AMRUS Cuore SUMMIT

Napoli, 1-2 ottobre 2021
Hotel Excelsior

Tavola rotonda 3

SGLT2 INIBITORI NEL PAZIENTE CON SCOMPENSO CARDIACO

- Il problema -

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Disclosures

Nothing to be declared.

Classification of HF

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF ≤40%	LVEF 41–49%[b]	LVEF ≥50%
	3	–	–	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c]

HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LV = left ventricle; LVEF = left ventricular ejection fraction.

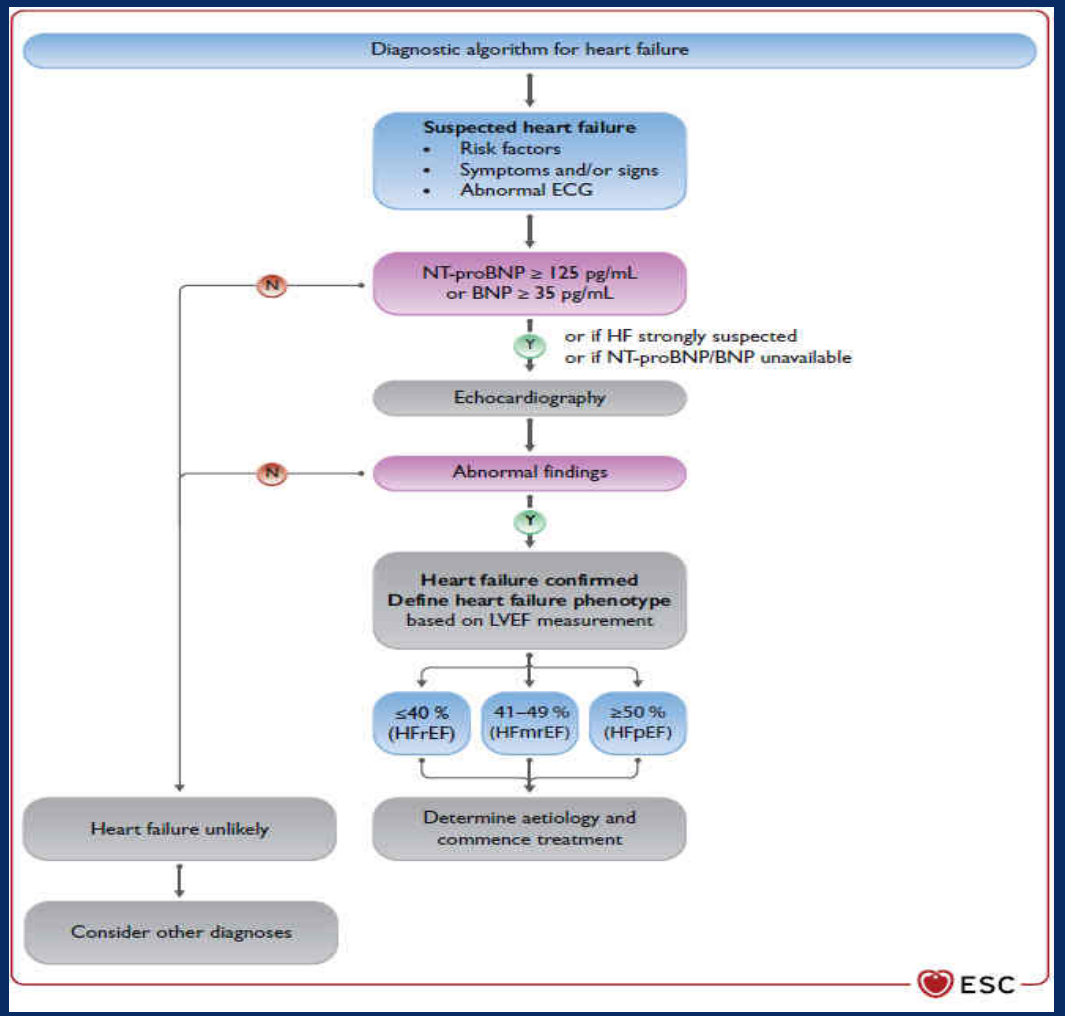
[a]Signs may not be present in the early stages of HF (especially in HFpEF) and in optimally treated patients.

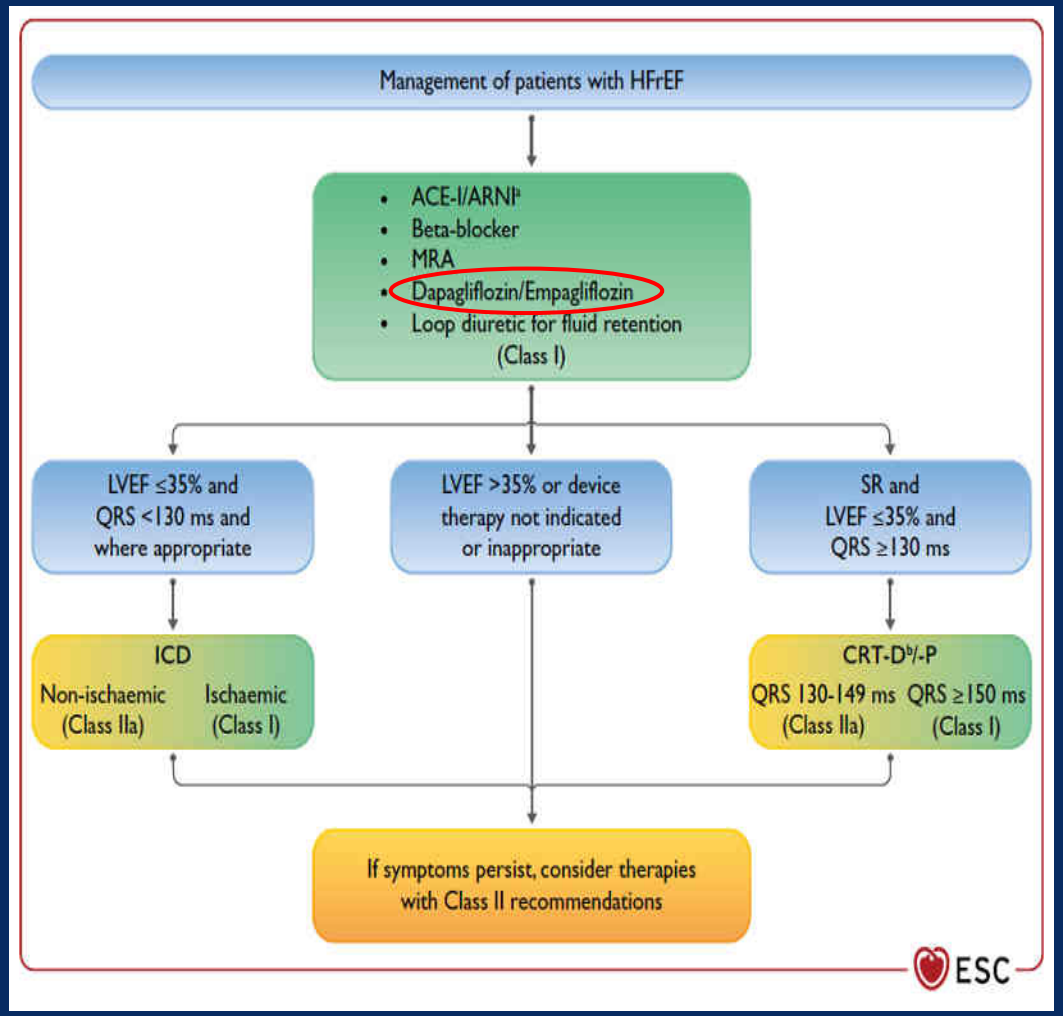
[b]For the diagnosis of HFmrEF, the presence of other evidence of structural heart disease (e.g. increased left atrial size, LV hypertrophy or echocardiographic measures of impaired LV filling) makes the diagnosis more likely.

[c]For the diagnosis of HFpEF, the greater the number of abnormalities present, the higher the likelihood of HFpEF.

McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021 Aug 27:ehab368.

Diagnosis & Management





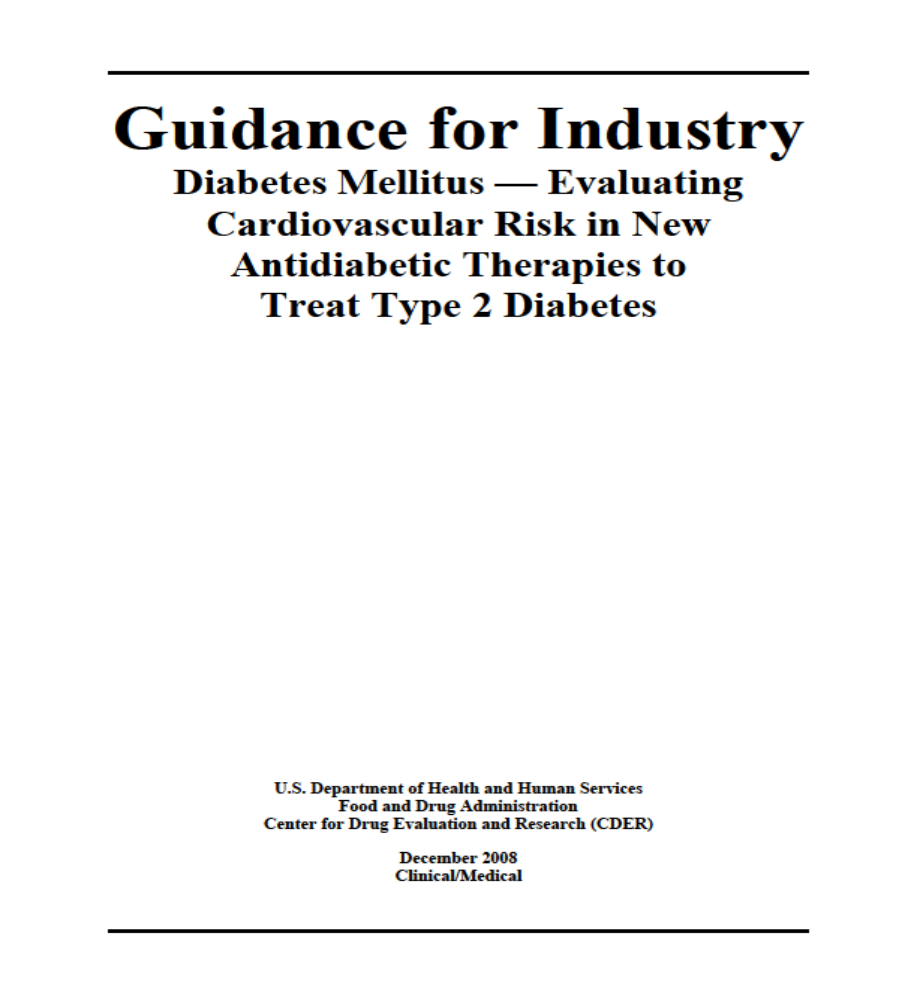
McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021 Aug 27:ehab368.

Pharmacological treatments of HFrEF

Recommendations	Class[a]	Level[b]
An ACE-I is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[110–113]	I	A
A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.[114–120]	I	A
An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[121,122]	I	A
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[108,109]	I	A
Sacubitril/valsartan is recommended as a replacement for an ACE-I in patients with HFrEF to reduce the risk of HF hospitalization and death.[105]	I	B

McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021 Aug 27:ehab368.

2008 FDA Guidance


Guidance for Industry

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

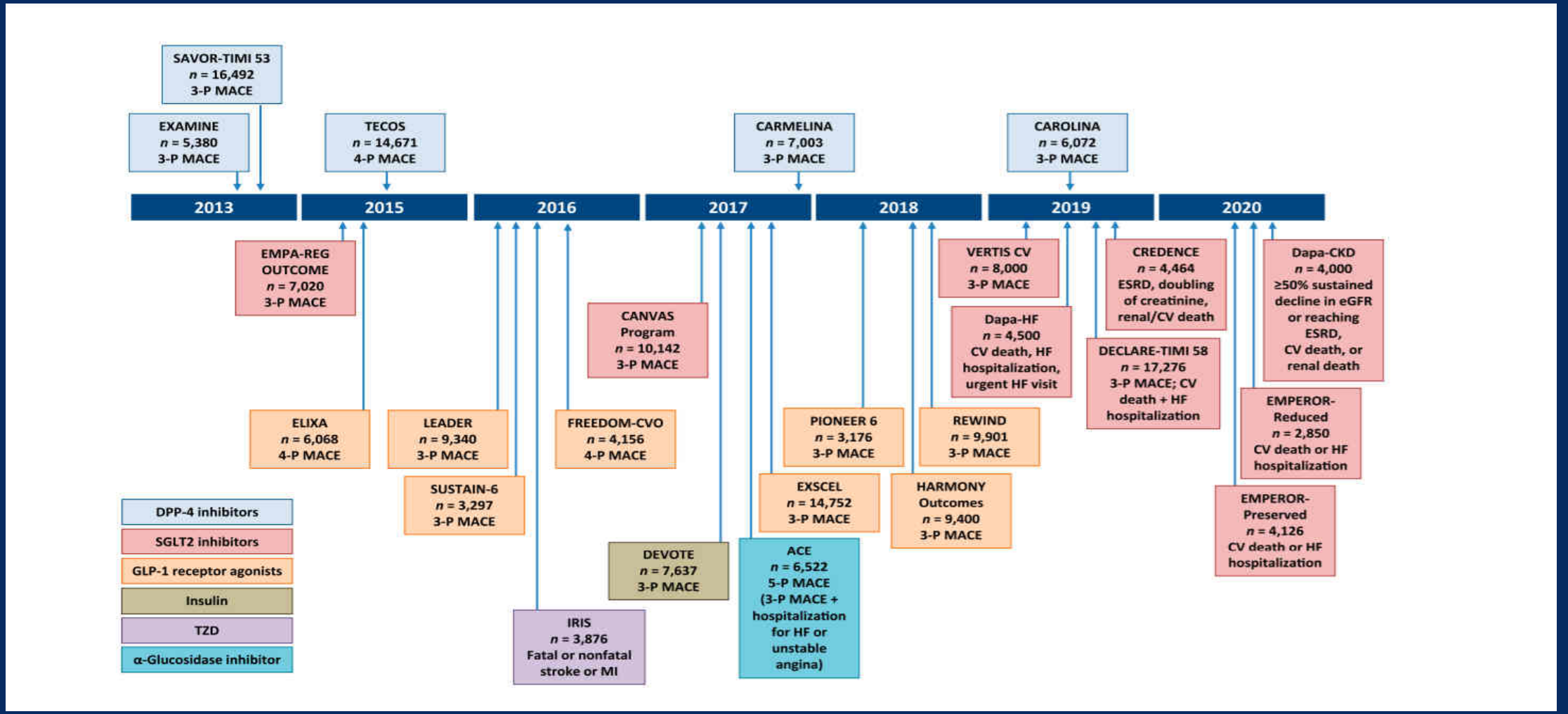
December 2008
Clinical/Medical

To establish the safety of a new antidiabetic therapy to treat type 2 diabetes, sponsors should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk. → **CVOTs (Cardiovascular Outcome Trials).**

- Independent cardiovascular endpoints (should include MACE) committee.
- Patients at higher risk of cardiovascular events (s.a. relatively advanced disease, elderly, renal impairment).
- Sponsors should perform a meta-analysis of the important cardiovascular events across phase 2 and phase 3 controlled clinical trials and explore similarities and/or differences in subgroups (e.g., age, sex, race), if possible.

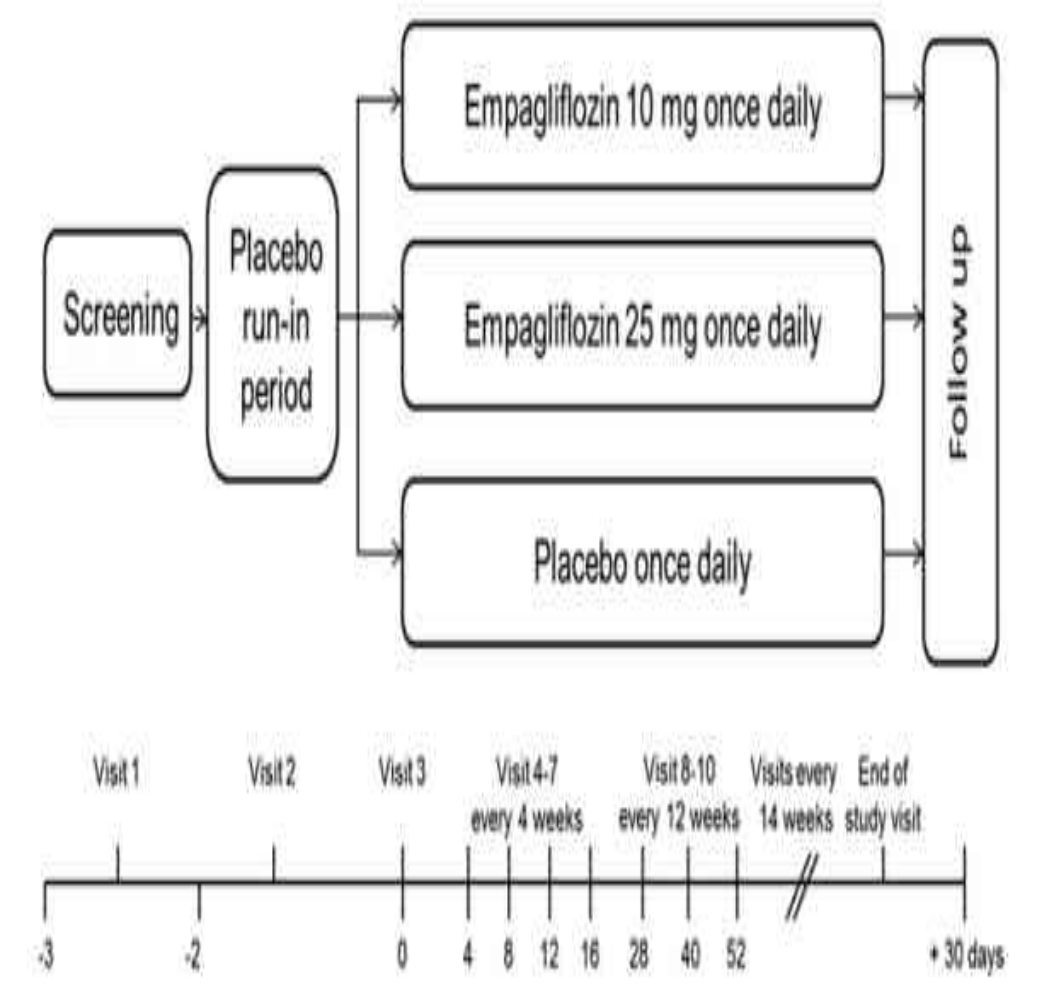
FDA. Guidance for Industry Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. 2008.

CVOTs Timeline



Cefalu WT, Kaul S, Gerstein HC, et al. Cardiovascular Outcomes Trials in Type 2 Diabetes: Where Do We Go From Here? Reflections From a *Diabetes Care* Editors' Expert Forum. Diabetes Care Jan 2018;41:14-31.

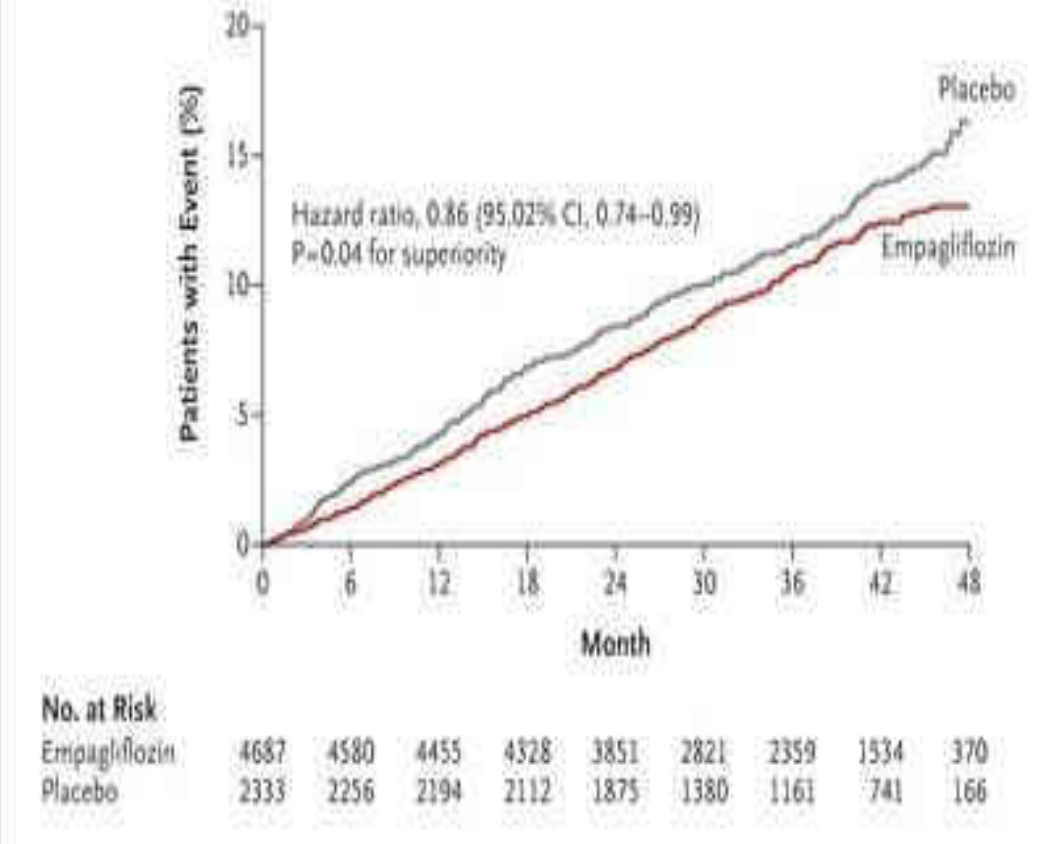
EMPA-REG OUTCOME



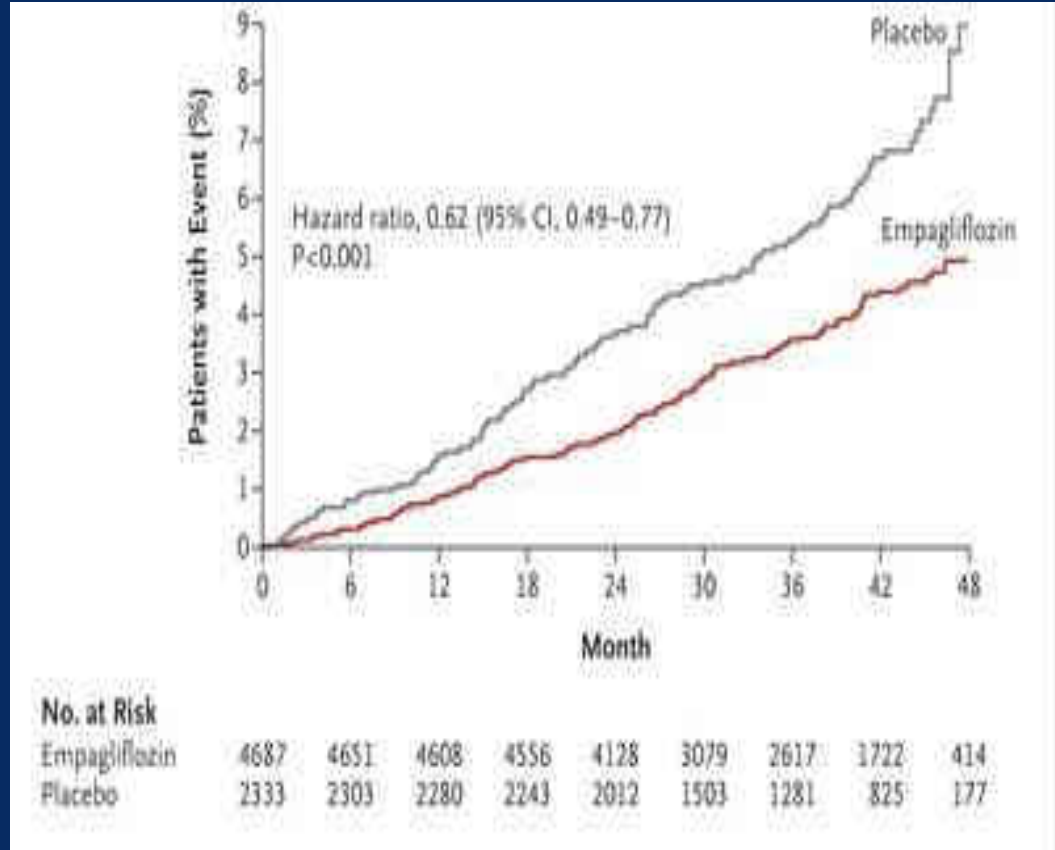
- Patients with T2DM, ≥18 years of age and high cardiovascular risk, BMI ≤45 Kg/m^2, eGFR ≥30 ml/min/1.73m^2.
- Mean age: 63.1 years; female: 28.5%; Median observation time: 3.1 years

Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med 2015; 373:2117-2128.

EMPA-REG OUTCOME



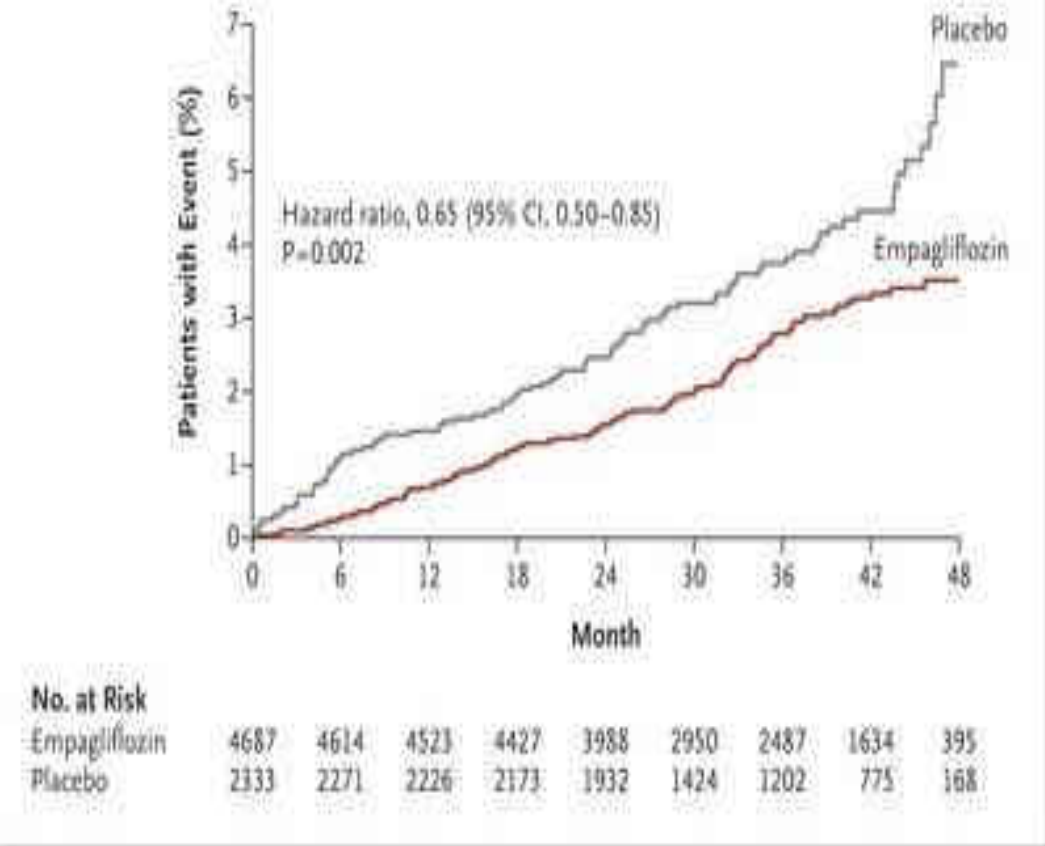
MACE -14%
(CV death, non-fatal MI, non- fatal stroke)



CV death -38%
Any death -32%

Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med 2015; 373:2117-2128.

EMPA-REG OUTCOME



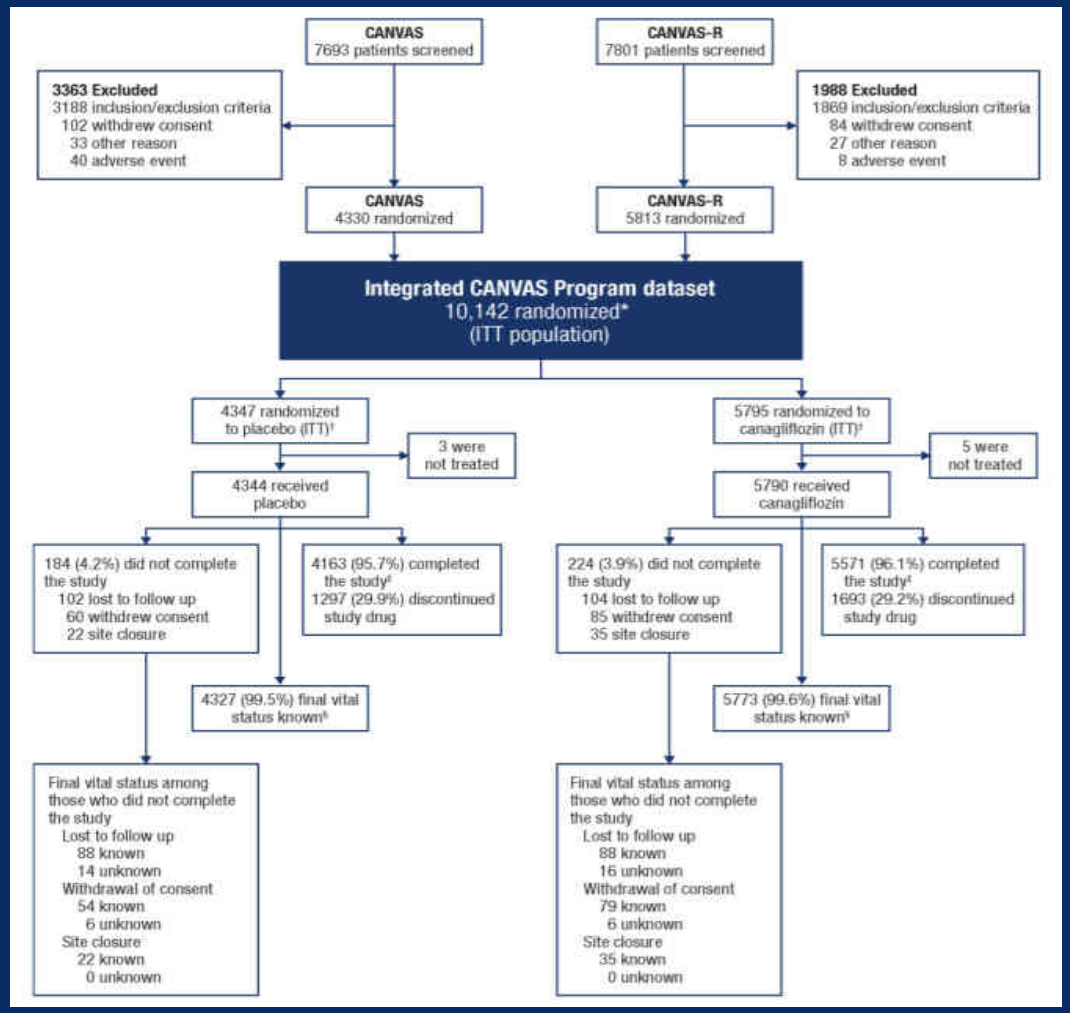
HHF -35%

Table 2. Adverse Events.*

Event	Placebo (N=2333)	Empagliflozin, 10 mg (N=2345)	Empagliflozin, 25 mg (N=2342)	Pooled Empagliflozin (N=4687)
	number of patients (percent)			
Any adverse event	2139 (91.7)	2112 (90.1)	2118 (90.4)	4230 (90.2)†
Severe adverse event	592 (25.4)	536 (22.9)	564 (24.1)	1100 (23.5)‡
Serious adverse event				
Any	988 (42.3)	876 (37.4)	913 (39.0)	1789 (38.2)†
Death	119 (5.1)	97 (4.1)	79 (3.4)	176 (3.8)§
Adverse event leading to discontinuation of a study drug	453 (19.4)	416 (17.7)	397 (17.0)	813 (17.3)§
Confirmed hypoglycemic adverse event¶				
Any	650 (27.9)	656 (28.0)	647 (27.6)	1303 (27.8)
Requiring assistance	36 (1.5)	33 (1.4)	30 (1.3)	63 (1.3)
Event consistent with urinary tract infection‖	423 (18.1)	426 (18.2)	416 (17.8)	842 (18.0)
Male patients	158 (9.4)	180 (10.9)	170 (10.1)	350 (10.5)
Female patients	265 (40.6)	246 (35.5)	246 (37.3)	492 (36.4)‡
Complicated urinary tract infection**	41 (1.8)	34 (1.4)	48 (2.0)	82 (1.7)
Event consistent with genital infection††	42 (1.8)	153 (6.5)	148 (6.3)	301 (6.4)†
Male patients	25 (1.5)	89 (5.4)	77 (4.6)	166 (5.0)†
Female patients	17 (2.6)	64 (9.2)	71 (10.8)	135 (10.0)†
Event consistent with volume depletion‡‡	115 (4.9)	115 (4.9)	124 (5.3)	239 (5.1)
Acute renal failure§§	155 (6.6)	121 (5.2)	125 (5.3)	246 (5.2)§
Acute kidney injury	37 (1.6)	26 (1.1)	19 (0.8)	45 (1.0)‡
Diabetic ketoacidosis¶¶	1 (<0.1)	3 (0.1)	1 (<0.1)	4 (0.1)
Thromboembolic event§§	20 (0.9)	9 (0.4)	21 (0.9)	30 (0.6)
Bone fracture‖‖	91 (3.9)	92 (3.9)	87 (3.7)	179 (3.8)

Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med 2015; 373:2117-2128.

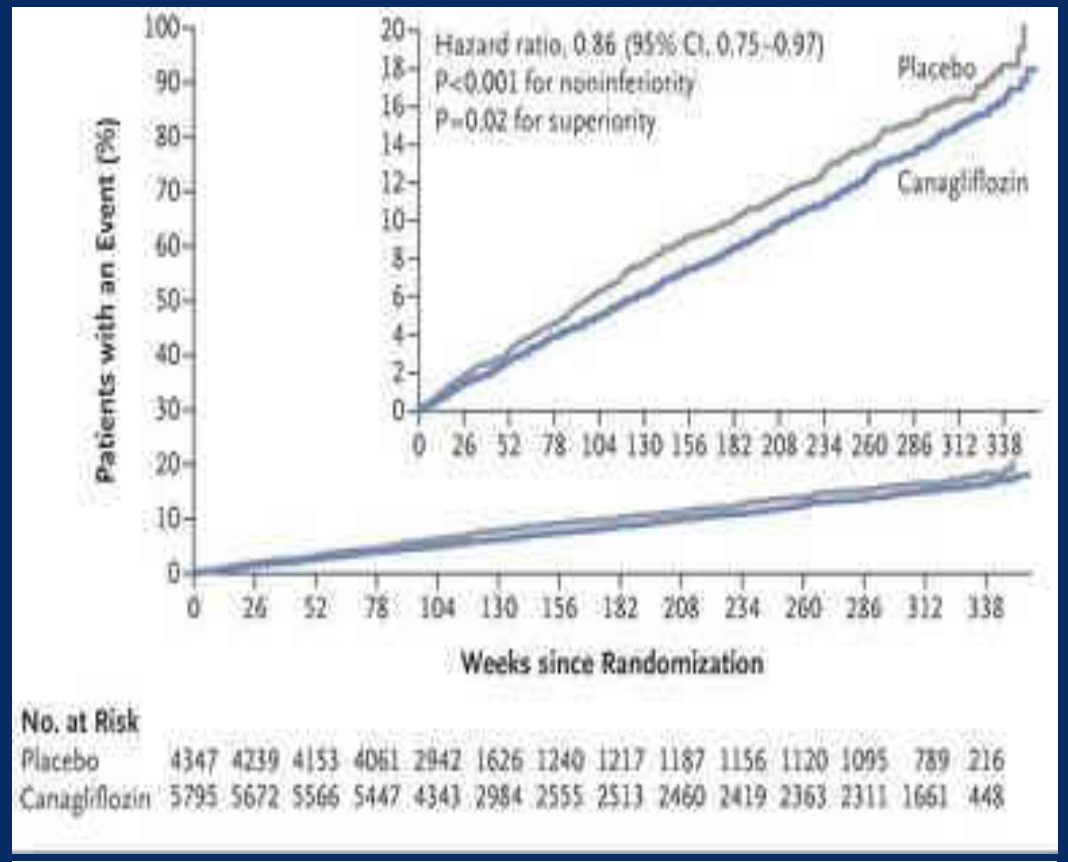
CANVAS Program



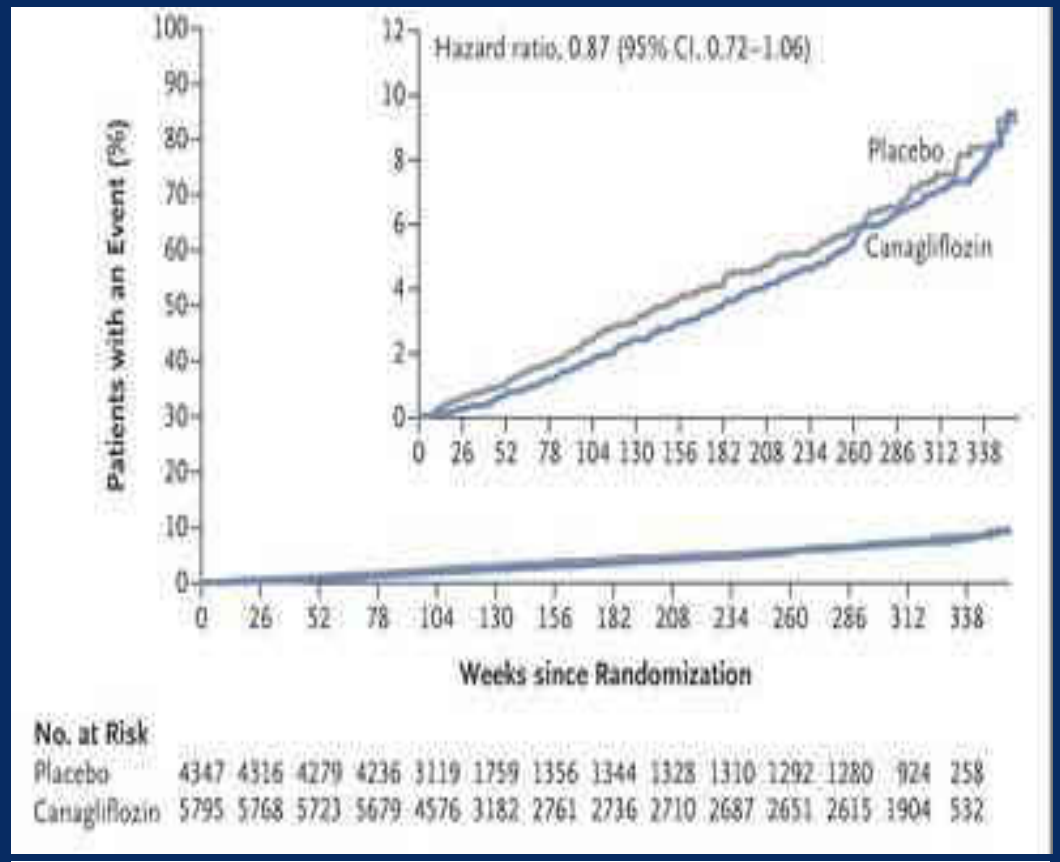
- T2DM, ≥30 years of age with history of CV disease (65.6%) or ≥ 50 years of age with 2 or more CV risk factors (34.4%), eGFR >30 ml/min/1.73m^2.
- Mean age: 63.3 years; women: 35.8%; median follow-up: 2.4 years.

Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017 Aug 17;377:644-657.

CANVAS Program



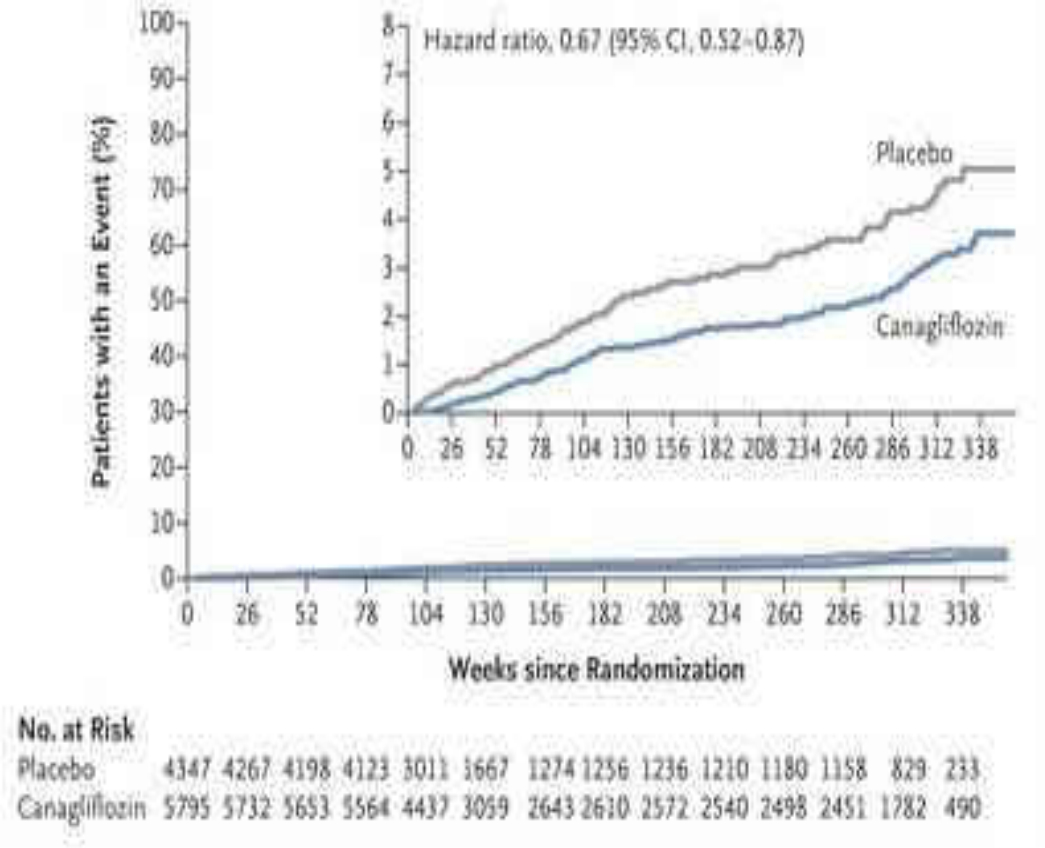
MACE -14%
(CV death, non-fatal MI, non- fatal stroke)



CV death – n.s.
Any death – n.s.

Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017 Aug 17;377:644-657.

CANVAS Program



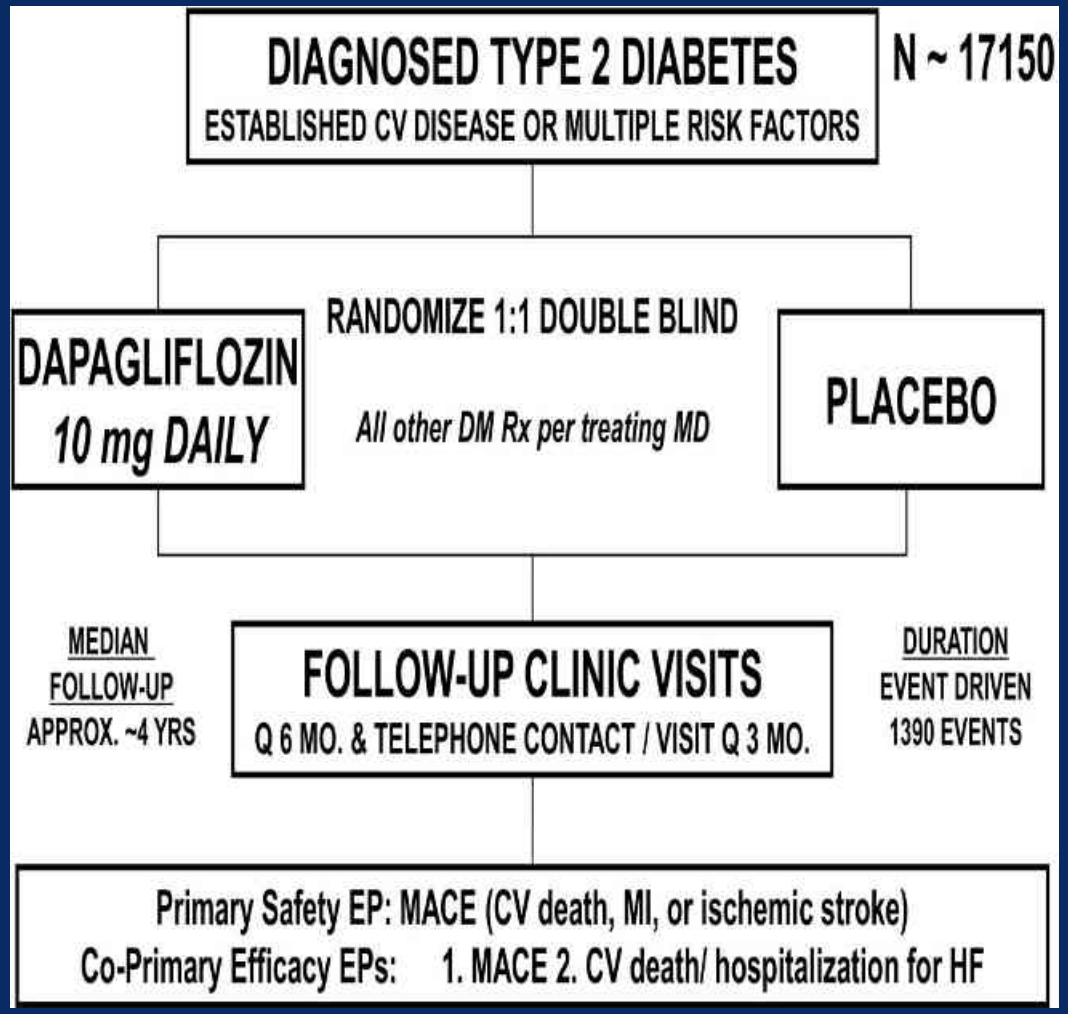
HHF -33%

Table 2. Adverse Events.*

Event	Canagliflozin	Placebo	P Value†
	event rate per 1000 patient-yr		
All serious adverse events	104.3	120.0	0.04
Adverse events leading to discontinuation	35.5	32.8	0.07
Serious and nonserious adverse events of interest recorded in the CANVAS Program			
Acute pancreatitis (adjudicated)	0.5	0.4	0.63
Cancer			
Renal cell	0.6	0.2	0.17
Bladder	1.0	1.1	0.74
Breast	3.1	2.6	0.65
Photosensitivity	1.0	0.3	0.07
Diabetic ketoacidosis (adjudicated)	0.6	0.3	0.14
Amputation	6.3	3.4	<0.001
Fracture (adjudicated)‡			
All	15.4	11.9	0.02
Low-trauma	11.6	9.2	0.06
Venous thromboembolic events	1.7	1.7	0.63
Infection of male genitalia§	34.9	10.8	<0.001
Serious and nonserious adverse events of interest collected in CANVAS alone¶			
Osmotic diuresis	34.5	13.3	<0.001
Volume depletion	26.0	18.5	0.009
Hypoglycemia	50.0	46.4	0.20
Acute kidney injury	3.0	4.1	0.33
Hyperkalemia	6.9	4.4	0.10
Urinary tract infection	40.0	37.0	0.38
Mycotic genital infection in women	68.8	17.5	<0.001
Severe hypersensitivity or cutaneous reaction	8.5	6.1	0.17
Hepatic injury	7.4	9.1	0.35
Renal-related (including acute kidney injury)	19.7	17.4	0.32

Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017 Aug 17;377:644-657.

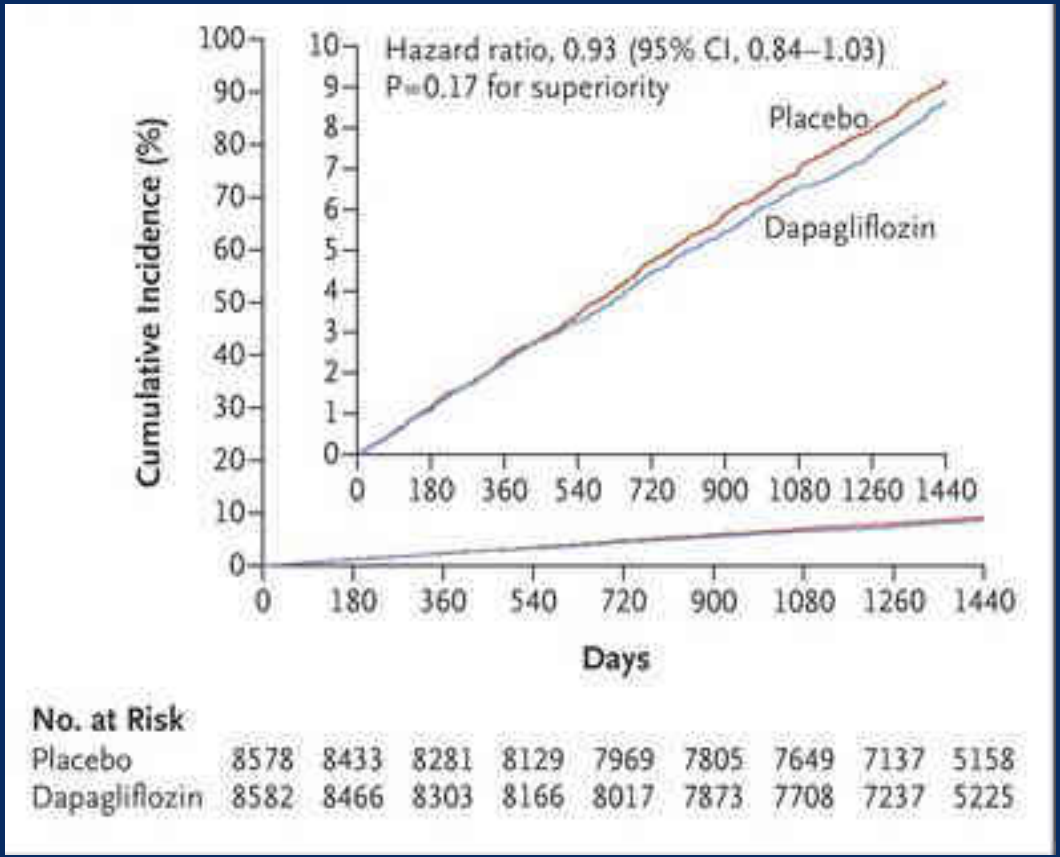
DECLARE-TIMI 58



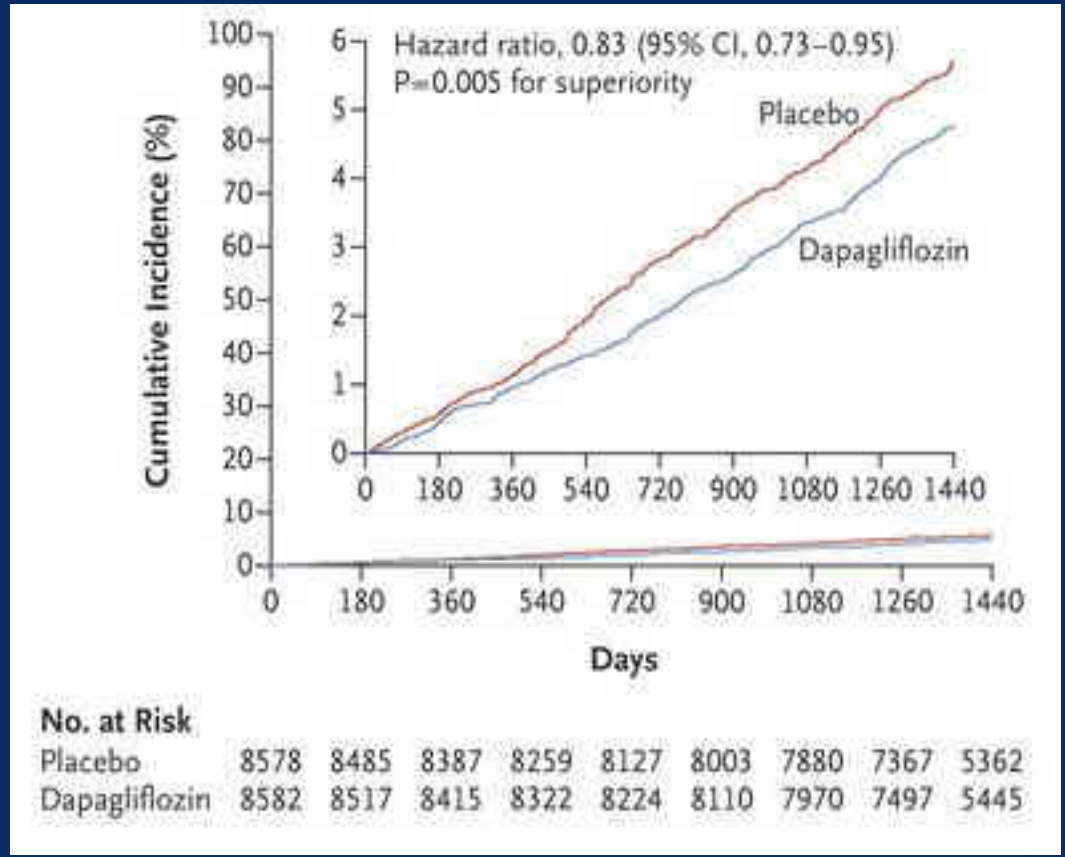
- T2DM, ≥ 40 years of age with established CV disease or with ≥1 traditional CV risk factors (men ≥ 55 years of age; women ≥ 60 years of age), eGFR >60 ml/min/1.73m^2.
- Mean age: 63.9 years; women: 37.4%; median follow-up: 4.2 years.

Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019 Jan 24;380:347-357.

DECLARE-TIMI 58



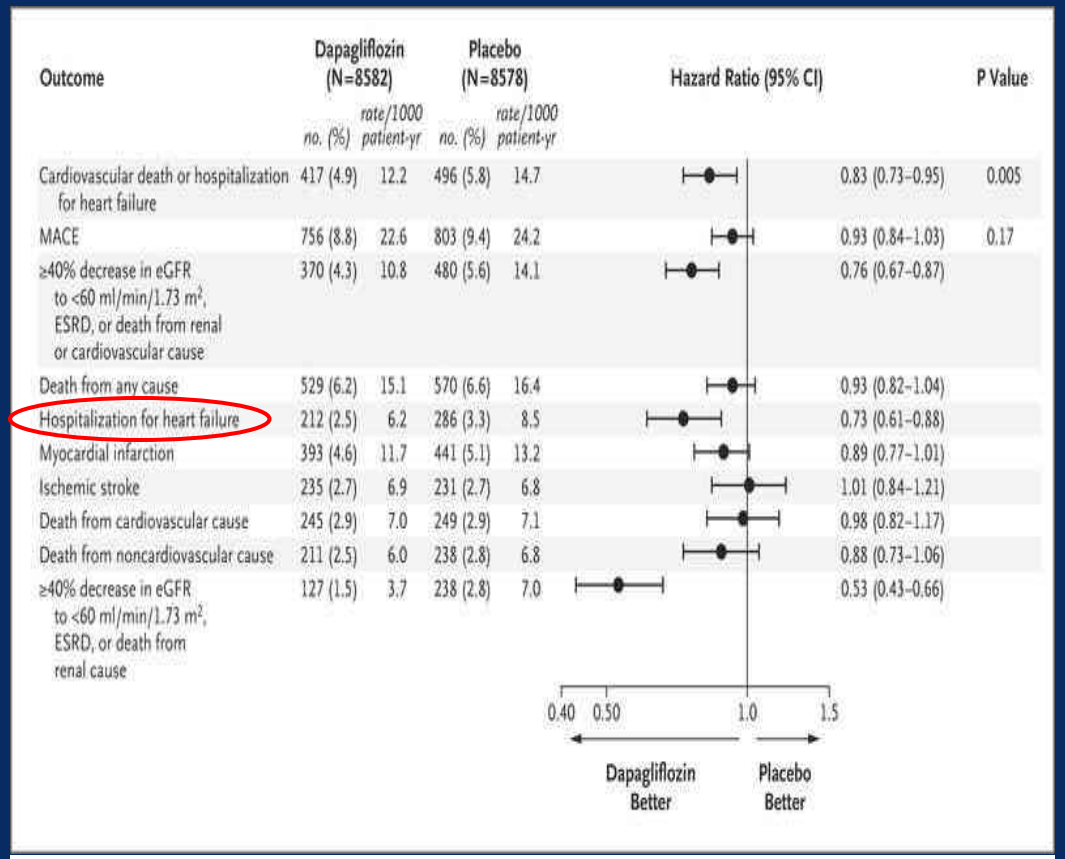
MACE – n.s.
(CV death, non-fatal MI, ischemic stroke)



CV death or HHF -17%
Any death – n.s.

Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019 Jan 24;380:347-357.

DECLARE-TIMI 58



Outcome	Dapagliflozin (N=8582) no. (%)	Dapagliflozin (N=8582) rate/1000 patient-yr	Placebo (N=8578) no. (%)	Placebo (N=8578) rate/1000 patient-yr	Hazard Ratio (95% CI)	P Value
Cardiovascular death or hospitalization for heart failure	417 (4.9)	12.2	496 (5.8)	14.7	0.83 (0.73–0.95)	0.005
MACE	756 (8.8)	22.6	803 (9.4)	24.2	0.93 (0.84–1.03)	0.17
≥40% decrease in eGFR to <60 ml/min/1.73 m², ESRD, or death from renal or cardiovascular cause	370 (4.3)	10.8	480 (5.6)	14.1	0.76 (0.67–0.87)	
Death from any cause	529 (6.2)	15.1	570 (6.6)	16.4	0.93 (0.82–1.04)	
Hospitalization for heart failure	212 (2.5)	6.2	286 (3.3)	8.5	0.73 (0.61–0.88)	
Myocardial infarction	393 (4.6)	11.7	441 (5.1)	13.2	0.89 (0.77–1.01)	
Ischemic stroke	235 (2.7)	6.9	231 (2.7)	6.8	1.01 (0.84–1.21)	
Death from cardiovascular cause	245 (2.9)	7.0	249 (2.9)	7.1	0.98 (0.82–1.17)	
Death from noncardiovascular cause	211 (2.5)	6.0	238 (2.8)	6.8	0.88 (0.73–1.06)	
≥40% decrease in eGFR to <60 ml/min/1.73 m², ESRD, or death from renal cause	127 (1.5)	3.7	238 (2.8)	7.0	0.53 (0.43–0.66)	

HHF -27%

Table 2. Safety Events.*

Event	Dapagliflozin (N=8574)	Placebo (N=8569)	Hazard Ratio (95% CI)	P Value
	no. (%)			
Serious adverse event	2925 (34.1)	3100 (36.2)	0.91 (0.87–0.96)	<0.001
Adverse event leading to discontinuation of trial regimen	693 (8.1)	592 (6.9)	1.15 (1.03–1.28)	0.01
Major hypoglycemic event	58 (0.7)	83 (1.0)	0.68 (0.49–0.95)	0.02
Diabetic ketoacidosis	27 (0.3)	12 (0.1)	2.18 (1.10–4.30)	0.02
Amputation	123 (1.4)	113 (1.3)	1.09 (0.84–1.40)	0.53
Fracture	457 (5.3)	440 (5.1)	1.04 (0.91–1.18)	0.59
Symptoms of volume depletion	213 (2.5)	207 (2.4)	1.00 (0.83–1.21)	0.99
Acute kidney injury	125 (1.5)	175 (2.0)	0.69 (0.55–0.87)	0.002
Genital infection	76 (0.9)	9 (0.1)	8.36 (4.19–16.68)	<0.001
Urinary tract infection	127 (1.5)	133 (1.6)	0.93 (0.73–1.18)	0.54
Cancer	481 (5.6)	486 (5.7)	0.99 (0.87–1.12)	0.83
Bladder cancer	26 (0.3)	45 (0.5)	0.57 (0.35–0.93)	0.02
Breast cancer	36 (0.4)	35 (0.4)	1.02 (0.64–1.63)	0.92
Hypersensitivity	32 (0.4)	36 (0.4)	0.87 (0.54–1.40)	0.57
Hepatic event	82 (1.0)	87 (1.0)	0.92 (0.68–1.25)	0.60

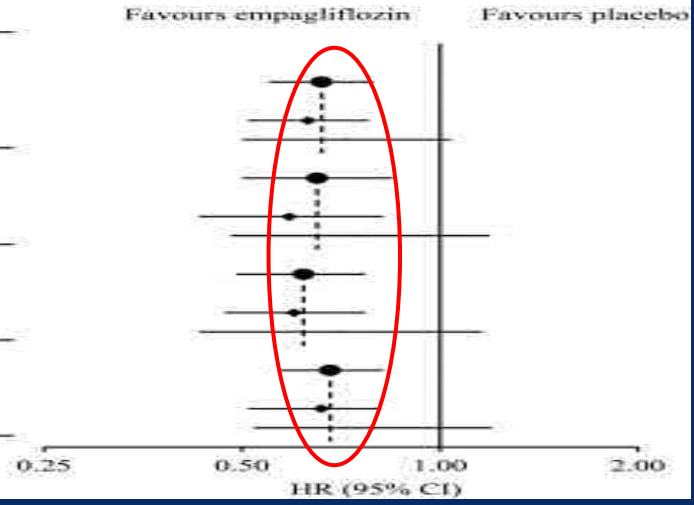
Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019 Jan 24;380:347-357.

Meta-analysis

	EMPA-REG OUTCOME[1]	CANVAS Program[2]	DECLARE-TIMI 58[3]
Drug	Empagliflozin	Canagliflozin	Dapagliflozin
Doses analysed	10 mg, 25 mg (once daily)	100 mg, 300 mg (once daily)	10 mg (once daily)
Median follow-up time, years	3·1	2·4	4·2
Trial participants	7020	10 142	17 160
Age, mean	63·1	63·3	63·9
Women	2004 (28·5%)	3633 (35·8%)	6422 (37·4%)
Patients with established atherosclerotic cardiovascular disease	7020 (100%)	6656 (65·6%)	6974 (40·6%)
Patients with a history of heart failure	706 (10·1%)	1461 (14·4%)	1724 (10·0%)
Patients with eGFR <60 mL/min per 1·73 m²	1819 (25·9%)	2039 (20·1%)	1265 (7·4%)

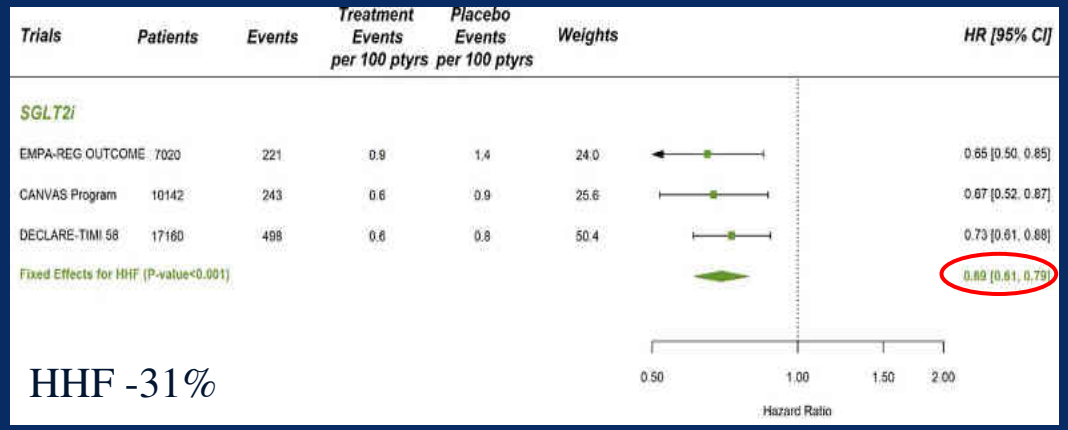
Data are n (%) unless otherwise specified. The CANVAS Program consisted of two trials, CANVAS and CANVAS-R, but are presented combined. eGFR=estimated glomerular filtration rate.

	Empagliflozin		Placebo		HR (95% CI)
	n with event/*n*	%	*n* with event/*n*	%	
Heart failure hospitalization or cardiovascular death					
All patients	265/4687	5.7	198/2333	8.5	0.66 (0.55–0.79)
Heart failure at baseline					
No	190/4225	4.5	149/2089	7.1	0.63 (0.51–0.78)
Yes	75/462	16.2	49/244	20.1	0.72 (0.50–1.04)
Hospitalization for heart failure					
All patients	126/4687	2.7	95/2333	4.1	0.65 (0.50–0.85)
Heart failure at baseline					
No	78/4225	1.8	65/2089	3.1	0.59 (0.43–0.82)
Yes	48/462	10.4	30/244	12.3	0.75 (0.48–1.19)
Cardiovascular death					
All patients	172/4687	3.7	137/2333	5.9	0.62 (0.49–0.77)
Heart failure at baseline					
No	134/4225	3.2	110/2089	5.3	0.60 (0.47–0.77)
Yes	38/462	8.2	27/244	11.1	0.71 (0.43–1.16)
All-cause mortality					
All patients	269/4687	5.7	194/2333	8.3	0.68 (0.57–0.82)
Heart failure at baseline					
No	213/4225	5.0	159/2089	7.6	0.66 (0.51–0.81)
Yes	56/462	12.1	35/244	14.3	0.79 (0.52–1.20)

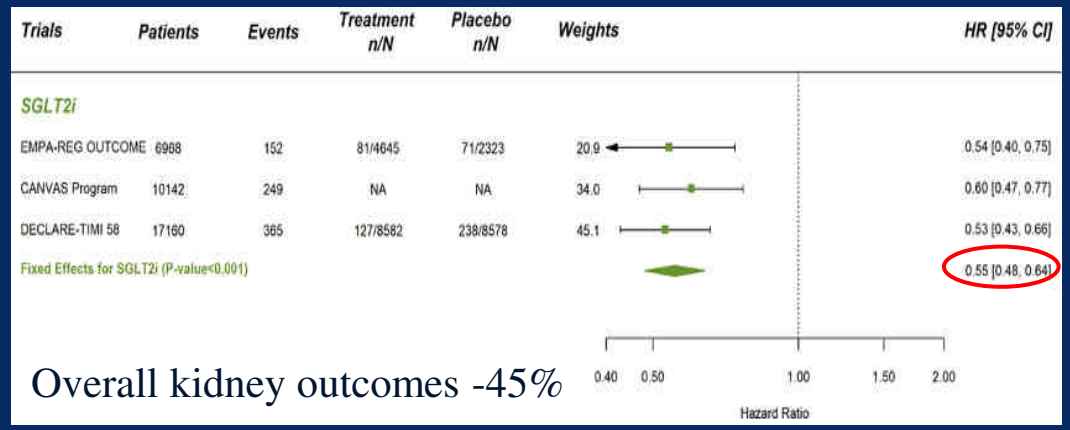


1.Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 2019 Jan 5;393:31-39.
2. Fitchett D, Zinman B, Wanner C, et al. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial. Eur Heart J. 2016 May 14;37:1526-34.

Meta-analysis

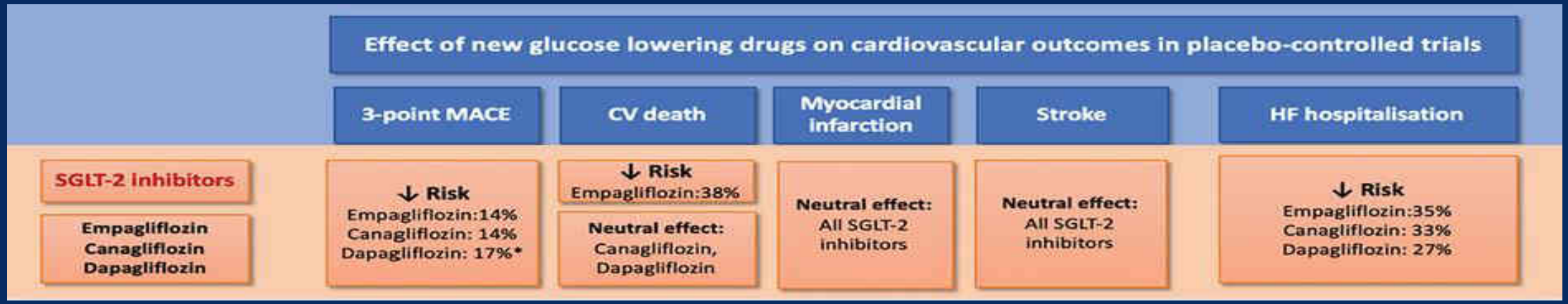


HHF -31%



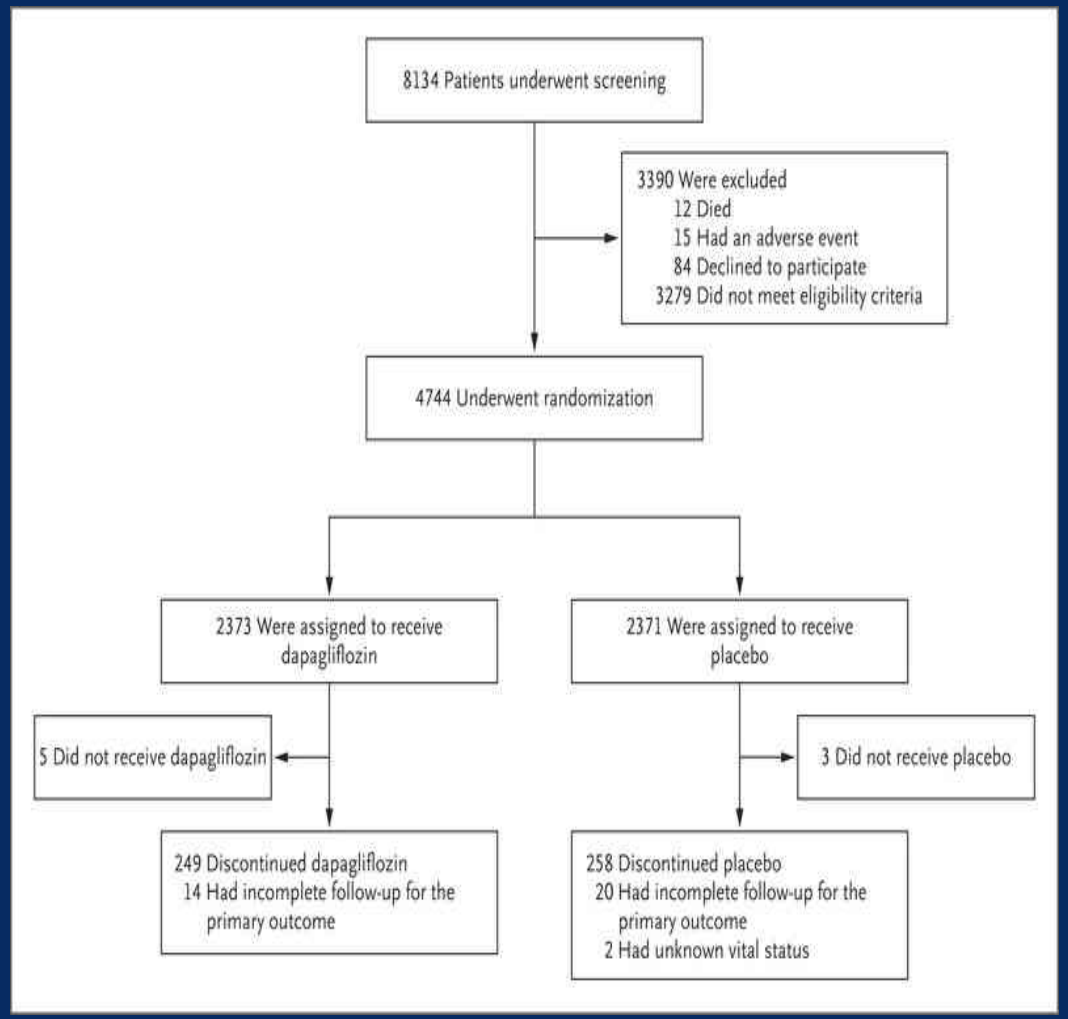
Overall kidney outcomes -45%

Modified: Zelniker TA, Wiviott SD, Raz I, et al. Comparison of the Effects of Glucagon-Like Peptide Receptor Agonists and Sodium-Glucose Cotransporter 2 Inhibitors for Prevention of Major Adverse Cardiovascular and Renal Outcomes in Type 2 Diabetes Mellitus. Circulation. 2019 Apr 23;139:2022-2031



Modified: Seferović PM, Coats AJS, Ponikowski P, et al. European Society of Cardiology/Heart Failure Association position paper on the role and safety of new glucose-lowering drugs in patients with heart failure. Eur J Heart Fail. 2020 Feb;22:196-213.

DAPA-HF



1. Provision of signed informed consent prior to any study specific procedures
2. Male or female, aged ≥18 years at the time of consent
3. Established documented diagnosis of symptomatic HFrEF (NYHA functional class II-IV)
4. LVEF≤40% (echocardiogram, radionuclide ventriculogram, contrast angiography or cardiac MRI) within the last 12 months prior to enrolment
5. NT-proBNP ≥600 pg/ml (or if hospitalized for heart failure within the previous 12 months, NT-proBNP ≥400 pg/ml) at enrolment (visit 1). If concomitant atrial fibrillation at Visit 1, NT-proBNP must be ≥900 pg/ml (irrespective of history of heart failure hospitalization)
6. Patients should receive background standard of care for HFrEF
7. eGFR ≥30 ml/min/1.73 m2 (CKD-EPI formula) at enrolment (visit 1)

McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019 Nov 21;381:1995-2008.

DAPA-HF

Characteristic	Dapagliflozin (N = 2373)	Placebo (N = 2371)
NYHA functional classification — no. (%)		
II	1606 (67.7)	1597 (67.4)
III	747 (31.5)	751 (31.7)
IV	20 (0.8)	23 (1.0)
Heart rate — beats/min	71.5±11.6	71.5±11.8
Systolic blood pressure — mm Hg	122.0±16.3	121.6±16.3
Left ventricular ejection fraction — %	31.2±6.7	30.9±6.9
Median NT-proBNP (IQR) — pg/ml	1428 (857–2655)	1446 (857–2641)

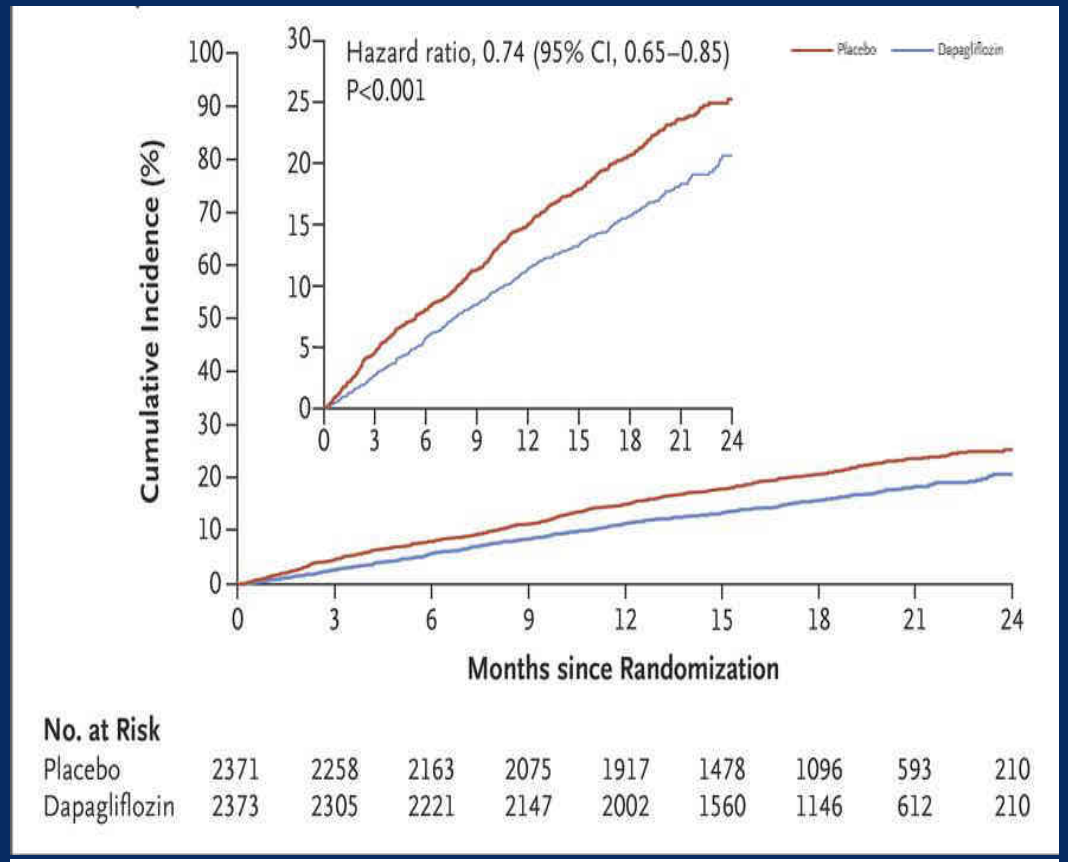
Mean age: 66.3 yrs
Women: 23.4%

41.8% diabetics
Median f-u: 18.2 m

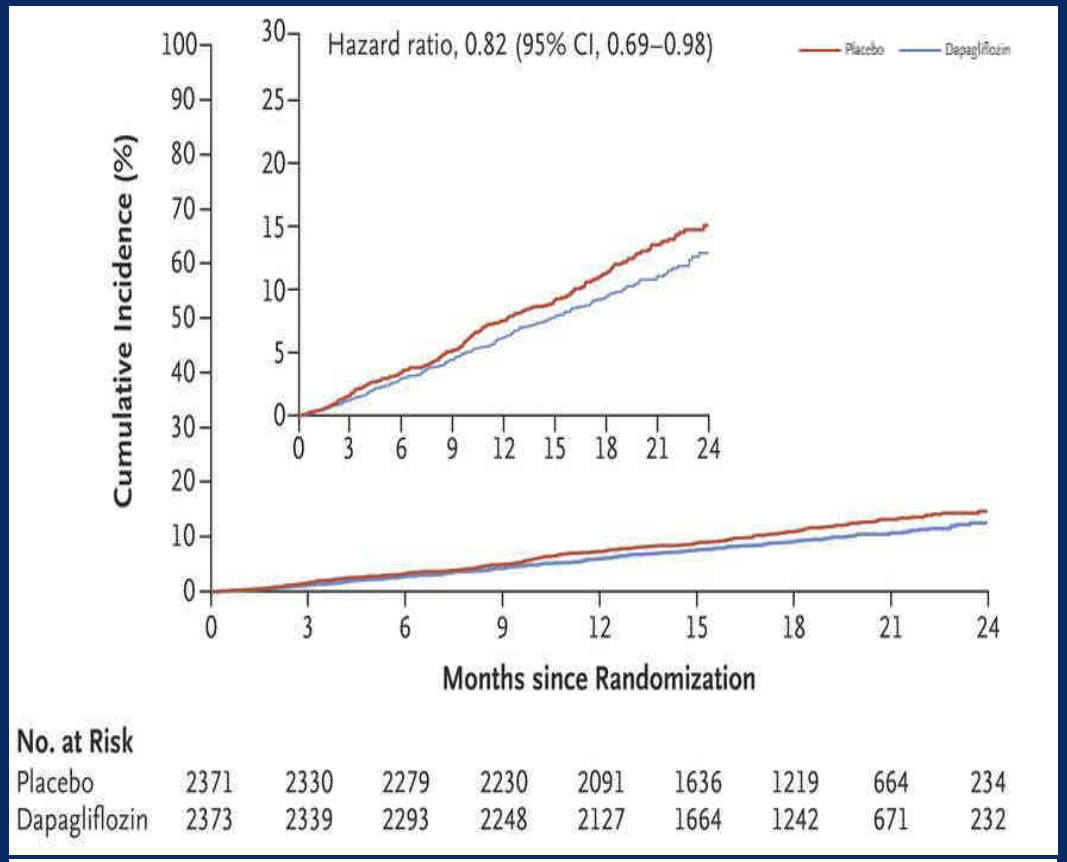
Characteristic	Dapagliflozin (N = 2373)	Placebo (N = 2371)
Heart failure medication — no. (%)		
Diuretic	2216 (93.4)	2217 (93.5)
ACE inhibitor	1332 (56.1)	1329 (56.1)
ARB	675 (28.4)	632 (26.7)
Sacubitril–valsartan	250 (10.5)	258 (10.9)
Beta-blocker	2278 (96.0)	2280 (96.2)
Mineralocorticoid receptor antagonist	1696 (71.5)	1674 (70.6)
Digitalis	445 (18.8)	442 (18.6)

McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019 Nov 21;381:1995-2008.

DAPA-HF



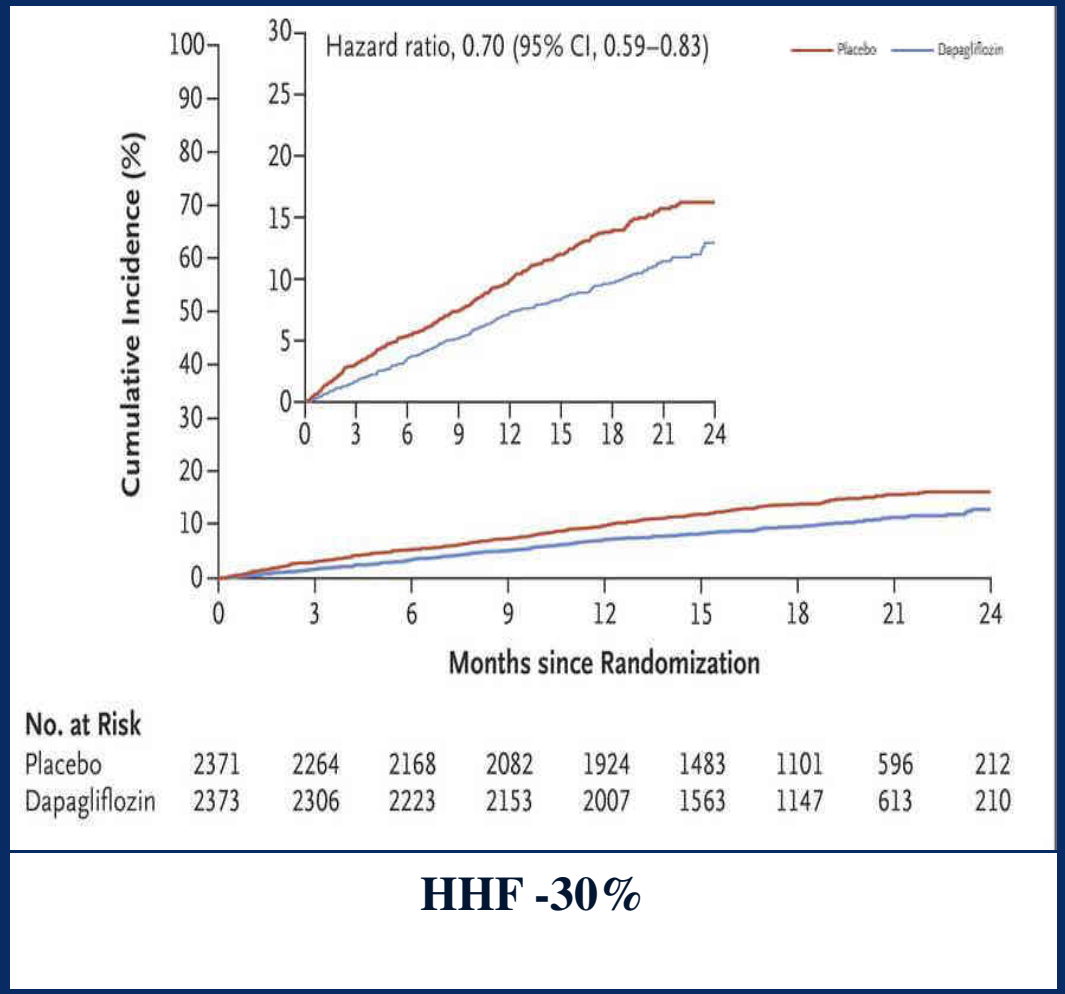
Primary outcome -26%
(CV death or worsening HF)



CV death -18%
Any death -17%

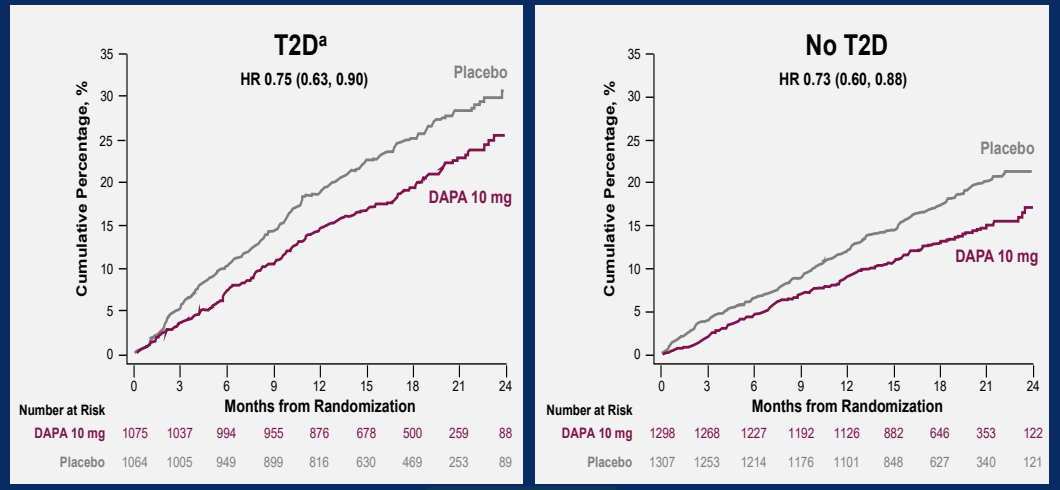
McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019 Nov 21;381:1995-2008.

DAPA-HF



HHF -30%

Dapagliflozin significantly reduced the primary endpoint, regardless of diabetes status



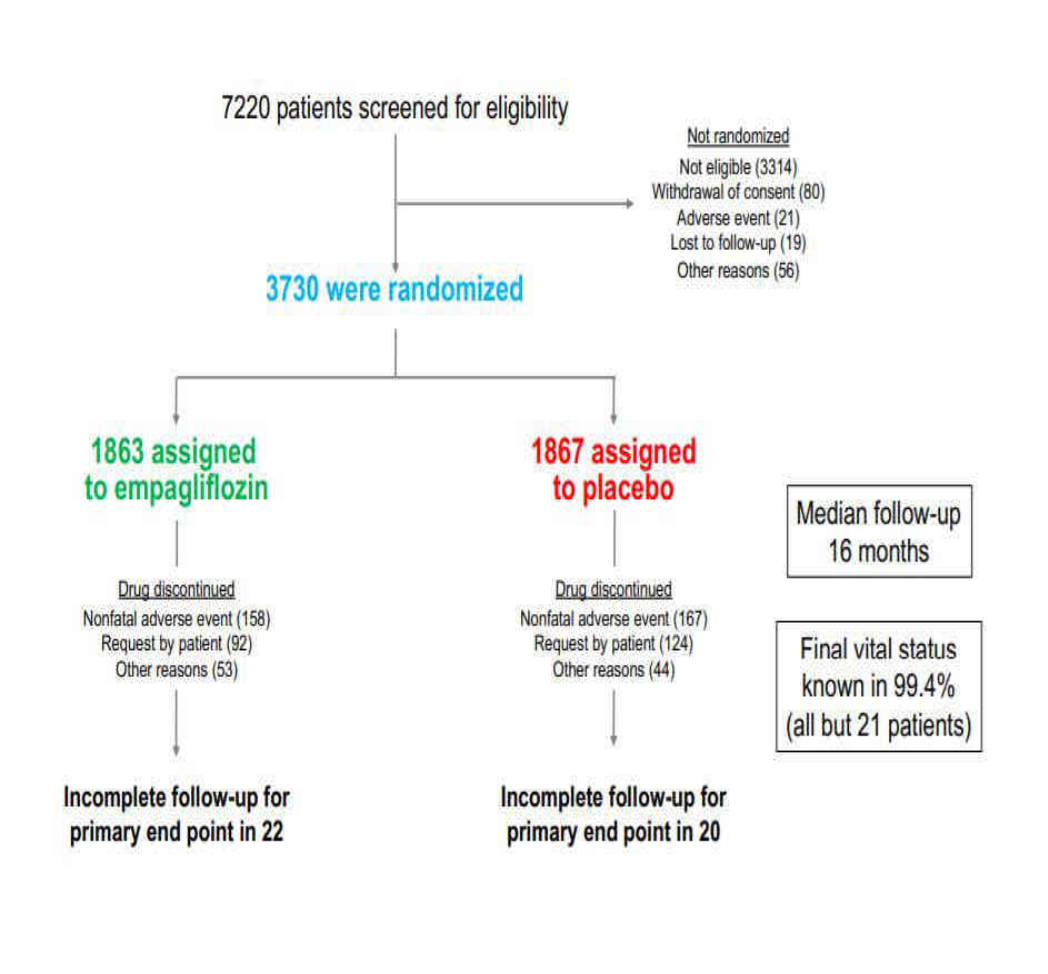
p-interaction=0.80

1. McMurray J. Presented at: AHA Scientific Sessions; November 16-18, 2019; Philadelphia, PA;
2. McMurray JJV et al. Online protocol. *N Engl J Med*. 2019.

Safety outcomes						
Discontinuation due to adverse event — no./total no. (%)	111/2368 (4.7)	—	116/2368 (4.9)	—	—	0.79
Adverse events of interest — no./total no. (%)						
Volume depletion	178/2368 (7.5)	—	162/2368 (6.8)	—	—	0.40
Renal adverse event	153/2368 (6.5)	—	170/2368 (7.2)	—	—	0.36
Fracture	49/2368 (2.1)		50/2368 (2.1)	—	—	1.00
Amputation	13/2368 (0.5)	—	12/2368 (0.5)	—	—	1.00
Major hypoglycemia[**]	4/2368 (0.2)	—	4/2368 (0.2)	—	—	NA
Diabetic ketoacidosis[††]	3/2368 (0.1)	—	0	—	—	NA
Fournier's gangrene	0	—	1/2368 (<0.1)	—	—	NA

McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019 Nov 21;381:1995-2008.

EMPEROR-Reduced



1. Age ≥ 18 years at screening. For Japan only: Age ≥ 20 years at screening
2. Men or women
3. Patients with CHF diagnosed for at least 3 months before Visit 1, and currently in NYHA functional class II, III or IV
4. Chronic heart failure with a reduced left ventricular ejection fraction (LVEF), defined as LVEF ≤ 40%
5. In addition to LVEF ≤ 40%, patients must have at least one of the following :
   a) If EF ≥36% to ≤40%: elevated NT-proBNP at Visit 1 ≥2500 pg/ml for patients without AF, OR ≥5000 pg/ml for patients with AF, analyzed at the Central Laboratory,
   b) If EF ≥31% to ≤35%: elevated NT-proBNP at Visit 1 ≥1000 pg/ml for patients without AF, OR ≥2000 pg/ml for patients with AF, analyzed at the Central Laboratory,
   c) If EF≤30%: elevated NT-proBNP at Visit 1 ≥600 pg/ml for patients without AF, OR ≥1200 pg/ml for patients with AF, analyzed at the Central Laboratory
   d) For EF≤ 40% and documented hospitalization for heart failure within 12 months prior to visit 1, elevated NT-proBNP at Visit 1 ≥600pg/ml for patients without AF and ≥1200 pg/ml for patients with AF
6. Appropriate dose of medical therapy for heart failure
7. Appropriate use of medical devices such as ICD or CRT
8. Body mass index (BMI) < 45 kg/m2 at Visit 1 (screening)
9. Signed and dated written ICF (informed consent) in accordance with GCP and local regulations, prior to admission to the trial

Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020 Oct 8;383:1413-1424.

EMPEROR-Reduced

Characteristic	Empagliflozin (N=1863)	Placebo (N=1867)
Left ventricular ejection fraction		
Mean value	27.7±6.0	27.2±6.1
Value of ≤30% — no. (%)	1337 (71.8)	1392 (74.6)
NT-proBNP		
Median value (IQR) — pg/ml	1887 (1077–3429)	1926 (1153–3525)
Value of ≥1000 pg/ml — no./total no. (%)	1463/1862 (78.6)	1488/1866 (79.7)
Estimated glomerular filtration rate		
Mean value — ml/min/1.73 m^2	61.8±21.7	62.2±21.5
Value of <60 ml/min/1.73 m^2 — no./total no. (%)	893/1862 (48.0)	906/1866 (48.6)

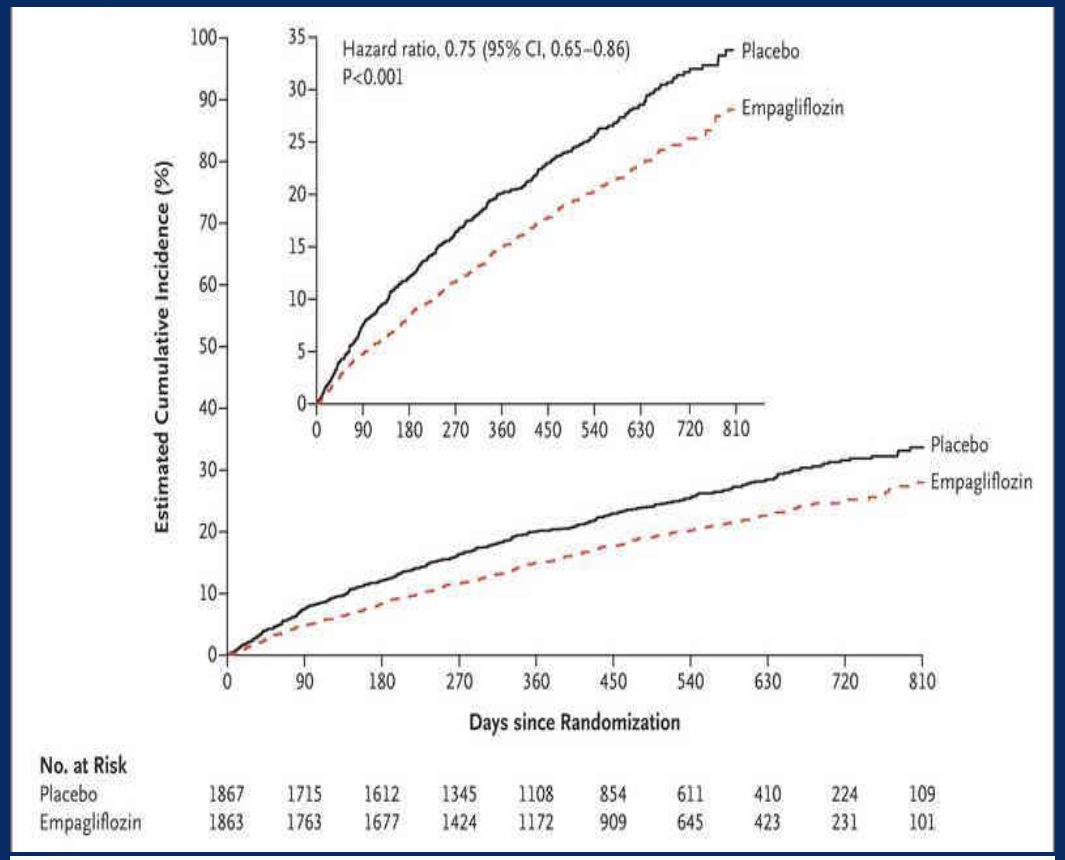
Mean age: 66.9 yrs
Women: 24%

49.8% diabetics
Median f-u: 16 m

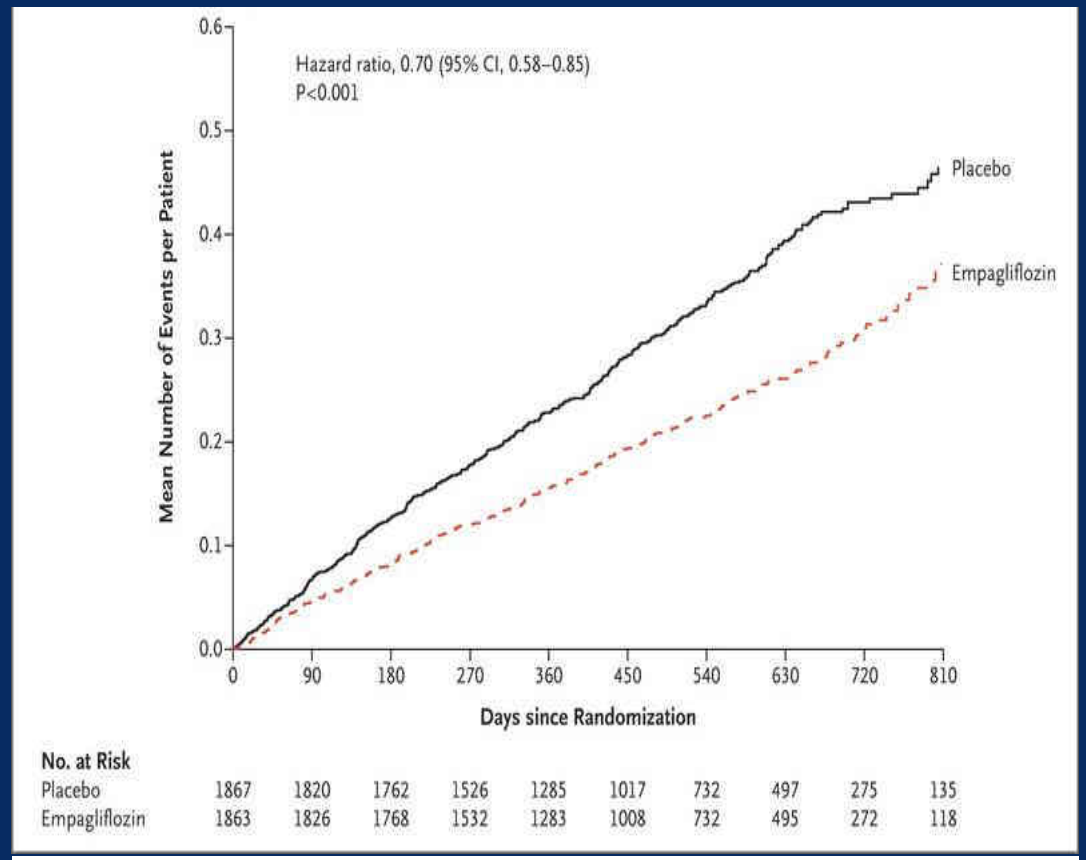
Characteristic	Empagliflozin (N=1863)	Placebo (N=1867)
Heart failure medication — no. (%)		
Renin–angiotensin inhibitor§		
Without neprilysin inhibitor	1314 (70.5)	1286 (68.9)
With neprilysin inhibitor	340 (18.3)	387 (20.7)
Mineralocorticoid receptor antagonist	1306 (70.1)	1355 (72.6)
Beta-blocker	1765 (94.7)	1768 (94.7)

Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020 Oct 8;383:1413-1424.

EMPEROR-Reduced



Primary outcome -25%
(time to CV death or HHF)

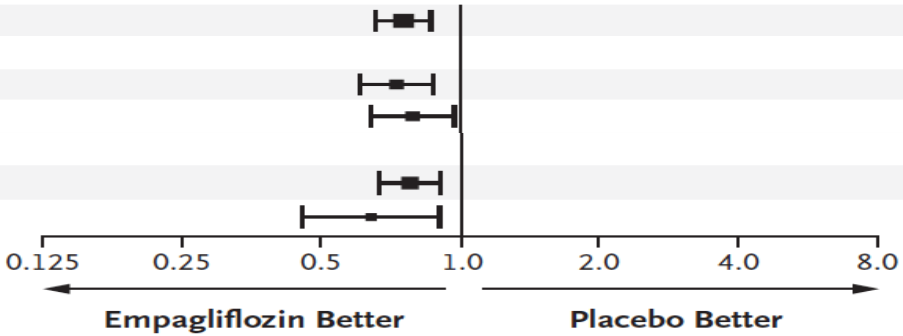


HHF -30%

Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020 Oct 8;383:1413-1424.

EMPEROR-Reduced

Subgroup	Empagliflozin	Placebo	Hazard Ratio (95% CI)
	no. of patients with events/total no.		
Overall	361/1863	462/1867	0.75 (0.65–0.86)
Baseline diabetes status			
Diabetes	200/927	265/929	0.72 (0.60–0.87)
No diabetes	161/936	197/938	0.78 (0.64–0.97)
Baseline use of ARNi			
No	310/1523	369/1480	0.77 (0.66–0.90)
Yes	51/340	93/387	0.64 (0.45–0.89)



Selected adverse events of interest

Hypotension	176 (9.4)	163 (8.7)
Symptomatic hypotension	106 (5.7)	103 (5.5)
Volume depletion	197 (10.6)	184 (9.9)
Ketoacidosis	0 (0.0)	0 (0.0)
Hypoglycemic events*	27 (1.4)	28 (1.5)
In patients with type 2 diabetes	20 (2.2)	22 (2.4)
In patients without type 2 diabetes	7 (0.7)	6 (0.6)
Urinary tract infections	91 (4.9)	83 (4.5)
Complicated urinary tract infections	19 (1.0)	15 (0.8)
Genital infections	31 (1.7)	12 (0.6)
Complicated genital infections	6 (0.3)	5 (0.3)
Bone fractures	45 (2.4)	42 (2.3)
Events leading to lower limb amputation	13 (0.7)	10 (0.5)

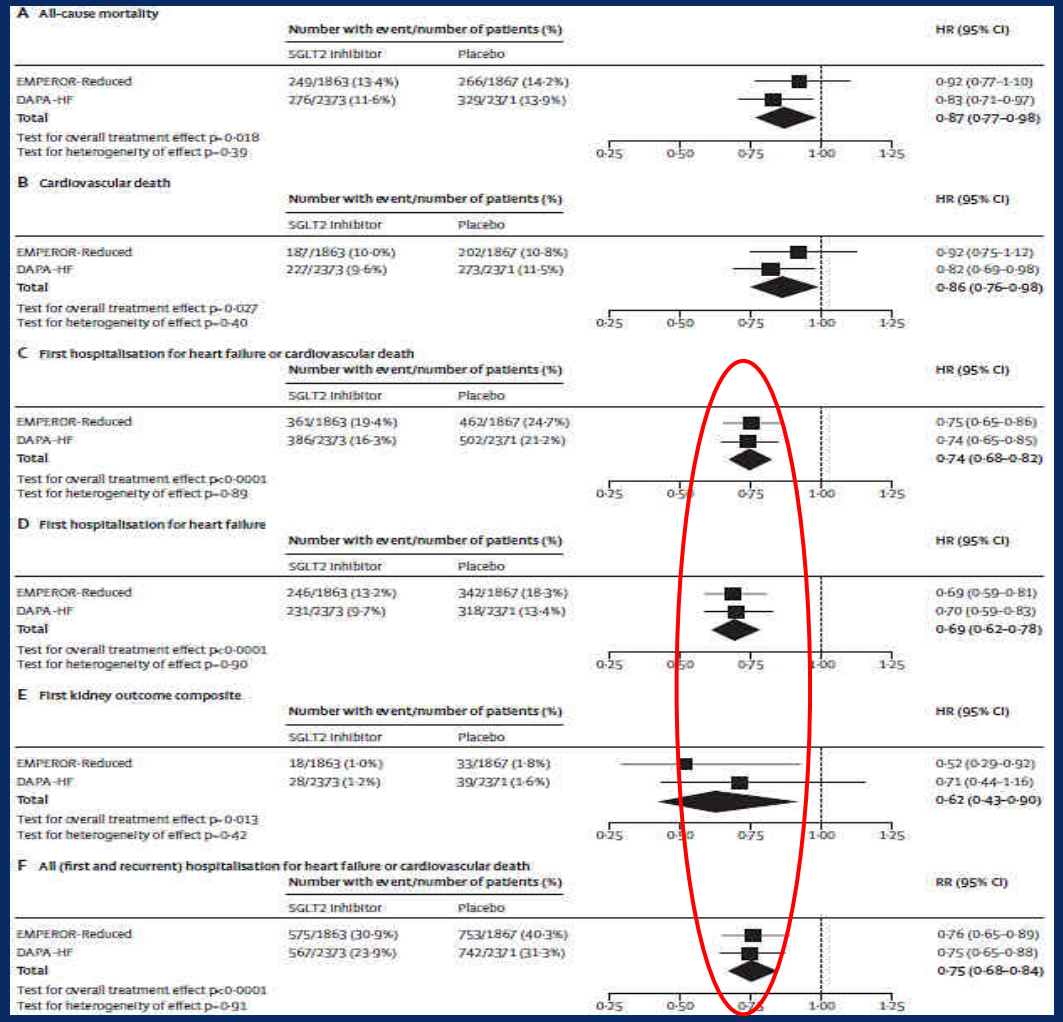
Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020 Oct 8;383:1413-1424.

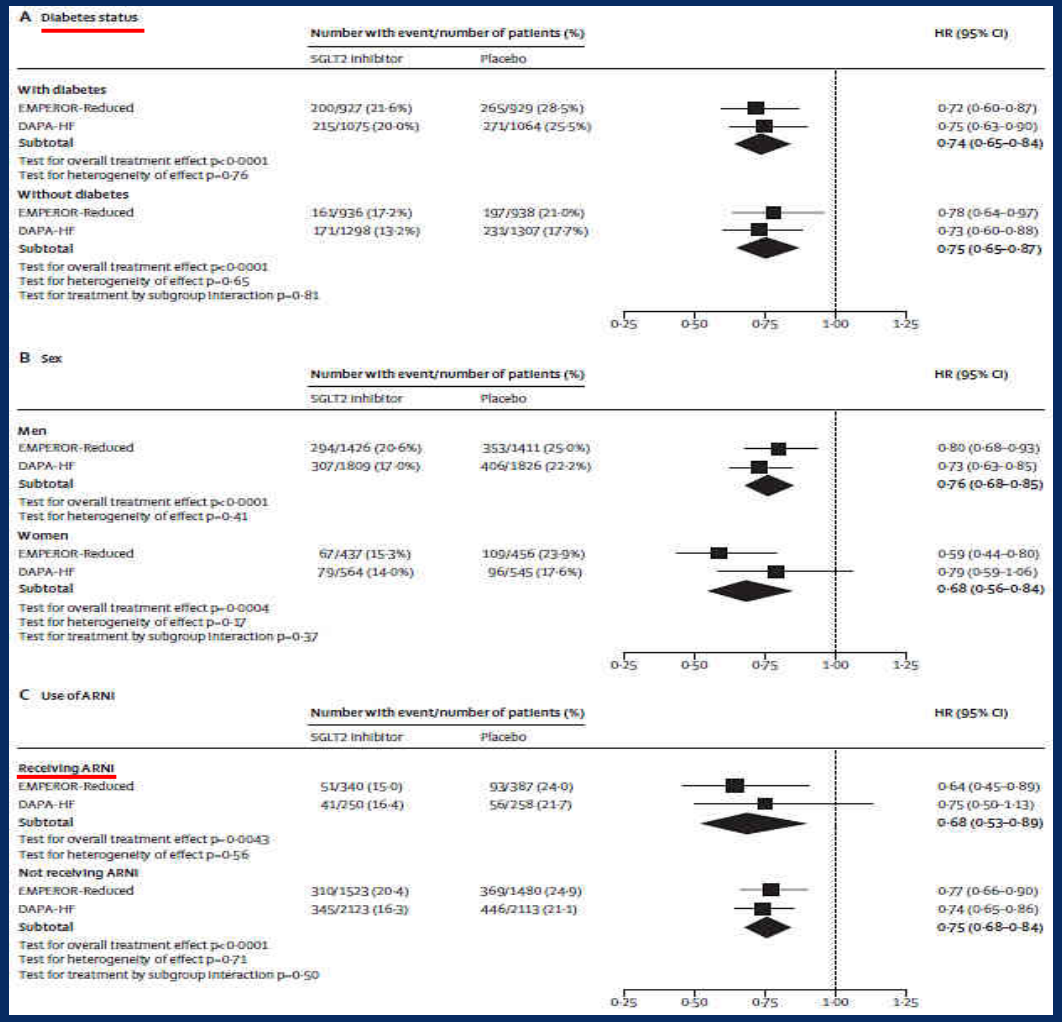
Comparison

	EMPEROR-Reduced N=3730	DAPA-HF N=4744
Median follow-up (mo)	≈16	≈18
Inclusion criteria	• LVEF ≤30% and NT-proBNP ≥600 pg/mL (without AF) and ≥1200 pg/mL (with AF) • LVEF 31%–35% and NT-proBNP ≥1000 pg/mL (without AF) and ≥2000 pg/mL (with AF) • LVEF 36%–40% and NT-proBNP ≥2500 pg/mL (without AF) and ≥5000 pg/mL (with AF) • LVEF ≤40% and HHF in past 12 mo and NT-proBNP ≥600 pg/mL (without AF) and ≥1200 pg/mL (with AF) • eGFR ≥20 mL·min^{-1}·1.73 m^{-2}	• LVEF ≤40% and NT-proBNP ≥600 pg/mL (without AF) or ≥900 pg/mL (with AF) • LVEF ≤40% and HHF in past 12 mo and NT-proBNP ≥400 pg/mL (without AF) or ≥900 pg/mL (with AF) • eGFR ≥30 mL·min^{-1}·1.73 m^{-2}
Demographics and key clinical history of the placebo groups*		
Age, y	66.5	66.5
Women, %	24.4	23.0
Body mass index, kg/m^2	27.8	28.1
eGFR, mL·min^{-1}·1.73 m^{-2}	62.2	65.5
Diabetes, %	49.8	41.8
Atrial fibrillation, %	37.8	38.0
Features of heart failure in the placebo groups		
Left ventricular ejection fraction (%)	27.2	30.9
Median NT-proBNP, pg/mL	1926	1446
Ischemic cardiomyopathy, %	50.7	57.3
HHF in previous 12 mo, %	30.7	27.4
NYHA class II/III/IV, %	75.0/24.4/0.6	67.4/31.7/1.0
Baseline heart failure therapies of the placebo groups, %		
ACE inhibitor or angiotensin receptor blocker without ARNI	68.9	82.8
β-Blocker	94.7	96.2
MRA	72.6	70.6
ARNI	20.7	10.9
Implantable cardioverter-defibrillator	31.8	26.1
Cardiac resynchronization therapy	11.9	6.9
Placebo event rates/100 patient-years, %		
Cardiovascular death or HHF	21.0	15.3
HHF	15.5	9.8
Cardiovascular death	8.1	7.9
All-cause mortality	10.7	9.5

Verma S, McGuire DK, Kosiborod MN. Two Tales: One Story: EMPEROR-Reduced and DAPA-HF. Circulation. 2020 Dec 8;142:2201-2204.

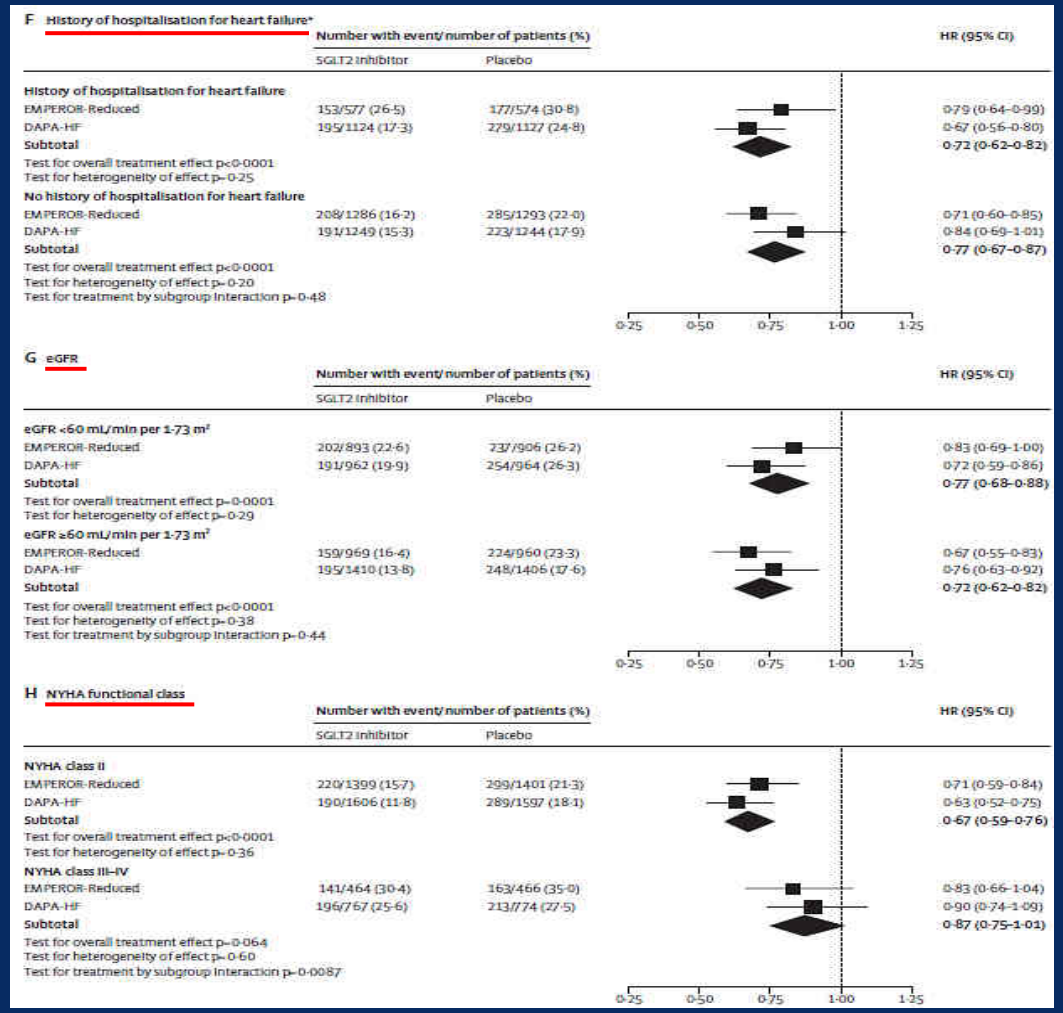
Meta-analysis





Zannad F, Ferreira JP, Pocock SJ, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. Lancet. 2020 Sep 19;396:819-829.

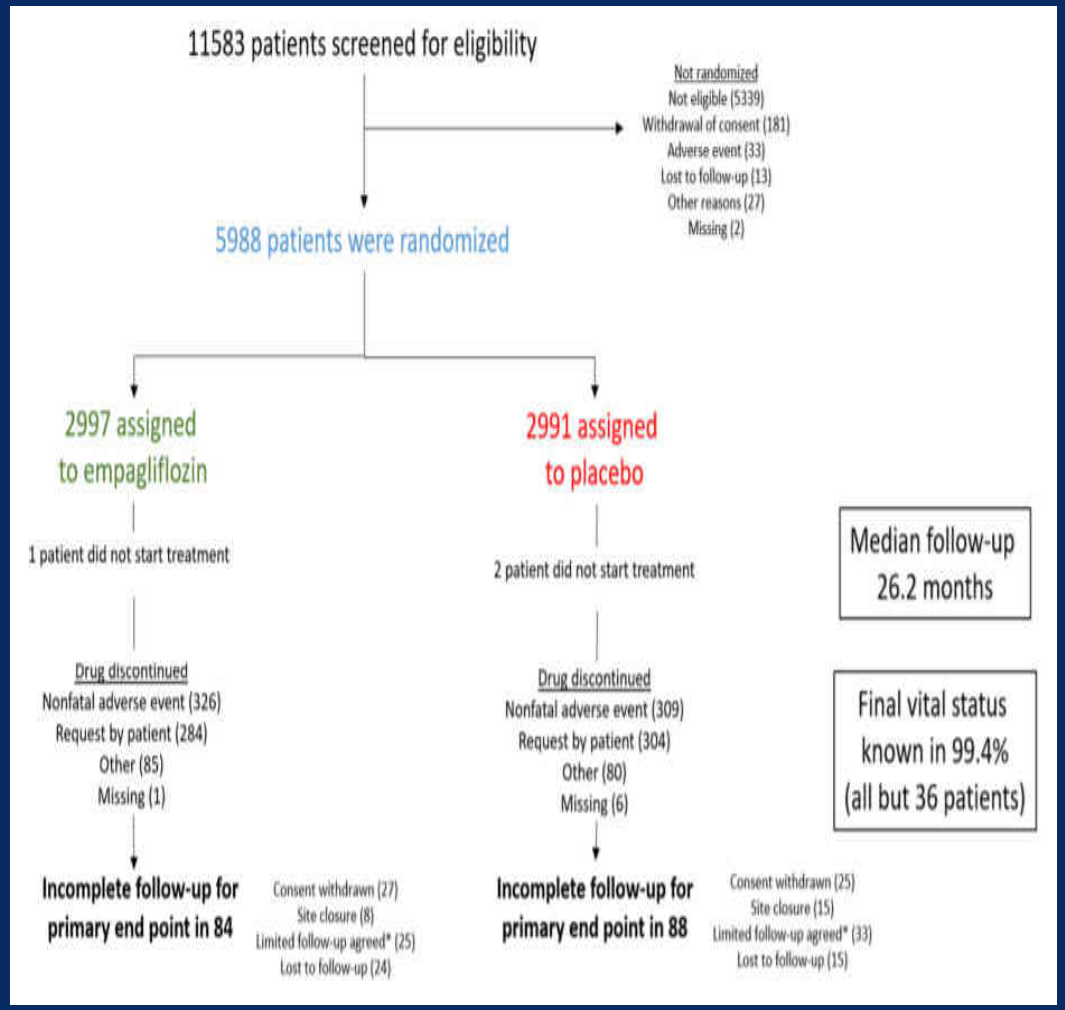
Meta-analysis



	EMPEROR-Reduced		DAPA-HF	
	Empagliflozin (n=1863)	Placebo (n=1867)	Dapagliflozin (n=2373)	Placebo (n=2371)
Serious adverse events	772 (41·4%)	896 (48·1%)	846 (35·7%)	951(40·2%)
Any renal adverse event	175 (9·4%)	192 (10·3%)	141 (6·0%)	158 (6·7%)
Volume depletion	197 (10·6%)	184 (9·9%)	170 (7·2%)	153 (6·5%)
Ketoacidosis	0	0	3 (0·1%)	0
Severe hypoglycaemic events	6 (0·3%)	7 (0·4%)	4 (0·2%)	4 (0·2%)
Bone fractures	45 (2·4%)	42 (2·3%)	48 (2·0%)	47 (2·0%)
Lower limb amputation	13 (0·7%)	10 (0·5%)	13 (0·5%)	12 (0·5%)
Fournier's Gangrene	1 (0·1%)	0	0	1 (0·1%)

Zannad F, Ferreira JP, Pocock SJ, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. Lancet. 2020 Sep 19;396:819-829.

EMPEROR-Preserved



1. Age ≥ 18 years at screening. For Japan only: Age ≥ 20 years
2. Male or female patients.
3. Patients with chronic HF diagnosed for at least 3 months before Visit 1, and currently in HF NYHA class II-IV
4. Chronic HF with preserved EF defined as LVEF > 40 %
5. Elevated NT-proBNP > 300 pg/ml for patients without AF, OR > 900 pg/ml for patients with AF, analysed at the Central laboratory at Visit 1
6. Patients must have at least one of the following evidence of HF:
   a. Structural heart disease (left atrial enlargement and/or left ventricular hypertrophy) documented by echocardiogram at Visit 1 or within 6 months prior to Visit 1, OR
   b. Documented HHF within 12 months prior to Visit 1
7. Oral diuretics, if prescribed to patient according to local guidelines and discretion of the Investigator, should be stable for at least 1 week prior to Visit 2 (Randomisation)
8. Body Mass Index (BMI) < 45 kg/m^2 at Visit 1
9. Signed and dated written ICF in accordance with GCP and local legislation prior to admission to the trial.

Anker SD, Butler J, Filippatos G, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021 Aug 27.

EMPEROR-Preserved

Characteristic	Empagliflozin (N = 2997)	Placebo (N = 2991)
NYHA functional classification — no. (%)		
Class I	3 (0.1)	1 (<0.1)
Class II	2432 (81.1)	2451 (81.9)
Class III	552 (18.4)	531 (17.8)
Class IV	10 (0.3)	8 (0.3)
Left ventricular ejection fraction		
Mean left ventricular ejection fraction — %	54.3±8.8	54.3±8.8
Left ventricular ejection fraction >40% to <50% — no. (%)§	995 (33.2)	988 (33.0)
Left ventricular ejection fraction ≥50% to <60% — no. (%)	1028 (34.3)	1030 (34.4)
Left ventricular ejection fraction ≥60% — no. (%)	974 (32.5)	973 (32.5)
Median NT-proBNP (interquartile range) — pg/ml	994 (501–1740)	946 (498–1725)
Heart failure category — no. (%)		
Ischemic	1079 (36.0)	1038 (34.7)
Nonischemic	1917 (64.0)	1953 (65.3)

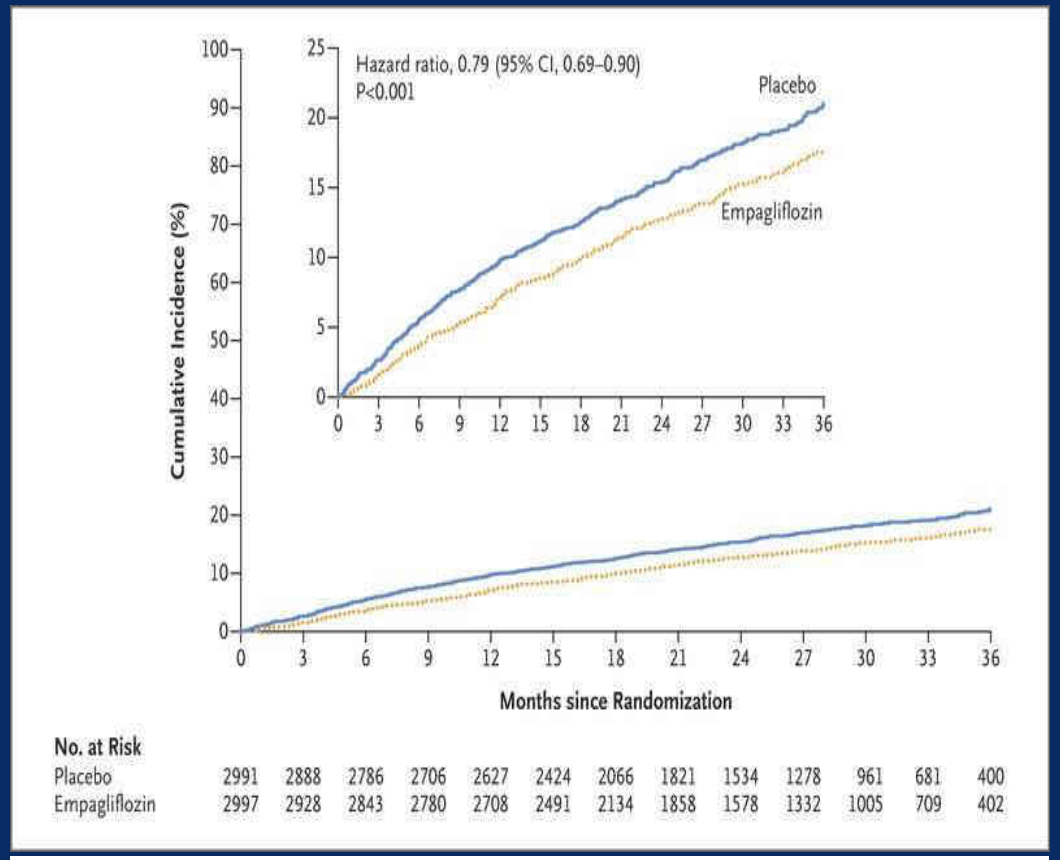
Mean age: 71.8 yrs
Women: 44.6%

Median f-u: 26.2 m

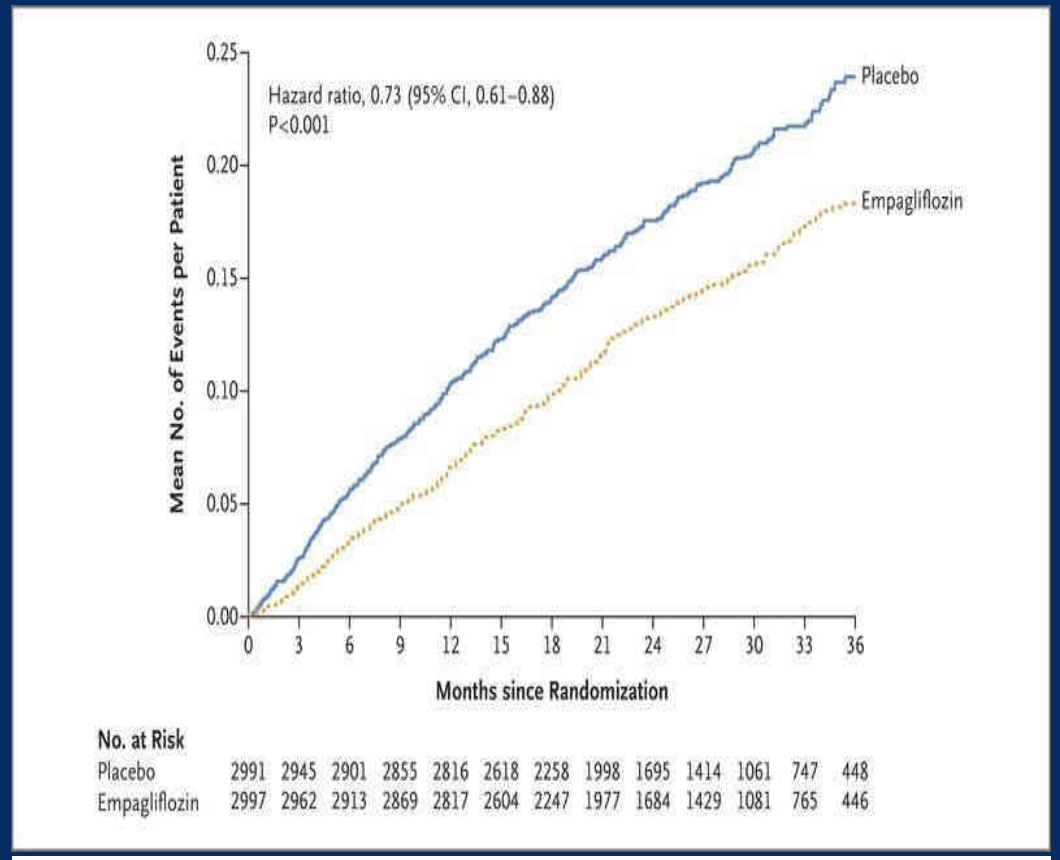
Characteristic	Empagliflozin (N = 2997)	Placebo (N = 2991)
Cardiovascular history — no. (%)		
Hospitalization for heart failure during previous 12 mo	699 (23.3)	670 (22.4)
Atrial fibrillation	1543 (51.5)	1514 (50.6)
Diabetes mellitus	1466 (48.9)	1472 (49.2)
Hypertension	2721 (90.8)	2701 (90.4)
Mean eGFR — ml/min/1.73 m^2	60.6±19.8	60.6±19.9
eGFR <60 ml/min/1.73 m^2 — no./total no. (%)	1504/2997 (50.2)	1484/2989 (49.6)

Anker SD, Butler J, Filippatos G, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021 Aug 27.

EMPEROR-Preserved



Primary outcome -21%
(time to CV death or HHF)



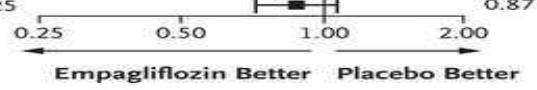
HHF -27%

Anker SD, Butler J, Filippatos G, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021 Aug 27.

EMPEROR-Preserved

Subgroup	Empagliflozin (no. of patients with events/total no.)	Placebo (no. of patients with events/total no.)	Hazard Ratio (95% CI)
Overall	415/2997	511/2991	0.79 (0.69–0.90)
Diabetes at baseline			
Yes	239/1466	291/1472	0.79 (0.67–0.94)
No	176/1531	220/1519	0.78 (0.64–0.95)
LVEF at baseline			
<50%	145/995	193/988	0.71 (0.57–0.88)
≥50% to <60%	138/1028	173/1030	0.80 (0.64–0.99)
≥60%	132/974	145/973	0.87 (0.69–1.10)

Subgroup	Empagliflozin (no. of patients with events/total no.)	Placebo (no. of patients with events/total no.)	Hazard Ratio (95% CI)
Hospitalization for heart failure ≤12 mo			
No	258/2298	319/2321	0.81 (0.68–0.95)
Yes	157/699	192/670	0.73 (0.59–0.90)
NYHA class at baseline			
II	275/2435	361/2452	0.75 (0.64–0.87)
III or IV	140/562	150/539	0.86 (0.68–1.09)
NT-proBNP at baseline (calculated by atrial fibrillation/flutter status)			
<Median	126/1477	168/1508	0.76 (0.61–0.96)
≥Median	288/1516	341/1476	0.78 (0.67–0.91)
Use of ACE-inhibitor, ARB, or ARNI at baseline			
No	90/569	121/587	0.75 (0.57–0.99)
Yes	325/2428	390/2404	0.80 (0.69–0.93)
Use of MRA at baseline			
No	233/1878	306/1866	0.73 (0.62–0.87)
Yes	182/1119	205/1125	0.87 (0.71–1.06)



Anker SD, Butler J, Filippatos G, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021 Aug 27.

Which, When, How to use?

- Naive patient
- Chronic heart failure
- Worsening heart failure