First drug in persons with Type 2 Diabetes Mellitus with HF/CKD: Metformin/SGLT2i from a Cardiologist and an Endocrinologist viewpoint.

Dr. Harry Jiménez, FACE

Medical Director HIMA San Pablo, Bayamón

DISCLOSURE

- Harry Jiménez MD, FACE
  - Has received honorarium as Speaker and/or Consultant for the following pharmaceutical companies:
    - Merck
    - Eli Lilly
    - Boehringer Ingelheim
    - Bristol-Myers Squibb
    - AstraZeneca
    - AbbVie
    - Janssen
    - Sanofi

OBJECTIVES

- Review SGLT2 clinical trial results.
- Discuss the ADA 2020 diabetic clinical guidelines and AACE 2020 clinical guidelines, European Society of Cardiology and European Association for the Study of Diabetes: New Guidelines 2019
- To give an opinion when Metformin or SGLT2 inhibitors could be the first drug for the treatment of diabetes type 2 mellitus

Cardiovascular benefits of Metformin:

Lessons from the UKPDS: positive legacy effect of early metformin therapy in patients with type 2 diabetes

UKPDS Trial Intervention 1977–1997

↓ Diabetes-related deaths (-42%)
↓ All-cause mortality (-36%)
↓ Myocardial infarction (-39%)

CV complications reduced and survival increased versus other therapies

UKPDS POST-Trial Monitoring 1977–2007

↓ Diabetes-related deaths (-30%)
↓ All-cause mortality (-27%)
↓ Myocardial infarction (-33%)

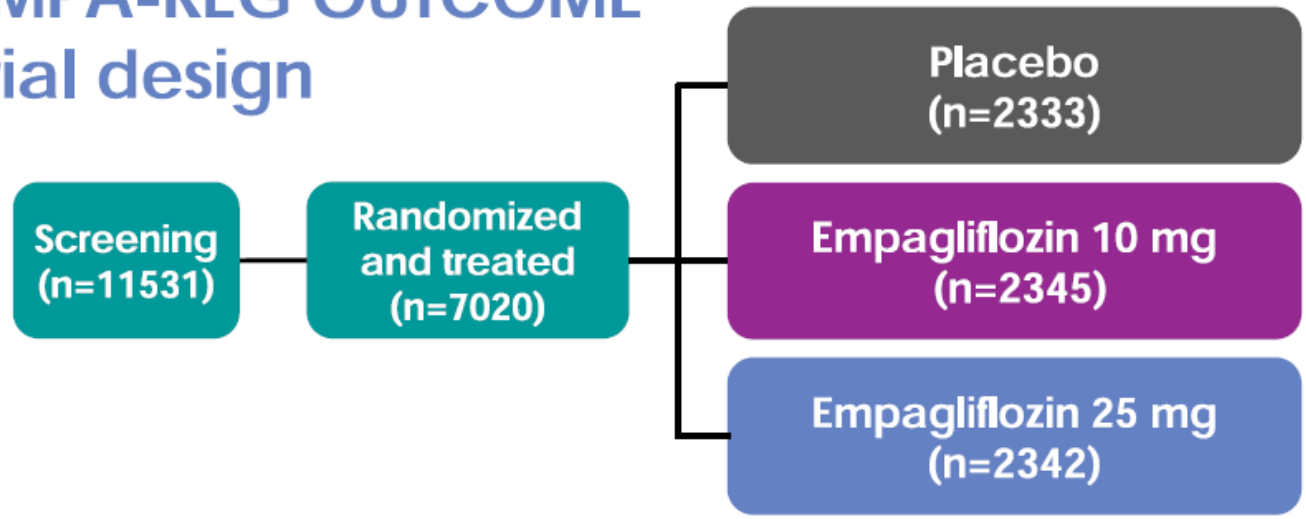
CV complications reduced and survival increase maintained

GLINT 2015–2022

Primary Prevention Trial in patients with Pre-diabetes and high CVD risk

UKPDS 34. Lancet 1998;352:854–65.
Holman RR, et al. UKPDS 80. N Engl J Med 2008;359:1577–89.
http://www.dtu.ox.ac.uk/GLINT/ (accessed 2014 Oct 12).

EMPA-REG OUTCOME®
Trial design

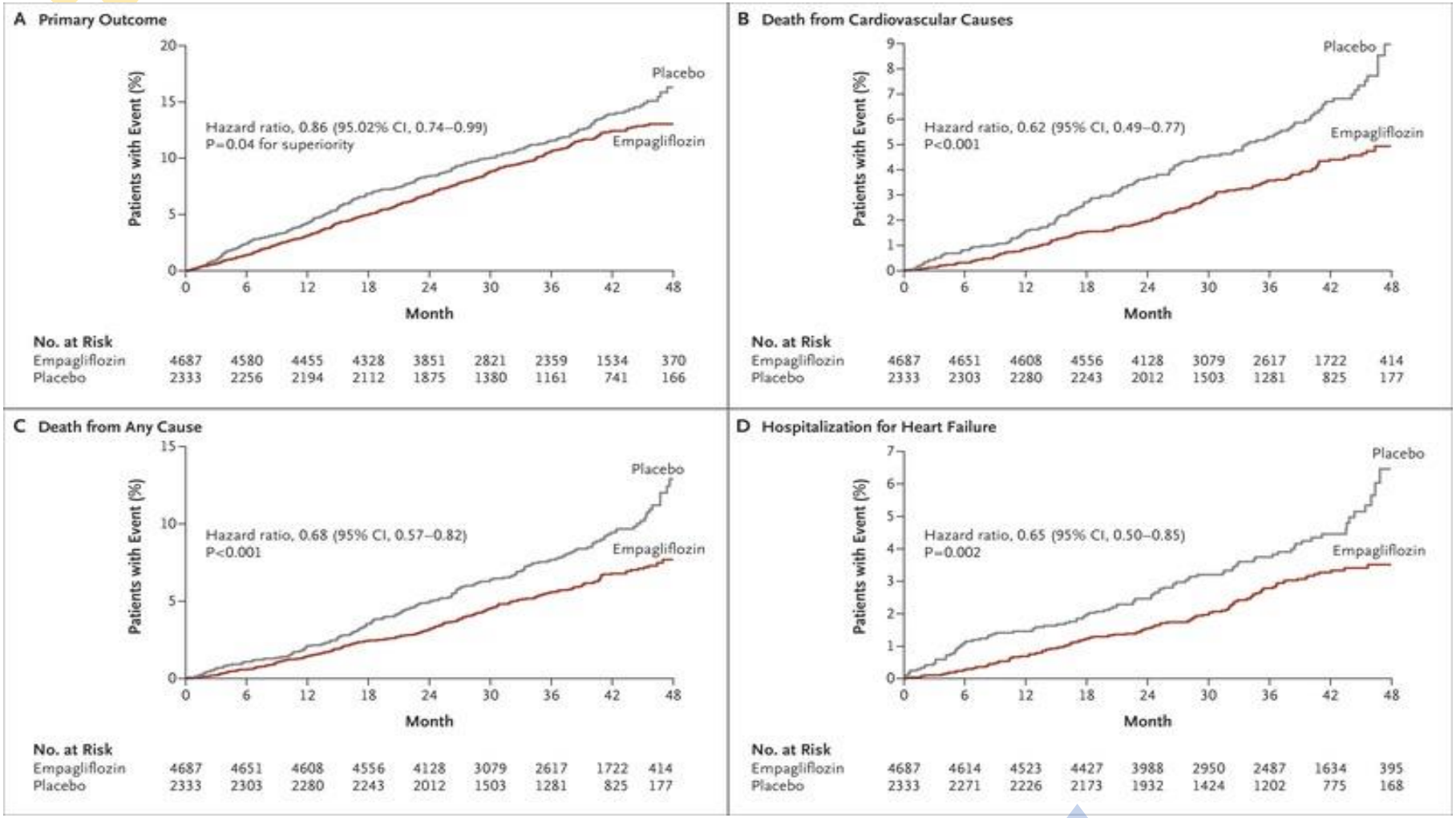


- **Study medication was given in addition to standard of care.**
- **The trial was to continue until ≥ 691 patients experienced an adjudicated primary outcome event.**
- **Key inclusion criteria:**
  - Adults with type 2 diabetes and established CVD
  - BMI ≤45 kg/m^2; HbA1c 7–10%; eGFR ≥30 mL/min/1.73m^2 (MDRD)

CV, cardiovascular; BMI, body mass index; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.
Zinman B et al. N Engl J Med 2015 [Epub ahead of print].

EMPA-REG OUTCOME®

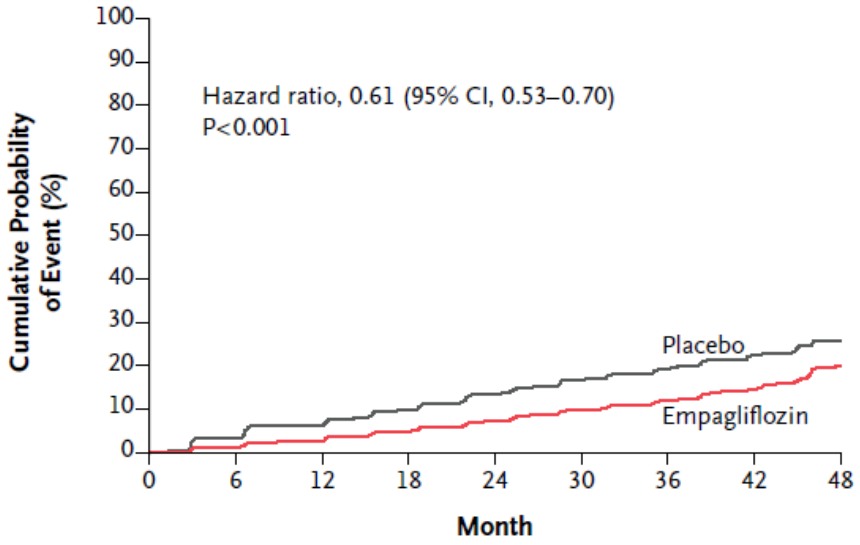
EMPA-REG OUTCOME: Trial Design



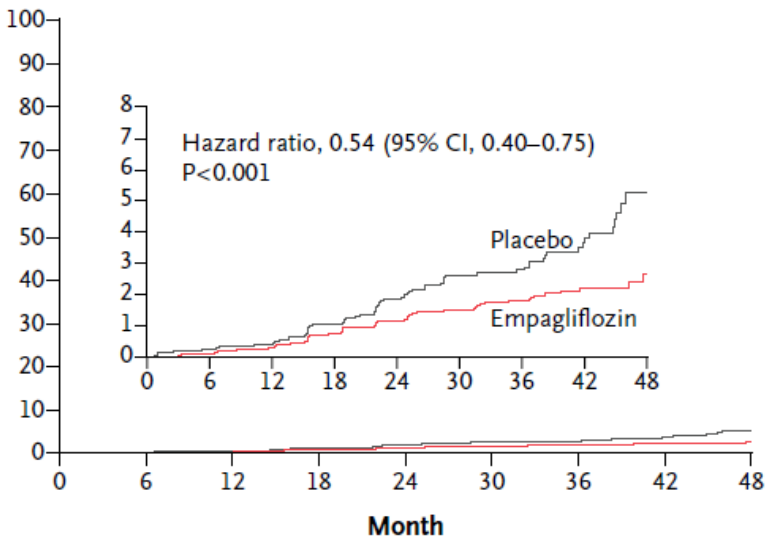
Renal Outcomes with Empagliflozin

EMPA-REG RENAL (N=7020)

Incident or Worsening Nephropathy



Post-hoc Renal Composite Outcome*



No. at Risk

Empagliflozin	4124	3994	3848	3669	3171	2279	1887	1219	290	4645	4500	4377	4241	3729	2715	2280	1496	360
Placebo	2061	1946	1836	1703	1433	1016	833	521	106	2323	2229	2146	2047	1771	1289	1079	680	144

*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; SCr, serum creatinine.

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

CANVAS: Study design

Aim
To determine CV risk associated with canagliflozin

Compound-specific

Main inclusion criteria[1]

1. Patients with T2D
2. Age ≥ 30 years with history of symptomatic atherosclerotic vascular disease
   or ≥ 50 years with 2 or more risk factors for CVD

Stable dose of background antihyperglycaemic agents administered for 8 weeks prior to screening

In addition to usual care for T2D, patients randomised 1:1:1 to

Canagliflozin (100 mg) | Canagliflozin (300 mg) | Placebo

N = 4365[2]; expected duration of follow-up 6-7 years

Primary endpoint: time to first occurrence of[1]**:**

- CV-related death
- Non-fatal stroke
- Non-fatal MI

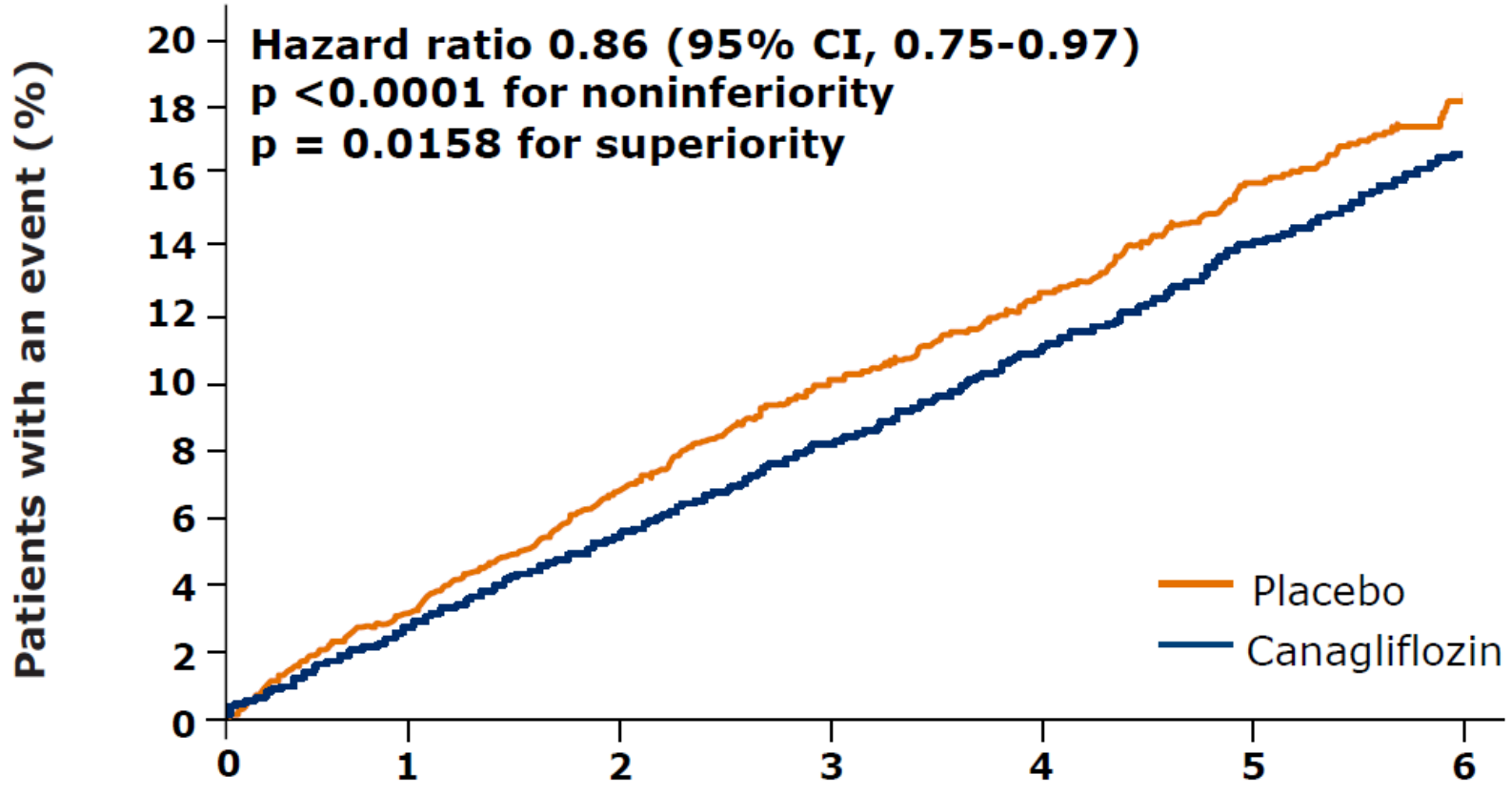
1. Neal et al. Am Heart J 2013;166:217–223.e11. 2. NCT01032629.

Back

ACROSS T2D

Primary MACE Outcome

CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke

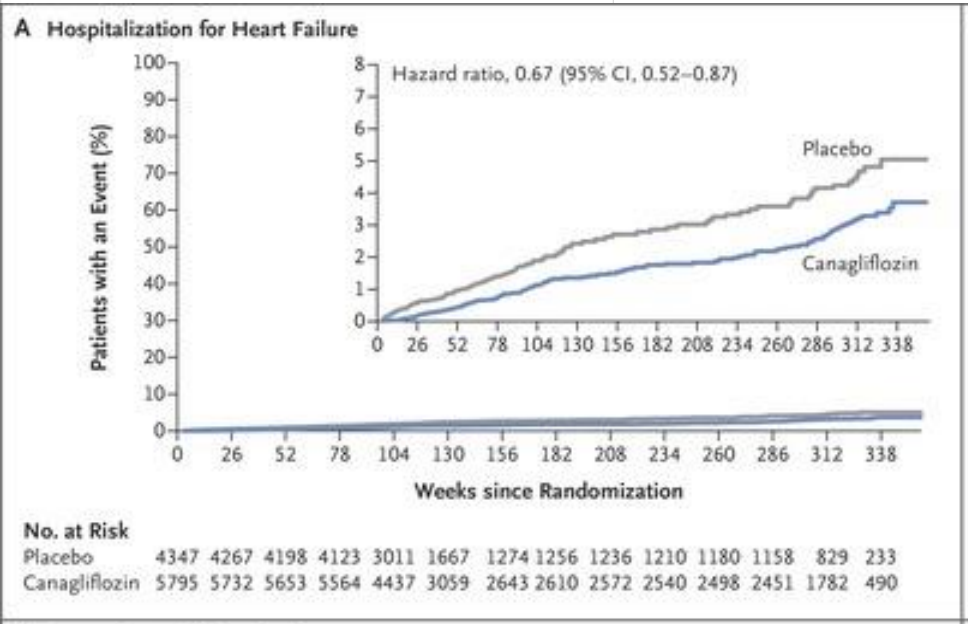


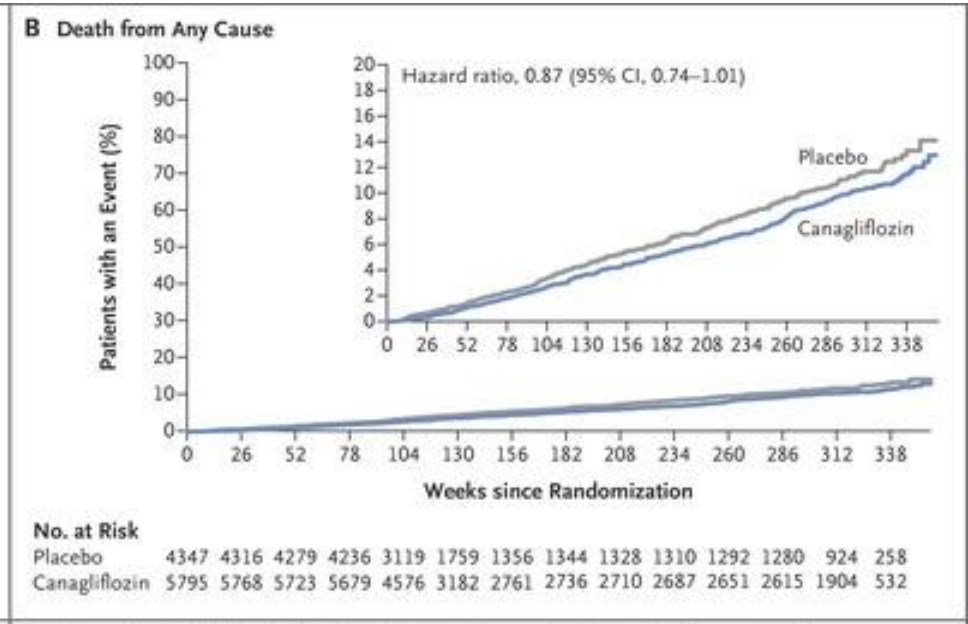
No. of patients							
Placebo	4347	4153	2942	1240	1187	1120	789
Canagliflozin	5795	5566	4343	2555	2460	2363	1661

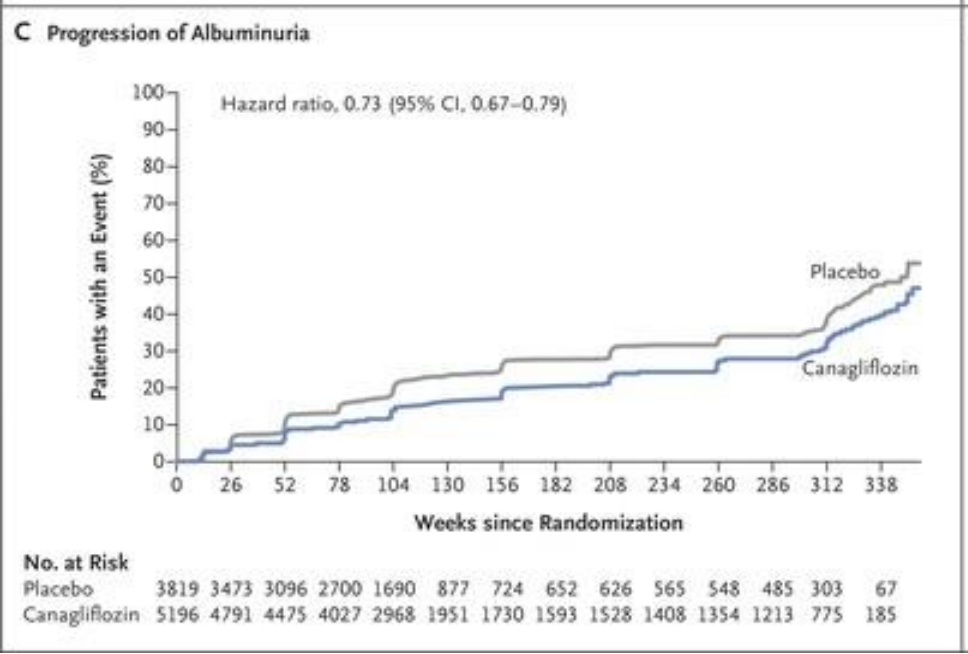
Intent-to-treat analysis

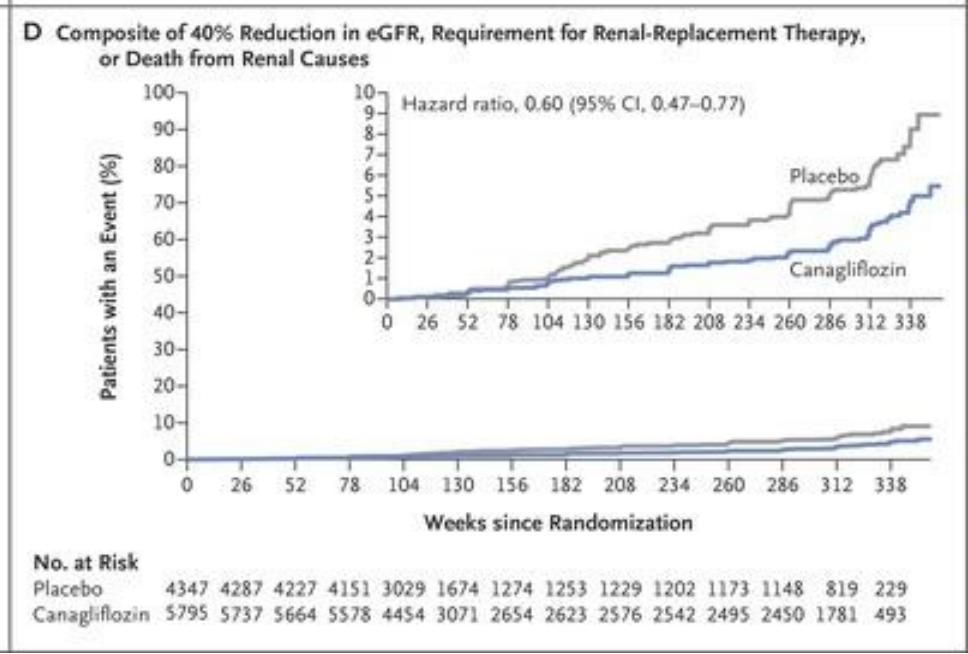
CANVAS Program

CANVAS Outcome Trial Design

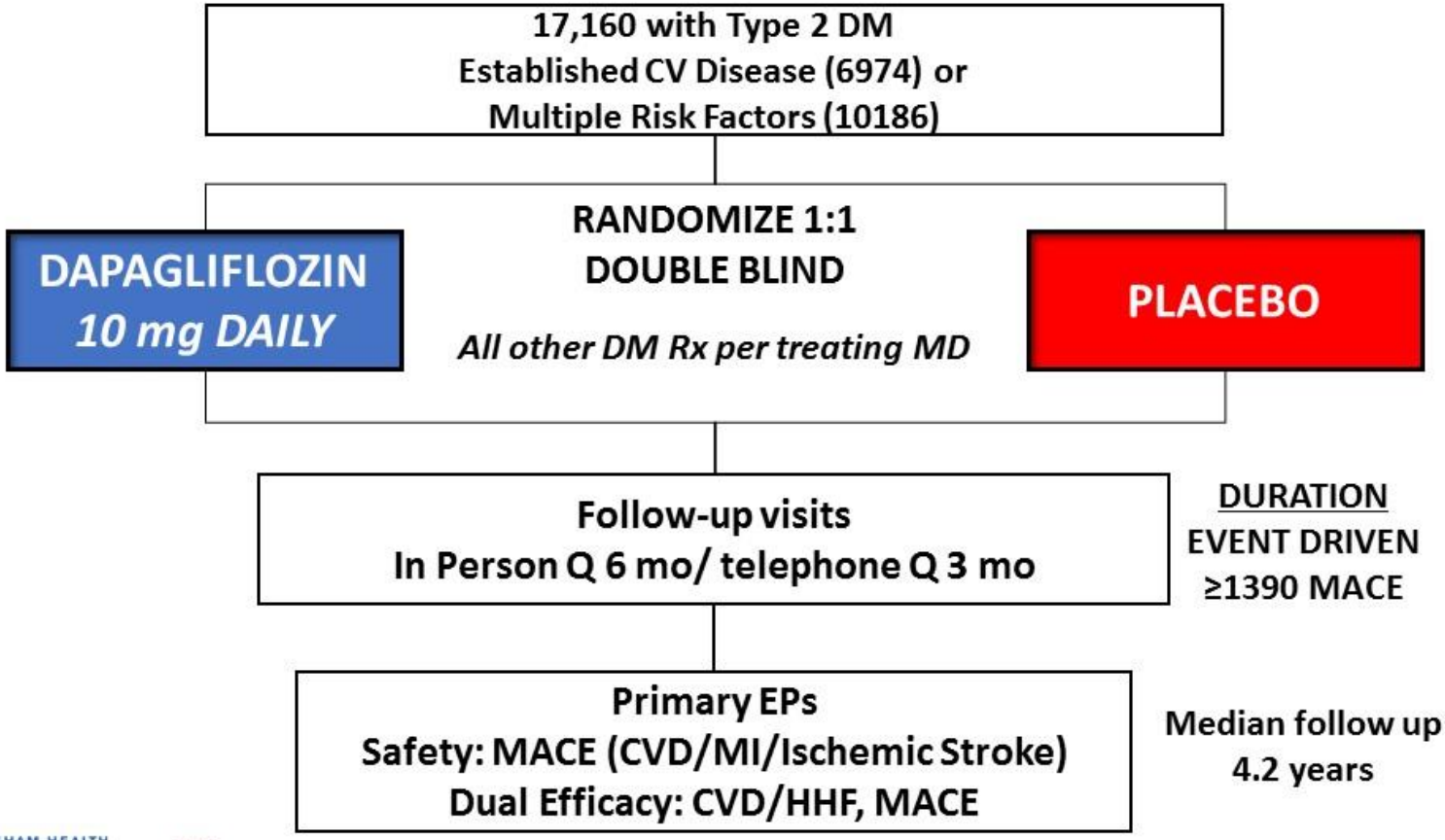








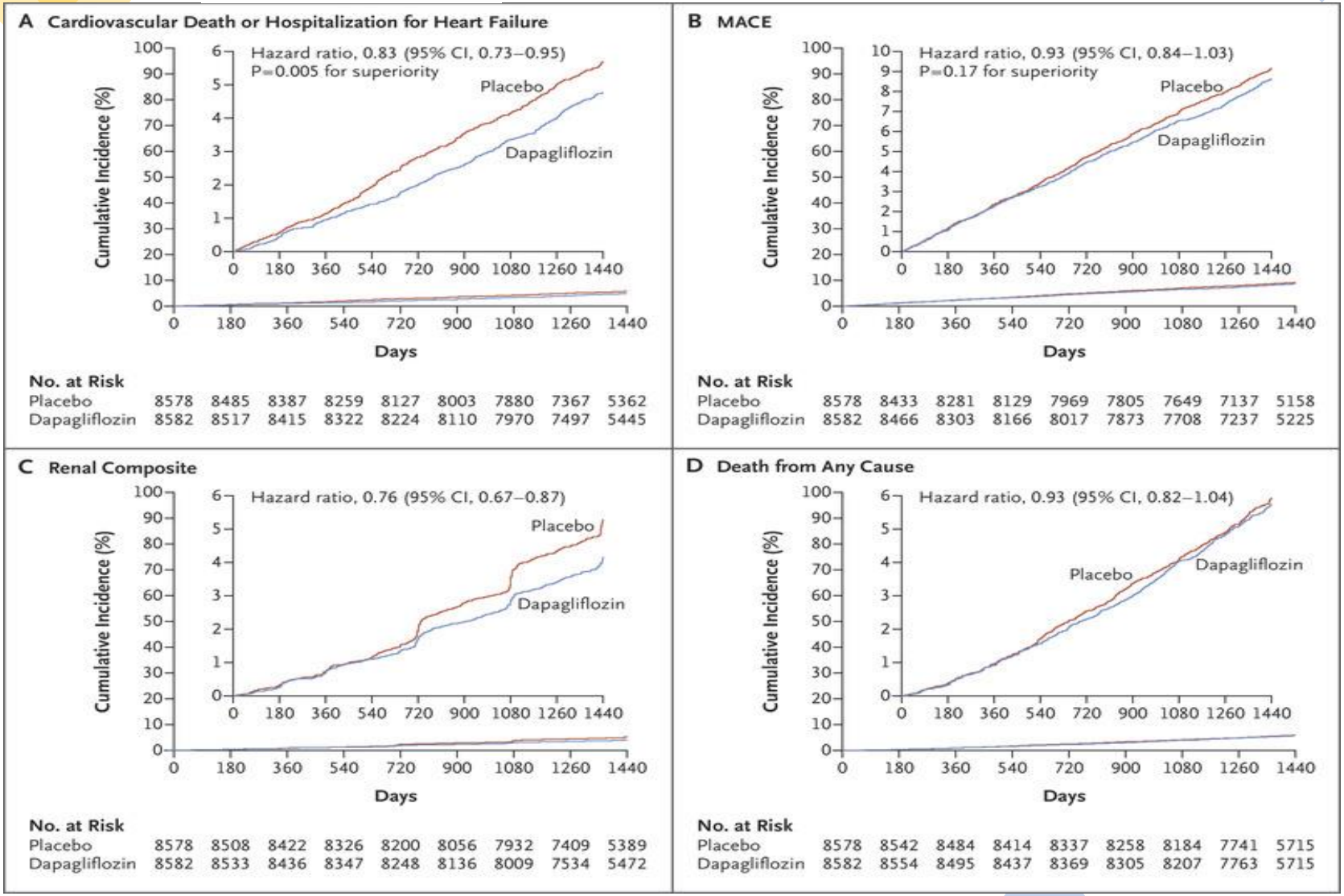
Trial Design



BRIGHAM HEALTH
BRIGHAM AND WOMEN'S HOSPITAL
HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Wiviott SD, Raz I...Sabatine MA, *AHJ* 2018

Outcome Trial Design



Study Design

CREDENCE

Key inclusion criteria
- ≥30 years of age
- T2DM and HbA1c 6.5% to 12.0%
- eGFR 30 to 90 mL/min/1.73 m^2
- UACR 300 to 5000 mg/g
- Stable max tolerated labelled dose of ACEi or ARB for ≥4 weeks

Key exclusion criteria
- Other kidney diseases, dialysis, or kidney transplant
- Dual ACEi and ARB; direct renin inhibitor; MRA
- Serum K^+ >5.5 mmol/L
- CV events within 12 weeks of screening
- NYHA class IV heart failure
- Diabetic ketoacidosis or T1DM

2-week placebo run-in

R

Double-blind randomization (1:1)

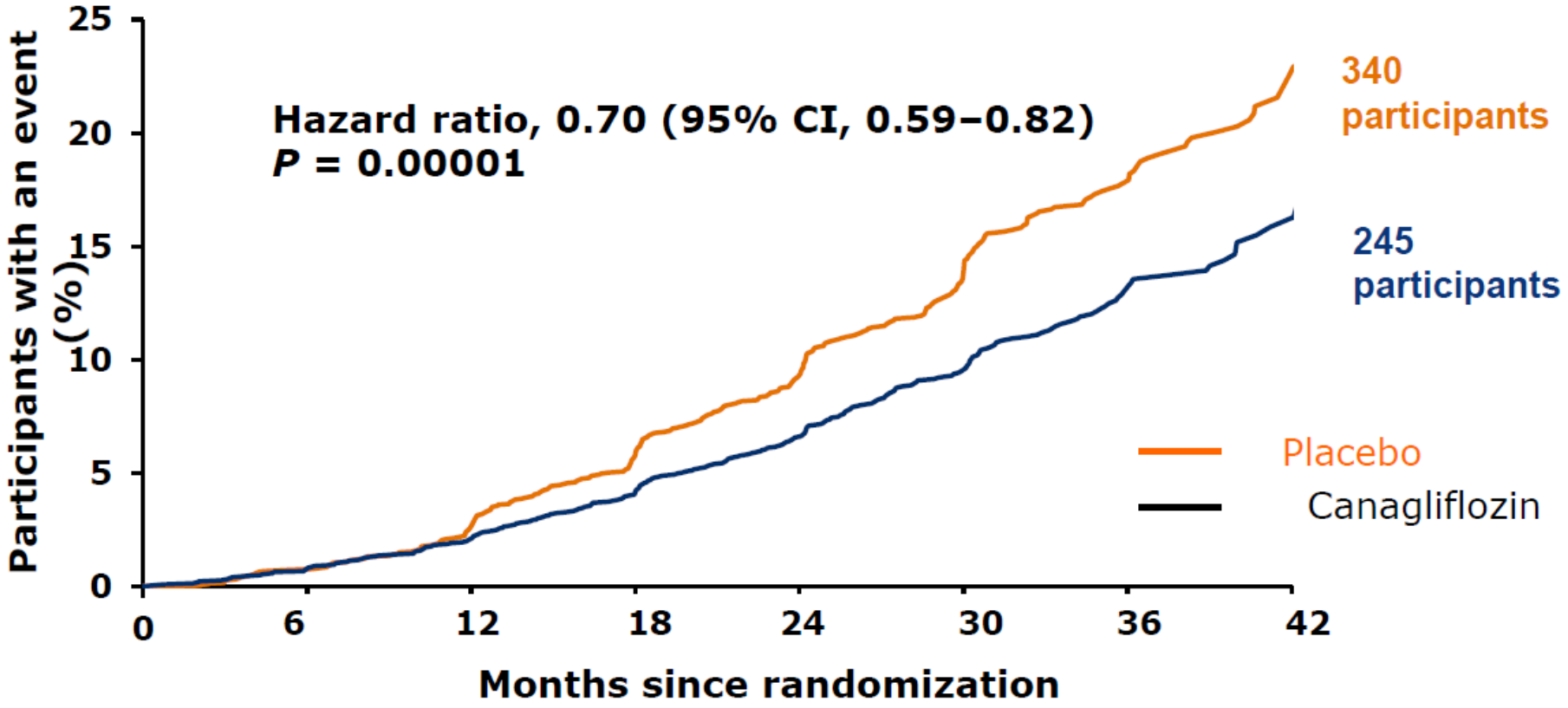
Canagliflozin 100 mg

Placebo

then every 13 weeks (alternating phone/F2F)

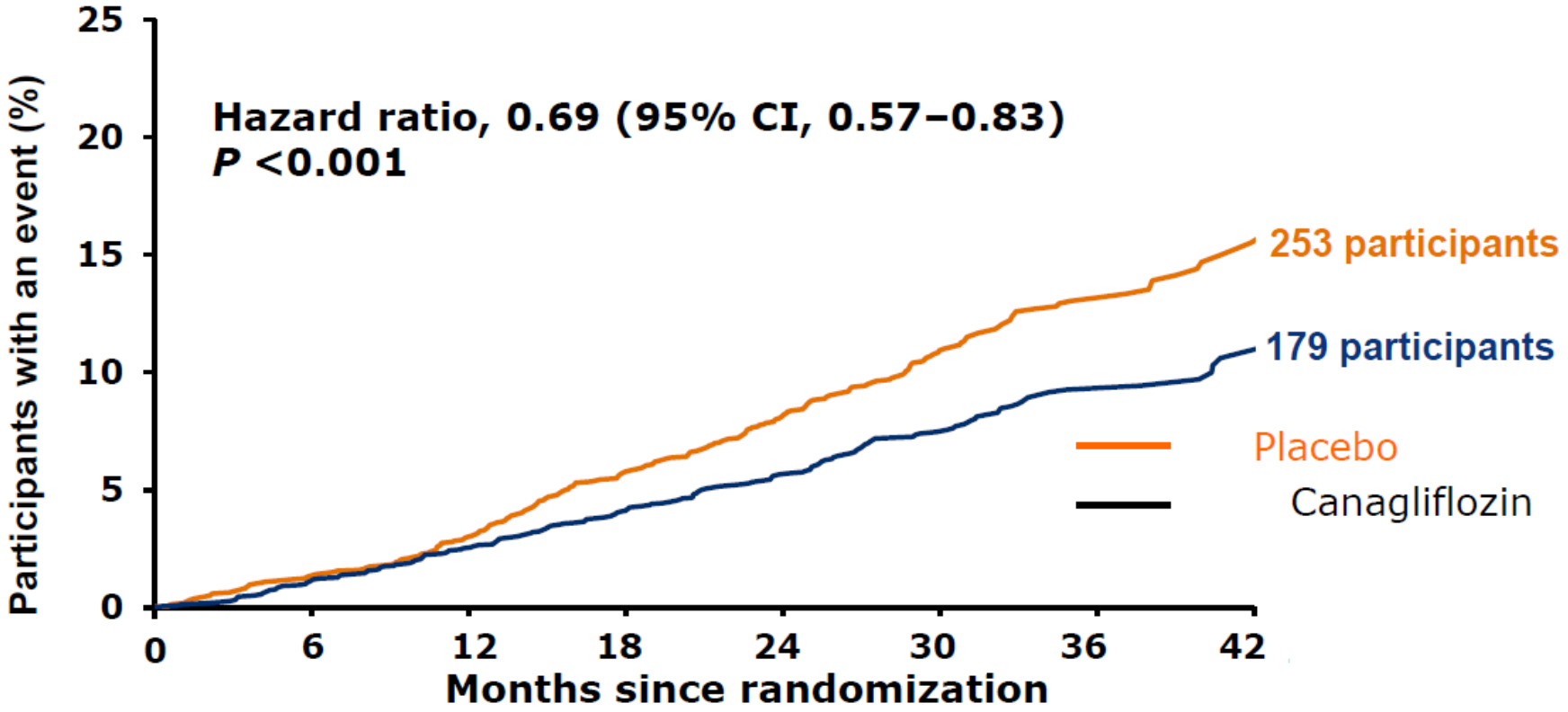
Participants continued treatment if eGFR was <30 mL/min/1.73 m^2 until chronic dialysis was initiated or kidney transplant occurred.

Primary Outcome:
ESKD, Doubling of Serum Creatinine, or Renal or CV Death



No. at risk								
Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

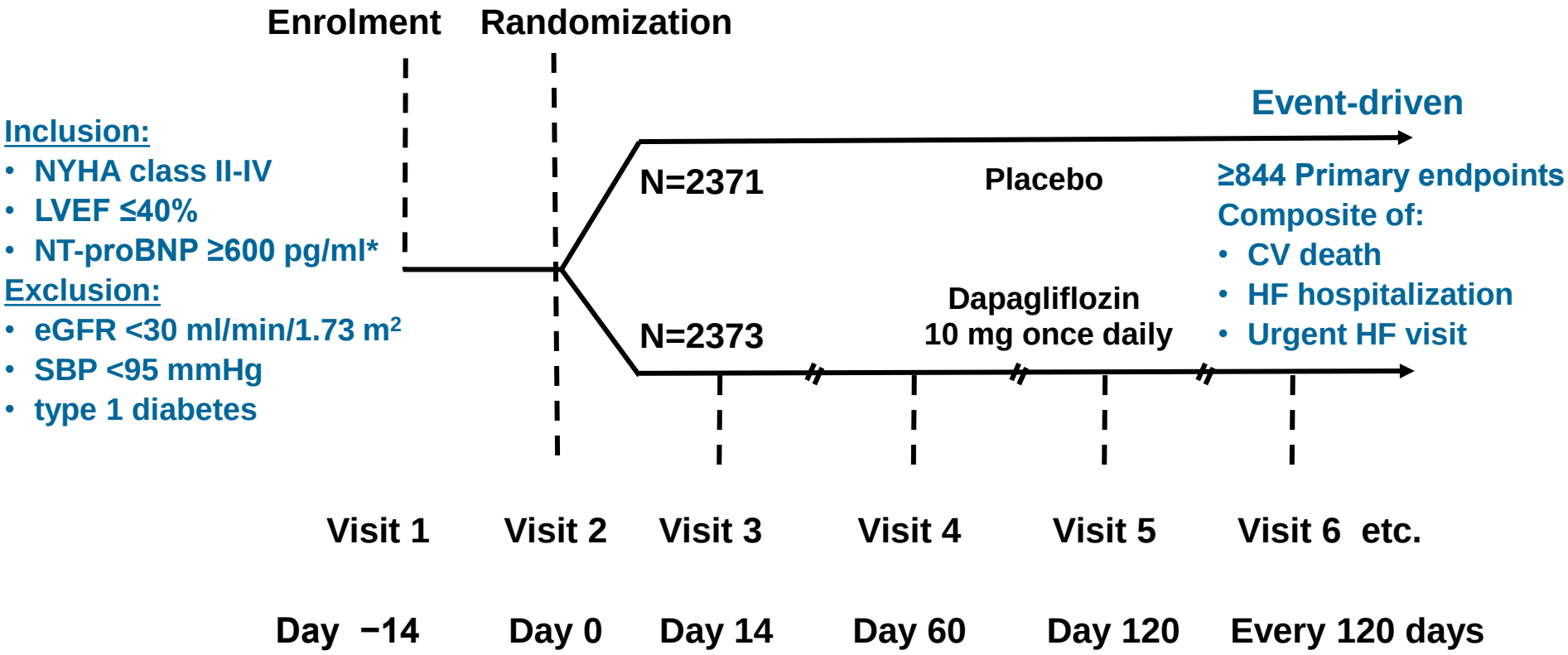
CV Death or Hospitalization for Heart Failure



No. at risk								
Placebo	2199	2165	2123	2044	1736	1147	638	170
Canagliflozin	2202	2171	2132	2077	1789	1226	668	199

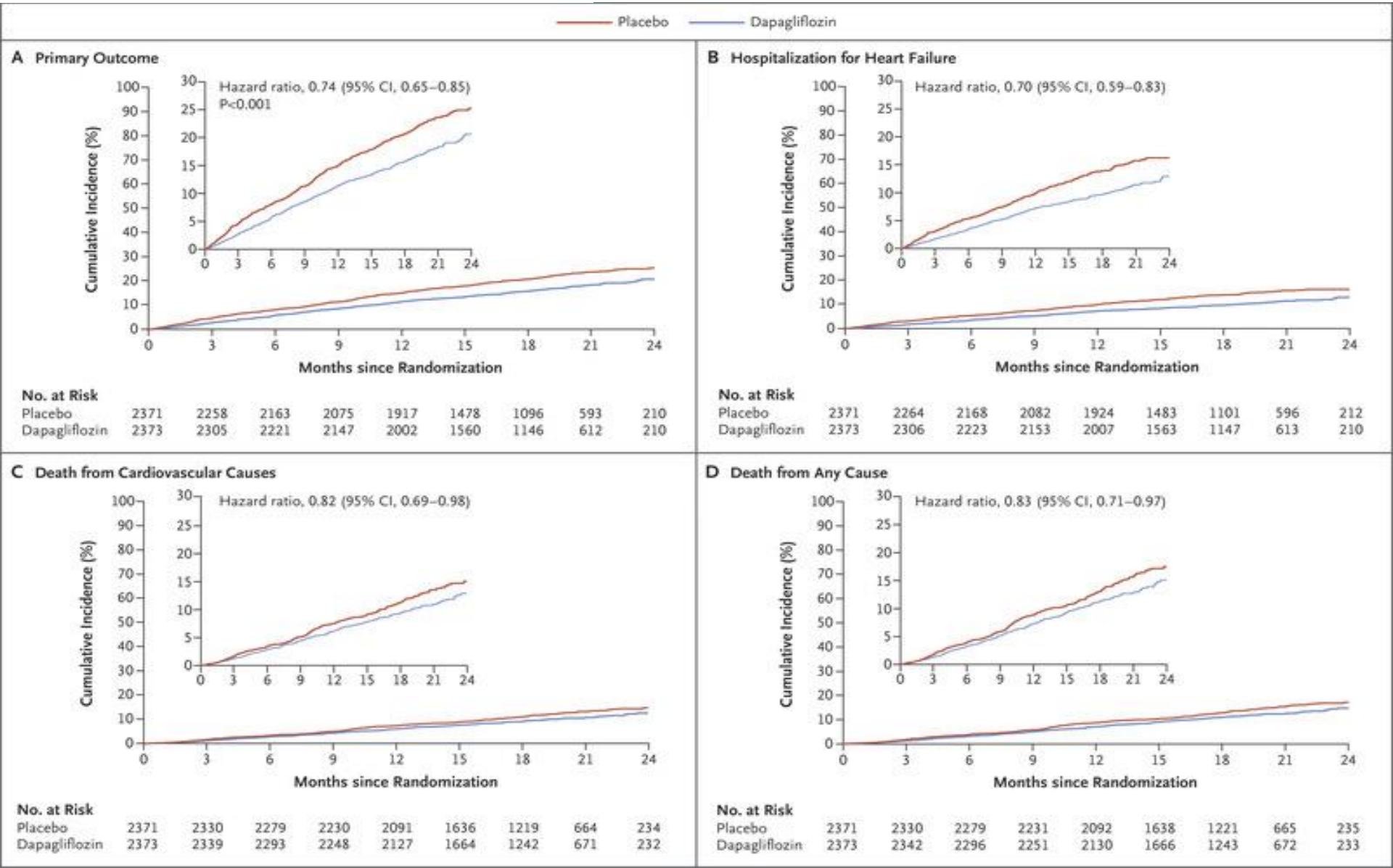
DAPA-HF Design

4,744 patients 20 countries



*≥400 pg/ml if HF hospitalization within ≤12 months; ≥900 pg/ml if atrial fibrillation/flutter

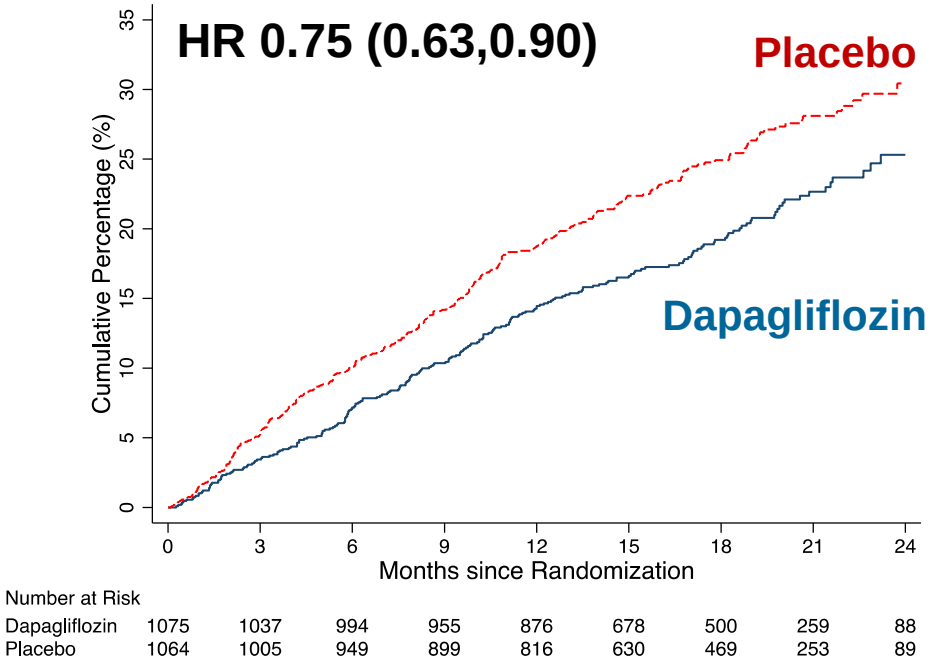
DAPAHF Outcome Trial Design



Primary composite outcome

CV Death/HF hospitalization/Urgent HF visit

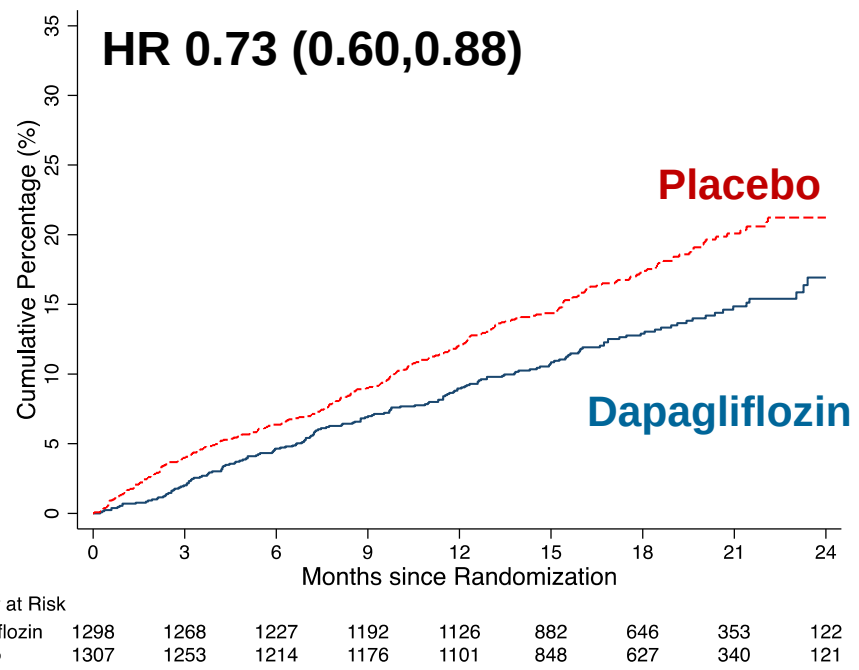
Diabetes



Number at Risk

Dapagliflozin	1075	1037	994	955	876	678	500	259	88
Placebo	1064	1005	949	899	816	630	469	253	89

No Diabetes



Number at Risk

Dapagliflozin	1298	1268	1227	1192	1126	882	646	353	122
Placebo	1307	1253	1214	1176	1101	848	627	340	121

P interaction 0.80

VERTIS

eValuation of ERTugliflozin efficacy and Safety

Presented during American Diabetes Association (ADA) Virtual 80th Scientific Sessions
June 16, 2020

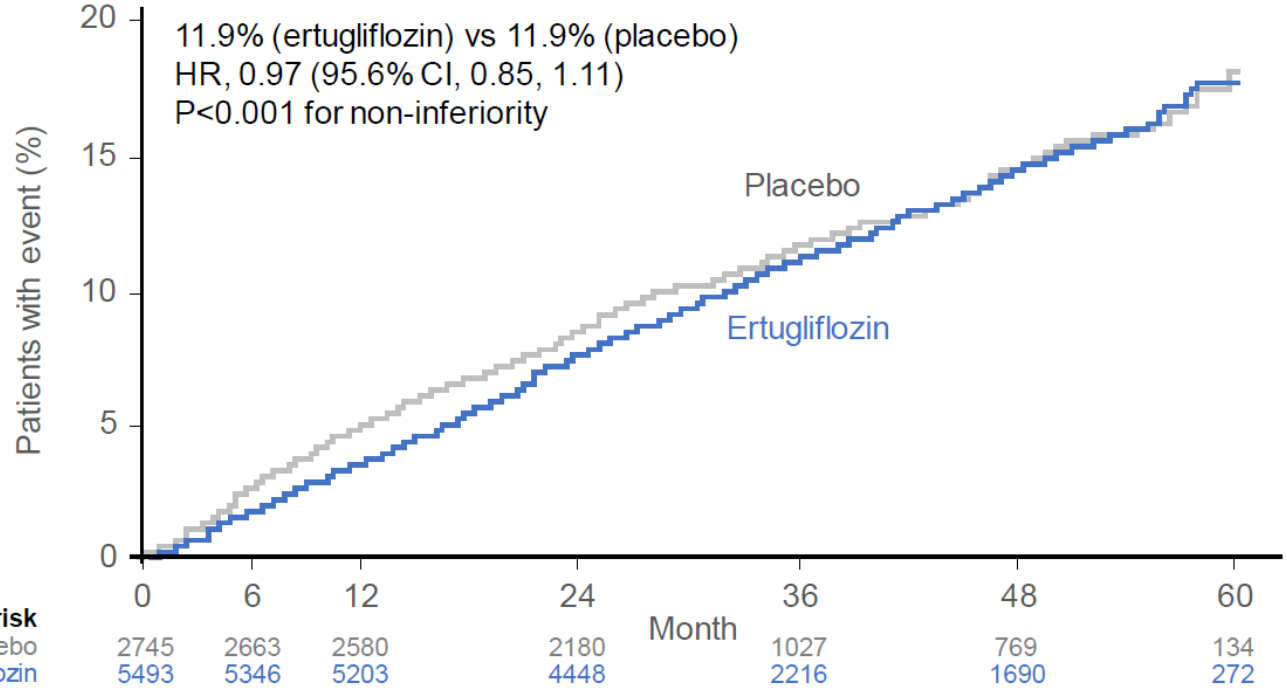
Multicentre, randomised, double-blind, placebo-controlled, event-driven trial.
Key inclusion criteria: T2DM; A1C 53–91 mmol/mol (7.0%–10.5%); age ≥40 years; established atherosclerotic vascular disease in the coronary, cerebral, or peripheral arteries

Primary endpoint (non-inferiority):
- MACE (CV death, nonfatal MI, nonfatal stroke) for non-inferiority.

Secondary endpoints (superiority):
- CV death/heart failure hospitalisation.
- CV death.
- Renal composite (renal death, dialysis/transplant, doubling of serum creatinine).

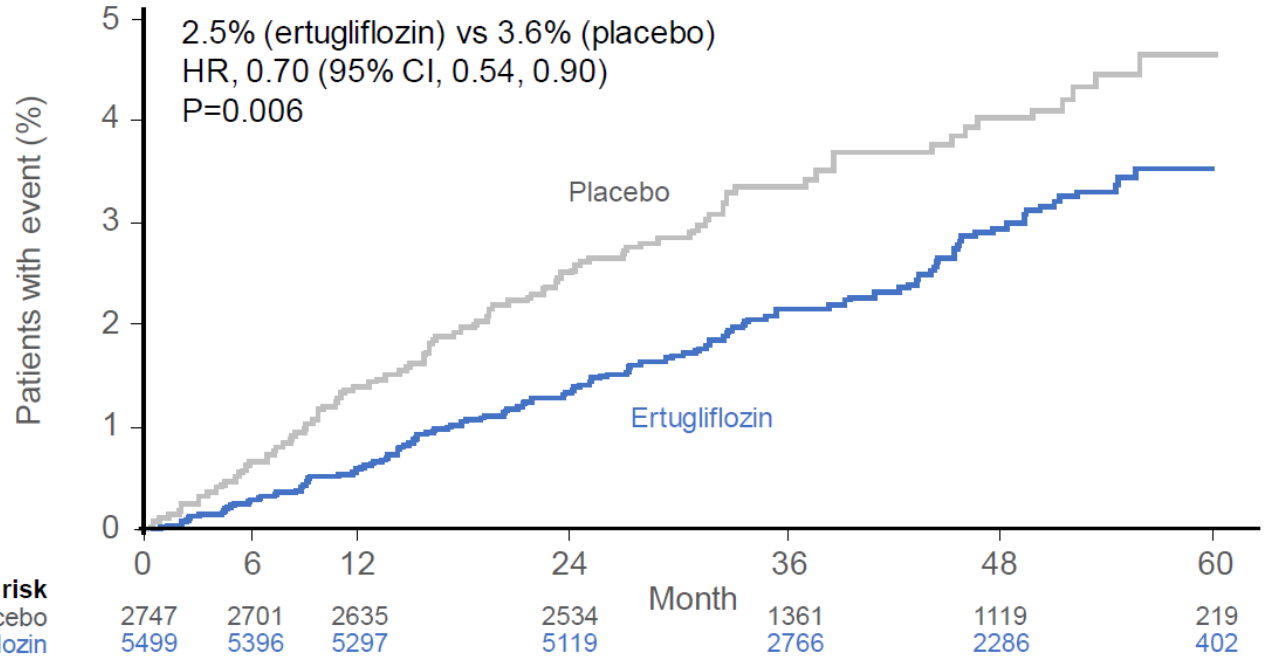
Primary outcome: MACE*

CV death, nonfatal MI, or nonfatal stroke



*Full analysis set included all randomized patients who received at least one dose of study medication (N=5493 for ertugliflozin and N=2745 for placebo). Only confirmed MACE events occurring up to 365 days after the last confirmed dose of study medication were included in the primary analysis.
CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction.

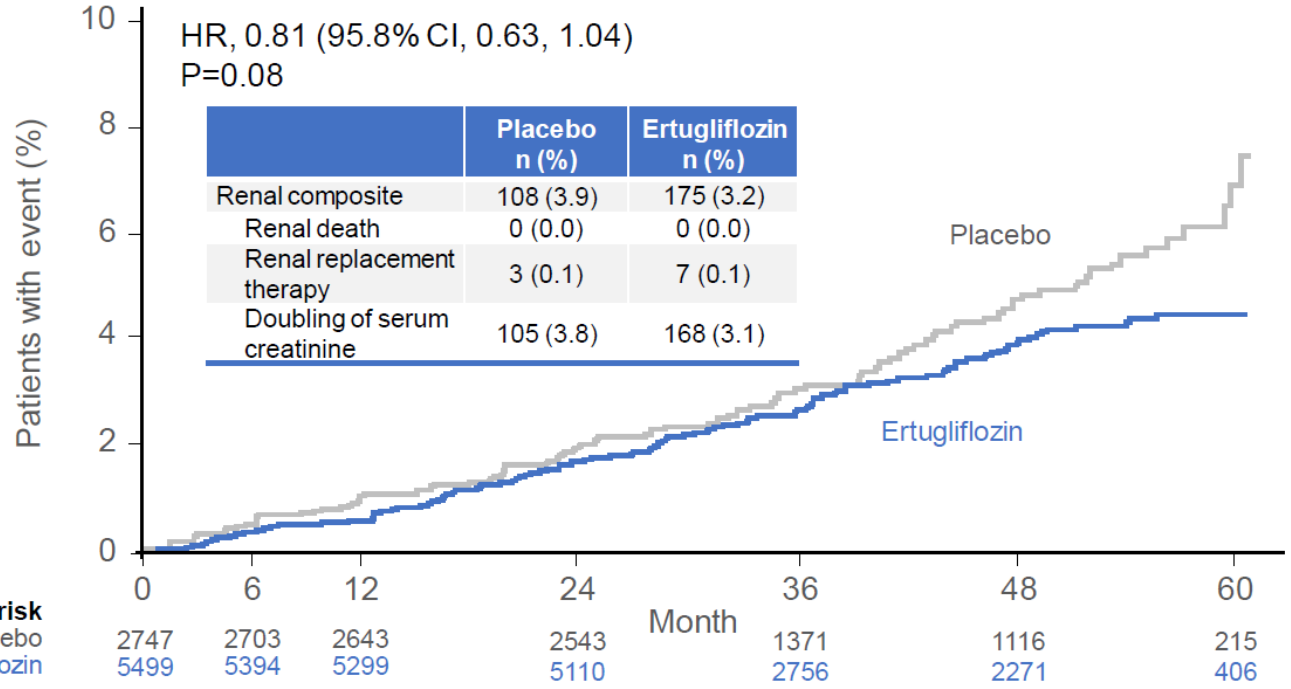
HHF*



*Intention-to-treat analysis set that included all randomized patients with no upper limit on the ascertainment window for the superiority outcomes (N=5499 for ertugliflozin and N=2747 for placebo).
CI, confidence interval; HHF, hospitalization for heart failure; HR, hazard ratio.

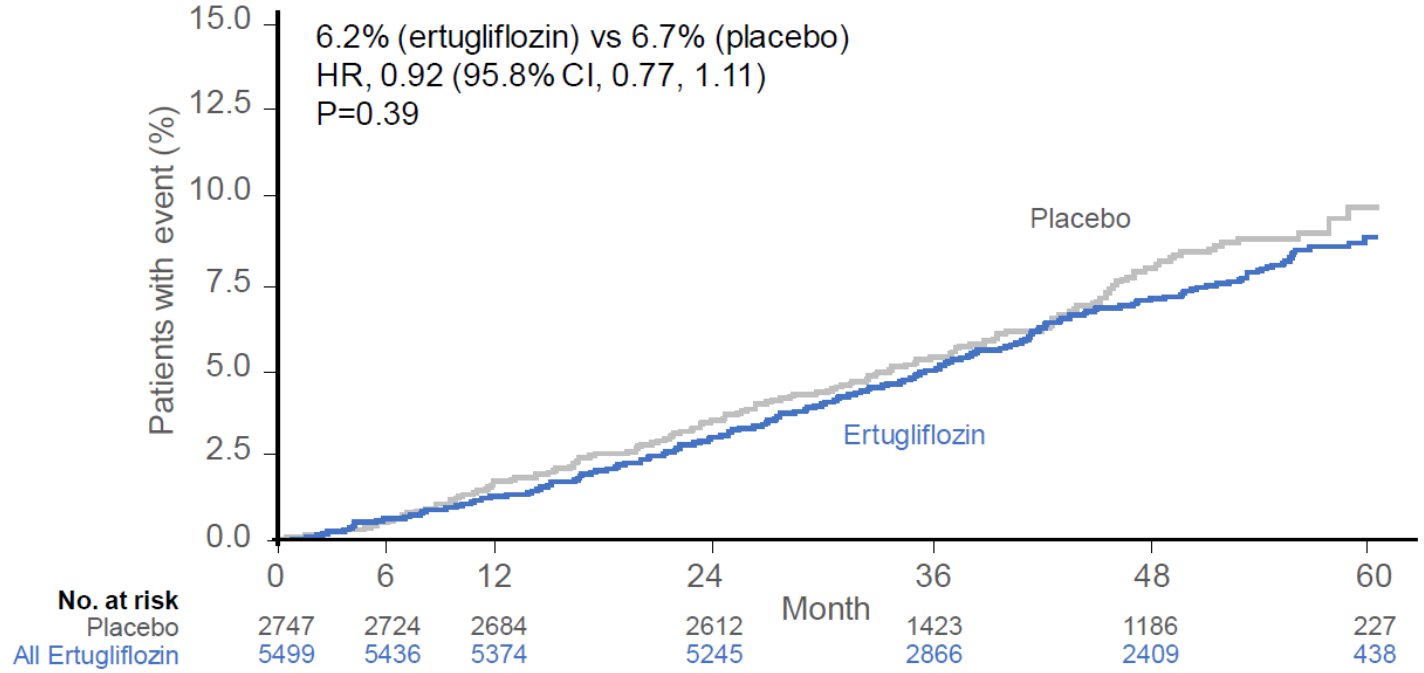
Renal composite*

Renal death, dialysis/transplant, or doubling of serum creatinine



*Intention-to-treat analysis set that included all randomized patients with no upper limit on the ascertainment window for the superiority outcomes (N=5499 for ertugliflozin and N=2747 for placebo).
CI (95.8%) for the alpha-protected tests was adjusted at the final analysis to account for the interim analysis as per the protocol.
CI, confidence interval; HR, hazard ratio.

CV death*



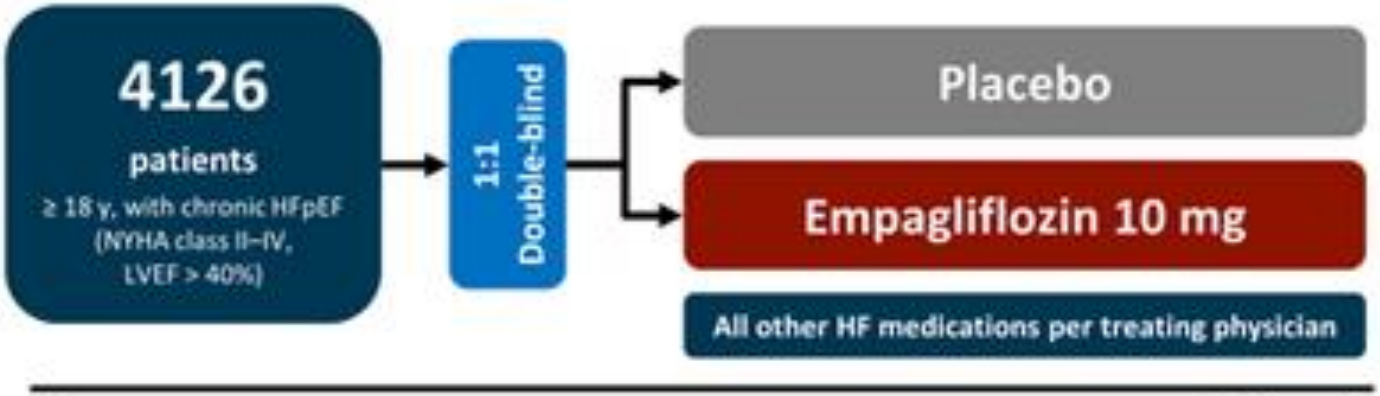
*Intention-to-treat analysis set that included all randomized patients with no upper limit on the ascertainment window for the superiority outcomes (N=5499 for ertugliflozin and N=2747 for placebo).
CI (95.8%) for the alpha-protected tests was adjusted at the final analysis to account for the interim analysis as per the protocol.
CI, confidence interval; CV, cardiovascular; HR, hazard ratio.

EMPEROR-Reduced Trial

Top-line results of the EMPEROR-Reduced trial released today show that treatment with 10 mg empagliflozin, added to standard care, significantly reduced the risk for cardiovascular (CV) death or heart failure hospitalization in patients with heart failure with reduced ejection fraction (HFrEF), with and without diabetes.

Positive Top-line Results for Another SGLT2 Inhibitor in HF
Medscape July 30, 2020.

EMPEROR-Preserved: Empagliflozin Outcome Trial in Patients With Chronic HFpEF



Primary endpoint:

- Time to first event of: CV death **OR** hospitalization for HF

Secondary endpoints:

- Occurrence of adjudicated hHF
- Change from baseline in eGFR
- Time to occurrence of sustained reduction in eGFR
- Time to occurrence of all-cause mortality
- Time to onset of T2D
- Change from baseline in KCCQ

ClinicalTrials.gov. NCT03057951.

TABLE 3 Selected Ongoing SGLT2i Trials

NCT Number	Trial Title	Trial Acronym	Anticipated Enrollment	Anticipated Completion	Drug
Cardiovascular outcomes trials					
NCT03982381	SGLT2 Inhibitor or Metformin as Standard Treatment of Early Stage Type 2 Diabetes	SMARTEST	4,300	September 20, 2024	Dapagliflozin
NCT03315143	Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk	SCORED	10,500	March 2022	Sotagliflozin
Heart failure trials					
NCT03619213	Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure	DELIVER	4,700	June 22, 2021	Dapagliflozin
NCT03057951	Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction	EMPEROR-Preserved	5,250	November 9, 2020	Empagliflozin
NCT03057977	Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction	EMPEROR-Reduced	3,600	July 20, 2020	
NCT03521934	Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure	SOLOIST-WHF	4,000	January 2021	Sotagliflozin
Chronic kidney disease trials					
NCT03036150	A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease	DAPA-CKD	4,000	November 27, 2020	Dapagliflozin
NCT03594110	The Study of Heart and Kidney Protection With Empagliflozin	EMPA-KIDNEY	5,000	June 30, 2022	Empagliflozin

NCT = national clinical trial; SGLT2i = sodium glucose cotransporter 2 inhibitor.

American Diabetes Association®

2020

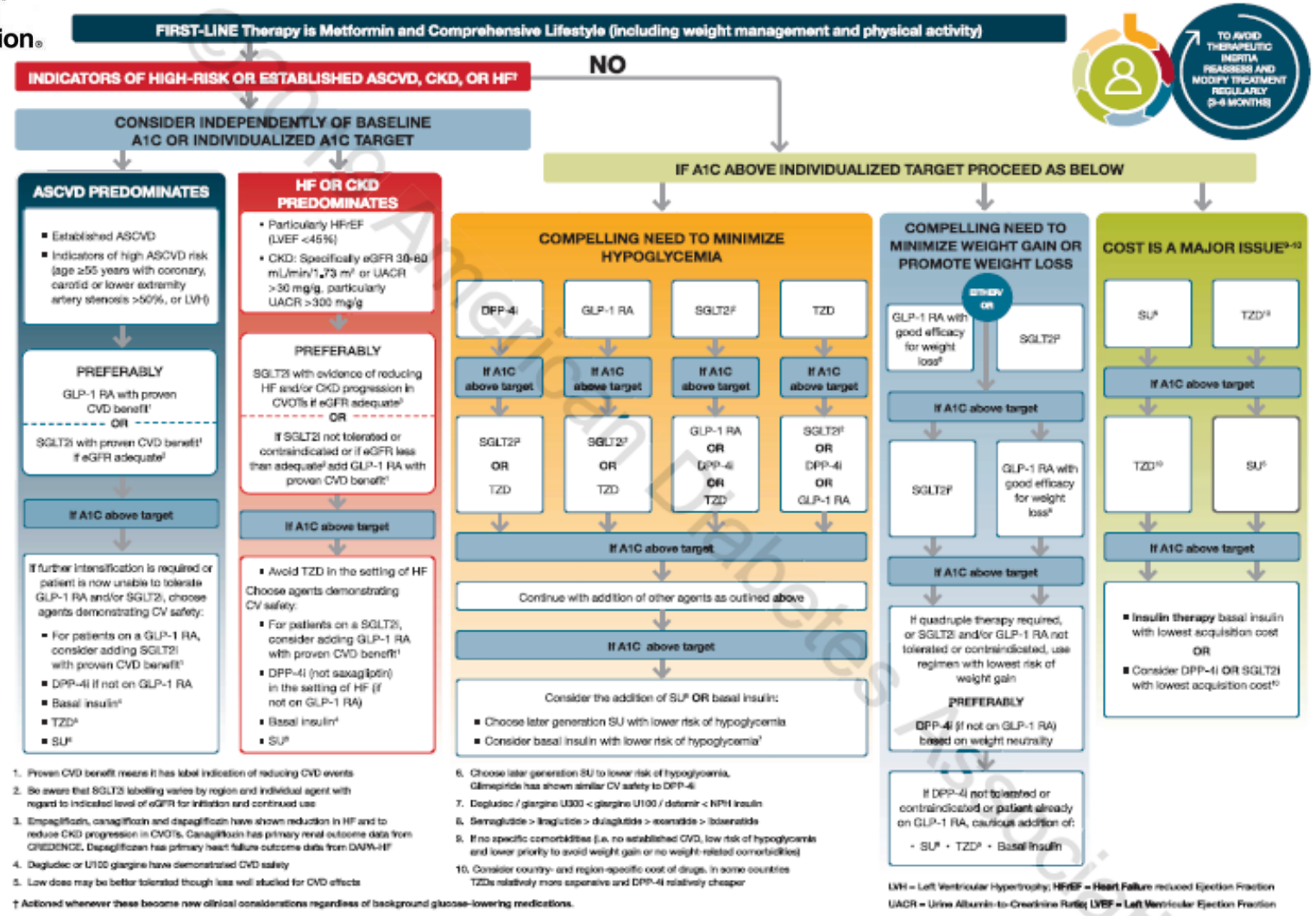
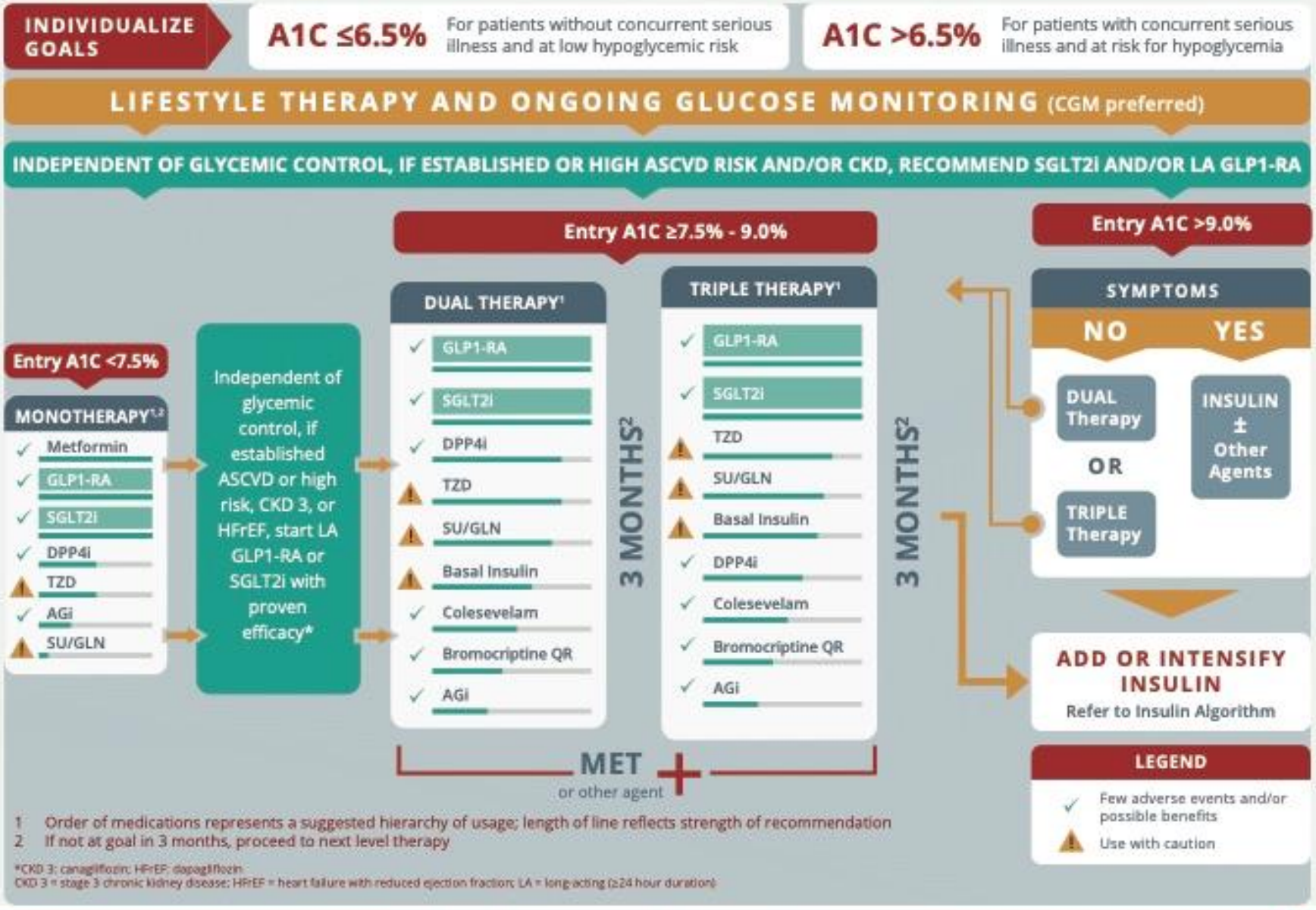
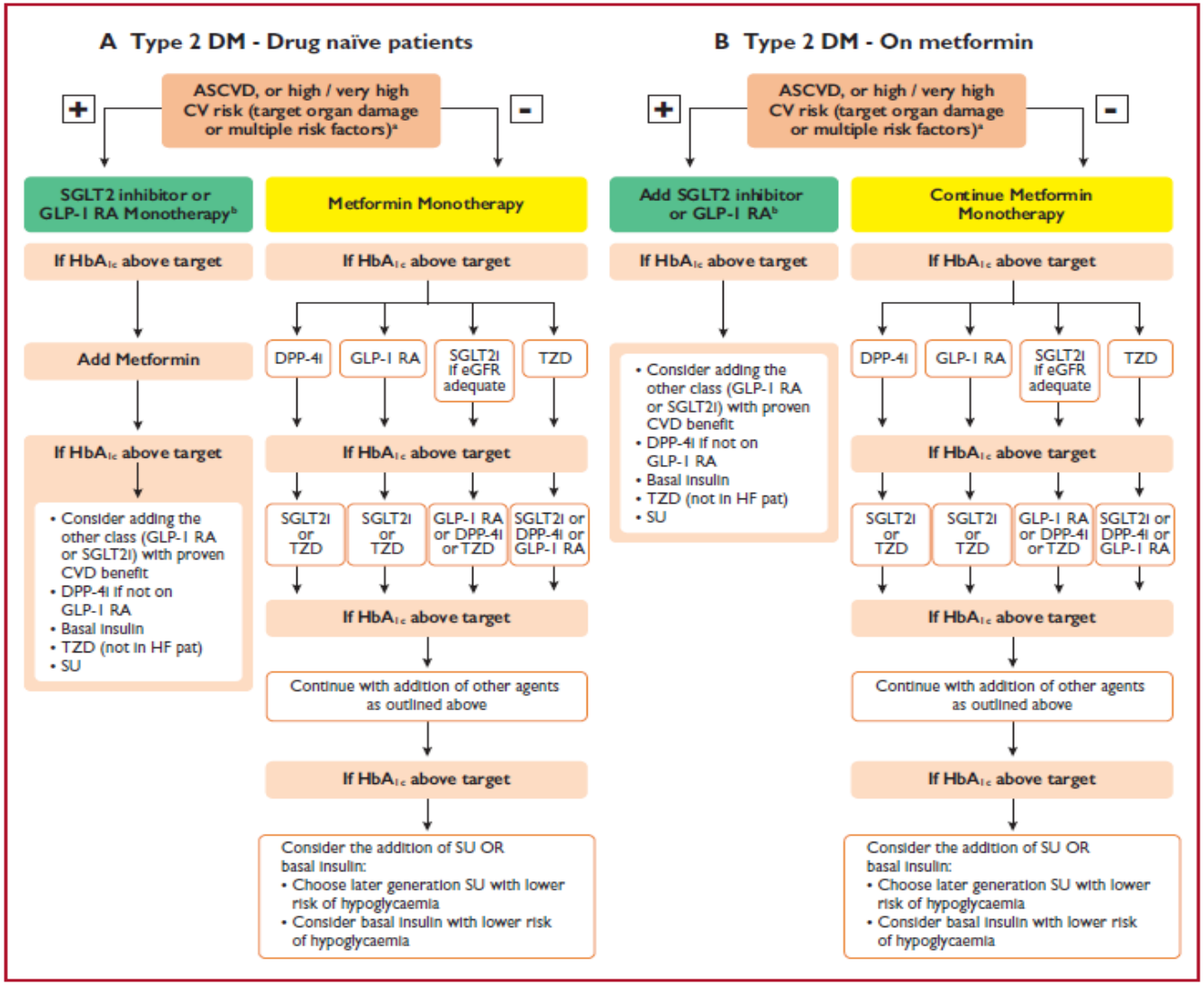


Figure 9.1—Glucose-lowering medication in type 2 diabetes: overall approach. For appropriate context, see Fig. 4.1. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOTs, cardiovascular outcomes trials; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione. Adapted from Davies and colleagues (33,34).

GLYCEMIC CONTROL ALGORITHM



European Society of Cardiology and European Association for the Study of Diabetes 2019



OPINION

- In patients with a recent diagnosis of diabetes without a history of CAD, heart failure or kidney disease, the therapy of choice as monotherapy should be metformin if the patient tolerates it.
- If the patient is in metformin and develops heart failure and/or kidney disease the second therapy of choice should be SGLT2.
- In naïve patients who debut with heart failure and/or kidney disease the monotherapy of choice should be SGLT2 if patient can afford it.
- If the patient is diabetic and develops heart failure and/or kidney disease, no matter the value of glycosylated A1C, SGLT2 should be added if is not contraindicated.
- SGLT2 Probably will emerge as a new alternative for cardiorenal syndrome.

POST-TEST

1. In patient with diabetic type 2 with ASCVD or high risk for ASCVD when HF or CKD predominate according to ADA 2020 the second prefer drug of choice is:
   a) Thiazolidine
   b) DPP4
   c) SGLT2
   d) GLP-1
2. Which diabetic guideline recommends as first line treatment the use of SGLT2 instead of Metformin in drug-naïve patient with type 2 diabetes, with establish cardiovascular disease:
   a) ADA Guidelines 2020
   b) AACE Guidelines 2020
   c) European Association Study of Diabetes Guidelines 2019
   d) None of the above