הטיפול בסכרת בחולה הקרדיו – וסקולרי :

תפקיד הקרדיולוג

פרופ׳ דורון זגר

מנהל המערך הקרדיולוגי

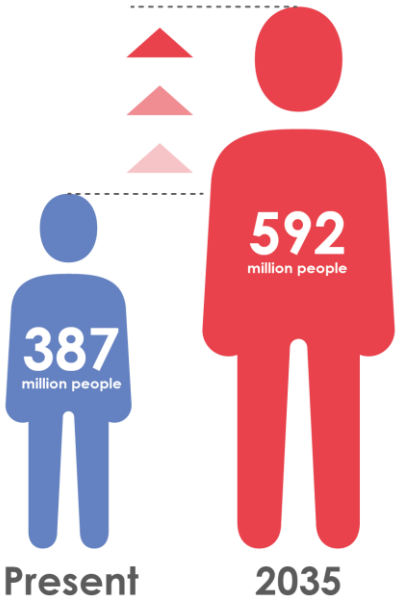
המרכז הרפואי האוניברסיטאי ״סורוקה״

תיאור מקרה

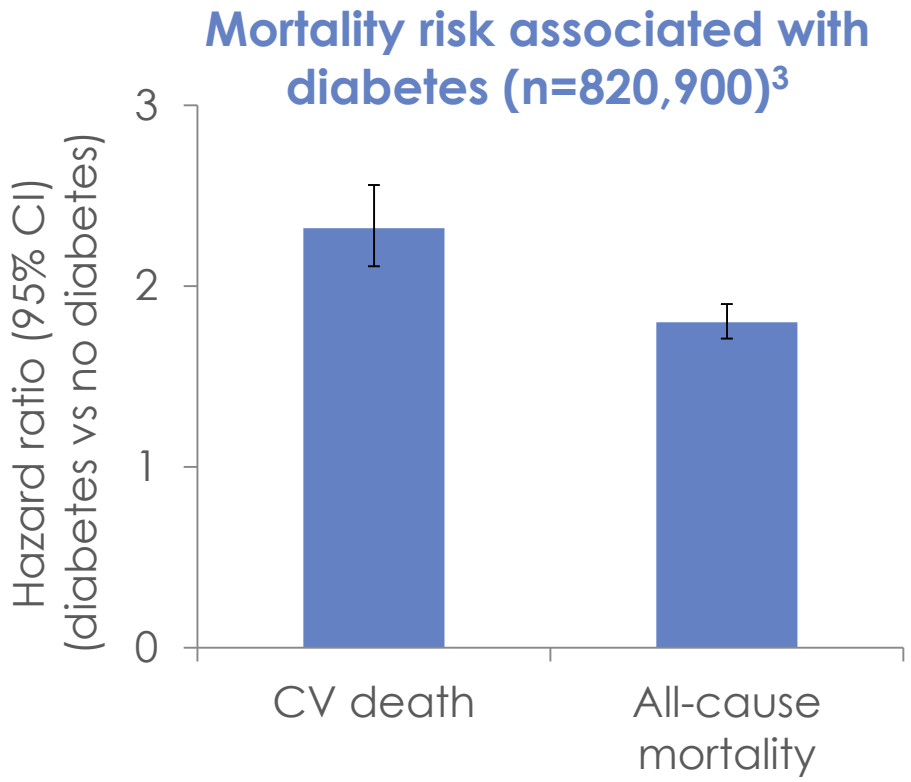
- אשה בת 65 פונה למרפאה למעקב לאחר אישפוז בו עברה אוטם לא חודר וניתוח מעקפים. תפקוד הלב היה ירוד במידה בינונית.
- מאז הניתוח היא חפשית מתעוקה או קוצר נשימה.
- ברקע – יתר ל.ד, דיסליפידמיה וסכרת.
- הטיפול בשחרור כולל אספירין, קרדילוק 2.5 מ״ג/יום מטפורמין 850 מ״ג*2/יום וקרסטור 20 מ״ג/יום.
- במעבדה: Creatinine: 1.3 mg/dl, T.C: 150,
- LDL: 68, HDL: 35, HBA1C: 8.0%

Type 2 diabetes is increasingly prevalent

- Globally, 387 million people are living with diabetes[1]
- At least 68% of people >65 years with diabetes die of heart disease[2]



This will rise to 592 million by 2035[1]



1. IDF Diabetes Atlas 6th Edition 2014 http://www.idf.org/diabetesatlas; 2. Centers for Disease Control and Prevention 2011; 3. Seshasai et al. N Engl J Med 2011;364:829-41

EMPA-REG OUTCOME®

Empagliflozin

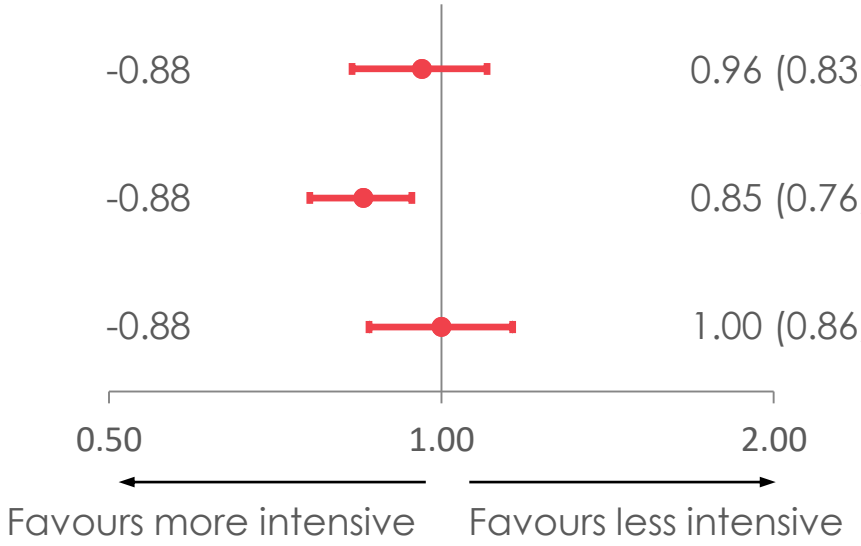
- Empagliflozin is a highly selective inhibitor of the sodium glucose cotransporter 2 (SGLT2) in the kidney
- Glucose reduction occurs by reducing renal glucose reabsorption and thus increasing urinary glucose excretion
- In patients with type 2 diabetes, empagliflozin leads to[1]:
  - Significant reductions in HbA1c
  - Weight loss
  - Reductions in blood pressure without increases in heart rate

1. Liakos A et al. Diabetes Obes Metab 2014;16:984-93

EMPA-REG OUTCOME®

Meta-analysis of intensive glucose control in T2DM: major CV events including heart failure

	Number of events			
	More intensive	Less intensive	Difference in HbA1c (%)	HR (95% CI)
Stroke	378	370	-0.88	0.96 (0.83, 1.10)
Myocardial infarction	730	745	-0.88	0.85 (0.76, 0.94)
Hospitalisation for or death from heart failure	459	446	-0.88	1.00 (0.86, 1.16)



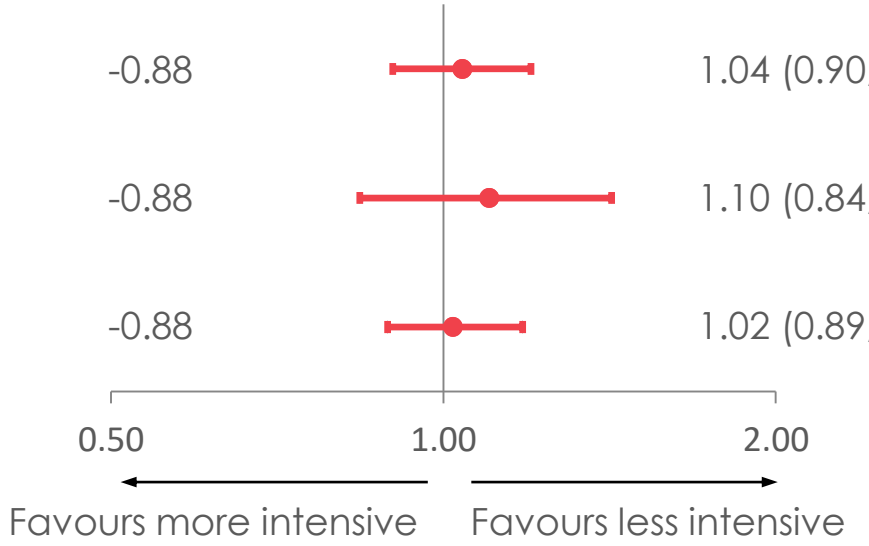
- Meta-analysis of 27,049 participants and 2370 major vascular events from:
  - ADVANCE
  - UKPDS
  - ACCORD
  - VADT

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

EMPA-REG OUTCOME®

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)



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

EMPA-REG OUTCOME®

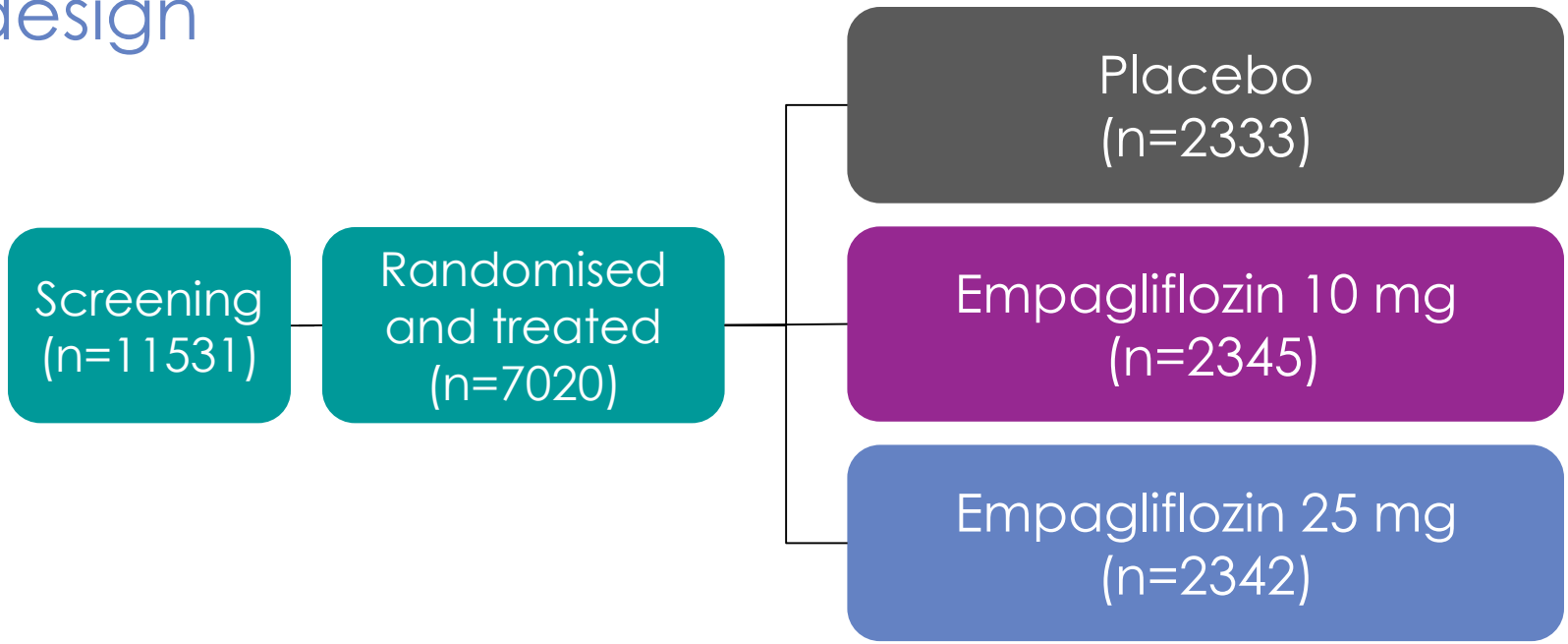
EMPA-REG OUTCOME®

- Randomised, double-blind, placebo-controlled CV outcomes trial

- **Objective**
  To examine the long-term effects of empagliflozin versus placebo, in addition to standard of care, on CV morbidity and mortality in patients with type 2 diabetes and high risk of CV events

CV, cardiovascular

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

EMPA-REG OUTCOME®

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/1.73m^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 randomisation or no change in dose for ≥12 weeks prior to randomisation or, in the case of insulin, unchanged by >10% compared to the dose at randomisation

EMPA-REG OUTCOME®

Pre-specified primary and key secondary outcomes

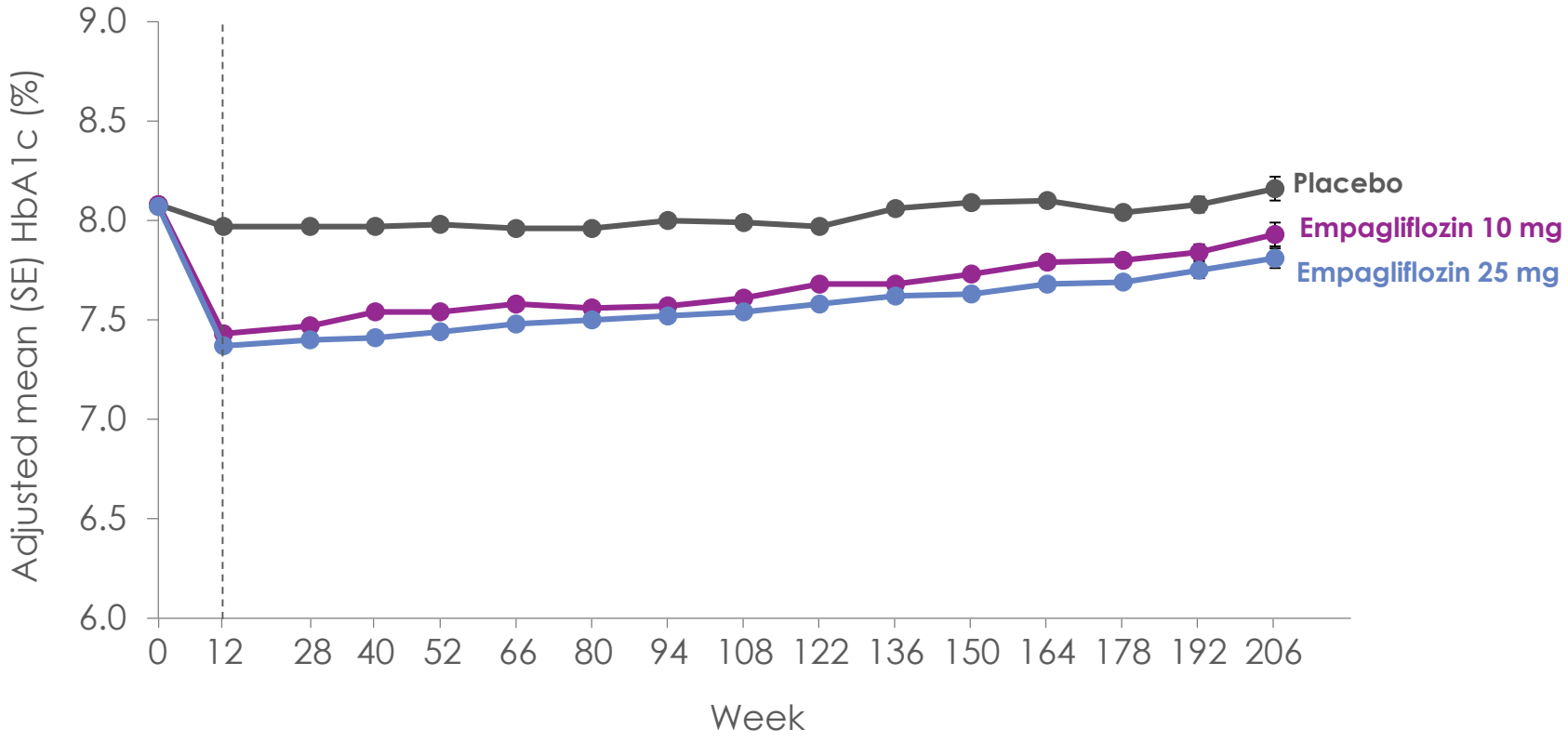
- Primary outcome
  - **3-point MACE:** Time to first occurrence of CV death, non-fatal MI or non-fatal stroke

- Key secondary outcome
  - **4-point MACE:** Time to first occurrence of CV death, non-fatal MI, non-fatal stroke or hospitalisation for unstable angina

CV, cardiovascular; MI, myocardial infarction; MACE, Major Adverse Cardiovascular Event

EMPA-REG OUTCOME®

HbA1c



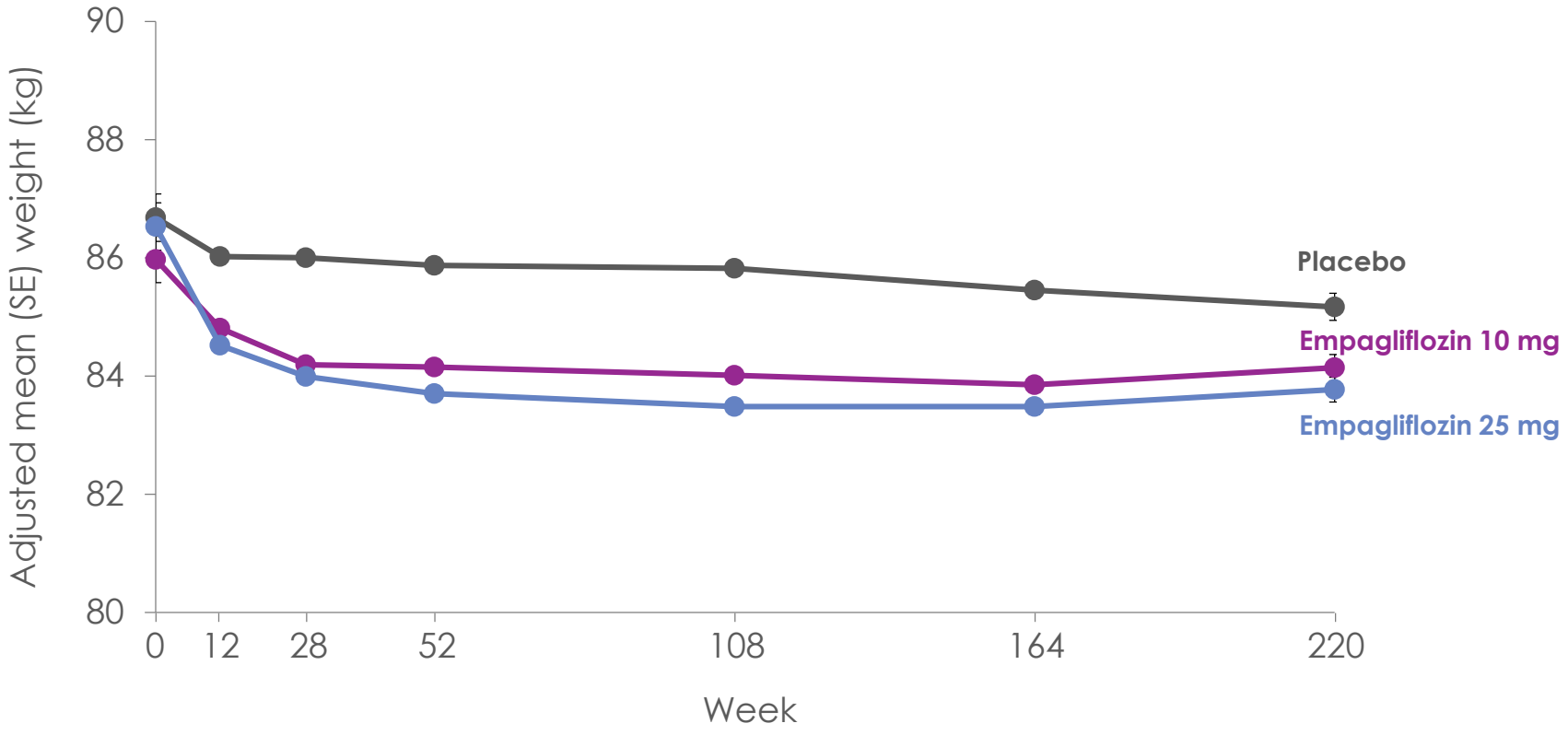
Placebo	2294	2272	2188	2133	2113	2063	2008	1967	1741	1456	1241	1109	962	705	420	151
Empagliflozin 10 mg	2296	2272	2218	2150	2155	2108	2072	2058	1805	1520	1297	1164	1006	749	488	170
Empagliflozin 25 mg	2296	2280	2212	2152	2150	2115	2080	2044	1842	1540	1327	1190	1043	795	498	195

All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent-to-treat) with reasonable amount of data available for pre-scheduled measurements

X-axis: timepoints

EMPA-REG OUTCOME®

Weight



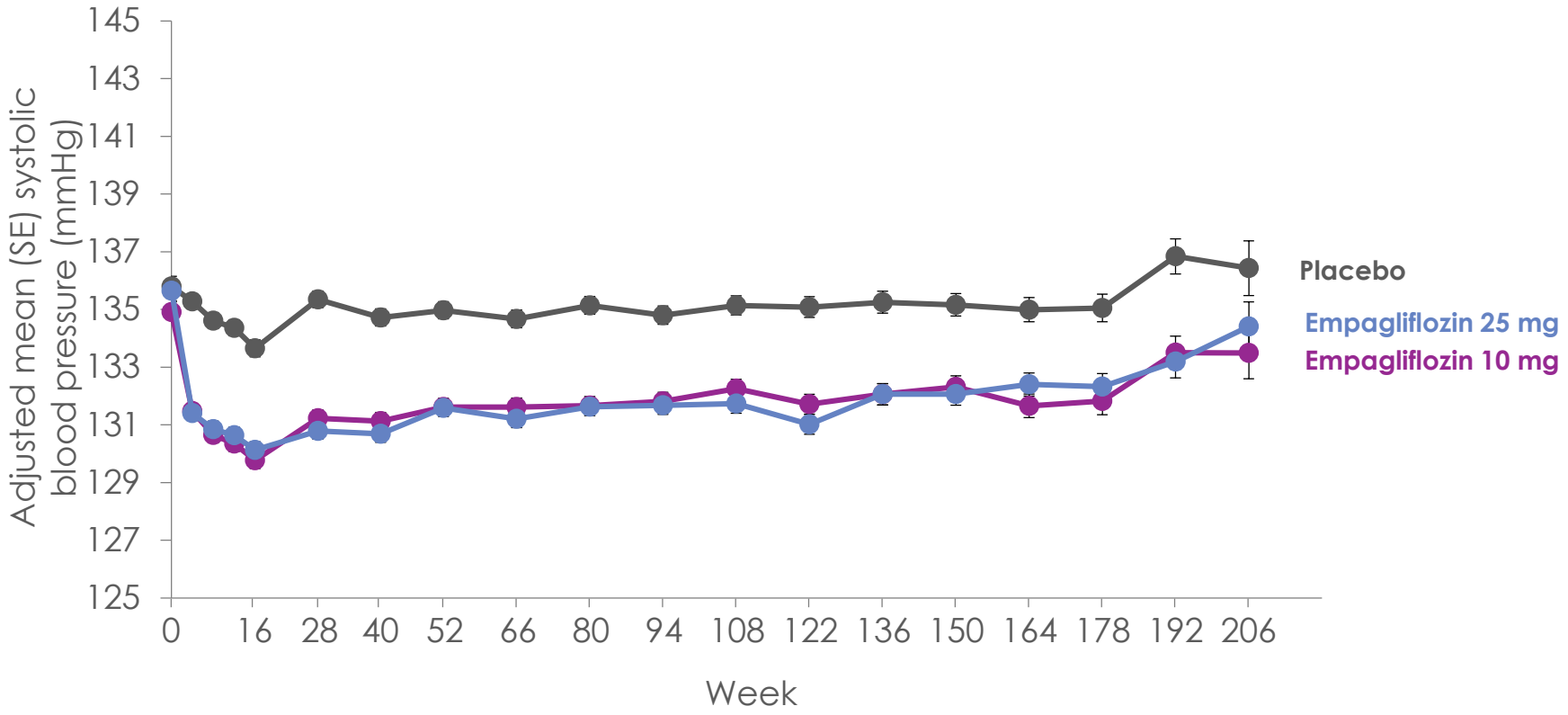
Placebo	2285	1915	2215	2138	1598	1239	425
Empagliflozin 10 mg	2290	1893	2238	2174	1673	1298	483
Empagliflozin 25 mg	2283	1891	2226	2178	1678	1335	489

All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent-to-treat) with reasonable amount of data available for pre-scheduled measurements

X-axis: timepoints

EMPA-REG OUTCOME®

Systolic blood pressure



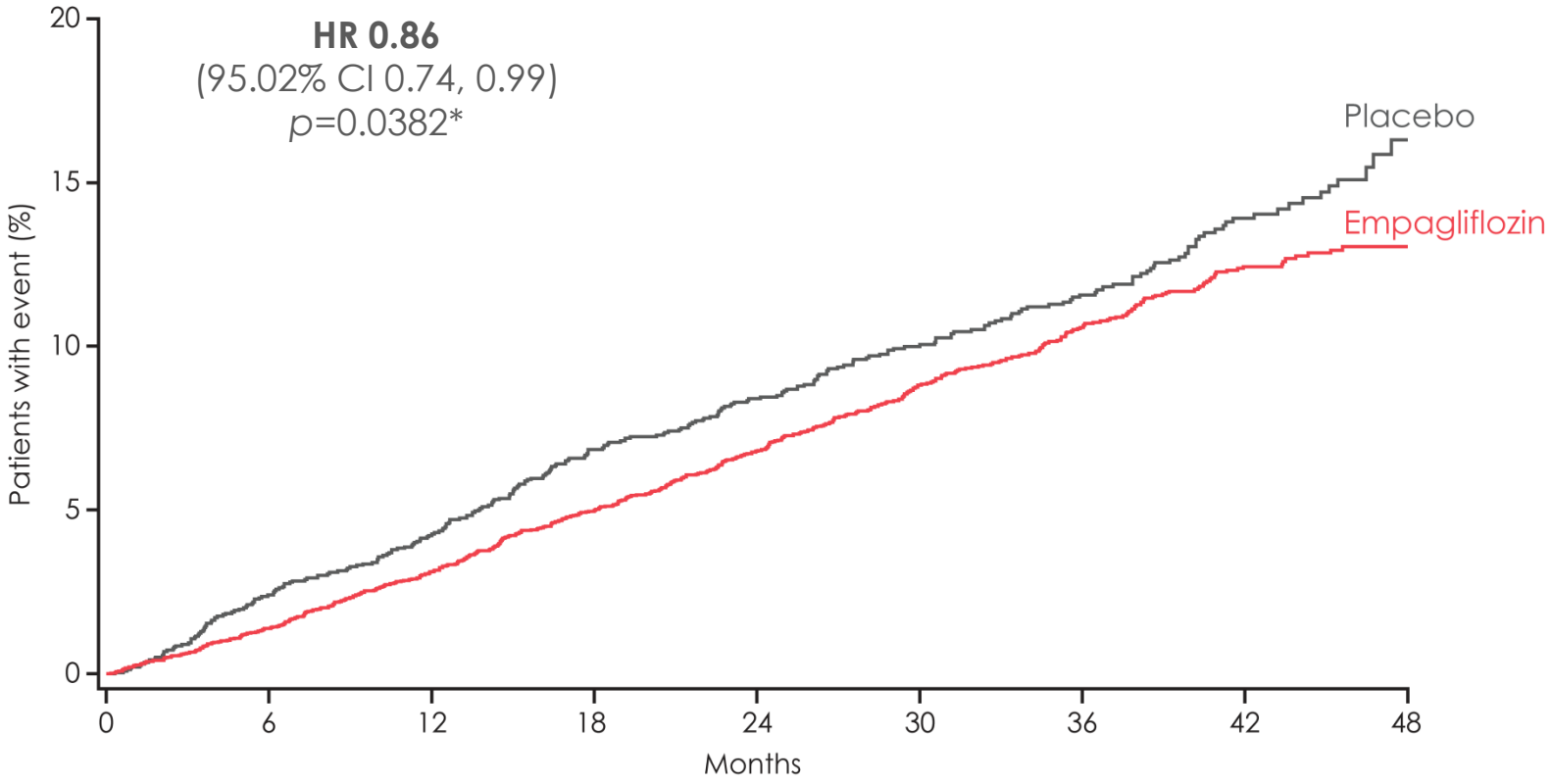
Placebo	2322	2235	2203	2161	2133	2073	2024	1974	1771	1492	1274	1126	981	735	450	171
Empagliflozin 10 mg	2322	2250	2235	2193	2174	2125	2095	2072	1853	1556	1327	1189	1034	790	518	199
Empagliflozin 25 mg	2323	2247	2221	2197	2169	2129	2102	2066	1878	1571	1351	1212	1070	842	528	216

All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent-to-treat) with reasonable amount of data available for pre-scheduled measurements

X-axis: timepoints

EMPA-REG OUTCOME®

Primary outcome: 3-point MACE

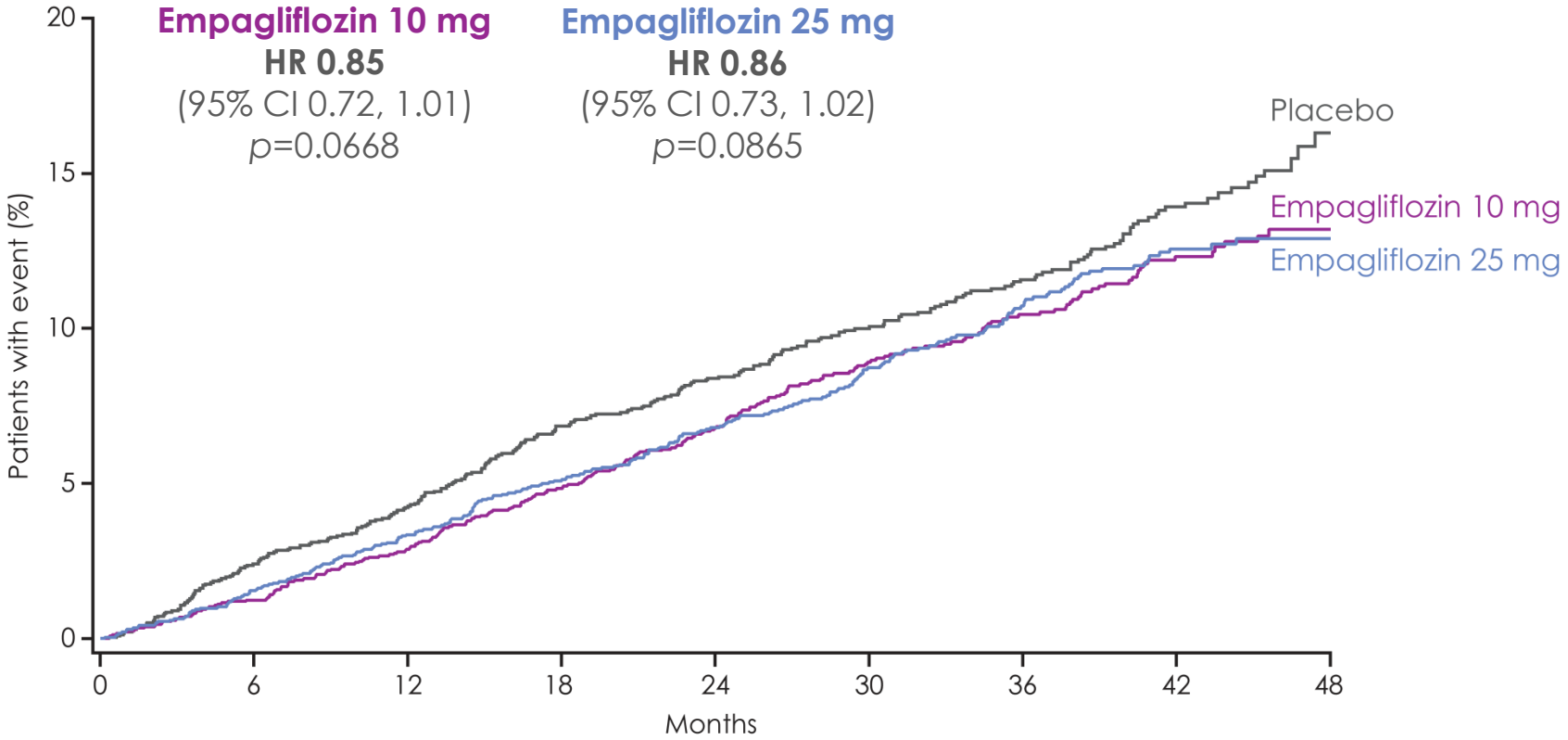


No. of patients									
Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

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)

EMPA-REG OUTCOME®

3-point MACE

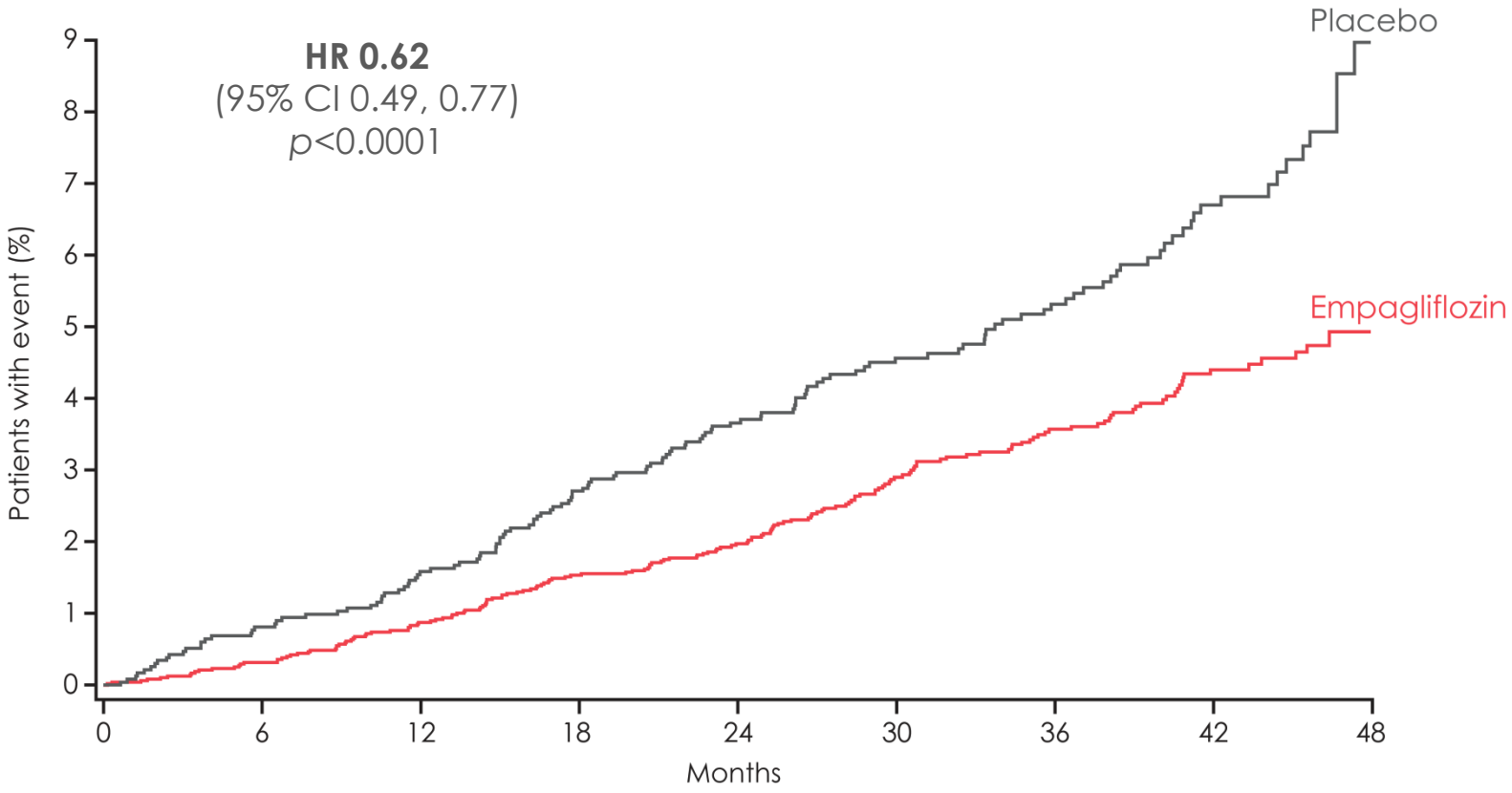


No. of patients									
Empagliflozin 10 mg	2345	2292	2233	2167	1918	1415	1177	753	178
Empagliflozin 25 mg	2342	2288	2222	2161	1933	1406	1182	781	192
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

Cumulative incidence function. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio

EMPA-REG OUTCOME®

CV death

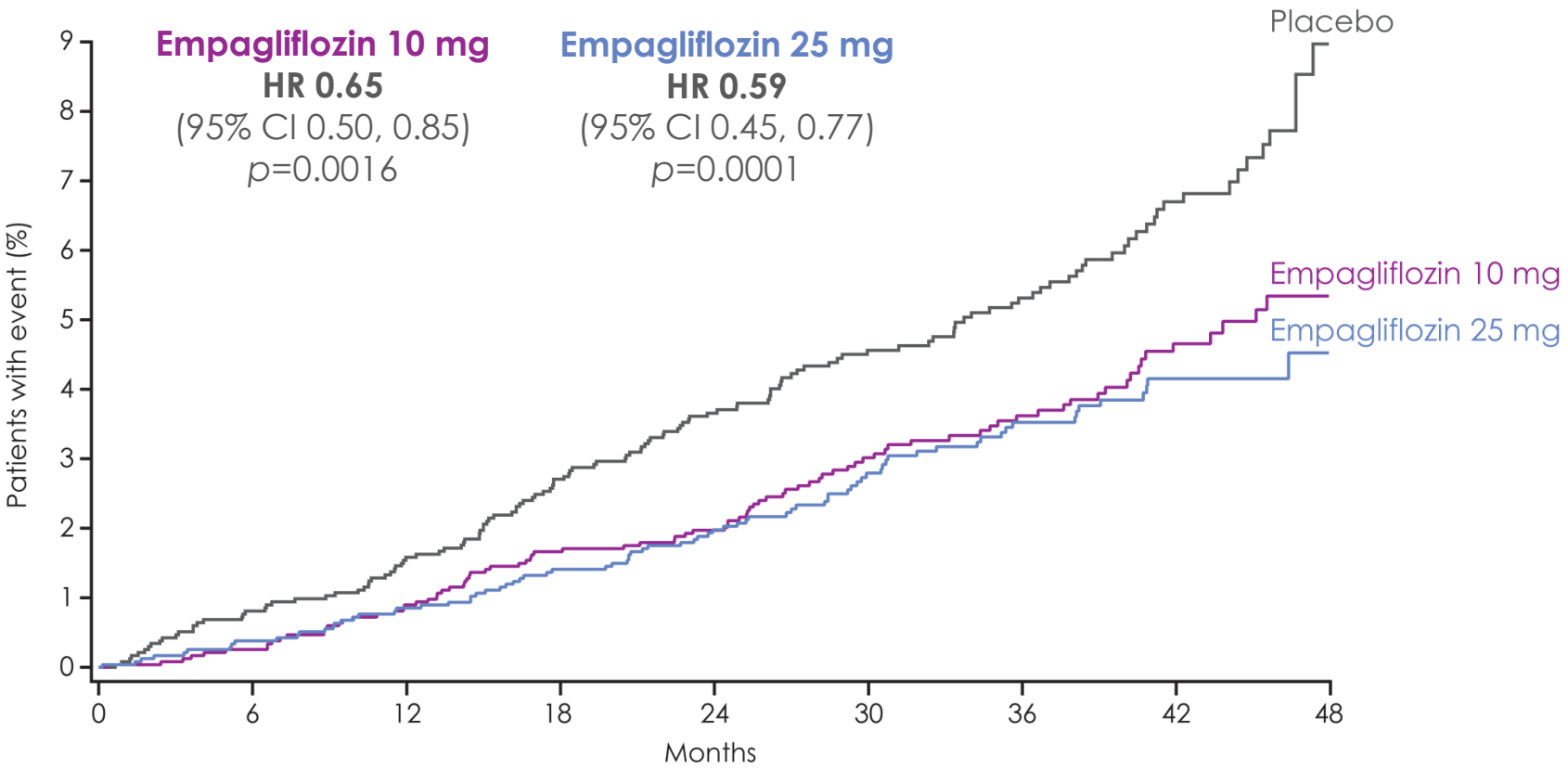


No. of patients									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

Cumulative incidence function. HR, hazard ratio

EMPA-REG OUTCOME®

CV death

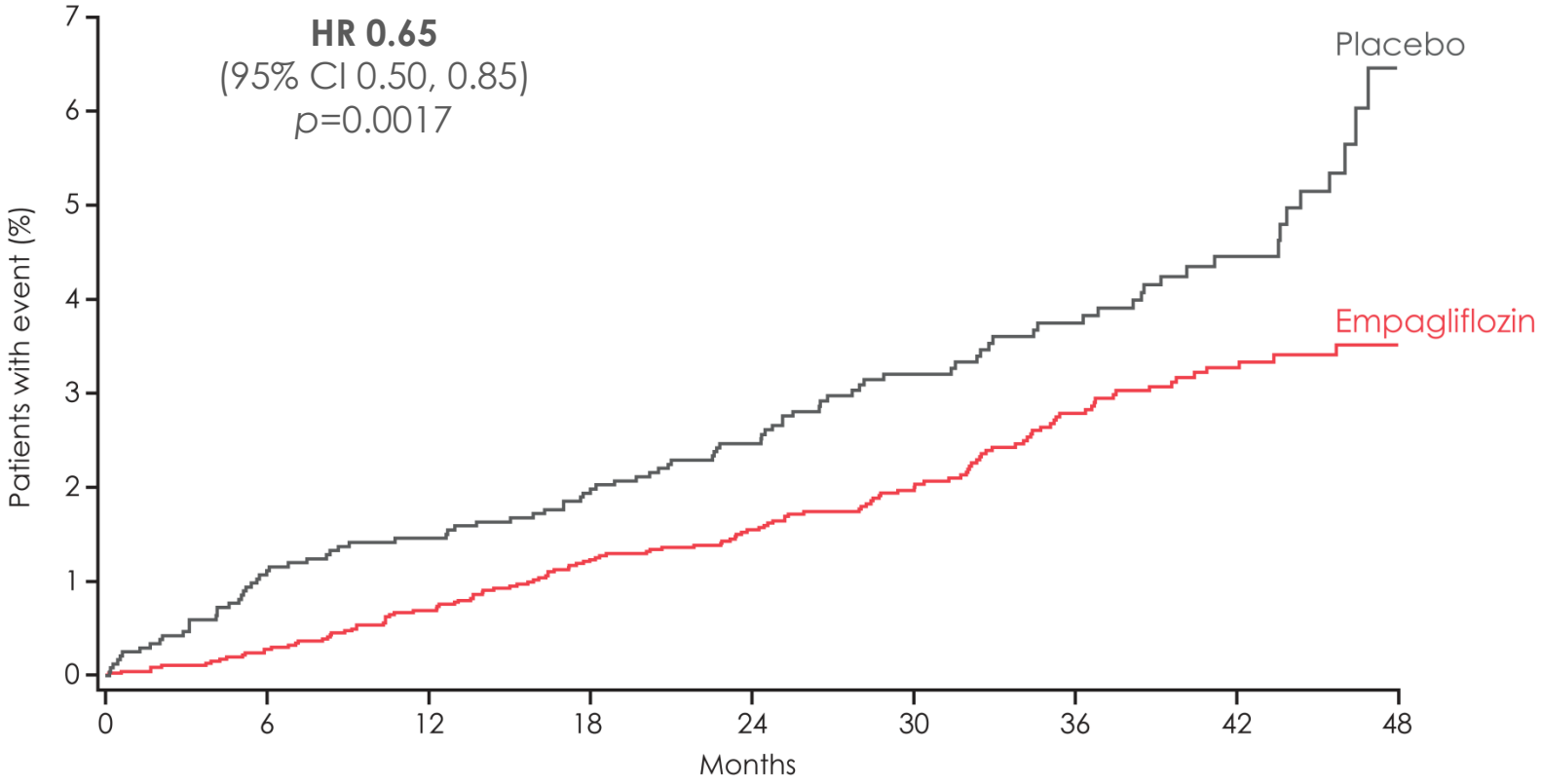


No. of patients									
Empagliflozin 10 mg	2345	2327	2305	2274	2055	1542	1303	847	201
Empagliflozin 25 mg	2342	2324	2303	2282	2073	1537	1314	875	213
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

Cumulative incidence function. HR, hazard ratio

EMPA-REG OUTCOME®

Hospitalisation for heart failure

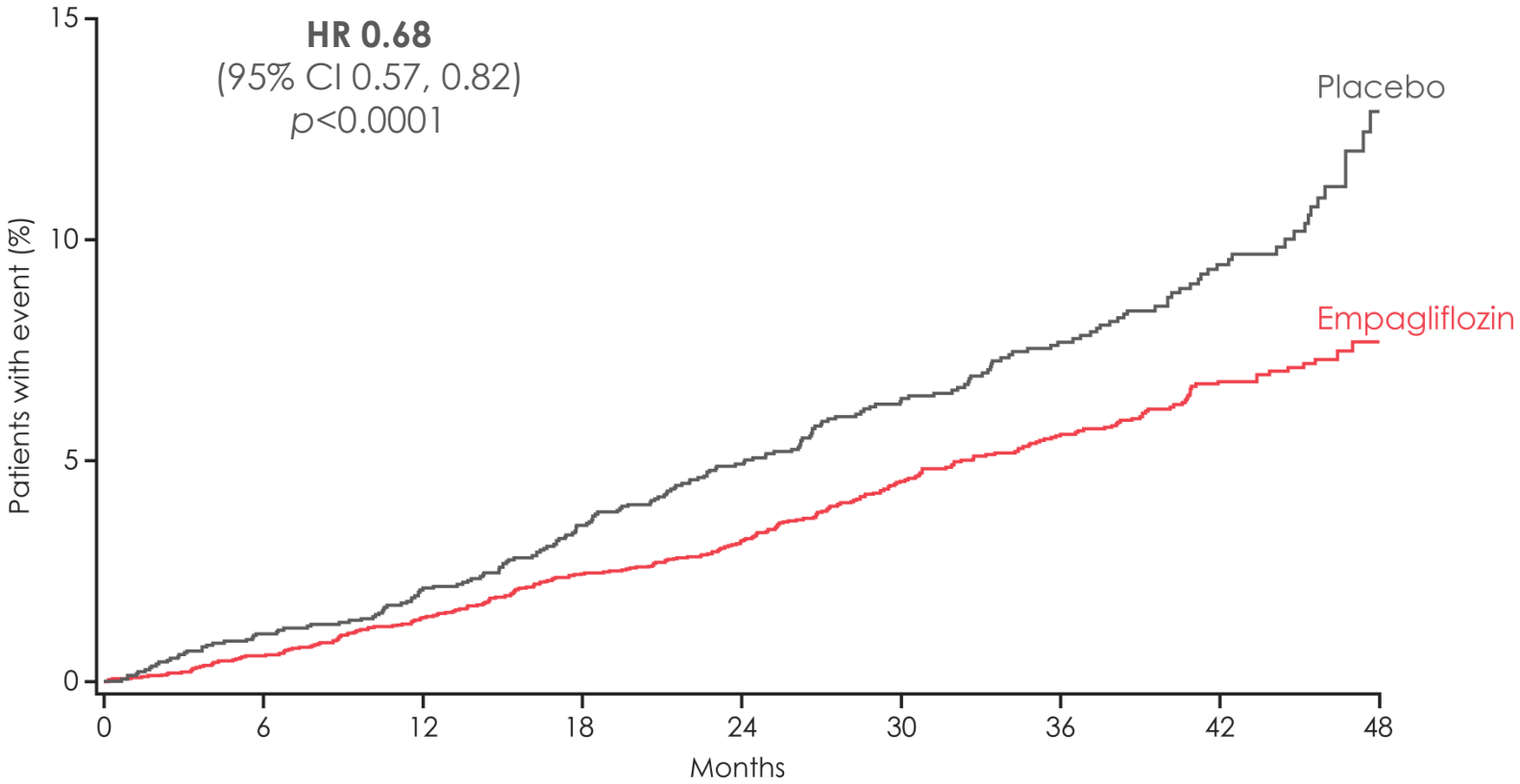


No. of patients									
Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

Cumulative incidence function. HR, hazard ratio

EMPA-REG OUTCOME®

All-cause mortality

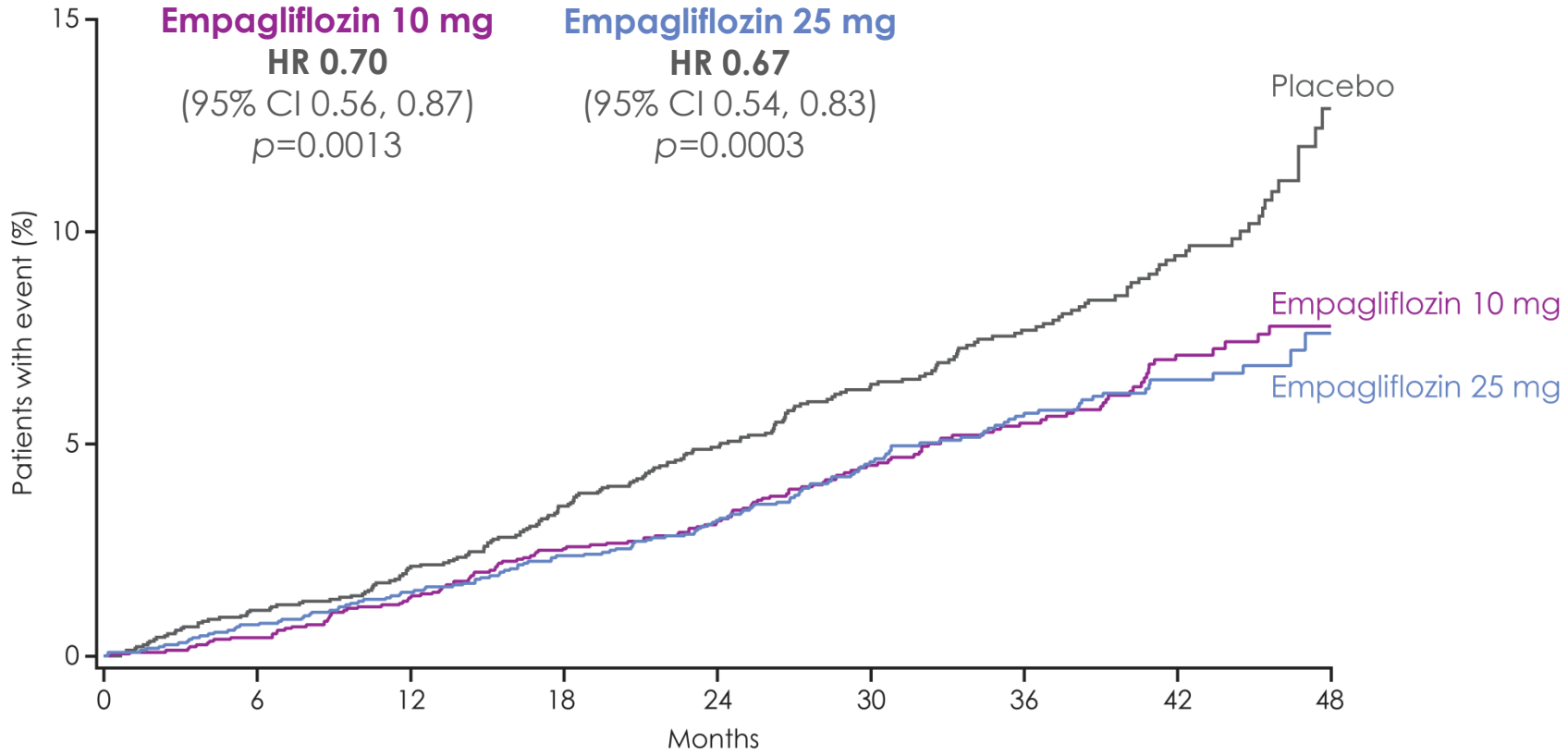


No. of patients									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

Kaplan-Meier estimate. HR, hazard ratio

EMPA-REG OUTCOME®

All-cause mortality



No. of patients									
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Empagliflozin 25 mg	2342	2324	2303	2282	2073	1537	1314	875	213
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

Kaplan-Meier estimate. HR, hazard ratio

EMPA-REG OUTCOME®

Adverse events

	Placebo (n=2333)		Empagliflozin 10 mg (n=2345)		Empagliflozin 25 mg (n=2342)	
	n (%)	Rate	n (%)	Rate	n (%)	Rate
One or more AEs	2139 (91.7%)	178.67	2112 (90.1%)	150.34	2118 (90.4%)	148.36
One or more drug-related* AEs	549 (23.5%)	11.33	666 (28.4%)	14.15	643 (27.5%)	13.38
One or more AEs leading to discontinuation	453 (19.4%)	8.26	416 (17.7%)	7.28	397 (17.0%)	6.89
One or more serious AEs	988 (42.3%)	22.34	876 (37.4%)	18.20	913 (39.0%)	19.39

Rate = per100 patient-years

*As reported by the investigator
Patients treated with ≥1 dose of study drug

EMPA-REG OUTCOME®

Adverse events consistent with genital infection

	Placebo (n=2333)		Empagliflozin 10 mg (n=2345)		Empagliflozin 25 mg (n=2342)	
	n (%)	Rate	n (%)	Rate	n (%)	Rate
Events consistent with genital infection	42 (1.8%)	0.73	153 (6.5%)	2.66	148 (6.3%)	2.55
Serious events	3 (0.1%)	0.05	5 (0.2%)	0.08	4 (0.2%)	0.07
Events leading to discontinuation	2 (0.1%)	0.03	19 (0.8%)	0.32	14 (0.6%)	0.23
By sex						
Male	25 (1.5%)	0.60	89 (5.4%)	2.16	77 (4.6%)	1.78
Female	17 (2.6%)	1.09	64 (9.2%)	3.93	71 (10.8%)	4.81

Rate = per100 patient-years

Patients treated with ≥1 dose of study drug
Based on 88 MedDRA preferred terms

EMPA-REG OUTCOME®

Confirmed hypoglycaemic adverse events

	Placebo (n=2333)	Empagliflozin 10 mg (n=2345)	Empagliflozin 25 mg (n=2342)
	n (%)		
Confirmed hypoglycaemic 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®

EMPA-REG OUTCOME®: summary

- Empagliflozin prevented hospitalization for heart failure by 35%
- Empagliflozin reduced CV death by 38%
- Empagliflozin improved survival by reducing all-cause mortality by 32%
- Empagliflozin was associated with a reduction in HbA1c without an increase in hypoglycaemia, reductions in weight and blood pressure, and small increases in LDL cholesterol and HDL cholesterol
- 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

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 71, NO. 23, 2018

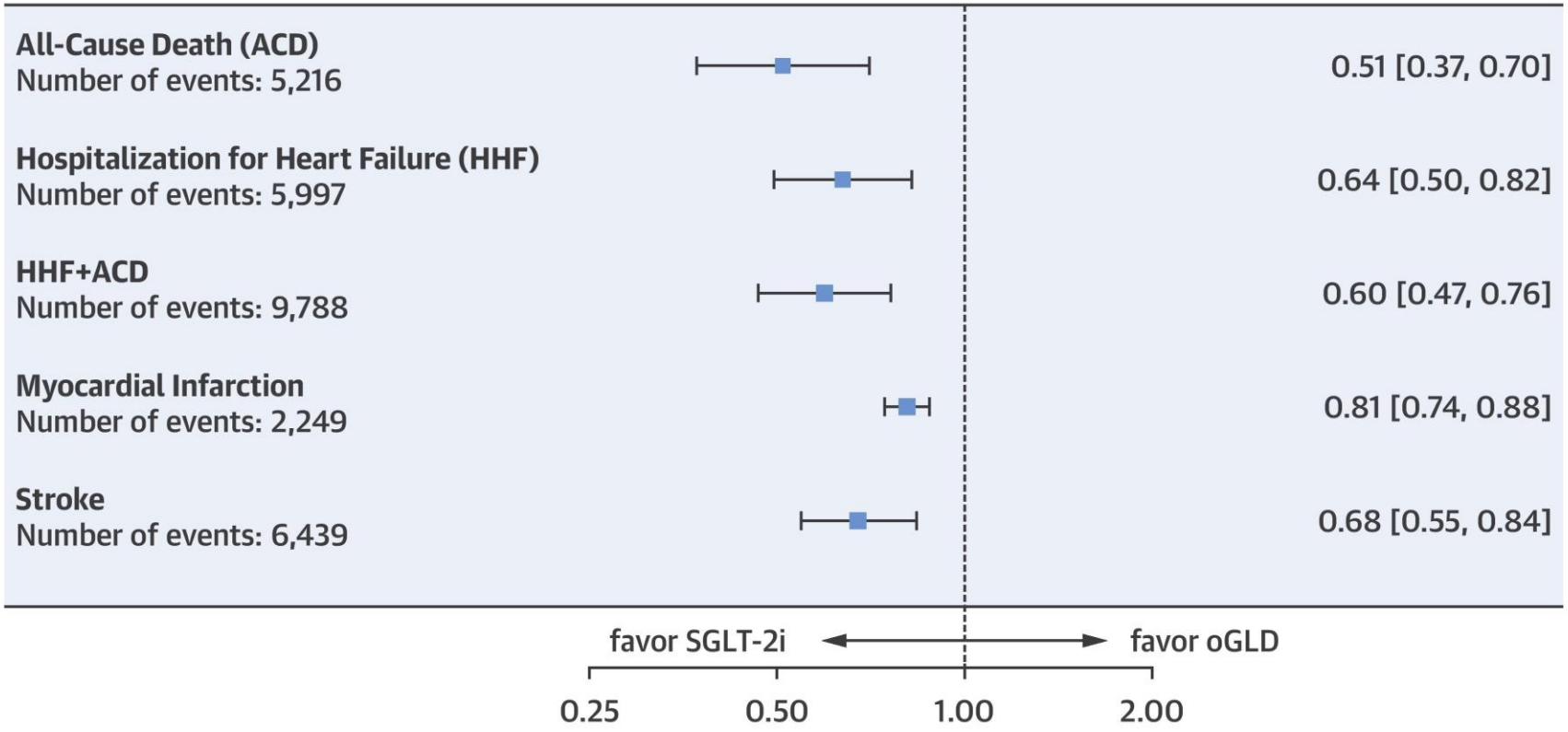
Cardiovascular Events Associated With SGLT-2 Inhibitors Versus Other Glucose-Lowering Drugs

The CVD-REAL 2 Study

Mikhail Kosiborod, MD,[a] Carolyn S.P. Lam, MBBS, PhD,[b,c] Shun Kohsaka, MD,[d] Dae Jung Kim, MD,[e] Avraham Karasik, MD,[f] Jonathan Shaw, MD,[g] Navdeep Tangri, MD, PhD,[h] Su-Yen Goh, MD,[i] Marcus Thuresson, PhD,[j] Hungta Chen, PhD,[k] Filip Surmont, MD,[l] Niklas Hammar, PhD,[m,n] Peter Fenici, MD,[o] on behalf of the CVD-REAL Investigators and Study Group

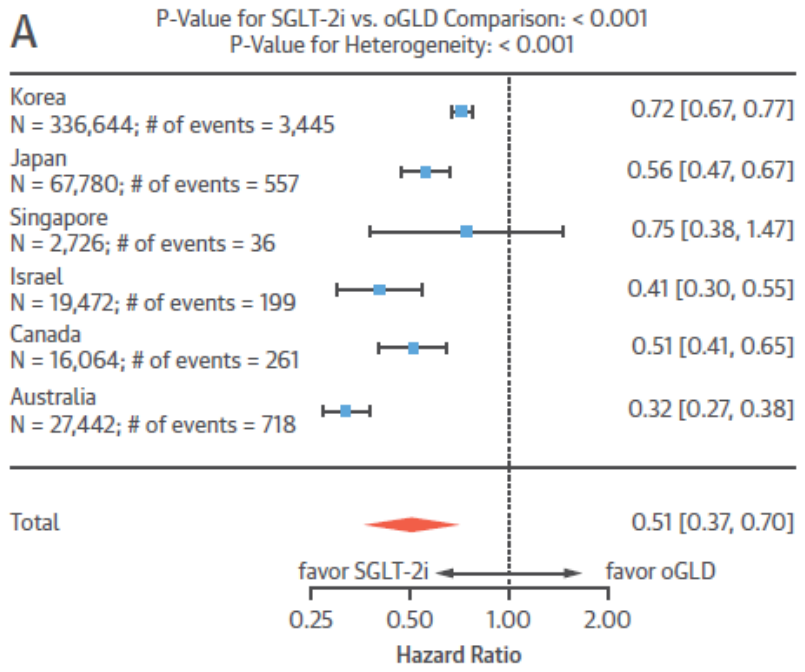
- Real world study in 6 countries
- 470,128 episodes of new treatment initiation for diabetes. One year follow up.
- Only 26% with CV disease
- Propensity matching of SGLT2 inhibitors vs. other medications

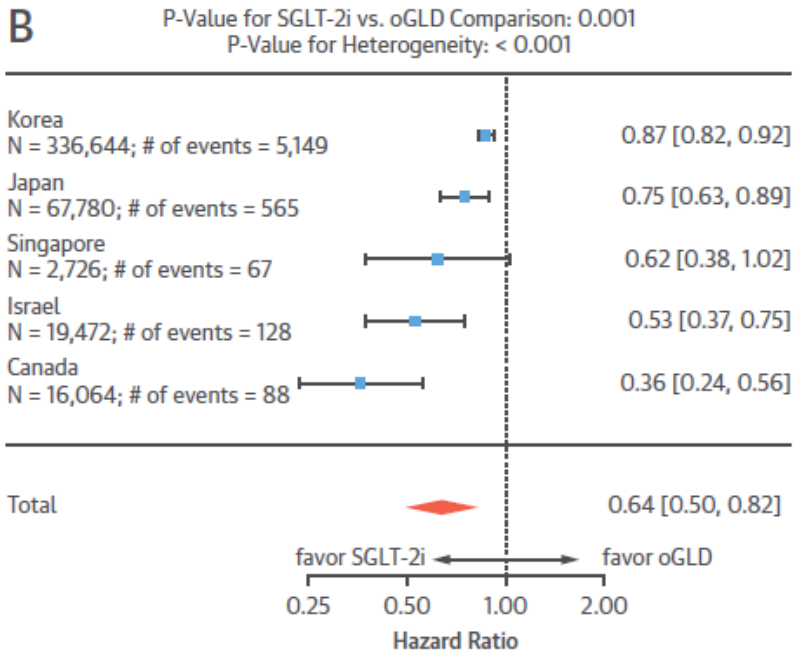
CENTRAL ILLUSTRATION: Lower Cardiovascular Risk Associated With SGLT-2 Inhibitors



Kosiborod, M. et al. J Am Coll Cardiol. 2018;71(23):2628-39.

FIGURE 2 Cardiovascular Outcomes Associated With SGLT-2i Versus Other Glucose-Lowering Drugs





Overall Death

Hospitalization for HF

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 71, NO. 22, 2018

SPECIAL FOCUS ISSUE: CARDIOVASCULAR HEALTH PROMOTION

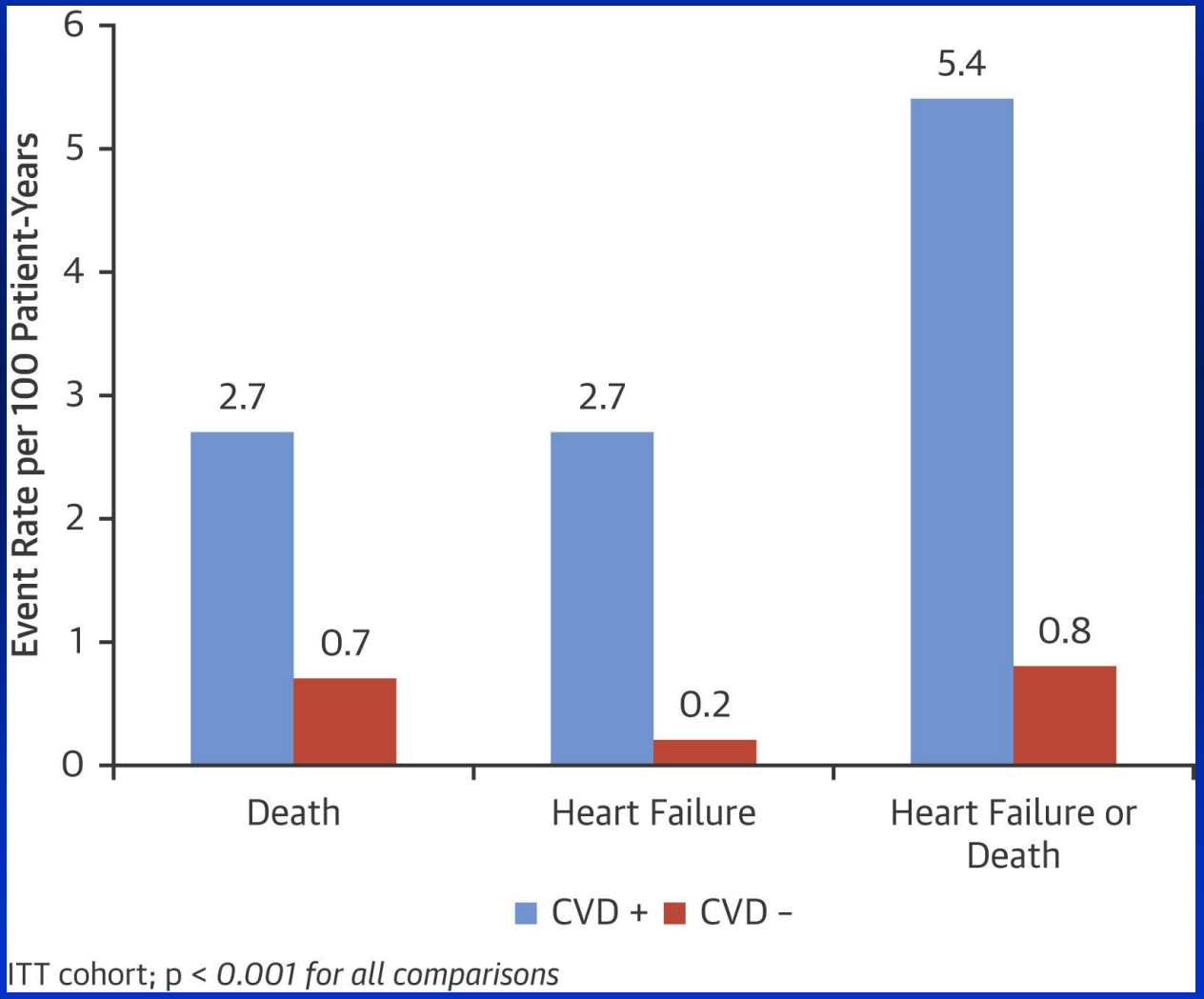
ORIGINAL INVESTIGATIONS

SGLT-2 Inhibitors and Cardiovascular Risk

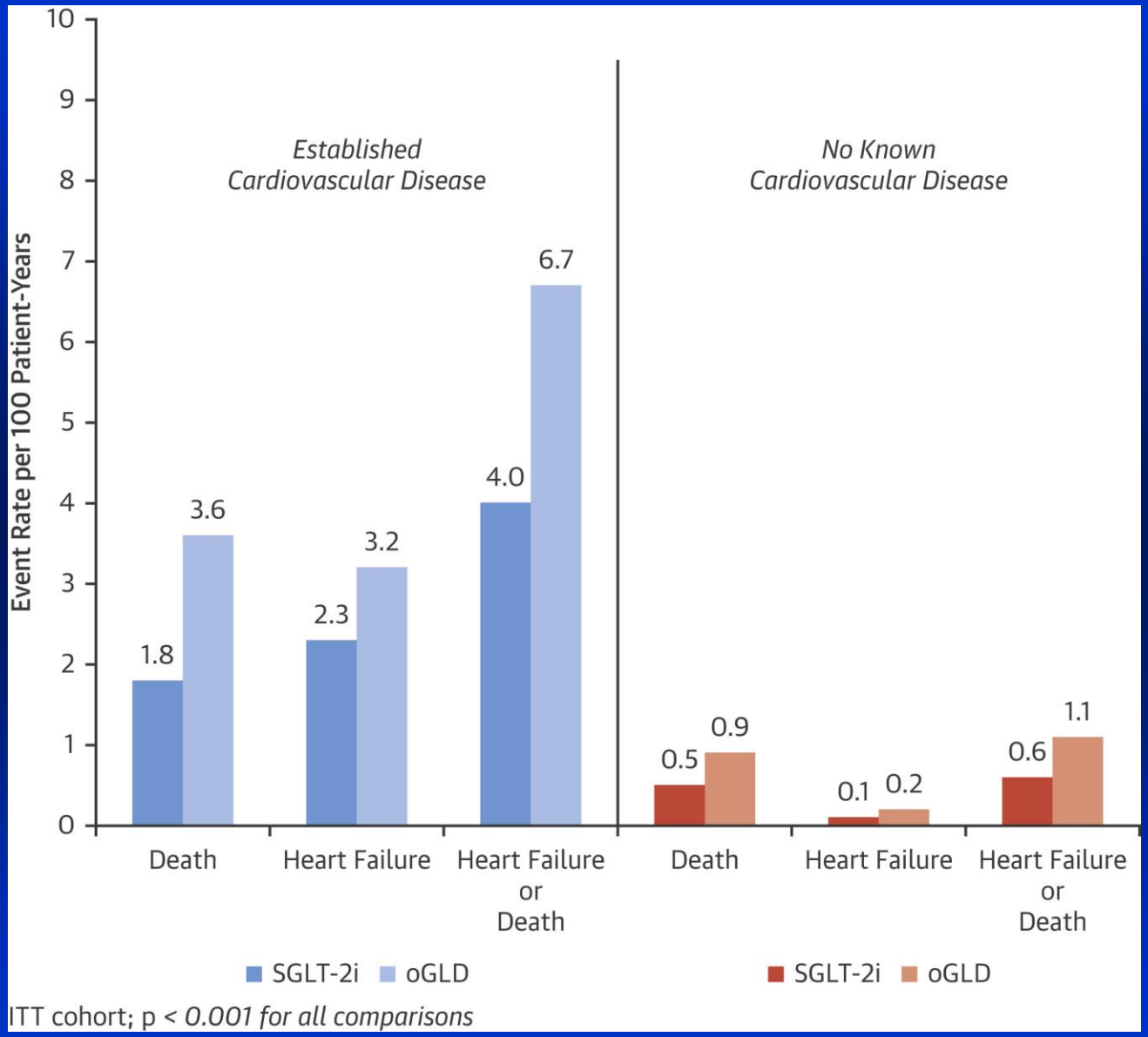
An Analysis of CVD-REAL

- This analysis sought to assess the impact of SGLT2 inhibition vs. other antidiabetic agents in patients with and without CVD.
- Propensity matching, 13% with established CVD, 87% without (39,293 vs. 266,863).

EVENT RATES IN PATIENTS WITH AND WITHOUT CVD

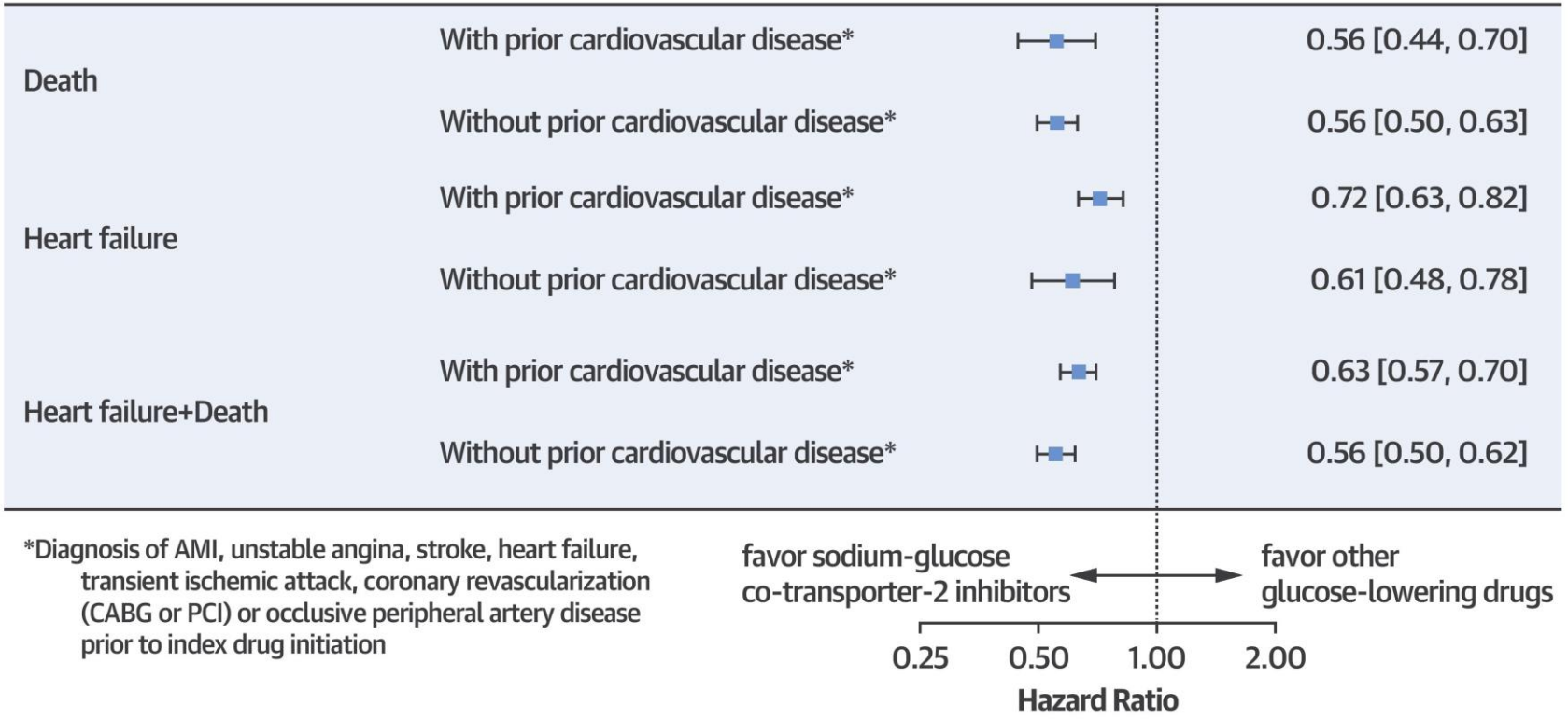


ITT cohort; p < *0.001 for all comparisons*



ITT cohort; p < *0.001 for all comparisons*

CENTRAL ILLUSTRATION: Sodium-Glucose Co-Transporter-2 Inhibitors in Patients With and Without Cardiovascular Disease

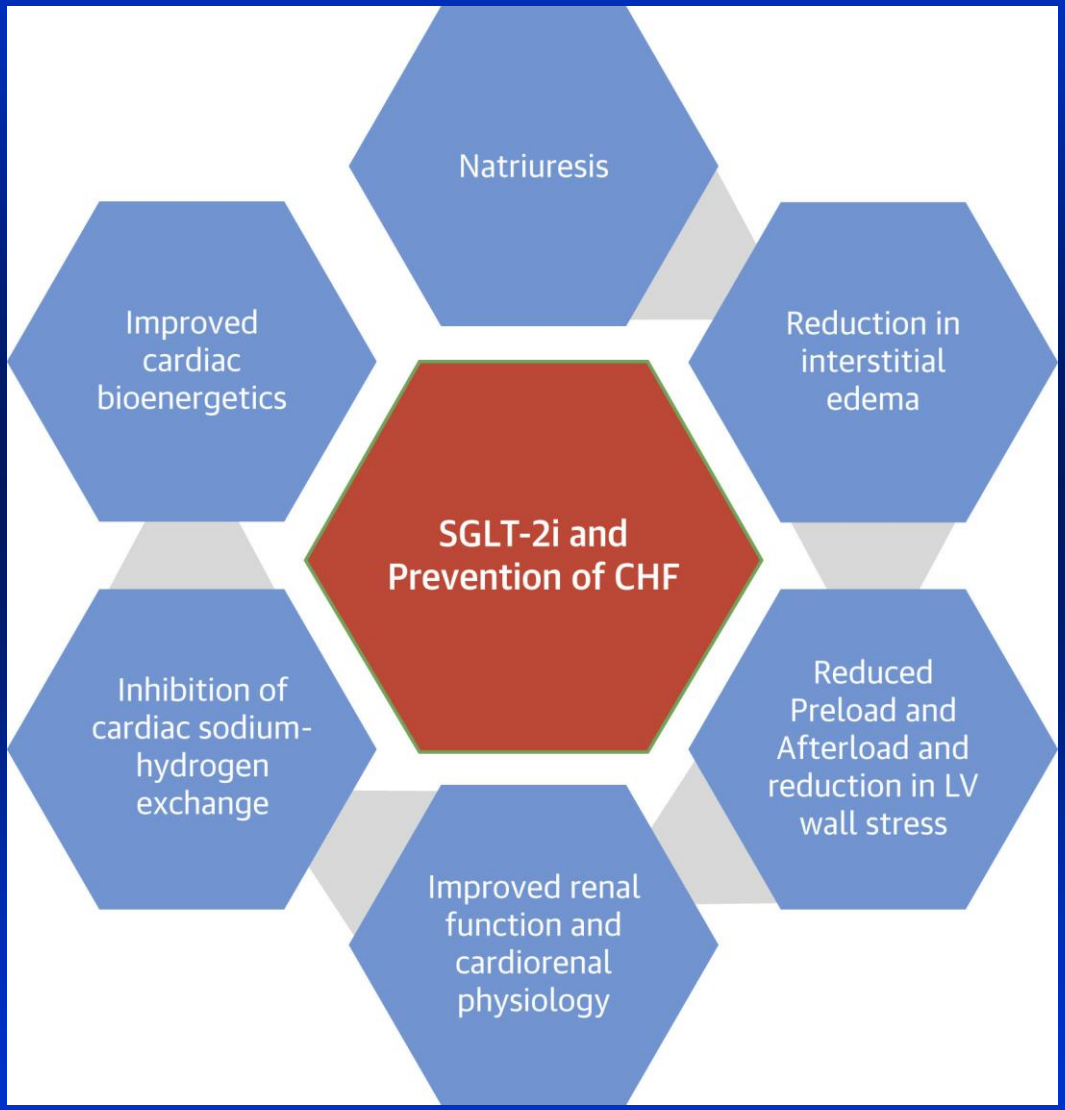


Cavender, M.A. et al. J Am Coll Cardiol. 2018;71(22):2497-506.

CONCLUSIONS

- In this observational analysis of the CVD-REAL study, most patients treated with SGLT-2i in clinical practice across 5 countries do not have established CVD.
- Patients with and without established CVD are at lower associated risk of both death and HF after initiation of SGLT-2i therapy compared to therapy with other GLDs.

SUGGESTED MECHANISMS BEYOND GLUCOSE LOWERING



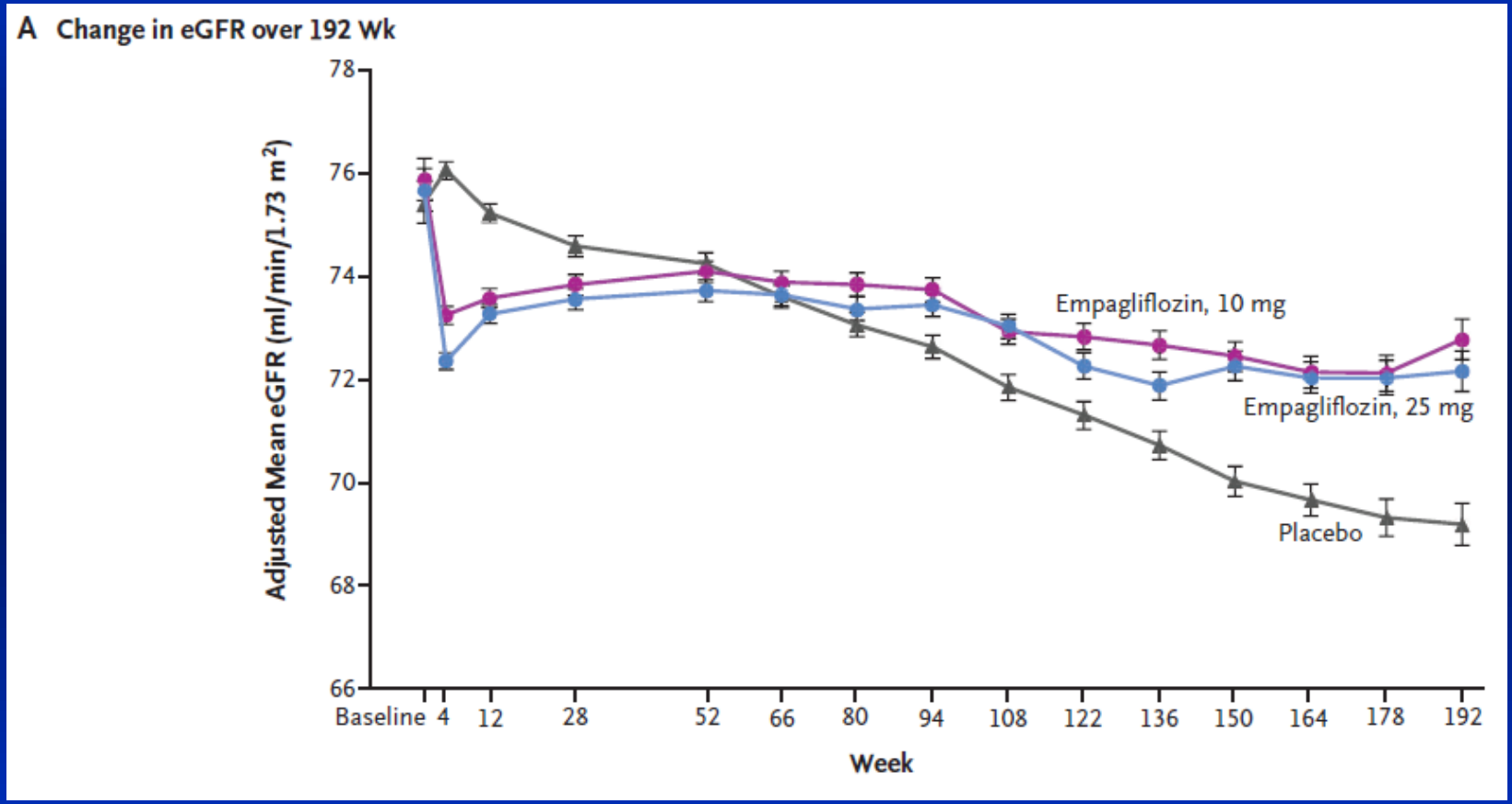
Farkouh and Verma JACC 2018; 2507

The NEW ENGLAND JOURNAL of MEDICINE

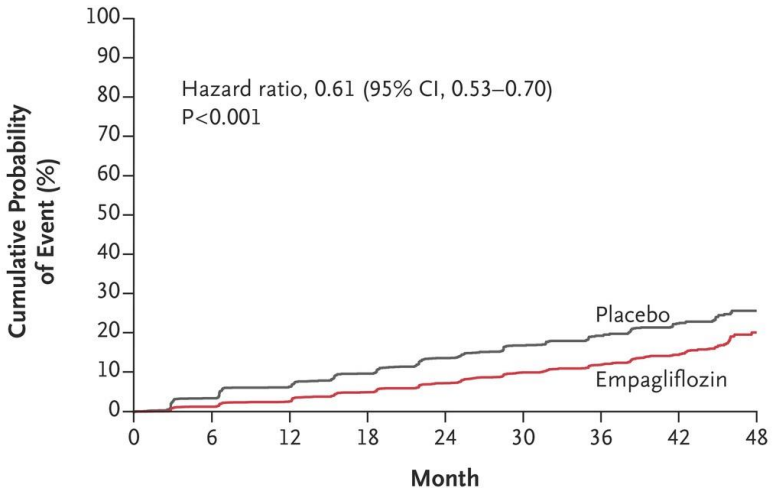
ORIGINAL ARTICLE

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

Christoph Wanner, M.D., Silvio E. Inzucchi, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Maximilian von Eynatten, M.D., Michaela Mattheus, Dipl. Biomath., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Bernard Zinman, M.D., for the EMPA-REG OUTCOME Investigators*

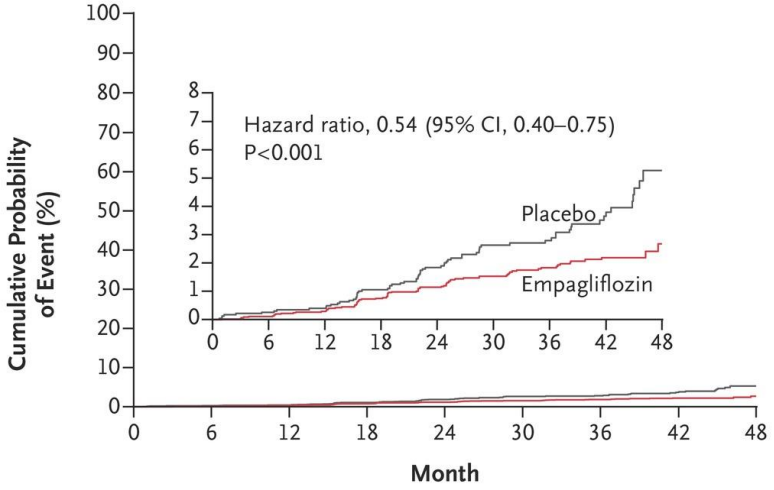

A Change in eGFR over 192 Wk
Adjusted Mean eGFR (ml/min/1.73 m²)
78
76
74
72
70
68
66
Empagliflozin, 10 mg
Empagliflozin, 25 mg
Placebo
Baseline 4 12 28 52 66 80 94 108 122 136 150 164 178 192
Week

A Incident or Worsening Nephropathy



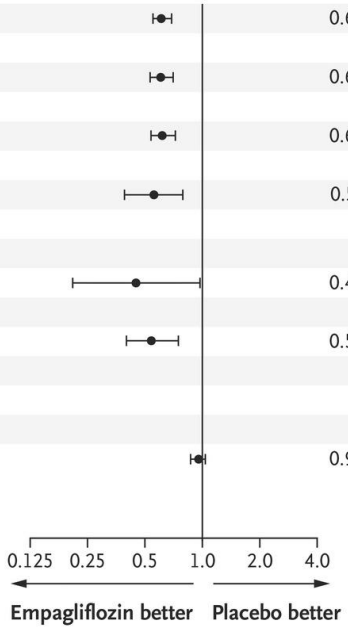
No. at Risk									
Empagliflozin	4124	3994	3848	3669	3171	2279	1887	1219	290
Placebo	2061	1946	1836	1703	1433	1016	833	521	106

B Post Hoc Renal Composite Outcome



No. at Risk									
Empagliflozin	4645	4500	4377	4241	3729	2715	2280	1496	360
Placebo	2323	2229	2146	2047	1771	1289	1079	680	144

Renal Outcome Measure	Empagliflozin		Placebo		Hazard Ratio (95% CI)	P Value
	no. with event/ no. analyzed (%)	*rate/1000 patient-yr*	*no. with event/ no. analyzed (%)*	*rate/1000 patient-yr*		
Incident or worsening nephropathy or cardiovascular death	675/4170 (16.2)	60.7	497/2102 (23.6)	95.9	0.61 (0.55–0.69)	<0.001
Incident or worsening nephropathy	525/4124 (12.7)	47.8	388/2061 (18.8)	76.0	0.61 (0.53–0.70)	<0.001
Progression to macroalbuminuria	459/4091 (11.2)	41.8	330/2033 (16.2)	64.9	0.62 (0.54–0.72)	<0.001
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2	70/4645 (1.5)	5.5	60/2323 (2.6)	9.7	0.56 (0.39–0.79)	<0.001
Initiation of renal-replacement therapy	13/4687 (0.3)	1.0	14/2333 (0.6)	2.1	0.45 (0.21–0.97)	0.04
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2, initiation of renal-replacement therapy, or death from renal disease	81/4645 (1.7)	6.3	71/2323 (3.1)	11.5	0.54 (0.40–0.75)	<0.001
Incident albuminuria in patients with a normal albumin level at baseline	1430/2779 (51.5)	252.5	703/1374 (51.2)	266.0	0.95 (0.87–1.04)	0.25



Conclusions

In patients with type 2 diabetes at high cardiovascular risk, empagliflozin was associated with slower progression of kidney disease and lower rates of clinically relevant renal events than was placebo when added to standard care.

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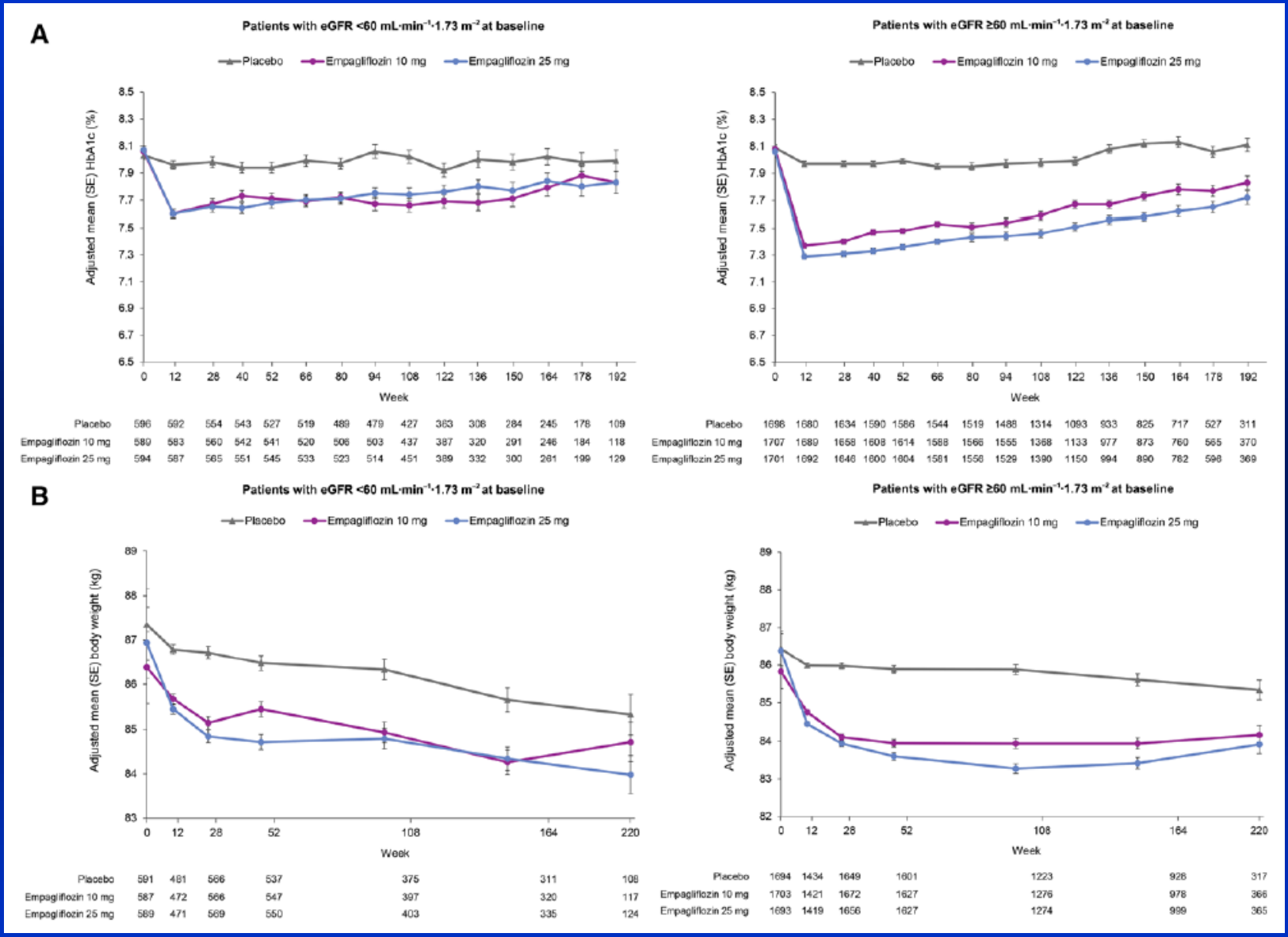
ORIGINAL RESEARCH ARTICLE

Empagliflozin and Clinical Outcomes in Patients With Type 2 Diabetes Mellitus, Established Cardiovascular Disease, and Chronic Kidney Disease

- Renal glucose excretion declines with declining renal function. Therefore, glucose lowering with empagliflozin also declines in these patients.
- However, there is evidence that the effects on albuminuria and BP are retained.
- This was a sub analysis of EMPAREG OUTCOME in patients with CKD (eGFR: 30-60)

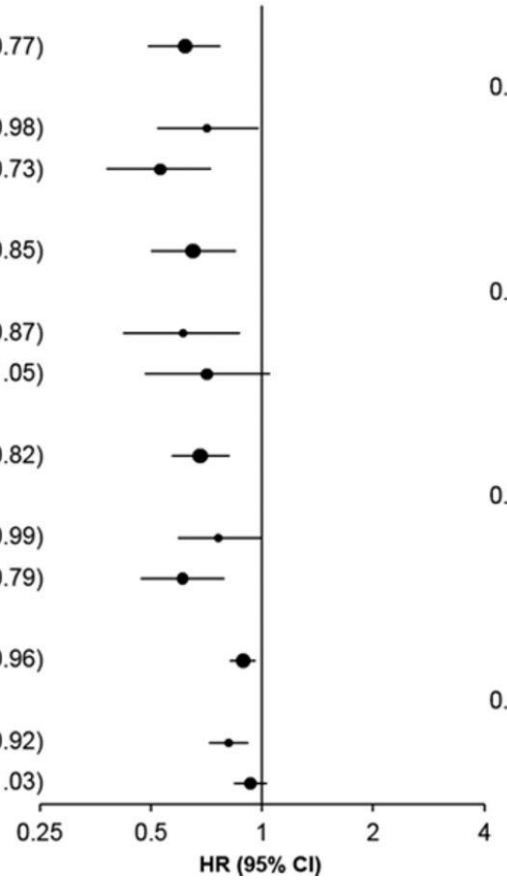
HBA1C

weight



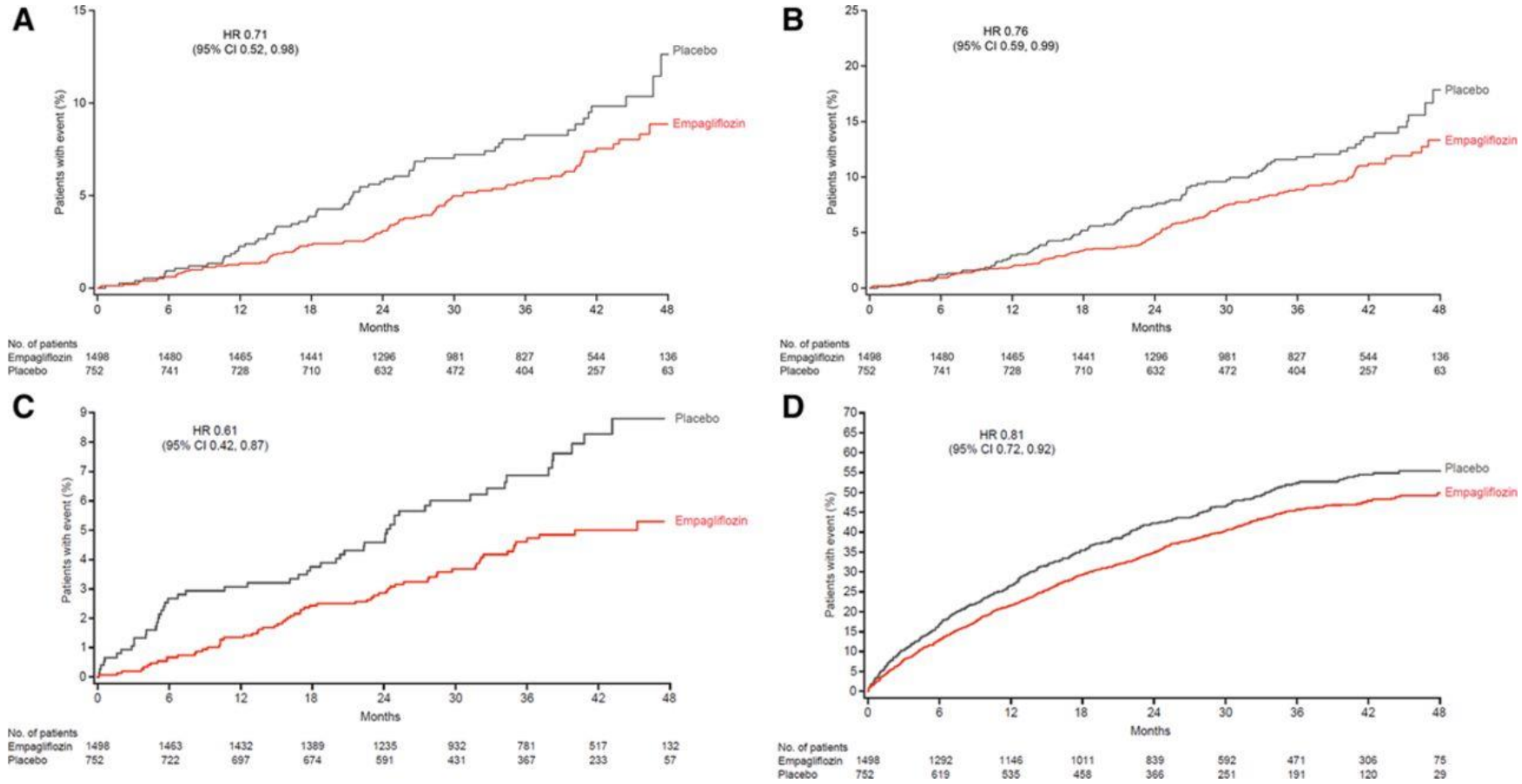
Cardiovascular death, hospitalization for heart failure, all-cause mortality, and all-cause hospitalization in patients with and without prevalent kidney disease (estimated glomerular filtration rate <60 mL·min−1·1.73 m−2 and/or macroalbuminuria [urine albumin-creatinine ratio >300 mg/g]) at baseline.

	Empagliflozin		Placebo			Interaction p-value
	n with event/N (%)	Rate/ 1000 pt-yr	n with event/N (%)	Rate/ 1000 pt-yr	HR (95% CI)	
Cardiovascular death						
All patients	172/4687 (3.7)	12.4	137/2333 (5.9)	20.2	0.62 (0.49, 0.77)	
Prevalent kidney disease*						0.1926
Yes	94/1498 (6.3)	21.4	65/752 (8.6)	30.1	0.71 (0.52, 0.98)	
No	77/3149 (2.4)	8.3	72/1569 (4.6)	15.7	0.53 (0.38, 0.73)	
Hospitalization for heart failure						
All patients	126/4687 (2.7)	9.4	95/2333 (4.1)	14.5	0.65 (0.50, 0.85)	
Prevalent kidney disease*						0.5780
Yes	66/1498 (4.4)	15.5	53/752 (7.0)	25.9	0.61 (0.42, 0.87)	
No	60/3149 (1.9)	6.6	42/1569 (2.7)	9.4	0.71 (0.48, 1.05)	
All-cause mortality						
All patients	269/4687 (5.7)	19.4	194/2333 (8.3)	28.6	0.68 (0.57, 0.82)	
Prevalent kidney disease*						0.2242
Yes	143/1498 (9.5)	32.5	92/752 (12.2)	42.5	0.76 (0.59, 0.99)	
No	125/3149 (4.0)	13.4	102/1569 (6.5)	22.2	0.61 (0.47, 0.79)	
All-cause hospitalization						
All patients	1725/4687 (36.8)	161.9	925/2333 (39.6)	183.3	0.89 (0.82, 0.96)	
Prevalent kidney disease*						0.1234
Yes	663/1498 (44.3)	208.4	375/752 (49.9)	258.9	0.81 (0.72, 0.92)	
No	1046/3149 (33.2)	141.8	549/1569 (35.0)	154.1	0.93 (0.84, 1.03)	



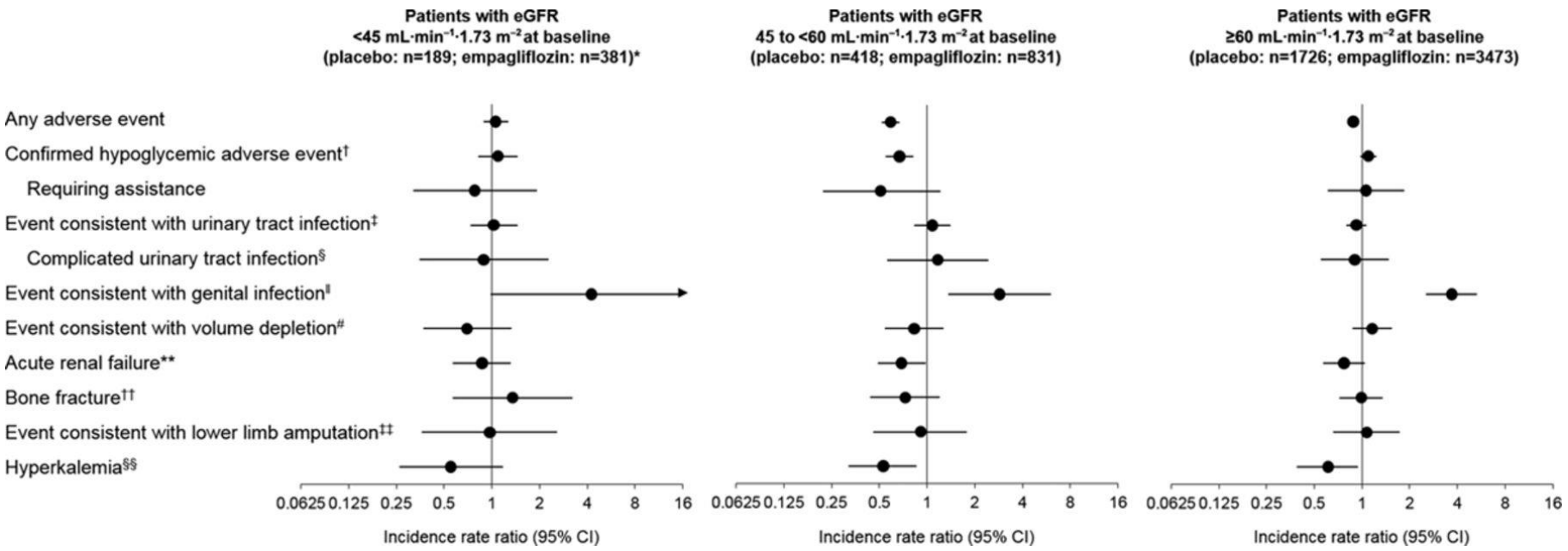
Christoph Wanner et al. Circulation. 2018;137:119-129

Time to cardiovascular death (A), all-cause mortality (B), hospitalization for heart failure (C), and all-cause hospitalization (D) with empagliflozin pooled and placebo in patients with prevalent kidney disease (estimated glomerular filtration rate<60 mL·min−1·1.73 m−2 and/or macroalbuminuria [urine albumin-creatinine ratio >300 mg/g]) at baseline.



Christoph Wanner et al. Circulation. 2018;137:119-129

Adverse events with empagliflozin pooled compared with placebo in patients with estimated glomerular filtration rate (eGFR) <45, 45 to <60, and ≥60 mL·min−1·1.73 m−2 at baseline.



Christoph Wanner et al. Circulation. 2018;137:119-129

CONCLUSIONS

- Empagliflozin safely reduced morbidity and mortality in patients with T2DM, established cardiovascular disease, and CKD.
- Despite diminishing glucose-lowering efficacy with declining renal function, improved outcomes with empagliflozin were consistent across subgroups of patients by baseline renal function

Diabetologia (2018) 61:1522–1527
https://doi.org/10.1007/s00125-018-4630-2

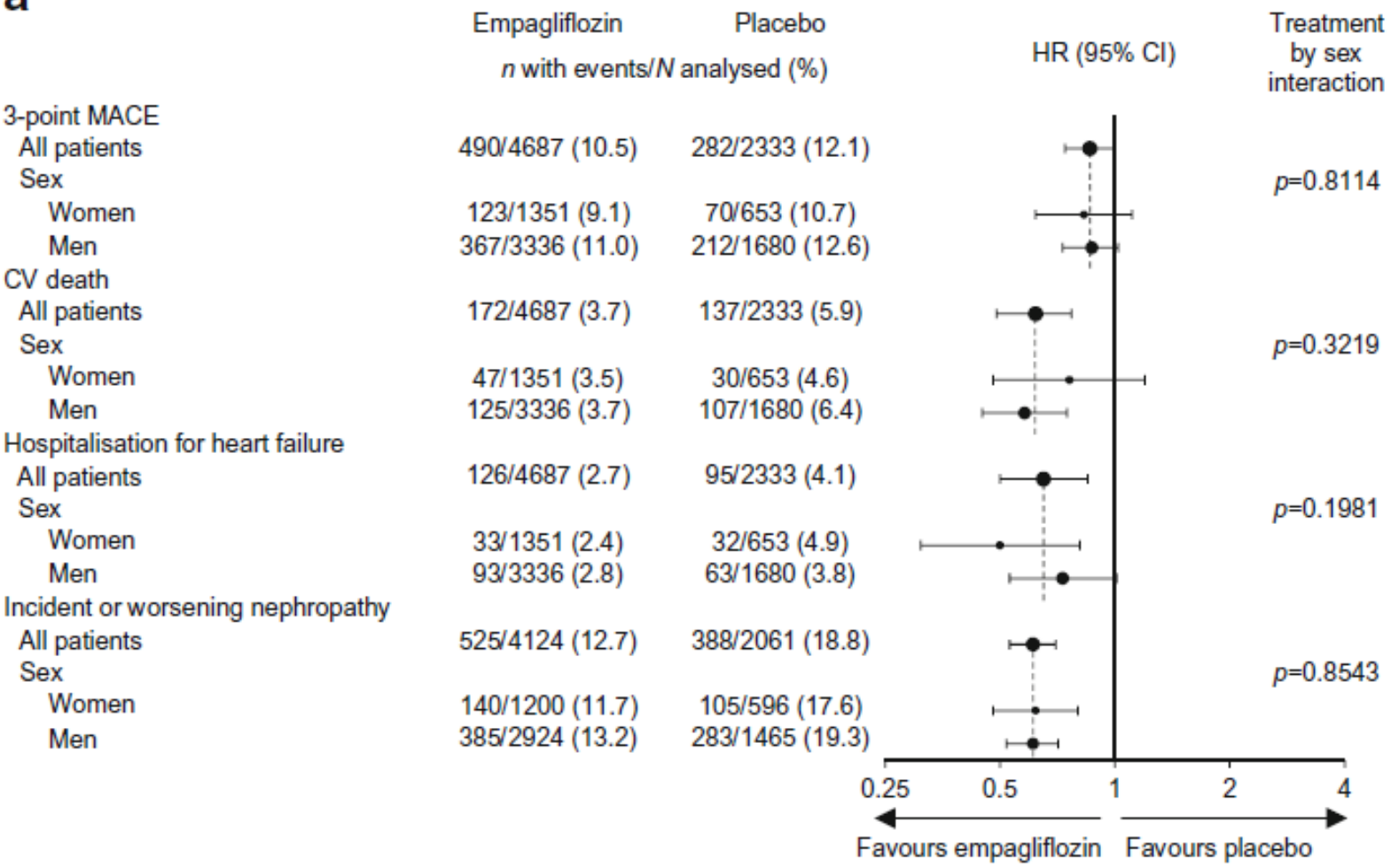
SHORT COMMUNICATION

Empagliflozin in women with type 2 diabetes and cardiovascular disease – an analysis of EMPA-REG OUTCOME®

Bernard Zinman[1] · Silvio E. Inzucchi[2] · Christoph Wanner[3] · Uwe Hehnke[4] · Jyothis T. George[4] · Odd Erik Johansen[5] · David Fitchett[6] · on behalf of the EMPA-REG OUTCOME® investigators

- **EMPAREG included 2004 women and 5026 men**

a


Empagliflozin
Placebo
n with events/N analysed (%)
HR (95% CI)
Treatment by sex interaction
3-point MACE
All patients 490/4687 (10.5) 282/2333 (12.1)
Sex
Women 123/1351 (9.1) 70/653 (10.7)
Men 367/3336 (11.0) 212/1680 (12.6)
p=0.8114
CV death
All patients 172/4687 (3.7) 137/2333 (5.9)
Sex
Women 47/1351 (3.5) 30/653 (4.6)
Men 125/3336 (3.7) 107/1680 (6.4)
p=0.3219
Hospitalisation for heart failure
All patients 126/4687 (2.7) 95/2333 (4.1)
Sex
Women 33/1351 (2.4) 32/653 (4.9)
Men 93/3336 (2.8) 63/1680 (3.8)
p=0.1981
Incident or worsening nephropathy
All patients 525/4124 (12.7) 388/2061 (18.8)
Sex
Women 140/1200 (11.7) 105/596 (17.6)
Men 385/2924 (13.2) 283/1465 (19.3)
p=0.8543
0.25
0.5
1
2
4
Favours empagliflozin
Favours placebo

Original Article

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D., Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D., Ngozi Erondu, M.D., Ph.D., Wayne Shaw, D.S.L., Gordon Law, Ph.D., Mehul Desai, M.D., David R. Matthews, D.Phil., B.M., B.Ch., for the CANVAS Program Collaborative Group

N Engl J Med
Volume 377(7):644-657
August 17, 2017

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Study Overview

- In this report of two randomized trials, patients with type 2 diabetes at risk for cardiovascular disease received the sodium–glucose cotransporter 2 inhibitor canagliflozin or placebo and were followed for 188 weeks.
- Baseline HBA1C in both groups was 8.2%.
- Canagliflozin reduced the risk of cardiovascular events.

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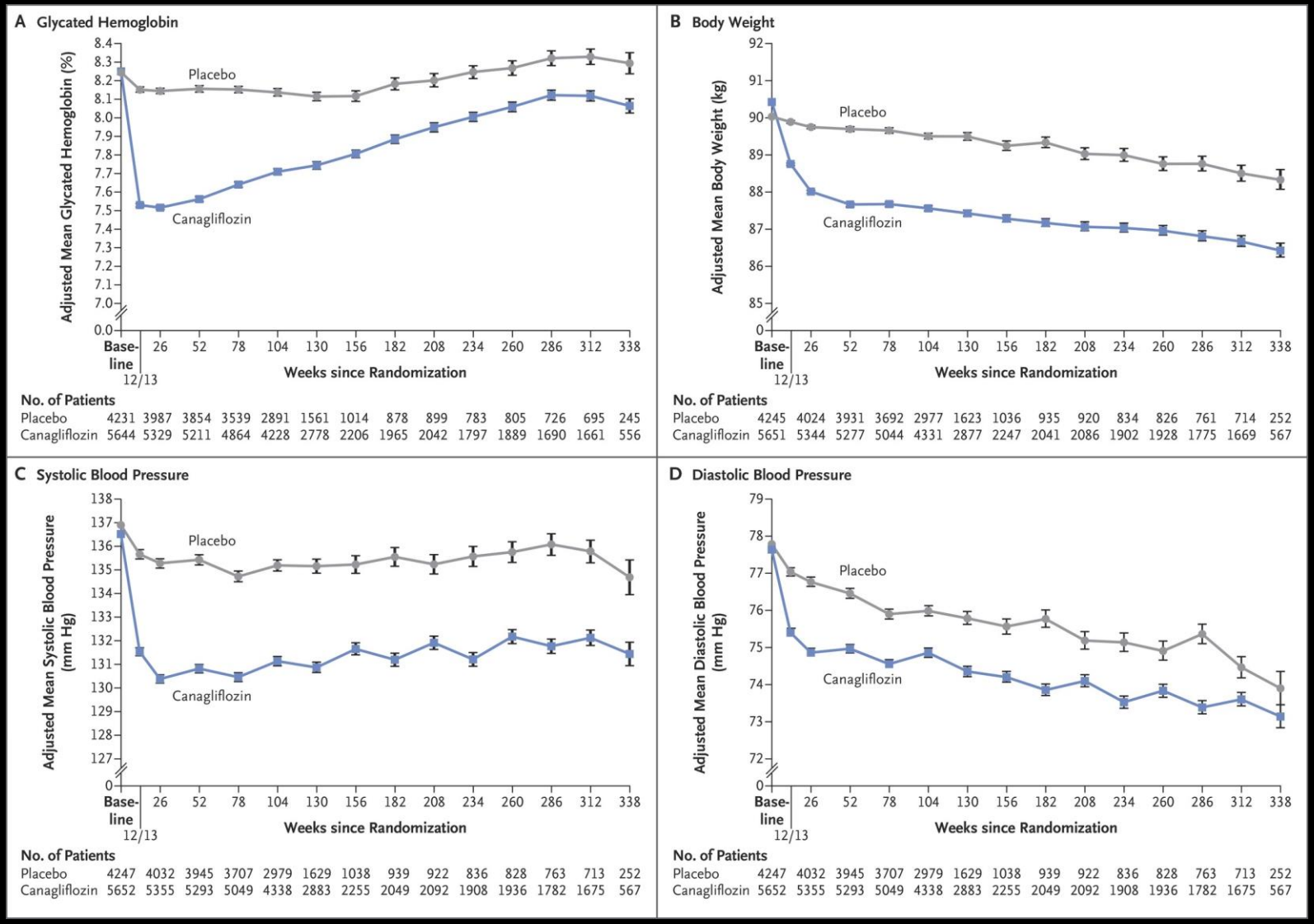
Effects of Canagliflozin on Glycated Hemoglobin Level, Body Weight, and Systolic and Diastolic Blood Pressure in the Integrated CANVAS Program.



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

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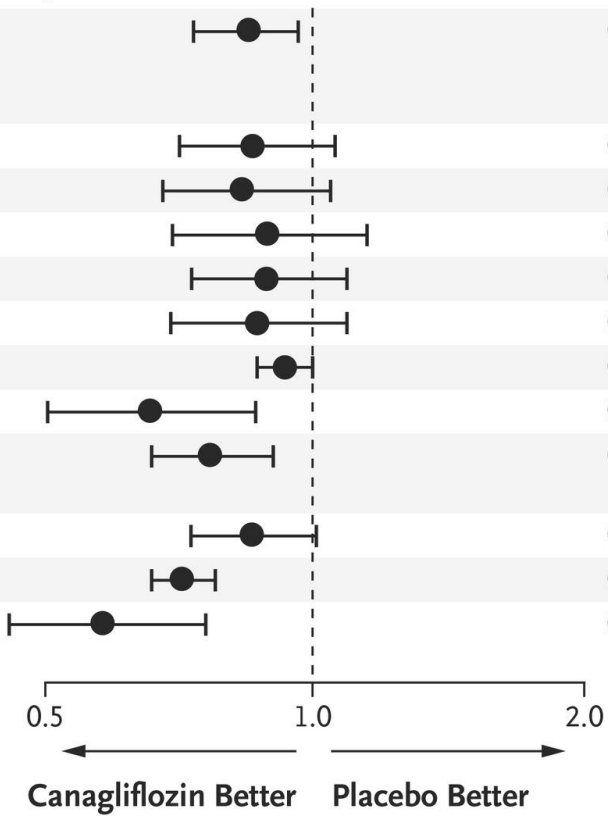
Effects of Canagliflozin on Cardiovascular, Renal, Hospitalization, and Death Events in the Integrated CANVAS Program.

Outcome	Canagliflozin (N=5795)	Placebo (N=4347)	Hazard Ratio (95% CI)
	no. of participants per 1000 patient-yr		
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	26.9	31.5	0.86 (0.75–0.97)
Death from cardiovascular causes	11.6	12.8	0.87 (0.72–1.06)
Nonfatal myocardial infarction	9.7	11.6	0.85 (0.69–1.05)
Nonfatal stroke	7.1	8.4	0.90 (0.71–1.15)
Fatal or nonfatal myocardial infarction	11.2	12.6	0.89 (0.73–1.09)
Fatal or nonfatal stroke	7.9	9.6	0.87 (0.69–1.09)
Hospitalization for any cause	118.7	131.1	0.94 (0.88–1.00)
Hospitalization for heart failure	5.5	8.7	0.67 (0.52–0.87)
Death from cardiovascular causes or hospitalization for heart failure	16.3	20.8	0.78 (0.67–0.91)
Death from any cause	17.3	19.5	0.87 (0.74–1.01)
Progression of albuminuria	89.4	128.7	0.73 (0.67–0.79)
40% reduction in eGFR, renal-replacement therapy, or renal death	5.5	9.0	0.60 (0.47–0.77)



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

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Adverse Events.

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

* Analyses were performed on data from the on-treatment data set (patients who had a safety outcome while they were receiving canagliflozin or placebo or within 30 days after discontinuation of the drug or placebo), except for fracture, amputation, cancer, and diabetic ketoacidosis outcomes, which included all events at any time point in all patients who underwent randomization and received at least one dose of canagliflozin or placebo.
† P values were estimated from Cox regression models.
‡ Low-trauma fracture was the prespecified primary fracture outcome, and all fracture was a secondary outcome.
§ Infection of male genitalia included balanitis, phimosis, and events leading to circumcision.
¶ For these adverse events, the annualized incidence rates are reported with data from CANVAS alone through January 7, 2014, because after this time, only serious adverse events or adverse events leading to discontinuation were collected. In CANVAS-R, only serious adverse events or adverse events leading to discontinuation were collected. Owing to the differences between the two trials in methods of collection of the data, an integrated analysis of these adverse events is not possible.

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

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Conclusions

- In two trials involving patients with type 2 diabetes and an elevated risk of cardiovascular disease, patients treated with canagliflozin had a lower risk of cardiovascular events than those who received placebo but a greater risk of amputation, primarily at the level of the toe or metatarsal.

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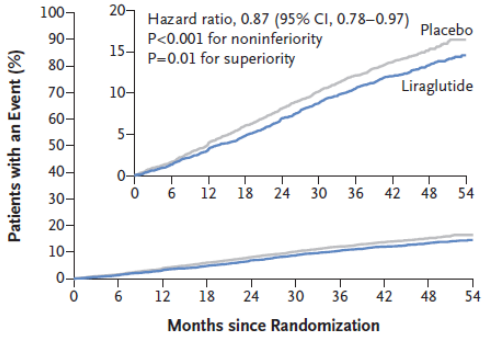
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 28, 2016 VOL. 375 NO. 4

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

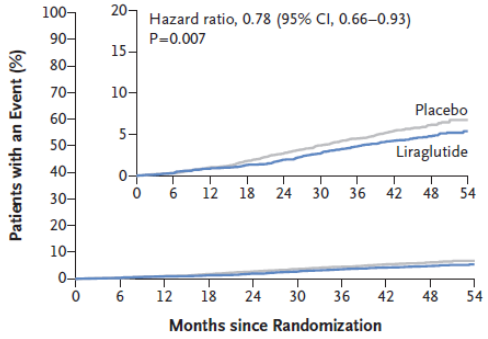
Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*

A Primary Outcome



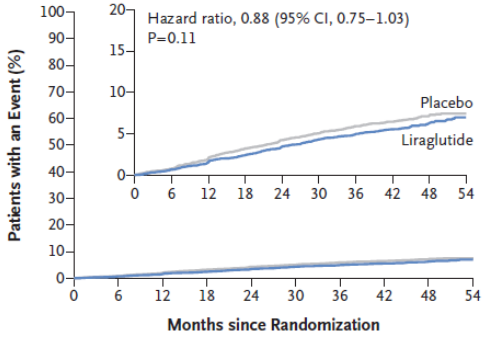
No. at Risk										
Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

B Death from Cardiovascular Causes



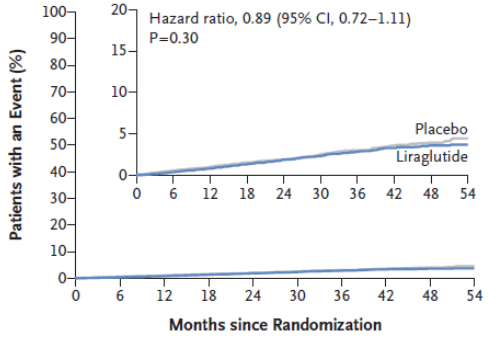
No. at Risk										
Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4267	1709	465

C Nonfatal Myocardial Infarction



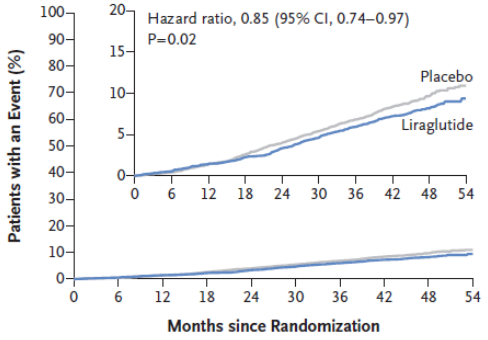
No. at Risk										
Liraglutide	4668	4609	4531	4454	4359	4263	4181	4102	1619	440
Placebo	4672	4613	4513	4407	4301	4202	4103	4020	1594	424

D Nonfatal Stroke



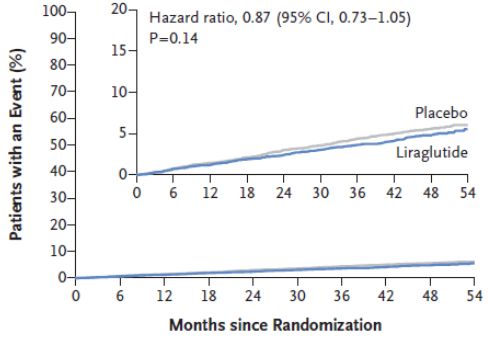
No. at Risk										
Liraglutide	4668	4624	4564	4504	4426	4351	4269	4194	1662	465
Placebo	4672	4622	4558	4484	4405	4314	4228	4141	1648	445

E Death from Any Cause



No. at Risk										
Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4268	1709	465

F Hospitalization for Heart Failure



No. at Risk										
Liraglutide	4668	4612	4550	4483	4414	4337	4258	4185	1662	467
Placebo	4672	4612	4540	4464	4372	4288	4187	4107	1647	442

לסיכום

- בחירת הטיפול לסכרת בחולים עם מחלה קרדיו וסקולרית צריכה לקחת בחשבון גם את התוצאות הקרדיו וסקולריות של הטיפול.
- Empagliflozine מוריד משמעותית את התמותה הכוללת, את התמותה הקרדיו וסקולרית ואת שיעור החמרת אי ספיקת הלב והחמרת התפקוד הכלייתי.
- גם ל GLP1 analogues ישנן תוצאות טובות אם כי לא הוכחה השפעה מובהקת על אי ספיקת הלב והתרופות ניתנות בזריקה.
- יש לשקול שימוש ב empagliflozine כקו שני אחרי מטפורמין בחולים שהפינוי הכלייתי שלהם הוא 30 מ"ל/דקה לפחות.

Management of diabetes (2)

Recommendations	Class	Level
Metformin is recommended as first-line therapy, if tolerated and not contra-indicated, following evaluation of renal function.	I	B
Avoidance of hypoglycaemia and excessive weight gain should be considered and individual approaches (with respect to both treatment targets and drug choices) should be considered in patients with advanced disease.	IIa	B
In patients with type 2 DM and CVD, the use of an SGLT2 inhibitor should be considered early in the course of the disease to reduce CV and total mortality.	IIa	B
Lipid lowering agents (principally statins) are recommended to reduce CV risk in all patients with type 2 or type 1 DM above the age of 40 years.	I	A
Lipid lowering agents (principally statins) may be considered also in individuals below 40 years of age if at significantly elevated risk, based on the presence of micro-vascular complications or of multiple CV risk factors.	IIb	A

European Heart Journal 2016;37:2315–2381-doi:10.1093/eurheartj/ehw106

תודה רבה!