR-Reduced Results

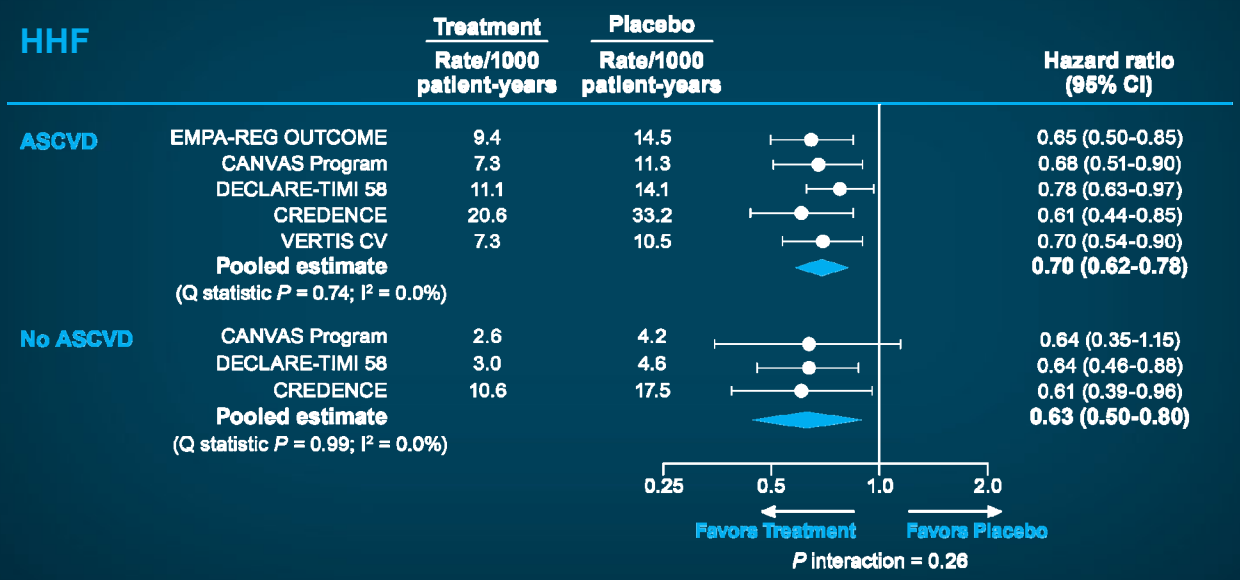
Effect of Empaglifiozin on the Combined Risk of Cardiovascular Death or Hospitalization for Heart Failure in Patients With or Without Recent Volume Overload at Baseline



Cumulative incidence plots, with hazard ratio (HR), 95% confidence interval (1), and p value for the comparison of empagliflozin and placebo. Interaction p value for the difference in the effect of empaglifiozin on the **left and right** is 0.34.

Packer M, et al. *J Am Coll Cardiol*. 2021;77(11):1381-1392.

Time to First HHF: Subgroup Analysis by ASCVD



McGuire DK, et al. *JAMA Cardiol*. 2021;6(2):148-158.

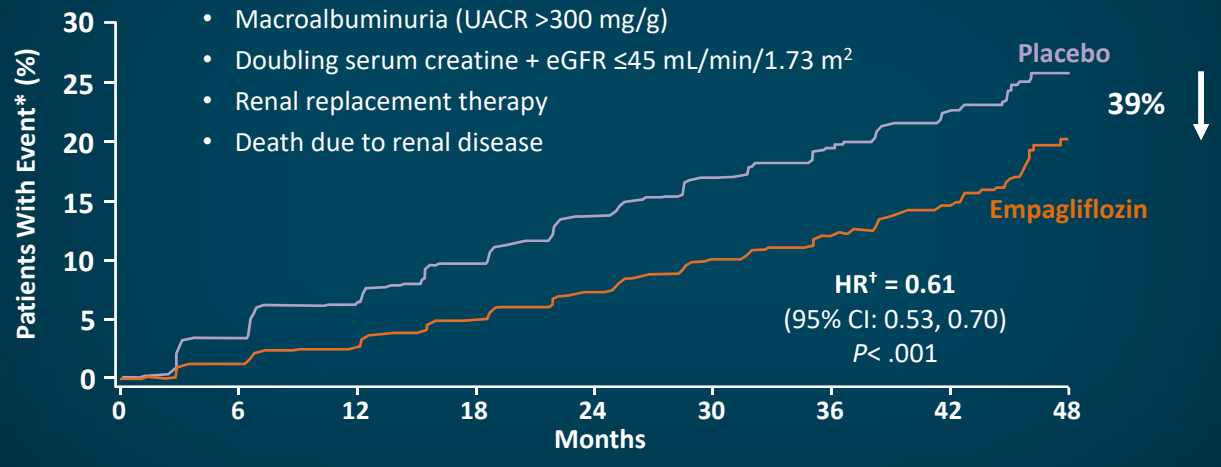
SGLT2 Inhibitors in Renal Disease

EMPA-REG OUTCOME: Secondary Outcome

Cumulative Incidence of Incident or Worsening Nephropathy

Incident or worsening nephropathy includes:

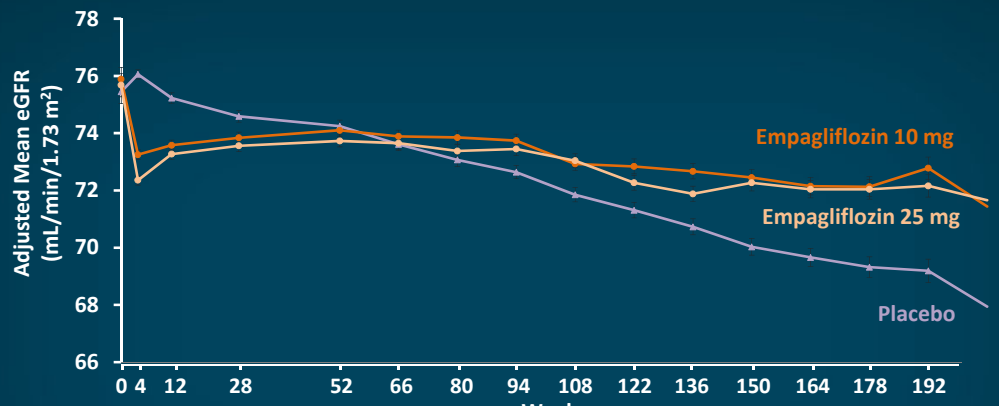
- Macroalbuminuria (UACR >300 mg/g)
- Doubling serum creatine + eGFR ≤45 mL/min/1.73 m^2
- Renal replacement therapy
- Death due to renal disease



*Kaplan-Meier estimate. †HR based on Cox regression analyses.

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

EMPA-REG: eGFR (CKD-EPI Formula) Over 192 Weeks



No. analyzed															
Placebo	2,323	2,295	2,267	2,205	2,121	2,064	1,927	1,981	1,763	1,479	1,262	1,123	977	731	448
Empagliflozin 10 mg	2,322	2,290	2,264	2,235	2,162	2,114	2,012	2,064	1,839	1,540	1,314	1,180	1,024	785	513
Empagliflozin 25 mg	2,322	2,288	2,269	2,216	2,156	2,111	2,006	2,067	1,871	1,563	1,340	1,207	1,063	838	524
No. in total follow-up for adverse/outcome events	7,020	7,020	6,996	6,931	6,864	6,765	6,696	6,651	6,068	5,114	4,443	3,961	3,488	2,707	1,703

Mixed-model repeated measures analysis.

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration.

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

Randomized Controlled Trials of SGLT2 Inhibitors in CKD

	CREDENCE[1,2]	Dapa-CKD[3]	EMPA-KIDNEY[4-6]
SGLT2 inhibitor	Canagliflozin	Dapagliflozin	Empagliflozin
Population	DKD	CKD	CKD
No. of patients	4,401	4,304	≈5,000
Key inclusion criteria	eGFR ≥30 to <90 mL/min/1.73 m² and UACR >300 to ≤5,000 mg/g	eGFR ≥25 to ≤75 mL/min/1.73 m² and UACR ≥200 to ≤5,000 mg/g	eGFR ≥20 to <45 mL/min/1.73 m² **OR** eGFR ≥45 to <90 mL/min/1.73 m² **AND** UACR ≥200 mg/g
Primary outcome	Doubling of serum creatinine, ESKD, or renal or CV death	eGFR decline of ≥50%, ESKD, or renal or CV death	eGFR decline of ≥40%, ESKD, or renal or CV death
Key secondary outcomes	• Composite of CV death and HHF • All-cause mortality	• Composite of CV death or HHF • All-cause mortality	• Composite of CV death or HHF • All-cause hospitalization • All-cause mortality
Start date Estimated completion	201[illegible] 018	201[illegible] 020	2019 2022

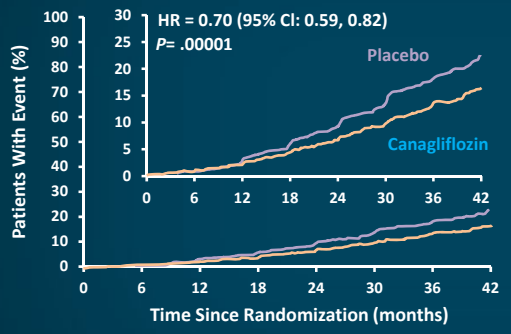
DKD = diabetic kidney disease.

1. Jardine MJ, et al. *Am J Nephrol*. 2017;46:462-472. 2. NCT02065791 (CREDENCE). 3. NCT03036150 (Dapa-CKD). 4. NCT03594110 (EMPA-KIDNEY). 5. Boehringer Ingelheim. 4. EMPA-KIDNEY. (https://www.empakidney.org/) 6. PACE-CME symposium. ERA-EDTA 2018 (https://pace-cme.org/2018/06/27/slides-addressing-the-remaining-questions-on-sglt2-ckd-a-review-of-new-outcome-trials//download-slides-addressing-the-remaining-questions-on-sglt2-ckd-a-review-of-new-outcome-trials.pdf). URLs accessed 9/21/2020.

CREDENCE: Progression of Nephropathy

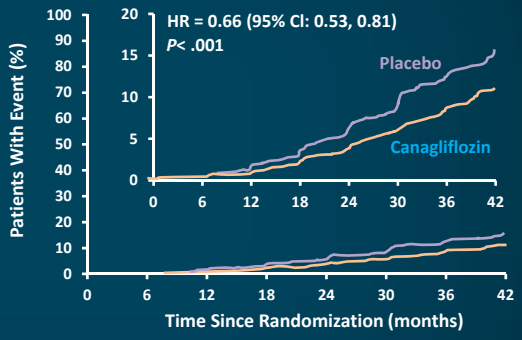
Primary and Secondary Endpoints

Primary composite outcome*



No. at risk								
Placebo	2,199	2,178	2,132	2,047	1,725	1,129	621	170
Canagliflozin	2,202	2,181	2,145	2,081	1,786	1,211	646	196

Renal-specific composite outcome*

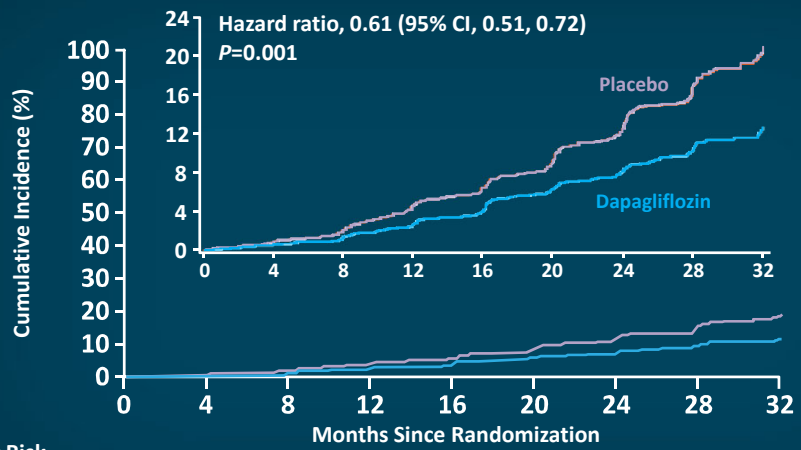


No. at risk								
Placebo	2,199	2,178	2,131	2,046	1,724	1,129	621	170
Canagliflozin	2,202	2,181	2,144	2,080	1,786	1,211	646	196

*Indicated to reduce risk of ESKD, doubling of serum creatinine, CV death, and HHF in adults with T2DM and diabetic nephropathy with albuminuria.

Perkovic V, et al. *N Engl J Med*. 2019;380:2295-2306. Canagliflozin (Invokana®) PI 2020 (www.janssenlabels.com/package-insert/product-monograph/prescribing-information/INVOKANA-pi.pdf). Accessed 9/18/2020.

DAPA-CKD: Primary Composite Outcome



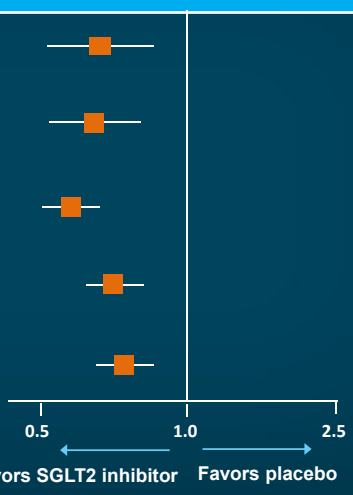
No. at Risk									
Dapagliflozin	2152	2001	1955	1898	1841	1701	1288	831	309
Placebo	2152	1993	1936	1858	1791	1664	1232	774	270

Primary outcome = composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes.

Heerspink HJL, et al. *N Engl J Med.* 2020;383:1436-1446.

Meta-analysis of Effects of SGLT2 Inhibitors on Major Kidney Outcomes in EMPA-REG OUTCOME, CANVAS, CREDENCE, and DECLARE-TIMI 58

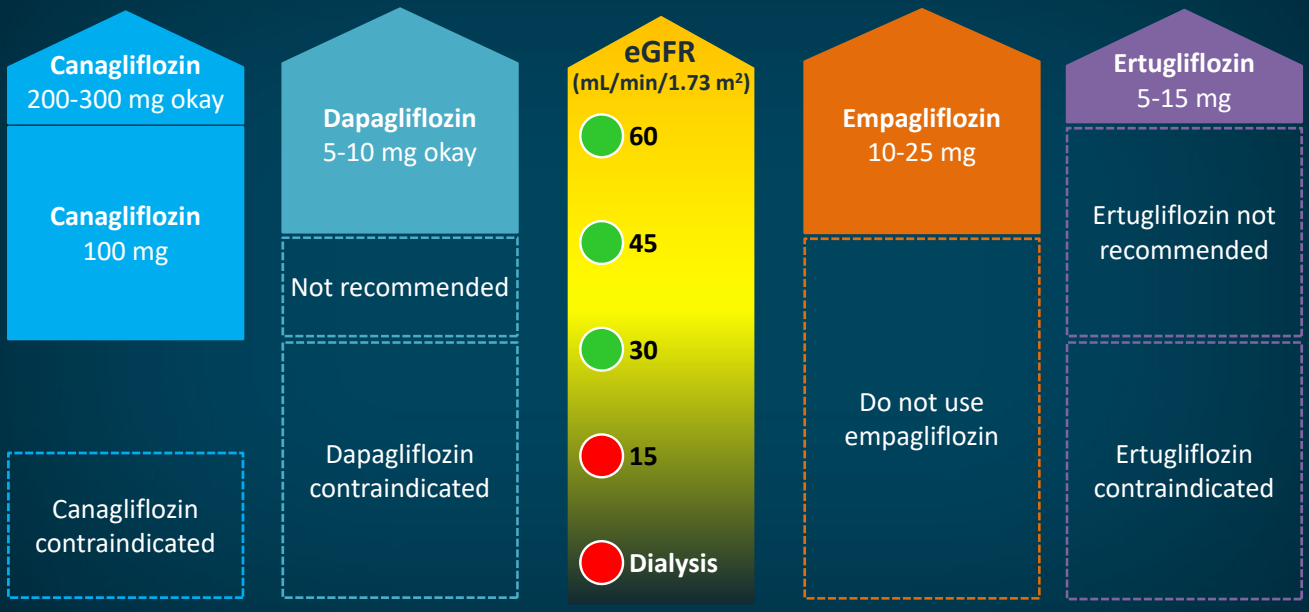
Major Kidney Outcomes	Events	Patients	RR (95% CI)
Dialysis, transplantation, or death due to kidney disease	252	38,723	0.67 (0.52, 0.86)
ESKD	335	38,723	0.65 (0.53, 0.81)
Substantial loss of kidney function, ESKD, or death due to kidney disease	967	38,671	0.58 (0.51, 0.66)
Substantial loss of kidney function, ESKD, or death due to CV or kidney disease	2323	38,676	0.71 (0.63, 0.82)
Acute kidney injury	943	38,684	0.75 (0.66, 0.85)



RR = relative risk.

Neuen BL, et al. *Lancet Diabetes Endocrinol*. 2019;7:845-854.

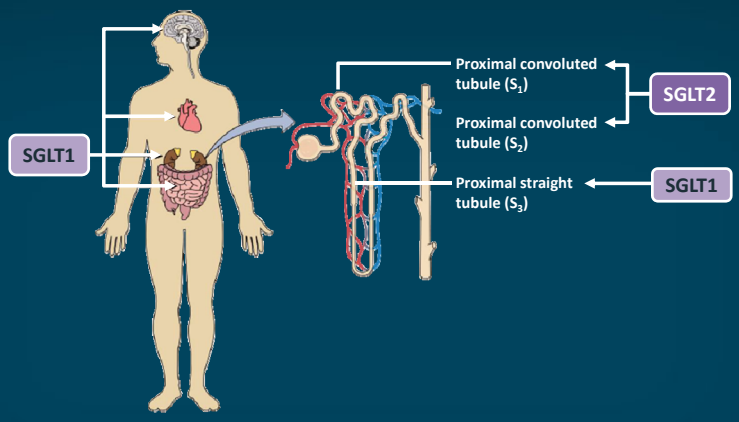
Current Renal Restrictions: SGLT2 Inhibitors



Prescribing information for these agents.

Looking Ahead

Sotagliflozin: Dual SGLT1 and SGLT2 Inhibitor



- SGLT1 is the primary transporter for absorption of glucose and galactose in the gastrointestinal tract
- Pharmacologic inhibition by sotagliflozin is independent of insulin and does not depend on kidney function
- Potential reduction in atherosclerotic risks

- SGLT2 is expressed in the kidney, where it reabsorbs 90% of filtered glucose

Pitt B, Bhatt DL. *Circulation*. 2021;144:4-6. Cefalo, CMA, et al. *Cardiovasc Diabetol.* 2019;18:20

SOLOIST-WHF: Trial Design

SOLOIST

1,222 patients with diabetes and HF

Double-blind randomization in-hospital or within 3 days after discharge

Placebo QD

Sotagliflozin 200 mg QD*

Primary Endpoint: Total Events
- CV death
- HHF
- Urgent HF visit

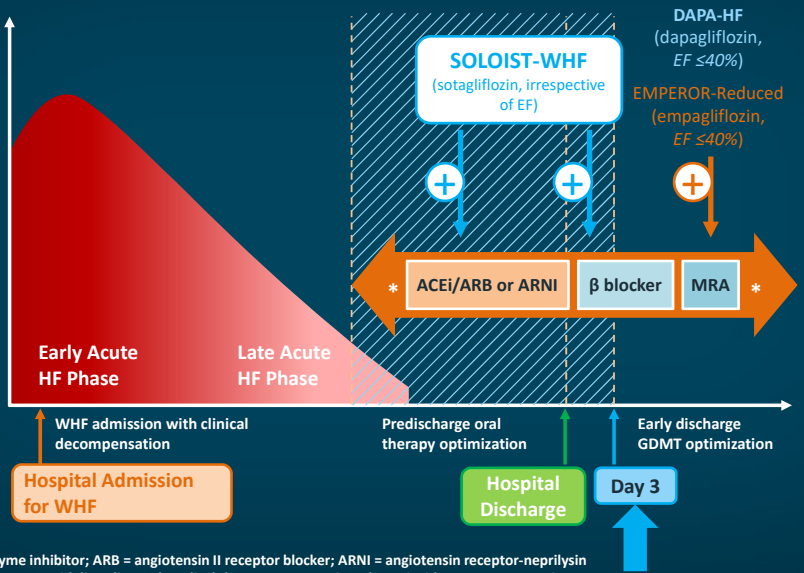
Median follow-up duration (IQR) = 9.0 (4.9-13.4) months

Key inclusion criteria:
- Admission with signs and symptoms of HF
- Treatment with IV diuretics
- Stabilized, off oxygen, transitioning to oral diuretics
- BNP ≥150 pg/mL (≥450 pg/mL if AF) or NT-proBNP ≥600 pg/mL (≥1,800 pg/mL if AF)
- T2D

Key exclusion criteria:
- End-stage HF
- Recent ACS, stroke, PCI, or CABG
- eGFR <30 mL/min/1.73 m^2

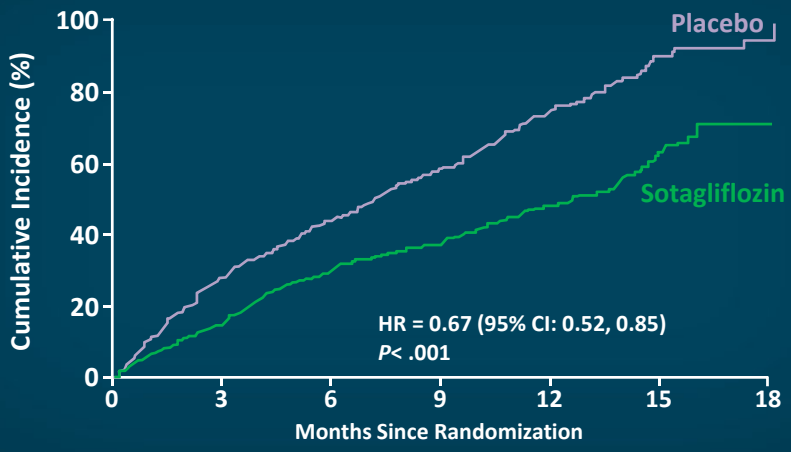
*Goal of dose increase to 400 mg QD.
ACS = acute coronary syndrome; CABG = coronary artery bypass graft; IQR = interquartile range; PCI = percutaneous coronary intervention.
Bhatt DL, et al. *N Engl J Med*. 2021;384:117-128. Bhatt DL, et al. AHA 2020, virtual; https://www.acc.org/Latest-in-Cardiology/Clinical-Trials/2020/11/11/22/00/SOLOIST-WHF

SOLOIST-WHF: Addressing the Vulnerable Period of an Admission for WHF



*Proven for HFrEF.
ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; EF = ejection fraction; GDMT = guideline-directed medical therapy; MRA = mineralocorticoid receptor antagonists.
Verma S, et al. *ESC Heart Fail*. 2020;7:3261-3267.

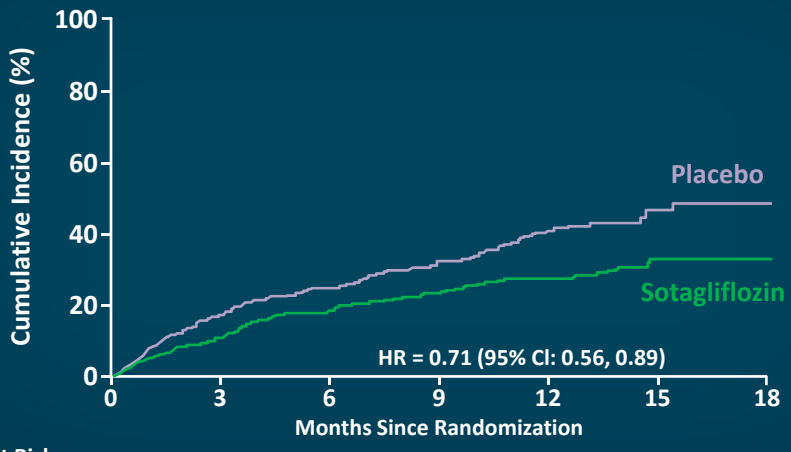
SOLOIST-WHF: Primary Efficacy Endpoints Total CV Death, HHF, and Urgent HF Visit



No. at Risk							
Placebo	614	524	416	305	195	100	25
Sotagliflozin	608	540	430	310	209	97	29

Bhatt DL, et al. *N Engl J Med*. 2021;384:117-128.

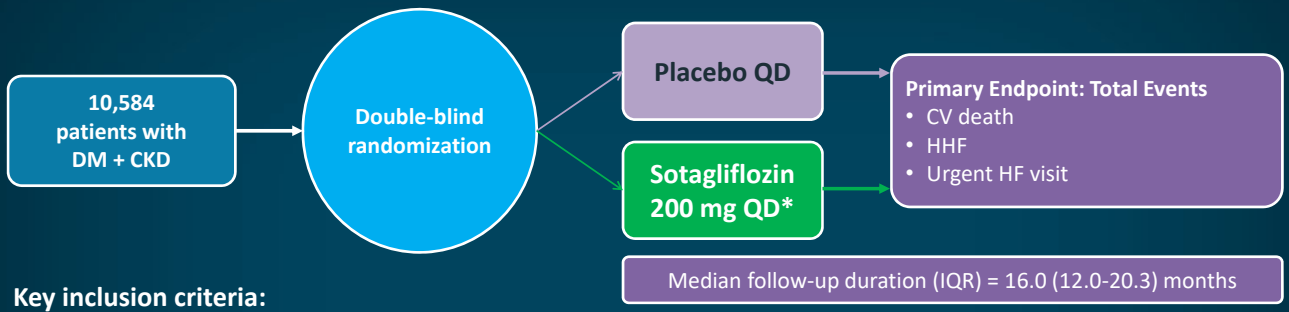
SOLOIST-WHF: First Occurrence of Either Death From CV Causes or HHF



No. at Risk							
Placebo	614	461	345	241	144	66	14
Sotagliflozin	608	498	374	266	171	76	25

Bhatt DL, et al. *N Engl J Med*. 2021;384:117-128.

SCORED: Trial Design



Key inclusion criteria:

- T2D with HbA_{1c} ≥7%
- eGFR 25-60 mL/min/1.73 m^2
  - With no requirement for macro- or microalbuminuria
- CV risk factors

Key exclusion criteria:

- Planned start of SGLT2 inhibitor

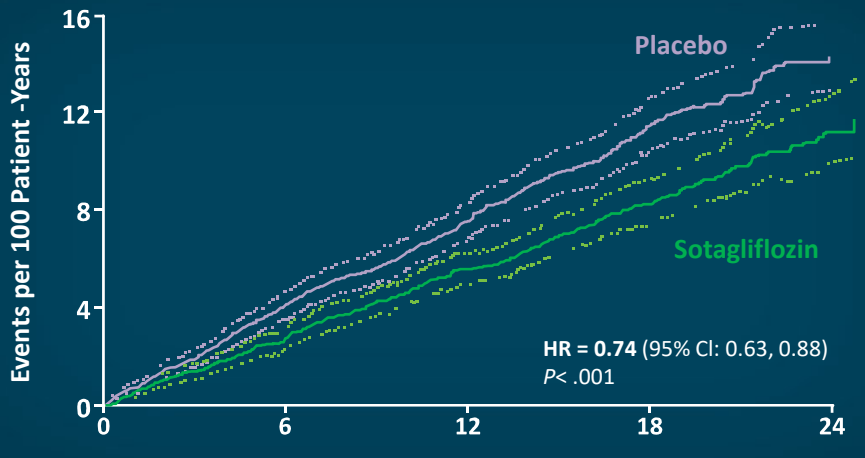
*Goal of dose increase to 400 mg QD.

SCORED = Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk.

Bhatt DL, et al. *N Engl J Med.* 2021;384:129-139. Bhatt DL, et al. AHA 2020, virtual.

SCORED: Primary Efficacy

Total CV Death, HHF, and Urgent HF Visit



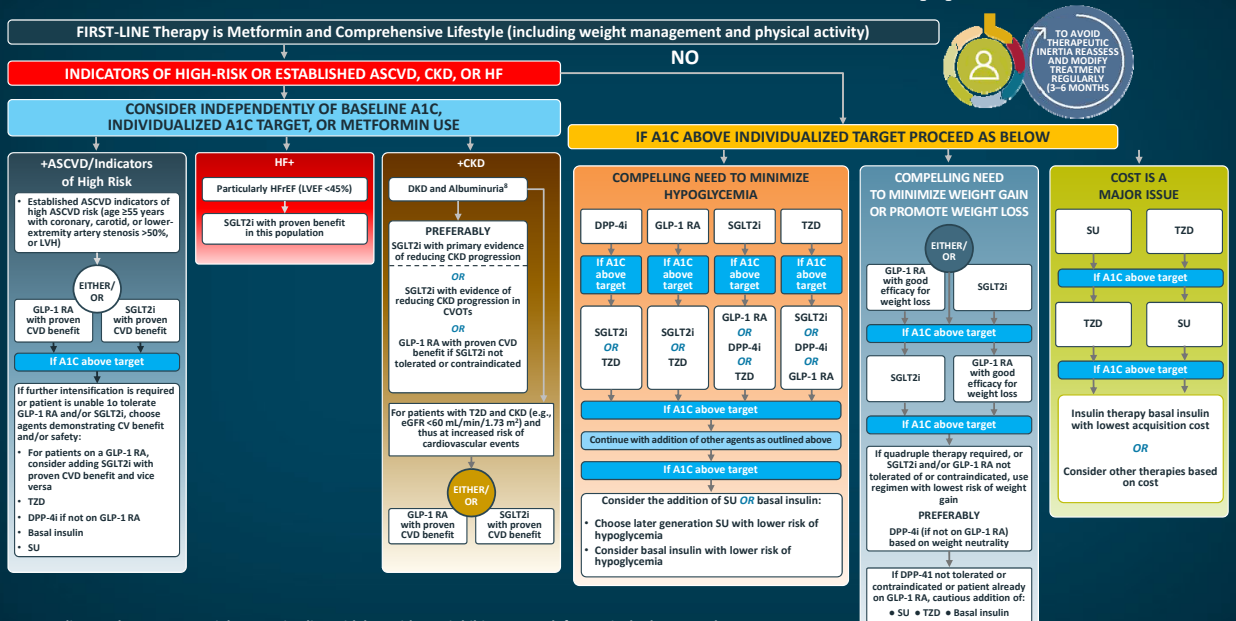
No. at Risk					
Placebo	5292	5160	3914	2061	441
Sotagliflozin	5292	5197	3965	2085	444

ARR = annualized relapse rate.

Bhatt DL, et al. *N Engl J Med.* 2021;384:129-139.

Current Guidelines

ADA 2021 Standards of Care: Overall Approach



CVOTs = cardiovascular outcomes trials; DPP-4i = dipeptidyl peptidase 4 inhibitor; LVH = left ventricular hypertrophy; SGLT2i = SGLT2 inhibitor; SU = sulfonylurea; TZD = thiazolidinedione.

American Diabetes Association (ADA). *Diabetes Care.* 2021;44(suppl 1):S111-S124.

ESC Guidelines 2019

Recommendations for Glucose-Lowering Treatment for Patients With DM

Recommendations	COR	LOE
SGLT2 inhibitor agents		
Empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with T2DM and CVD, or those at very high/high CV risk, to reduce CV events	I	A
Empagliflozin is recommended in patients with T2DM and CVD to reduce risk of death	I	B
GLP-1 RA agents		
Liraglutide, semaglutide, or dulaglutide are recommended in patients with T2DM and CVD, or those at very high/high CV risk, to reduce CV events	I	A
Liraglutide is recommended in patients with T2DM and CVD, or those at very high/high CV risk, to reduce the risk of death	I	B
Biguanides		
Consider metformin in patients with T2DM who are overweight, without CVD, and at moderate CV risk	IIa	C
Insulin		
Insulin-based glycemic control should be considered in patients with ACS with significant hyperglycemia (>180 mg/dL [>10 mmol/L]), adapting target according to comorbidities	IIa	C
TZDs		
TZDs are not recommended in patients with HF	III	A
DPP-4i		
Saxagliptin is not recommended in patients with T2DM and a high risk of HF	III	B

Class of Recommendation (COR)	
I	Recommended or is indicated
IIa	Should be considered
IIb	May be considered
III	Is not recommended

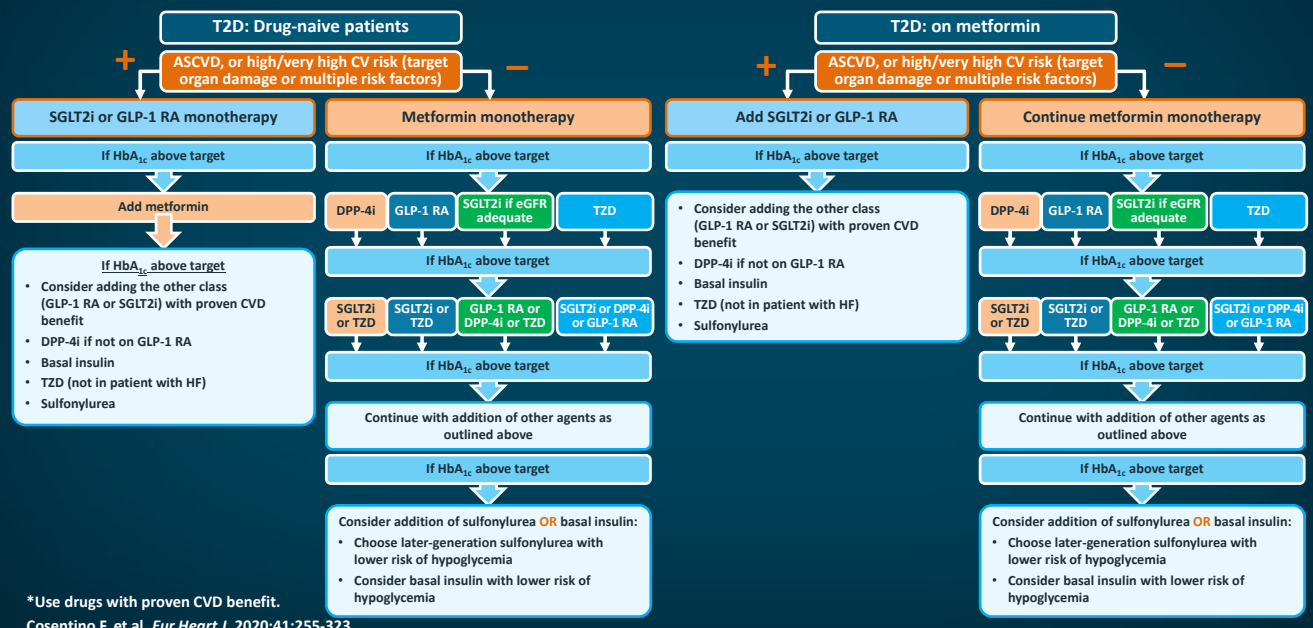
Level of Evidence (LOE)	
A	Multiple RCTs and meta-analyses
B	Single RCT or large non-randomized studies
C	Expert opinion and/or small and/or retrospective studies, registries

ESC = European Society of Cardiology; RCT = randomized controlled trial.

Cosentino F, et al. *Eur Heart J.* 2020;41:255-323.

ESC Guidelines 2019

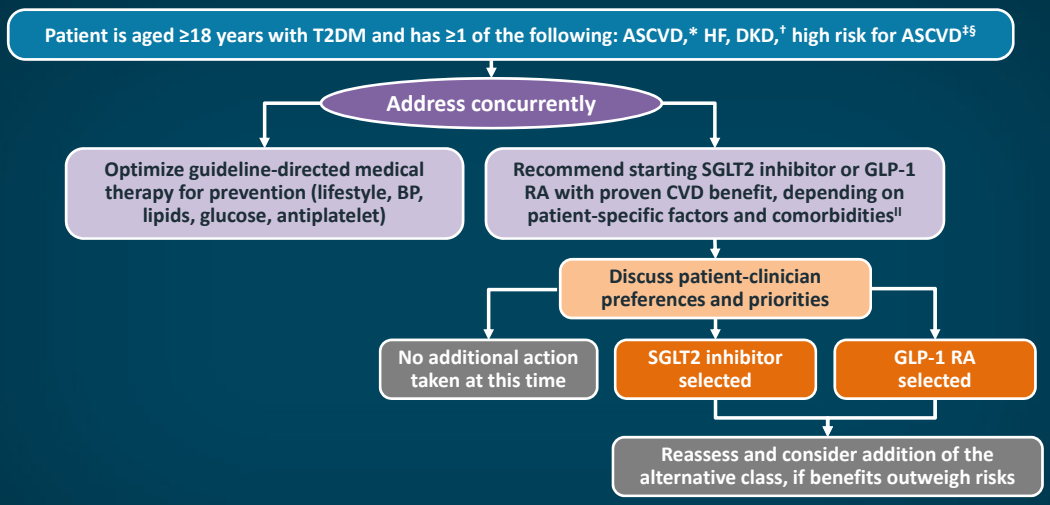
Recommended Treatment Pathway in Patients With T2D



*Use drugs with proven CVD benefit.

Cosentino F, et al. *Eur Heart J.* 2020;41:255-323.

American College of Cardiology Clinical Decision Pathway



*ASCVD is defined as a history of ACS or MI, stable or unstable angina, coronary heart disease ± revascularization, other arterial revascularization, stroke, or PAD assumed to be atherosclerotic in origin. †DKD is clinical diagnosis marked by reduced eGFR, presence of albuminuria, or both. ‡Consider an SGLT2 inhibitor when patient has established ASCVD, HF, DKD, or is at high risk for ASCVD, and consider a GLP-1 RA when your patient has established ASCVD or is at high risk for ASCVD. §Patients at high risk for ASCVD include those with end-organ damage (eg, LVH or retinopathy) or with multiple CV risk factors (eg, age, hypertension, smoking, dyslipidemia, obesity). ‖Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

Das SR, et al. *J Am Coll Cardiol*. 2020;76:1117-1145.

AHA/ACC Guideline on the Primary Prevention of CVD

Recommendations for Adults With T2DM		
COR	**LOE**	**Recommendations**
I	A	1. For all adults with T2DM, a tailored nutrition plan focusing on a heart-healthy dietary pattern is recommended to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors.
I	A	2. Adults with T2DM should perform at least 150 min/wk of moderate-intensity physical activity or 75 minutes of vigorous-intensity physical activity to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors.
IIa	B-R	3. For adults with T2DM, it is reasonable to initiate metformin as first-line therapy along with lifestyle therapies at the time of diagnosis to improve glycemic control and reduce ASCVD risk.
IIb	B-R	4. For adults with T2DM and additional ASCVD risk factors who require glucose-lowering therapy despite initial lifestyle modifications and metformin, it may be reasonable to initiate an SGLT2 inhibitor or a GLP-1 RA to improve glycemic control and reduce CVD risk.

Class of Recommendation (COR)	
I (strong)	Recommended or is indicated
IIa (moderate)	Is reasonable and can be useful
IIb (weak)	May be reasonable and may be considered

Level of Evidence (LOE)	
A	Multiple RCTs and meta-analyses
B-R	≥1 RCT or meta-analyses of moderate-quality RCTs

AHA/ACC = American Heart Association/American College of Cardiology.

Arnett DK, et al. *J Am Coll Cardiol*. 2019;74:e177-e232.

SGLT2 Inhibitor Use in Patients With COVID-19

SGLT2 inhibitors

- These include canagliflozin, dapagliflozin, and empaglifiozin
- There is a risk of dehydration and diabetic ketoacidosis during illness, so patients should stop taking the drugs and follow sick day rules
- Patients should avoid initiating therapy during respiratory illness
- Renal function should be carefully monitored for acute kidney injury

Bornstein SR, et al. *Lancet Diabetes Endocrinol.* 2020;8:546-550.

Cross-Specialty Coordination

"From the patient's perspective, there is a great need for coordination and facilitation of the care, not only to reduce disease progression but also to improve quality of life. Person-centred integrated clinics for patients with cardiovascular disease, renal dysfunction and diabetes are a promising approach for complex chronic disease management."

Novel combined management approaches to patients with diabetes, chronic kidney disease and cardiovascular disease

J Spaak[1]

Spaak J. *J R Coll Physicians Edinb.* 2017;47:83-87.

Case 1: EP

- 74-year-old man with a 1-year history of T2DM who recently developed worsening DOE and pedal edema
- Past medical history
  - NSTEMI ≈1 year ago: DES x 2, Circ and LAD
  - Hypertension
  - Hypercholesterolemia
  - Prior smoker (quit 1 year ago)
- Medications
  - Atorvastatin 40 mg/d
  - Losartan 100 mg/d
  - Metoprolol XR 100 BID
  - Aspirin 81 mg/d
  - Ticagrelor 60 mg BID
  - Metformin 1,000 mg BID

Case 1: EP
(continued)

- Physical examination
  - BMI: 37.4 kg/m^2
  - BP: 144/2 mm Hg
  - Heart: normal S1, S2, no murmurs
  - Lungs: clear
  - Extremities: pulses diminished, 1-2+ edema bilaterally
- Laboratory results
  - Fasting plasma glucose: 154 mg/dL
  - HbA_{1c}: 7.4%
  - CMP, CBC normal
  - LDL-C: 101; HDL-C: 40; TG: 198
  - eGFR: 58 mL/min/1.73 m^2; UACR: 31 mg/g

Case 1: EP—Questions to Consider

- What is an optimal HbA1c for this patient?
- Should his metformin be stopped or adjusted?
- Is this patient a candidate for an SGLT2 inhibitor?
- What clinical considerations would lead you to select an SGLT2 inhibitor?

Key Points

- CVD, HF, and CKD remain leading complications of DM associated with increased morbidity, mortality and costs.
- CVD, HF, and CKD often co-exist, complicating management. Drugs with beneficial effects that overlap these complications are highly desirable.
- Guidelines are transitioning from a gluco-centric focus to one emphasizing patient-relevant outcomes, including CVD, HF, and CKD.
- SGLT2 inhibitors have proven benefits to reduce risk for CVD, HHF, and CKD progression and should be considered in high-risk patients regardless of glycemic control.

SGLT2 Inhibitors:
Reviewing Their Role in Type 2 Diabetes, Heart Failure, and Chronic Kidney Disease

Diabetes and Cardiovascular Disease/Risk

Reference	Address
Afkarian M, Sachs MC, Kestenbaum B, et al. Kidney disease and increased mortality risk in type 2 diabetes. *J Am Soc Nephrol*. 2013;24(2):302-308.	https://pubmed.ncbi.nlm.nih.gov/23362314/
American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes-2021*. *Diabetes Care*. 2021;44(suppl 1):S111-S124.	https://pubmed.ncbi.nlm.nih.gov/33298420/
Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2019;74:e177-e232.	https://www.sciencedirect.com/science/article/pii/S073510971933877X
Baigent C. Addressing the remaining questions on SGLT2 & CKD: A review of new outcome trials. Presented at: ERA-EDTA; June 27, 2018; Copenhagen, Denmark.	https://pace-cme.org/2018/06/27/slides-addressing-the-remaining-questions-on-sglt2-ckd-a-review-of-new-outcome-trials//download-slides-addressing-the-remaining-questions-on-sglt2-ckd-a-review-of-new-outcome-trials.pdf
Bauters C, Lamblin N, Mc Fadden EP, Van Belle E, Millaire A, de Groote P. Influence of diabetes mellitus on heart failure risk and outcome. *Cardiovasc Diabetol*. 2003;2:1.	https://pubmed.ncbi.nlm.nih.gov/12556246/
Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med*. 2021;384(2):117-128	https://pubmed.ncbi.nlm.nih.gov/33200892/
Bhatt DL, Verma S, Braunwald E. The DAPA-HF trial: A momentous victory in the war against heart failure. *Cell Metab*. 2019;30(5):847-849	https://pubmed.ncbi.nlm.nih.gov/31693879/
Bornstein SR, Rubino F, Khunti K, et al. Practical recommendations for the management of diabetes in patients with	https://pubmed.ncbi.nlm.nih.gov/32334646/

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Burke KR, Schumacher CA, Harpe SE. SGLT2 inhibitors: A systematic review of diabetic ketoacidosis and related risk factors in the primary literature. *Pharmacotherapy.* 2017;37:187-194.	https://accpjournals.onlinelibrary.wiley.com/doi/abs/10.1002/phar.1881
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Control Group, Turnbull FM, Abraira C, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia*. 2009;52(11):2288-2298.	https://pubmed.ncbi.nlm.nih.gov/19655124/
Cosentino F, Cannon CP, Cherney DZI, et al. Efficacy of ertugliflozin on heart failure-related events in patients with type 2 diabetes mellitus and established atherosclerotic cardiovascular disease: Results of the VERTIS CV trial. *Circulation*. 2020;142(23):2205-2215.	https://pubmed.ncbi.nlm.nih.gov/33026243/
Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J*. 2020;41(2):255-323.	https://pubmed.ncbi.nlm.nih.gov/31497854/
Das SR, Everett BM, Birtcher KK, et al. 2020 Expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes: A report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2020;76(9):1117-1145.	https://pubmed.ncbi.nlm.nih.gov/32771263/

Dauriz M, Targher G, Laroche C, et al. Association between diabetes and 1-year adverse clinical outcomes in a multinational cohort of ambulatory patients with chronic heart failure: Results from the ESC-HFA Heart Failure Long-Term Registry. *Diabetes Care*. 2017;40(5):671-678.	https://pubmed.ncbi.nlm.nih.gov/28255009/
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Clinical Trials

Resource	Address

CANagliflozin cardioVascular Assessment Study (CANVAS) NCT01032629	https://clinicaltrials.gov/ct2/show/NCT01032629
Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CREDENCE) NCT02065791	https://clinicaltrials.gov/ct2/show/NCT02065791
A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease (DAPA-CKD) NCT03036150	https://clinicaltrials.gov/ct2/show/NCT03036150
Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure (DAPA-HF) NCT03036124	https://clinicaltrials.gov/ct2/show/NCT03036124
Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI58) NCT01730534	https://clinicaltrials.gov/ct2/show/NCT01730534
Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure. (DELIVER) NCT03619213	https://clinicaltrials.gov/ct2/show/NCT03619213
The Study of Heart and Kidney Protection With Empagliflozin (EMPA-KIDNEY) NCT03594110	https://clinicaltrials.gov/ct2/show/NCT03594110
BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) NCT01131676	https://clinicaltrials.gov/ct2/show/NCT01131676
EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction (EMPEROR-Preserved) NCT03057951	https://clinicaltrials.gov/ct2/show/NCT03057951
EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction (EMPEROR-Reduced) NCT03057977	https://clinicaltrials.gov/ct2/show/NCT03057977
Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes	https://clinicaltrials.gov/ct2/show/NCT01986881

Mellitus Participants With Vascular Disease (VERTIS CV) NCT01986881	

Patient Resources

Resource	Address
American Diabetes Association (ADA). Resources.	https://www.diabetes.org/resources
American Diabetes Association (ADA). Diabetes Tools and Resources.	https://www.heart.org/en/health-topics/diabetes/diabetes-tools--resources
American Heart Association (AHA). About Prediabetes.	https://www.heart.org/en/health-topics/diabetes/about-diabetes/about-prediabetes
Association of Diabetes Care & Education Specialists (ADCES). Resources for People Living with Diabetes.	https://www.diabeteseducator.org/living-with-diabetes
Centers for Disease Control and Prevention (CDC). Diabetes.	https://www.cdc.gov/diabetes/index.html

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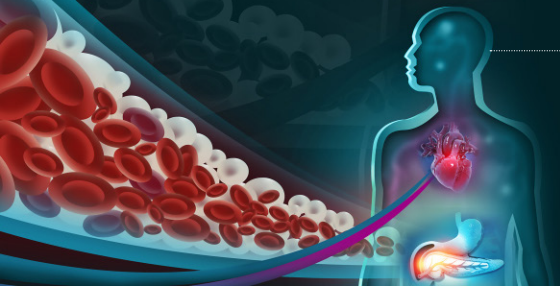

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