Update on Diabetes CV Outcome Trials

Update on Diabetes CV Outcome Trials

Woodrow Corey M.D.; FACC

FINANCIAL DISCLOSURE**:**

Speaker Bureau for Boehringer Ingelheim, Amarin, and Eli Lilly

Live Content Slide

When playing as a slideshow, this slide will display live content

Poll: A patient with Type 2 DM and a prior MI has a reduced life expectancy of how many years?

Live Content Slide

When playing as a slideshow, this slide will display live content

Poll: Relative to a nondiabetic patient, a patient with CHF and Type 2 DM has what increased risk of CV death?

Live Content Slide

When playing as a slideshow, this slide will display live content

Poll: Lower Hemoglobin A1C and glycemic control have been shown to reduce CV death?

Causes of death in people with T2D

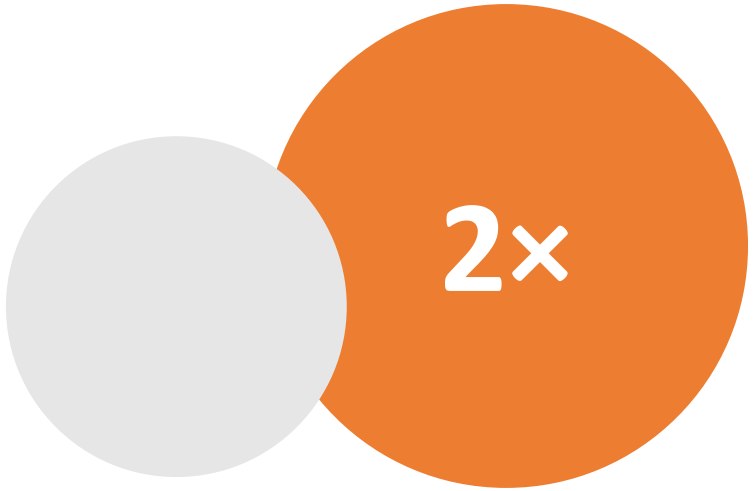
% of deaths of people with T2D[1]

CVD
52–80%

Renal disease
10–20%

Cerebrovascular
15%

T2D doubles the risk of CVD compared with adults without T2D[1]



1. Nwaneri et al. Br J Diabetes Vasc Dis 2013;13:192

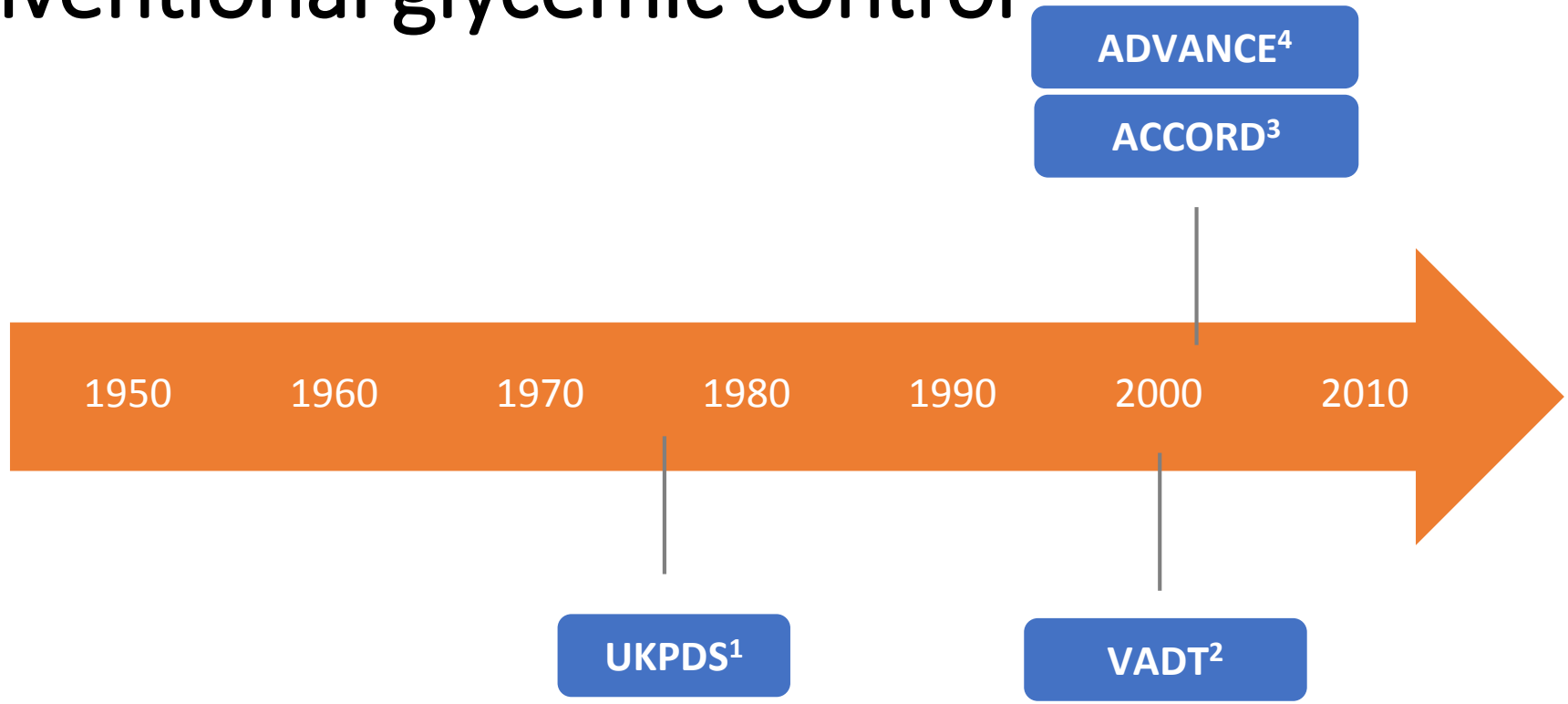
SIGNIFICANTLY REDUCED LIFE EXPECTANCY WITH HIGH CV RISK

CV disease is represented by myocardial infarction (MI) or stroke.

*Based on ~60 years of age and adjusted for sex.

1. The Emerging Risk Factors Collaboration. JAMA. 2015;314(1):52-60; 2. World Heart Federation. Cardiovascular disease risk factors. http://www.world-heart-federation.org/cardiovascular-health/cardiovascular-disease-risk-factors/ Accessed September 21, 2016.

Major T2D CV outcome trials focused on intensive vs conventional glycemic control

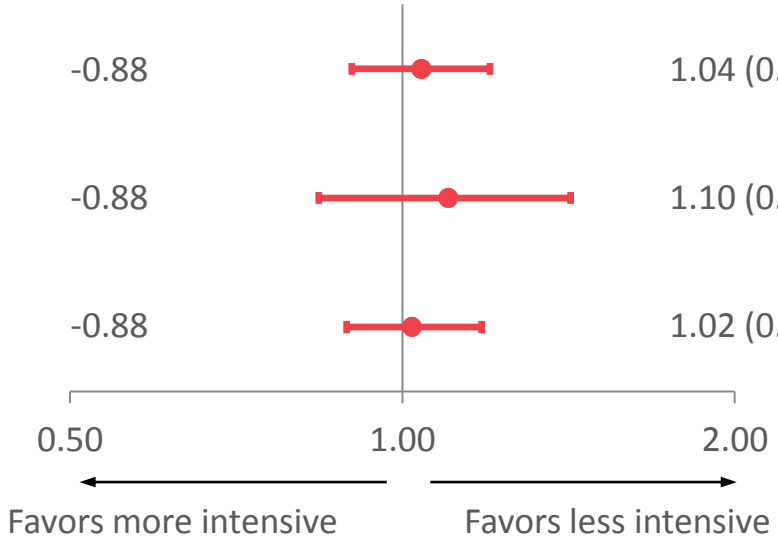


Date of first patient enrolment

- 1. UKPDS 33. Lancet 1998;352:837–53. 2. Duckworth et al. N Engl J Med 2009;360:129–39. 3. Gerstein for ACCORD. N Engl J Med 2008;358:2545–59. 4. Patel for ADVANCE. N Engl J Med 2008;358:2560–72

Meta-analysis of intensive glucose control in T2DM: mortality

	Number of events			
	More intensive	Less intensive	Difference in HbA1c (%)	HR (95% CI)
All-cause mortality	980	884	-0.88	1.04 (0.90,1.20)
CV death	497	441	-0.88	1.10 (0.84,1.42)
Non-CV death	476	432	-0.88	1.02 (0.89,1.18)



- Meta-analysis of 27,049 participants and 2,370 major vascular events from
  - ADVANCE
  - UKPDS
  - ACCORD
  - VADT

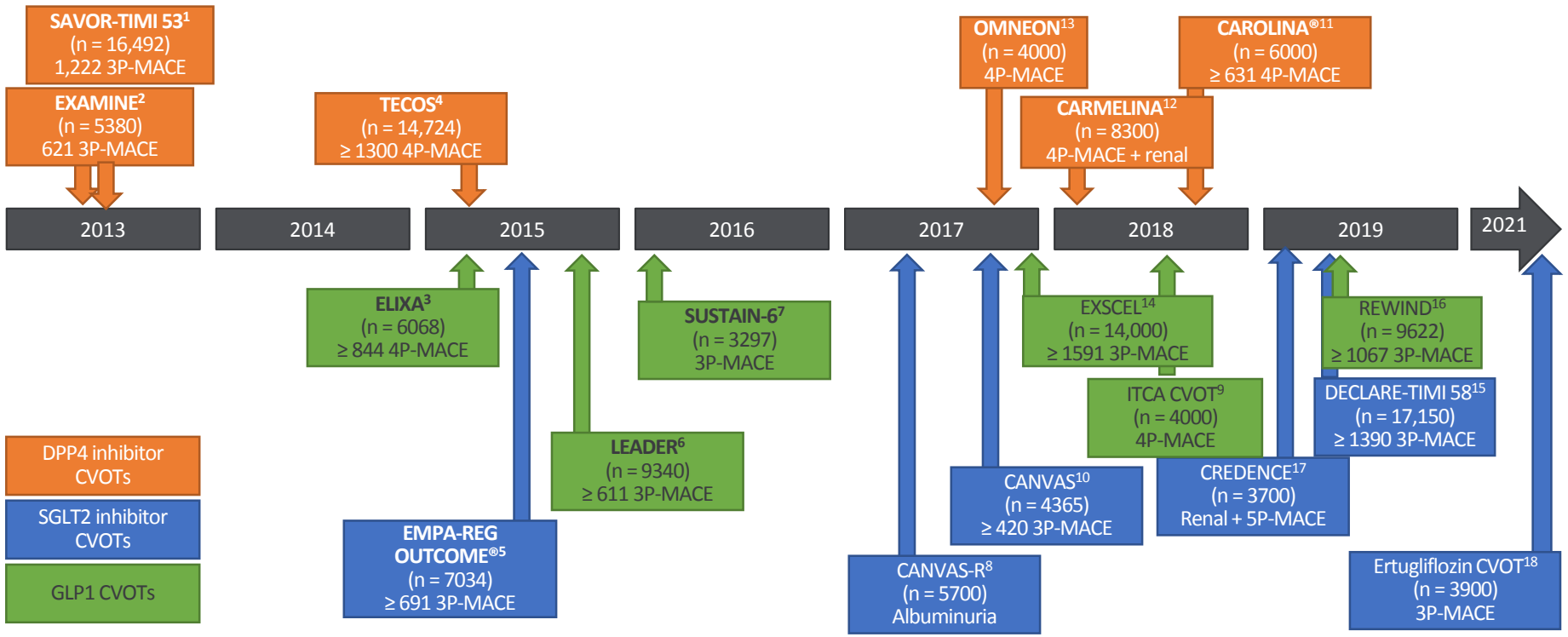
HR, hazard ratio; CV, cardiovascular
Turnbull FM et al. Diabetologia 2009;52:2288–2298

FDA Guidance for CVD Risk

Upper bound of a 2-sided 95% confidence interval for estimated CV risk	
>1.8	The data are inadequate to support approval. A large safety trial should be conducted
1.3 – 1.8	The potential for CV harm may still exist. An adequately powered and designed post-marketing trial is necessary to show an upper bound < 1.3*
<1.3	A post-marketing trial is generally not needed*
*with a reassuring point estimate for overall CV risk	

FDA Guidance for Industry: Diabetes Mellitus – Evaluating CV risk in new antidiabetic therapies to treat type 2 diabetes.
www.fda.gov

CV safety trials are being conducted for each compound within the newer classes



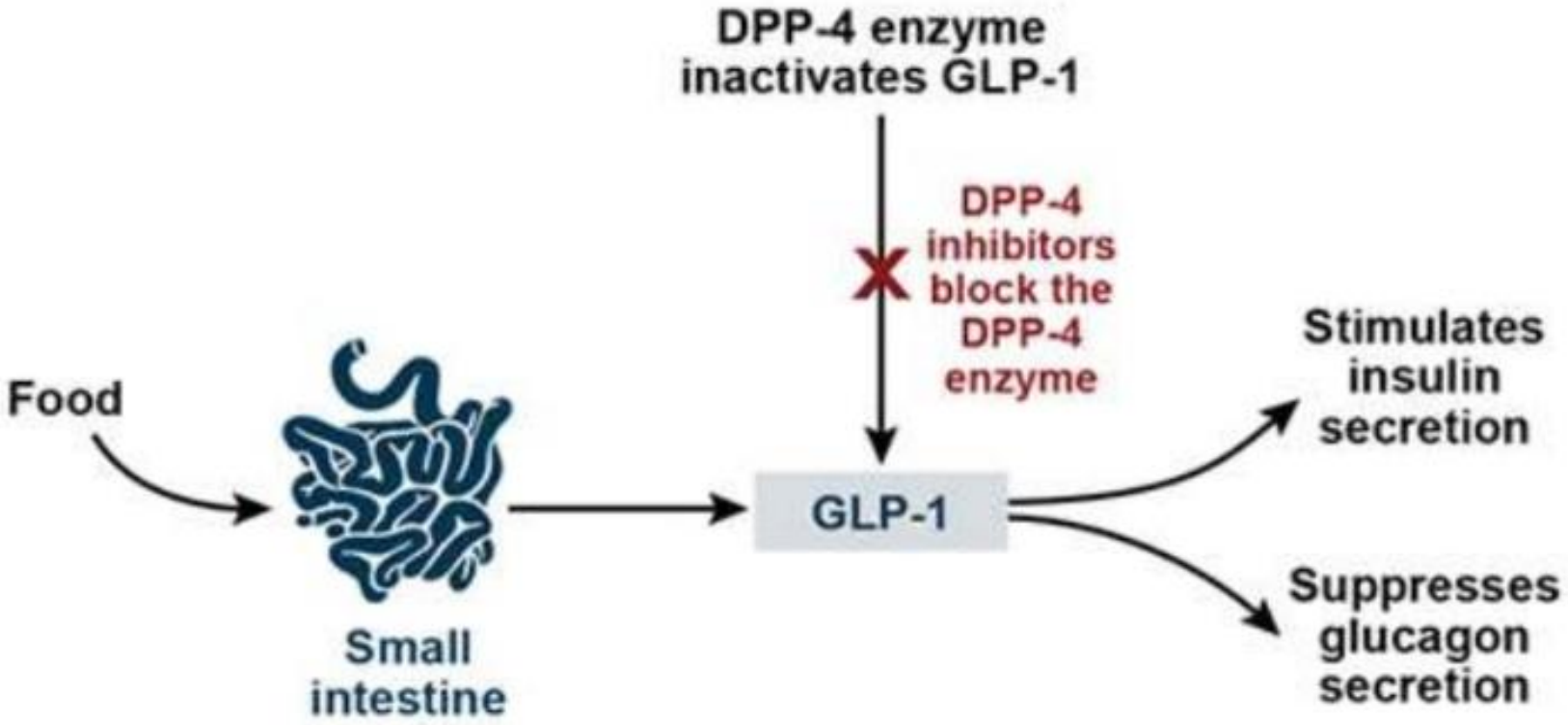
- Timings represent estimated completion dates as per ClinicalTrials.gov
- Adapted from Johansen. World J Diabetes 2015; in press (references 1–18 expanded in slide notes)

Cardiovascular Outcomes Trials

Name of trial	Drug	Estimated enrollment
SAVOR TIMI-53	Saxagliptin	18,206
CAROLINA	Linagliptin	6,000
CARMELINA	Linagliptin	8,300
TECOS	Sitagliptin	14,000
EXAMINE	Alogliptin	5,380
EXSCEL	Exenatide-QW	14,000
REWIND	Dulaglutide	9,622
LEADER	Liraglutide	9,340
SUSTAIN	Semaglutide	3,297
ELIXA	Lixisenatide	6,000
DECLARE TIMI-58	Dapagliflozin	27,000
CANVAS	Canagliflozin	4,335
CANVAS-R	Canagliflozin	5,700
CREDENCE	Canagliflozin	3,627
EMPA-REG OUTCOME	Empagliflozin	7,000

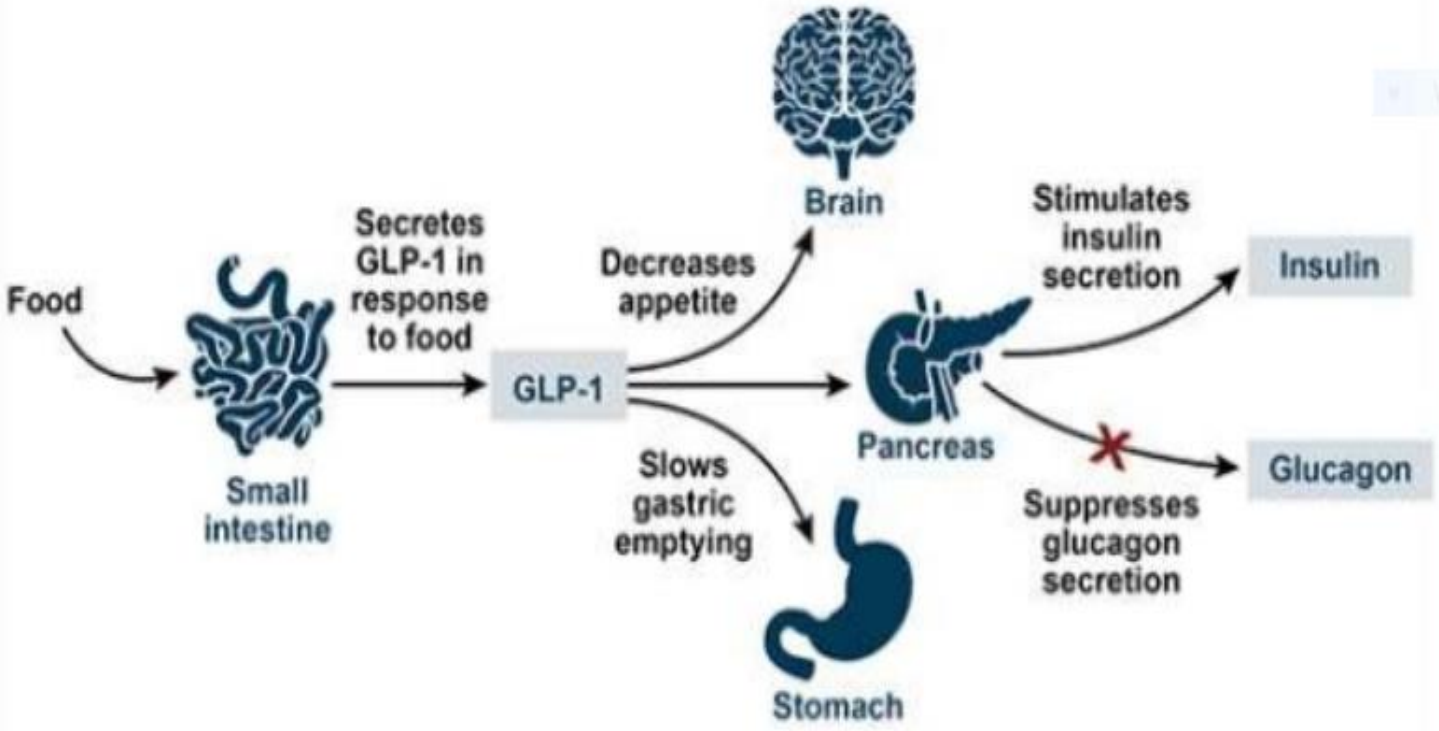
DPP-4 Inhibitors

Mechanism of Action



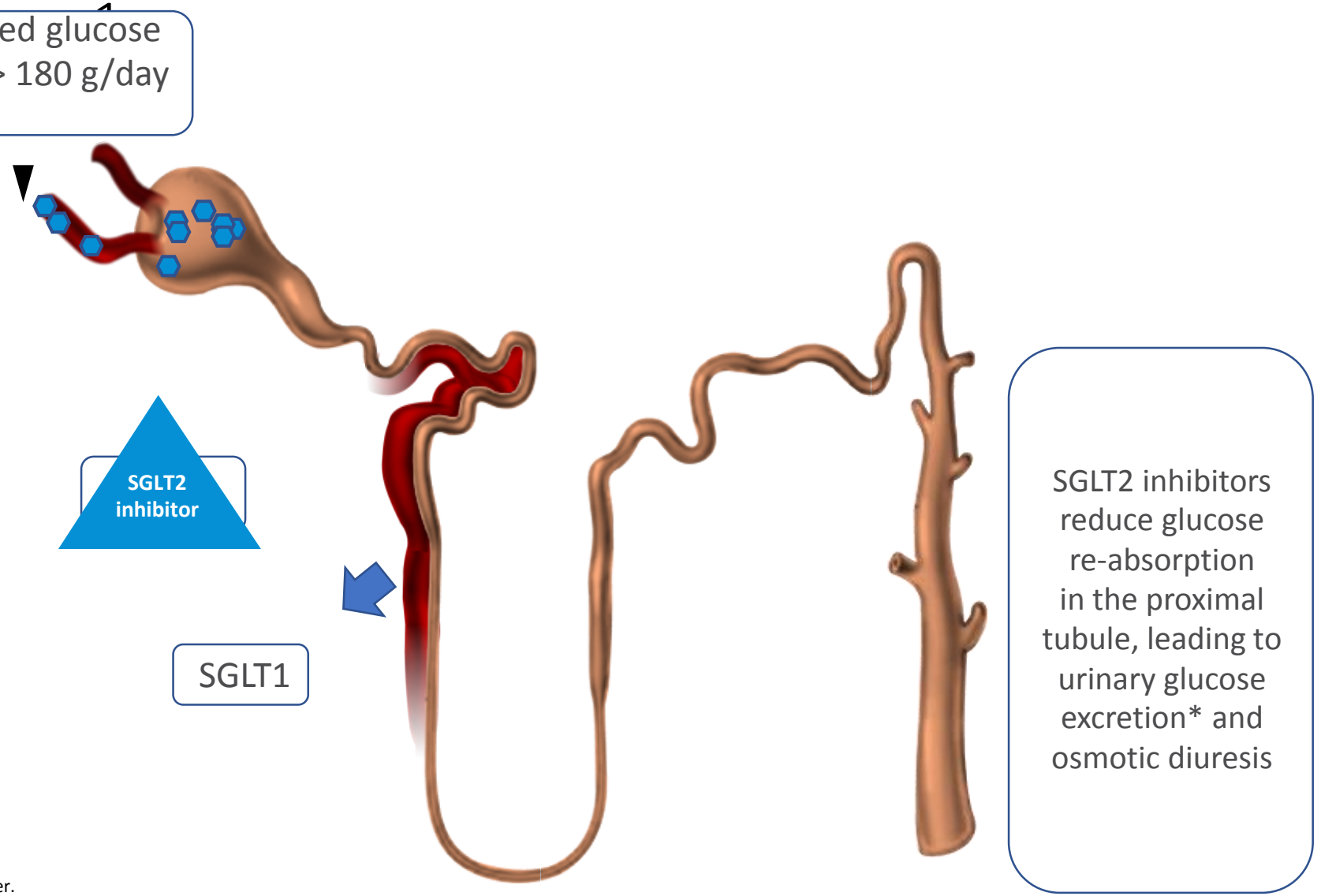
Drucker DJ. *Diabetes Care*. 2007;30:1335-1343.

GLP-1 RAs
Mechanism of Action



Meier JJ. *Nat Rev Endocrinol*. 2012;8:728-742.

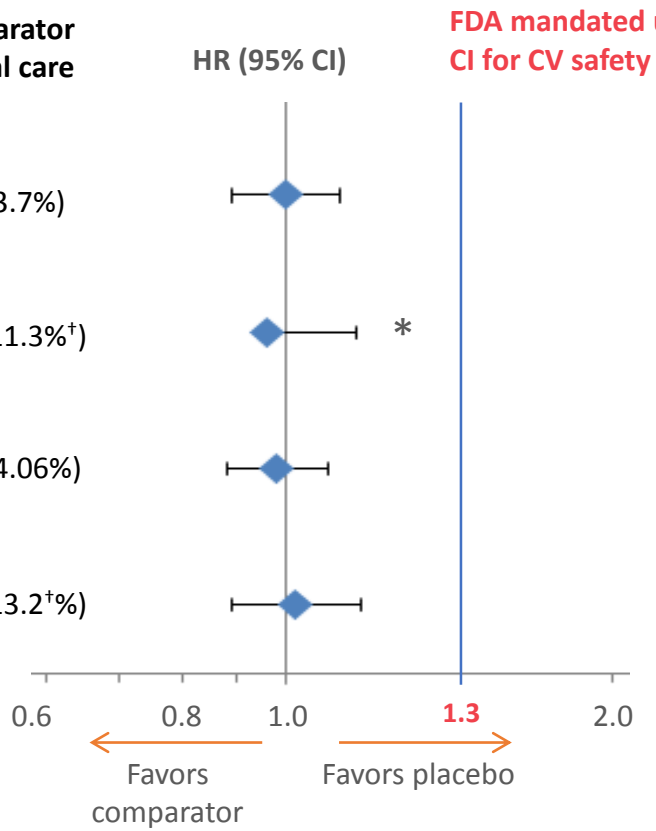
Urinary glucose excretion via SGLT2 inhibition[1]



SGLT, sodium glucose cotransporter.
*Loss of ~ 80 g of glucose per day = 240 cal/day.
1. Bakris GL, et al. *Kidney Int*. 2009;75;1272–1277.

Initial CVOT Trials completed

	Number of events (event rate, % per 100 person-years)	
	Placebo + usual care	Comparator + usual care
DPP4 inhibitor trials		
SAVOR-TIMI 53[1]	609 (3.7%)	613 (3.7%)
EXAMINE[2]	316 (11.8%†)	305 (11.3%†)
TECOS[3]	851 (4.17%)	839 (4.06%)
GLP1 agonist trials		
ELIXA[4]	406 (13.4†%)	399 (13.2†%)



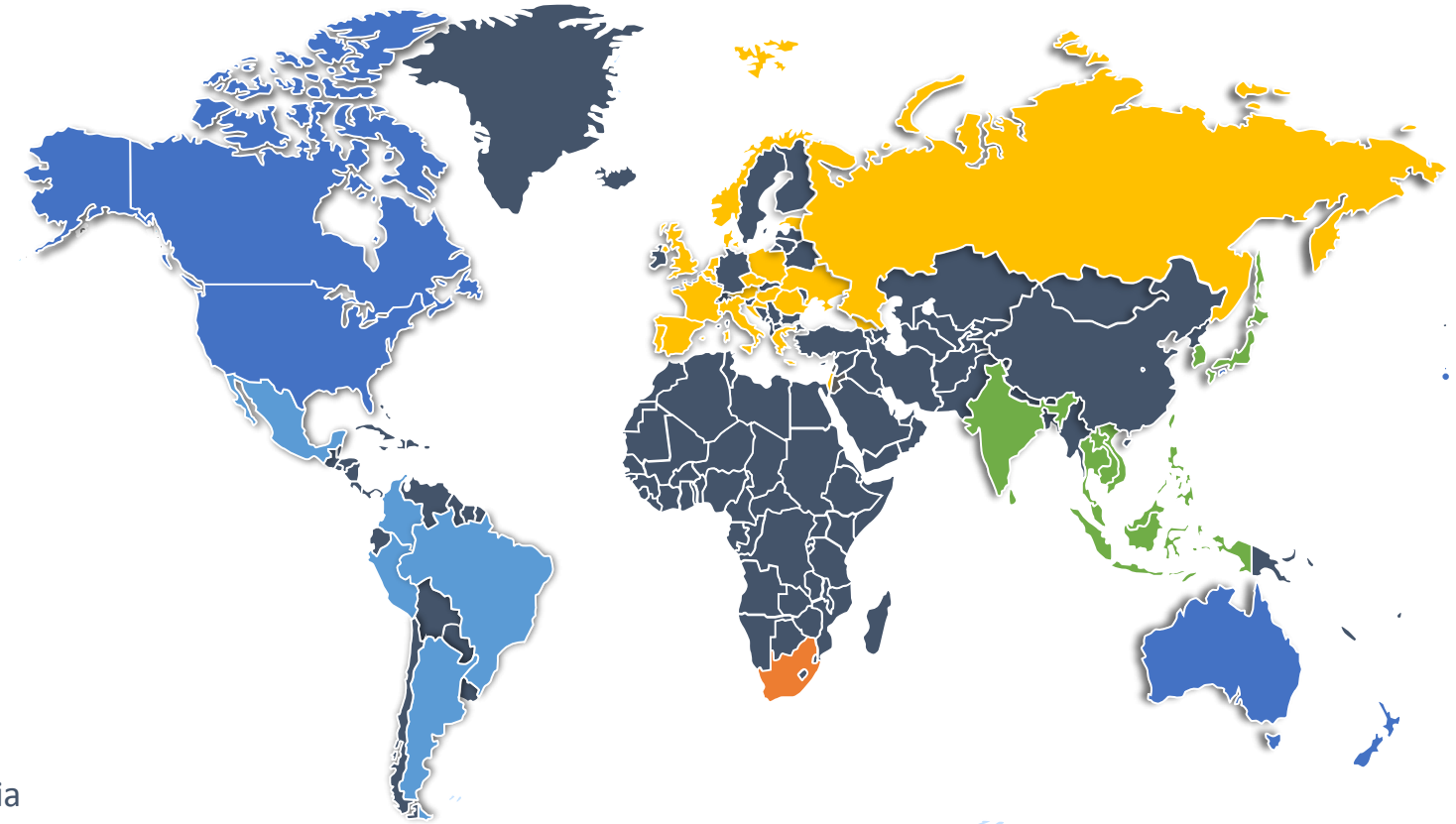
*Upper boundary of 1-sided repeated CI.

†Total event rate, %.

1. Scirica et al. N Engl J Med 2013;369:1317–26. 2. White et al. N Engl J Med 2013;369:1327–35.
3. Green et al. N Engl J Med 2015; DOI: 10.1056/NEJMoa1501352. 4. Pfeffer et al. ADA, 8 Jun 2015, Boston, USA (oral presentation).

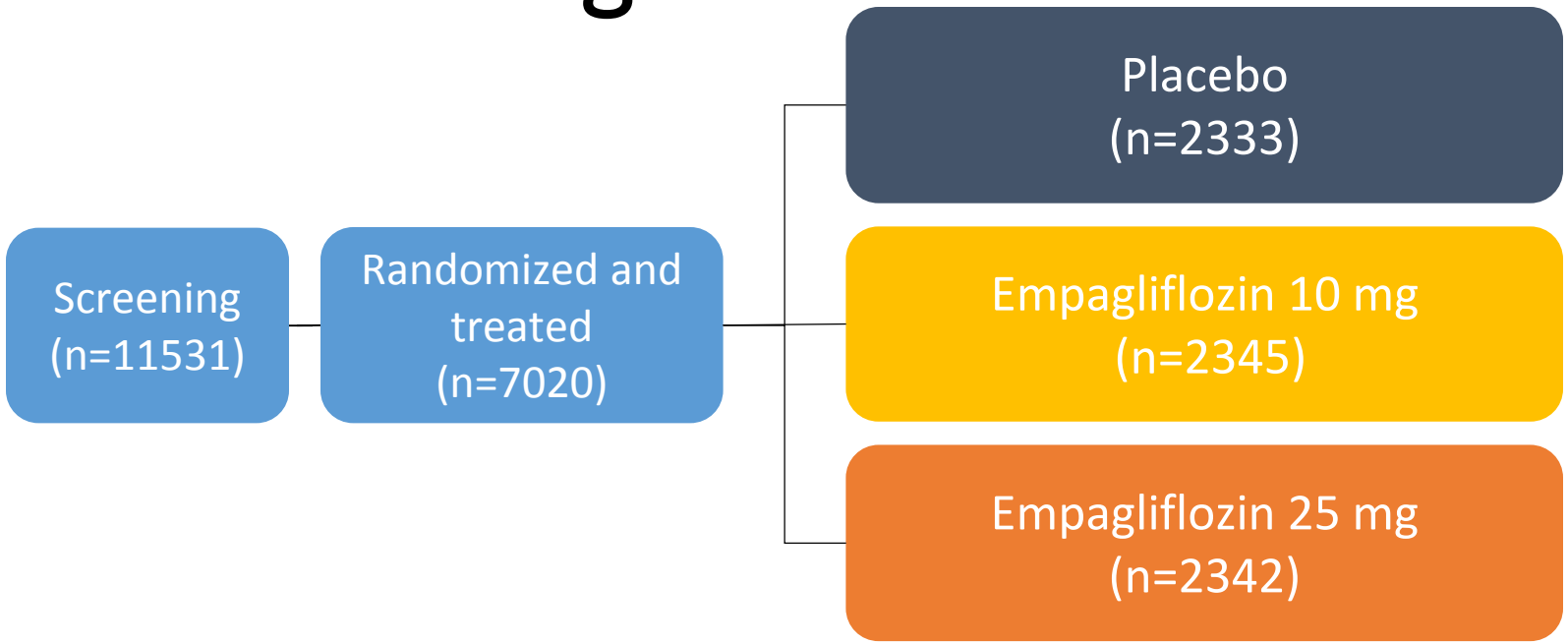
EMPA-REG OUTCOME®
Participating countries

590 sites in 42 countries



- Asia
- North America, Australia, New Zealand
- Latin America
- Europe
- Africa

Trial design



- Study medication was given in addition to standard of care
  - Glucose-lowering therapy was to remain unchanged for first 12 weeks
- Treatment assignment double-masked
- The trial was to continue until at least 691 patients experienced an adjudicated primary outcome event

Key inclusion and exclusion criteria

- Key inclusion criteria
  - Adults with type 2 diabetes
  - BMI ≤45 kg/m^2
  - HbA1c 7–10%*
  - Established cardiovascular disease
    - Prior myocardial infarction, coronary artery disease, stroke, unstable angina or occlusive peripheral arterial disease

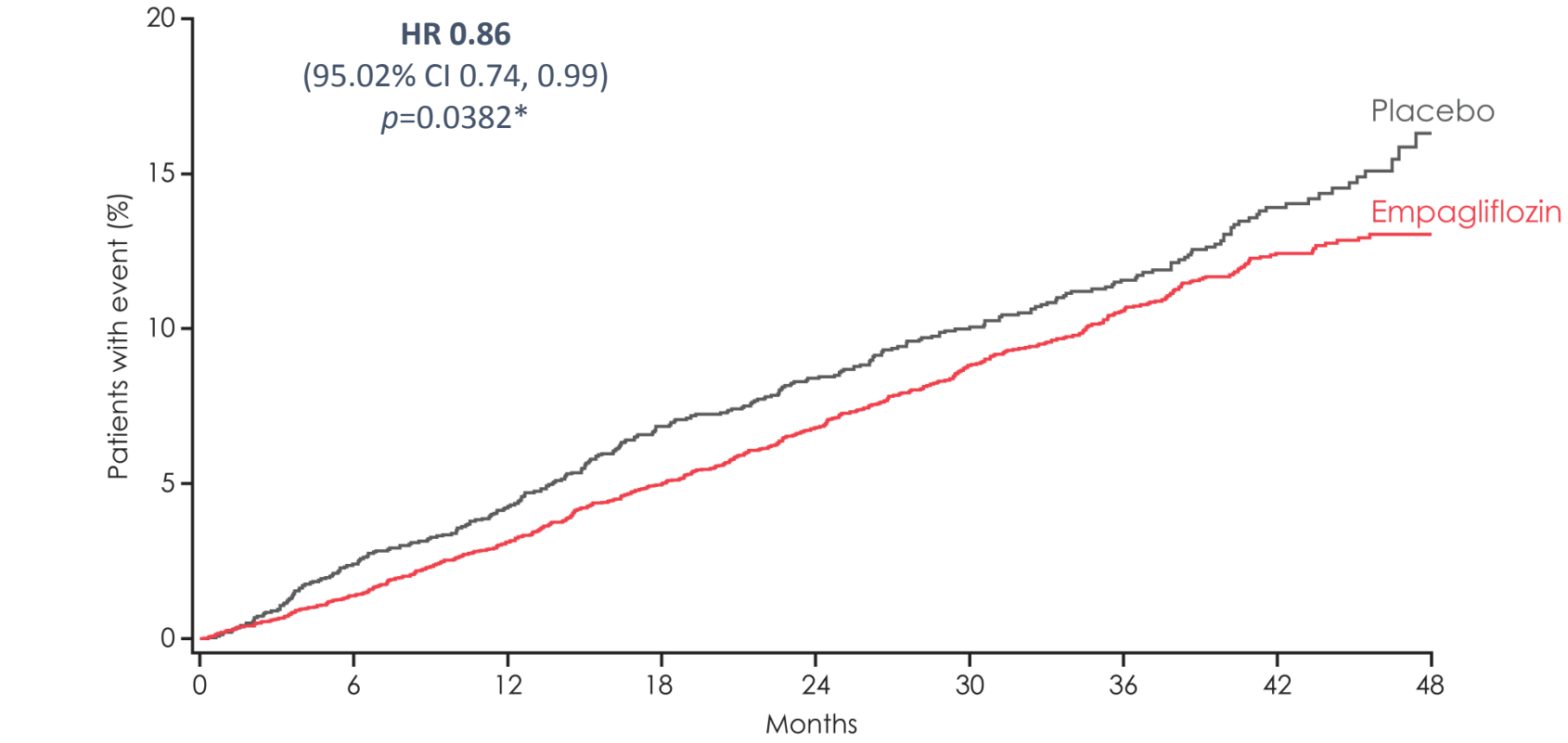
- Key exclusion criteria
  - eGFR <30 mL/min/1.73 m^2 (MDRD)

BMI, body mass index; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease
*No glucose-lowering therapy for ≥12 weeks prior to randomization or no change in dose for ≥12 weeks prior to randomization or, in the case of insulin, unchanged by >10% compared with the dose at randomization

BASELINE THERAPIES

	PLACEBO N=2,333	JARDIANCE N=4,687
Any antihypertensive therapy (%)	95	95
ACE inhibitors/ARBs	80	81
Beta-blockers	64	65
Diuretics	42	44
Any lipid-lowering therapy (%)	80	82
Statins	76	77
Aspirin	83	83
Glucose-lowering therapy (alone/combination, %)		
Metformin	74	74
Insulin	49	48
Sulfonylurea	43	43

Primary outcome: 3-point MACE

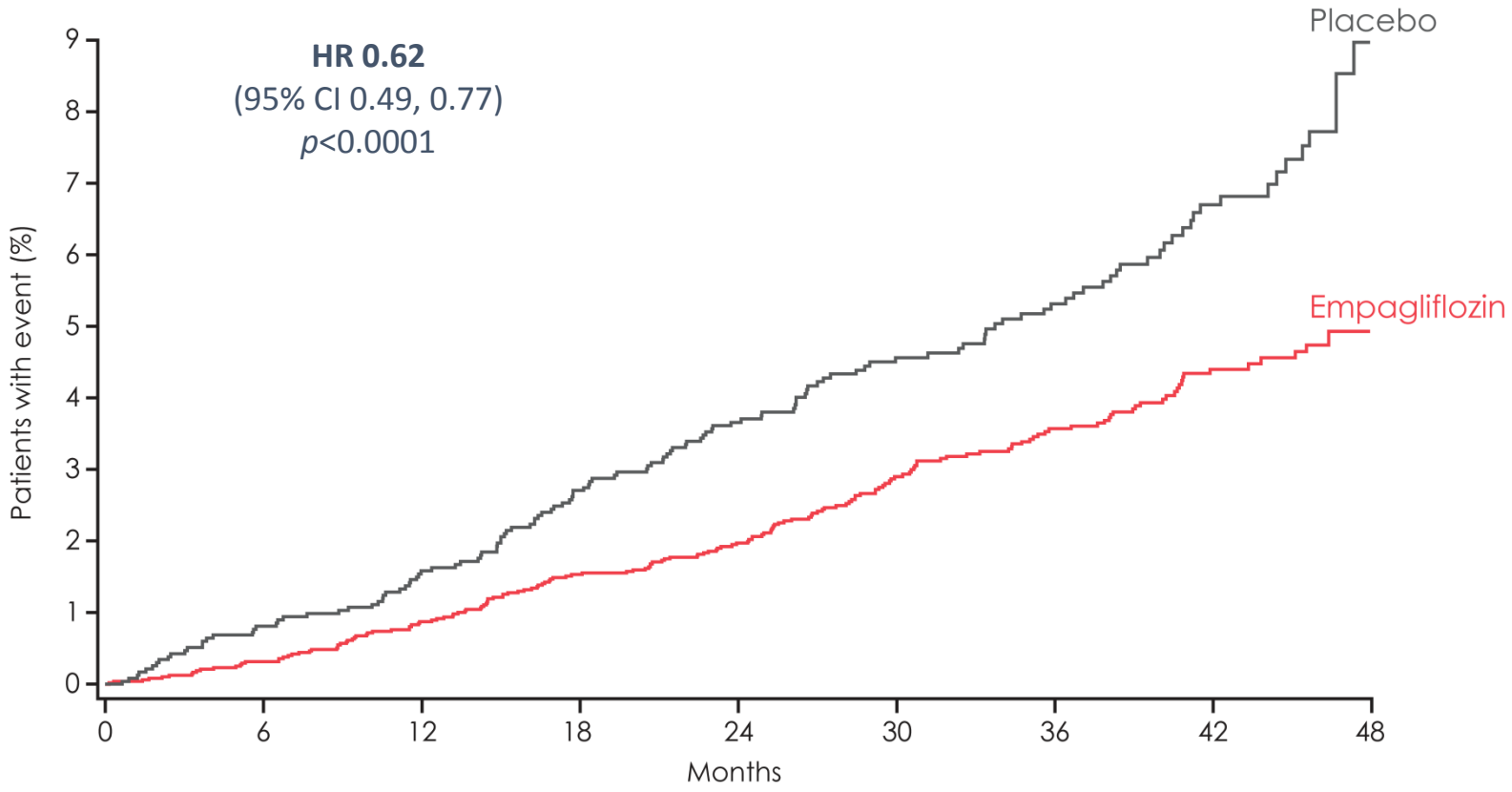


No. of patients									
Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

Cumulative incidence function. MACE, major adverse cardiovascular event; HR, hazard ratio

* Two-sided tests for superiority were conducted (statistical significance was indicated if p≤0.0498)

CV death

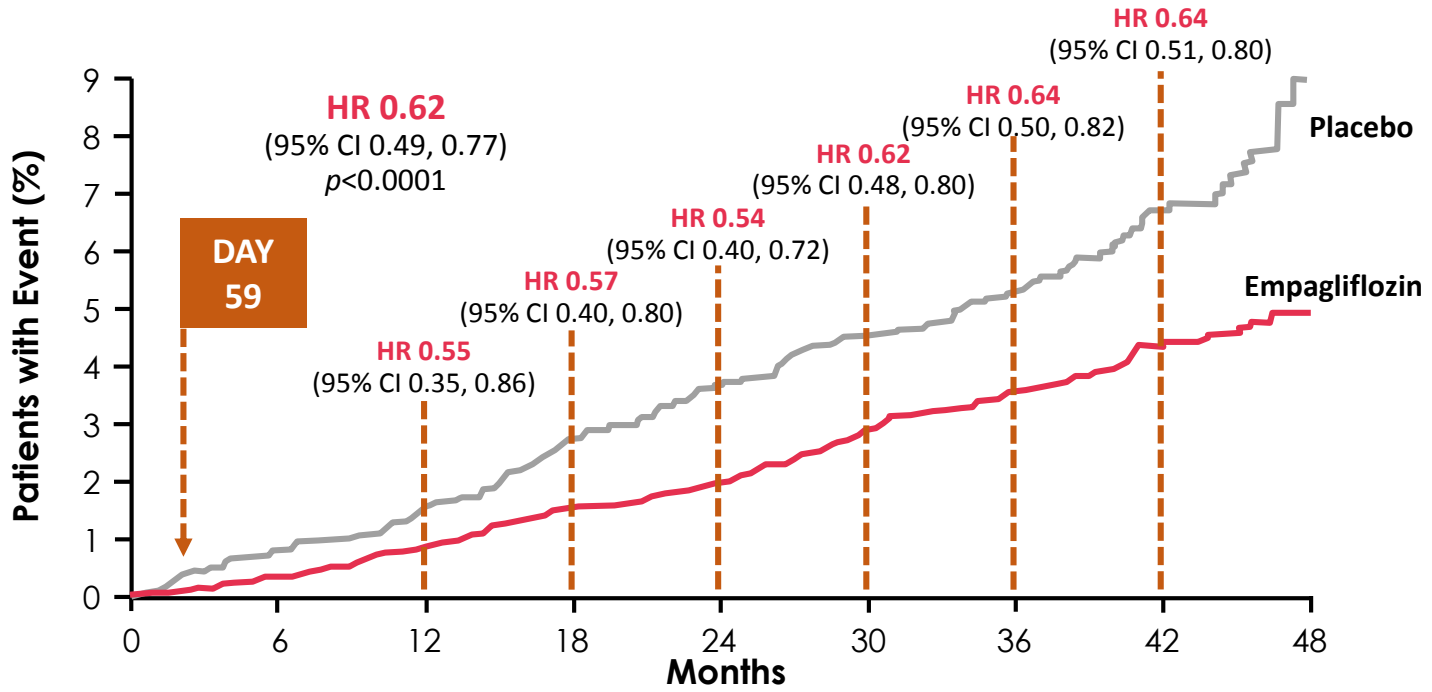


No. of patients									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

Cumulative incidence function. HR, hazard ratio

CV death: Early and sustained reduction in the risk versus placebo

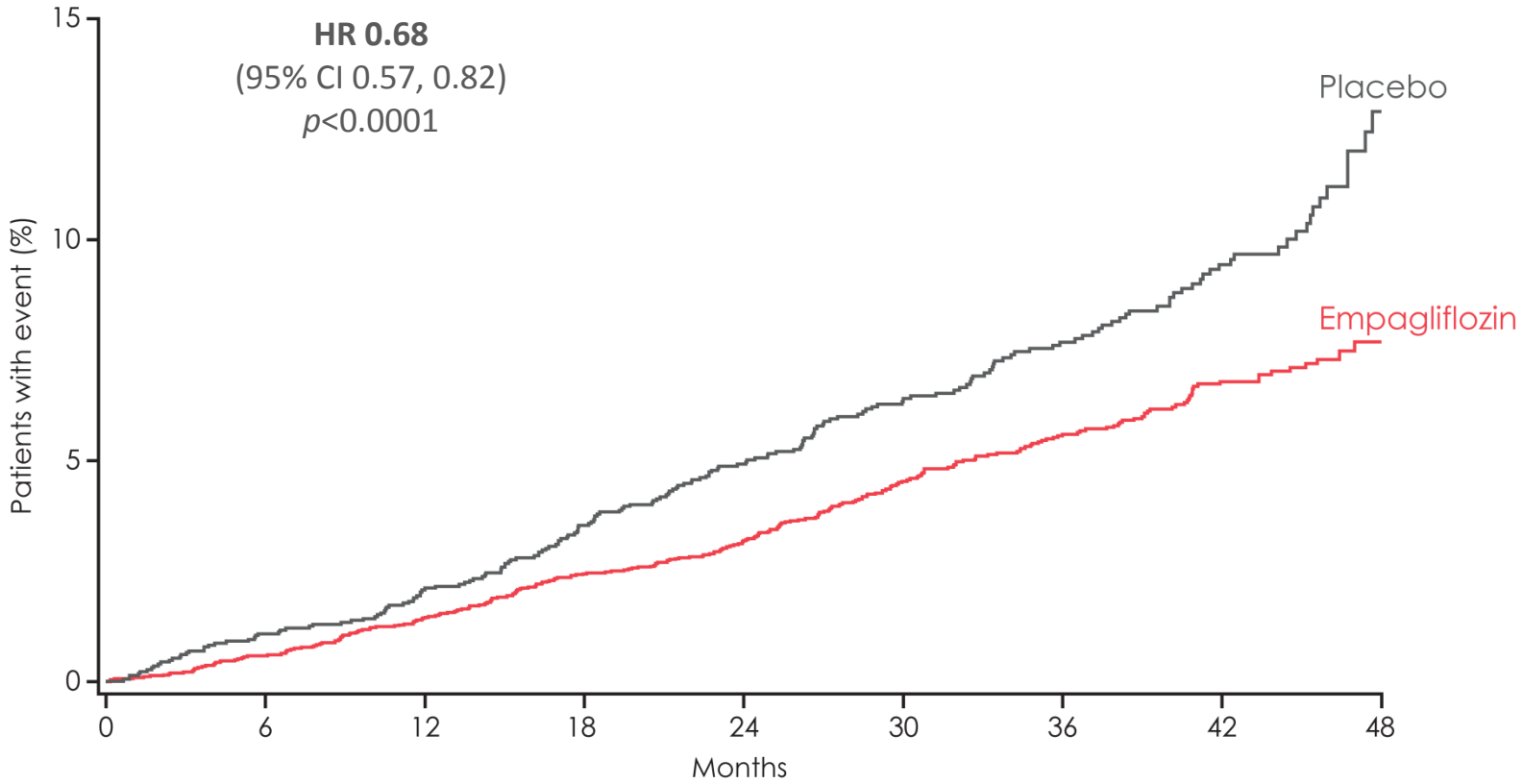
As early as **DAY 59,** there were statistically fewer CV deaths with empagliflozin vs. placebo[2]



No. of patients									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

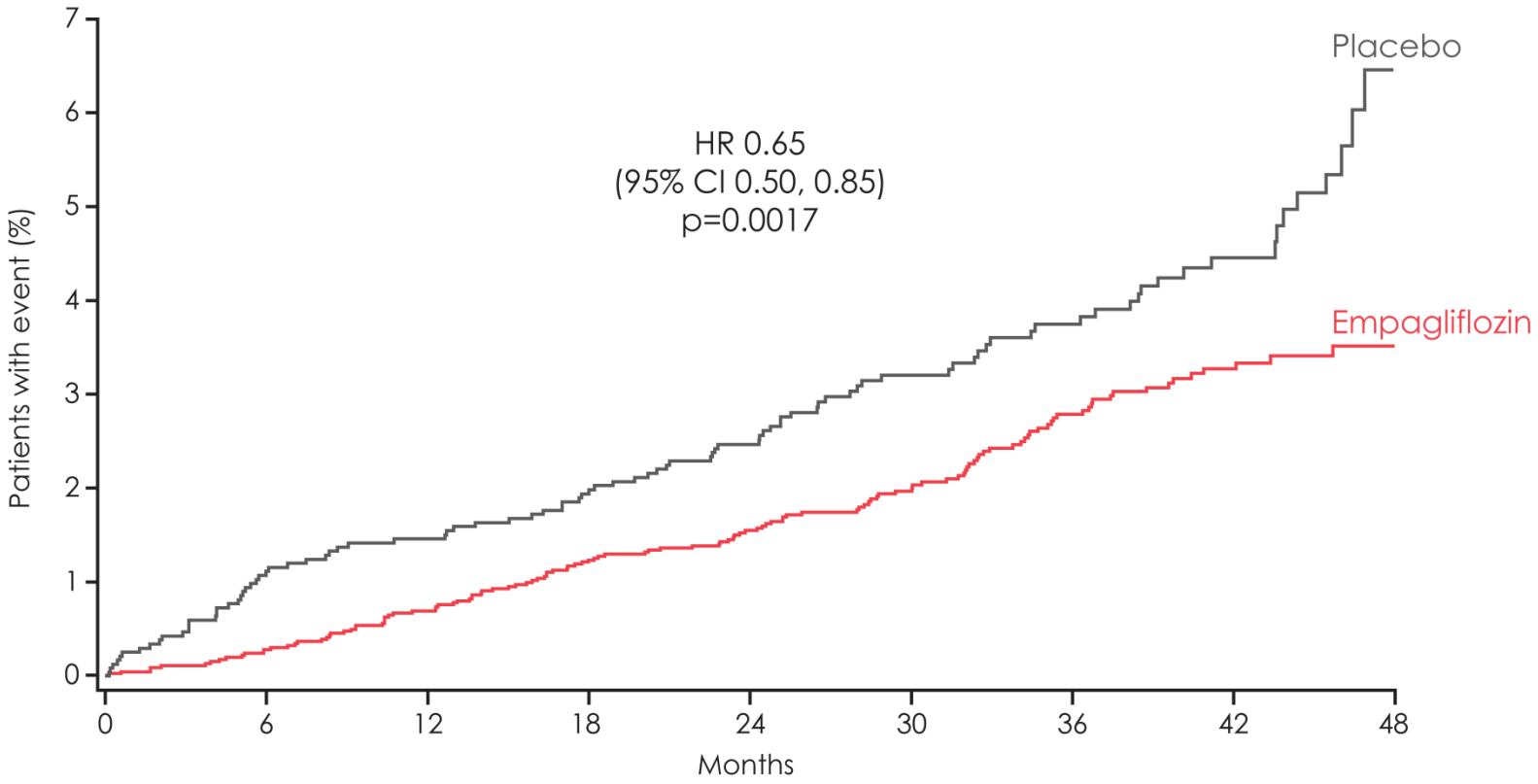
1. van de Borne et al. Presented at: Heart Failure 2016 & 3rd World Congress on Acute Heart Failure; May 21-24, 2016; Florence, Italy; 2. Data on File, Boehringer Ingelheim Pharmaceuticals, Inc.

All-cause mortality



Kaplan-Meier estimate. HR, hazard ratio

Hospitalization for heart failure

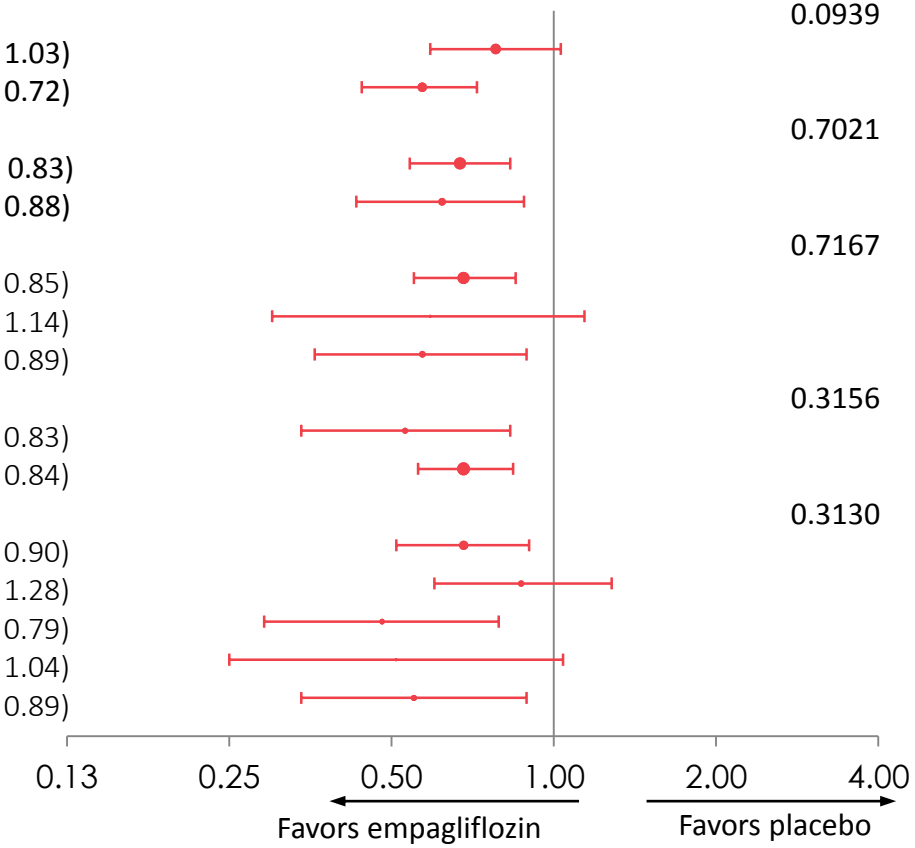


No. of patients									
Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

Hospitalization for heart failure or CV death by subgroups

Age at baseline, sex, race, ethnicity and region

	n event/n analyzed Empagliflozin	Placebo	HR	(95% CI)	p-value for interaction
Age (years)					0.0939
<65	127/2596	81/1297	0.78	(0.59, 1.03)	
≥65	138/2091	117/1036	0.57	(0.44, 0.72)	
Sex					0.7021
Male	197/3336	145/1680	0.67	(0.54, 0.83)	
Female	68/1351,	53/ 653	0.62	(0.43, 0.88)	
Race					0.7167
White	204/3403	145/1678	0.68	(0.55, 0.85)	
Black/African American	19/ 237	16/ 120	0.59	(0.30, 1.14)	
Asian	39/1006	35/ 511	0.57	(0.36, 0.89)	
Ethnicity					0.3156
Hispanic/Latino	40/ 847	35/ 418	0.53	(0.34, 0.83)	
Not Hispanic/Latino	225/3835,	163/1912	0.68	(0.56, 0.84)	
Region					0.3130
Europe	112/1926	82/959	0.68	(0.51, 0.90)	
North America	73/ 932	42/462	0.87	(0.60, 1.28)	
Latin America	30/ 721	29/360	0.48	(0.29, 0.79)	
Africa	16/ 211	14/102	0.51	(0.25, 1.04)	
Asia	34/ 897	31/450	0.55	(0.34, 0.89)	

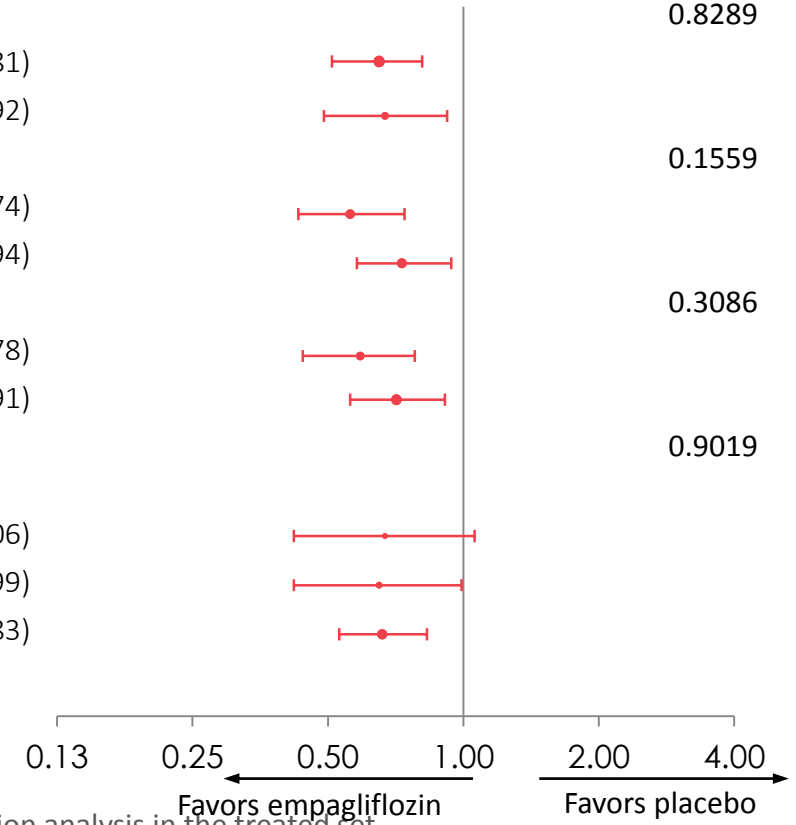


Cox regression analysis in the treated set.
HR, hazard ratio.

Hospitalization for heart failure or CV death by subgroups

HbA1c, BMI, BP and time since diagnosis of T2DM at baseline

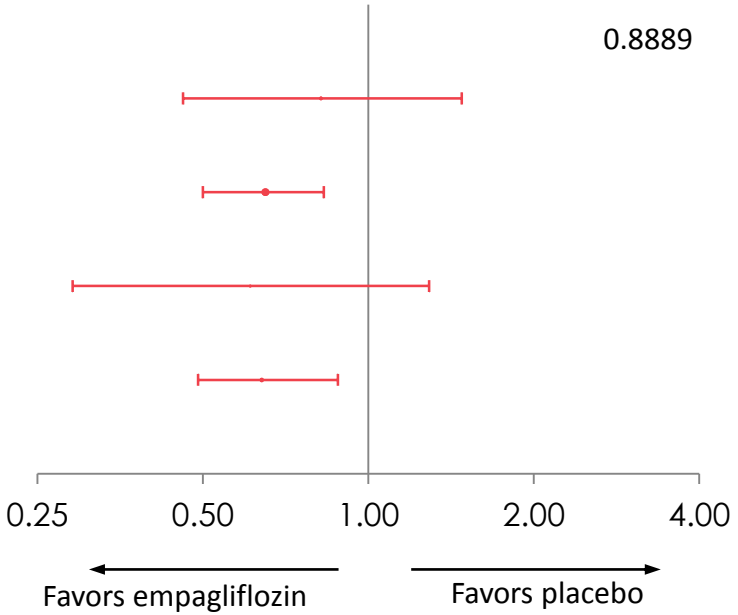
	n event/n analyzed		HR	(95% CI)	p-value for interaction
	Empagliflozin	Placebo			
HbA1c (%)					0.8289
<8.5	171/3212	131/1607	0.65	(0.51, 0.81)	
≥8.5	94/1475	67/ 726	0.67	(0.49, 0.92)	
BMI (kg/m²)					0.1559
<30	108/2279	93/1120	0.56	(0.43, 0.74)	
≥30	157/2408	105/1213	0.74	(0.58, 0.94)	
BP (mmHg)					0.3086
SBP ≥140 and/or DBP ≥90	105/1780	89/ 934	0.59	(0.44, 0.78)	
SBP <140 and DBP <90	160/2907	109/1399	0.71	(0.56, 0.91)	
Time since diagnosis of T2DM (years)					0.9019
≤5	42/ 840	31/ 423	0.67	(0.42, 1.06)	
>5 to 10	51/1175	36/ 571	0.65	(0.42, 0.99)	
>10	172/2672	131/1339	0.66	(0.53, 0.83)	



Cox regression analysis in the treated set.
T2DM, type 2 diabetes; HR, hazard ratio; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Hospitalization for heart failure or CV death by subgroups
CV risk at baseline

	n event/n analyzed		HR	(95% CI)	p-value for interaction
	Empagliflozin	Placebo			
CV risk					0.8889
Only cerebrovascular disease	29/ 635	18/ 325	0.82	(0.46, 1.48)	
Only coronary artery disease	135/2732	102/1340	0.65	(0.50, 0.83)	
Only peripheral artery disease	17/ 412	12/ 191	0.61	(0.29, 1.29)	
2 or 3 CV high risk categories	82/ 878	63/ 451	0.64	(0.46, 0.88)	

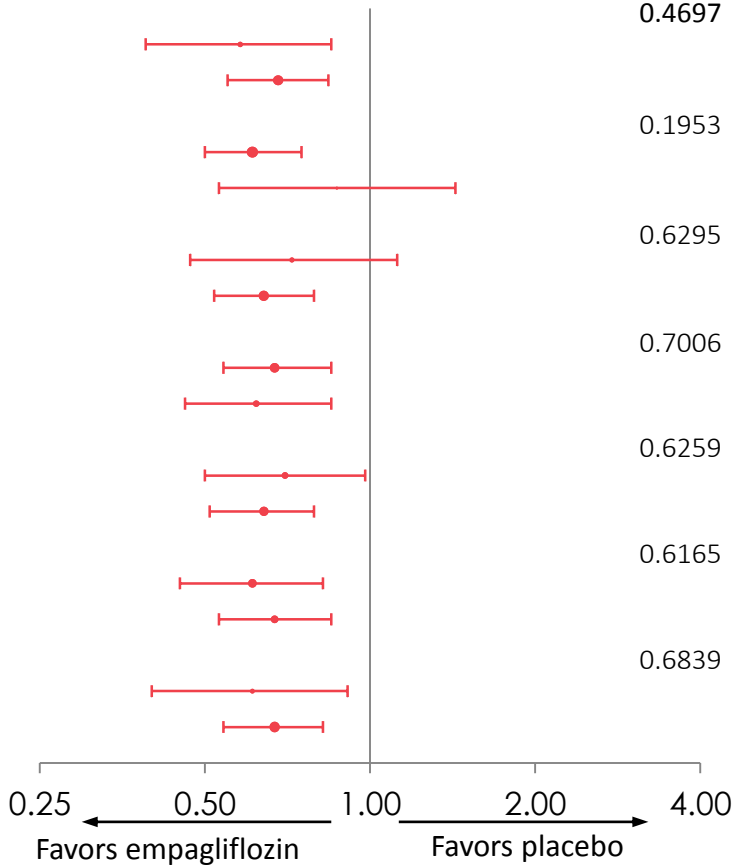


Cox regression analysis in the treated set. HR, hazard ratio; CV, cardiovascular.

Hospitalization for heart failure or CV death by subgroups

CV medication at baseline

	n event/n analyzed		HR	(95% CI)	p-value for interaction
	Empagliflozin	Placebo			
Statins/ezetemibe					0.4697
No	52/1029	48/ 551	0.58	(0.39, 0.85)	
Yes	213/3658	150/1782	0.68	(0.55, 0.84)	
Mineralocorticoid receptor antagonist					0.1953
No	49/ 305	23/ 136	0.61	(0.50, 0.75)	
Yes	216/4382	175/2197	0.87	(0.53, 1.43)	
ACE inhibitor/ARB					0.6295
No	47/ 889	34/ 465	0.72	(0.47, 1.12)	
Yes	218/3798	164/1868	0.64	(0.52, 0.79)	
Calcium channel blockers					0.7006
No	173/3158	125/1545	0.67	(0.54, 0.85)	
Yes	92/1529	73/ 788	0.62	(0.46, 0.85)	
Beta blockers					0.6259
No	82/1631	59/ 835	0.70	(0.50, 0.98)	
Yes	183/3056	139/1498	0.64	(0.51, 0.79)	
Diuretics					0.6165
No	93/2640	77/1345	0.61	(0.45, 0.82)	
Yes	172/2047	121/ 988	0.67	(0.53, 0.85)	
Acetylsalicylic acid					0.6839
No	53/ 811	41/ 406	0.61	(0.40, 0.91)	
Yes	212/3876	157/1927	0.67	(0.54, 0.82)	



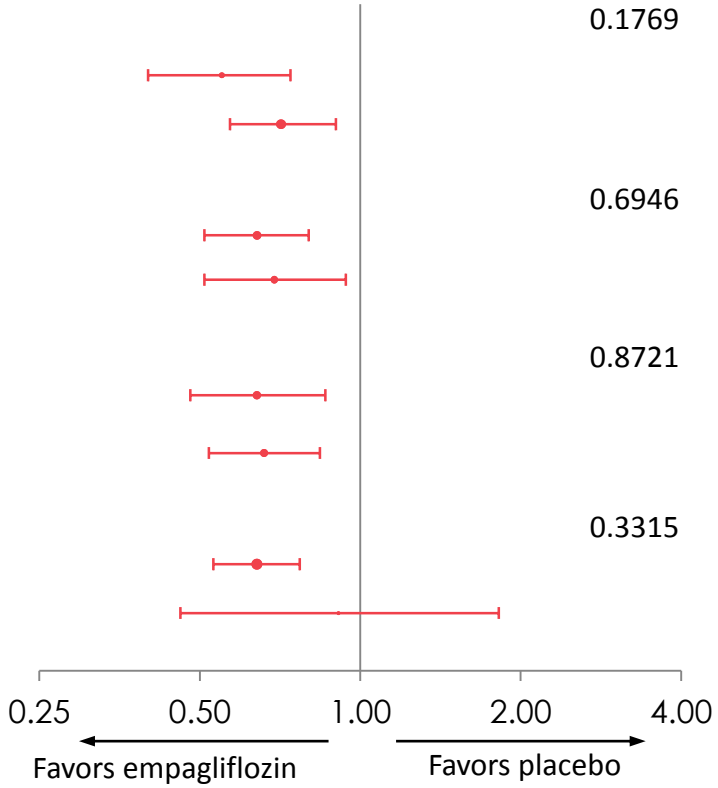
Subgroup by antihypertensive medication:
HR and 95% CI were not analyzed as there was ≥1 group with <14 events.

Cox regression analysis in the treated set.
HR, hazard ratio; ACE, angiotensin-converting-enzyme; ARB, angiotensin receptor blocker;

Hospitalization for heart failure or CV death by subgroups

Glucose-lowering medication at baseline

	n event/n analyzed		HR	(95% CI)	p-value for interaction
	Empagliflozin	Placebo			
Metformin					0.1769
No	92/1228	75/ 599	0.55	(0.40, 0.74)	
Yes	173/3459	123/1734	0.71	(0.57, 0.90)	
Sulphonylurea					0.6946
No	169/2673	131/1341	0.64	(0.51, 0.80)	
Yes	96/2014	67/ 992	0.69	(0.51, 0.94)	
Insulin					0.8721
No	105/2435	80/1198	0.64	(0.48, 0.86)	
Yes	160/2252	118/1135	0.66	(0.52, 0.84)	
DPP-4 inhibitor					0.3315
No	243/4158	185/2066	0.64	(0.53, 0.77)	
Yes	22/ 529	13/ 267	0.91	(0.46, 1.80)	

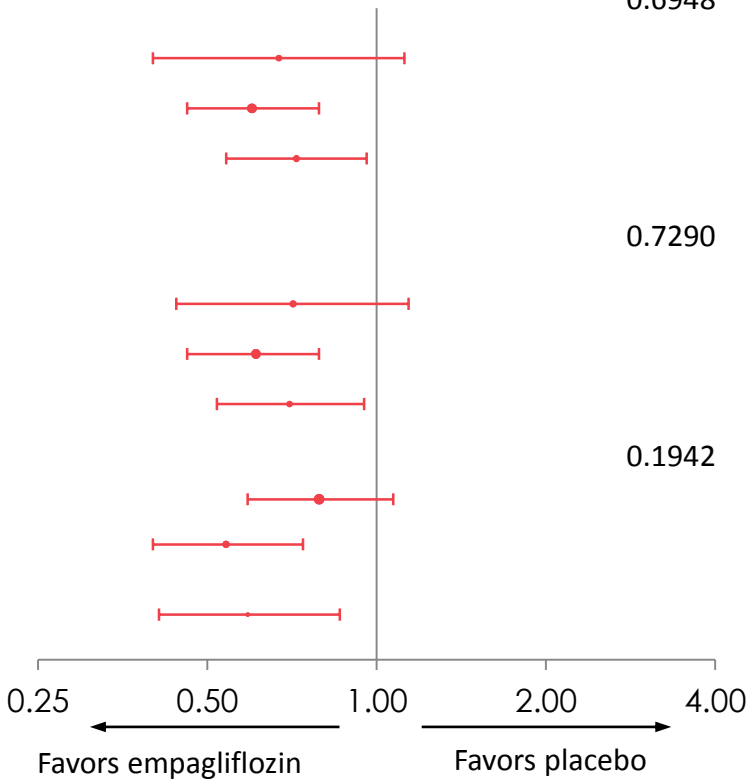


Cox regression analysis in the treated set. HR, hazard ratio.

Hospitalization for heart failure or CV death by subgroups

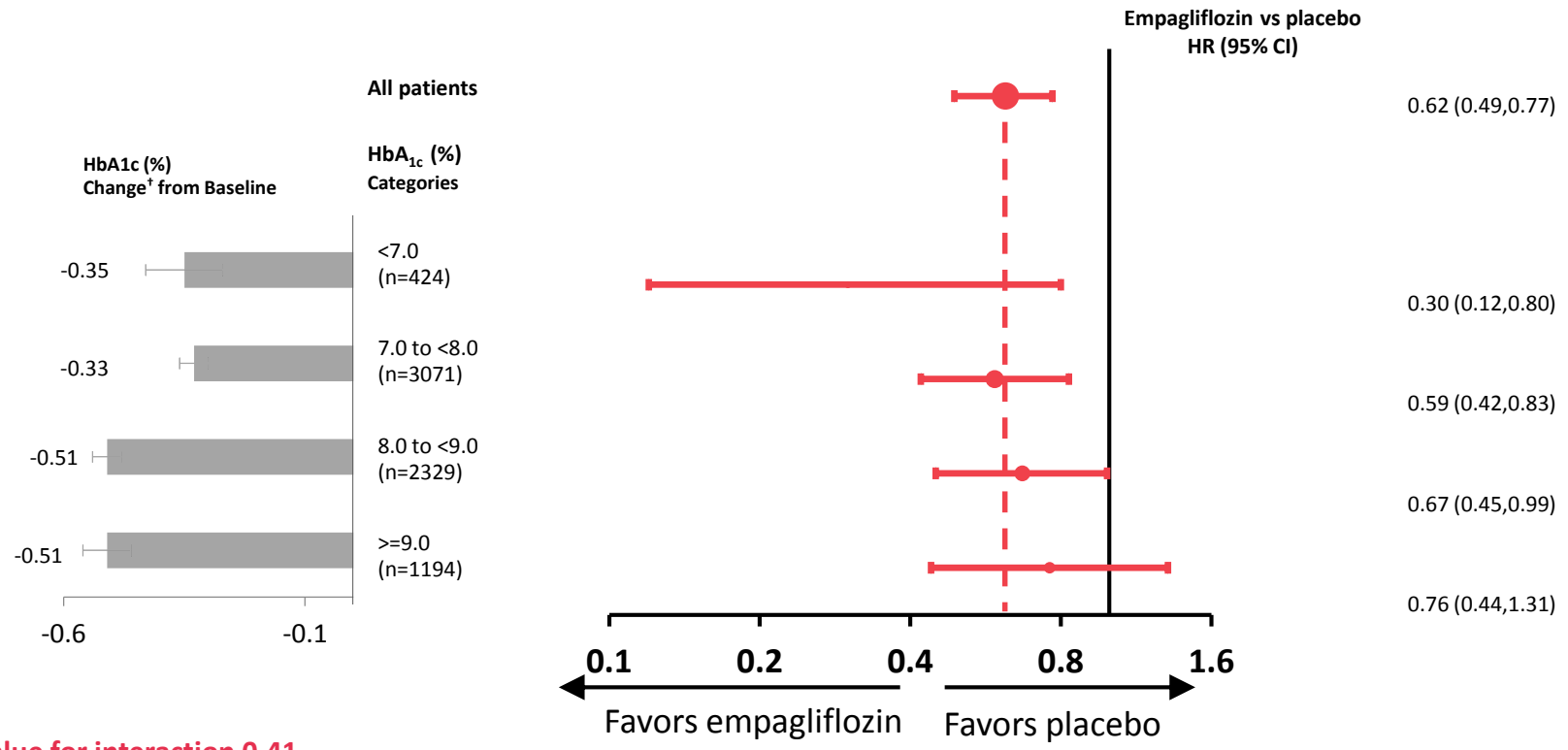
eGFR and UACR at baseline

	n event/n analyzed		HR	(95% CI)	p-value for interaction
	Empagliflozin	Placebo			
eGFR (MDRD; mL/min/1.73m²)*					0.6948
≥90 (normal)	36/1050	25/ 488	0.67	(0.40, 1.12)	
60 to <90 (mild)	117/2425	96/1238	0.60	(0.46, 0.79)	
<60 (moderate/severe)	112/1212	77/ 607	0.72	(0.54, 0.96)	
eGFR (CKD-EPI; mL/min/1.73m²)*					0.7290
≥90 (normal)	43/1294	29/ 627	0.71	(0.44, 1.14)	
60 to <90 (mild)	119/2325	95/1162	0.61	(0.46, 0.79)	
<60 (moderate/severe)	103/1066	74/ 544	0.70	(0.52, 0.95)	
UACR (mg/g)†					0.1942
Normal (<30)	112/2789	70/1382	0.79	(0.59, 1.07)	
Microalbuminuria (≥30 to 300)	84/1338	78/ 675	0.54	(0.40, 0.74)	
Macroalbuminuria (>300)	67/ 509	50/ 260	0.59	(0.41, 0.86)	



Cox regression analysis in the treated set. HR, hazard ratio; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; CKD-EPI, chronic kidney disease epidemiology collaboration; UACR, urine albumin–to–creatinine ratio.
*2 patients were excluded as the subgroup variable was missing.
†67 patients were excluded as the subgroup variable was missing.

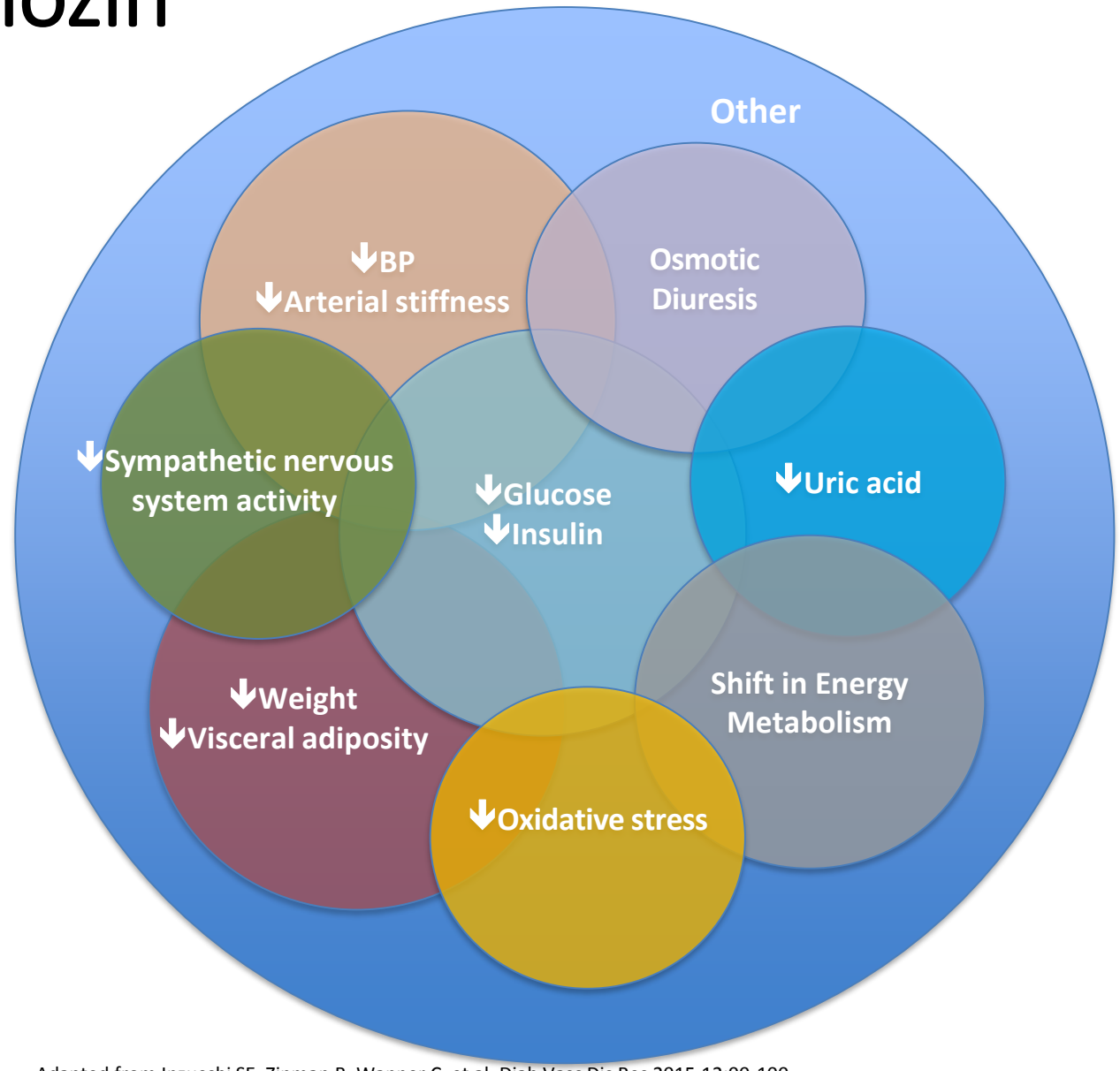
CV Death Reduction: Independent of Baseline HbA1c



p-value for interaction 0.41

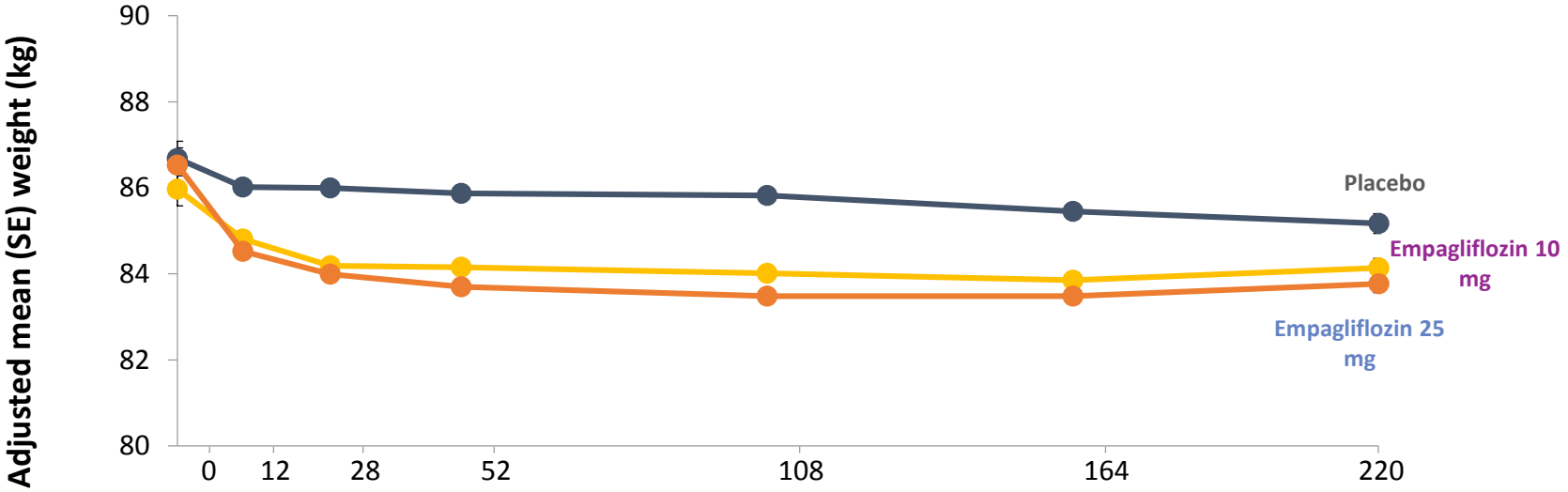
† HbA1c (%) placebo-adjusted mean +/- SE of weighted HbA1c change from baseline
Cox regression analysis in the treated set. HR, hazard ratio. CI, confidence interval.

Factors related to CV risk that are modified by empagliflozin



Adapted from Inzucchi SE, Zinman B, Wanner C, et al. Diab Vasc Dis Res 2015;12:90-100

Adjusted mean weight

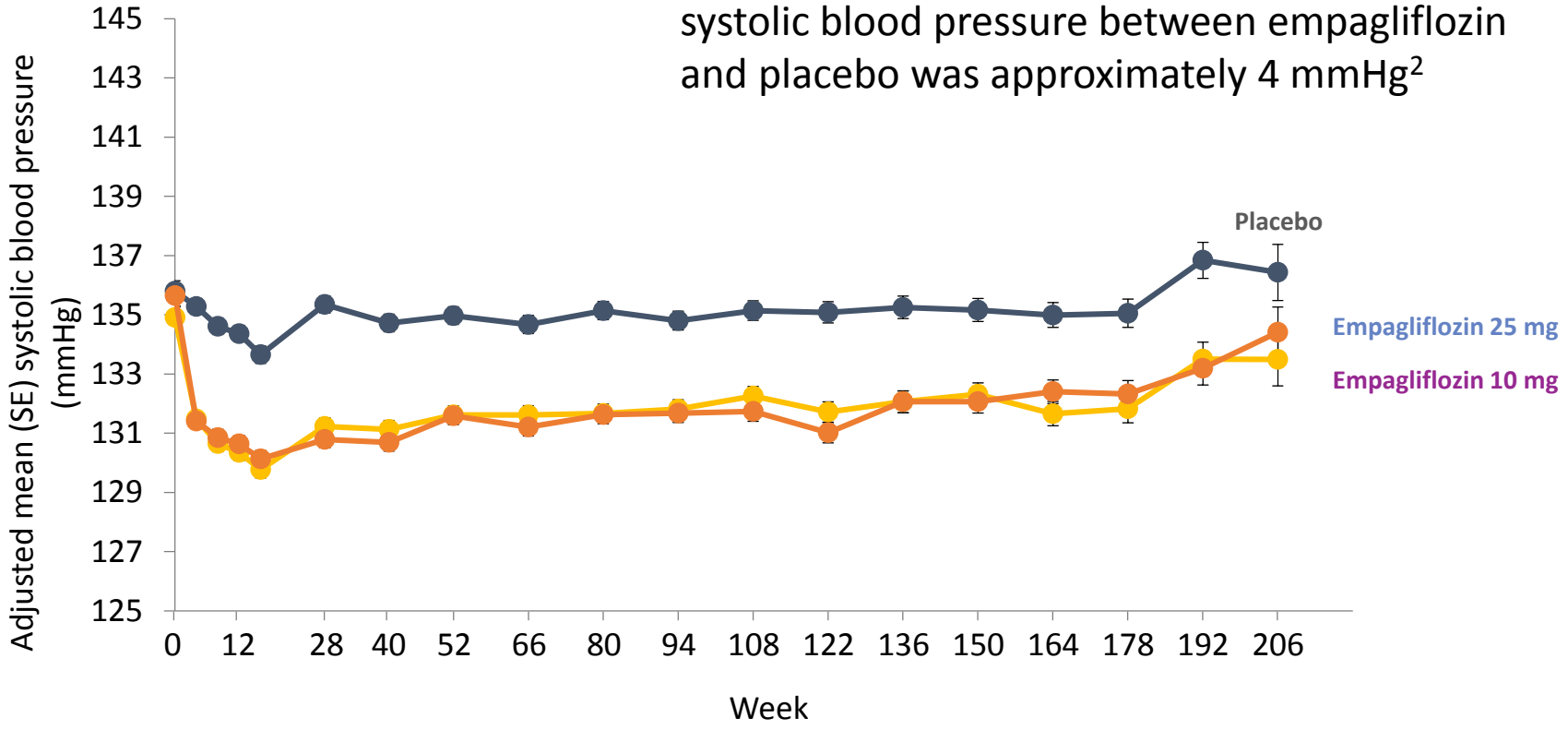


Placebo	2285	1915	2215	2138	1598	1239	425
Empagliflozin 10 mg	2290	1893	2238	2174	1673	1298	483
Empagliflozin 25 mg	2283	1891	2226	2178	1678	1335	489

All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent-to-treat).
X-axis: time points with reasonable amount of data available for prescheduled measurements.
Zinman et al. N Engl J Med. 2015;373(22):2117-28.

Changes in adjusted mean systolic blood pressure

At study end, the observed difference in mean systolic blood pressure between empagliflozin and placebo was approximately 4 mmHg[2]

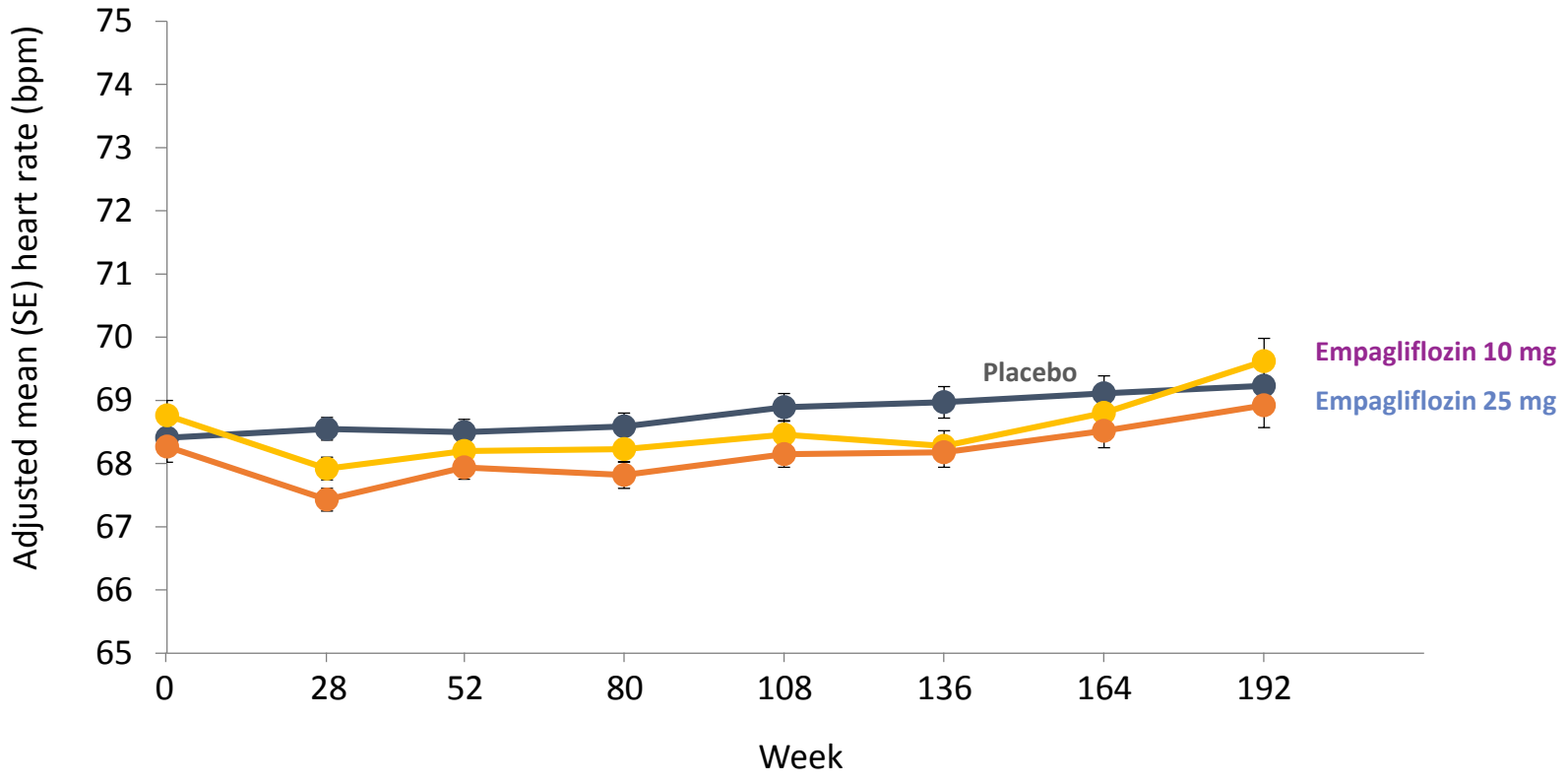


Placebo	2322	2235	2203	2161	2133	2073	2024	1974	1771	1492	1274	1126	981	735	450	171
Empagliflozin 10 mg	2322	2250	2235	2193	2174	2125	2095	2072	1853	1556	1327	1189	1034	790	518	199
Empagliflozin 25 mg	2323	2247	2221	2197	2169	2129	2102	2066	1878	1571	1351	1212	1070	842	528	216

MMRM in the treated set (OC-AD). SBP, systolic blood pressure.

1. Zinman *et al N Engl J Med* 2015; doi: 10.1056/NEJMoa1504720; 2. Data on File. **For Internal Use Only**.

Changes in heart rate

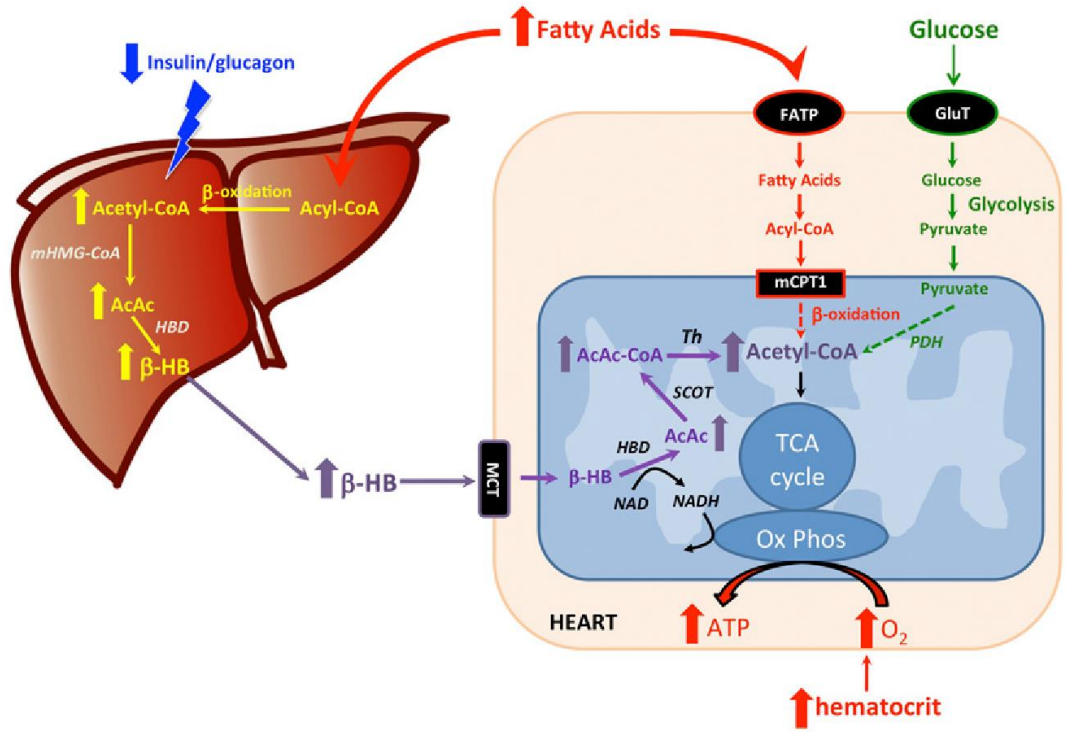


Placebo	2174	2127	2032	1928	1796	1300	1002	552
Empagliflozin 10 mg	2205	2137	2064	2006	1877	1366	1045	597
Empagliflozin 25 mg	2192	2127	2066	2006	1907	1383	1086	633

MMRM in the treated set (OC-AD).
Zinman *et al N Engl J Med* 2015; doi: 10.1056/NEJMoa1504720

Potential MOA CV effect: Shift from glucose to lipid metabolism

- Empagliflozin increases β-HB production in the liver
- Increased β-HB and FFA uptake into the heart
- Meanwhile, empagliflozin increases hematocrit increasing oxygen delivery to the heart



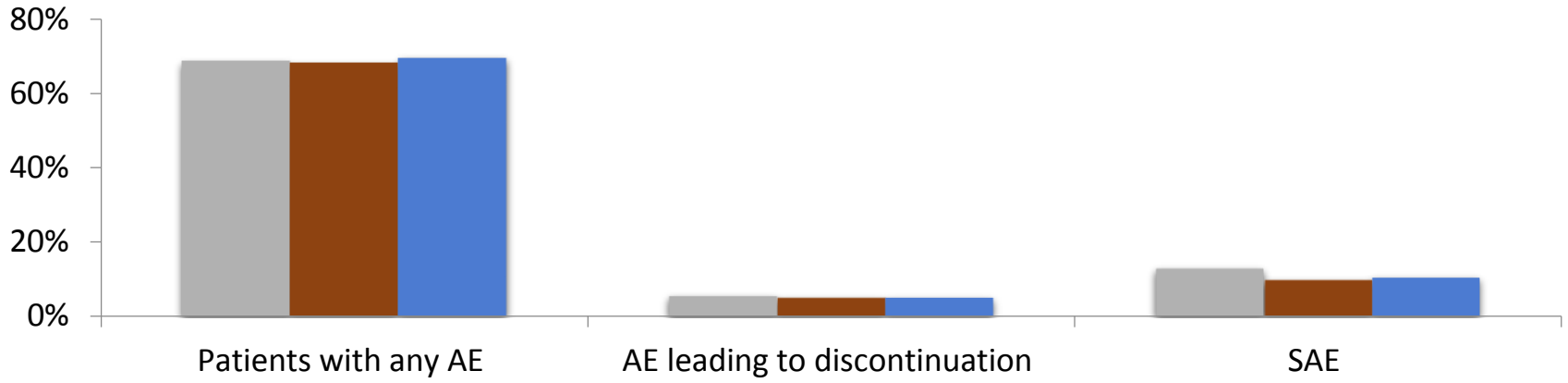
β-HB, beta-hydroxybutyrate; FFA, free fatty acids.

Ferrannini et al. Diabetes Care. 2016;39(7):1108-14.

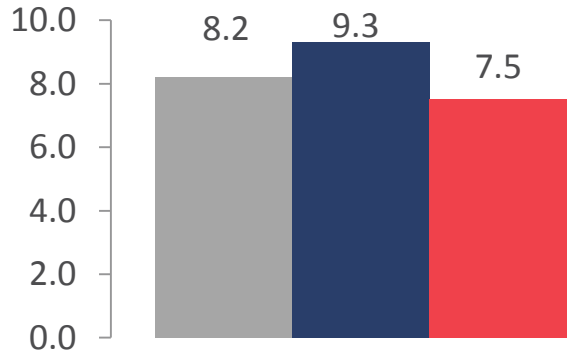
Safety and tolerability

Empagliflozin – safety profile

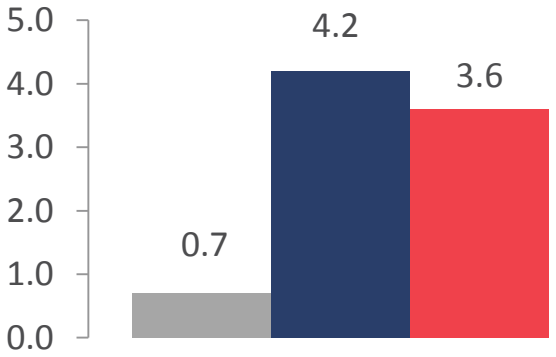
Overall AEs, AEs leading to discontinuation and serious AEs [% of patients]



AEs consistent with UTIs [% of patients]



AEs consistent with genital infections [% of patients]



Placebo

Empagliflozin 10 mg

Empagliflozin 25 mg

Confirmed hypoglycemic adverse events

	Placebo (n=2333)	**Empagliflozin 10 mg (n=2345)**	**Empagliflozin 25 mg (n=2342)**
	n (%)		
Confirmed hypoglycemic adverse events	650 (27.9%)	656 (28.0%)	647 (27.6%)
Events requiring assistance	36 (1.5%)	33 (1.4%)	30 (1.3%)
Patients taking insulin at baseline			
Total	483 (42.6%)	494 (43.6%)	464 (41.4%)
Events requiring assistance	28 (2.5%)	27 (2.4%)	25 (2.2%)

Patients treated with ≥1 dose of study drug
Plasma glucose <3.9 mmol/L (70 mg/dL) and/or requiring assistance

EMPA-REG OUTCOME®: Summary

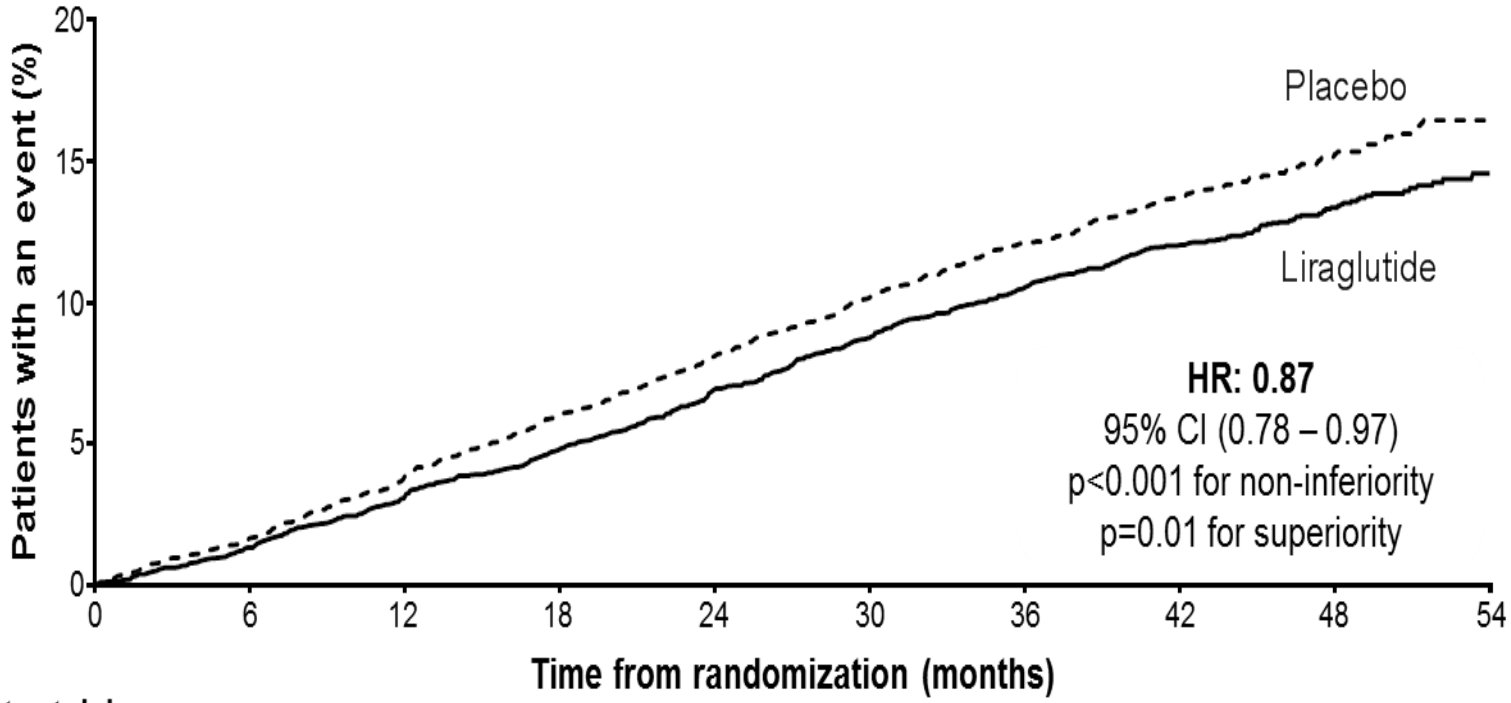
- **Empagliflozin reduced risk for 3-point MACE by 14%**
- **Empagliflozin reduced CV death by 38%**
- **Empagliflozin improved survival by reducing all-cause mortality by 32%**
- **Empagliflozin reduced hospitalization for heart failure by 35%**
- **Empagliflozin was associated with an increase in genital infections but was otherwise well tolerated**

MACE, major adverse cardiovascular event; HDL, high-density lipoprotein; LDL, low-density lipoprotein

LEADER TRIAL: Liraglutide vs Placebo

Primary outcome

CV death, non-fatal myocardial infarction, or non-fatal stroke

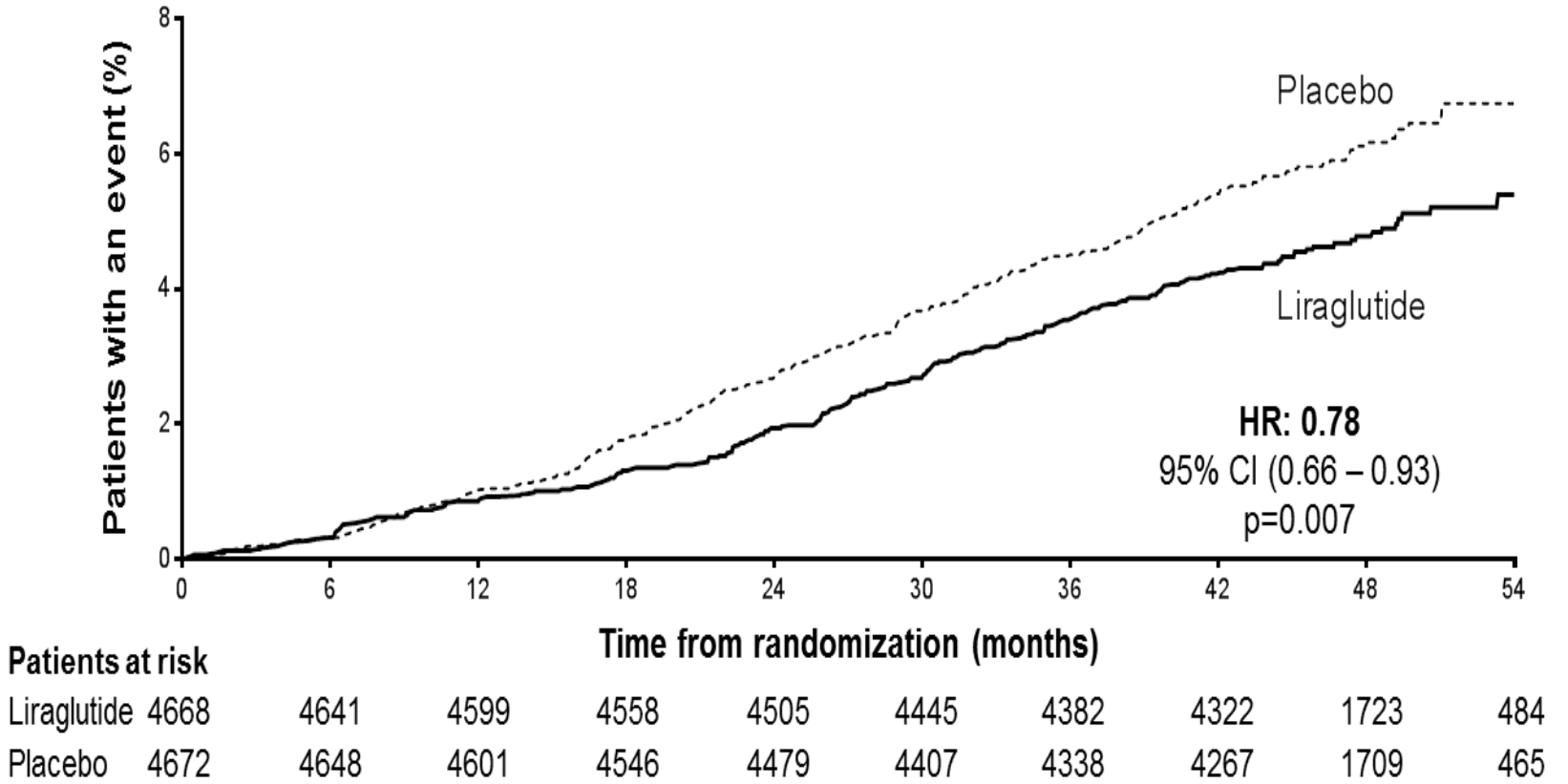


Patients at risk										
Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months. CI: confidence interval; CV: cardiovascular; HR: hazard ratio.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

CV death

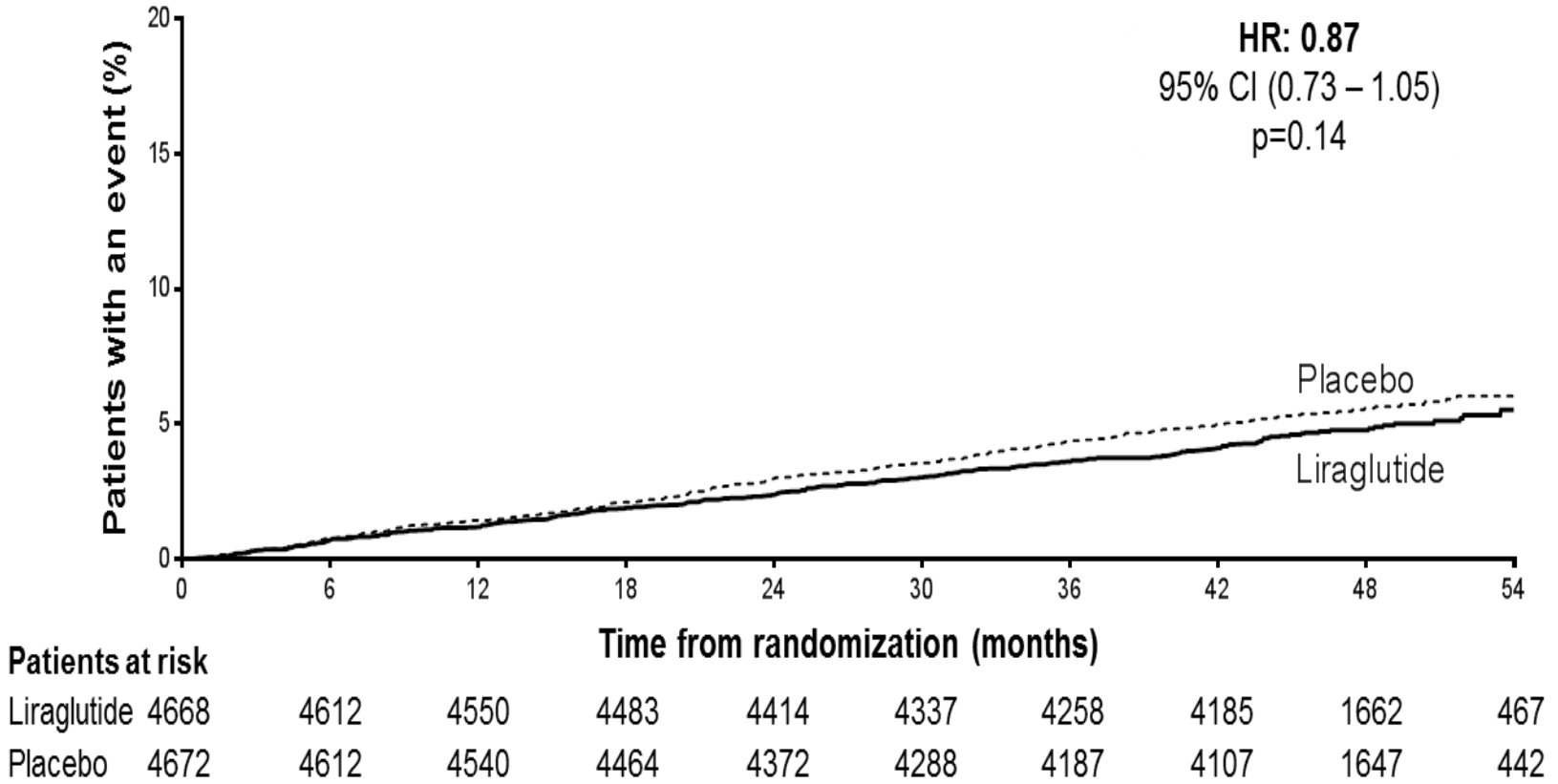


Patients at risk										
Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4267	1709	465

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months.
CI: confidence interval; CV: cardiovascular; HR: hazard ratio.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

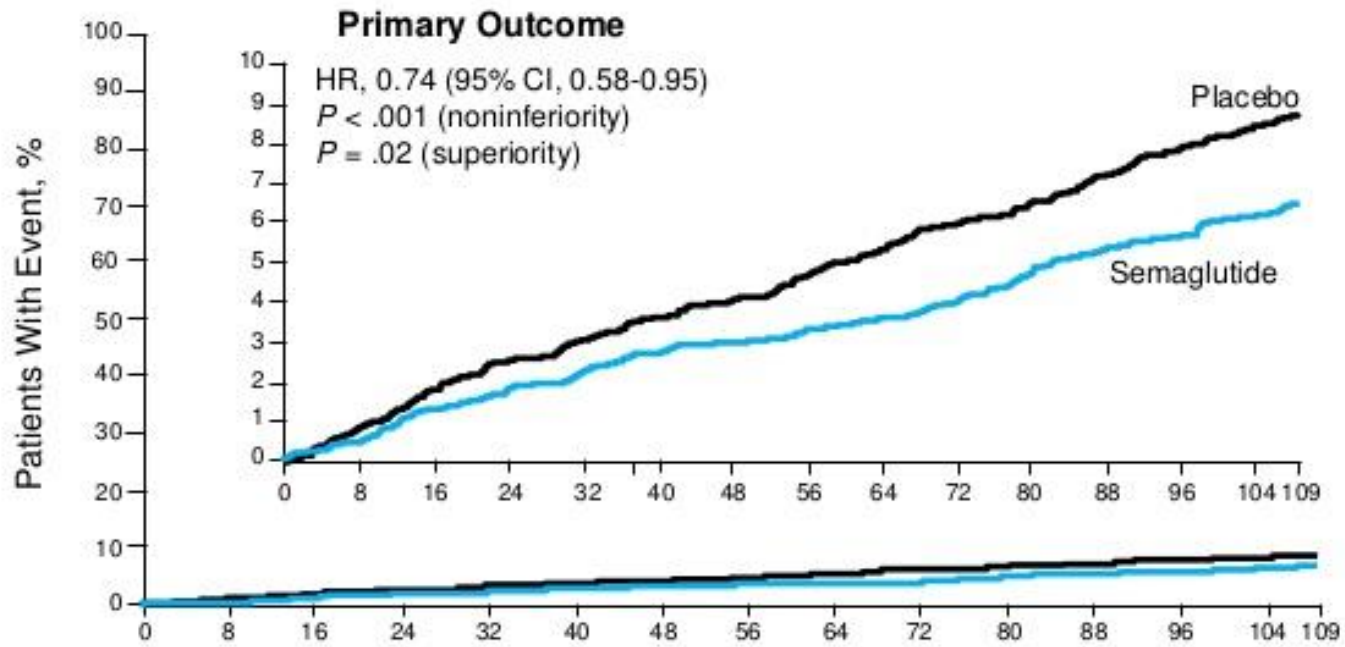
Hospitalization for heart failure



The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months. CI: confidence interval; HR: hazard ratio.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

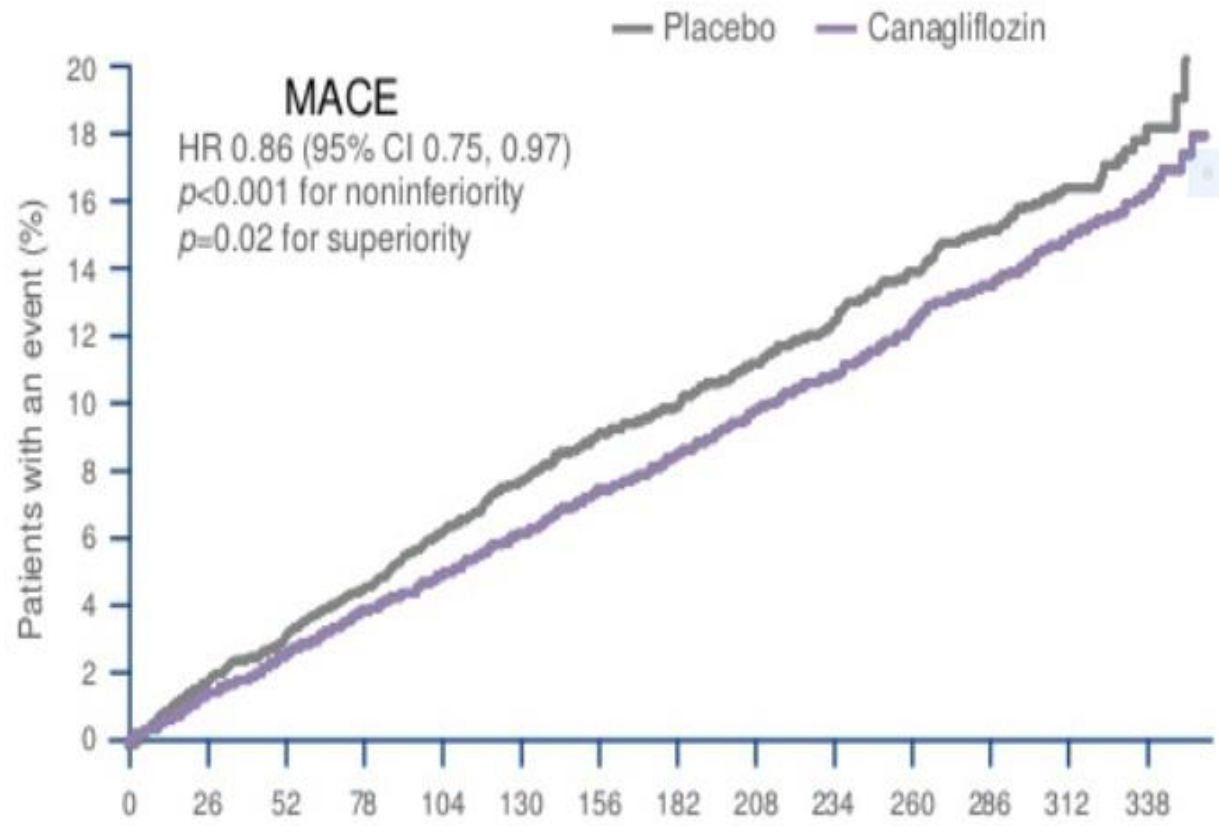
SUSTAIN-6: Semaglutide vs. Placebo



No. at Risk							
Placebo	1649	1616	1586	1567	1534	1508	1479
Semaglutide	1648	1619	1601	1584	1568	1543	1524

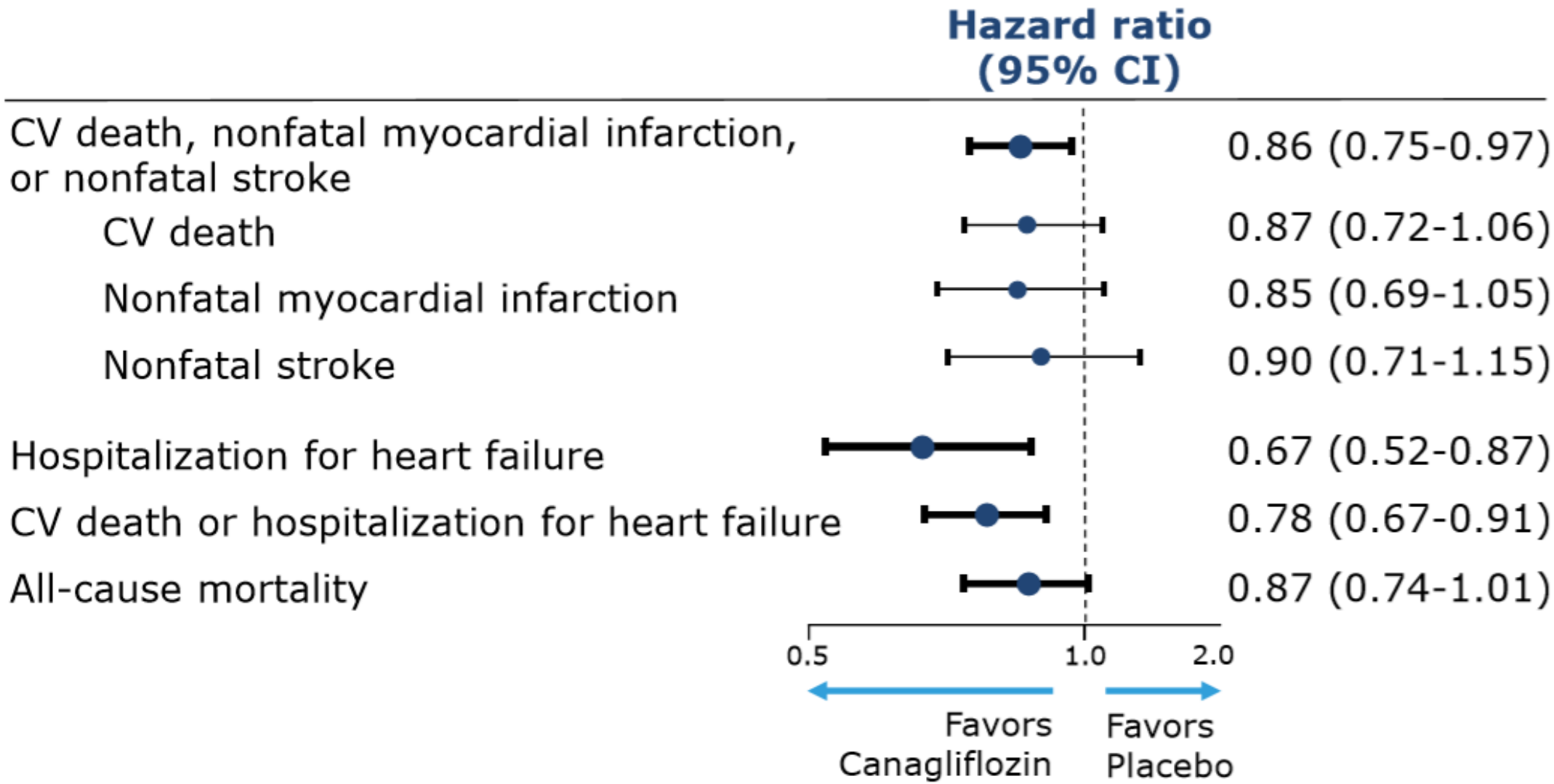
Marso SP, et al. N Engl J Med 2016 375: 1834-1844

CANVAS Program: Canagliflozin vs. Placebo



No. at risk														
Canagliflozin	5795	5672	5566	5447	4343	2984	2555	2513	2460	2419	2363	2311	1661	448
Placebo	4347	4239	4153	4061	2942	1626	1240	1217	1187	1156	1120	1095	789	216

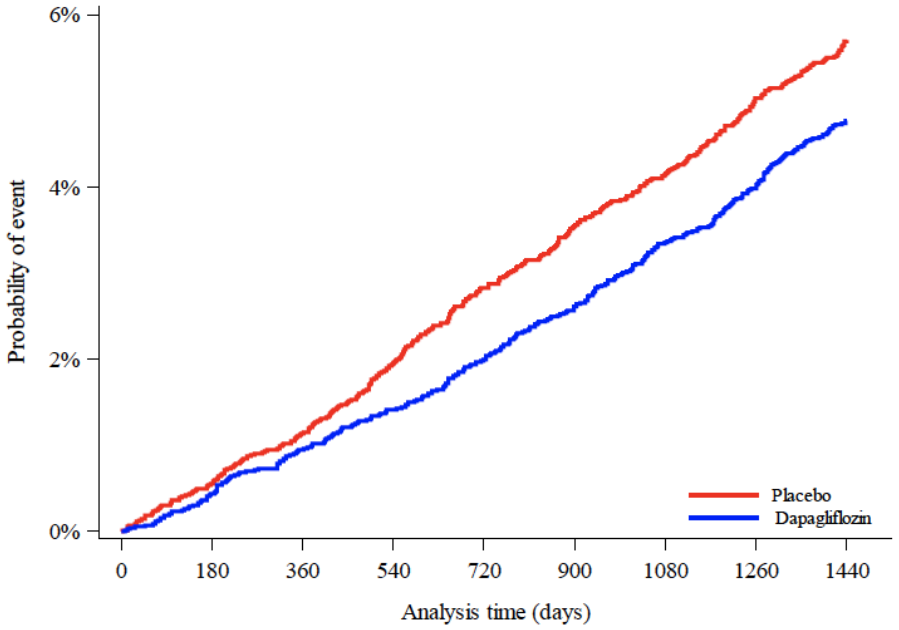
Other vascular events and death



DECLARE-TIMI 58 Primary Endpoints

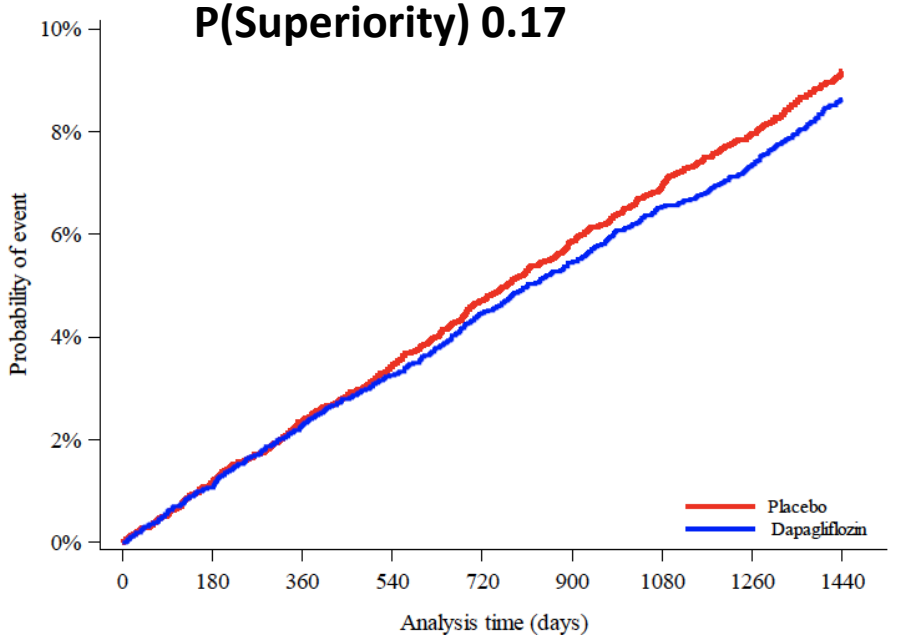
CVD/HHF

4.9% vs 5.8%
HR 0.83 (0.73-0.95)
P(Superiority) 0.005



MACE

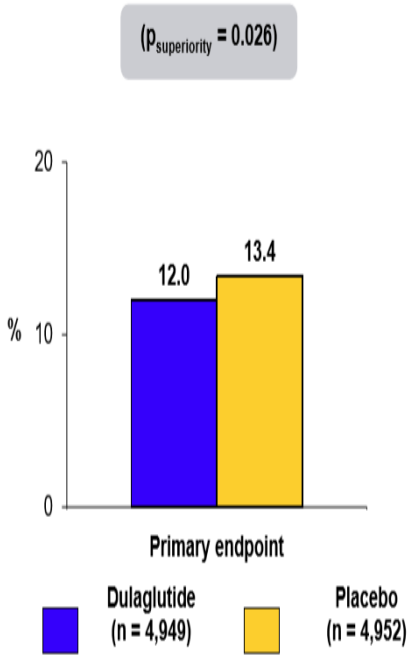
8.8% vs 9.4%
HR 0.93 (0.84-1.03)
P(Noninferiority) <0.001
P(Superiority) 0.17



REWIND

AMERICAN COLLEGE of CARDIOLOGY

Trial Description: Patients with type 2 diabetes mellitus (DM2) and higher cardiovascular (CV) risk were randomized in a 1:1 fashion to either subcutaneous dulaglutide 1.5 mg once weekly or matching placebo. They were followed for 5.4 years.



RESULTS

- Primary endpoint, CV death, MI, or stroke, for dulaglutide vs. placebo: 12.0% vs. 13.4%, $p_{superiority}$ = 0.026; CV death: 6.4% vs. 7.0% (p = 0.21); nonfatal MI: 4.1% vs. 4.3% (p = 0.65); nonfatal stroke: 2.7% vs. 3.5% (p = 0.017)
- CHF hospitalization/urgent visit: 4.3% vs. 4.6% (p = 0.46); composite microvascular outcome (eye or kidney): 18.4% vs. 20.6% (p = 0.002)
- Composite renal outcome: 17.1% vs. 19.6% (p = 0.0004)

CONCLUSIONS

- Dulaglutide (GLP-1 agonist) is superior to placebo in improving glycemic control and ↓ CV events (particularly stroke) in patients with DM2 and higher CV risk
- These are really important findings and suggest that dulaglutide may need to be considered for the management of DM2 in similar high-risk patients going forward

Gerstein HC, et al. Lancet 2019;Jun 9:[Epub]

The PIONEER 6 trial investigated cardiovascular safety of oral semaglutide vs placebo

PIONEER 6 trial design

Trial objective

Confirm the cardiovascular safety of oral semaglutide in patients with type 2 diabetes

Inclusion criteria

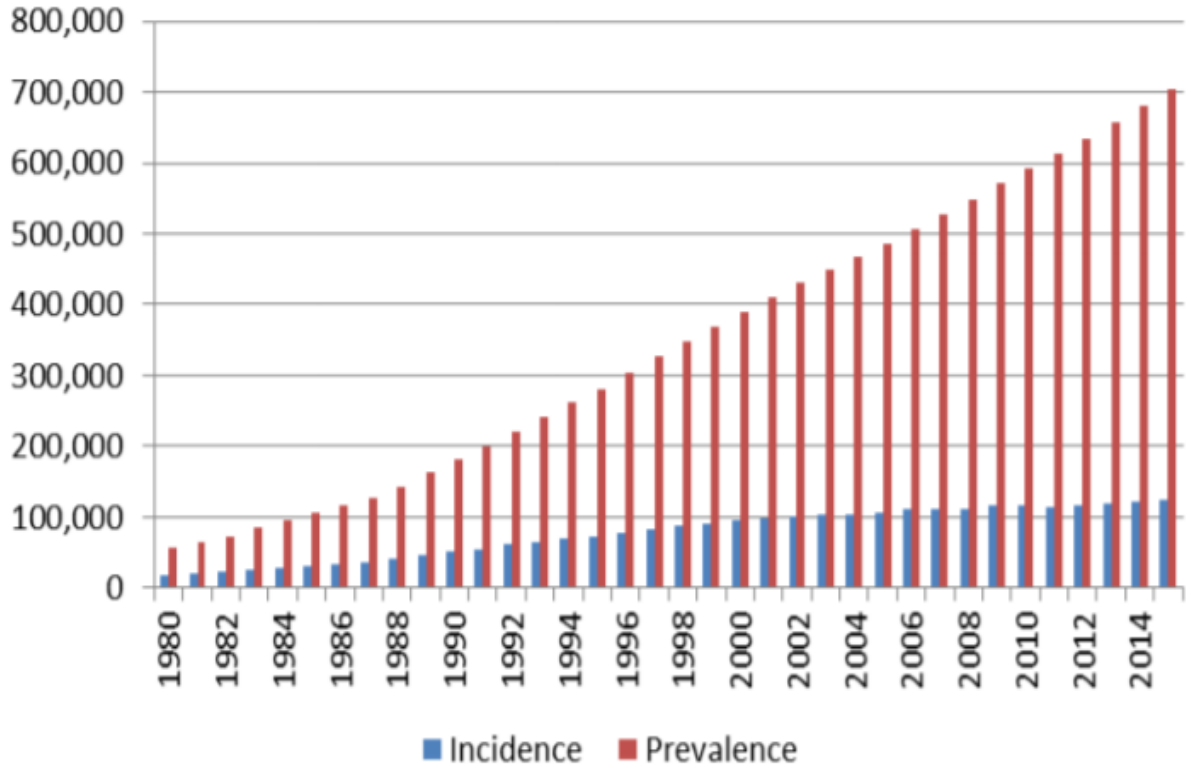
- Age ≥50 years and clinical evidence of CV disease or age ≥50 years and subclinical evidence of CV disease
- Antidiabetic drug-naïve or current treatment with one or more oral or injectable antidiabetic agent(s) (excl. DPP-4 and GLP-1)

PIONEER 6 headline results

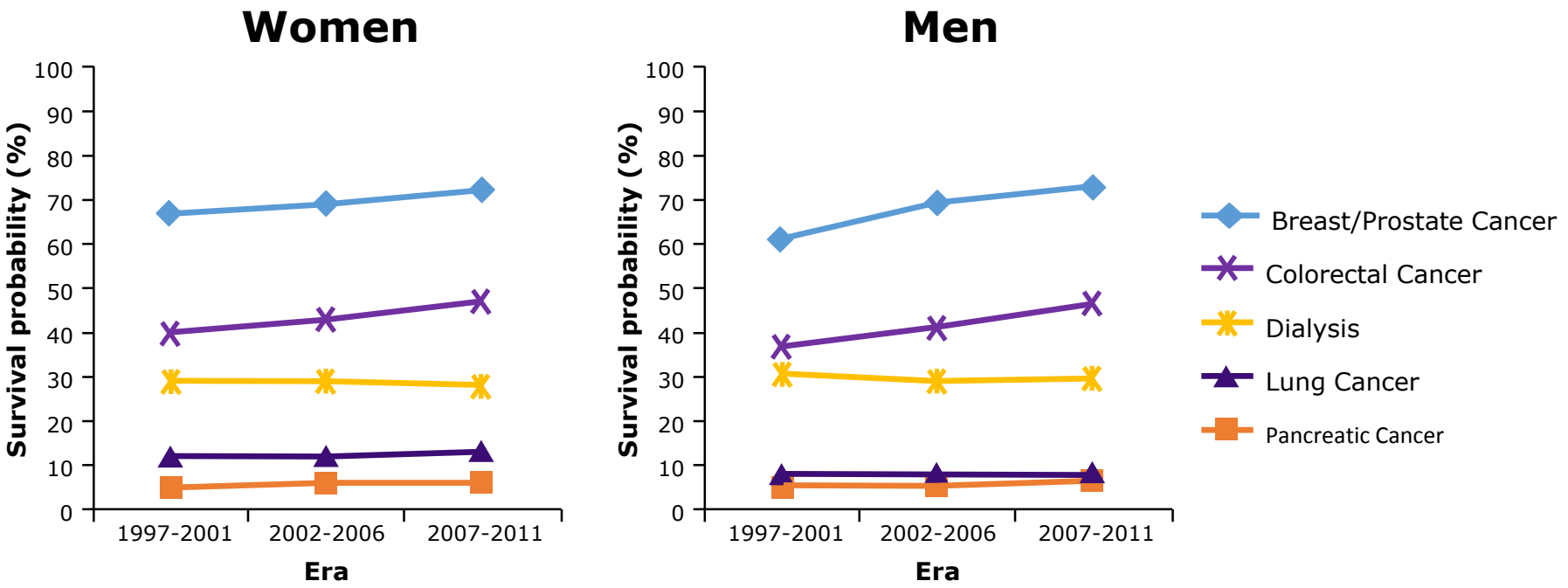
- 21% non-significant reduction of primary endpoint[1] for oral semaglutide-treated patients compared to placebo-treated subjects (HR: 0.79)
  - CV death – significant (HR: 0.49)
  - Non-fatal MI – non-significant (HR: 1.18)
  - Non-fatal stroke – non-significant (HR: 0.74)
- All-cause mortality – significant (HR: 0.51)
- Results were based on 137 MACE with median follow-up of 16 months

[1] The primary endpoint of the PIONEER 6 trial was defined as the MACE composite outcome of the first occurrence of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke.
CV: cardiovascular; DPP-4: dipeptidyl peptidase-4 inhibitor; GLP-1: glucagon-like peptide-1; MACE: major cardiovascular event; HR: hazard ratio; MI: myocardial infarction; PIONEER: peptide innovation for early diabetes treatment

Increasing Incidence and Prevalence of ESKD: US Data



Dialysis Survival Compared to Common Cancers



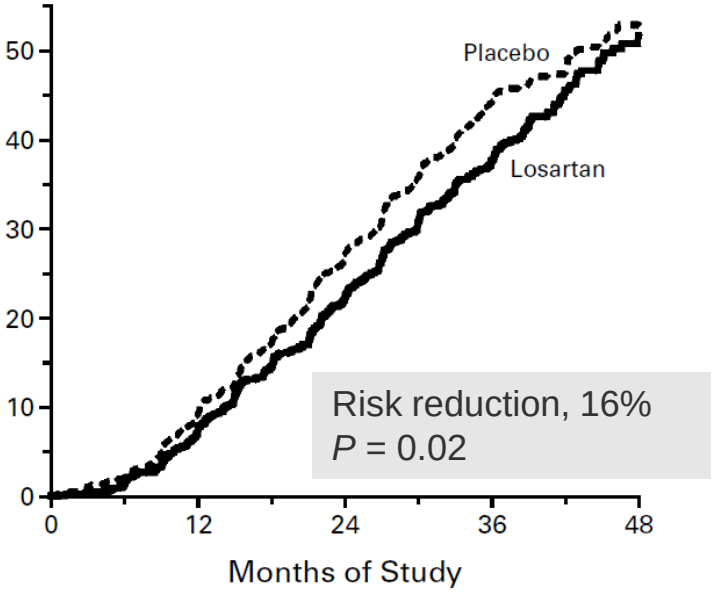
Unadjusted 10-year survival for all-cause mortality in Canada

N = 33,500 incident maintenance dialysis patients; 532,452 incident cancer patients

The Only Proven Treatment for Renoprotection in T2DM: RENAAL & IDNT

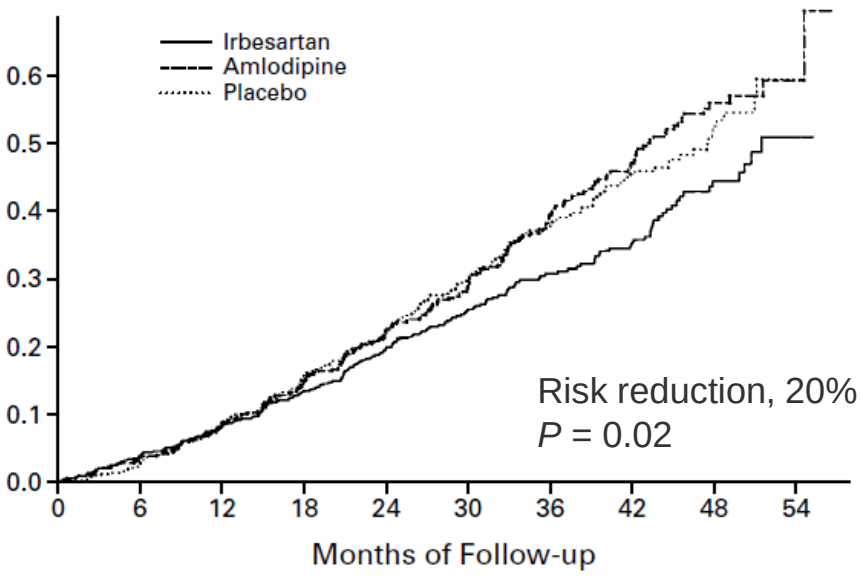
Doubling of serum creatinine, ESKD, or death

RENAAL



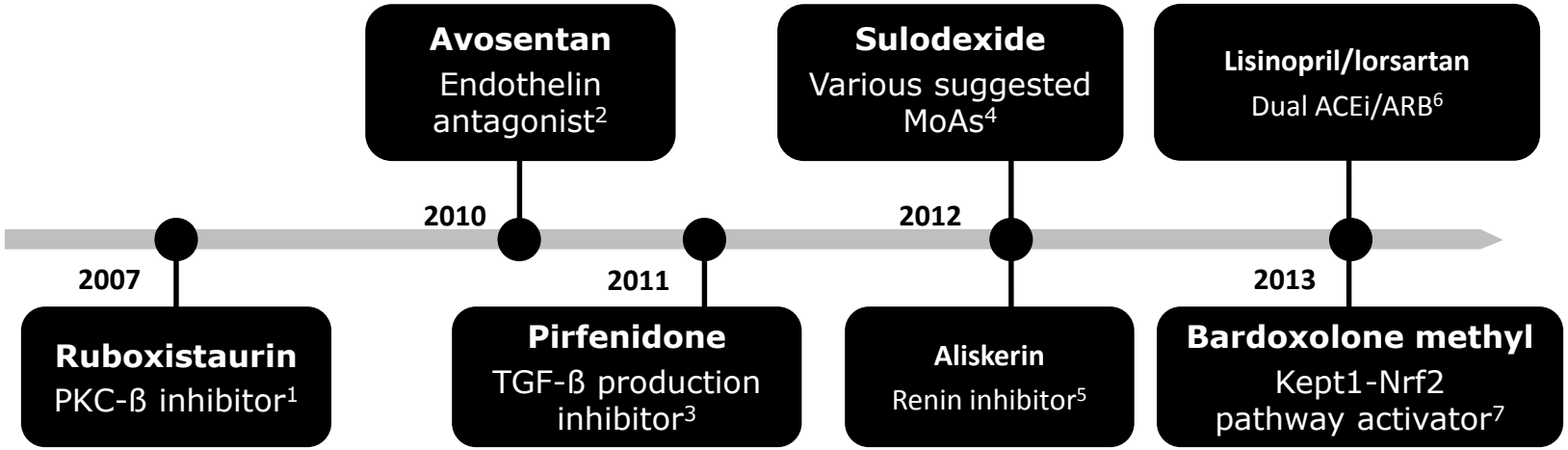
Brenner B, et al. *N Engl J Med*. 2001;345(12):861-869.

IDNT

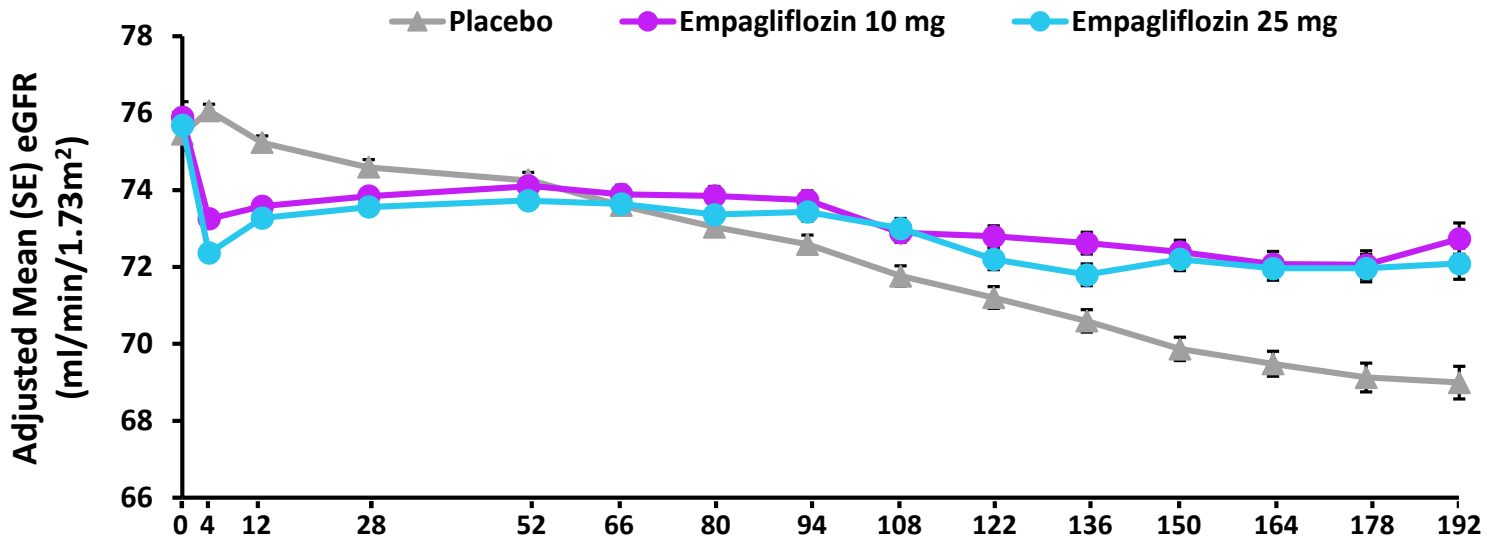


Lewis EJ, et al. *N Eng J Med*. 2001;345(12):851-860.

Since RENAAL and IDNT, New Therapeutic Strategies for Patients With T2DM and CKD Have Failed



Renal function: eGFR (CKD-EPI formula) over time



No. of Patients															
Placebo	2323	2295	2267	2205	2121	2064	1927	1981	1763	1479	1262	1123	977	731	448
Empagliflozin 10 mg	2322	2290	2264	2235	2162	2114	2012	2064	1839	1540	1314	1180	1024	785	513
Empagliflozin 25 mg	2322	2288	2269	2216	2156	2111	2006	2067	1871	1563	1340	1207	1063	838	524

eGFR calculated with CKD-EPI formula. MMRM analysis following the intention-to-treat principle.
CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MMRM, mixed-model repeated measure; SE, standard error.

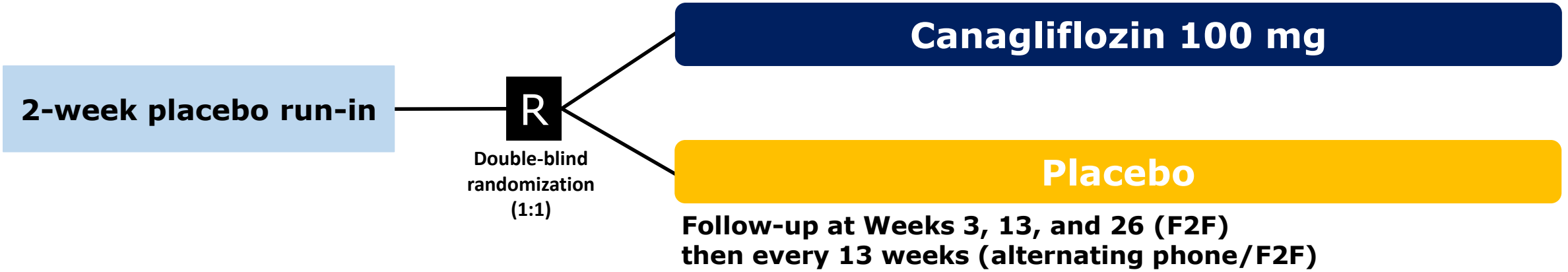
Wanner et al. N Engl J Med. 2016;375(4):323-34.

CREDENCE TRIAL: Canagliflozin vs Placebo

Study Design

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



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

Primary Endpoint Definitions

- **ESKD**
  - Chronic dialysis for ≥30 days
  - Kidney transplantation
  - eGFR <15 mL/min/1.73 m^2 sustained for ≥30 days by central laboratory assessment
- **Doubling of serum creatinine**
  - Doubling from the baseline average sustained for ≥30 days by central laboratory assessment
- **Renal death**
  - Deaths in patients who have reached ESKD who die prior to initiating renal replacement therapy and no other cause of death is adjudicated
- **CV death**
  - Death due to MI, stroke, heart failure, sudden death, death during a CV procedure or as a result of procedure-related complications, presumed sudden CV death, death of unknown cause, or death resulting from a documented CV cause other than those listed

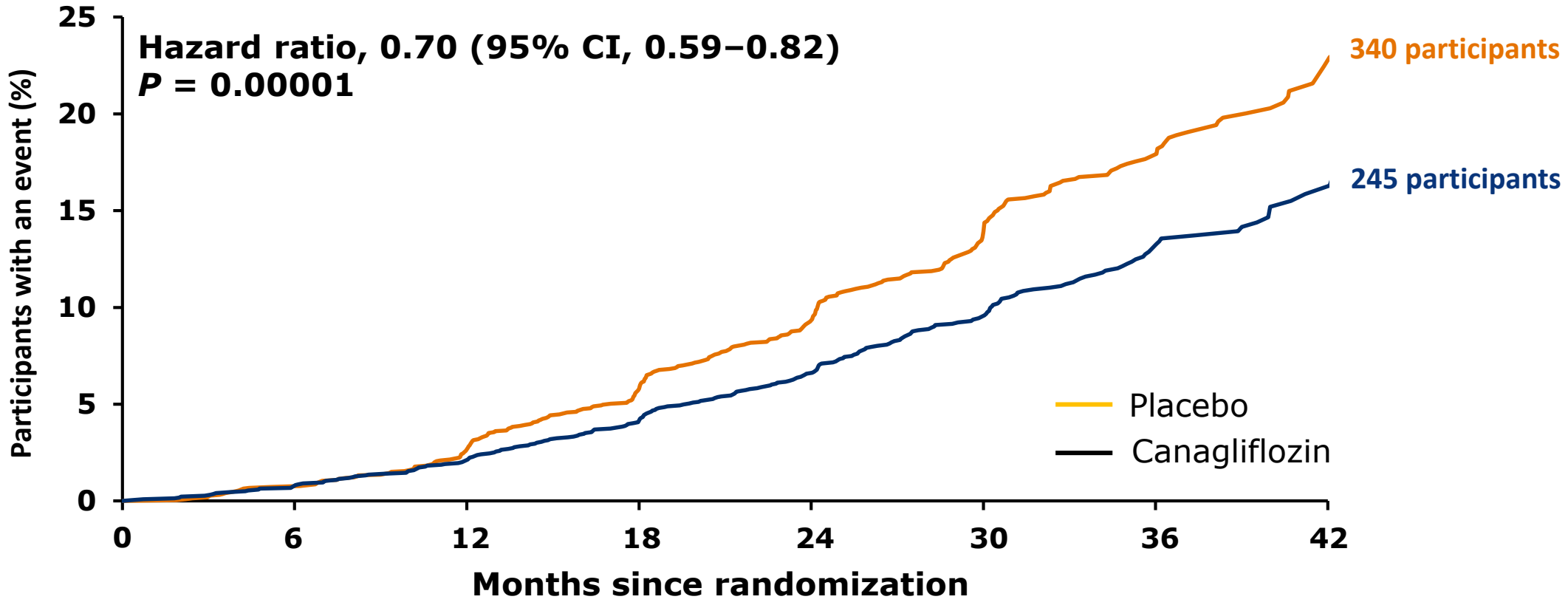
Interim Analysis

- Planned interim analysis to occur after 405 confirmed primary efficacy endpoints and 2 years of exposure
- Reviewed by an Independent Data Monitoring Committee
- Prespecified stopping guidance included
  - Primary composite: 2-sided $P < 0.01$

  AND

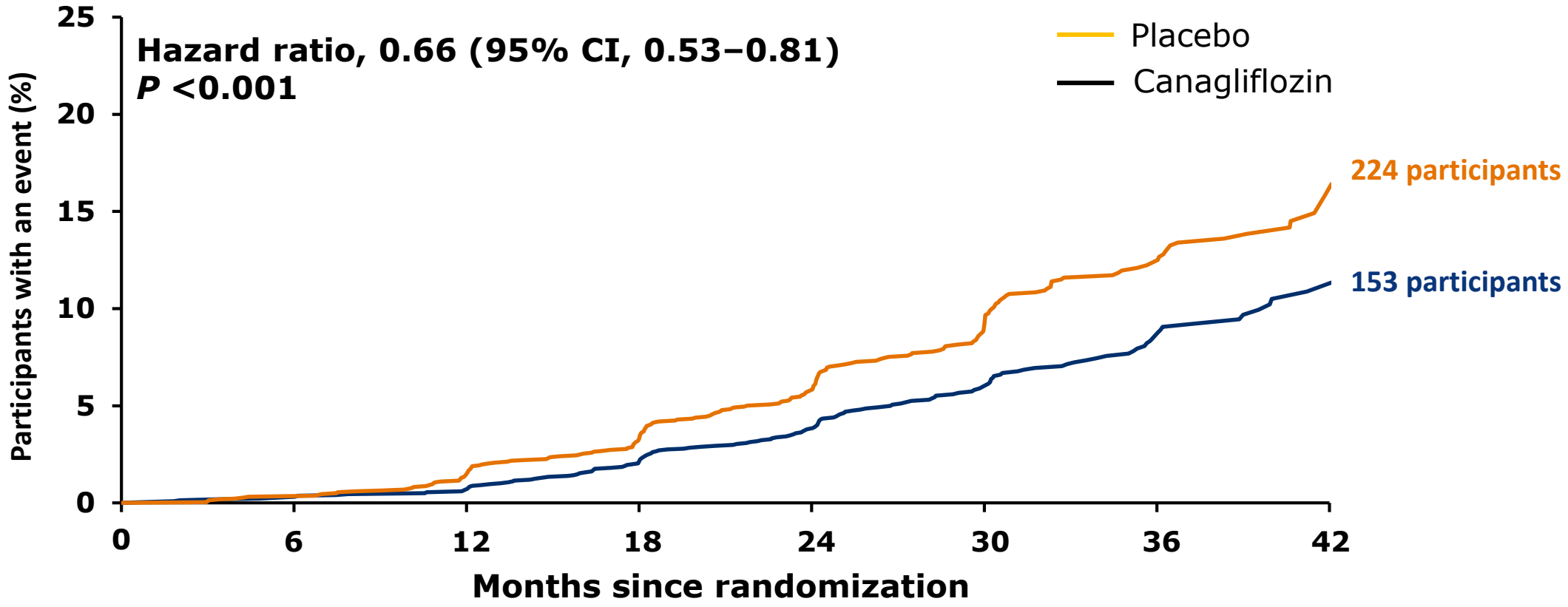
  Composite of ESKD, renal death, or CV death: 2-sided $P < 0.025$
  - Global assessment of benefit and safety

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



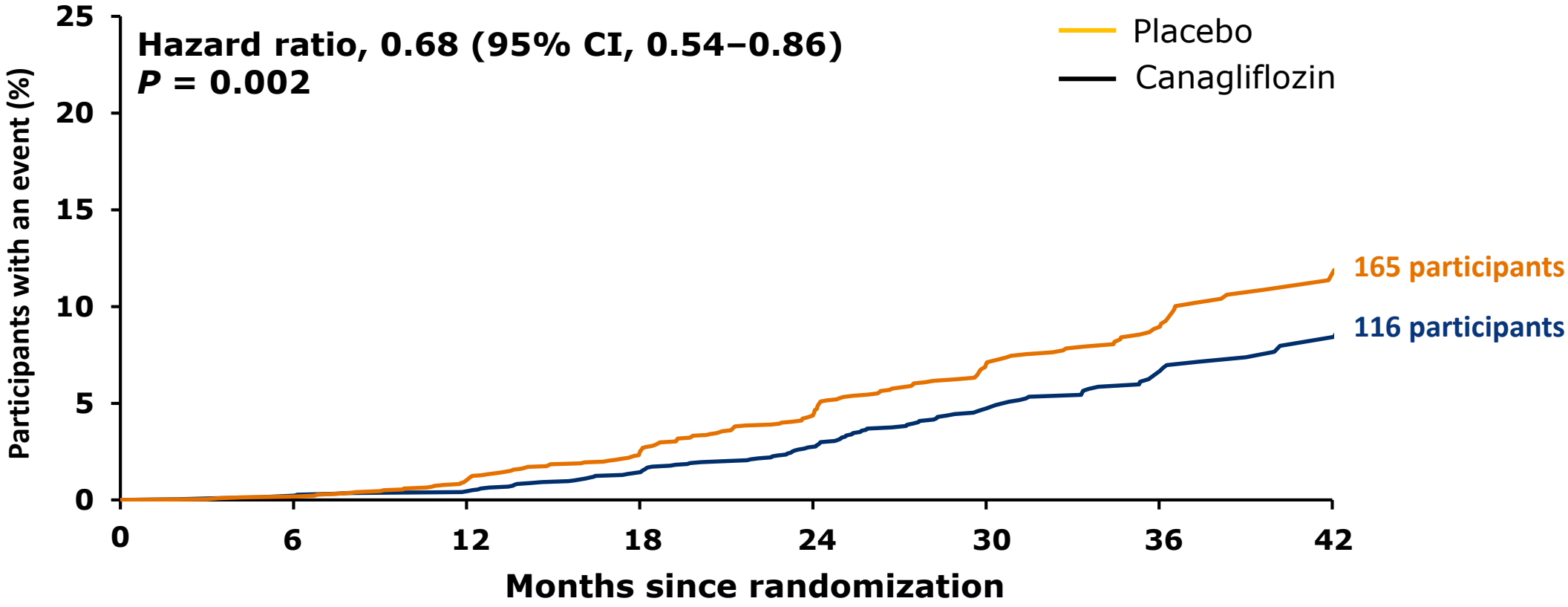
No. at risk								
Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

ESKD, Doubling of Serum Creatinine, or Renal Death



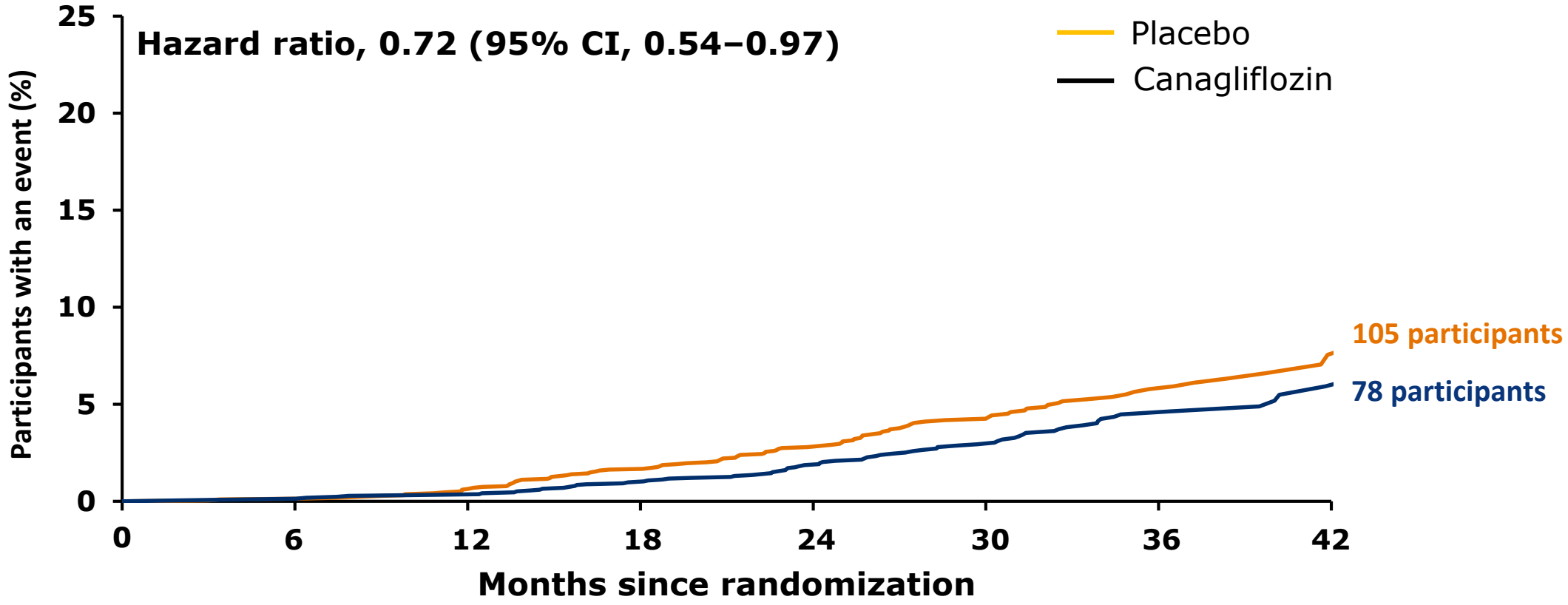
No. at risk								
Placebo	2199	2178	2131	2046	1724	1129	621	170
Canagliflozin	2202	2181	2144	2080	1786	1211	646	196

End-stage Kidney Disease



No. at risk								
Placebo	2199	2182	2141	2063	1752	1152	641	178
Canagliflozin	2202	2182	2146	2091	1798	1217	654	199

Dialysis, Kidney Transplantation, or Renal Death



No. at risk								
Placebo	2199	2183	2147	2077	1776	1178	653	180
Canagliflozin	2202	2184	2148	2100	1811	1236	661	199

Summary

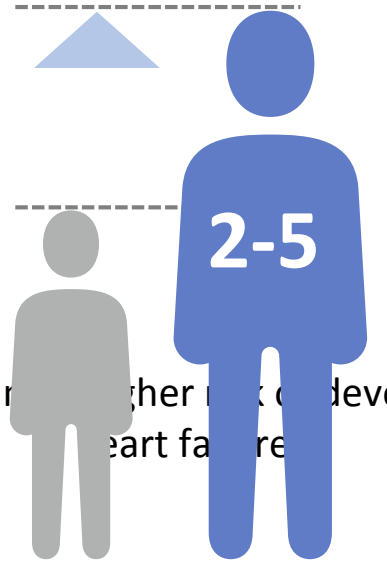
- Canagliflozin **reduced the risk of the primary outcome** of ESKD, doubling of serum creatinine, or renal or CV death **by 30%** (*P* = 0.00001)
  - The results were consistent across a broad range of prespecified subgroups

- Canagliflozin also **reduced the risk of the secondary outcome** of ESKD, doubling of serum creatinine, or renal death **by 34%** (*P* <0.001)

- Similar risk reductions were seen for exploratory outcomes assessing components of the primary outcome
  - **ESKD: 32% lower** (95% CI, 14–46)
  - **Dialysis, transplantation, or renal death: 28% lower** (95% CI, 3–46)

- Canagliflozin **attenuated the slope of chronic eGFR decline** by 2.7 mL/min/1.73 m^2/year (1.9 vs 4.6)

Type 2 diabetes and heart failure



2 to 5 ti gher developing
eart fa re

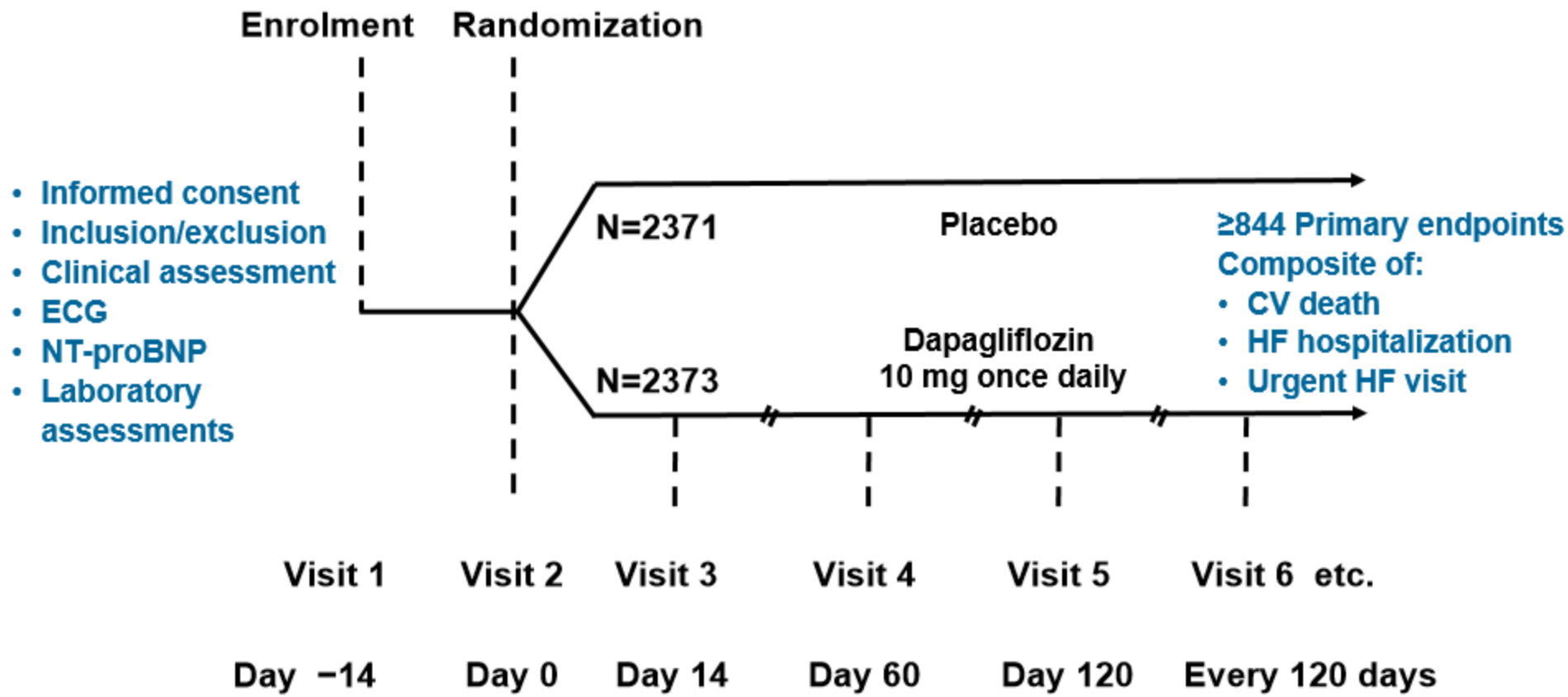
*Synthesized based on data from two clinical studies

In diabetes + heart failure
2 times greater probability of cardiovascular death and all-cause mortality[2,3]

1. Kannel et al. Am J Cardiol. 1974;34:29-34
2. Cubbon et al. Diab Vasc Dis Res. 2013;10:330-6
3. MacDonald et al. Eur Heart J. 2008;29:1377-85.

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

DAPA-HF Design



Key baseline characteristics

Characteristic	Dapagliflozin (n=2373)	Placebo (n=2371)
Mean age (yr)	66	67
Male (%)	76	77
NYHA class II/III/IV (%)	68/31/1	67/32/1
Mean LVEF (%)	31	31
Median NT pro BNP (pg/ml)	1428	1446
Mean systolic BP (mmHg)	122	122
Ischaemic aetiology (%)	55	57
Mean eGFR (ml/min/1.73m^2)	66	66
Prior diagnosis T2D (%)	42	42
Any baseline T2D (%)*	45	45

*includes 82 dapagliflozin and 74 placebo patients with previously undiagnosed diabetes i.e. two HbA1c ≥6.5% (≥48 mmol/mol)

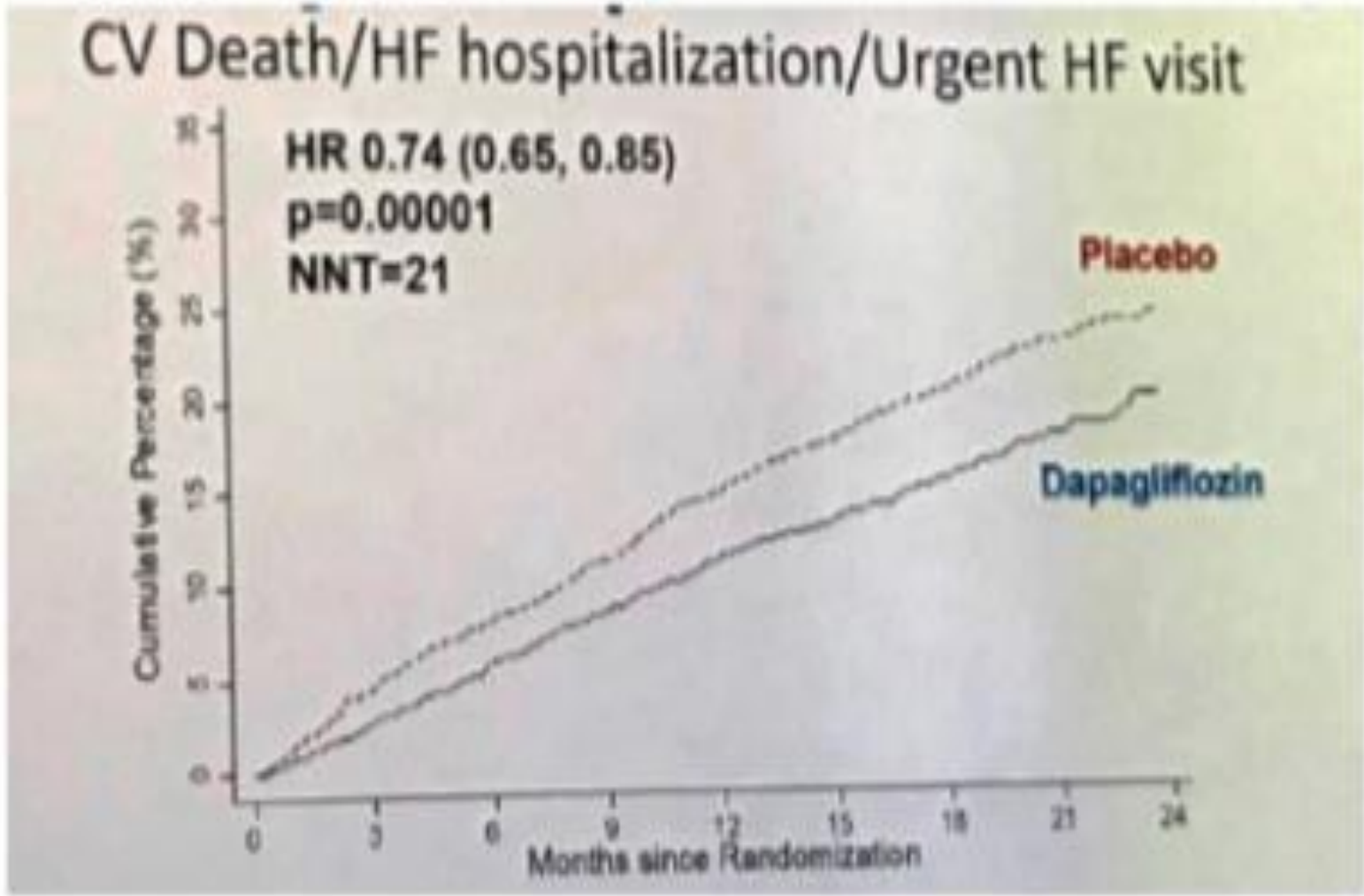
Baseline treatment

Treatment (%)	Dapagliflozin (n=2373)	Placebo (n=2371)
Diuretic	93	94
ACE-inhibitor/ARB/ARNI[+]	94	93
ACE inhibitor	56	56
ARB	28	27
Sacubitril/valsartan	11	11
Beta-blocker	96	96
MRA	71	71
ICD*	26	26
CRT**	8	7

[+]ARNI = angiotensin receptor neprilysin inhibitor
*ICD or CRT-D **CRT-P or CRT-D

For full details see McMurray JJV et al
Eur J Heart Fail.2019 Jul 15. doi: 10.1002/ejhf.1548

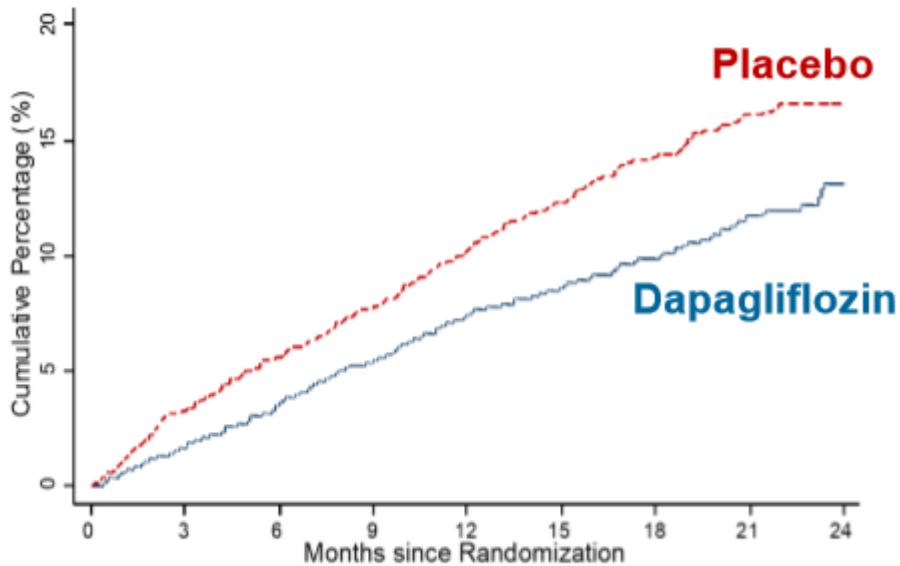
Primary composite outcome



Components of primary outcome

Worsening HF event

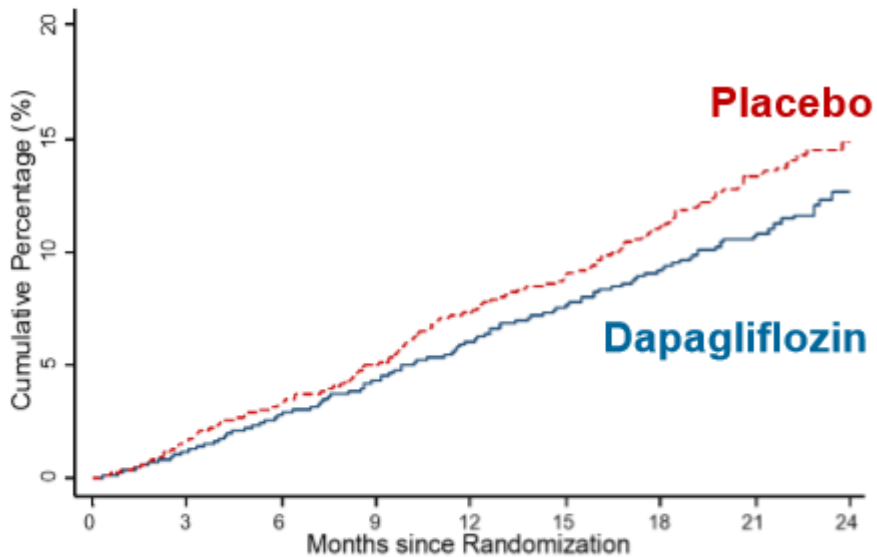
HR 0.70 (0.59, 0.83); p=0.00003



Number at Risk									
Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

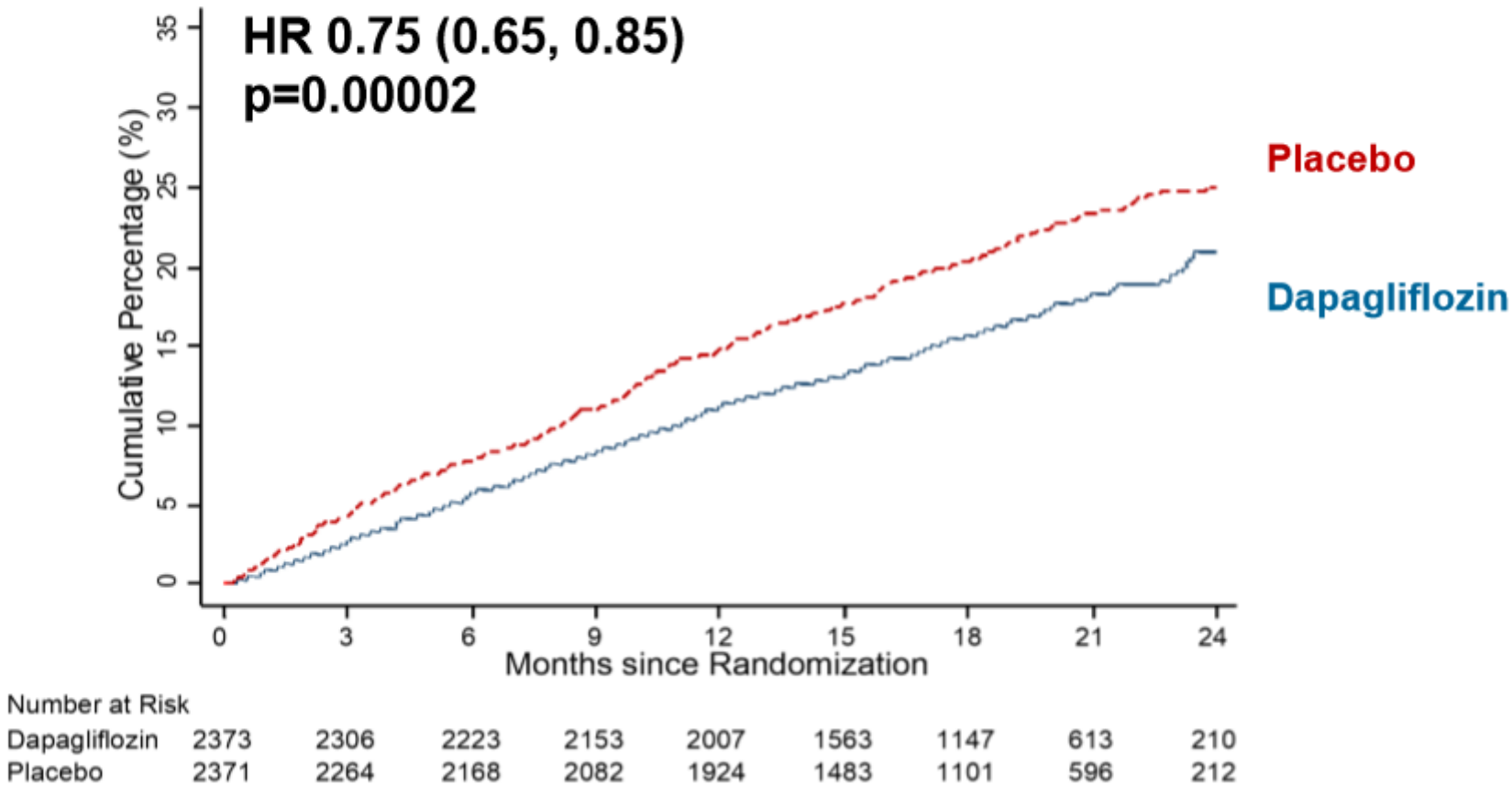
Cardiovascular death

HR 0.82 (0.69, 0.98); p=0.029

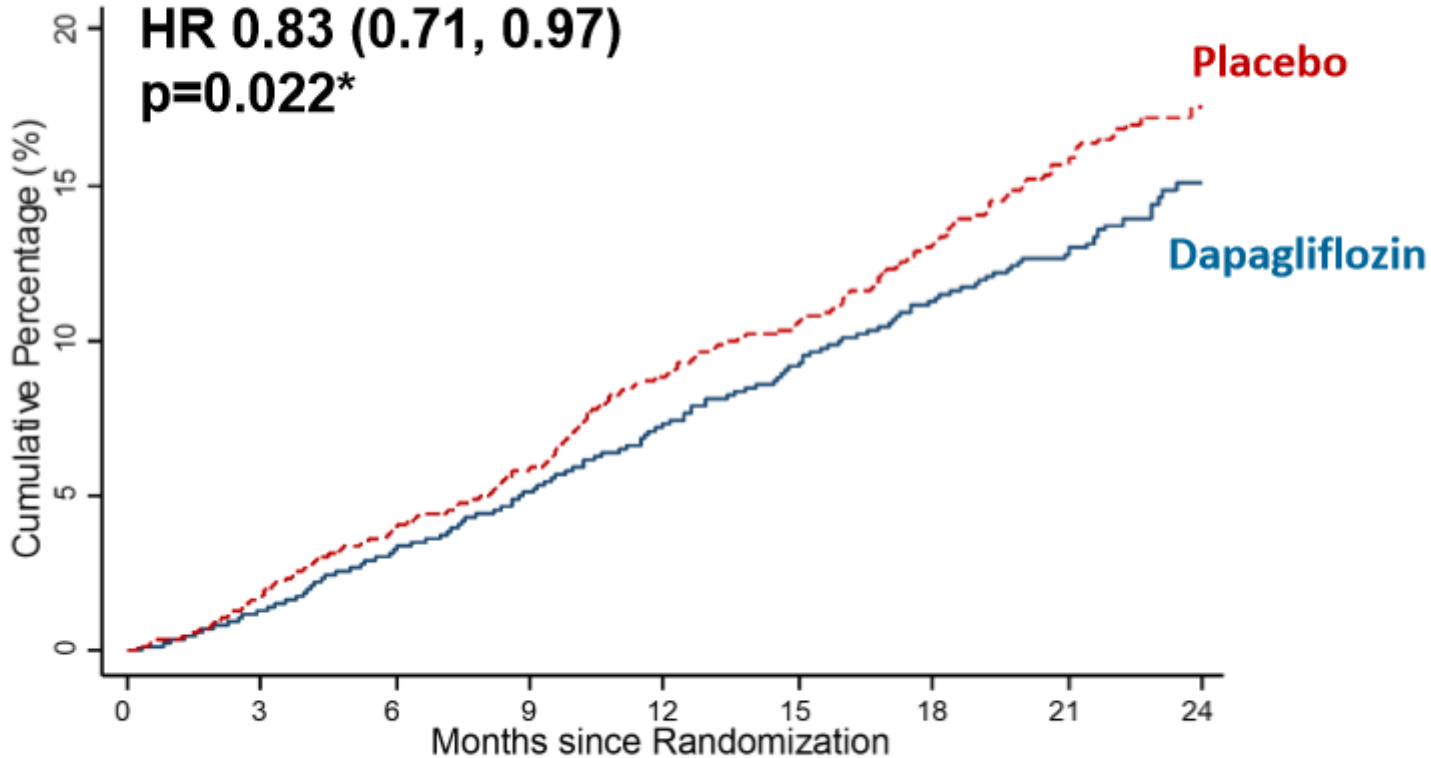


	2373	2339	2293	2248	2127	1664	1242	671	232
	2371	2330	2279	2230	2091	1636	1219	664	234

CV death or HF hospitalization



All-cause death

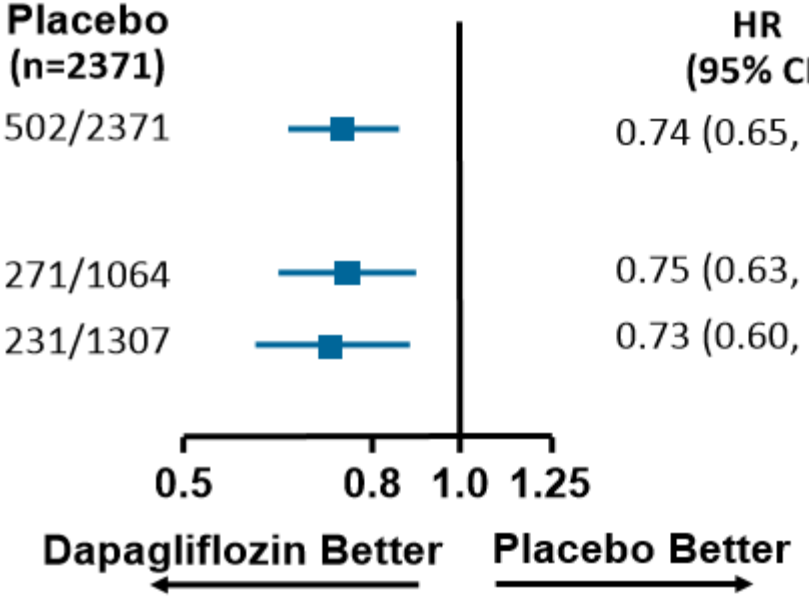


Number at Risk									
Dapagliflozin	2373	2342	2296	2251	2130	1666	1243	672	233
Placebo	2371	2330	2279	2231	2092	1638	1221	665	235

*Nominal p value

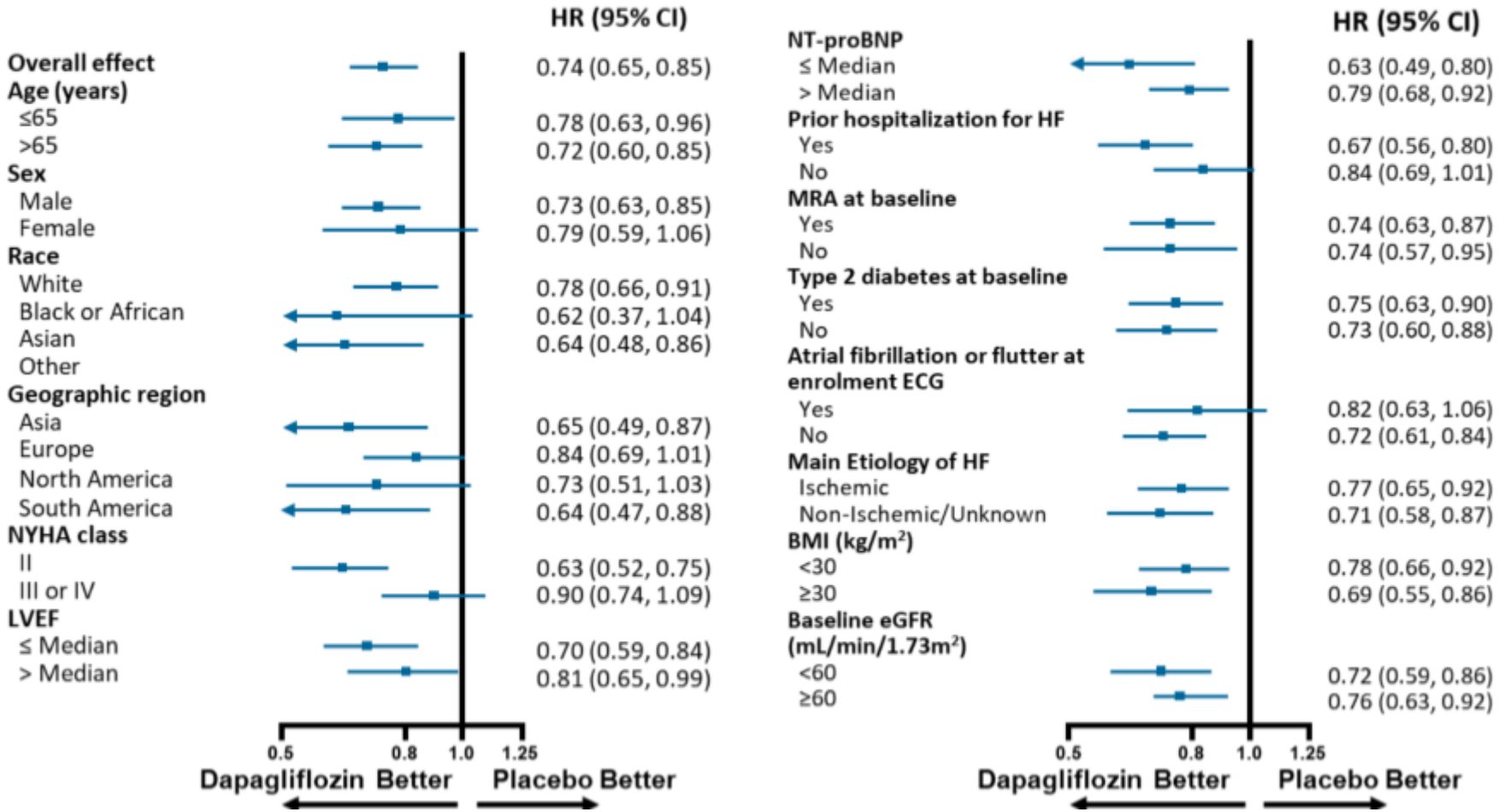
No diabetes/diabetes subgroup: Primary endpoint

	Dapagliflozin (n=2373)	Placebo (n=2371)	HR (95% CI)
All patients	386/2373	502/2371	0.74 (0.65, 0.85)
Type 2 diabetes at baseline*			
Yes	215/1075	271/1064	0.75 (0.63, 0.90)
No	171/1298	231/1307	0.73 (0.60, 0.88)



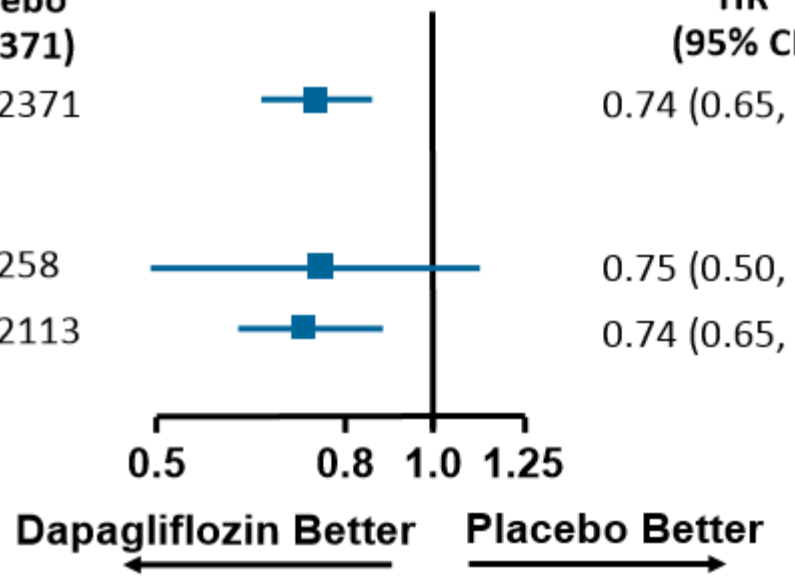
*Defined as history of type 2 diabetes or HbA1c ≥6.5% at **both** enrollment and randomization visits.

Primary Endpoint: Prespecified subgroups



ARNI/no ARNI *post hoc* subgroup: Primary endpoint

	Dapagliflozin (n=2373)	Placebo (n=2371)	HR (95% CI)
All patients	386/2373	502/2371	0.74 (0.65, 0.85)
Angiotensin Receptor Neprilysin Inhibitor (ARNI)			
Yes	41/250	56/258	0.75 (0.50, 1.13)
No	345/2123	446/2113	0.74 (0.65, 0.86)



Patients exposed to at least one dose of study drug	Dapagliflozin (n=2368)	Placebo (n=2368)	p-value
Adverse events (AE) of interest (%)			
Volume depletion[+]	7.5	6.8	0.40
Renal AE[‡]	6.5	7.2	0.36
Fracture	2.1	2.1	1.00
Amputation	0.5	0.5	1.00
Major hypoglycaemia	0.2	0.2	-
Diabetic ketoacidosis	0.1	0.0	-
AE leading to treatment discontinuation (%)	4.7	4.9	0.79
Any serious adverse event (incl. death) (%)	38	42	<0.01

[+] Volume depletion serious AEs in 29 dapagliflozin patients (1.2%) and 40 placebo patients (1.7%), p=0.23

[‡] Renal serious AEs in 38 dapagliflozin patients (1.6%) and 65 placebo patients (2.7%), p=0.009

Summary and conclusions

- Dapagliflozin reduced the risk of worsening heart failure events and cardiovascular death, and improved symptoms, in patients with HFrEF, when added to standard therapy
- The relative and absolute risk reductions in death and hospitalization were substantial, clinically important, and consistent across important subgroups, including patients ***without*** T2D
- Dapagliflozin was well tolerated and the rate of treatment discontinuation was low
- Dapagliflozin offers a new approach to the treatment of HFrEF

SUMMARY

DPP4 Inhibitors

Trial	Result
TECOS (Sitagliptin)	NEUTRAL
SAVOR-TIMI 53 (Saxagliptin)	NEUTRAL (↑ HF Risk)
EXAMINE (Alogliptin)	NEUTRAL
CARMELINA (Linagliptin)	NEUTRAL

GLP1 Agonists

Trial	Result
ELIXA (Lixisenatide)	NEUTRAL
LEADER (Liraglutide)	POSITIVE
SUSTAIN-6 (Semaglutide)	POSITIVE
EXSCEL (Exenatide)	NEUTRAL (POS for ACM)
REWIND (Dulaglutide)	POSITIVE
HARMONY (Albiglutide)	POSITIVE
PIONEER 6 (Semaglutide PO)	NEUTRAL

SGLT2 Inhibitors

Trial	Result
EMPA-REG Outcome (Empagliflozin)	POSITIVE
CANVAS, CANVAS-R (Canagliflozin)	POSITIVE
DECLARE-TIMI 58 (Dapagliflozin)	+/-POSITIVE
VERTIS CV (Ertugliflozin)	(Q4 2019)
SCORED (Sotagliflozin)	(Q1 2022)
DAPA HF (Dapagliflozin)	POSITIVE
CREDENCE (Canagliflozin)	POSITIVE

ADA & EASD Guidelines

New recommendations call for use of a glucose lowering agent with proven cardiovascular benefit such as the GLP-1 Liraglutide and or one with mortality reduction such as that observed with the SGLT-2 inhibitor Empagliflozin in type 2 diabetes patients with established ASCVD who do not meet glycemic targets with lifestyle modification and Metformin.

American College of Cardiology recommends empagliflozin as preferred SGLT2 inhibitor for adults with type 2 diabetes and established cardiovascular disease in new Expert Consensus Decision Pathway

Nov 27th, 2018

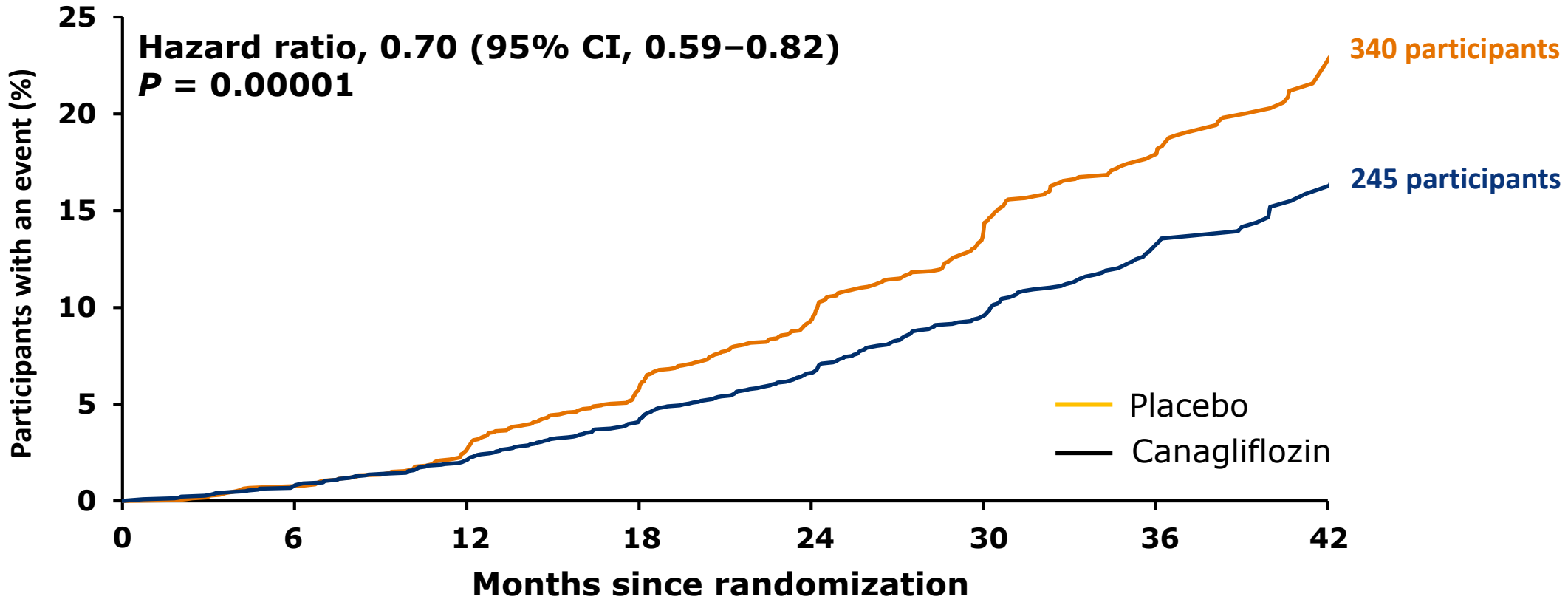
Cardiometabolic Center

Back up Slides

Primary Endpoint Definitions

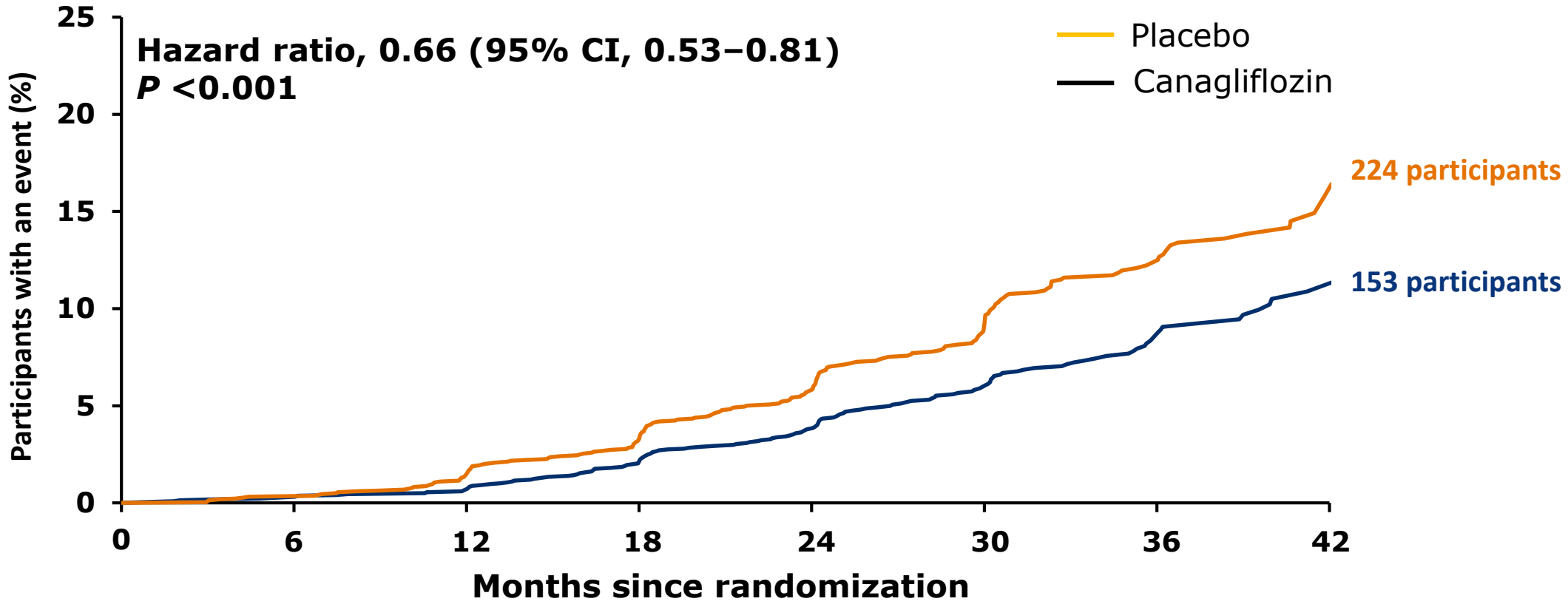
- **ESKD**
  - Chronic dialysis for ≥30 days
  - Kidney transplantation
  - eGFR <15 mL/min/1.73 m^2 sustained for ≥30 days by central laboratory assessment
- **Doubling of serum creatinine**
  - Doubling from the baseline average sustained for ≥30 days by central laboratory assessment
- **Renal death**
  - Deaths in patients who have reached ESKD who die prior to initiating renal replacement therapy and no other cause of death is adjudicated
- **CV death**
  - Death due to MI, stroke, heart failure, sudden death, death during a CV procedure or as a result of procedure-related complications, presumed sudden CV death, death of unknown cause, or death resulting from a documented CV cause other than those listed

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



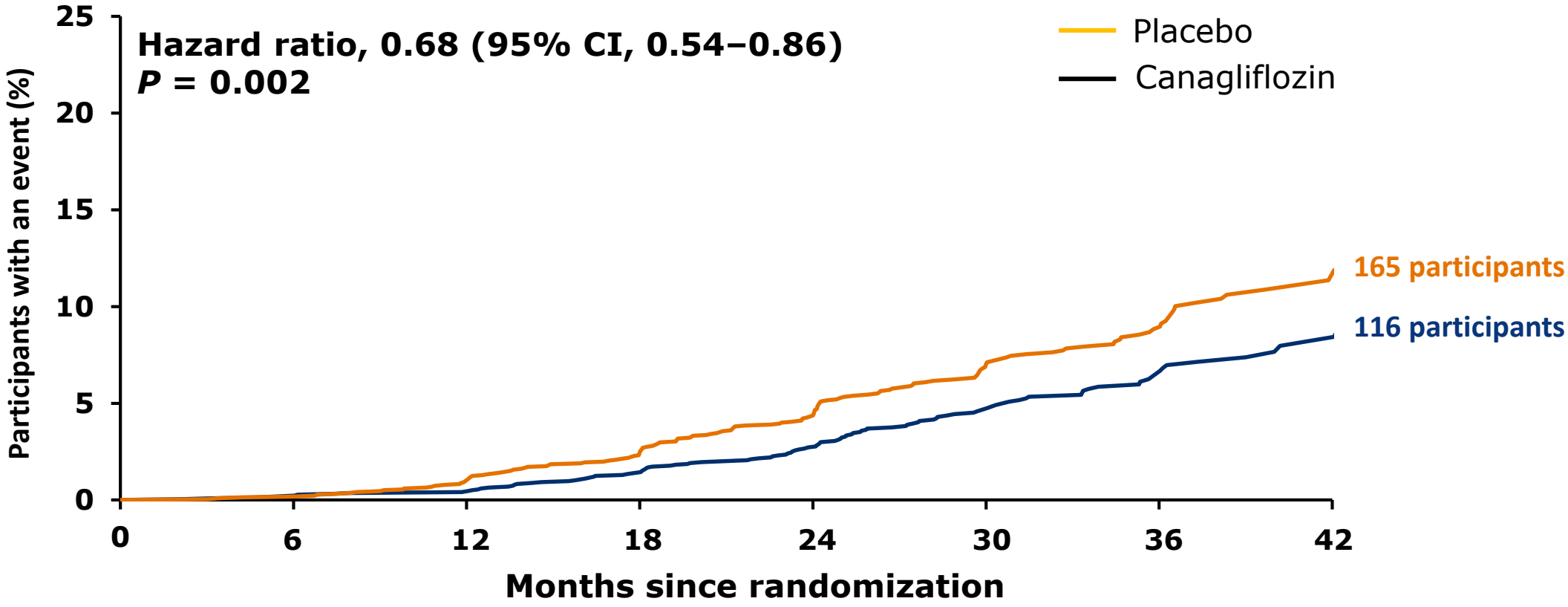
No. at risk								
Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

ESKD, Doubling of Serum Creatinine, or Renal Death



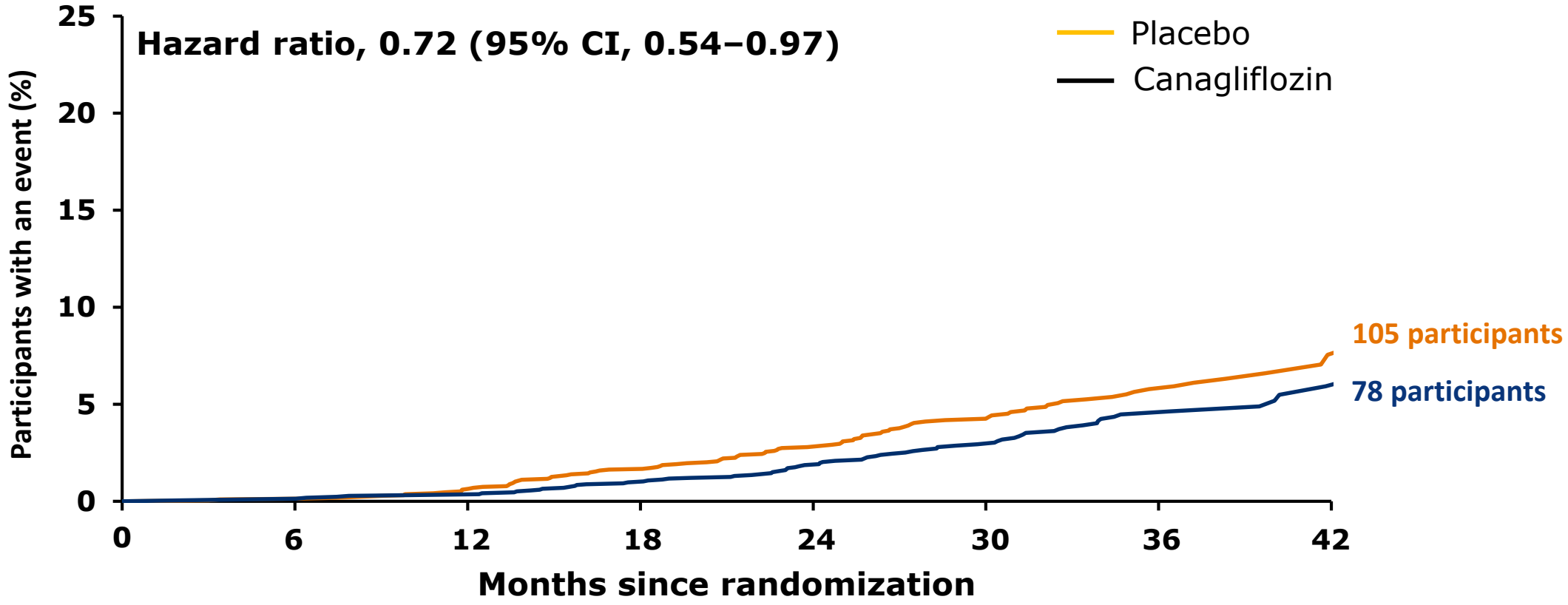
No. at risk								
Placebo	2199	2178	2131	2046	1724	1129	621	170
Canagliflozin	2202	2181	2144	2080	1786	1211	646	196

End-stage Kidney Disease



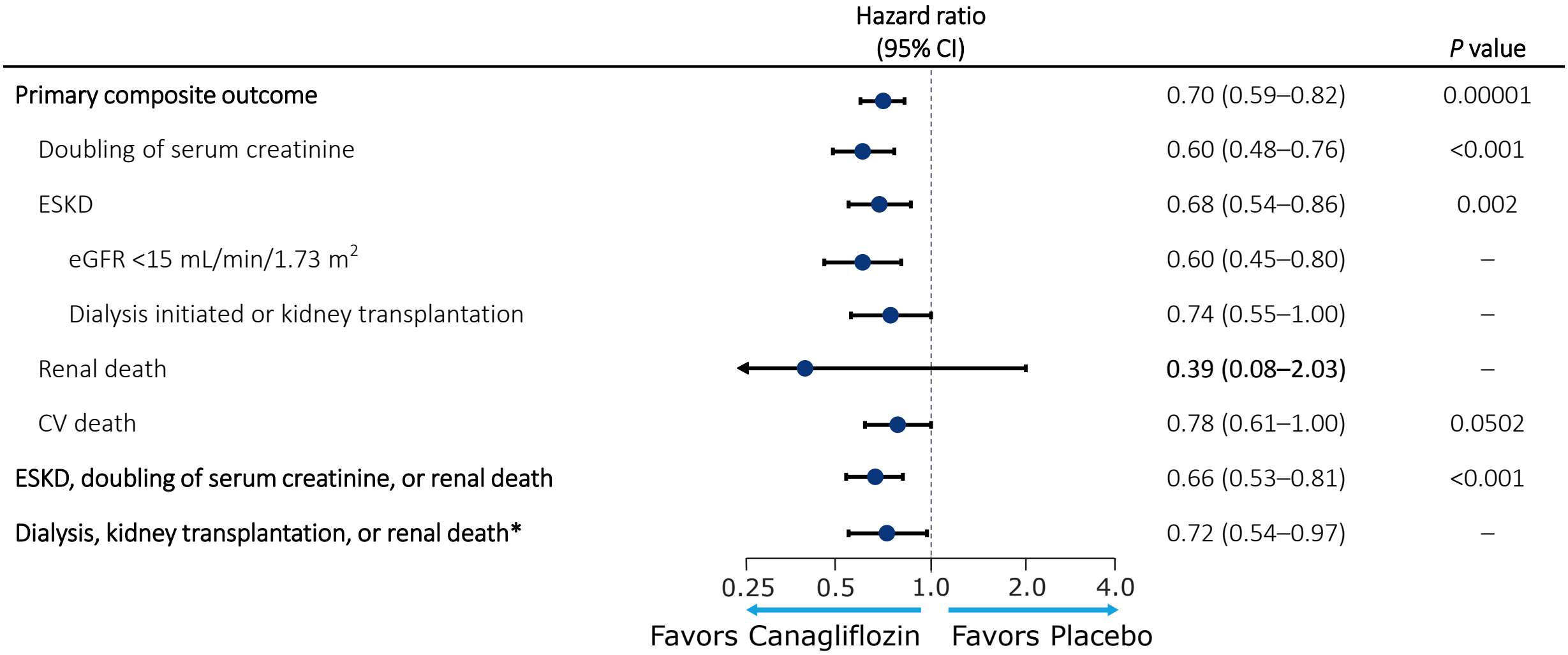
No. at risk								
Placebo	2199	2182	2141	2063	1752	1152	641	178
Canagliflozin	2202	2182	2146	2091	1798	1217	654	199

Dialysis, Kidney Transplantation, or Renal Death

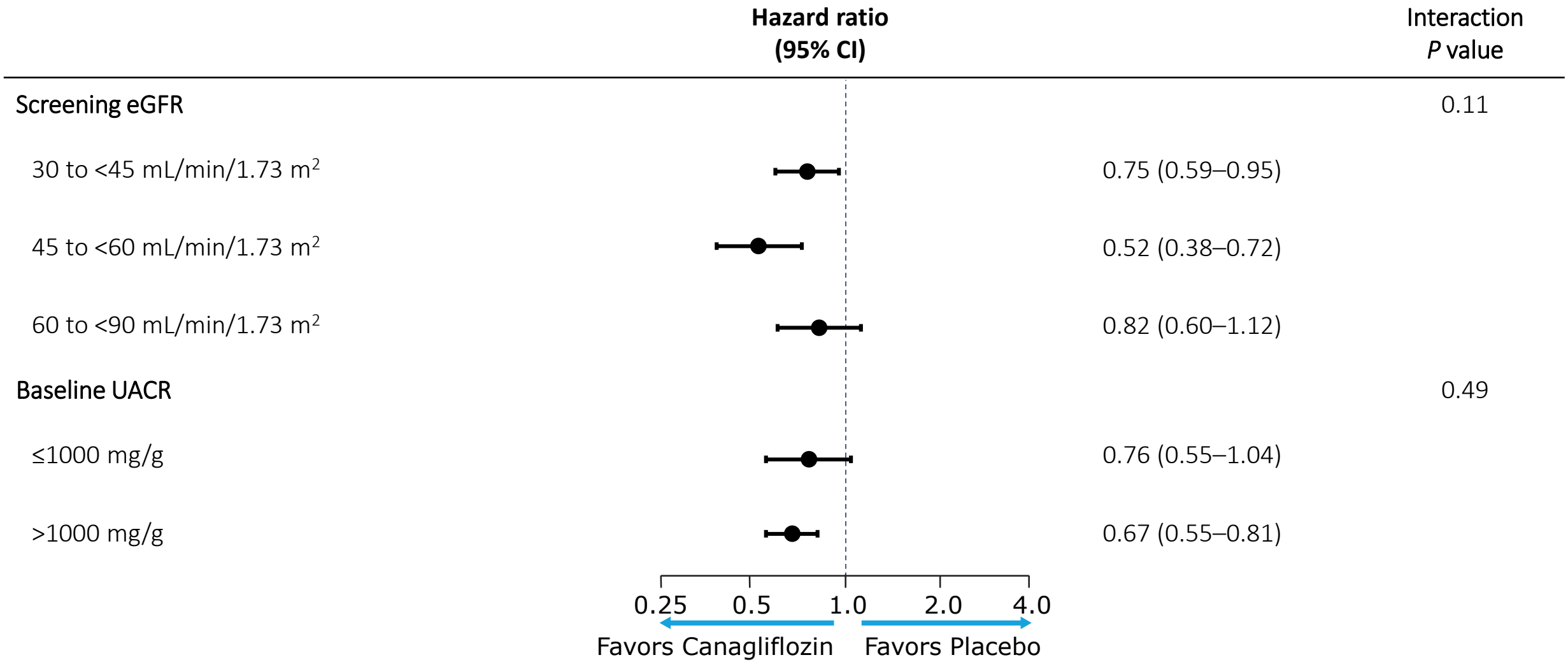


No. at risk								
Placebo	2199	2183	2147	2077	1776	1178	653	180
Canagliflozin	2202	2184	2148	2100	1811	1236	661	199

Summary Forest Plot



Primary Outcome by Screening eGFR and Albuminuria



SUMMARY

DPP4 Inhibitors

Trial	Result
TECOS (Sitagliptin)	**NEUTRAL**
SAVOR-TIMI 53 (Saxagliptin)	**NEUTRAL (↑ HF Risk)**
EXAMINE (Alogliptin)	**NEUTRAL**
CARMELINA (Linagliptin)	(Q1 2018)

GLP1 Agonists

Trial	Result
ELIXA (Lixisenatide)	**NEUTRAL**
LEADER (Liraglutide)	**POSITIVE**
SUSTAIN-6 (Semaglutide)	**POSITIVE**
EXSCEL (Exenatide)	**NEUTRAL (POS for ACM)**
REWIND (Dulaglutide)	(Q3 2018)
HARMONY (Albiglutide)	(Q2 2019)
PIONEER 6 (Semaglutide PO)	(Q3 2018)

SGLT2 Inhibitors

Trial	Result
EMPA-REG Outcome (Empagliflozin)	**POSITIVE**
CANVAS, CANVAS-R (Canagliflozin)	**POSITIVE**
DECLARE-TIMI 58 (Dapagliflozin)	(Q2 2019)
VERTIS CV (Ertugliflozin)	(Q4 2019)
SCORED (Sotagliflozin)	(Q1 2022)

Comparison of post-hoc analyses of SUSTAIN 6, LEADER and REWIND for prior and no prior MI/stroke subgroups

SUSTAIN 6

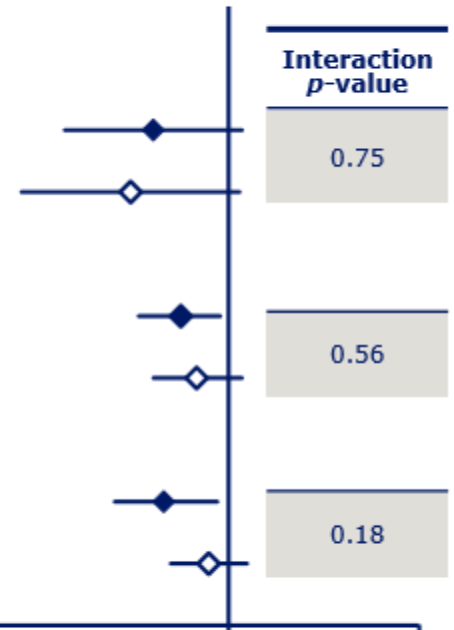
Outcome	Prior MI/stroke	No. events* Sema	Pbo	Hazard ratio (95% CI)	Interaction *p*-value
3-point MACE	With	66	88	0.76 (0.55 ; 1.05)	0.75
	Without	42	58	0.70 (0.47 ; 1.04)	

LEADER

Outcome	Prior MI/stroke	No. events* Lira	Pbo	Hazard ratio (95% CI)	Interaction *p*-value
3-point MACE	With	322	372	0.84 (0.72 ; 0.97)	0.56
	Without	286	322	0.89 (0.76 ; 1.05)	

REWIND

Outcome	Prior MI/stroke	No. events* Dula	Pbo	Hazard ratio (95% CI)	Interaction *p*-value
3-point MACE	With	196	236	0.79 (0.66 ; 0.96)	0.18
	Without	396	423	0.93 (0.81 ; 1.07)	



With prior MI/stroke
Lira N=1,865; Sema N=673; Dula N=1,028
Pbo N=1,827; Pbo N=694; Pbo N=1,007

Without prior MI/stroke
Lira N=2803; Sema N=975; Dula N=3,896
Pbo N=2845; Pbo N=955; Pbo N=3,920

*First events

Poulter N et al. Abstract 86477, presented at the European Society of Cardiology Congress, Barcelona, 28 August 2017
Leiter L et al. 2019. Cardiovascular Risk Reduction with only once weekly semaglutide in subjects with type 2 diabetes: a post hoc analysis of gender, age, and baseline CV risk profile in the SUSTAIN 6 trial. *Cardiovasc Diabeto* 18:73. https://doi.org/10.1186/s12933-019-0871-8;
Supplement appendix to: Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomized placebo-controlled trial. Lancet 2019; published online June 10.

CI: confidence interval; CV: cardiovascular; MI: myocardial infarction; PYO: patient-years of observation; Lira: Liraglutide; Sema: Semaglutide; Dula: dulaglutide Pbo: Placebo

GLP1 Agonists

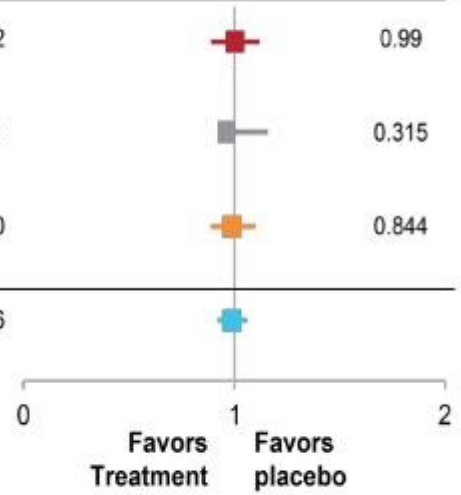
Generic	Trade Name	Trial
Lixisenatide	AdlyxinTM	ELIXA
Liraglutide	Victoza	LEADER
Semaglutide	Ozempic	SUSTAIN-6
Exenatide	Bydureon/Byetta	EXSCEL
Dulaglutide	Trulicity	REWIND
Lixisenatide	AdlyxinTM	ELIXA
Albiglutide	Tanzeum	HARMONY
Semaglutide PO		PIONEER 6

DPP4 Inhibitors

Generic	Trade Name	Trial
Sitagliptin	Januvia	TECOS
Saxagliptin	Onglyza	SAVOR-TIMI 53
Alogliptin	Nesina	EXAMINE
Linagliptin	Tradjenta	CARMELINA

DPP4 Inhibitor Trials: MACE

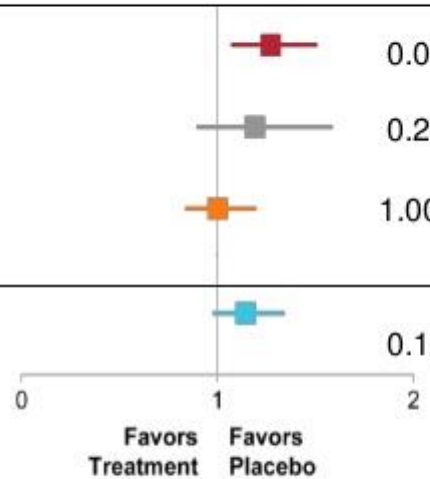
	Study Drug n/N (%)	Placebo n/N (%)	Hazard Ratio	95% CI	P Value
SAVOR-TIMI (saxagliptin vs. placebo)	613/8280 (7.4%)	609/8212 (7.4%)	1.00	0.89, 1.12	0.99
EXAMINE (alogliptin vs. placebo)	305/2701 (11.3%)	316/2679 (11.8%)	0.96	NA, 1.16	0.315
TECOS (sitagliptin vs. placebo)	745/7332 (10.2%)	746/7339 (10.2%)	0.99	0.89, 1.10	0.844
SAVOR + EXAMINE + TECOS	1663/18313 (9.1%)	1671/18230 (9.2%)	0.99	0.92, 1.06	



Scirica BM et al. N Engl J Med 2013; 369: 1317–1326
White WB et al. N Engl J Med 2013; 369: 1327–1335
Green JB et al. N Engl J Med 2015; 373: 232-42

DPP4 Inhibitor Trials: HF Hospitalization

Trial	HR (95% CI)	P-Value	Events (n)
SAVOR-TIMI 53	1.27 (1.07–1.51)	0.007	517
EXAMINE	1.19 (0.89–1.59)	0.235	195
TECOS	1.00 (0.84–1.20)	1.000	457
SAVOR-TIMI + EXAMINE + TECOS	1.14 (0.97–1.34)	0.102	1169



Test for heterogeneity for 3 trials: p=0.16, I^2=44.9

McGuire DK, et al. JAMA Cardiol 2016; 1: 126-135.

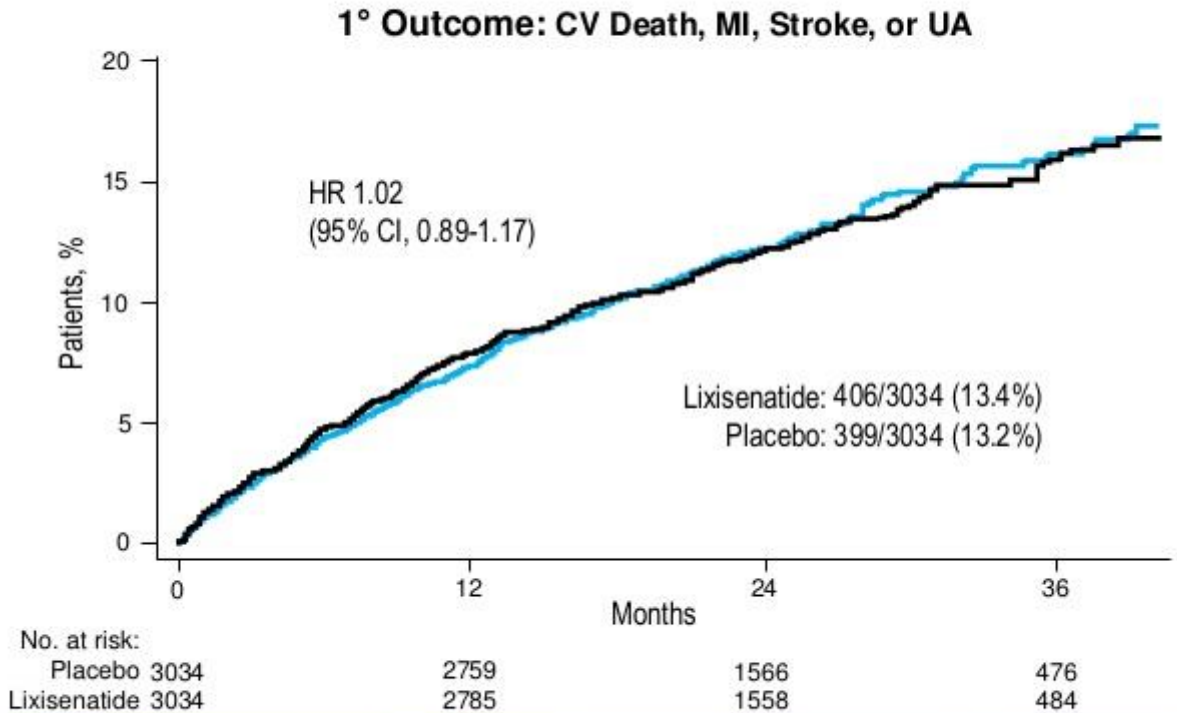
DPP4 Inhibitors

Generic	Trade Name	Trial	Result
Sitagliptin	Januvia	TECOS	**NEUTRAL**
Saxagliptin	Onglyza	SAVOR-TIMI 53	**NEUTRAL** **(↑ HF Risk)**
Alogliptin	Nesina	EXAMINE	**NEUTRAL**
Linagliptin	Tradjenta	CARMELINA	(Q1 2018)

GLP1 Agonists

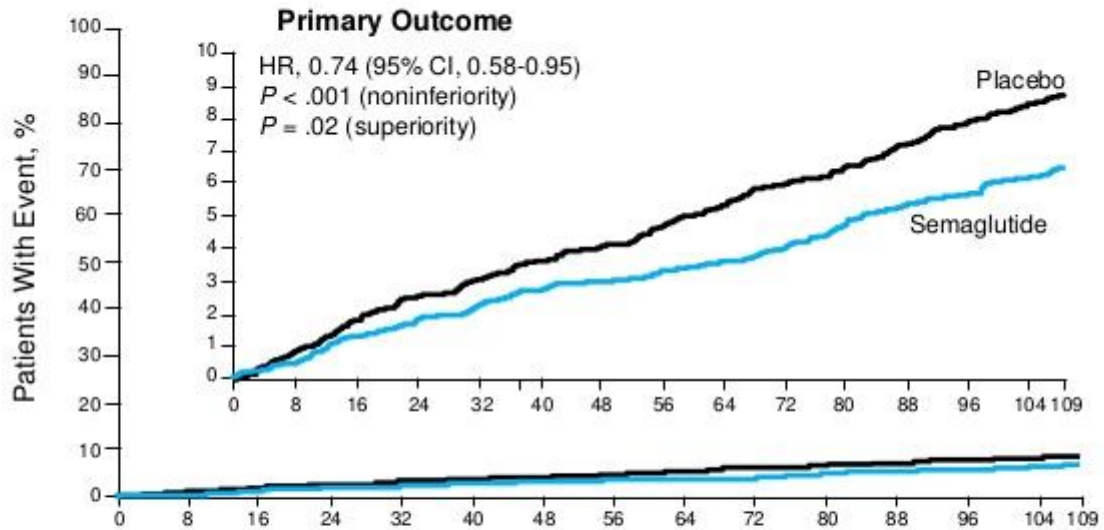
Generic	Trade Name	Trial
Lixisenatide	AdlyxinTM	ELIXA
Liraglutide	Victoza	LEADER
Semaglutide	Ozempic	SUSTAIN-6
Exenatide	Bydureon/Byetta	EXSCEL
Dulaglutide	Trulicity	REWIND
Lixisenatide	AdlyxinTM	ELIXA
Albiglutide	Tanzeum	HARMONY
Semaglutide PO		PIONEER 6

ELIXA: Lixisenatide vs. Placebo



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

SUSTAIN-6: Semaglutide vs. Placebo

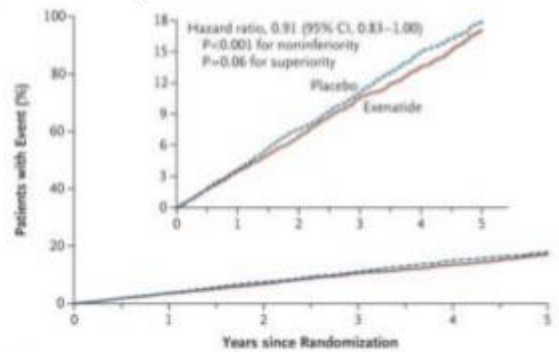


No. at Risk							
Placebo	1649	1616	1586	1567	1534	1508	1479
Semaglutide	1648	1619	1601	1584	1568	1543	1524

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

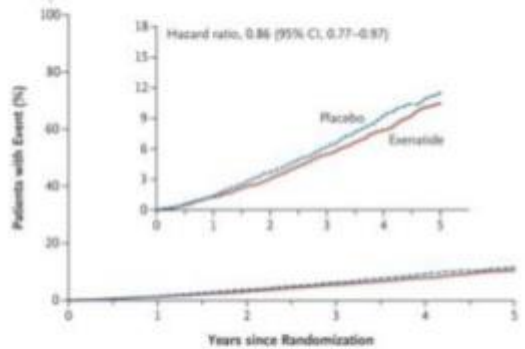
EXSCEL: Exenatide ER vs. Placebo

Primary Outcome



No. at Risk											
Placebo	7396	7120	6897	6565	5908	4468	3565	2961	2209	1366	687
Exenatide	7356	7101	6893	6580	5912	4475	3595	3053	2281	1417	727

All-Cause Death



No. at Risk											
Placebo	7396	7344	7178	7058	6470	5019	4091	3478	2666	1695	892
Exenatide	7356	7304	7234	7028	6433	4991	4095	3518	2698	1726	907

Holman R, et al. N Engl J Med 2017 377: 1228-1239.

GLP1 Agonists

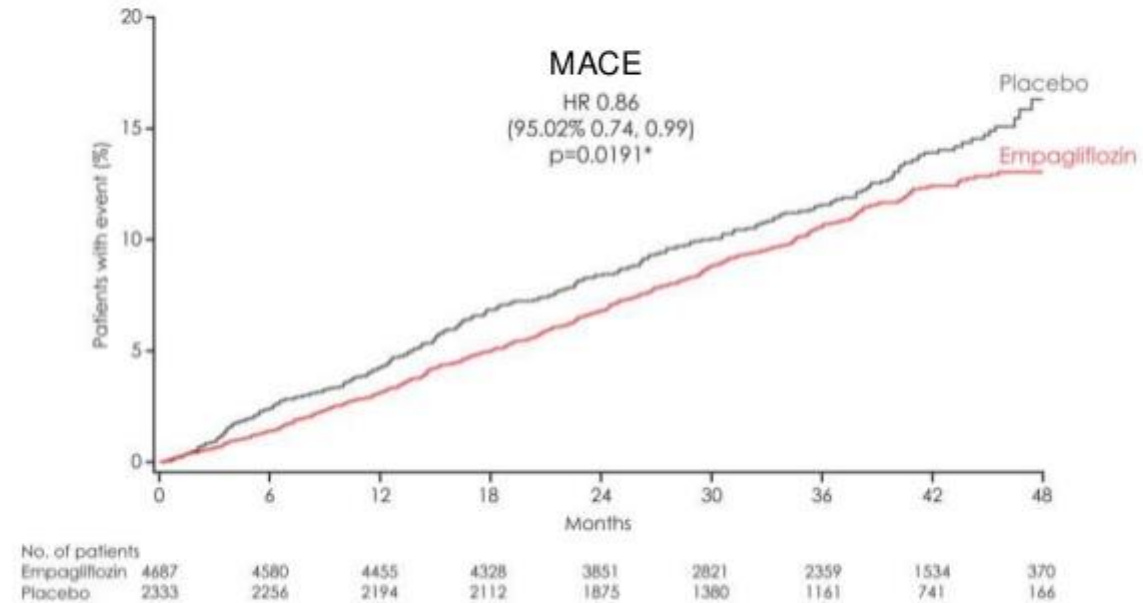
Generic	Trade Name	Trial	Result
Lixisenatide	AdlyxinTM	ELIXA	**NEUTRAL**
Liraglutide	Victoza	LEADER	**POSITIVE**
Semaglutide	Ozempic	SUSTAIN-6	**POSITIVE**
Exenatide	Bydureon/Byetta	EXSCEL	**NEUTRAL (POS for ACM)**
Dulaglutide	Trulicity	REWIND	(Q3 2018)
Albiglutide	Tanzeum	HARMONY	(Q2 2019)
Semaglutide PO		PIONEER 6	(Q3 2018)

SGLT2 Inhibitors

Generic	Trade Name	Trial
Empagliflozin	Jardiance	EMPA-REG Outcome
Canagliflozin	Invokana	CANVAS, CANVAS-R
Dapagliflozin	Forxiga	DECLARE-TIMI 58
Ertugliflozin	Steglatro	VERTIS CV
Sotagliflozin*		SCORED

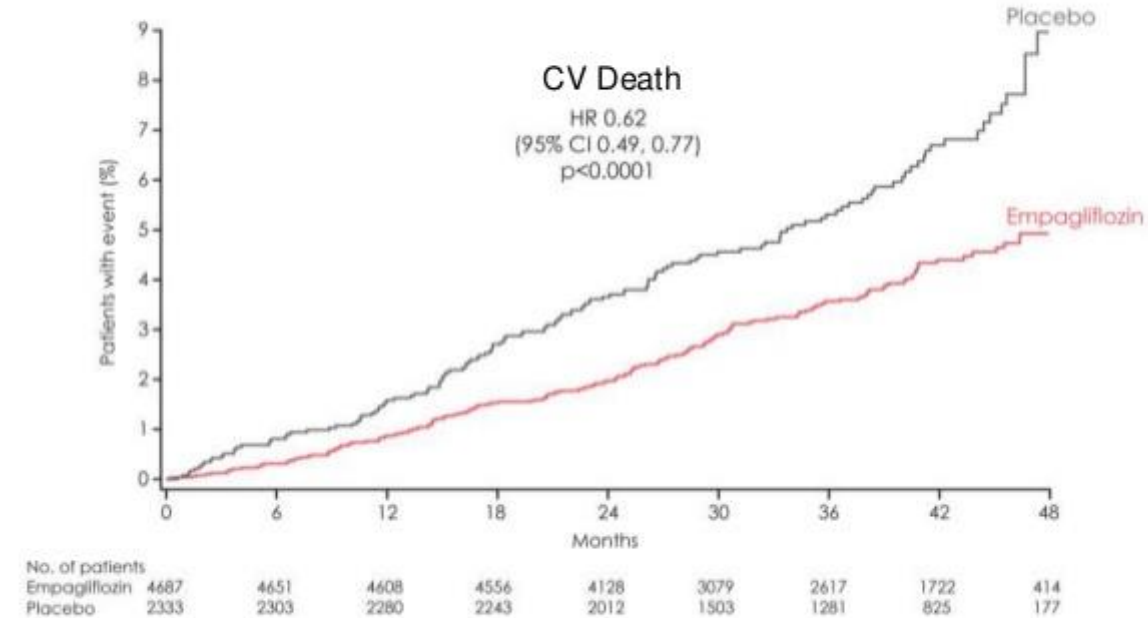
*Dual SGLT1 and SGLT2 inhibitor.

EMPA-REG Outcomes: Empagliflozin vs. Placebo



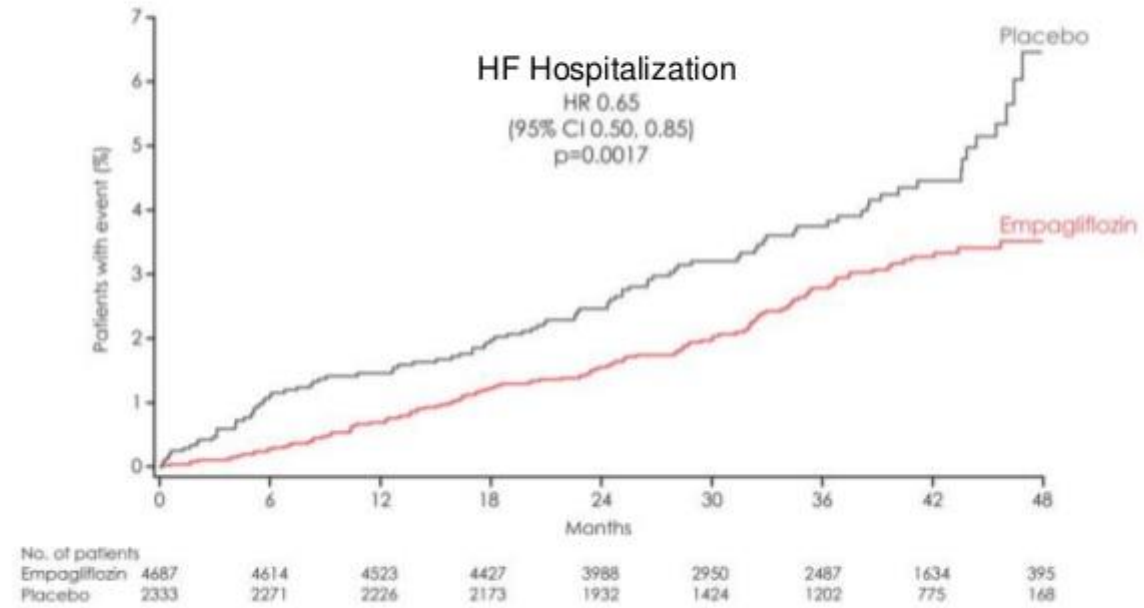
Zinman B et al. N Engl J Med 2015; 373: 2117-28

EMPA-REG Outcomes: Empagliflozin vs. Placebo



Zinman B et al. N Engl J Med 2015; 373: 2117-28

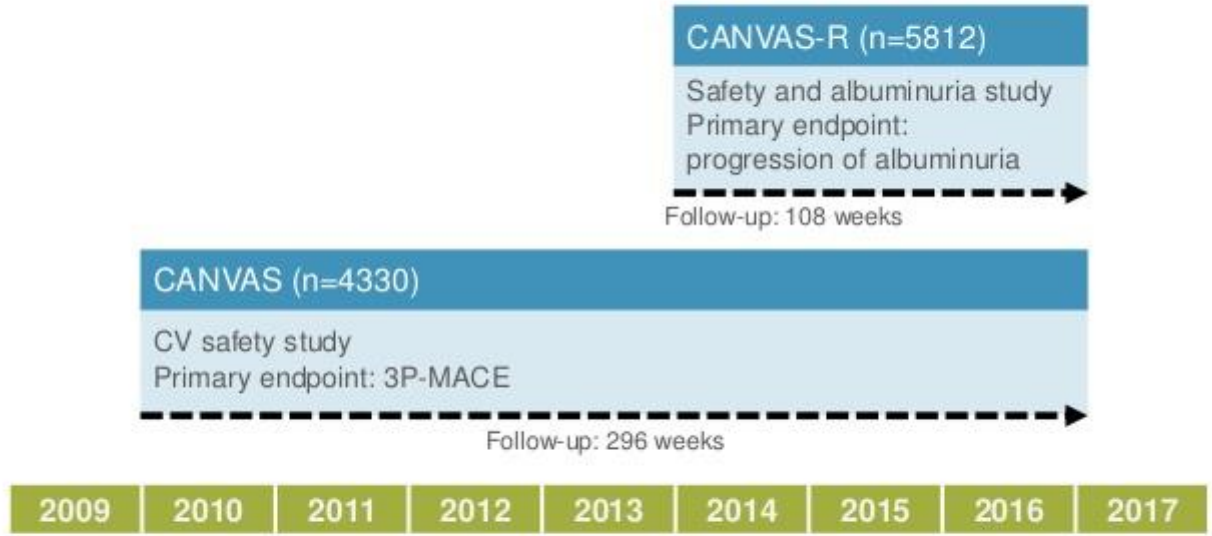
EMPA-REG Outcomes: Empagliflozin vs. Placebo



Zinman B et al. N Engl J Med 2015; 373: 2117-28

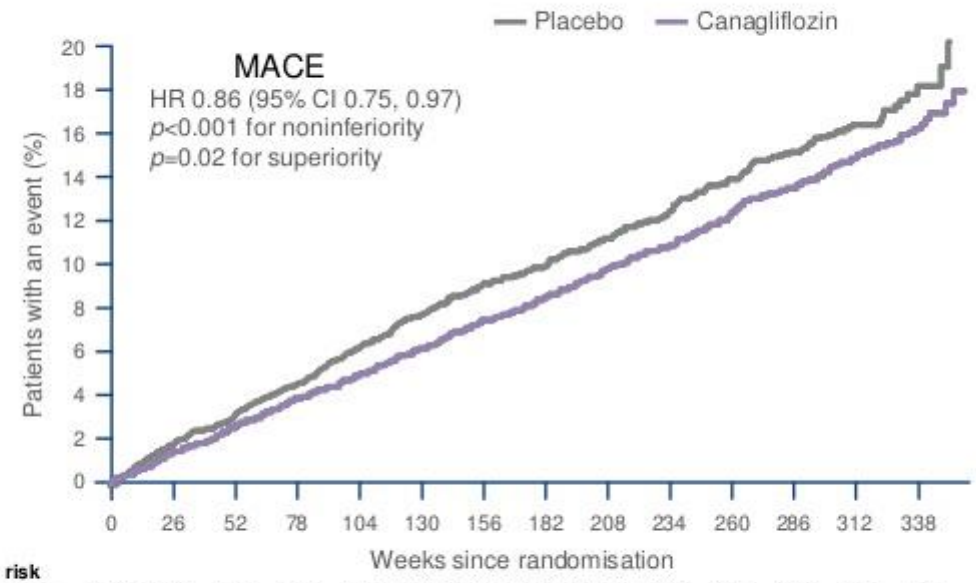
CANVAS Program: Canagliflozin vs. Placebo

The CANVAS Program consisted of two randomised, double-blind, placebo-controlled trials.



Neal B et al. N Engl J Med 2017; 377: 644-657

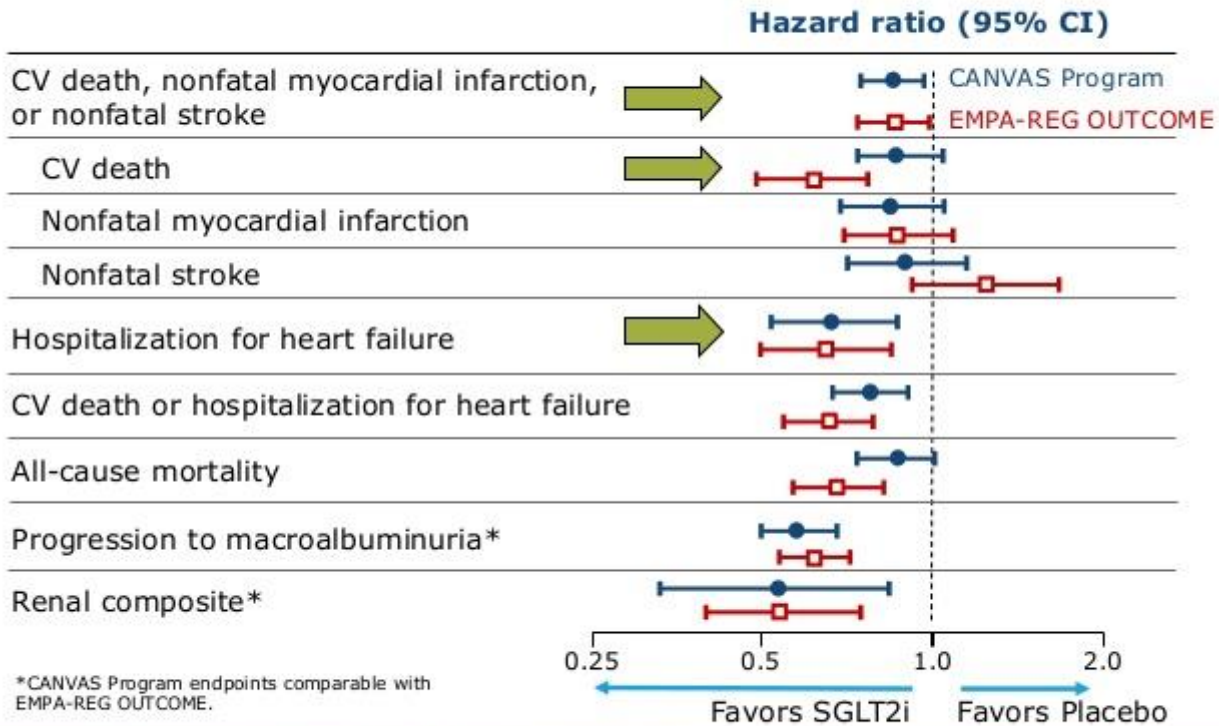
CANVAS Program: Canagliflozin vs. Placebo



No. at risk														
Canagliflozin	5795	5672	5566	5447	4343	2984	2555	2513	2460	2419	2363	2311	1661	448
Placebo	4347	4239	4153	4061	2942	1626	1240	1217	1187	1156	1120	1095	789	216

Neal B et al. N Engl J Med 2017; 377: 644-657

Key Outcomes: EMPA-REG vs CANVAS



Zinman Bet al. N Engl J Med. 2015 ;373(22):2117-2128.
Neal B et al. N Engl J Med 2017; 377: 644-657

SGLT2 Inhibitors

Generic	Trade Name	Trial	Result
Empagliflozin	Jardiance	EMPA-REG Outcome	**POSITIVE**
Canagliflozin	Invokana	CANVAS, CANVAS-R	**POSITIVE**
Dapagliflozin	Forxiga	DECLARE-TIMI 58	**(Q2 2019)**
Ertugliflozin	Steglatro	VERTIS CV	**(Q4 2019)**
Sotagliflozin*		SCORED	**(Q1 2022)**

*Dual SGLT1 and SGLT2 inhibitor.

SUMMARY

DPP4 Inhibitors

Trial	Result
TECOS (Sitagliptin)	**NEUTRAL**
SAVOR-TIMI 53 (Saxagliptin)	**NEUTRAL (↑ HF Risk)**
EXAMINE (Alogliptin)	**NEUTRAL**
CARMELINA (Linagliptin)	(Q1 2018)

GLP1 Agonists

Trial	Result
ELIXA (Lixisenatide)	**NEUTRAL**
LEADER (Liraglutide)	**POSITIVE**
SUSTAIN-6 (Semaglutide)	**POSITIVE**
EXSCEL (Exenatide)	**NEUTRAL (POS for ACM)**
REWIND (Dulaglutide)	(Q3 2018)
HARMONY (Albiglutide)	(Q2 2019)
PIONEER 6 (Semaglutide PO)	(Q3 2018)

SGLT2 Inhibitors

Trial	Result
EMPA-REG Outcome (Empagliflozin)	**POSITIVE**
CANVAS, CANVAS-R (Canagliflozin)	**POSITIVE**
DECLARE-TIMI 58 (Dapagliflozin)	(Q2 2019)
VERTIS CV (Ertugliflozin)	(Q4 2019)
SCORED (Sotagliflozin)	(Q1 2022)

Rewind Study

- CVOT trial to assess Dulaglutide
- 9901 patients enrolled
- 2/3 of patients had no history of CV disease
- Primary endpoint CV death, nonfatal stroke, nonfatal MI
- 5 year duration
- Top line data released 11-4-18 and superiority met

Summary

Primary	Hazard ratio (95% CI)	*P* value	
1. ESKD, doubling of serum creatinine, or renal or CV death	0.70 (0.59–0.82)	0.00001	✓
Secondary			
2. CV death or hospitalization for heart failure	0.69 (0.57–0.83)	<0.001	✓
3. CV death, MI, or stroke	0.80 (0.67–0.95)	0.01	✓
4. Hospitalization for heart failure	0.61 (0.47–0.80)	<0.001	✓
5. ESKD, doubling of serum creatinine, or renal death	0.66 (0.53–0.81)	<0.001	✓
6. CV death	0.78 (0.61–1.00)	0.0502	Not significant
7. All-cause mortality	0.83 (0.68–1.02)	–	Not formally tested
8. CV death, MI, stroke, hospitalization for heart failure, or hospitalization for unstable angina	0.74 (0.63–0.86)	–	Not formally tested

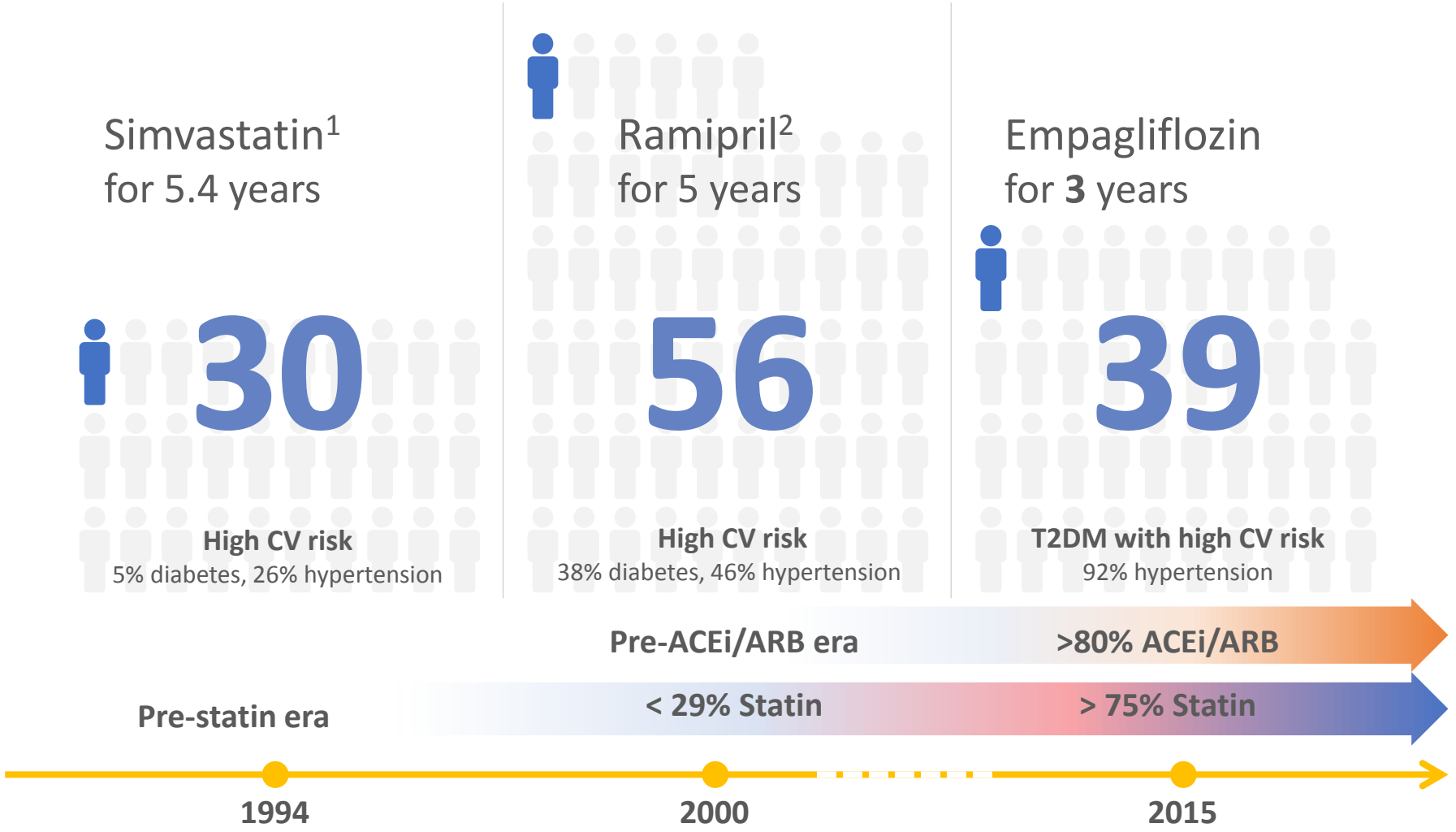
Baseline characteristics: type 2 diabetes

	Placebo (n=2333)	Empagliflozin 10 mg (n=2345)	Empagliflozin 25 mg (n=2342)
HbA1c, %	8.08 (0.84)	8.07 (0.86)	8.06 (0.84)
Time since diagnosis of type 2 diabetes, years			
≤5	423 (18.1)	406 (17.3)	434 (18.6)
>5 to 10	571 (24.5)	585 (24.9)	590 (25.2)
>10	1339 (57.4)	1354 (57.7)	1318 (56.3)
Glucose-lowering medication*			
Metformin	1734 (74.3)	1729 (73.7)	1730 (73.9)
Sulfonylurea	992 (42.5)	985 (42.0)	1029 (43.9)
Thiazolidinedione	101 (4.3)	96 (4.1)	102 (4.4)
Insulin	1135 (48.6)	1132 (48.3)	1120 (47.8)
Mean daily dose, U**	65 (50.6)	65 (47.9)	66 (48.9)

Data are n (%) or mean (SD) in patients treated with ≥1 dose of study drug

*Medication taken alone or in combination
**Placebo, n=1135; empagliflozin 10 mg, n=1132; empagliflozin 25 mg, n=1120

Number needed to treat (NNT) to prevent one patient death across landmark trials in patients with high CV risk



1. 4S investigator. Lancet 1994; 344: 1383-89, http://www.trialresultscenter.org/study2590-4S.htm; 2. HOPE investigator N Engl J Med 2000;342:145-53, EBM2000;5:47 http://www.trialresultscenter.org/study2606-HOPE.htm

SUMMARY

DPP4 Inhibitors

Trial	Result
TECOS (Sitagliptin)	NEUTRAL
SAVOR-TIMI 53 (Saxagliptin)	NEUTRAL (↑ HF Risk)
EXAMINE (Alogliptin)	NEUTRAL
CARMELINA (Linagliptin)	NEUTRAL

GLP1 Agonists

Trial	Result
ELIXA (Lixisenatide)	NEUTRAL
LEADER (Liraglutide)	POSITIVE
SUSTAIN-6 (Semaglutide)	POSITIVE
EXSCEL (Exenatide)	NEUTRAL (POS for ACM)
REWIND (Dulaglutide)	POSITIVE
HARMONY (Albiglutide)	POSITIVE
PIONEER 6 (Semaglutide PO)	NEUTRAL

SGLT2 Inhibitors

Trial	Result
EMPA-REG Outcome (Empagliflozin)	POSITIVE
CANVAS, CANVAS-R (Canagliflozin)	POSITIVE
DECLARE-TIMI 58 (Dapagliflozin)	+/-POSITIVE
VERTIS CV (Ertugliflozin)	(Q4 2019)
SCORED (Sotagliflozin)	(Q1 2022)

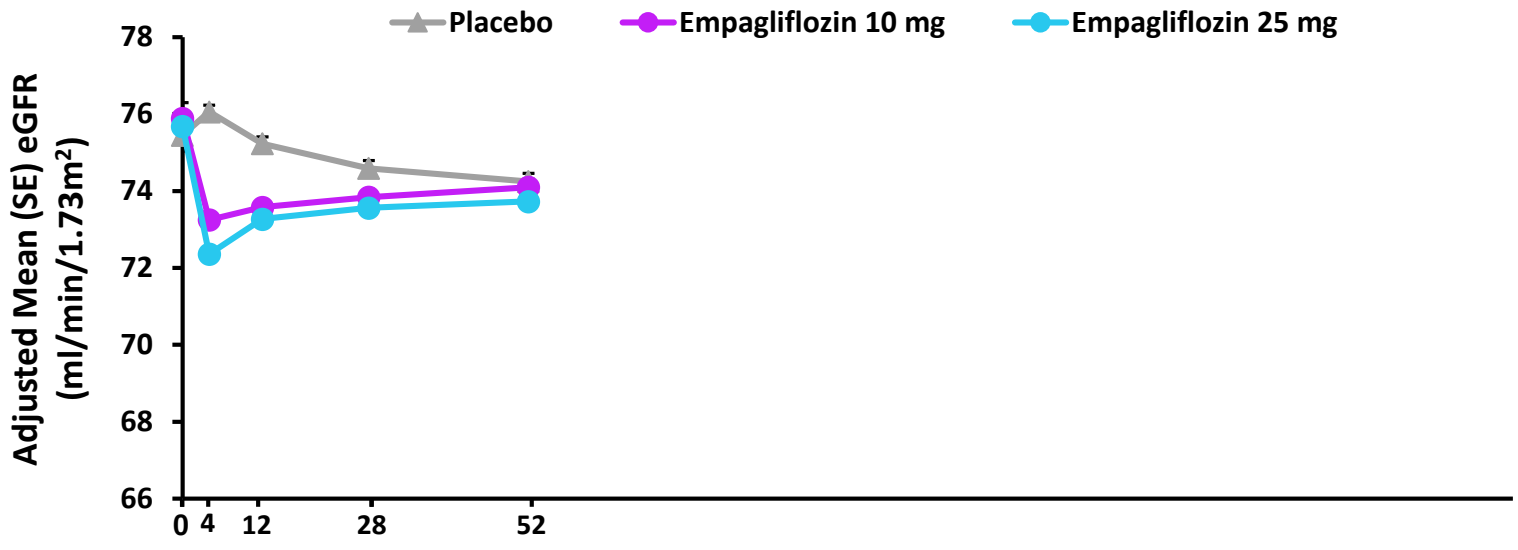
Ongoing CV Clinical Trials with Empagliflozin

Emperor Trials

-HFrEF

-HFpEF

Renal function: eGFR (CKD-EPI formula) over time



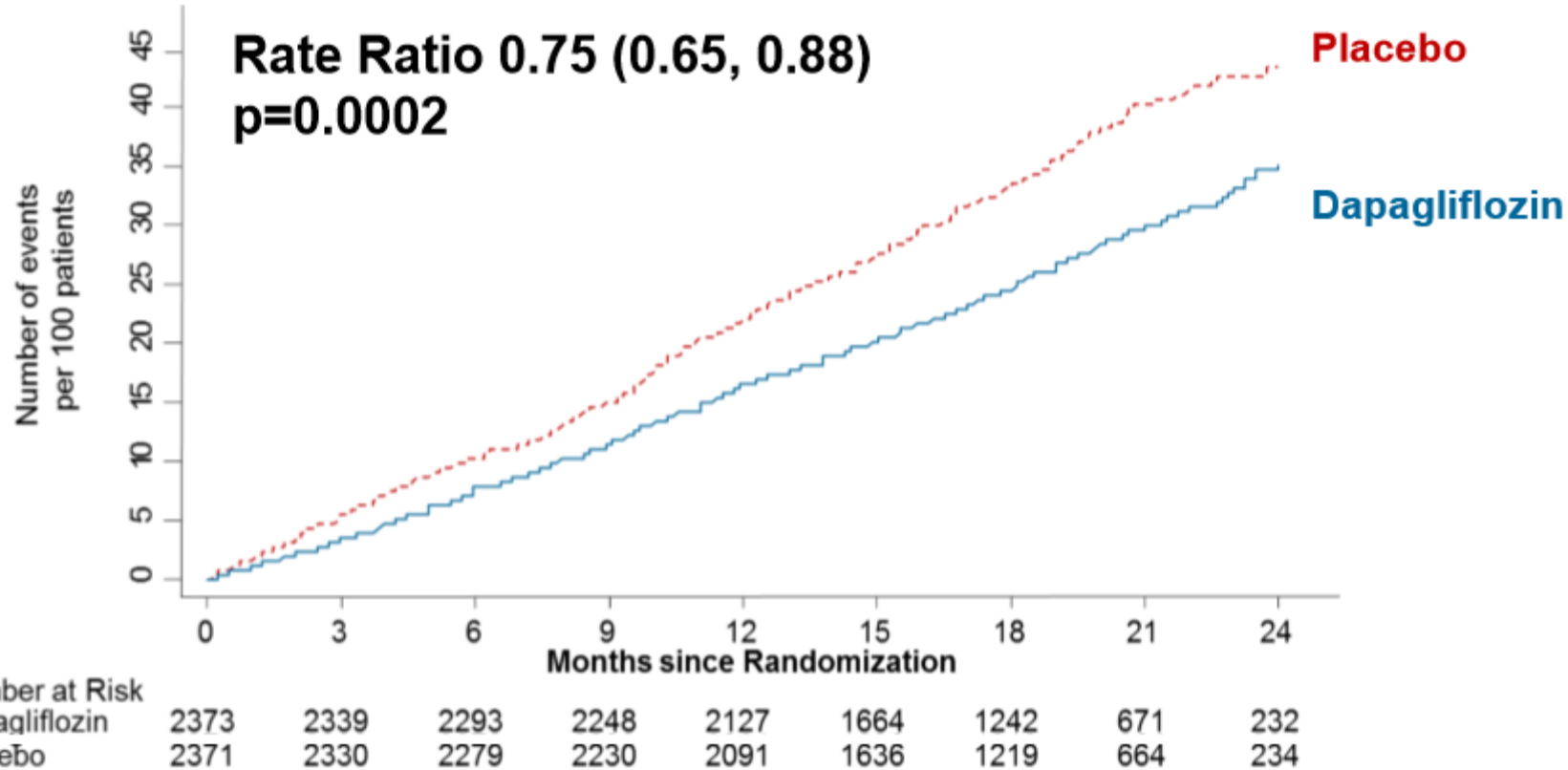
No. of Patients					
Placebo	2323	2295	2267	2205	2121
Empagliflozin 10 mg	2322	2290	2264	2235	2162
Empagliflozin 25 mg	2322	2288	2269	2216	2156

eGFR calculated with CKD-EPI formula. MMRM analysis following the intention-to-treat principle.
CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MMRM, mixed-model repeated measure; SE, standard error.

Wanner et al. N Engl J Med. 2016;375(4):323-34.

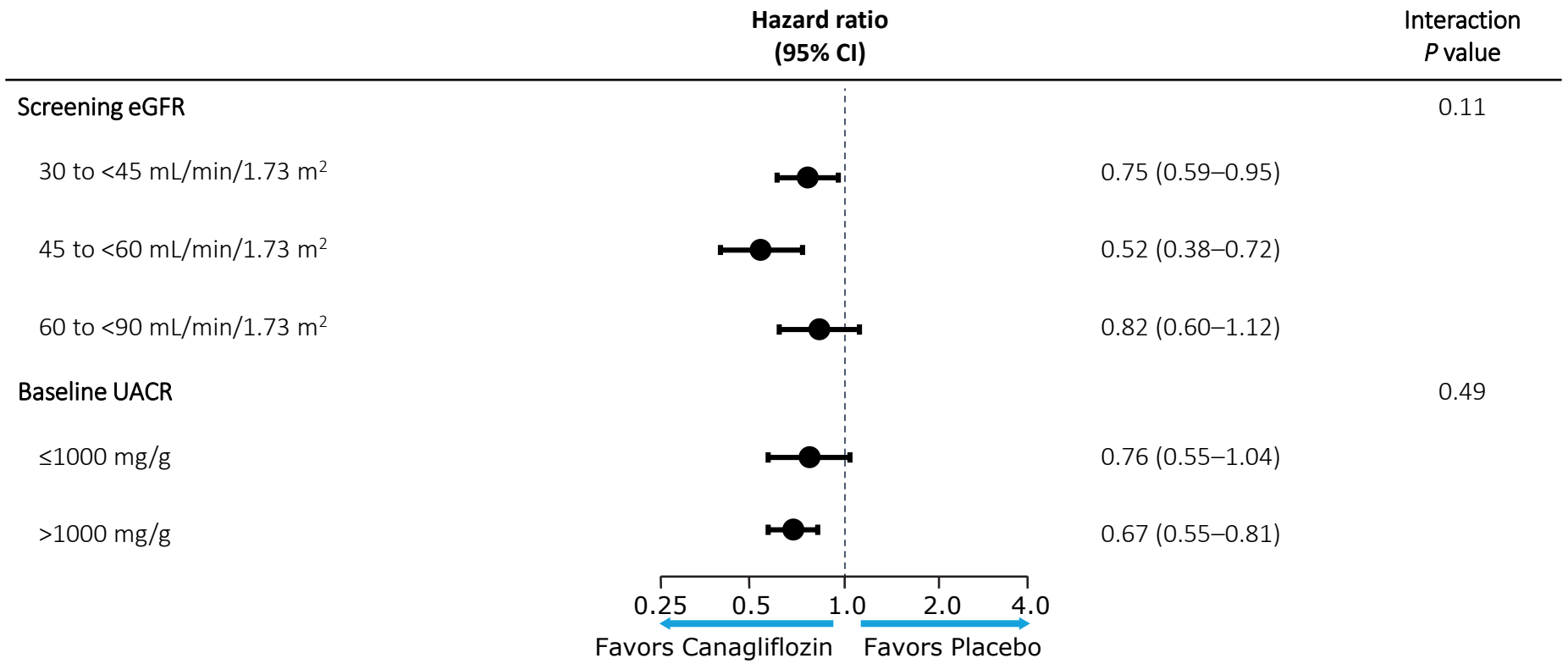
Total HF hospitalizations and CV death

Including first and repeat hospitalizations

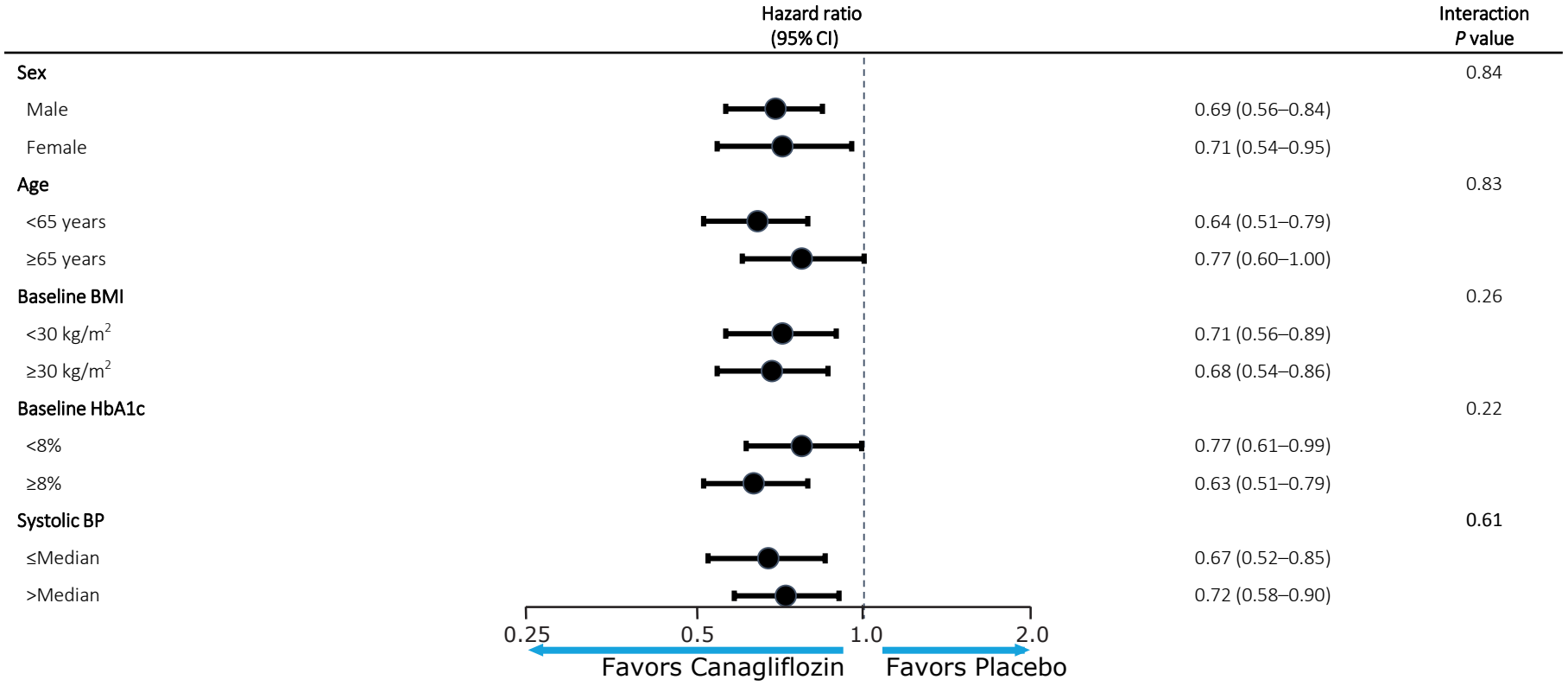


Number at Risk									
Dapagliflozin	2373	2339	2293	2248	2127	1664	1242	671	232
Placebo	2371	2330	2279	2230	2091	1636	1219	664	234

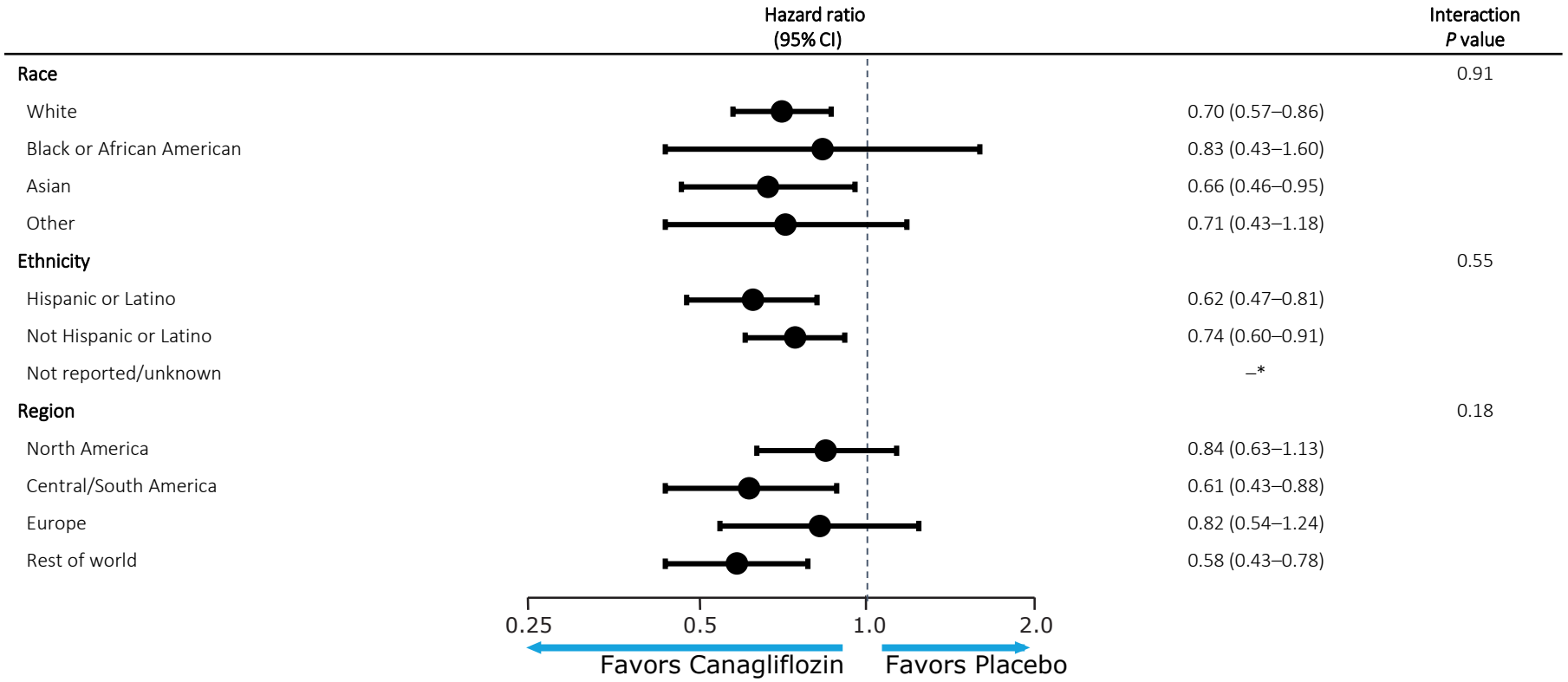
Primary Outcome by Screening eGFR and Albuminuria



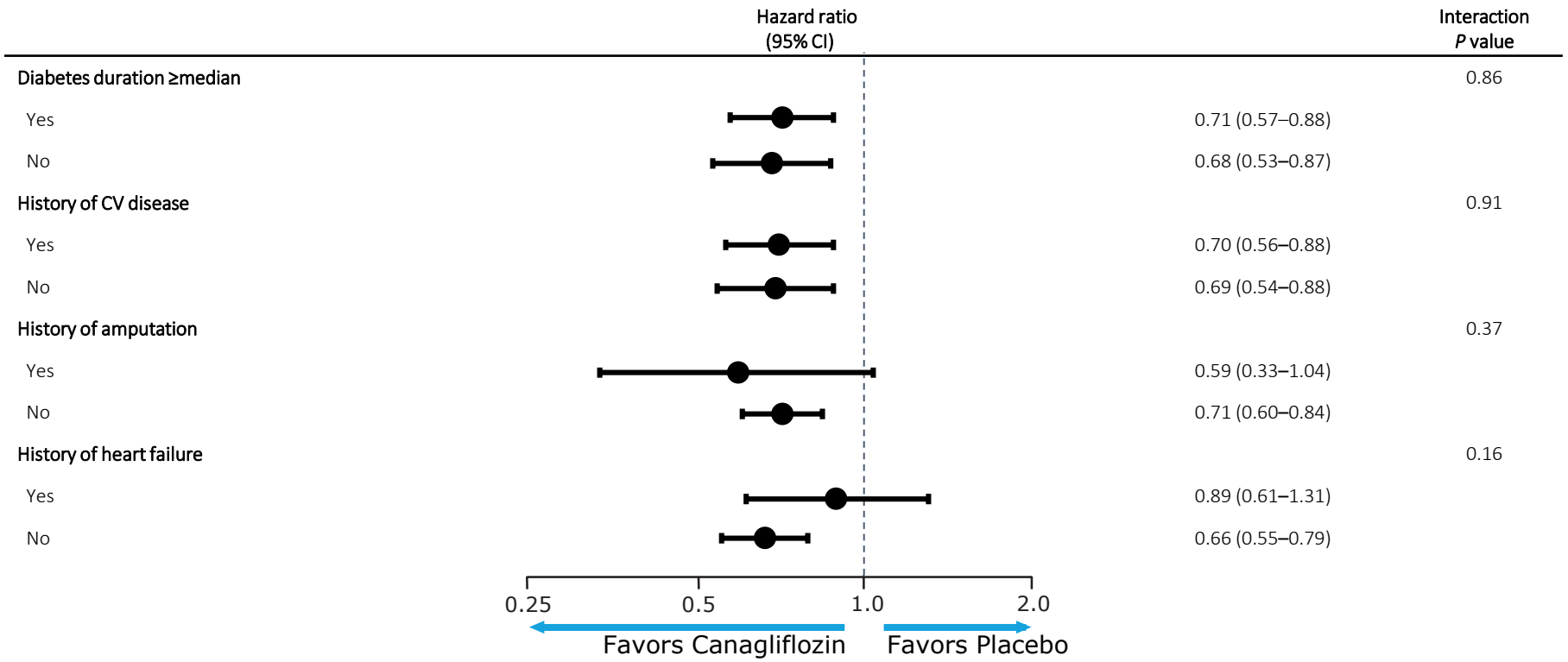
Primary Outcome: Demographic and Risk Factor Subgroups



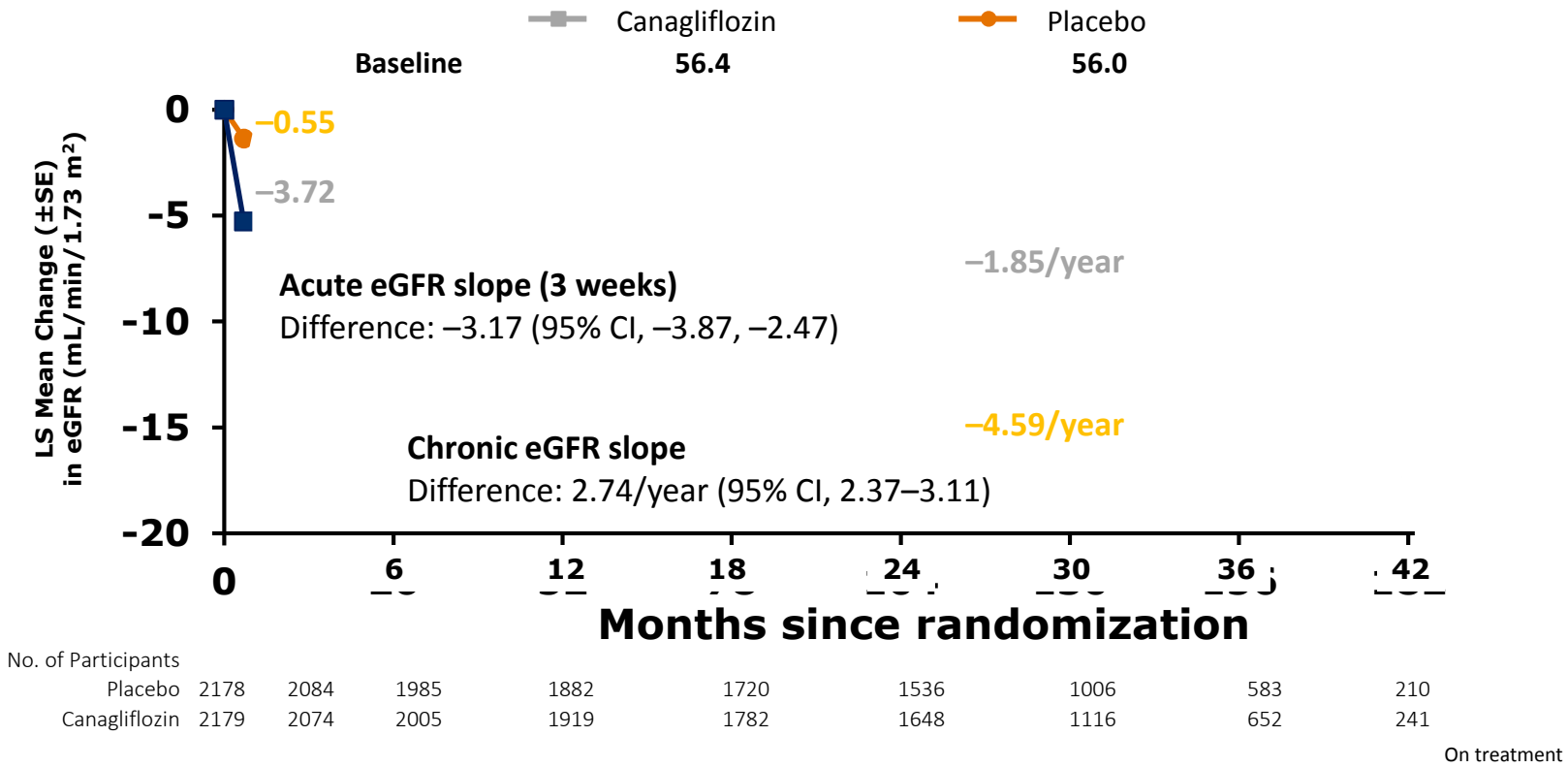
Primary Outcome: Demographic Subgroups



Primary Outcome: Disease History Subgroups



Effects on eGFR

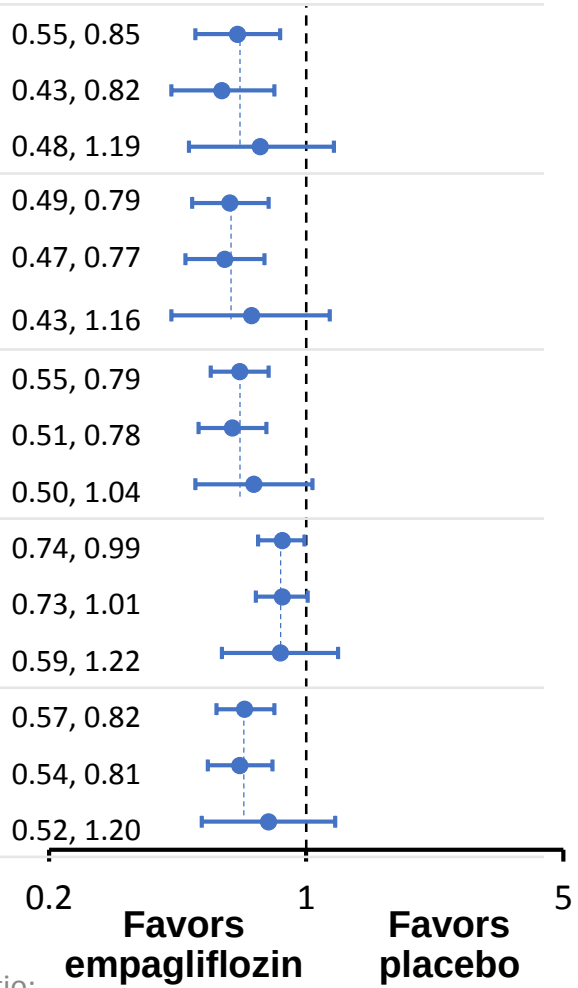


No. of Participants									
Placebo	2178	2084	1985	1882	1720	1536	1006	583	210
Canagliflozin	2179	2074	2005	1919	1782	1648	1116	652	241

On treatment

CV outcomes in patients with or without history of cardiac failure at baseline

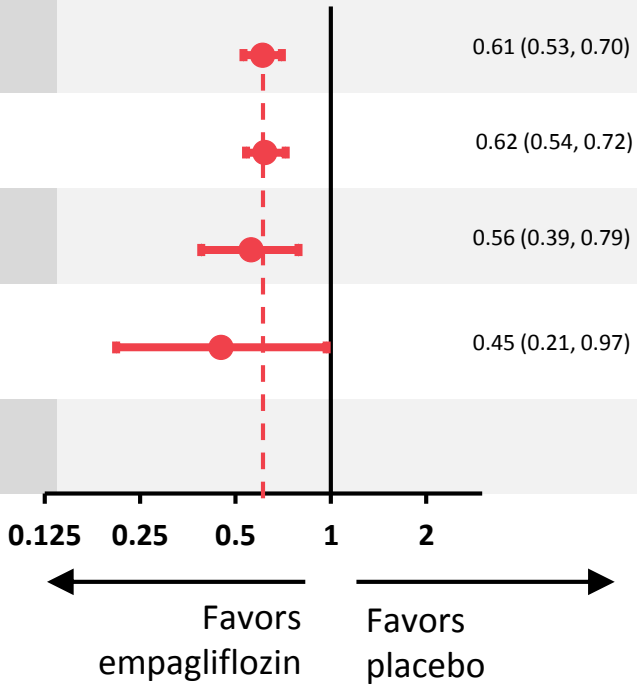
		Empagliflozin n/N	Placebo n/N	HR	95% CI
HHF	**Overall**	126/4687	95/2333	0.65	0.55, 0.85
	No cardiac failure at BL	78/4225	65/2089	0.59	0.43, 0.82
	Cardiac failure at BL	48/462	30/244	0.75	0.48, 1.19
CV death	**Overall**	172/4687	137/2333	0.62	0.49, 0.79
	No cardiac failure at BL	134/4225	110/2089	0.60	0.47, 0.77
	Cardiac failure at BL	38/462	27/244	0.71	0.43, 1.16
HHF+ CV death	**Overall**	265/4687	198/2333	0.66	0.55, 0.79
	No cardiac failure at BL	190/4225	149/2089	0.63	0.51, 0.78
	Cardiac failure at BL	75/462	49/244	0.72	0.50, 1.04
3P MACE	**Overall**	490/4687	282/2333	0.86	0.74, 0.99
	No cardiac failure at BL	412/4225	237/2089	0.86	0.73, 1.01
	Cardiac failure at BL	78/462	45/244	0.85	0.59, 1.22
All-cause death	**Overall**	269/4687	194/2333	0.68	0.57, 0.82
	No cardiac failure at BL	213/4225	159/2089	0.66	0.54, 0.81
	Cardiac failure at BL	56/462	35/244	0.79	0.52, 1.20



CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiovascular event

Pre-specified endpoint: New or worsening nephropathy

	Empagliflozin		Placebo		HR (95% CI)	*p*-value
	Patients with Events	Rate/ 100 PY	Patients with Events	Rate/ 100 PY		
New onset or worsening of nephropathy	525/4124 (12.7%)	4.78	388/2061 (18.8%)	7.6	0.61 (0.53, 0.70)	<0.0001
New onset macroalbuminuria*	459/4091 (11.2%)	4.18	330/2033 (16.2%)	6.49	0.62 (0.54, 0.72)	<0.0001
Doubling of serum-creatinine†	70/4645 (1.5%)	0.55	60/2323 (2.6%)	0.97	0.56 (0.39, 0.79)	0.0009
Initiation of renal replacement therapy	13/4687 (0.3%)	0.10	14/2333 (0.6%)	0.21	0.45 (0.21, 0.97)	0.0409
Death due to renal disease‡	3/4687 (0.1%)	-	0/2333 (0.0%)	-		–



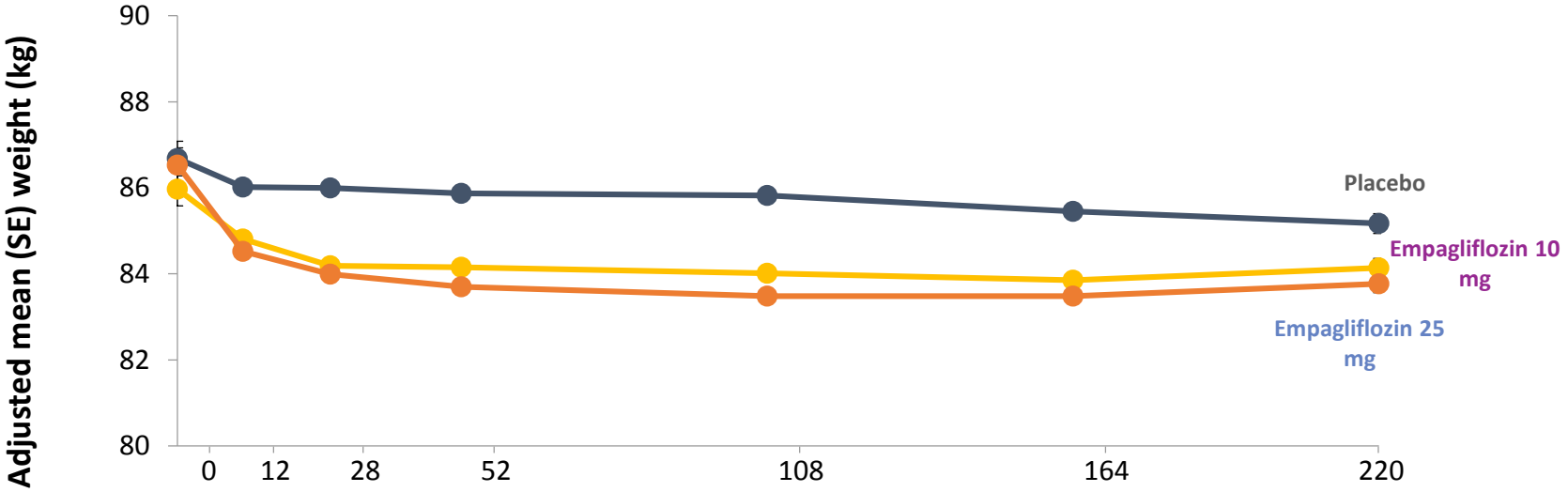
Cox regression analysis in the treated set. Nominal p values reported.
PY, patient years; CI, confidence interval; HR, hazard ratio.
*Macroalbuminuria defined as UACR >300 mg/g;
†Accompanied by estimated glomerular filtration rate (MDRD) ≤45 mL/min/1.73m^2;
‡HR and 95% CI were not analysed as the total number of events was <7.

FDA Guidance on CVOTs

Guidance for Industry Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

December 2008

Adjusted mean weight

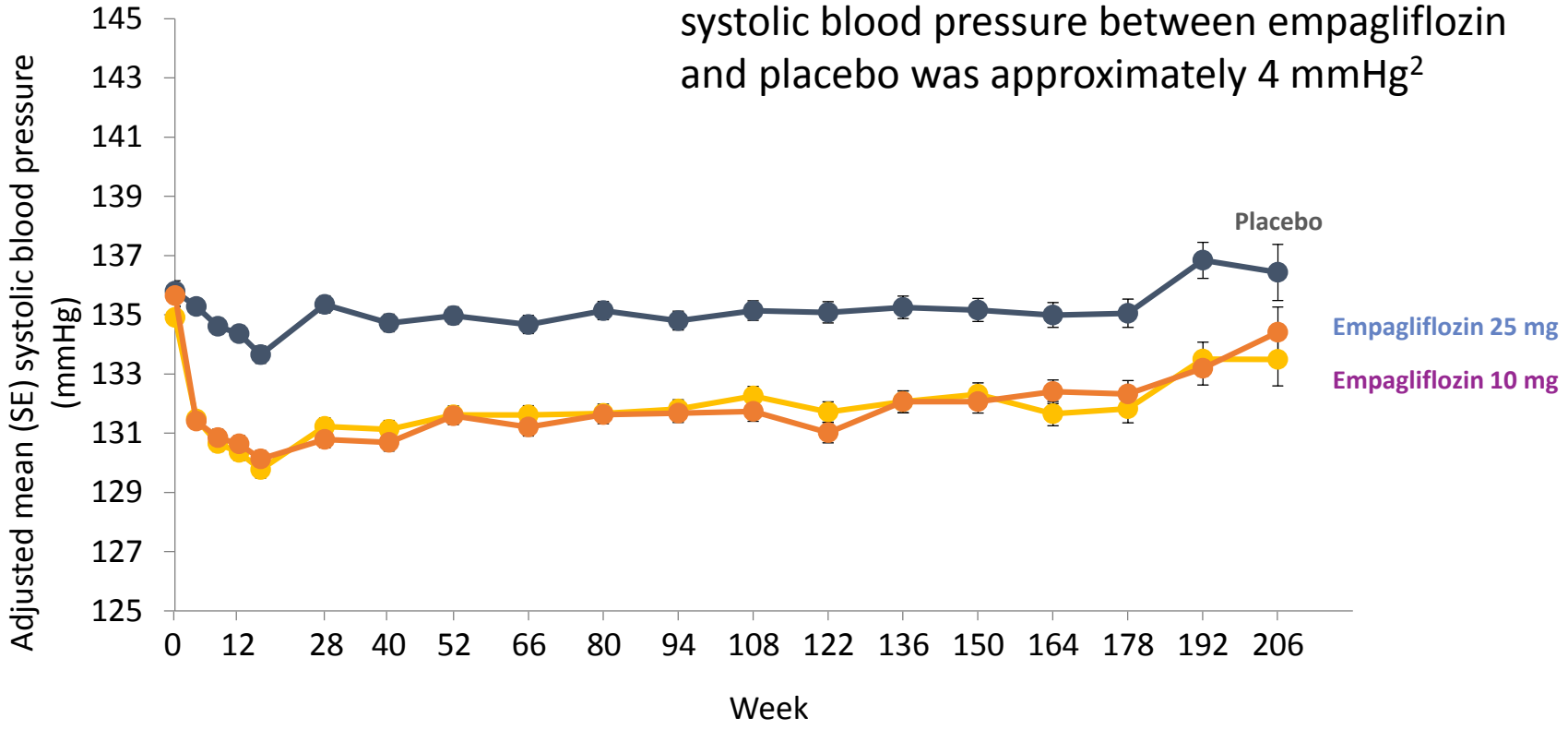


Placebo	2285	1915	2215	2138	1598	1239	425
Empagliflozin 10 mg	2290	1893	2238	2174	1673	1298	483
Empagliflozin 25 mg	2283	1891	2226	2178	1678	1335	489

All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent-to-treat).
X-axis: time points with reasonable amount of data available for prescheduled measurements.
Zinman et al. N Engl J Med. 2015;373(22):2117-28.

Changes in adjusted mean systolic blood pressure

At study end, the observed difference in mean systolic blood pressure between empagliflozin and placebo was approximately 4 mmHg[2]

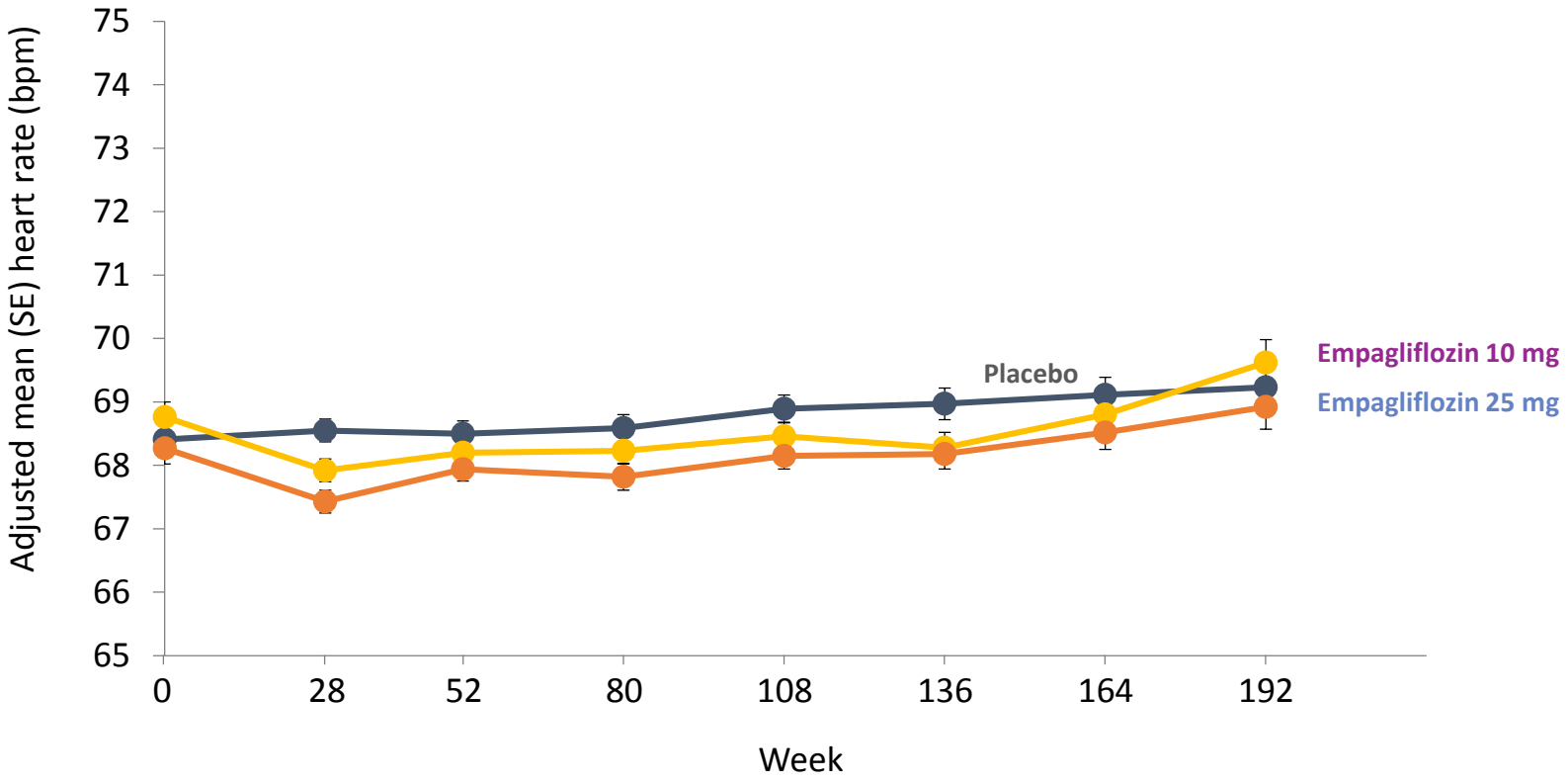


Placebo	2322	2235	2203	2161	2133	2073	2024	1974	1771	1492	1274	1126	981	735	450	171
Empagliflozin 10 mg	2322	2250	2235	2193	2174	2125	2095	2072	1853	1556	1327	1189	1034	790	518	199
Empagliflozin 25 mg	2323	2247	2221	2197	2169	2129	2102	2066	1878	1571	1351	1212	1070	842	528	216

MMRM in the treated set (OC-AD). SBP, systolic blood pressure.

1. Zinman *et al N Engl J Med* 2015; doi: 10.1056/NEJMoa1504720; 2. Data on File. **For Internal Use Only**.

Changes in heart rate

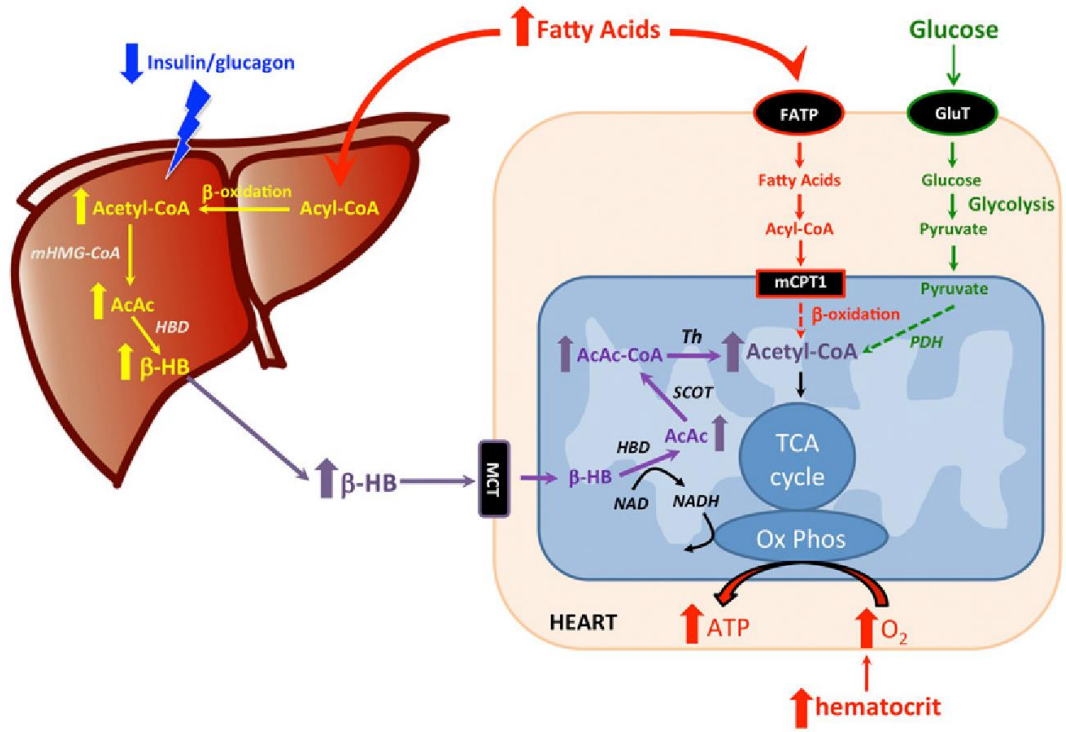


Placebo	2174	2127	2032	1928	1796	1300	1002	552
Empagliflozin 10 mg	2205	2137	2064	2006	1877	1366	1045	597
Empagliflozin 25 mg	2192	2127	2066	2006	1907	1383	1086	633

MMRM in the treated set (OC-AD).
Zinman *et al N Engl J Med* 2015; doi: 10.1056/NEJMoa1504720

Potential MOA CV effect: Shift from glucose to lipid metabolism

- Empagliflozin increases β-HB production in the liver
- Increased β-HB and FFA uptake into the heart
- Meanwhile, empagliflozin increases hematocrit increasing oxygen delivery to the heart



β-HB, beta-hydroxybutyrate; FFA, free fatty acids.

Ferrannini et al. Diabetes Care. 2016;39(7):1108-14.