SGLT2'S: Diabetes and Beyond

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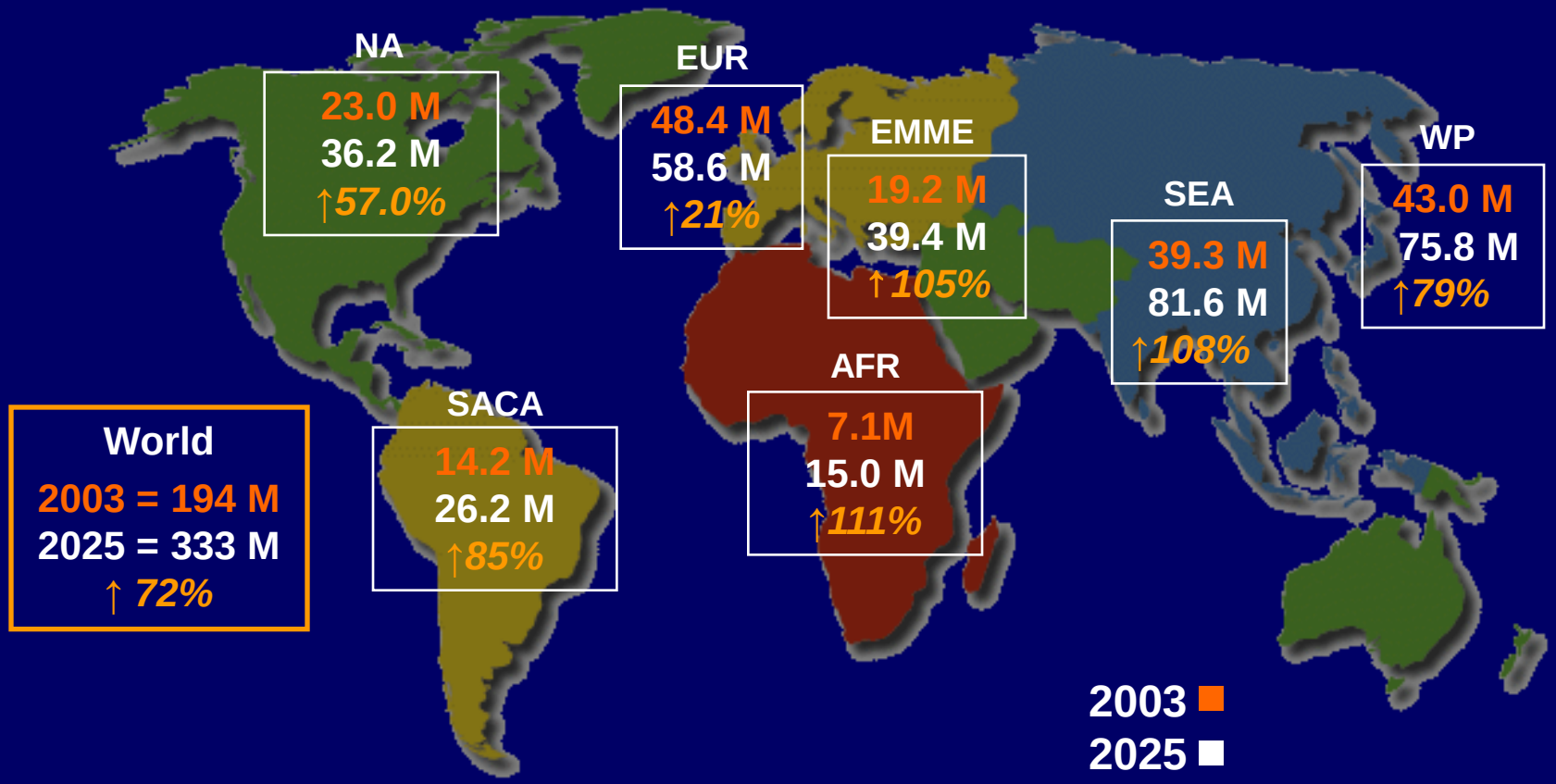
Grand Rounds

Boca Raton Regional Hospital

September 24th 2019

Global Projections for the Diabetes Epidemic: 2003-2025



M = million, AFR = Africa, NA = North America, EUR = Europe,
SACA = South and Central America, EMME = Eastern Mediterranean and Middle East,
SEA = South-East Asia, WP = Western Pacific

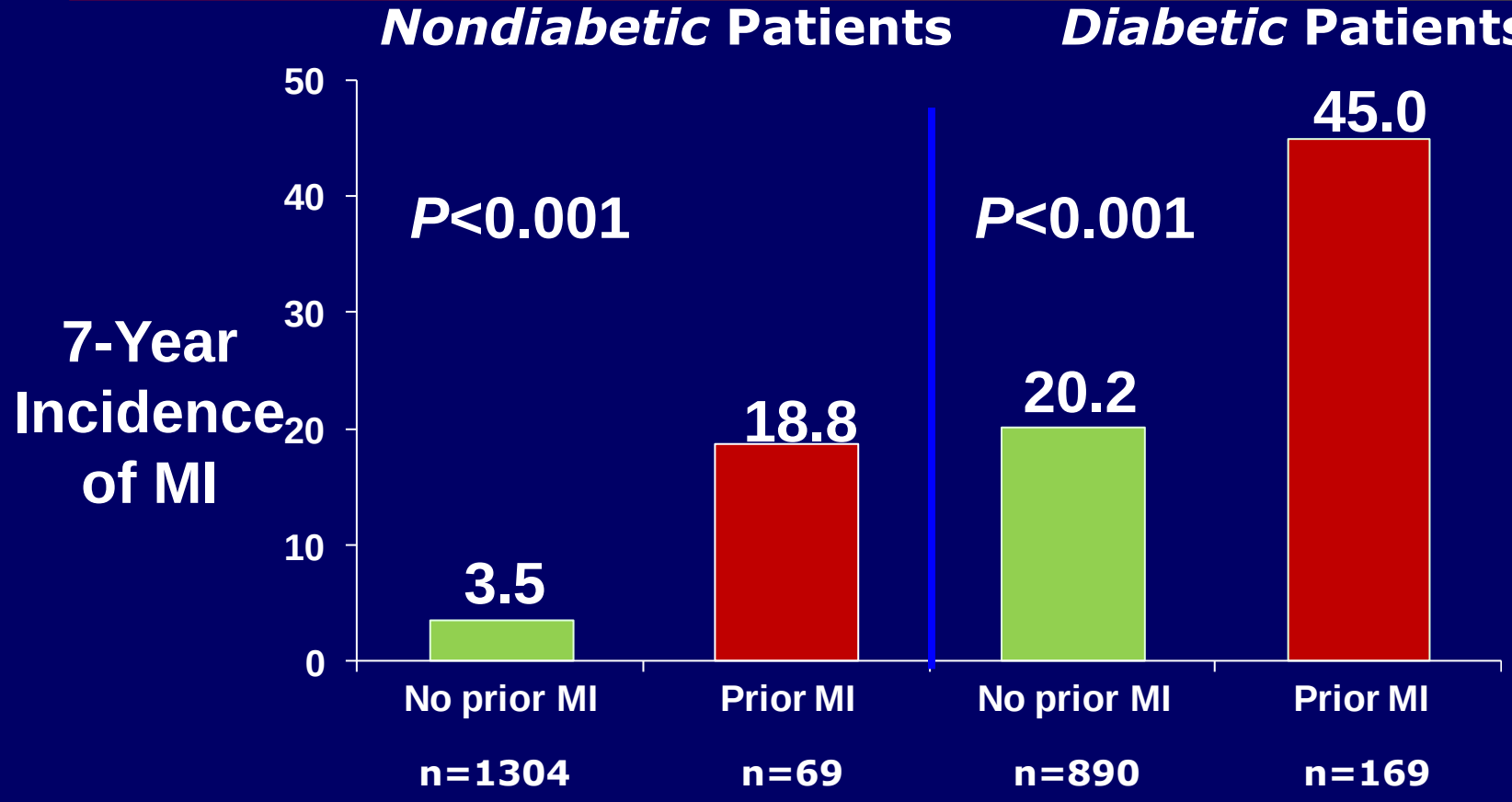
Diabetes Atlas Committee. *Diabetes Atlas 2nd Edition:* IDF 2003.

In a Single Year in the United States…

- 86,000 amputations are performed because of diabetes
- 12,000-24,000 people lose their eyesight from diabetes
- 41,000 people begin treatment for end-stage kidney disease
- 213,000 people die from diabetes and its complications

American Diabetes Association. National Diabetes Fact Sheet. Available at http://www.diabetes.org/diabetes-statistics. Accessed April 29, 2005.

Diabetes = CVD Risk



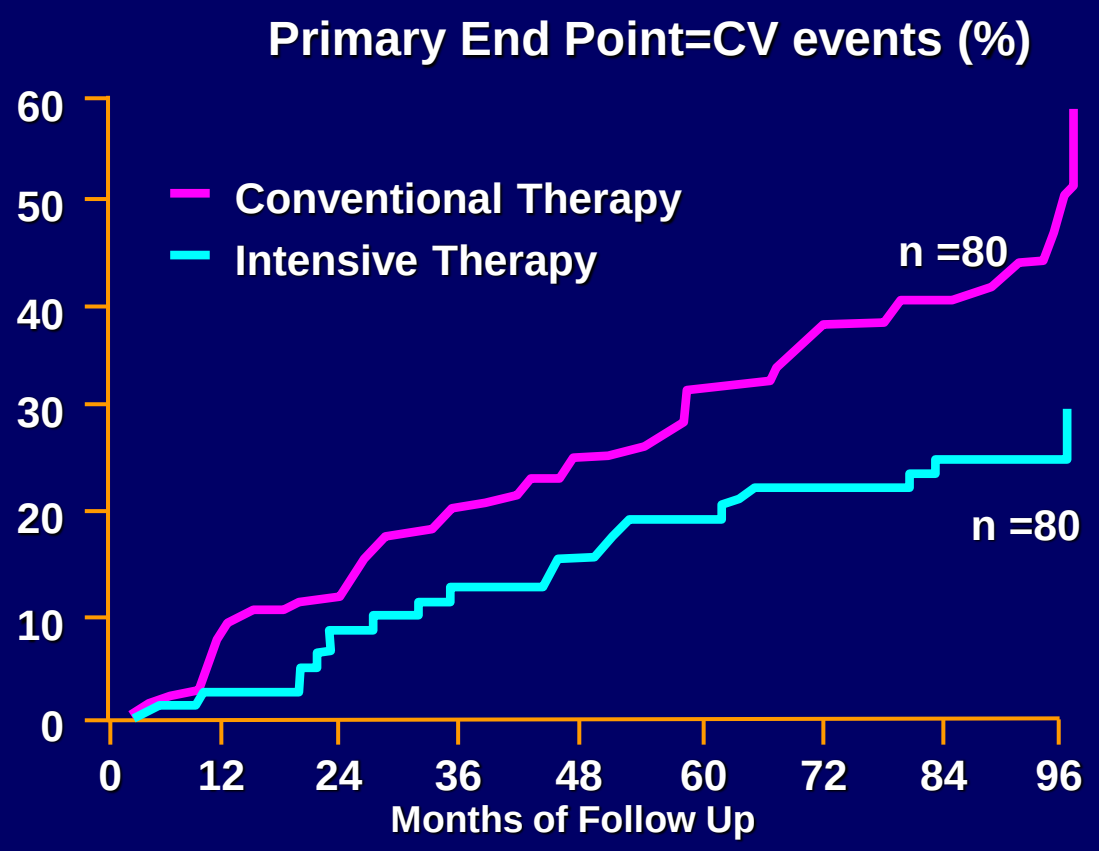
More recent studies suggest that this is perhaps only true for those with fairly long-standing diabetes – duration over ten years.

Haffner SM et al. *N Engl J Med.* 1998;339:229; *Arch Intern Med.* 2011;171:404.

Benefit of Comprehensive, Intensive Management: STENO 2 Study

Treatment Goals:

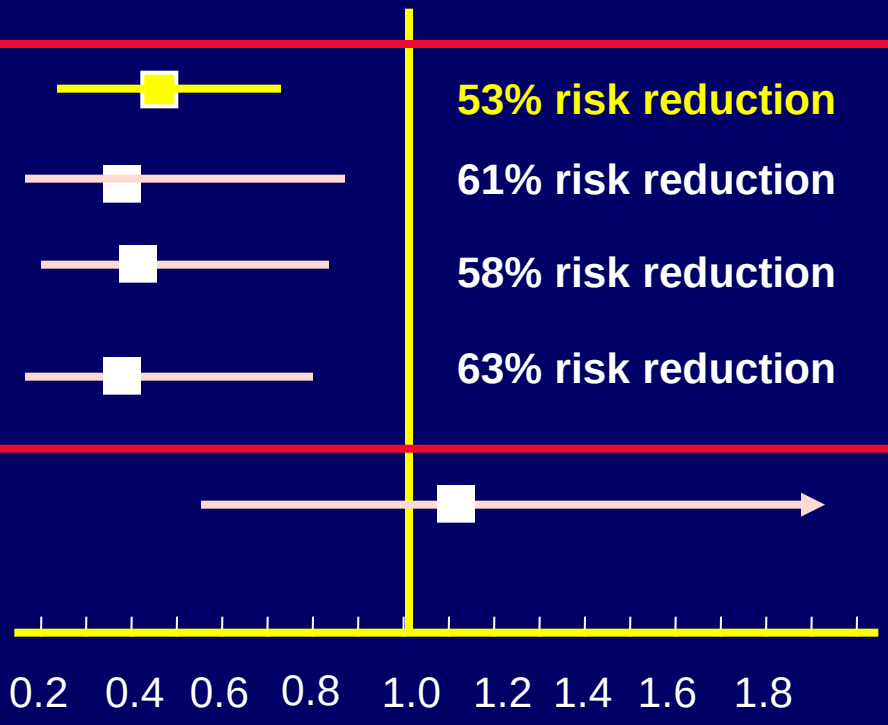
- Intensive TLC
- HgbA1c <6.5%
- Cholesterol <175
- Triglycerides <150
- BP <130/80



Gaede, P. et al, NEJM 2003;348:390-393

Main Results Steno – 2 Study

Complication	Risk ratio (95% CI)	p value	
1° Endpoint	0.47 (0.24 – 0.73)	0.008	**53% risk reduction**
Nephropathy	0.39 (0.17 – 0.87)	0.003	**61% risk reduction**
Retinopathy	0.42 (0.21 – 0.86)	0.02	**58% risk reduction**
Autonomic neuropathy	0.37 (0.18 – 0.79)	0.002	**63% risk reduction**
Peripheral neuropathy	1.09 (0.54 – 2.22	0.66	

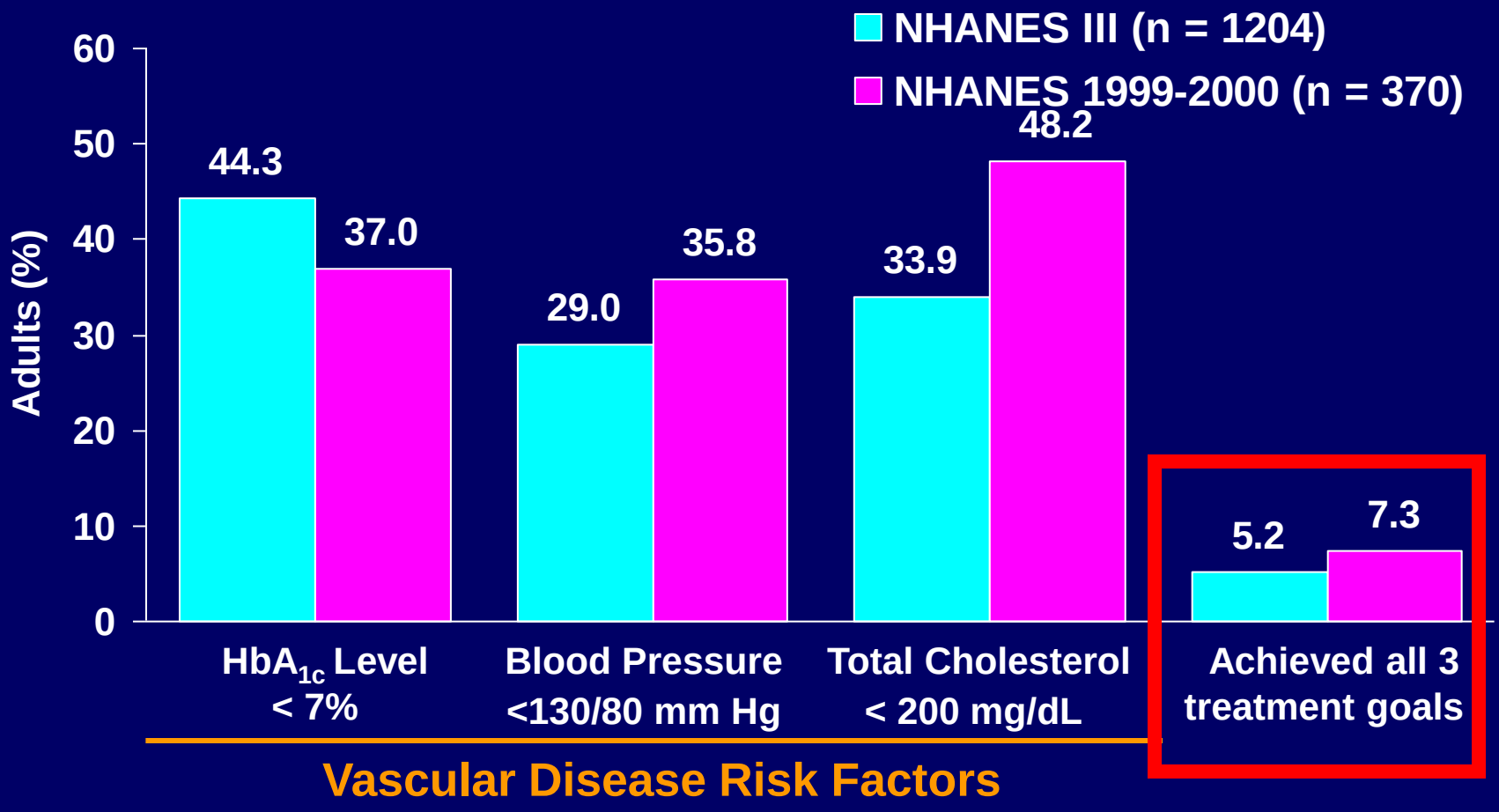


1° endpoint: CVD death, non-fatal MI, CABG, PTCA, non-fatal stroke, amputation, any bypass

Gaede P et al. *NEJM* 348:5, 2003. Leiter LA. Diabetes Res. Clin Practice. The role for lipid lowering for microvascular complications.

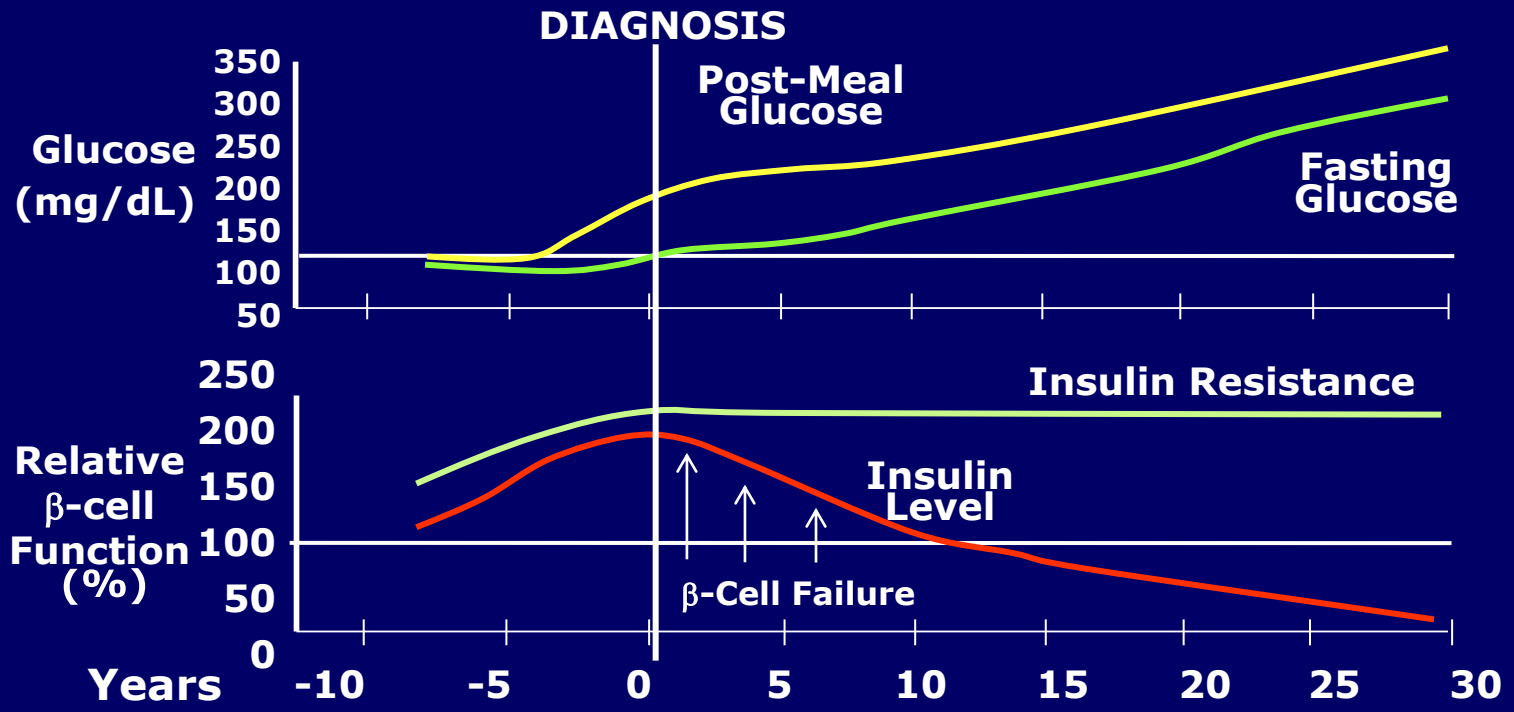
Reaching Goal of CV Risk Factor Levels Among Adults With Diagnosed Diabetes

Fewer than half of the adults with diabetes achieve treatment goals for CV risk factors



Saydah et al. *JAMA.* 2004;291:335-342.

Natural Progression of Type 2 Diabetes

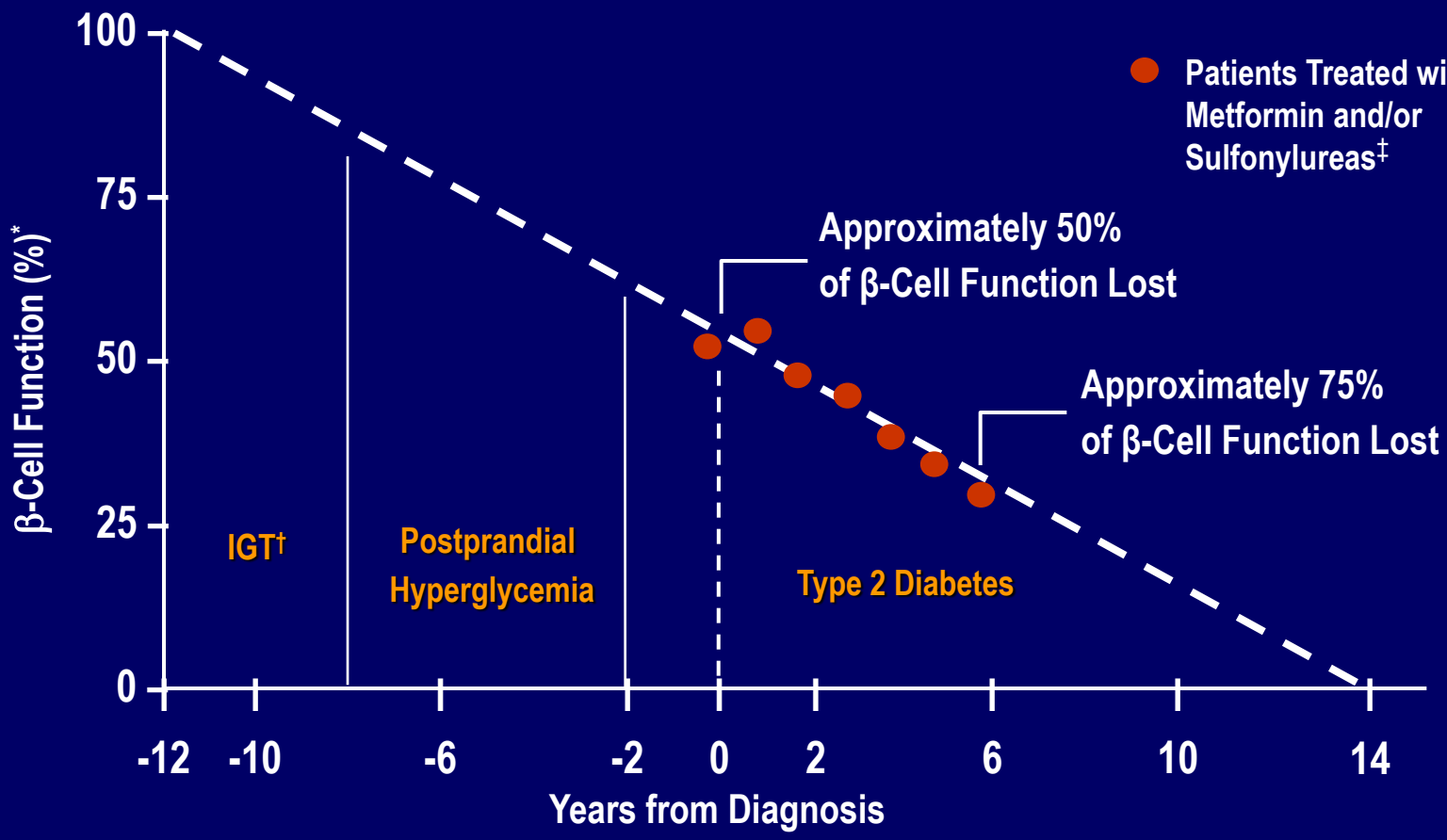


Adapted from *Type 2 Diabetes BASICS*. Minneapolis, Minn: International Diabetes Center; 2000.

Mermaid in Copenhagen where NPH Insulin was invented by Hans Christian Hagedorn

"Neutral Protamine Hagedorn"

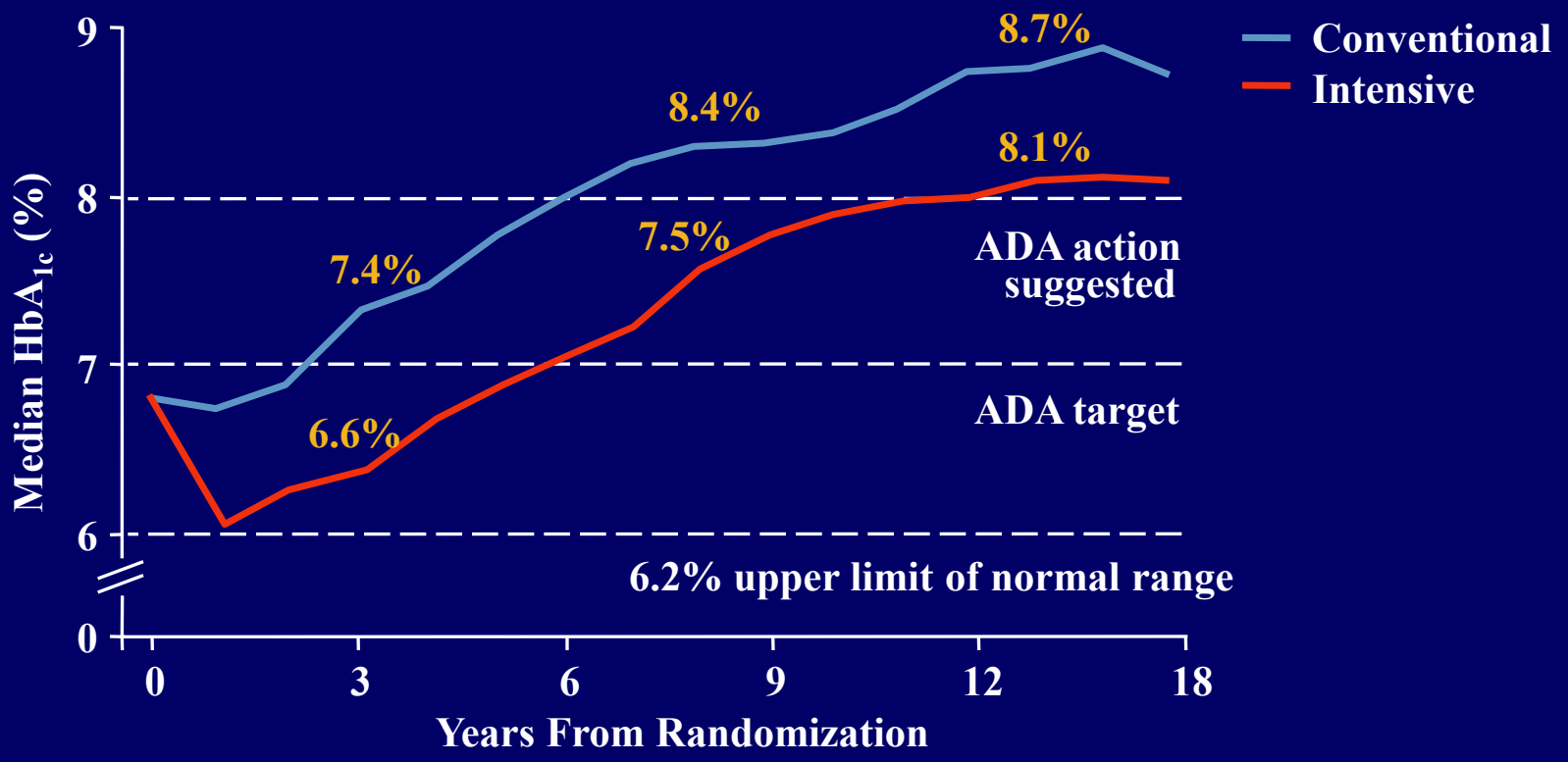
β-Cell Function Declines Over Time



*Dashed line shows extrapolation backward from year 0 and forward from year 6 from diagnosis based on Homeostasis Model Assessment (HOMA) data from UKPDS. †IGT = impaired glucose tolerance. ‡The data points for the time of diagnosis (0) and the subsequent 6 years are taken from the obese subset of the UKPDS population and were determined by the HOMA model.

Adapted from Lebovitz HE. *Diabetes Rev.* 1999;7:139-153.

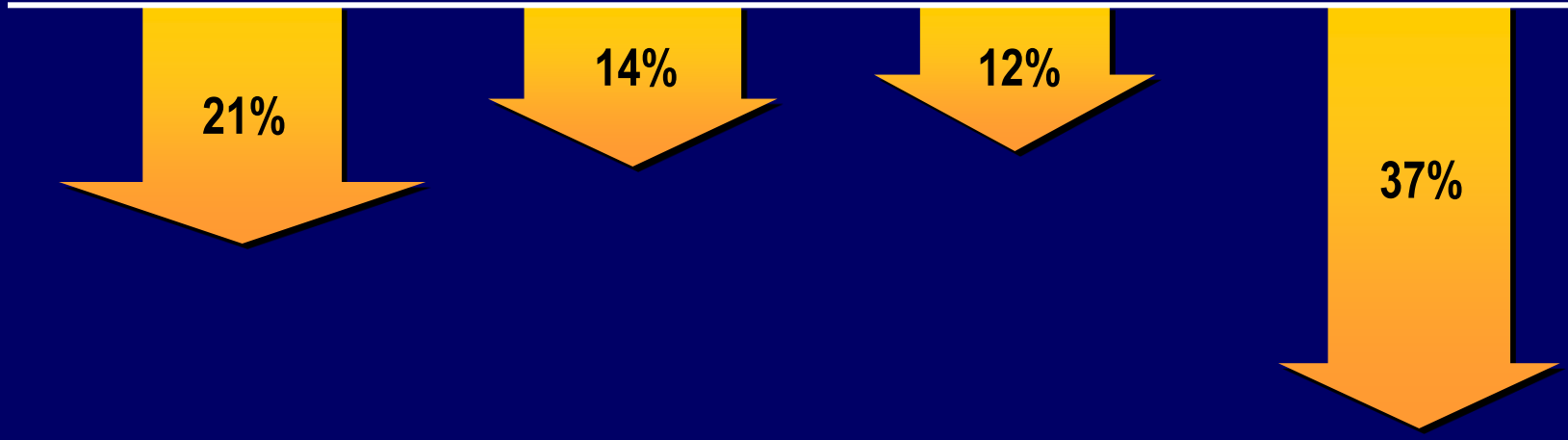
HbA_{1c} in the UKPDS



Adapted from UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352:837-853.

The Need for Tight Glycemic Control

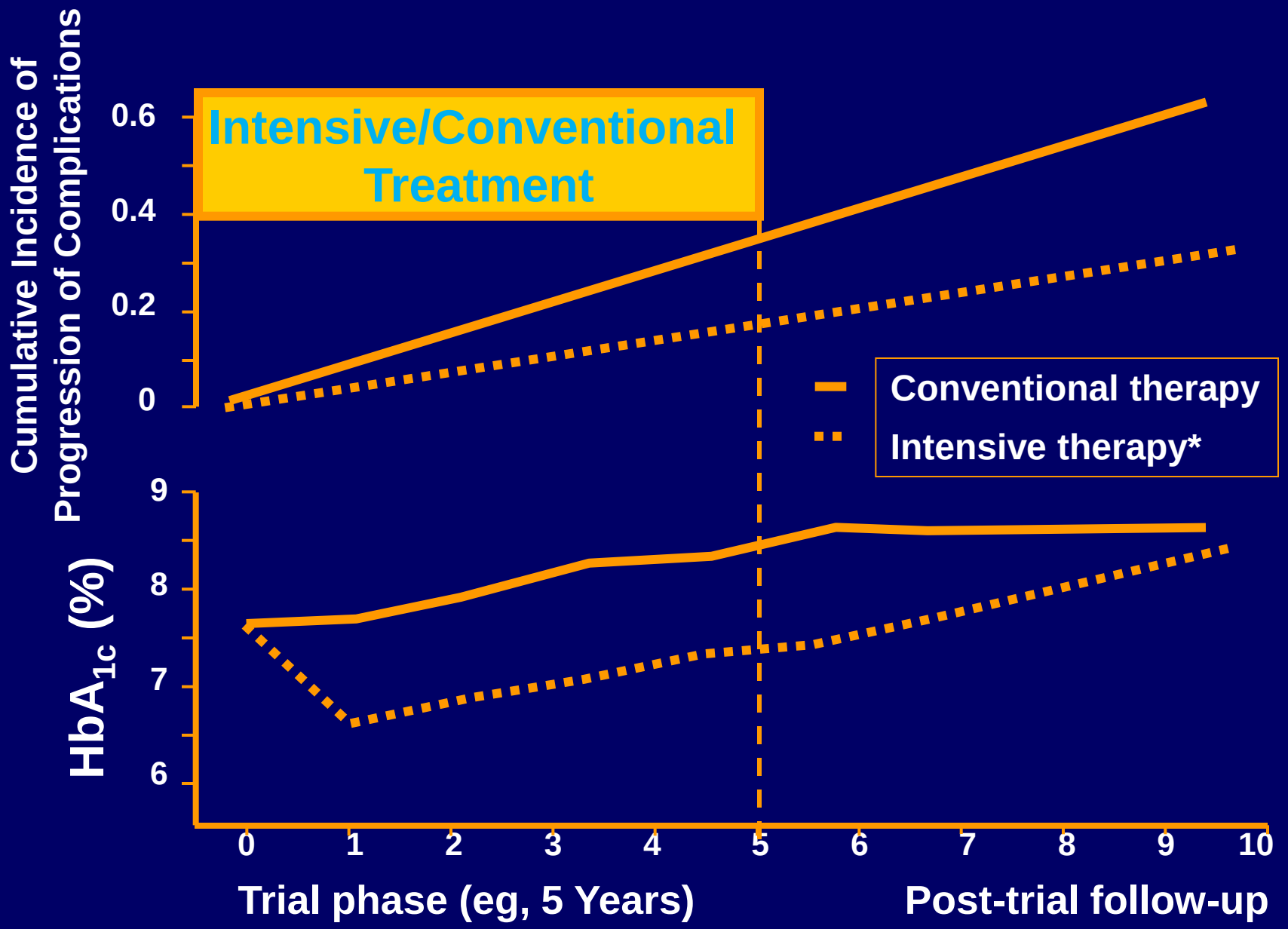
According to the United Kingdom Prospective Diabetes Study (UKPDS) 35, Every 1% Decrease in A1C Resulted in:



- Decrease in risk of any diabetes-related end point (*P*<.0001)
- Decrease in risk of MI (*P*<.0001)
- Decrease in risk of stroke (*P*=.04)
- Decrease in risk of microvascular complications (*P*<.0001)

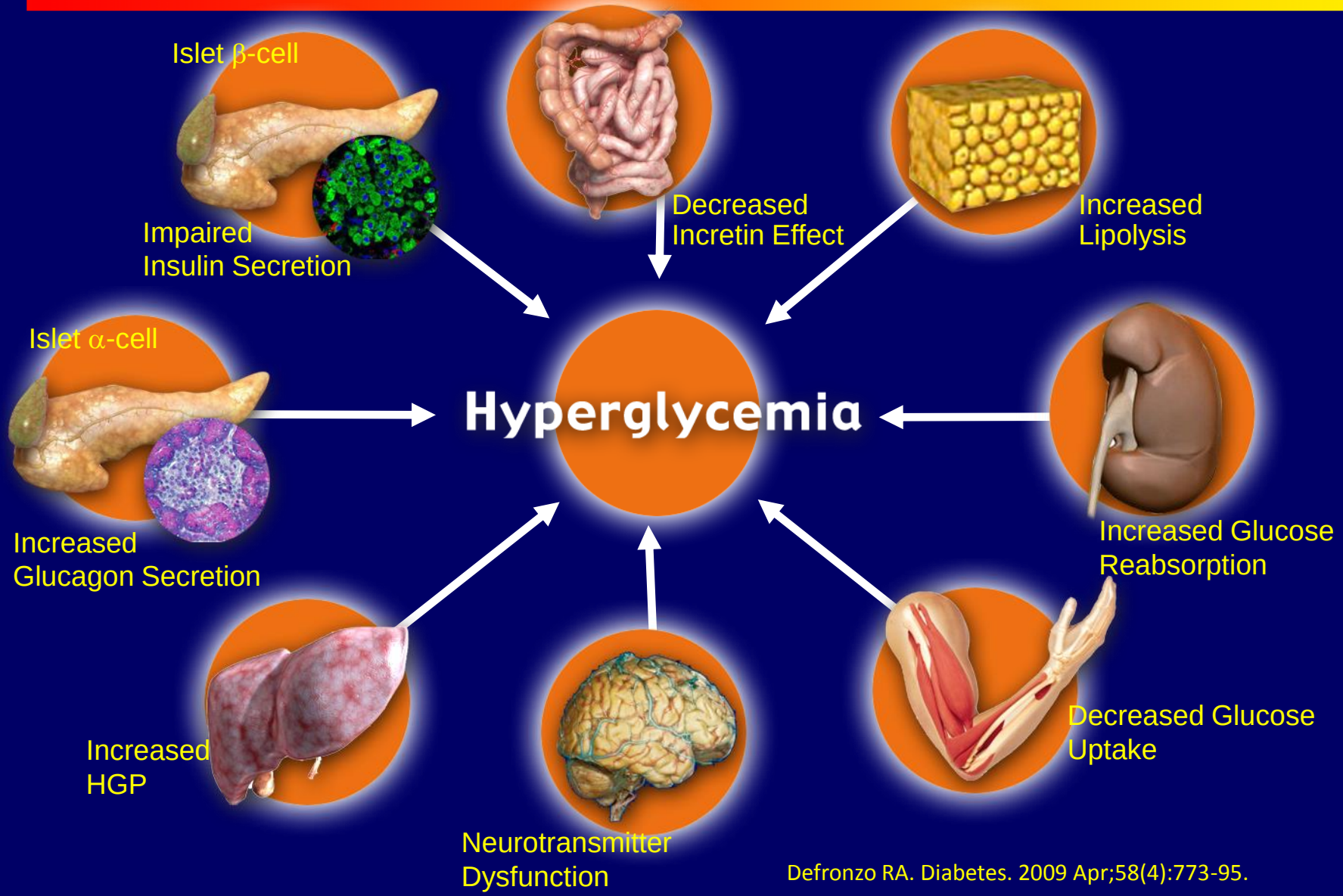
United Kingdom Prospective Diabetes Study. Stratton IM et al. *BMJ.* 2000;321:405-412.

Metabolic Memory Counts



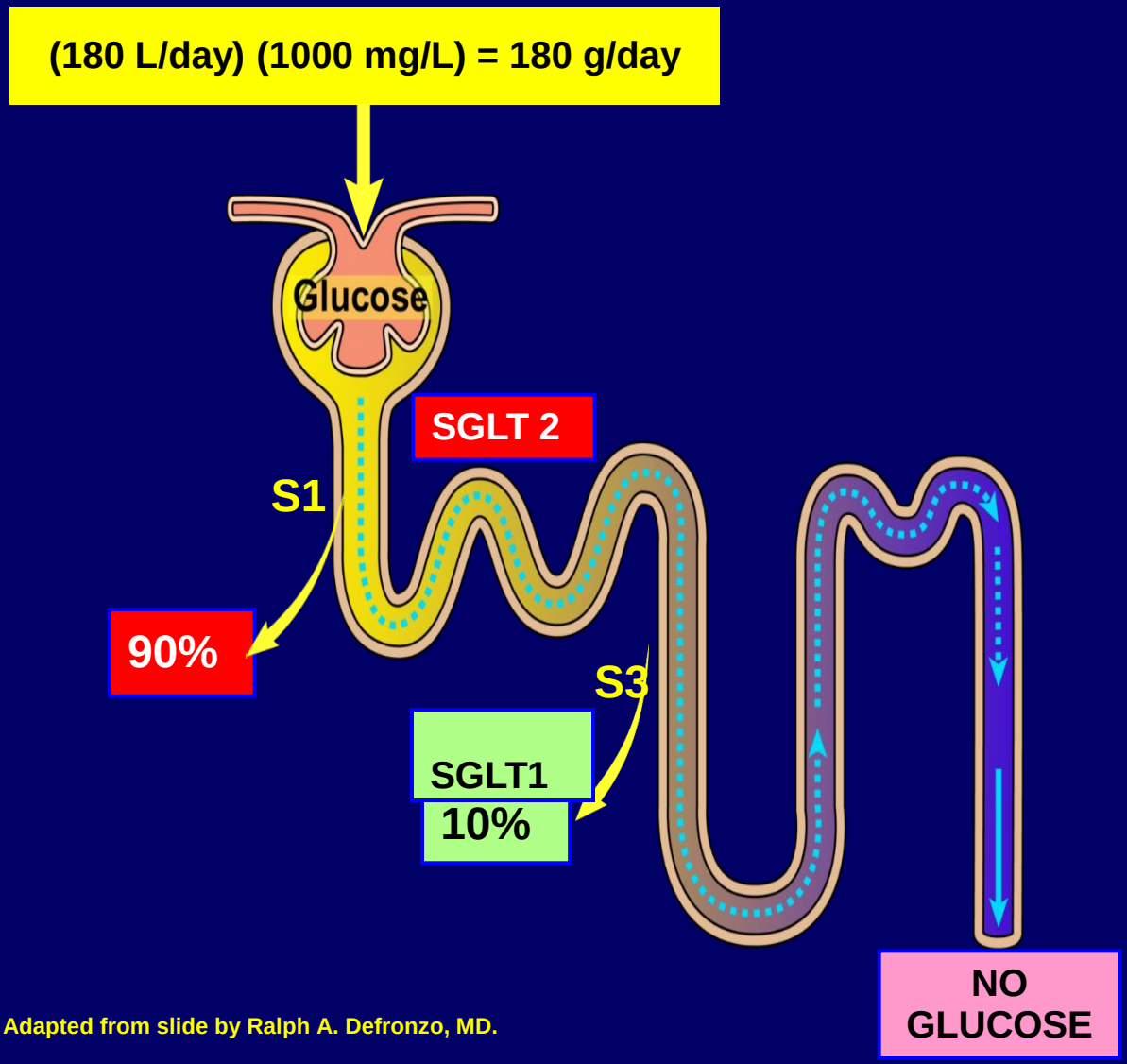
Leroith, Fonseca, Al Vinik JDiabetes, Metab Res Rev, 2005: 21, 85-90,

Main Pathophysiological Defects in T2DM
"The Ominous Octet"



Defronzo RA. Diabetes. 2009 Apr;58(4):773-95.

Renal Handling of Glucose



Adapted from slide by Ralph A. Defronzo, MD.

Summary of Observed Efficacy of SGLT2 Inhibitors

- Similar to other oral antihyperglycemic agents in A1C reduction
  - Reduces both FPG and PPG
  - Certainly equivalent efficacy to metformin, sulfonylurea and DPP-4 inhibitors
- Modest weight loss
  - ~3 kg at 26 weeks vs placebo; slightly greater weight loss at 52 weeks
- Modest blood pressure reduction
  - 2-7 mm Hg vs placebo
- No intrinsic increased risk of hypoglycemia

Hasan FM, Alsahli M, Gerich JE. Diabetes Res Clin Pract. 2014 Jun;104(3):297-322. Tahrani AA, Barnett AH, Bailey CJ. Lancet Diabetes Endocrinol. 2013 Oct;1(2):140-51.

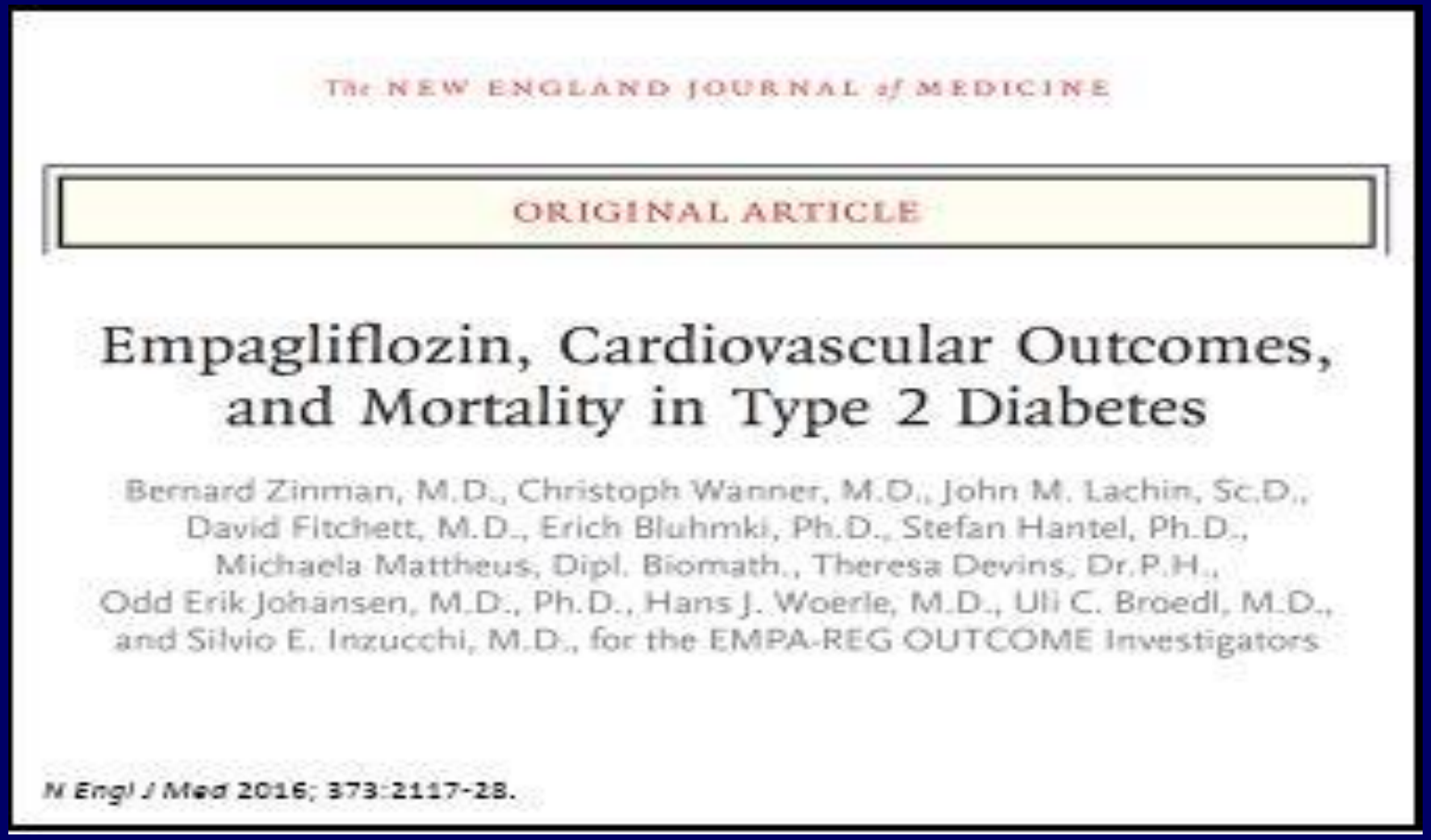
Safety Concerns Raised with SGLT2 inhibitors

	Cana-gliflozin	Dapa-gliflozin	Empa-gliflozin
Hypotension	C	D	E
Ketoacidosis	C	D	E
Acute kidney injury	C	D	-
Impairment of renal function	-	-	E
Hyperkalemia	C	-	-
Urosepsis	C	D	E
Hypoglycemia	C	D	E
Genital mycotic infection	C	D	E
Bone fractures	C	?	-
Increased LDL	C	D	E
Amputations*	?	-	-
Bladder cancer	-	D	-
Macrovascular outcomes	-	?	?

Package inserts; *http://www.fda.gov/Drugs/DrugSafety/ucm500965.htm;

Timeline of Major SGLT2 Inhibitor Trials

EMPA-REG (empagliflozin)



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

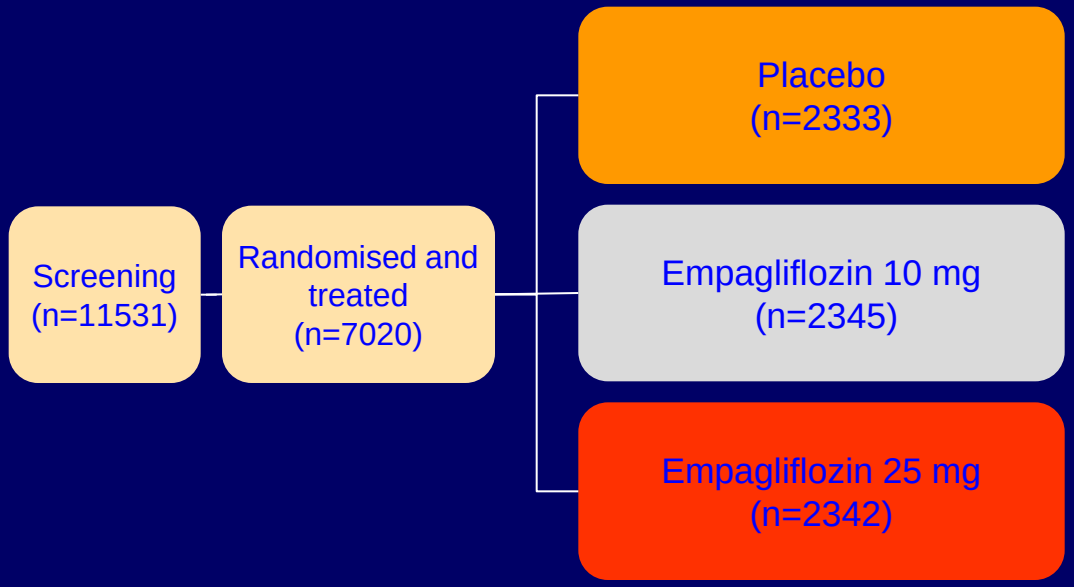
Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

N Engl J Med 2016; 373:2117-28.

Primary outcome: 3-point MACE = Nonfatal stroke, Nonfatal myocardial infarction, and Cardiovascular death

Zinman B, et al. *N Engl J Med.* 2015. 373(22):2117-28.

EMPA-REG (empagliflozin) Randomization



Study medication was given in addition to standard of care

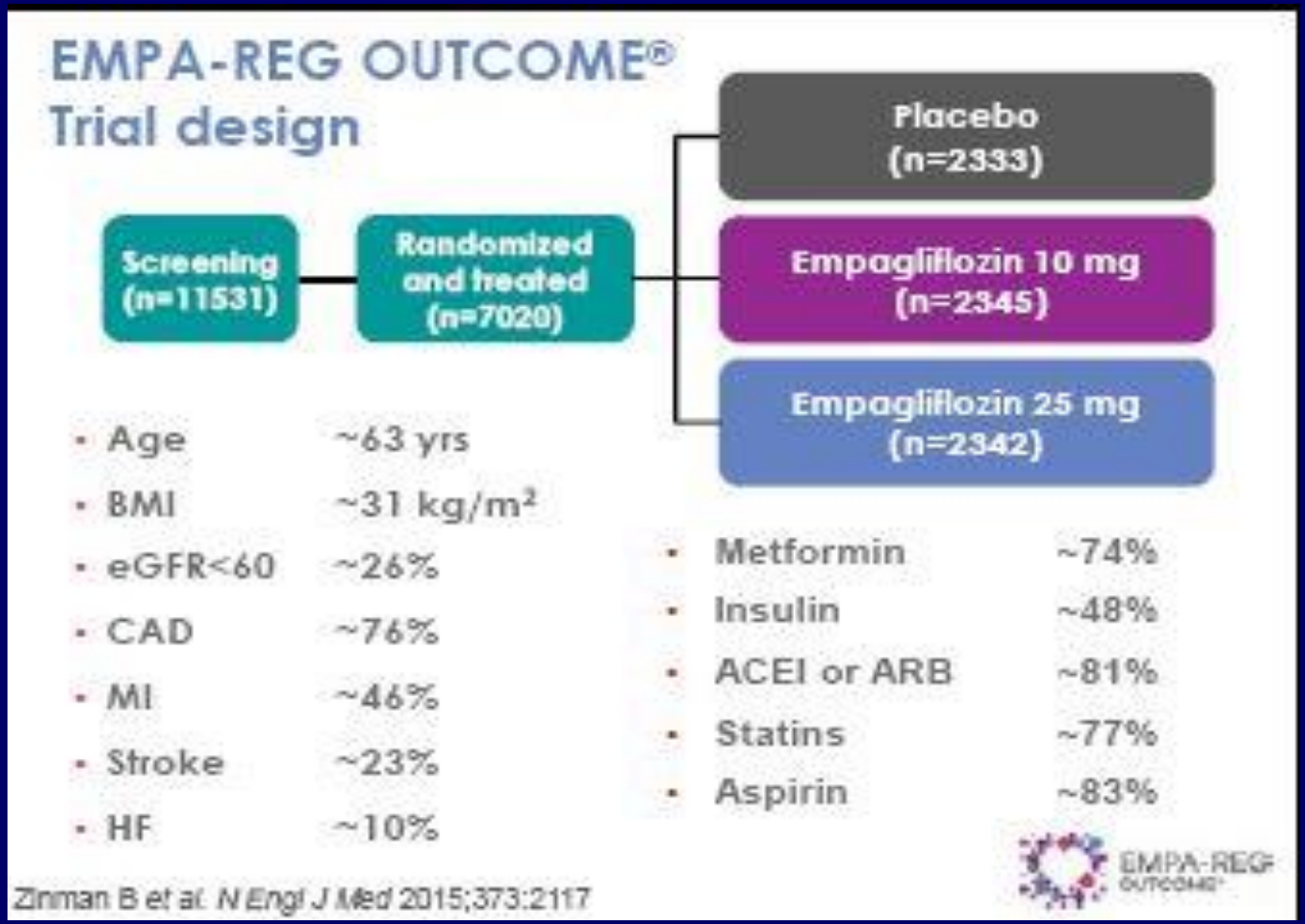
- Glucose-lowering therapy was to remain unchanged for first 12 weeks

Treatment assignment double masked

The trial was to continue until at least 691 patients experienced an adjudicated primary outcome event

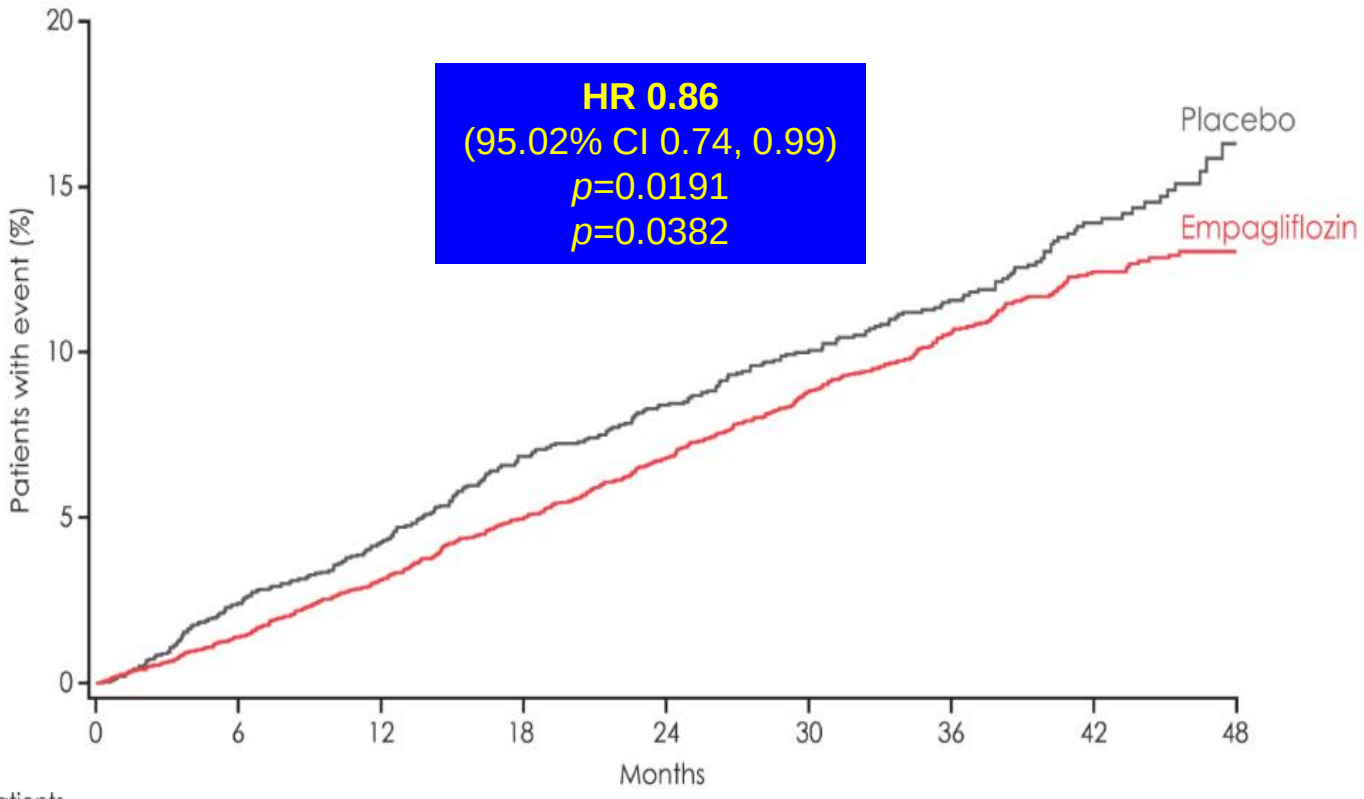
Zinman B, et al. *N Engl J Med.* 2015. 373(22):2117-28.

EMPA-REG Baseline Demographics



Zinman B, et al. *N Engl J Med.* 2015. 373(22):2117-28.

EMPA-REG (empagliflozin)
Primary outcome: 3-point MACE



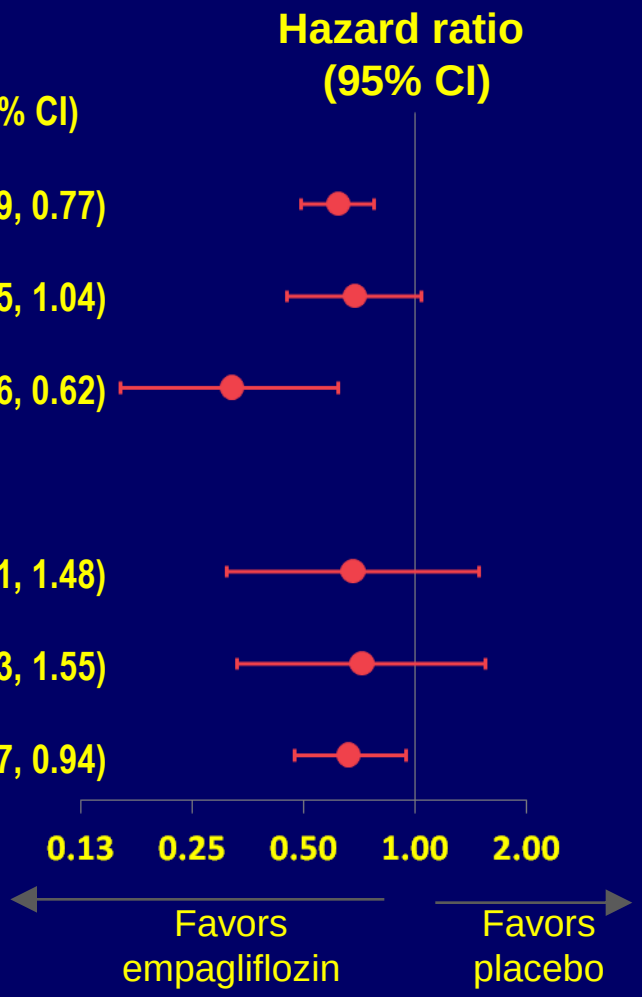
No. of patients									
Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

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)

Zinman B, et al. *N Engl J Med.* 2015. 373(22):2117-28.

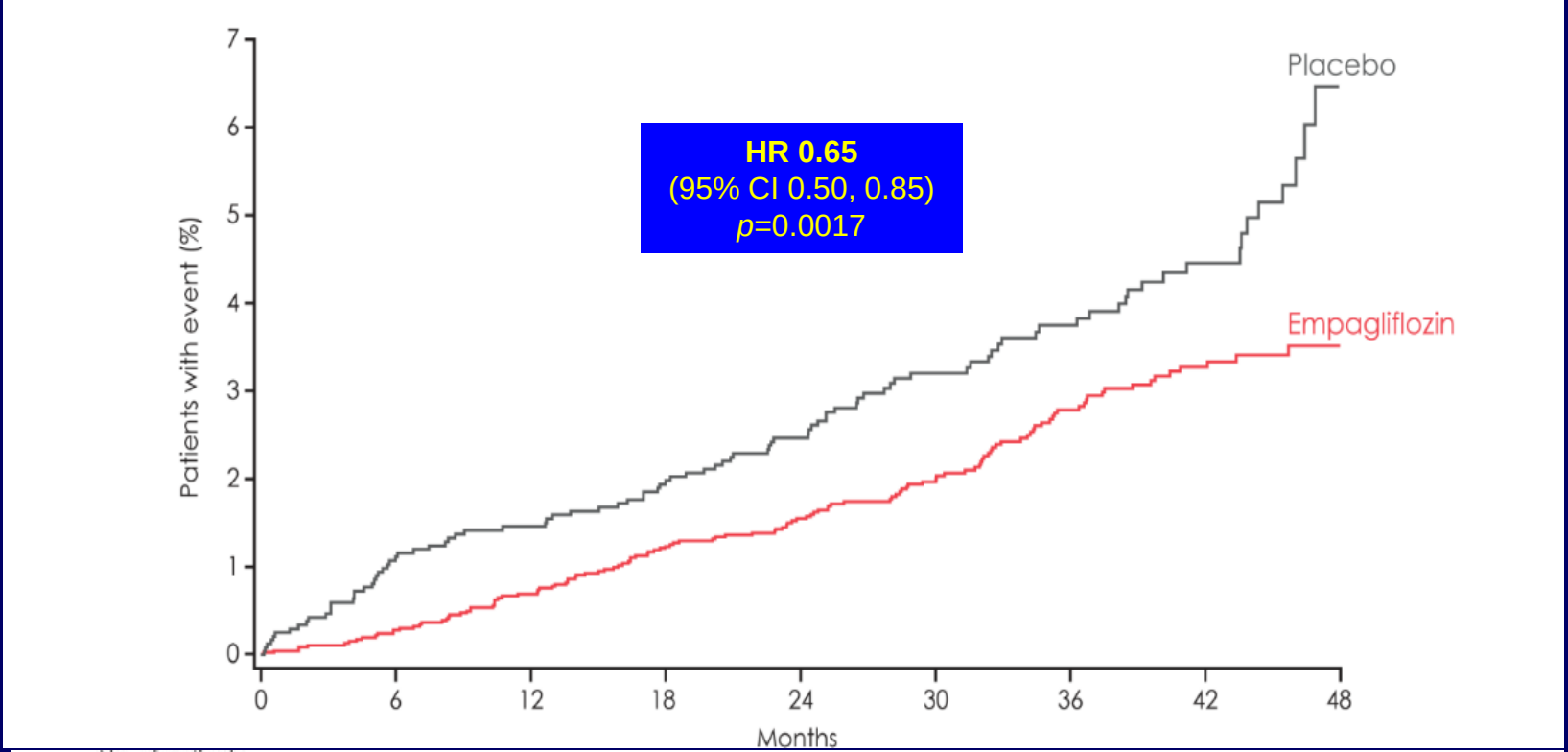
EMPA-REG (empagliflozin)
Categories of CV death

	Patients with event (%) Empagliflozin (N=4687)	Patients with event (%) Placebo (N=2333)	HR (95% CI)
CV death	172 (3.7%)	137 (5.9%)	0.62 (0.49, 0.77)
Sudden death	53 (1.1%)	38 (1.6%)	0.69 (0.45, 1.04)
Worsening of heart failure or cardiogenic shock	14 (0.3%)	22 (0.9%)	0.32 (0.16, 0.62)
Acute MI	15 (0.3%)	11 (0.5%)	0.68 (0.31, 1.48)
Stroke	16 (0.3%)	11 (0.5%)	0.72 (0.33, 1.55)
Other*	74 (1.6%)	55 (2.4%)	0.66 (0.47, 0.94)



Cox regression analysis.
*1.5% on empagliflozin and 2.3% on placebo were presumed CV death (insufficient data for the adjudication committee to categorize cause of death).
Fitchett D et al. J Am Coll Cardiol 2016;67:1869.

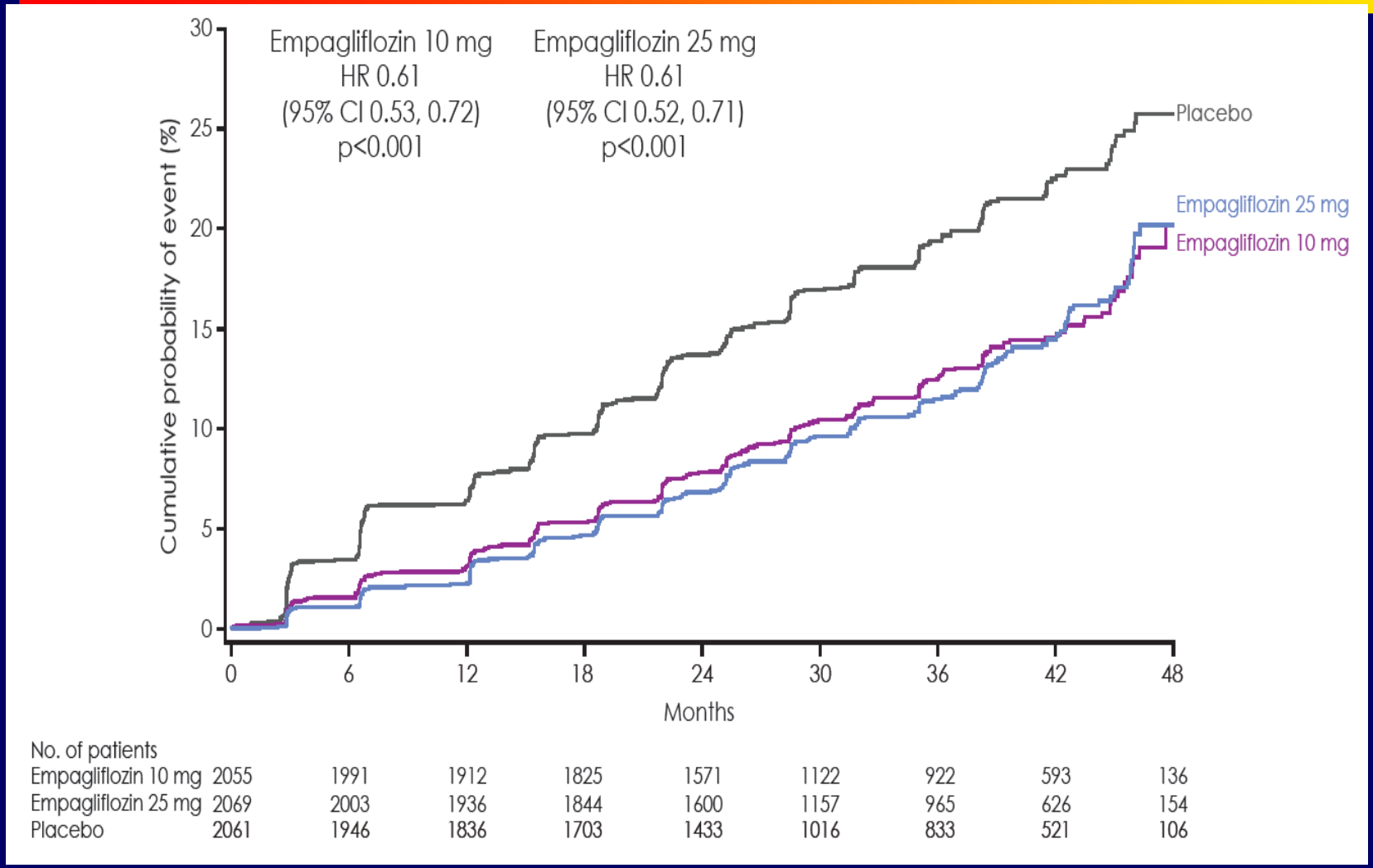
EMPA-REG (empagliflozin)
Hospitalization for heart failure



Cumulative incidence function. HR, hazard ratio

Zinman B, et al. *N Engl J Med.* 2015. 373(22):2117-28.

EMPA-REG (empagliflozin)
Incident or Worsening Nephropathy



Kaplan-Meier estimate. Hazard ratios based on pre-specified Cox regression analyses.

Wanner C, et al. *NEJM* 2016

Canagliflozin for Primary and Secondary Prevention of Cardiovascular Events in Type 2 Diabetes: Results From the CANVAS Program

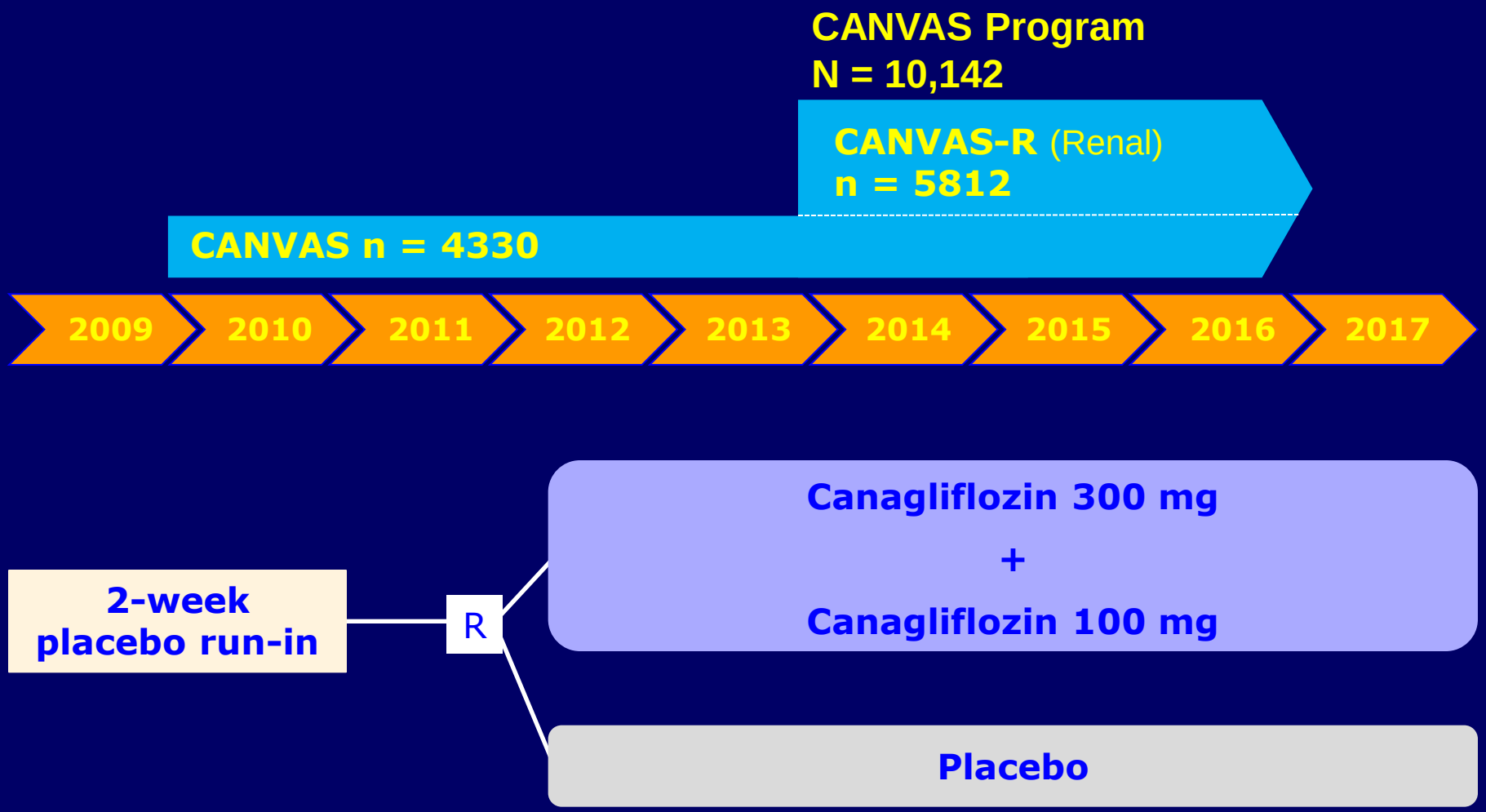
Kenneth W. Mahaffey, Bruce Neal, Vlado Perkovic, Dick de Zeeuw, Greg Fulcher, Ngozi Erondu, Wayne Shaw, Tao Sun, Mehul Desai, David R. Matthews, on behalf of the CANVAS Program collaborative group

November 13, 2017

DOI: 10.1161/CIRCULATIONAHA.117.032038

CANVAS Program

CANVAS Program



Neal B. *NEJM*. 2017.

CANVAS Participants

Patients with type 2 diabetes

- HbA1c ≥7.0% to ≤10.5%
- eGFR ≥30 mL/min/1.73 m^2
- Secondary prevention: Age ≥30 years and history of prior CV event

  OR

  Primary prevention: Age ≥50 years with ≥2 CV risk factors*

Of 10,142 patients enrolled

- 6656 (66%) secondary prevention
- 3486 (34%) primary prevention

*Diabetes duration ≥10 years, SBP >140 mmHg on ≥1 medication, current smoker, micro- or macroalbuminuria, or HDL-C <39 mg/dL

Neal B. *NEJM*. 2017.

Baseline Characteristics

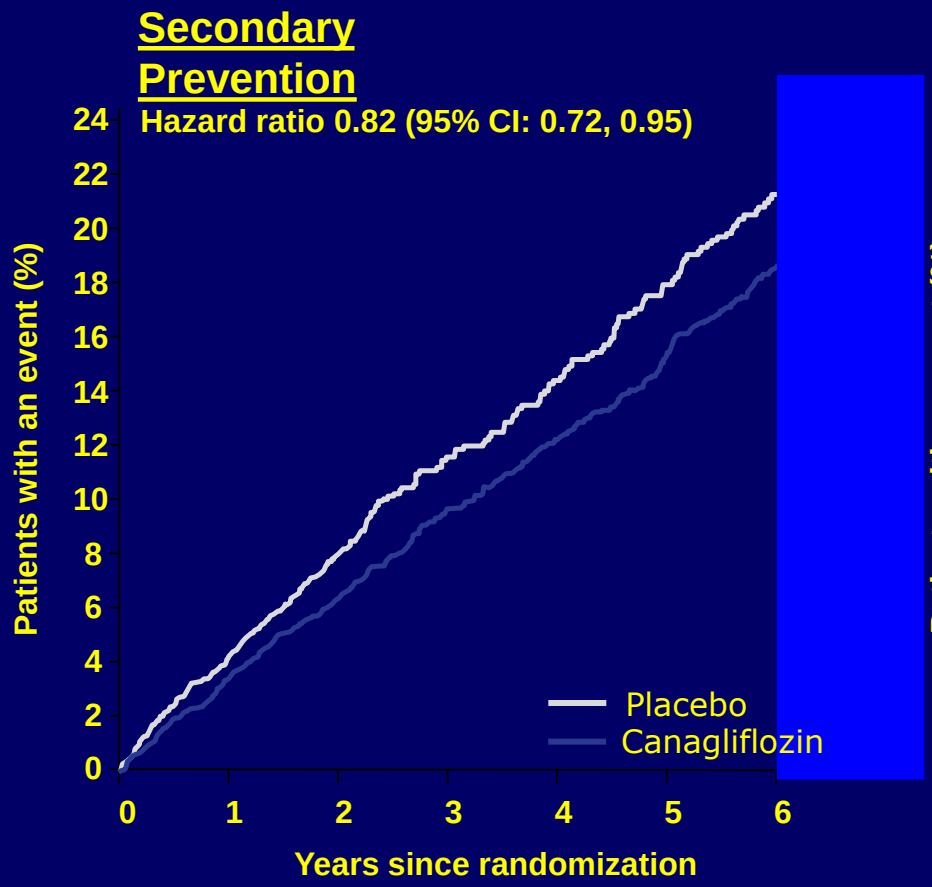
	Secondary prevention (n = 6656)	Primary prevention (n = 3486)
Mean age, y	64	63
Female, %	31	45
Mean duration of diabetes, y	13	14
Mean HbA1c, %	8.2	8.3
Hypertension, %	89	91
Antihyperglycemic agents, %	98	99
Cardioprotective agents, %		
RAAS inhibitor	80	81
Statin	81	63
Antithrombotic	87	49
Beta blocker	64	33
Diuretic	44	44

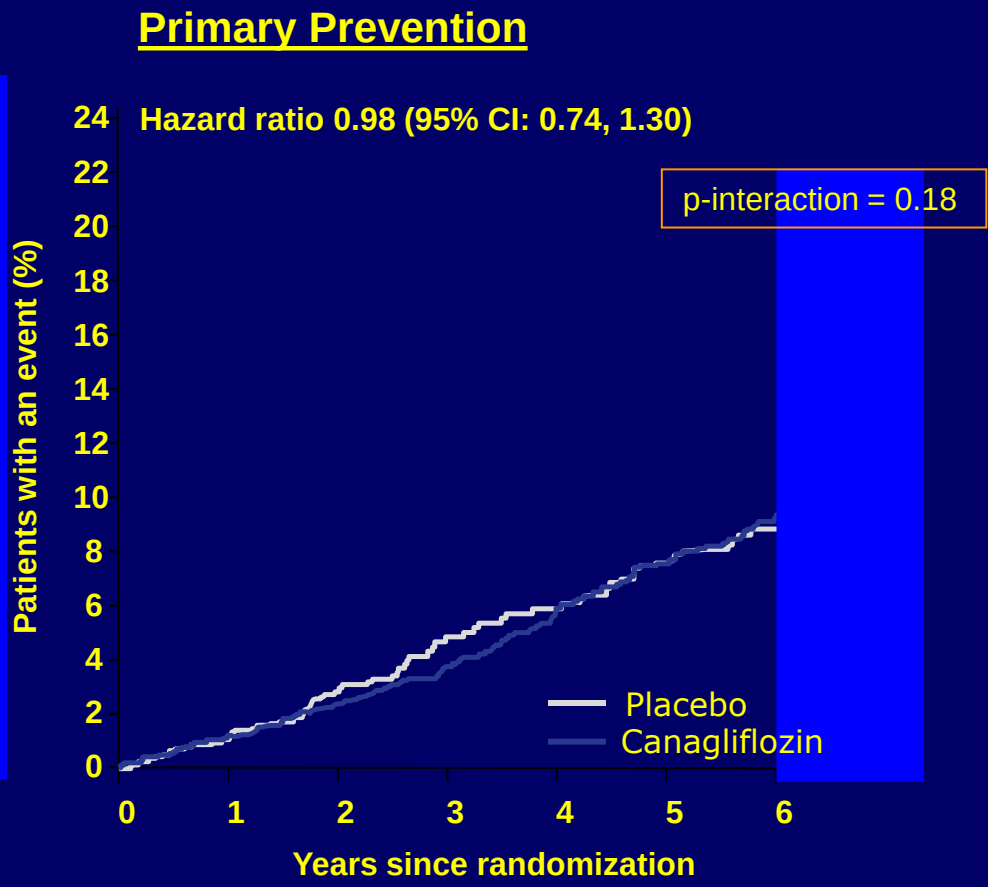
Baseline CV Disease History

	Secondary prevention (n = 6656)	Primary prevention (n = 3486)
Myocardial infarction	44	0.5
Hospitalization for USA	11	0
Coronary revascularization	54	0.1
PCI	38	0.1
CABG	21	<0.1
Stroke	19	0.4
Carotid revascularization	1	0
Peripheral revascularization (surgical or percutaneous)	8	0.1
Amputation	3	0.6

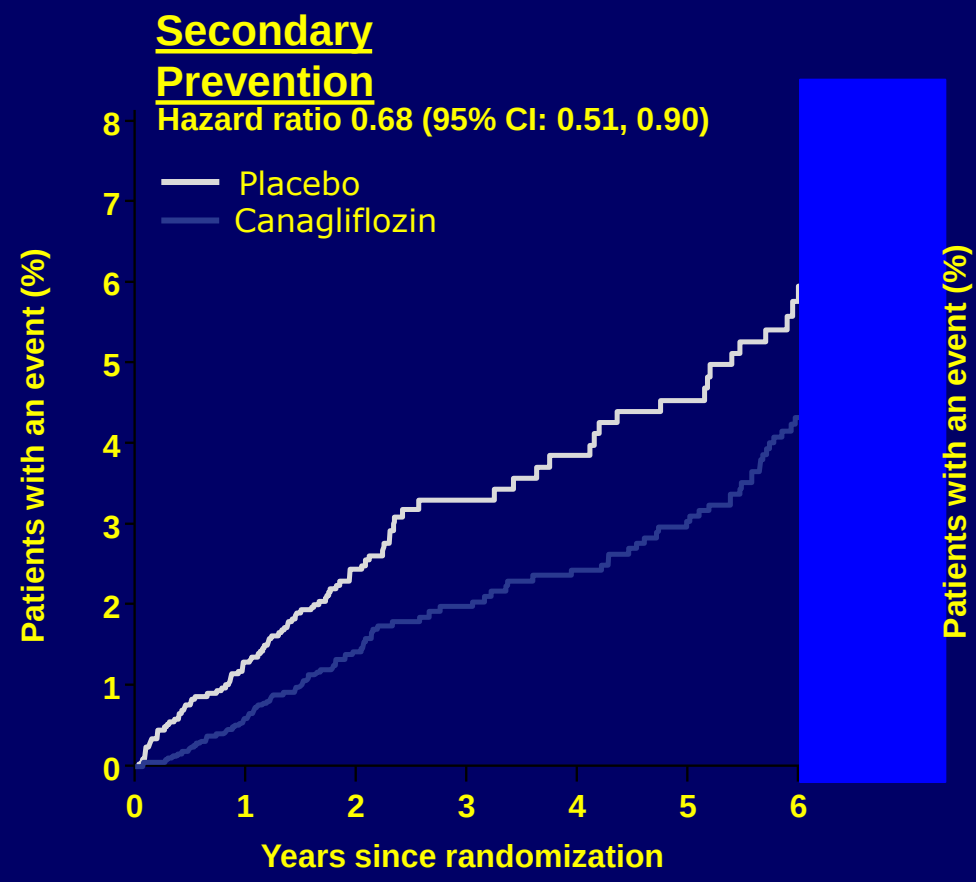
Data are percentage of participants.

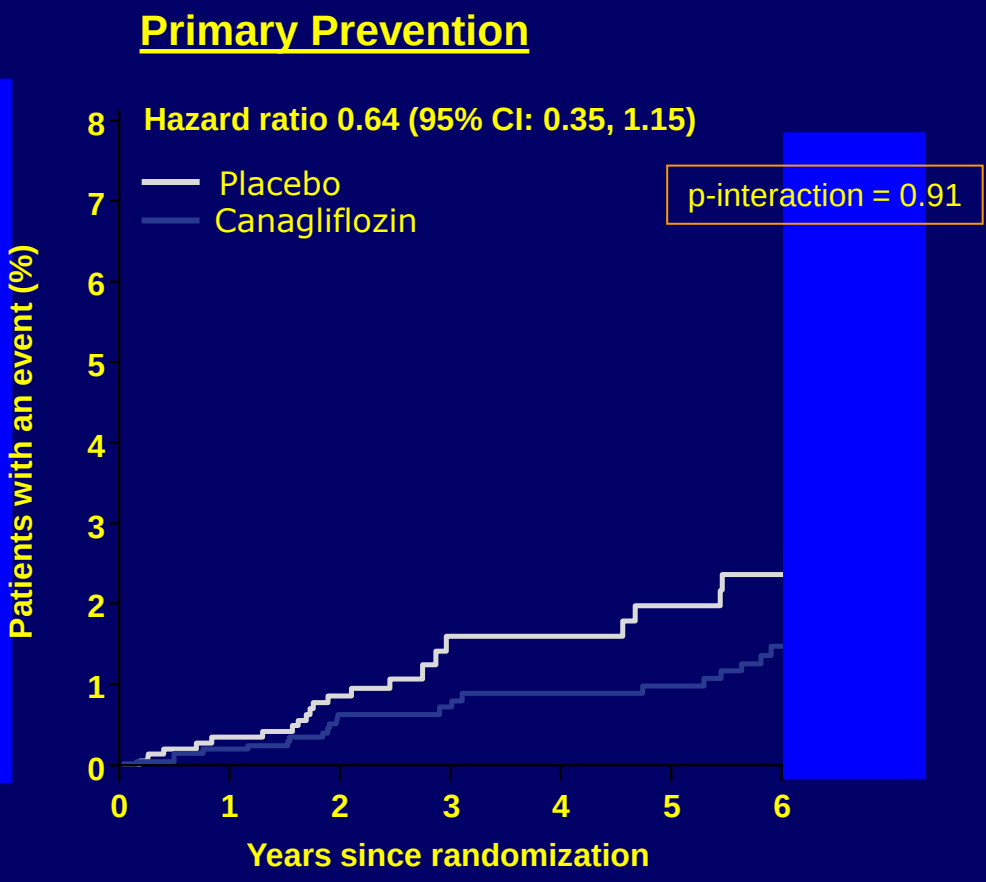
CV Death, Nonfatal MI, or Nonfatal Stroke



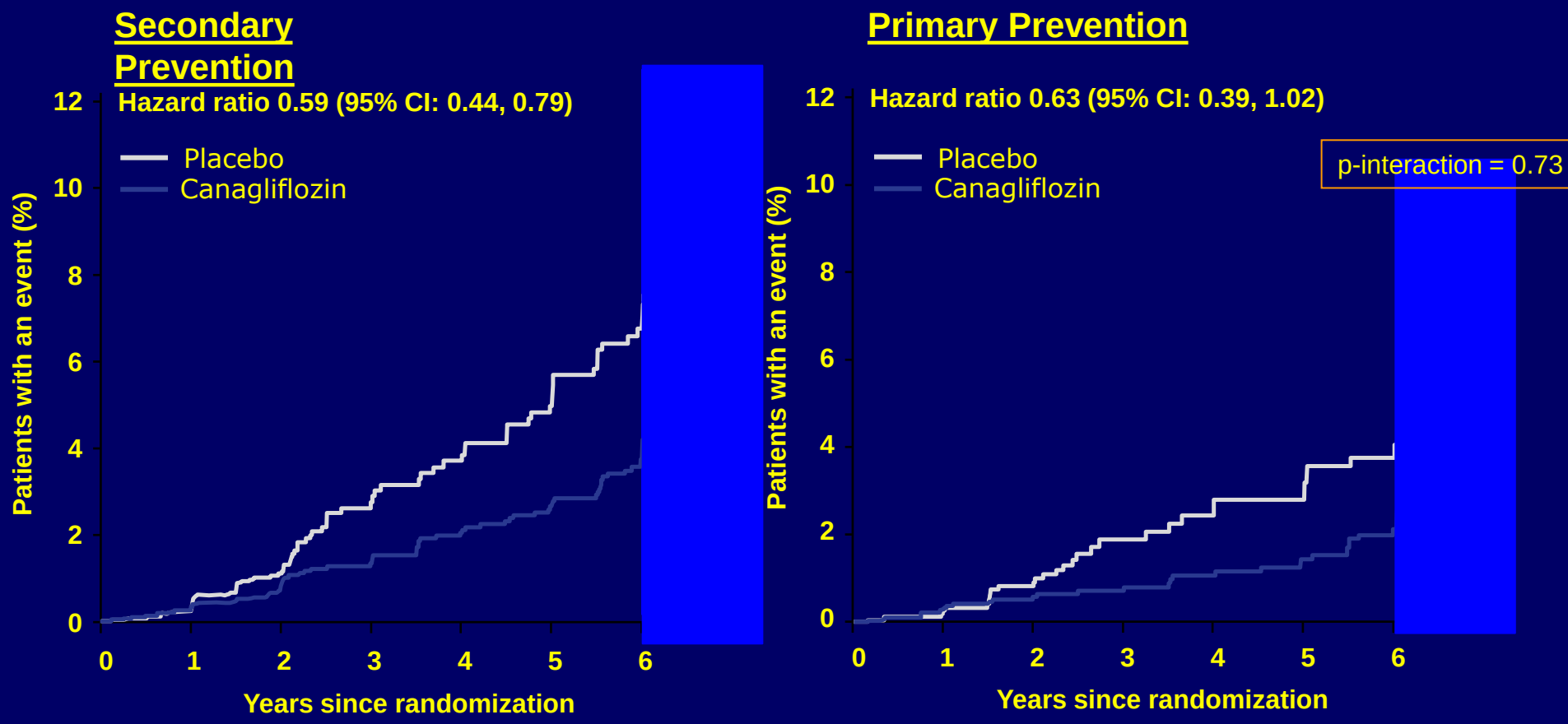


Hospitalization for HF



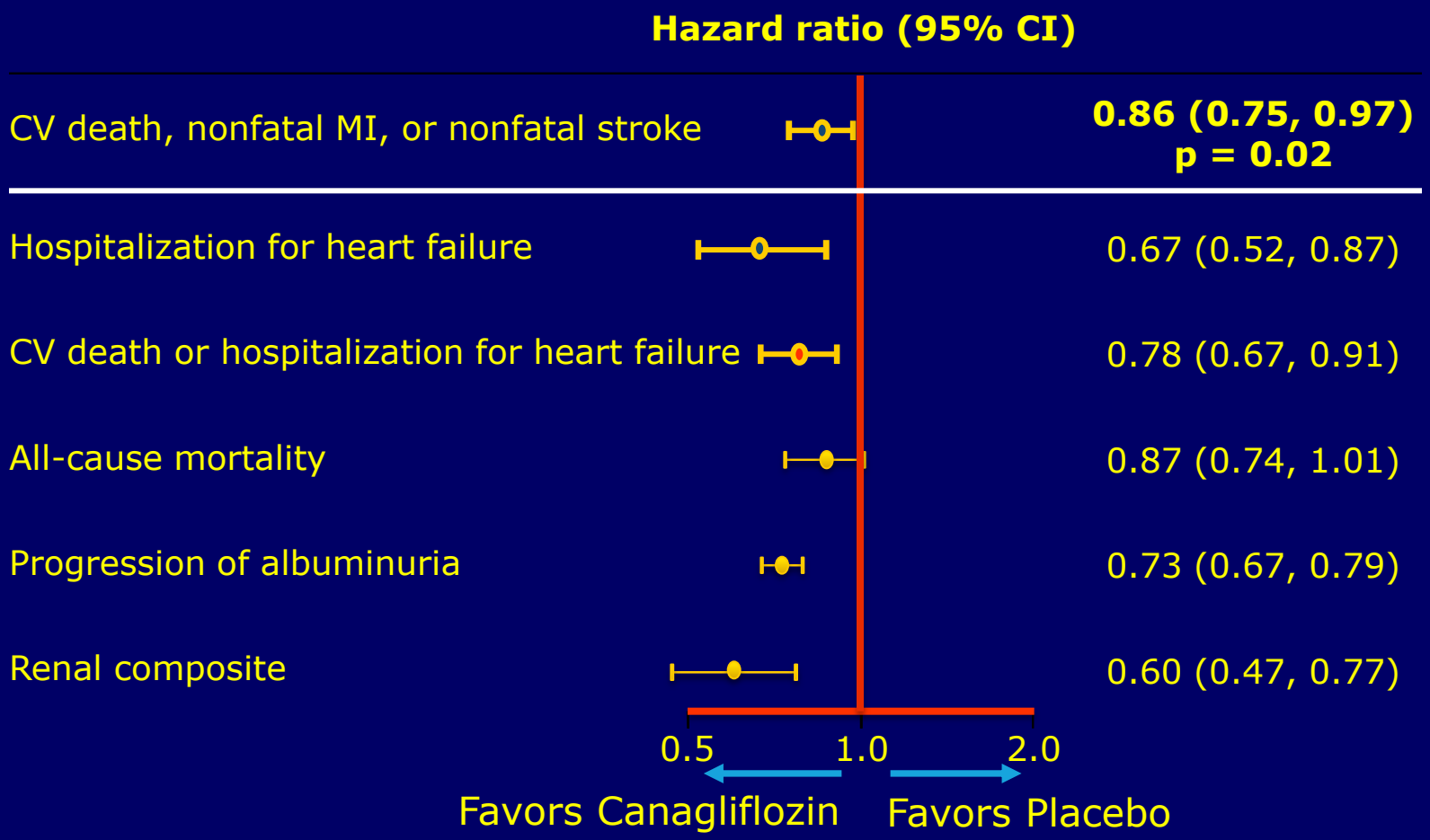


Renal Composite Outcome



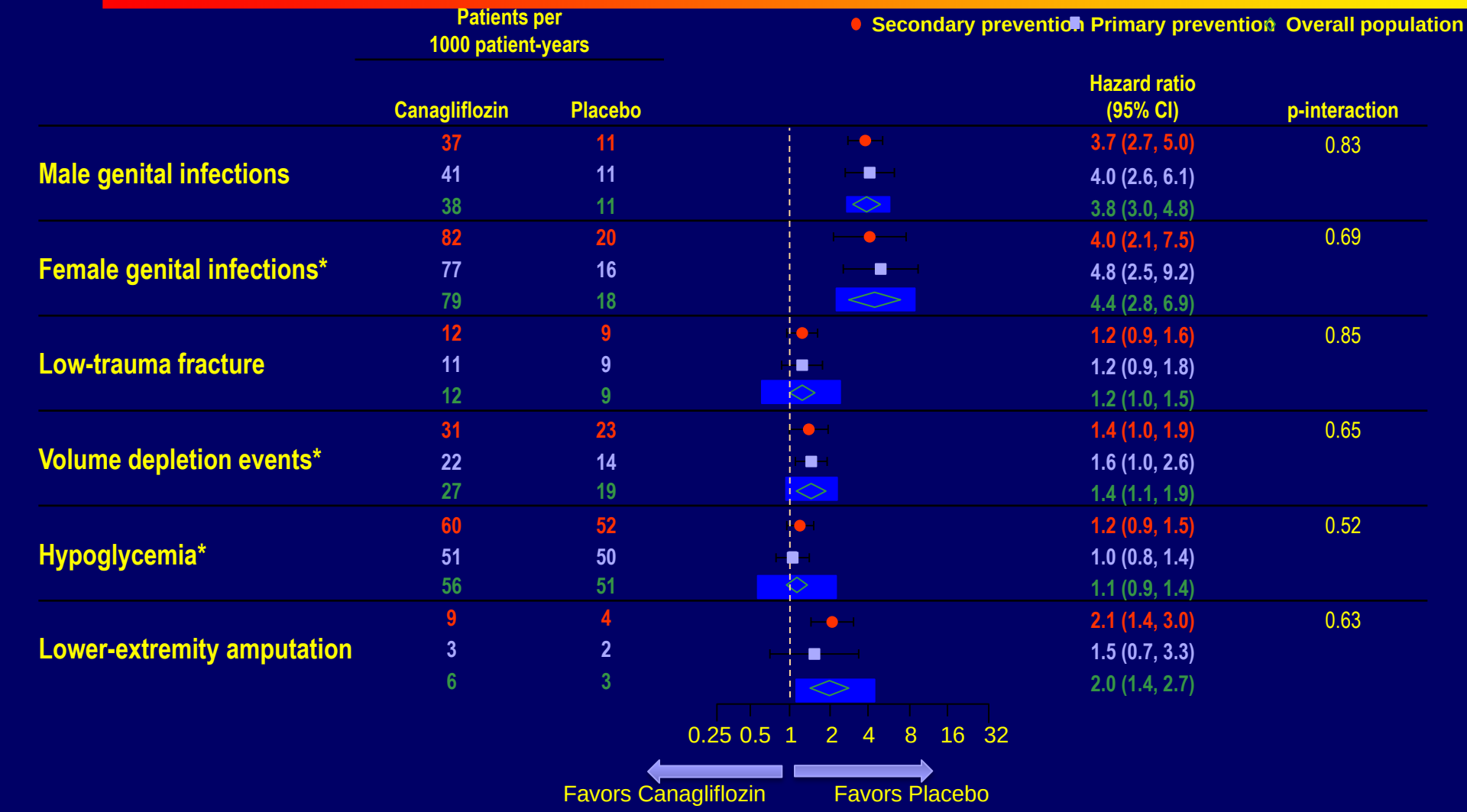
Renal composite outcome includes 40% reduction in eGFR, renal replacement therapy, or renal death.

CV and Renal Outcomes



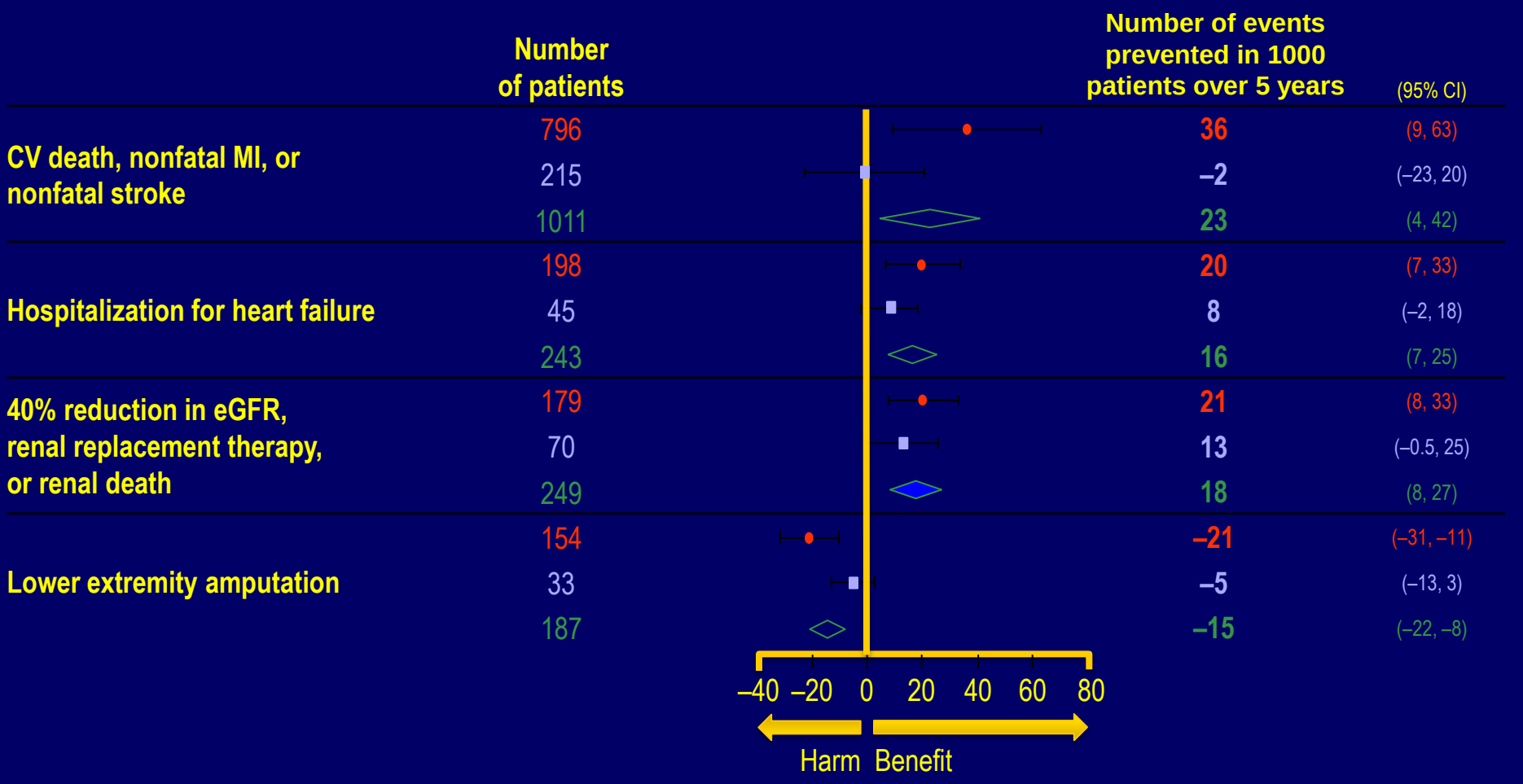
Neal B. *NEJM*. 2017.

Safety Events



*Serious and nonserious adverse events of interest collected in CANVAS only.

Benefit Risk: Risk Differences



CREDENCE: Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation

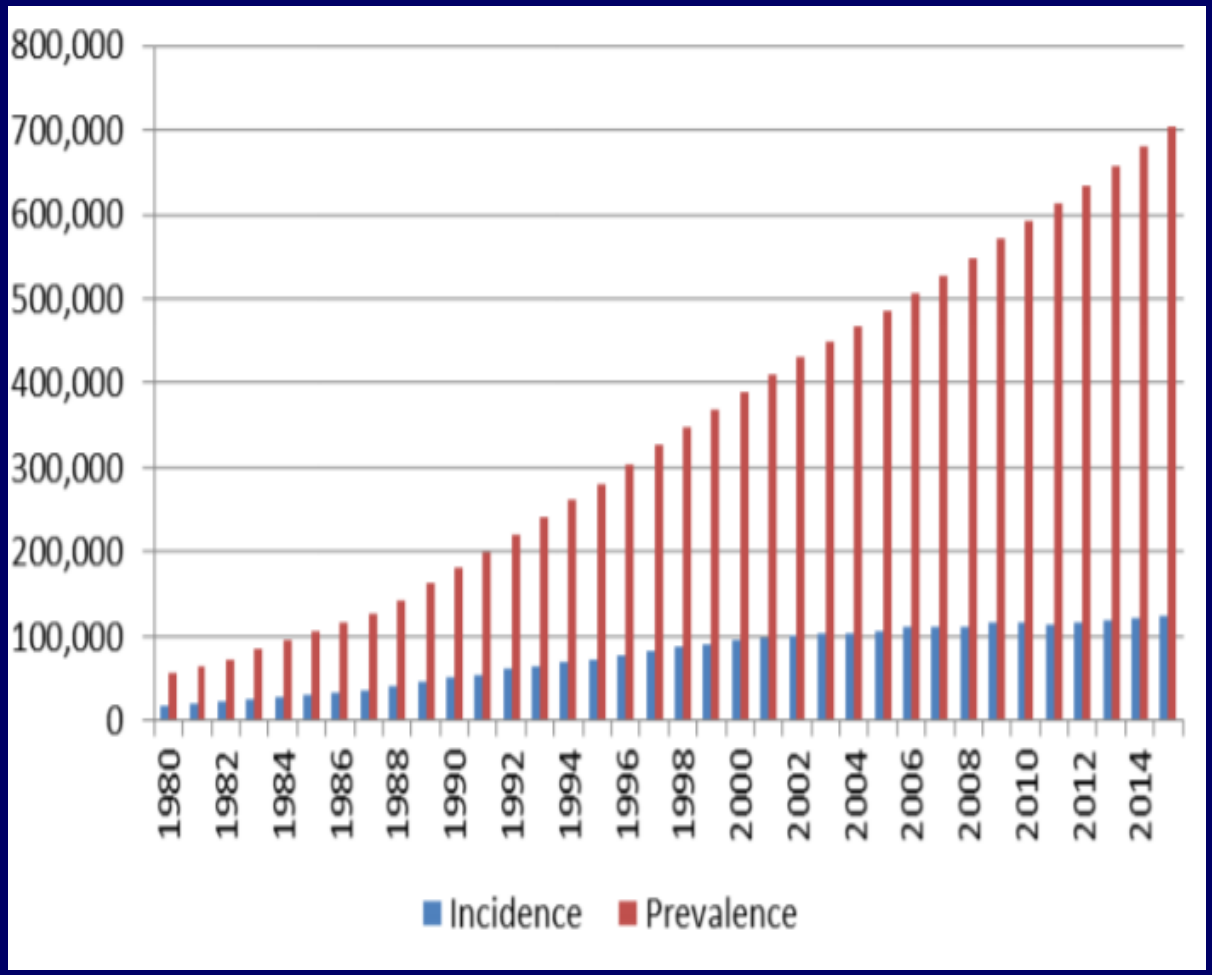
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

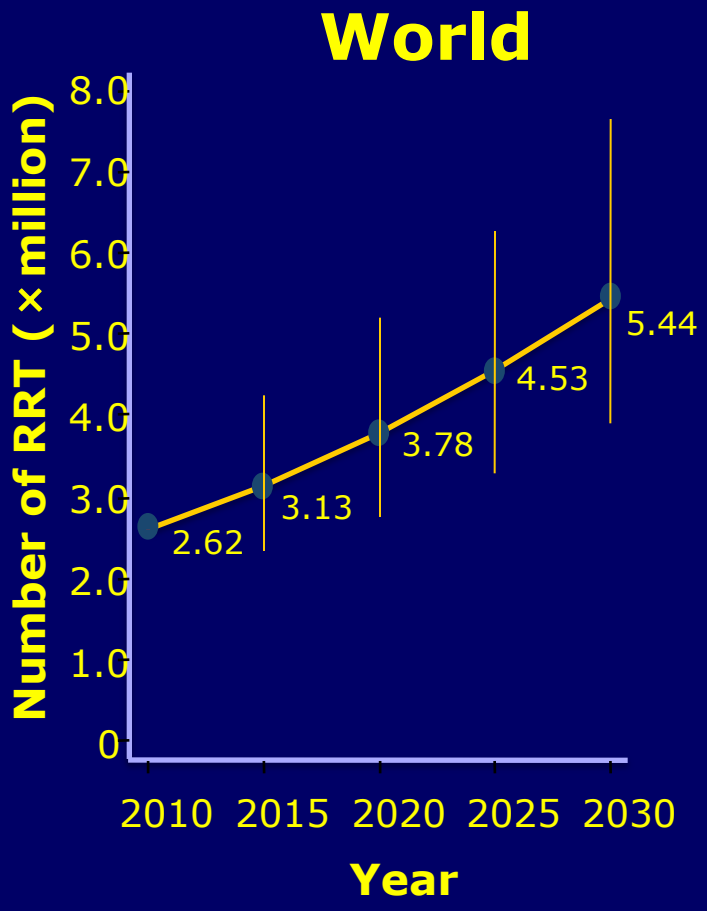
V. Perkovic, M.J. Jardine, B. Neal, S. Bompoint, H.J.L. Heerspink, D.M. Charytan, R. Edwards, R. Agarwal, G. Bakris, S. Bull, C.P. Cannon, G. Capuano, P.-L. Chu, D. de Zeeuw, T. Greene, A. Levin, C. Pollock, D.C. Wheeler, Y. Yavin, H. Zhang, B. Zinman, G. Meininger, B.M. Brenner, and K.W. Mahaffey, for the CREDENCE Trial Investigators*

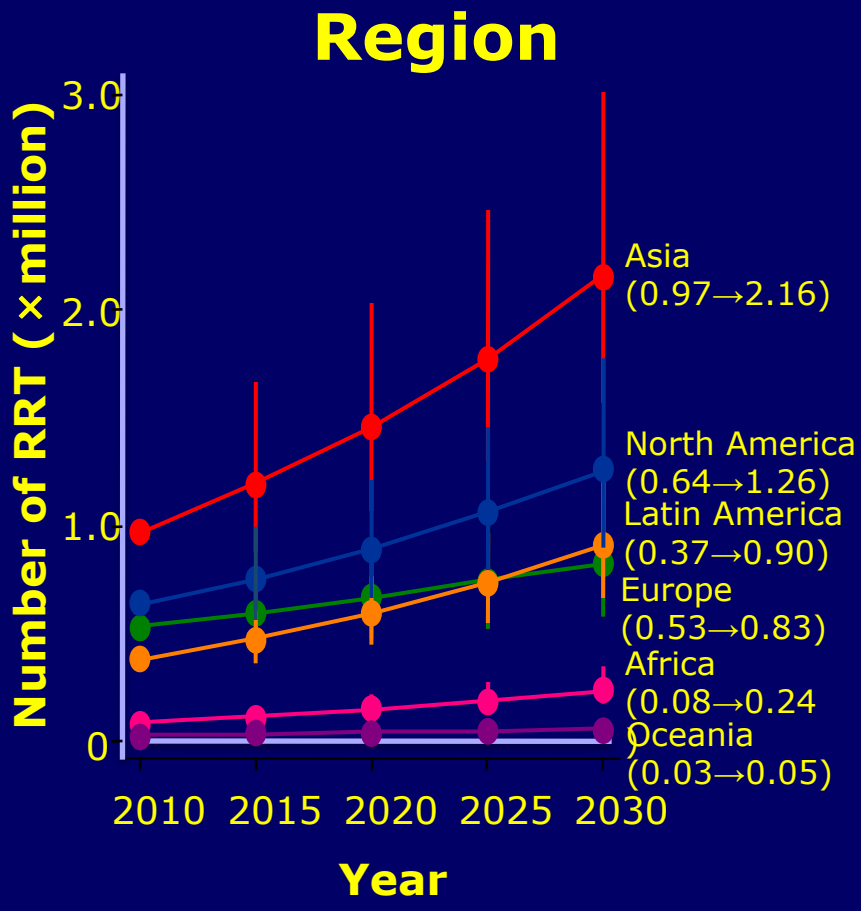
Increasing Incidence and Prevalence of ESKD: US Data



Kirchhoff S. Medicare coverage of end-stage renal disease (ESRD). https://fas.org/sgp/crs/misc/R45290.pdf. Accessed February 13, 2019.

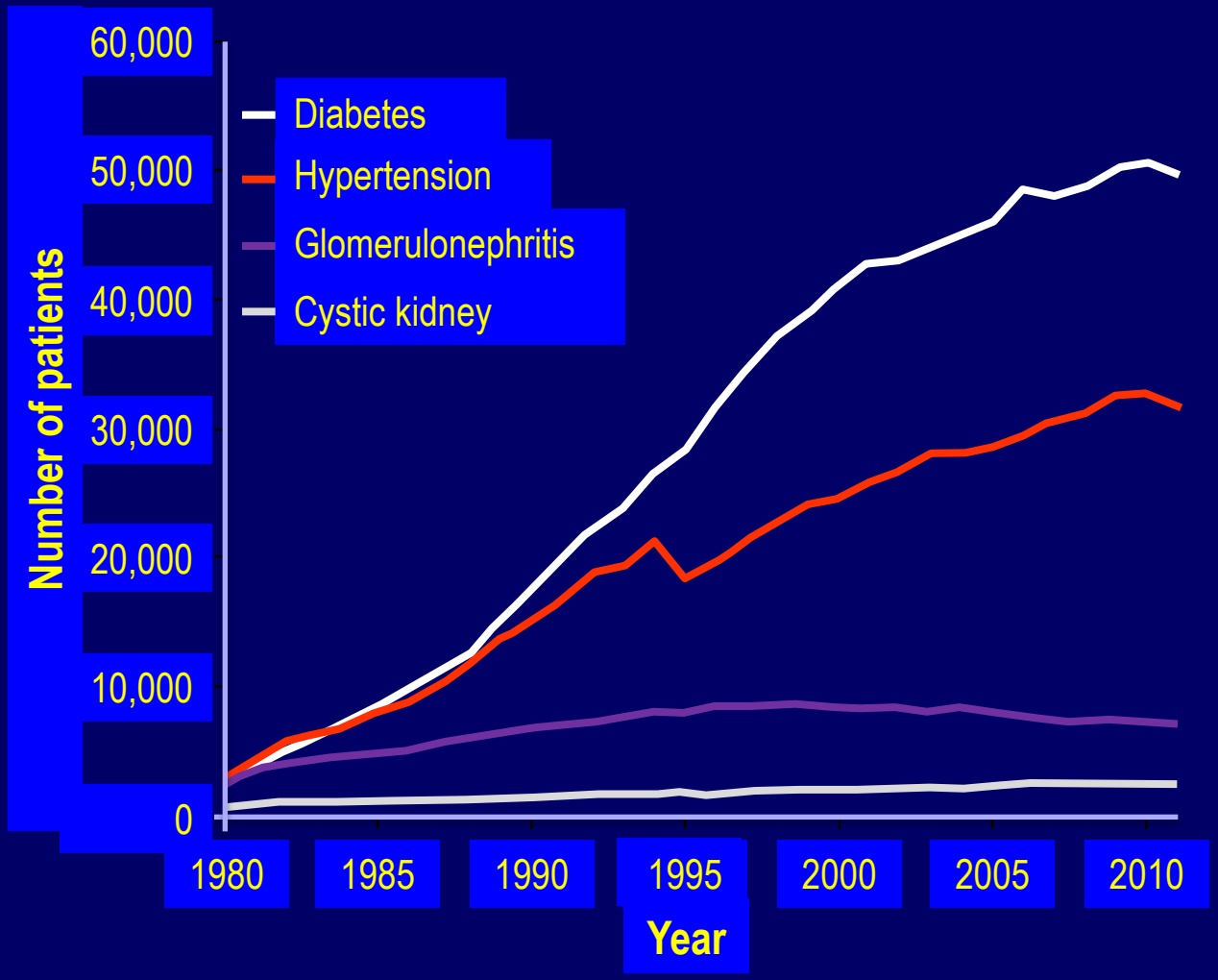
Number of People Receiving Renal Replacement Therapy Is Projected to Double





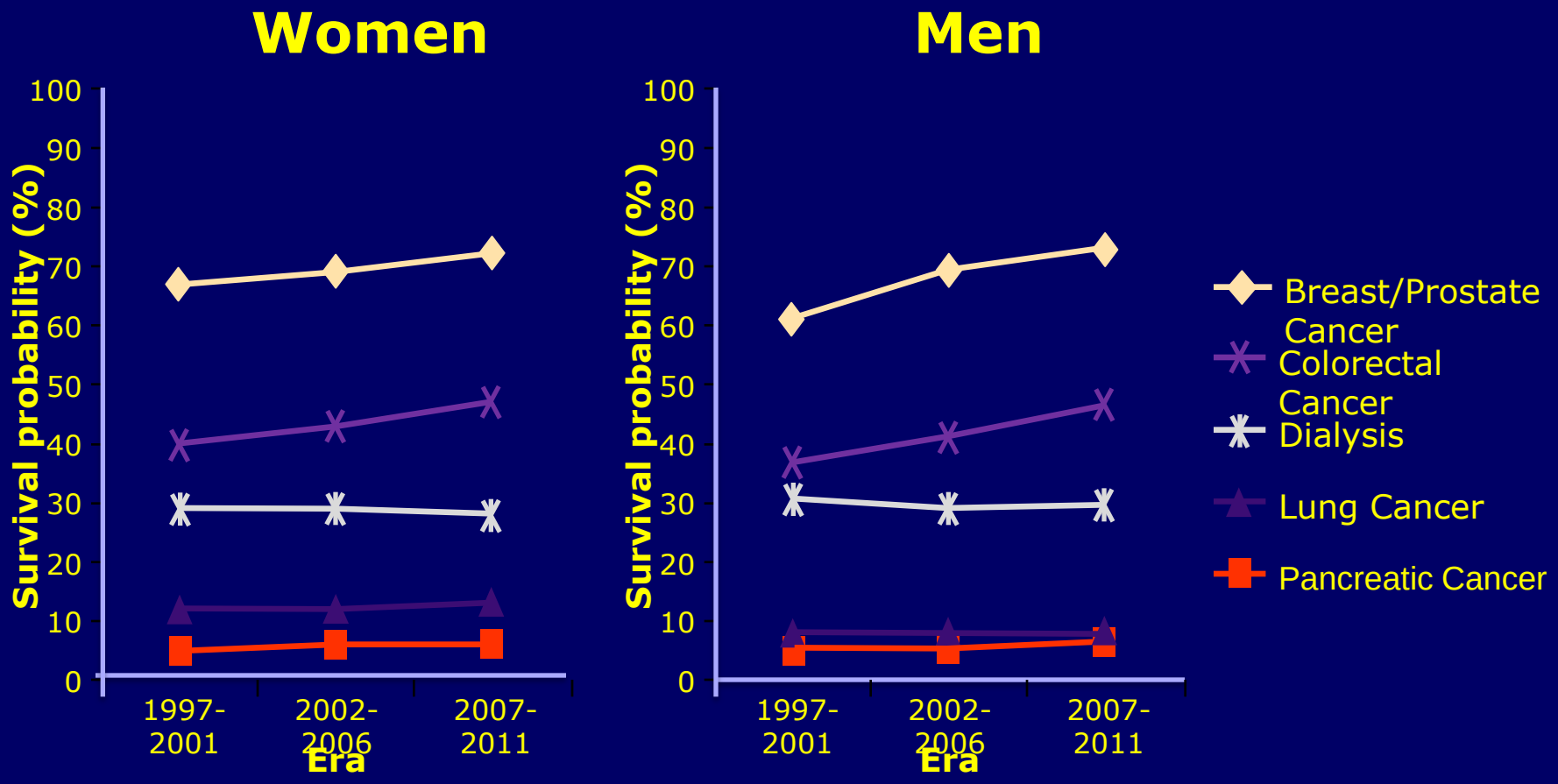
Liyanage T, et al. *Lancet*. 2015;385(9981):1975-1982.

Diabetes Is the Leading Cause of Kidney Failure: US Data



United States Renal Data System (USRDS). USRDS Annual Report, Chapter 1. https://www.usrds.org/2012/pdf/v2_ch1_12.pdf. Accessed March 15, 2019.

Dialysis Survival Compared to Common Cancers

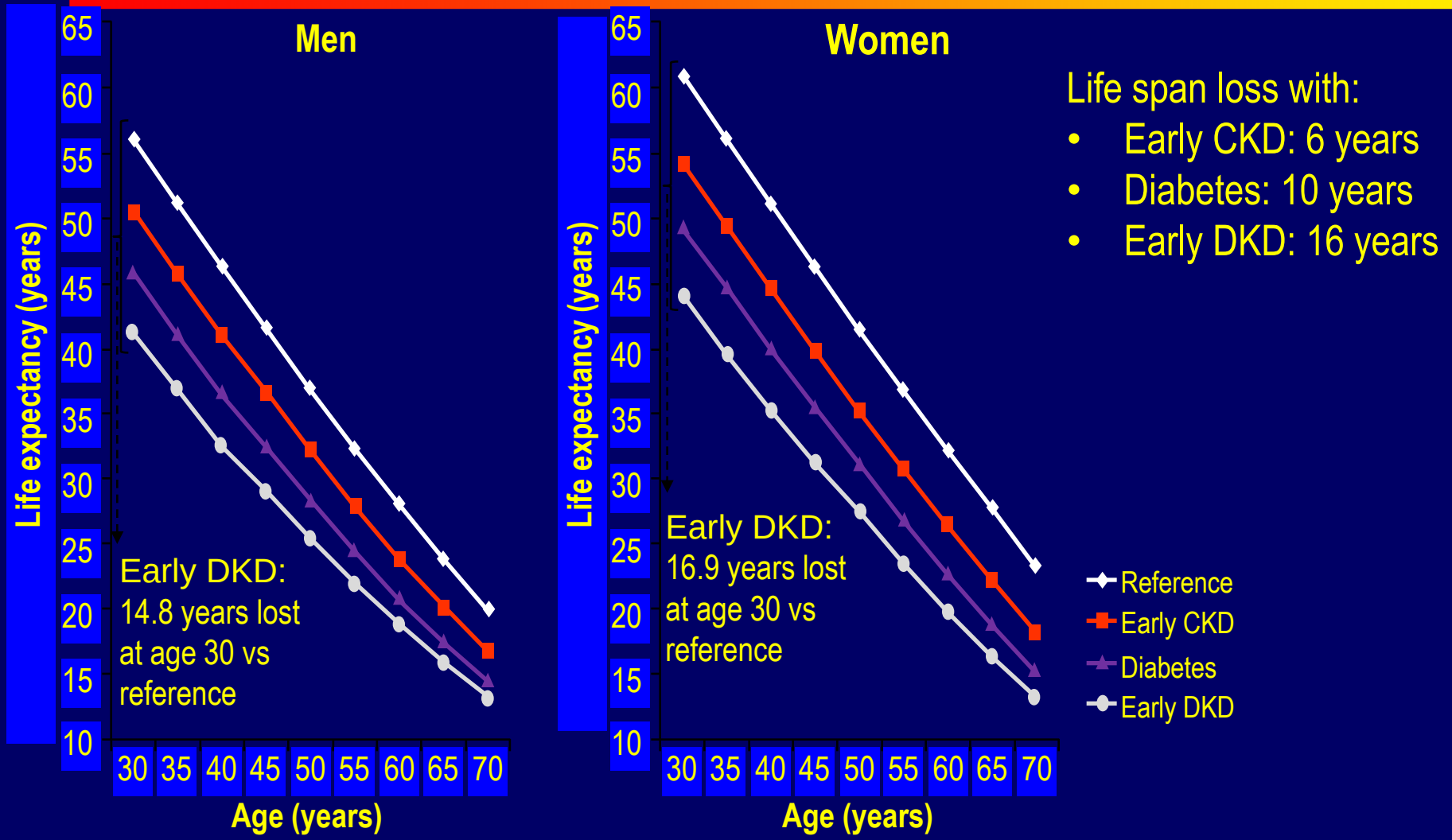


Unadjusted 10-year survival for all-cause mortality in Canada

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

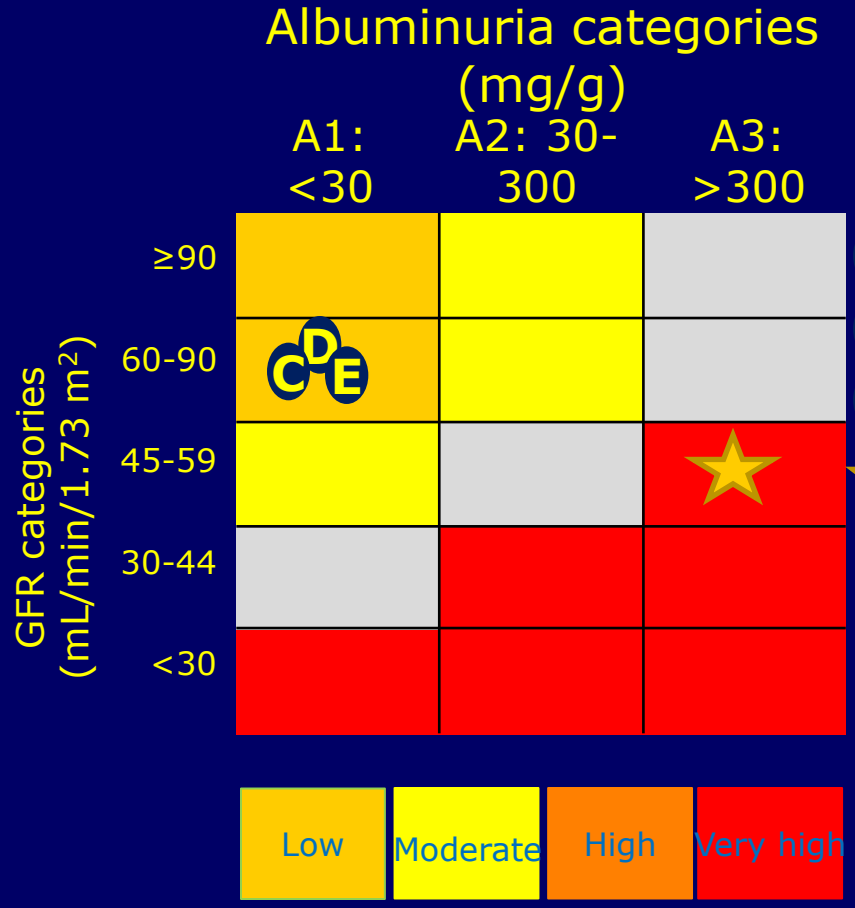
Naylor KL, et al. *Am J Kidney Dis.* 2019. Epub ahead of print. doi:10.1053/j.ajkd.2018.12.011.

Diabetic Kidney Disease Shortens Life Span by 16 Years



Wen CP, et al. *Kidney Int.* 2017;92(2):388-396.

Low Renal Risk Populations in Other CV Outcomes Trials



		Mean eGFR (mL/min/1.73 m²)	Median UACR (mg/g)
D	DECLARE	85	13
C	CANVAS Program	76	12
E	EMPA-REG OUTCOME	74	18
★	CREDENCE		

Sustained RRT Events 29

DECLARE	Not reported
CANVAS Program	18
EMPA-REG OUTCOME	11

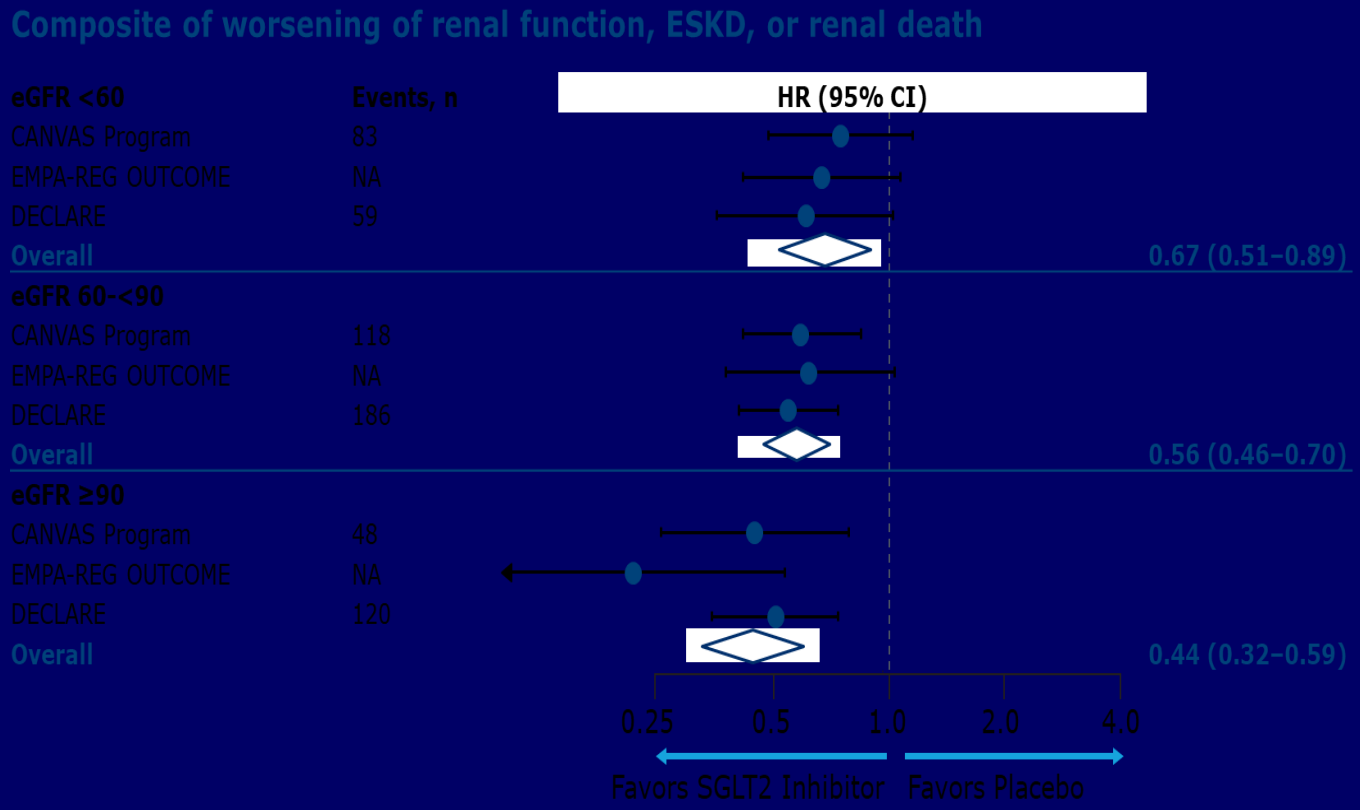
Timeline of Major SGLT2 Inhibitor Trials

CREDENCE began before any CV outcomes trials had reported

Renal effects were not the primary focus of the CV outcomes trials

Why Is CREDENCE Important?

CV outcomes trial results suggested possible attenuation of renal effects in patients with reduced kidney function



Interaction
P value = 0.0258

Zelniker TA, et al. *Lancet.* 2019;393(10166):31-39.

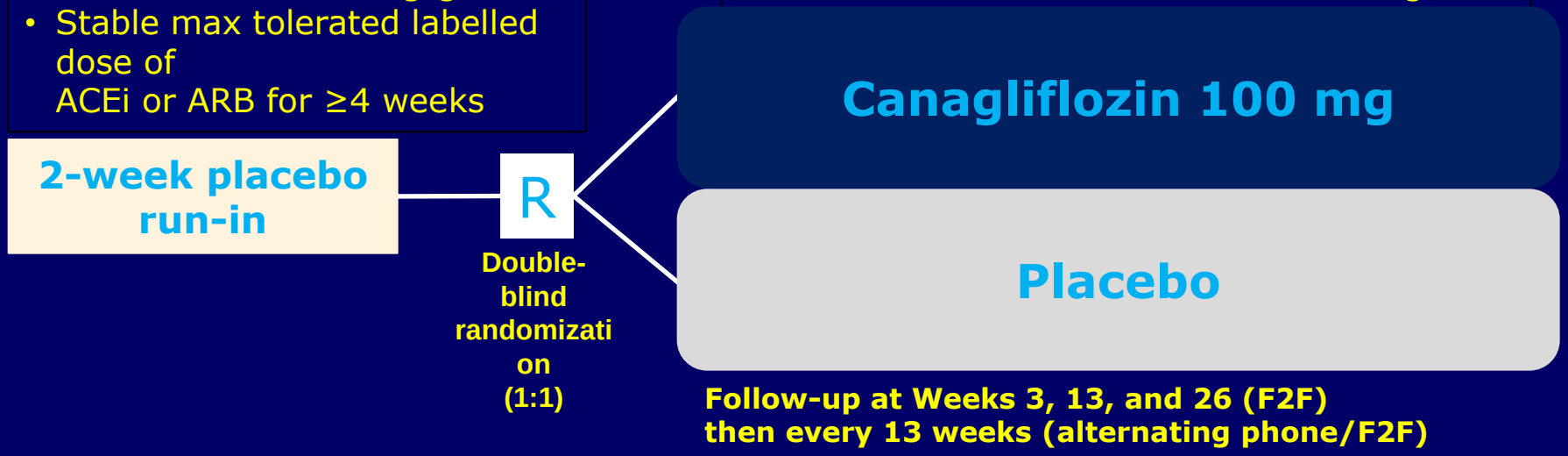
Primary Aim of the CREDENCE Trial

To assess the effects of the SGLT2 inhibitor, canagliflozin, on clinically important renal outcomes in people with T2DM and established CKD

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



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

Jardine MJ, et al. *Am J Nephrol.* 2017;46(6):462-472.

Demographics and Disease History

	Canagliflozin (n = 2202)	Placebo (n = 2199)	Total (N = 4401)
Mean age, years	63	63	**63**
Female, %	35	33	**34**
Mean duration of diabetes, years	16	16	**16**
Hypertension, %	97	97	**97**
Heart failure (NYHA I-III), %	15	15	**15**
CV disease, %	51	50	**50**
Prior amputation, %	5	5	**5**

Demographics

	Canagliflozin (n = 2202)	Placebo (n = 2199)	Total (N = 4401)
Race, %			
White	68	66	**67**
Asian	19	21	**20**
Black or African American	5	5	**5**
Other	8	9	**8**
Geographic region, %			
North America	26	28	**27**
Central/South America	22	21	**21**
Europe	21	19	**20**
Rest of world	32	33	**32**

Baseline Therapies

	Canagliflozin (n = 2202)	Placebo (n = 2199)	Total (N = 4401)
Glucose-lowering agents, %			
Insulin	66	65	**66**
Metformin	58	58	**58**
Sulfonylurea	28	30	**29**
DPP-4 inhibitor	17	17	**17**
GLP-1 receptor agonist	4	4	**4**
Renal and CV protective agents, %			
RAAS inhibitor	>99.9	99.8	**99.9**
Statin	70	68	**69**
Antithrombotic	61	58	**60**
Beta blocker	40	40	**40**
Diuretic	47	47	**47**

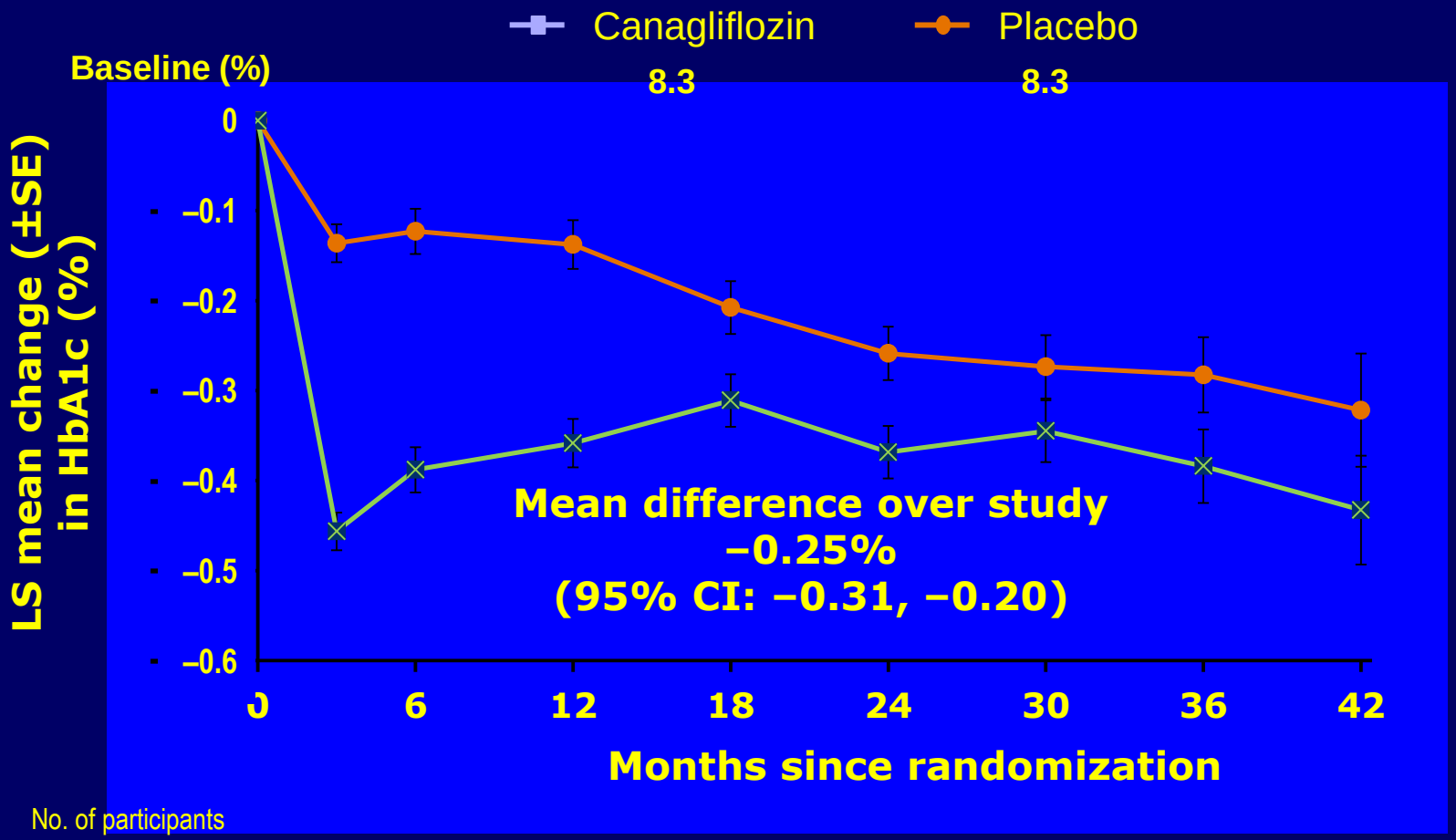
Baseline Risk Factors

	Canagliflozin (n = 2202)	Placebo (n = 2199)	Total (N = 4401)
HbA1c, %	8.3	8.3	**8.3**
BMI, kg/m^2	31.4	31.3	**31.3**
Systolic BP, mmHg	140	140	**140**
Diastolic BP, mmHg	78	78	**78**
Total cholesterol, mmol/L	4.7	4.6	**4.7**
HDL-C, mmol/L	1.2	1.2	**1.2**
LDL-C, mmol/L	2.5	2.5	**2.5**
Triglycerides, mmol/L	2.2	2.2	**2.2**

Baseline Renal Characteristics

	Canagliflozin (n = 2202)	Placebo (n = 2199)	Total (N = 4401)
Mean eGFR, mL/min/1.73 m²	**56**	**56**	**56**
eGFR ≥90, %	5	5	5
eGFR ≥60 to <90, %	36	35	35
eGFR ≥45 to <60, %	29	29	29
eGFR ≥30 to <45, %	27	27	27
eGFR <30, %	4	4	4
Median UACR (IQR), mg/g	**923 (459-1794)**	**931 (473-1868)**	**927 (463-1833)**
UACR <30, %	<1	<1	<1
UACR 30-300, %	11	11	11
UACR >300-≤3000, %	77	76	77
UACR >3000, %	11	12	11

Effects on HbA1c

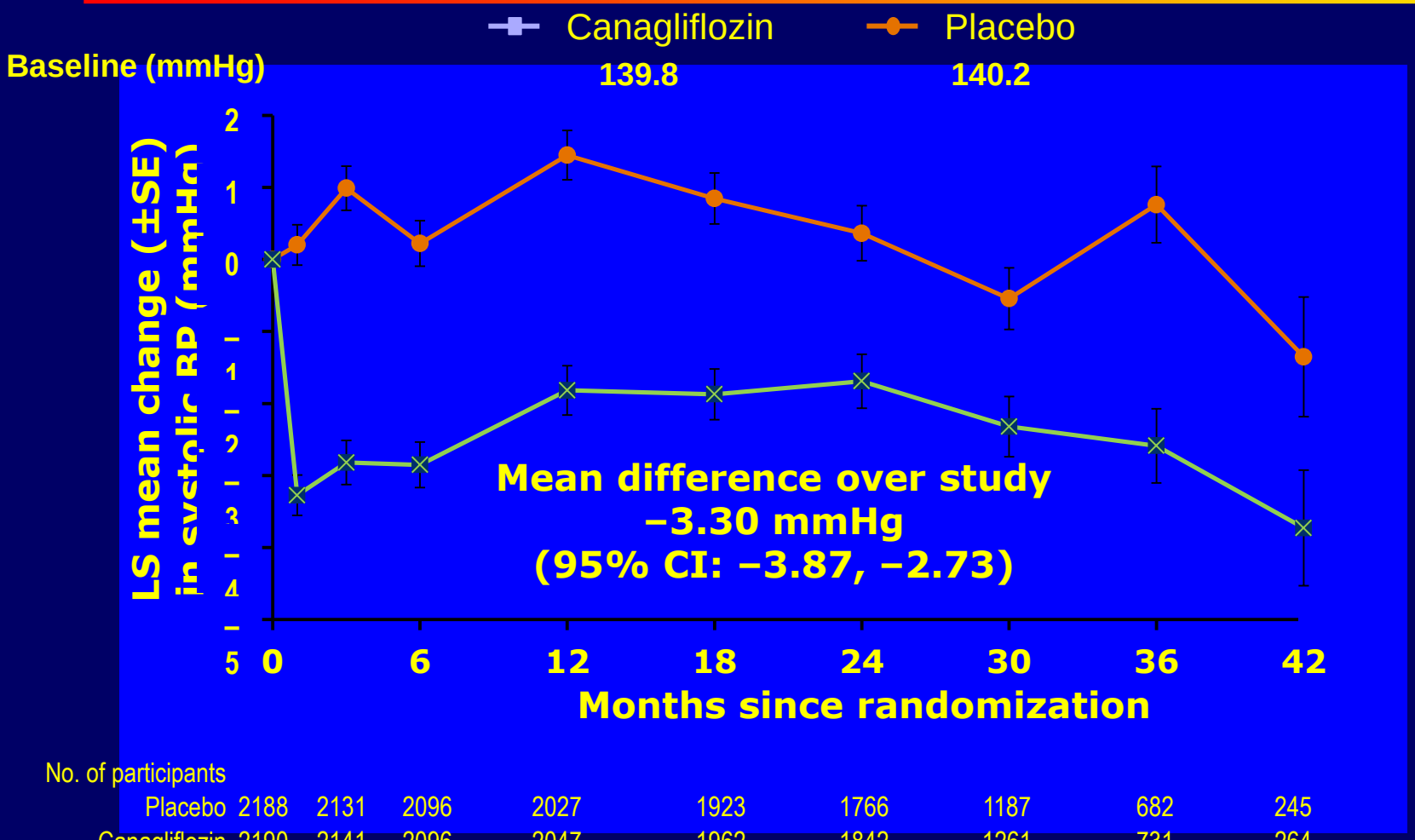


No. of participants

Placebo	2150	2103	2066	1981	1882	1728	1172	688	252
Canagliflozin	2154	2108	2074	2024	1909	1817	1254	729	274

ITT analysis

Effects on Systolic BP

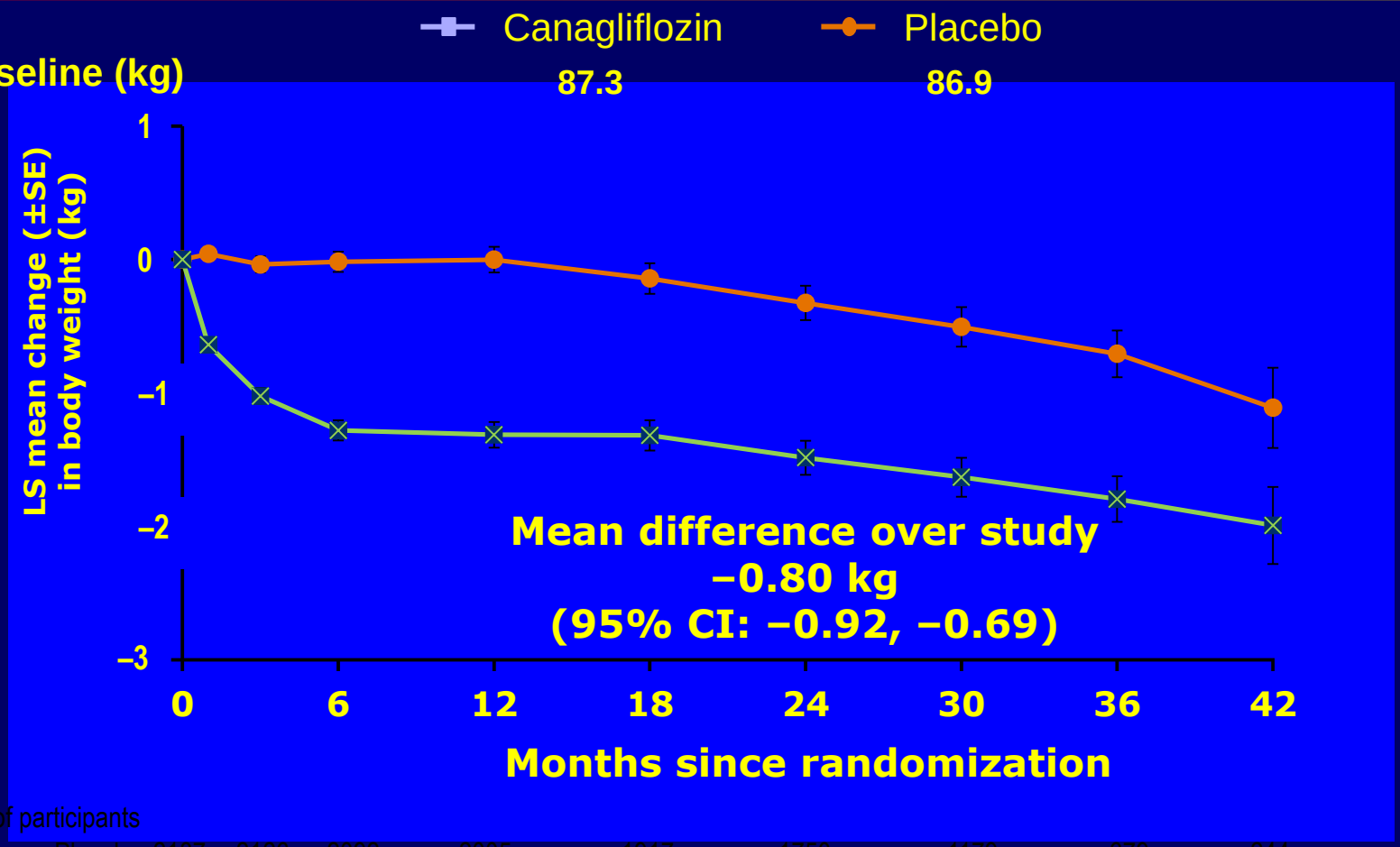


No. of participants

Placebo	2188	2131	2096	2027	1923	1766	1187	682	245
Canagliflozin	2190	2141	2096	2047	1962	1842	1261	731	264

ITT analysis

Effects on Body Weight

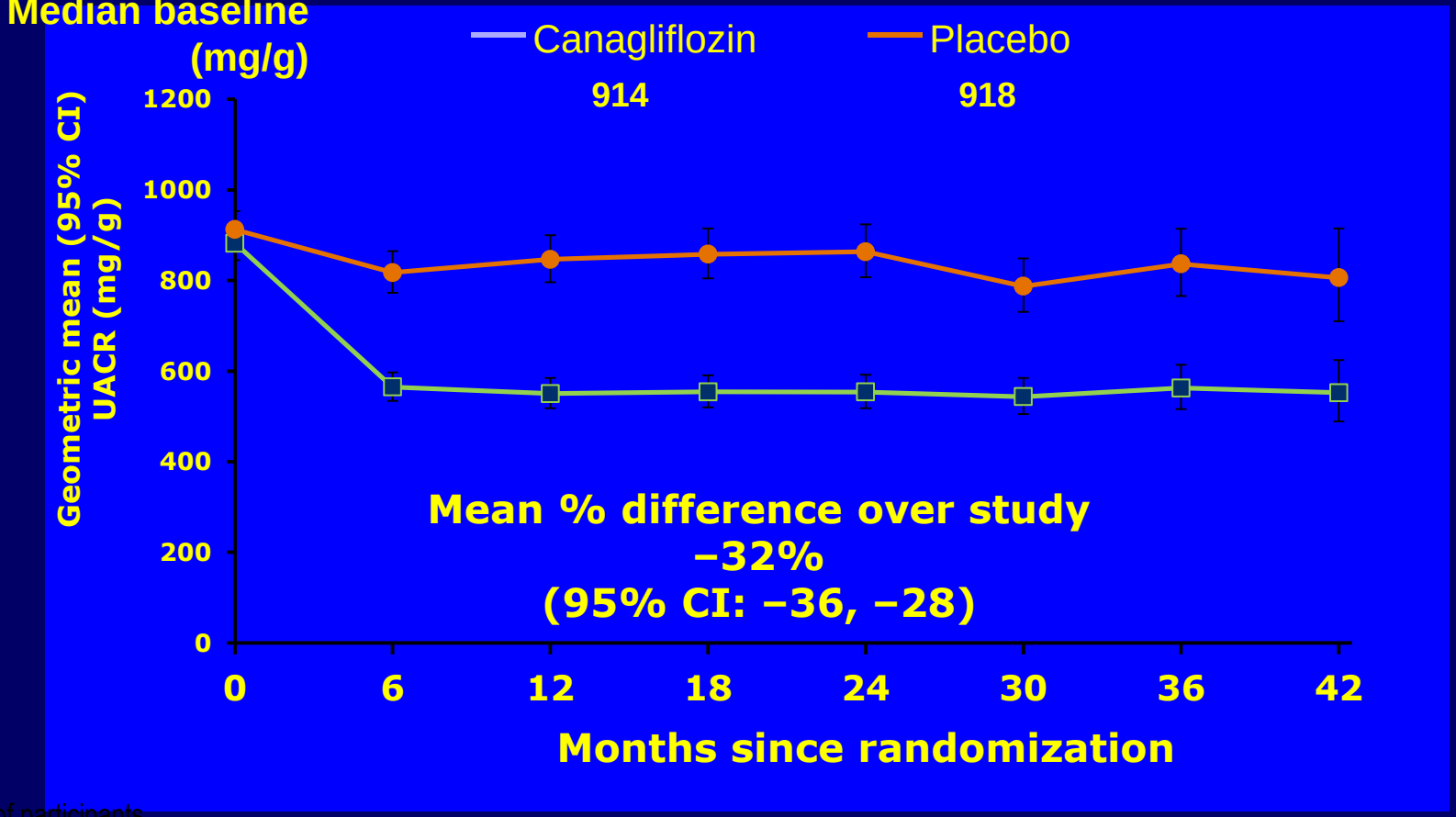


No. of participants

Placebo	2187	2126	2092	2005	1917	1750	1179	679	244
Canagliflozin	2188	2134	2091	2023	1957	1830	1256	731	263

ITT analysis

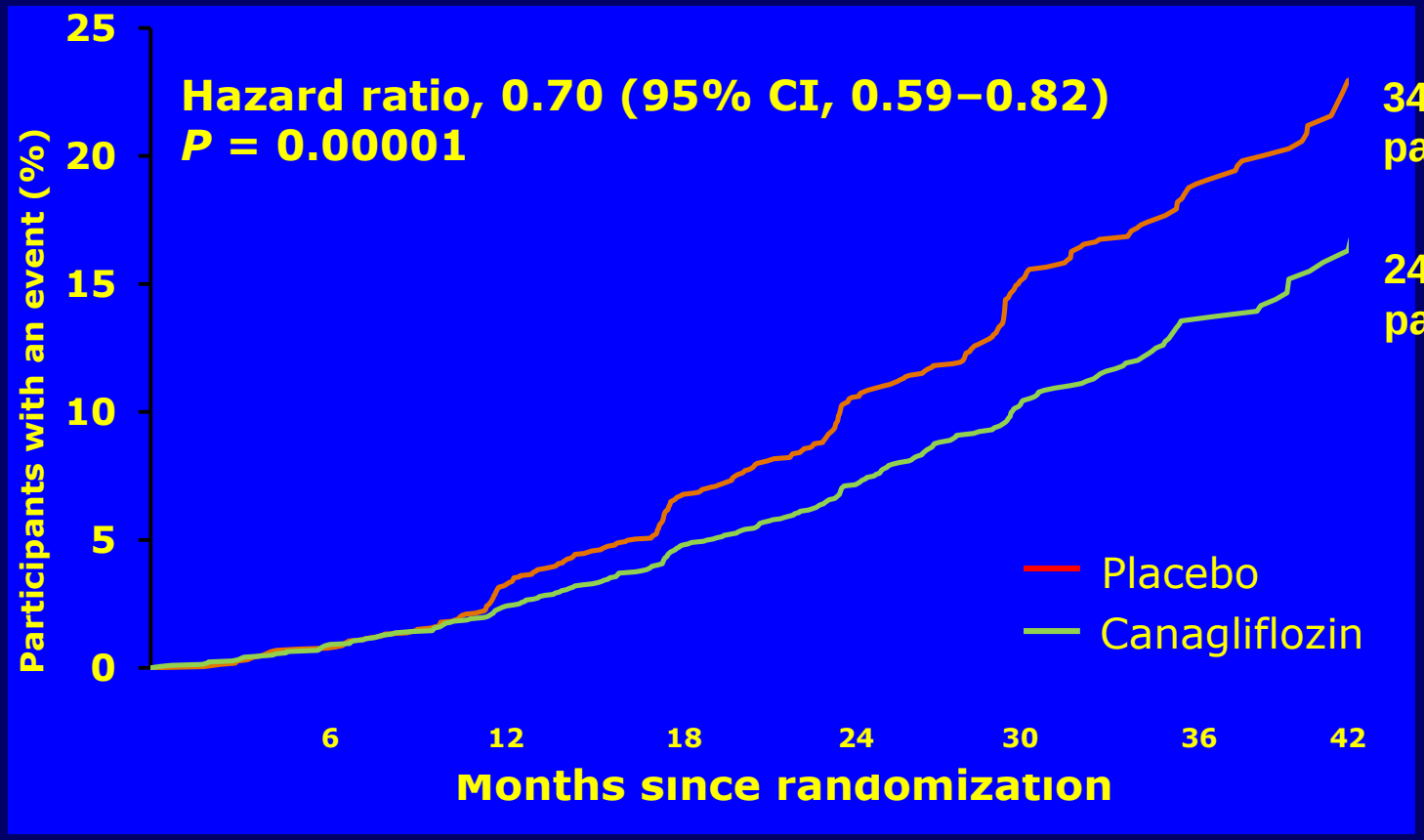
Effects on Albuminuria (UACR)



No. of participants								
Placebo	2113	2061	1986	1865	1714	1158	685	251
Canagliflozin	2114	2070	2019	1917	1819	1245	730	271

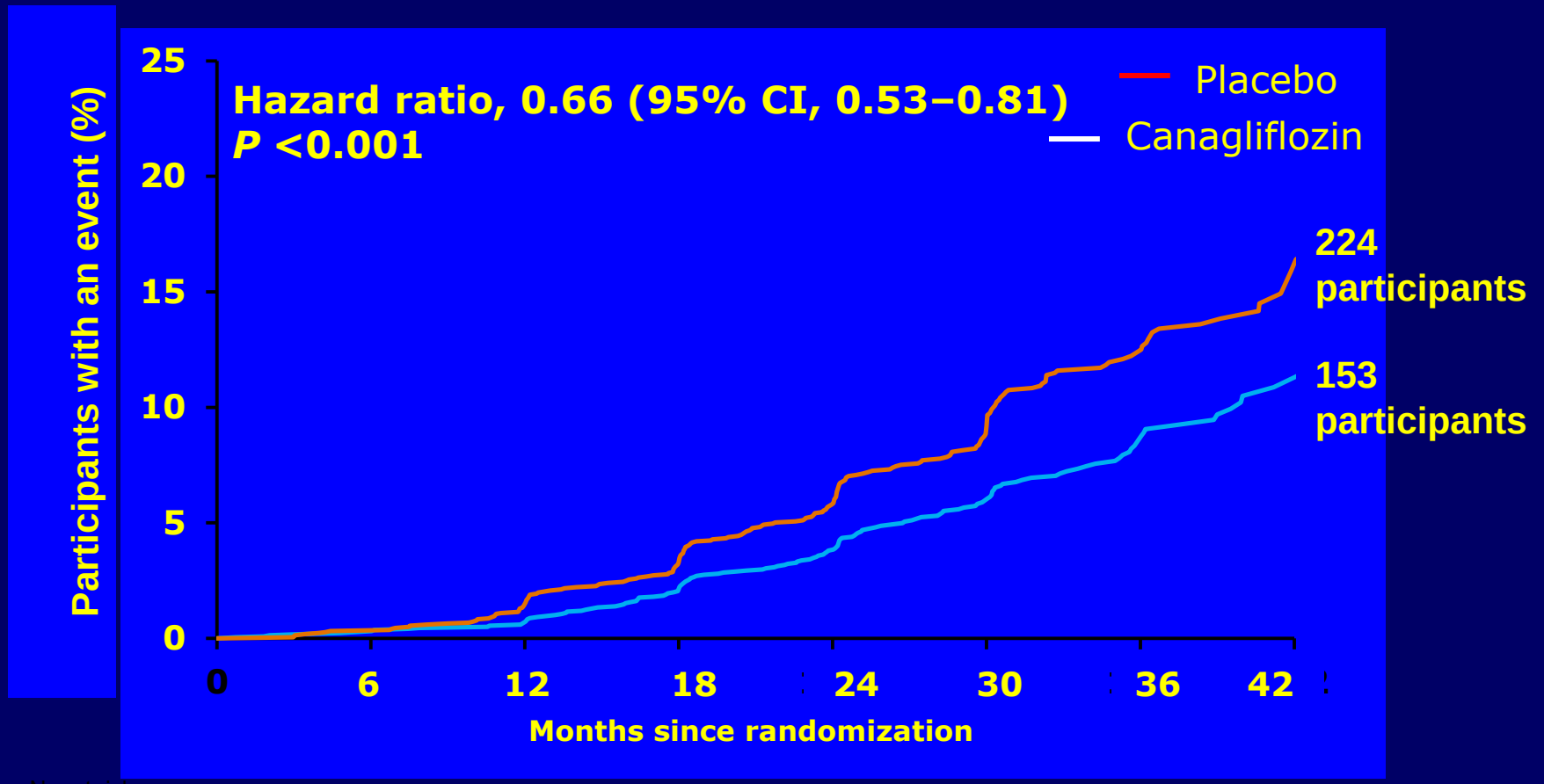
ITT analysis

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



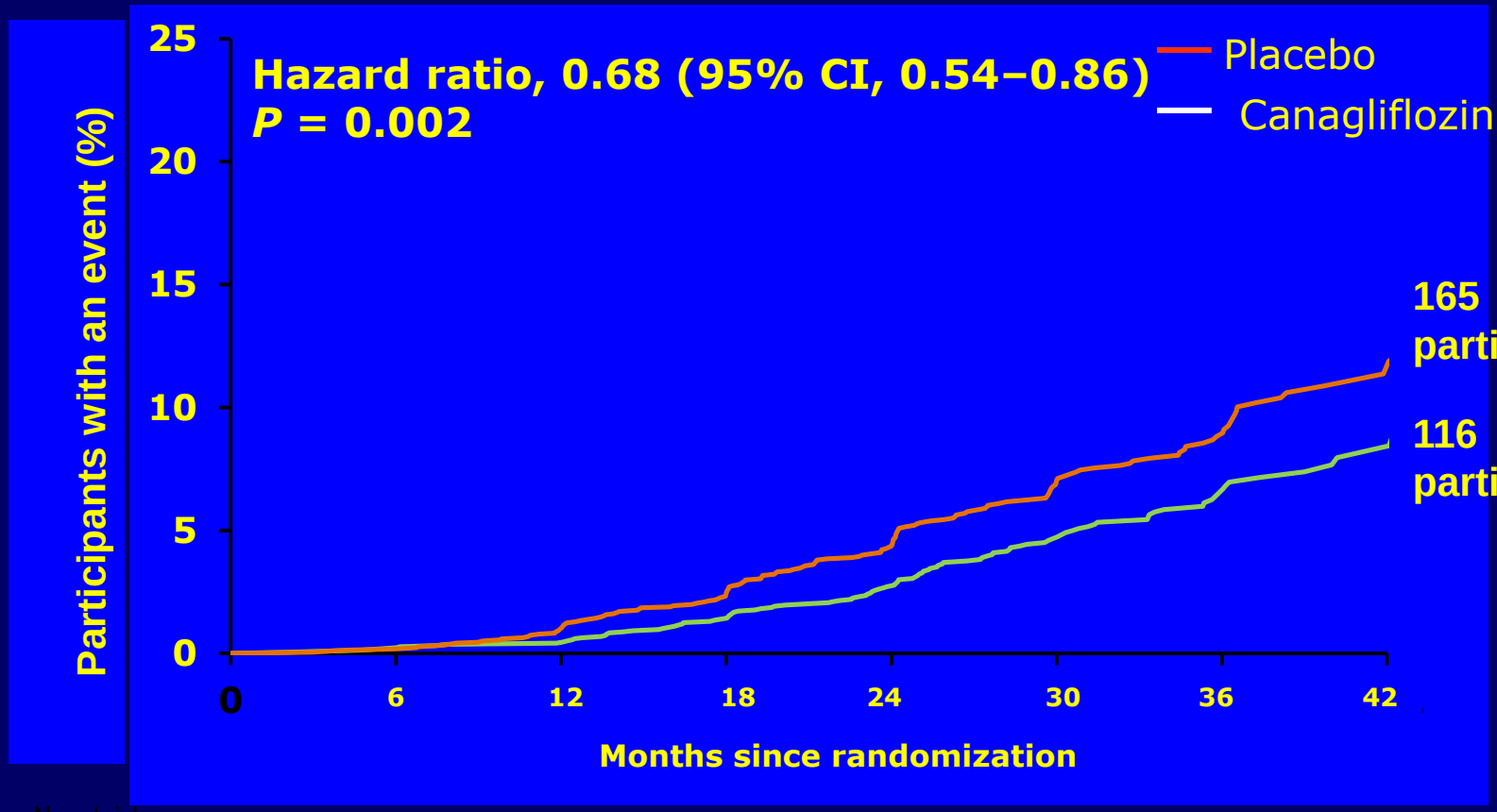
No. at risk								
Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

ESKD, Doubling of Serum Creatinine, or Renal Death



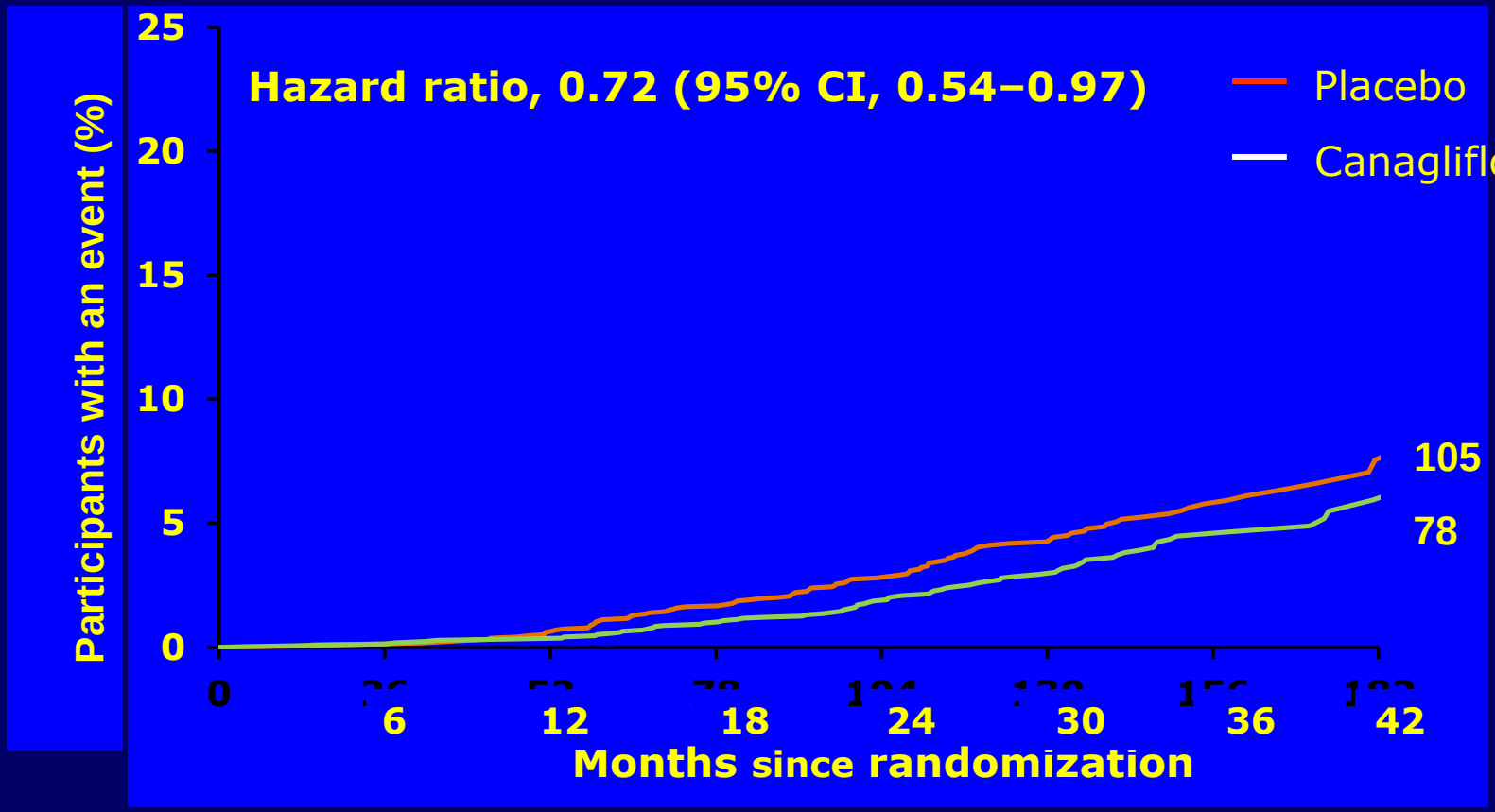
No. at risk								
Placebo	2199	2178	2131	2046	1724	1129	621	170
Canagliflozin	2202	2181	2144	2080	1786	1211	646	196

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

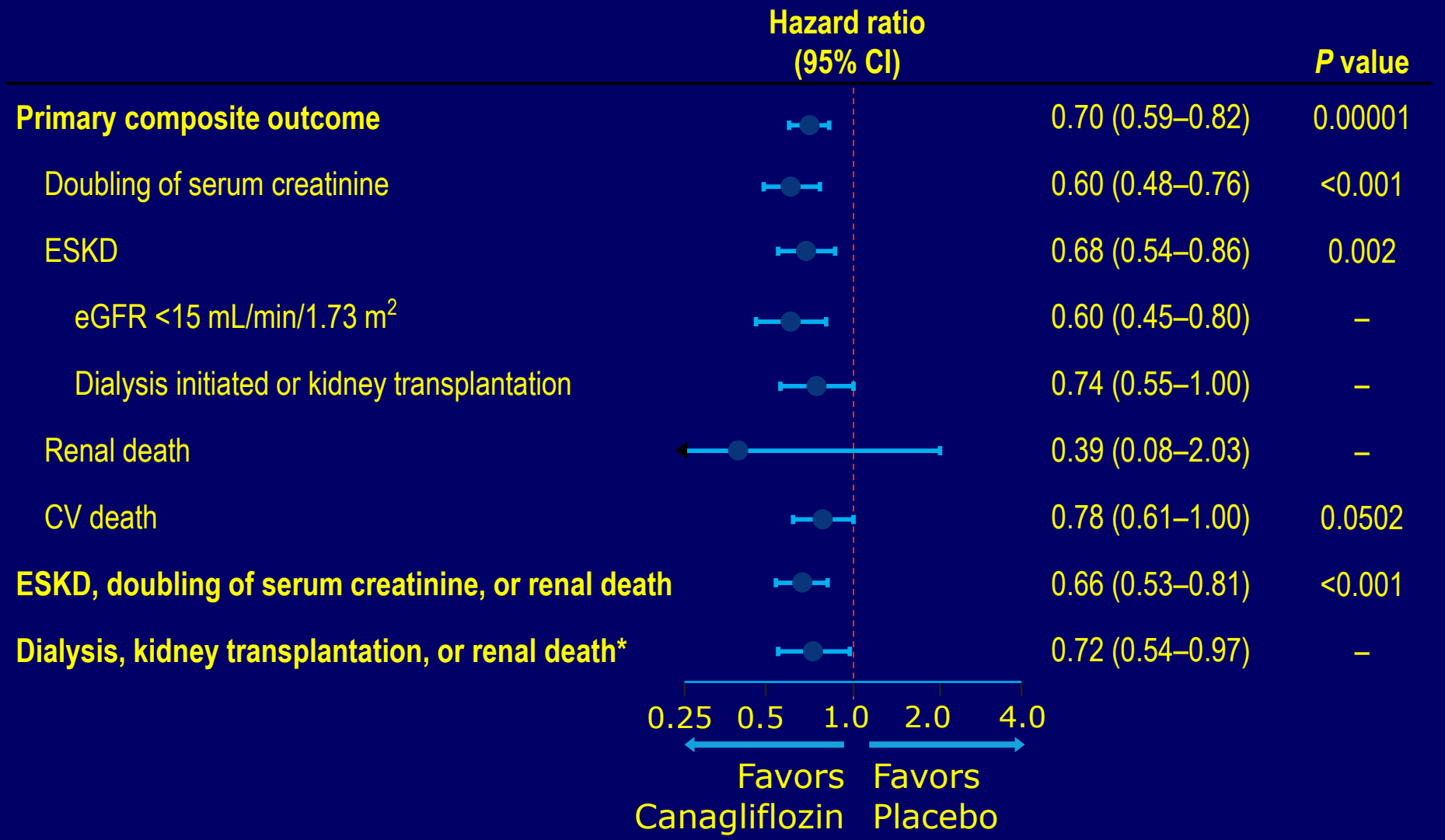
Dialysis, Kidney Transplantation, or Renal Death*



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

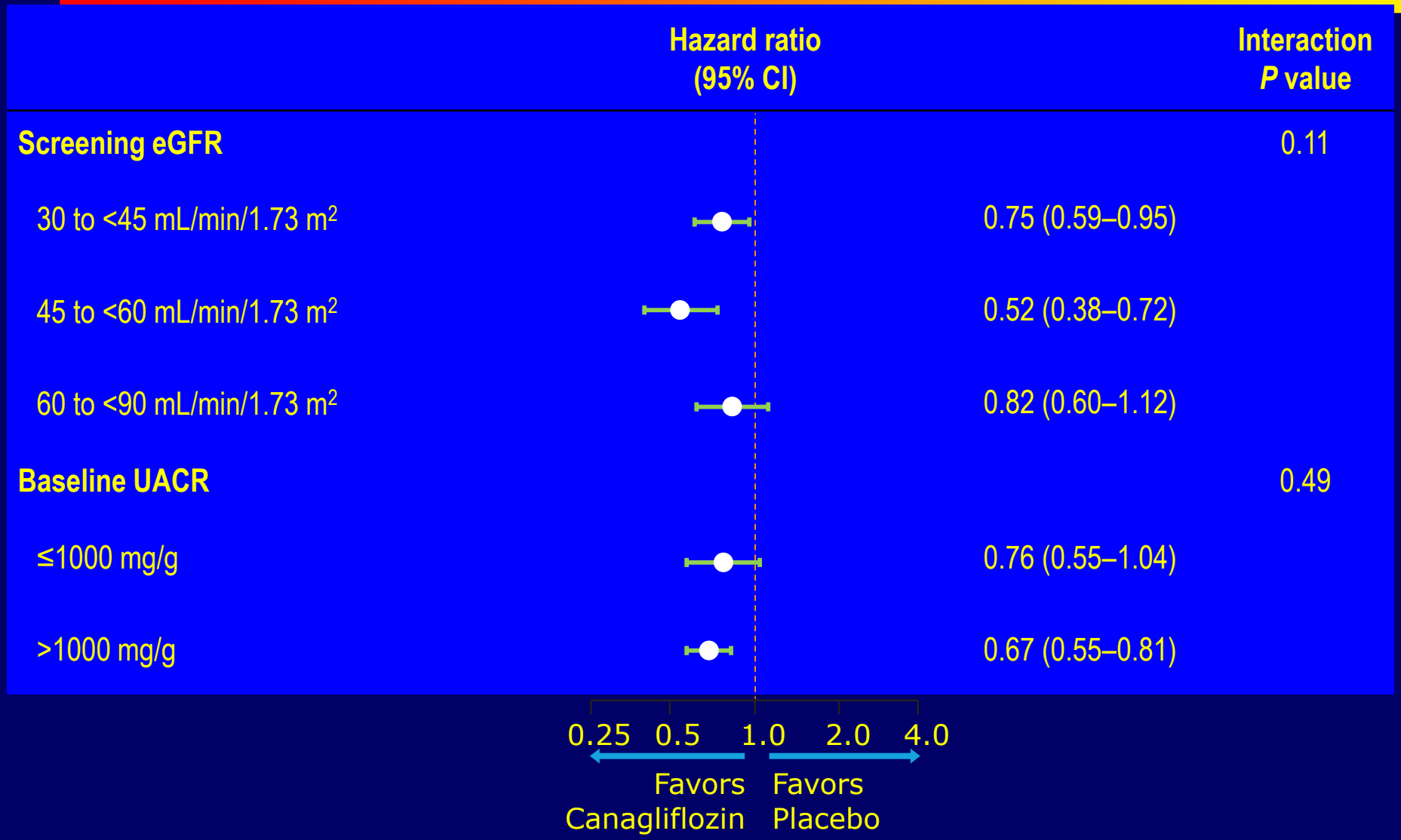
*Post hoc analysis.

Summary Forest Plot

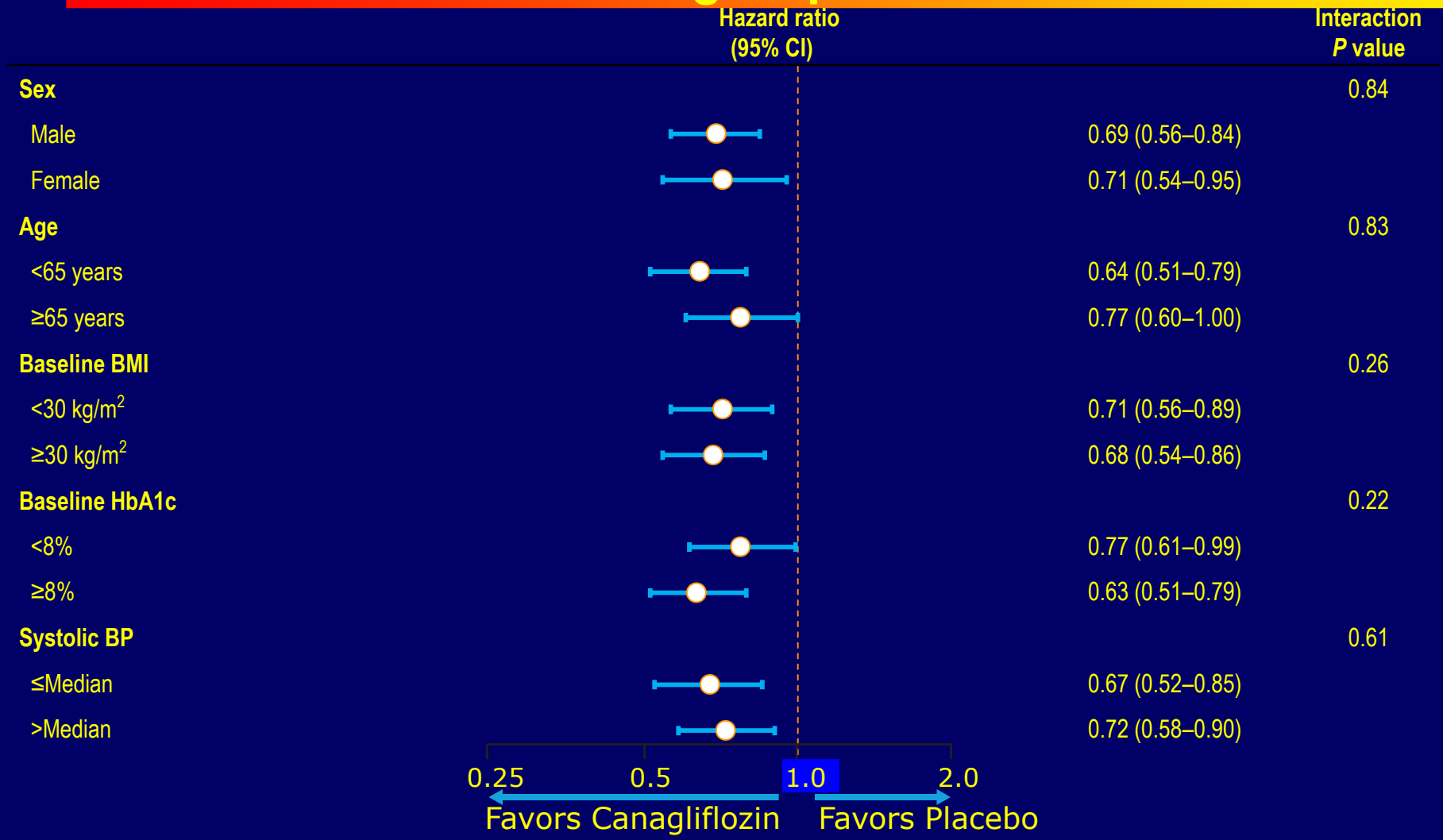


*Post hoc analysis.

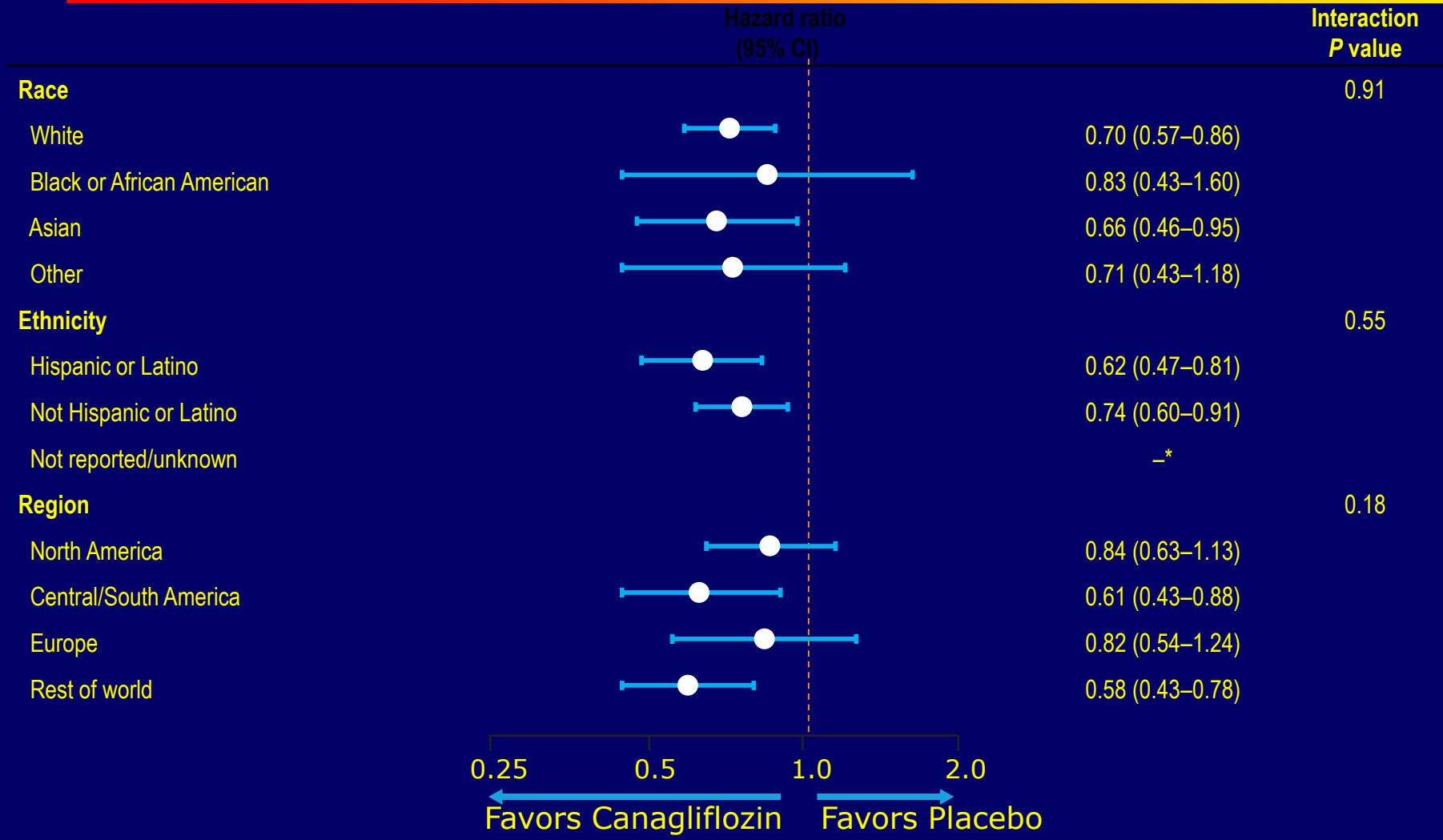
Primary Outcome by Screening eGFR and Albuminuria



Primary Outcome: Demographic and Risk Factor Subgroups

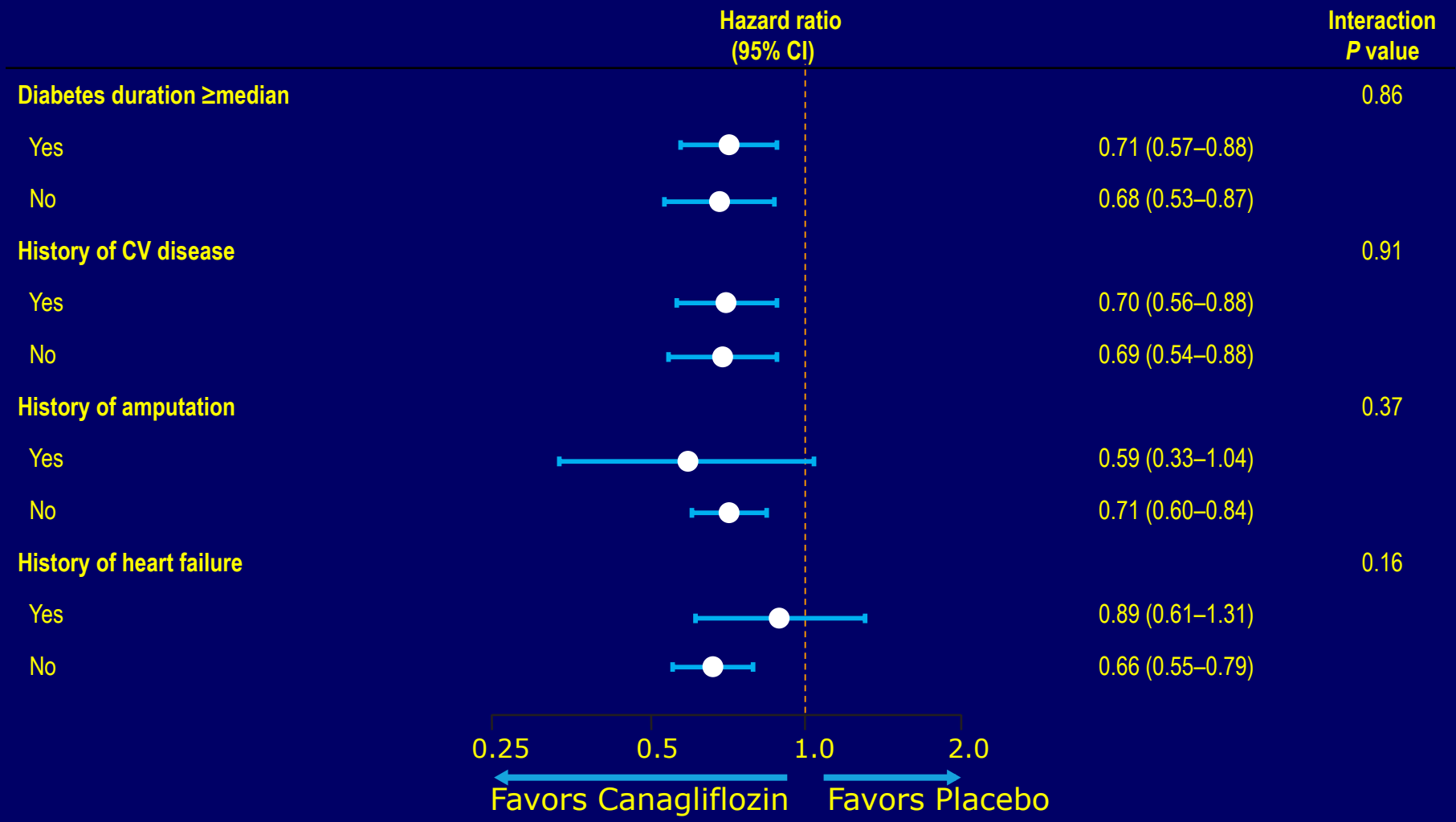


Primary Outcome: Demographic Subgroups

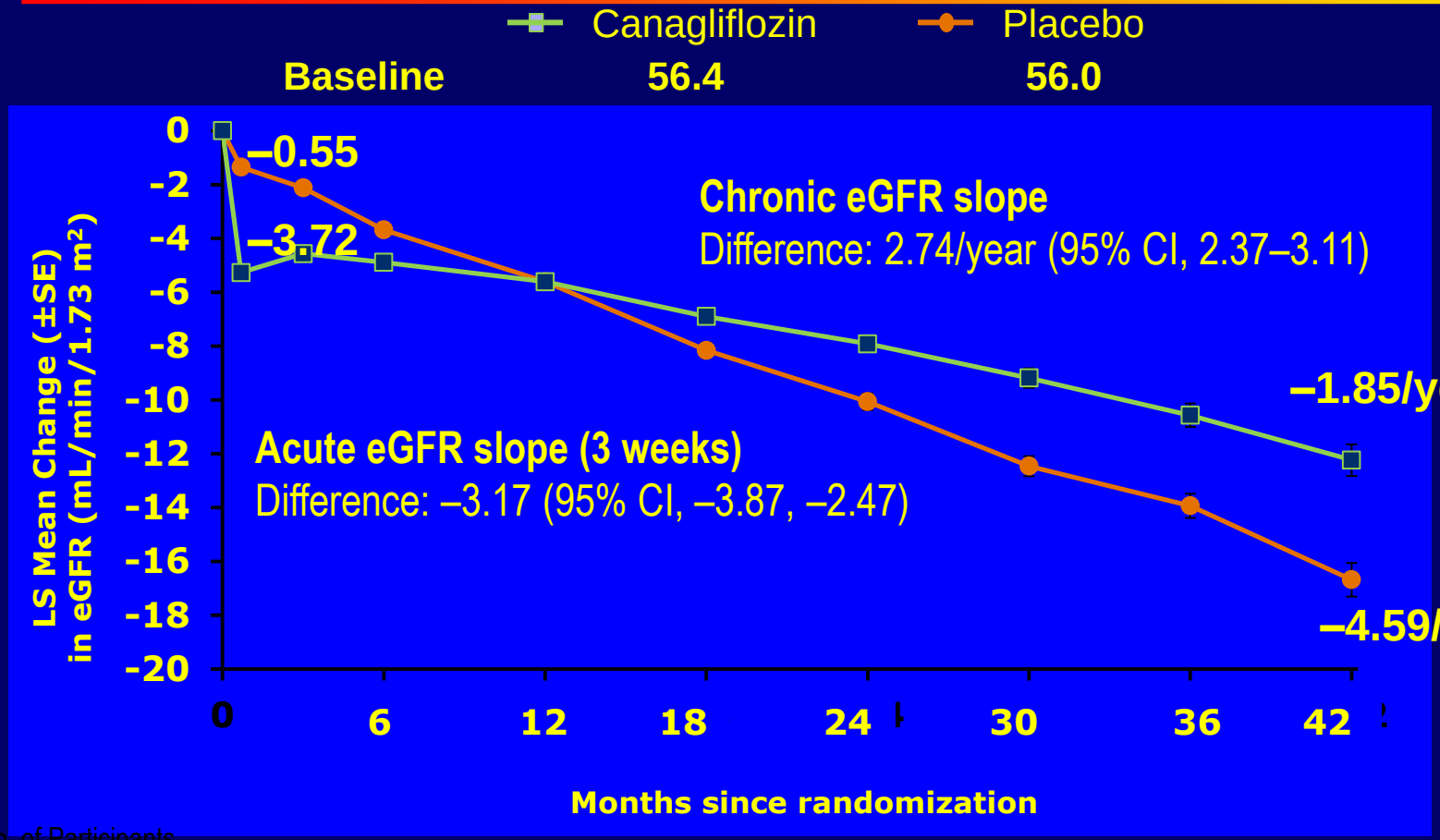


*Hazard ratios and 95% CIs were calculated for outcomes with >10 events.

Primary Outcome: Disease History Subgroups



Effects on eGFR

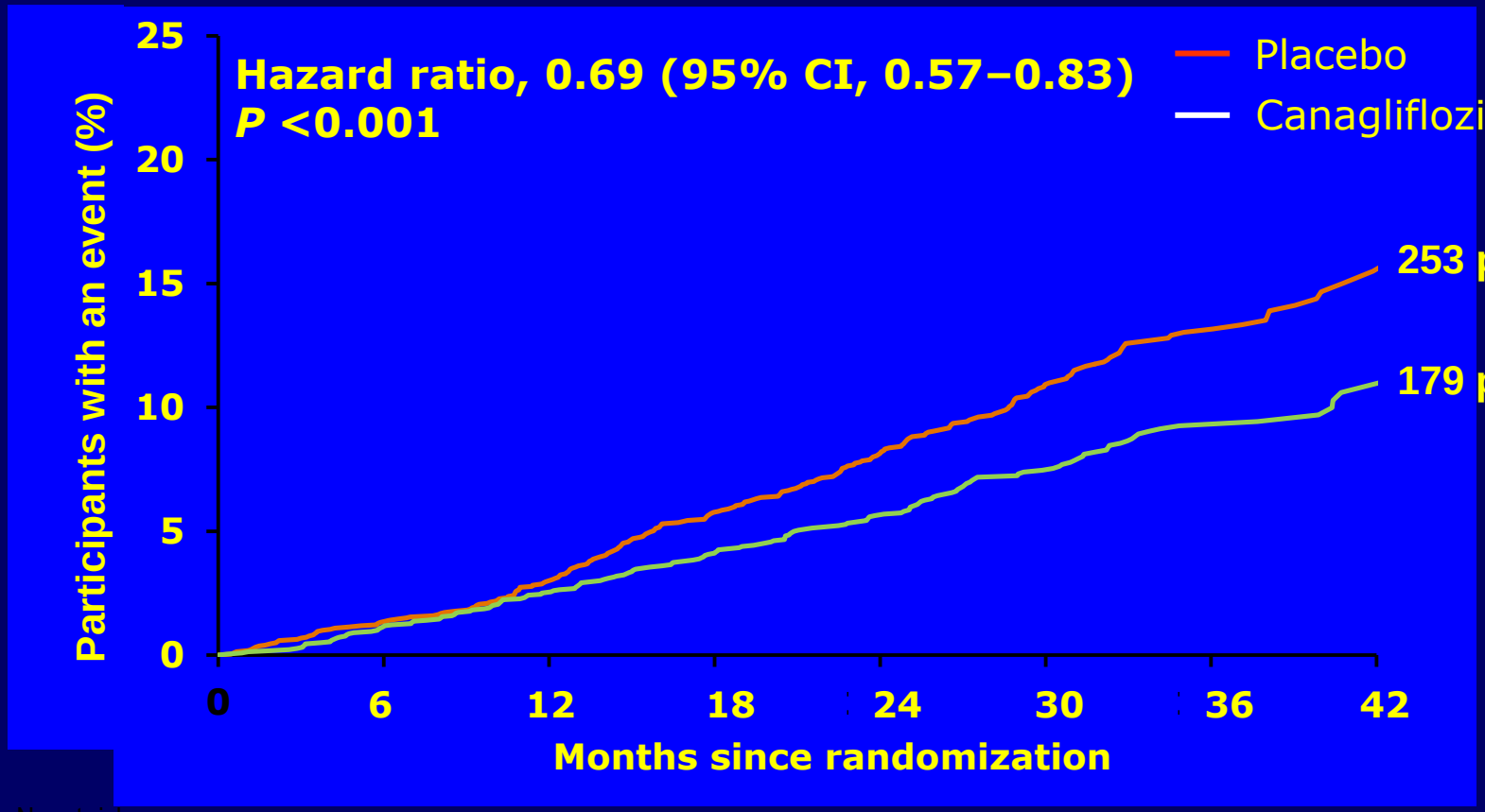


No. of Participants

Placebo	2178	2084	1985	1882	1720	1536	1006	583	210
Canagliflozin	2179	2074	2005	1919	1782	1648	1116	652	241

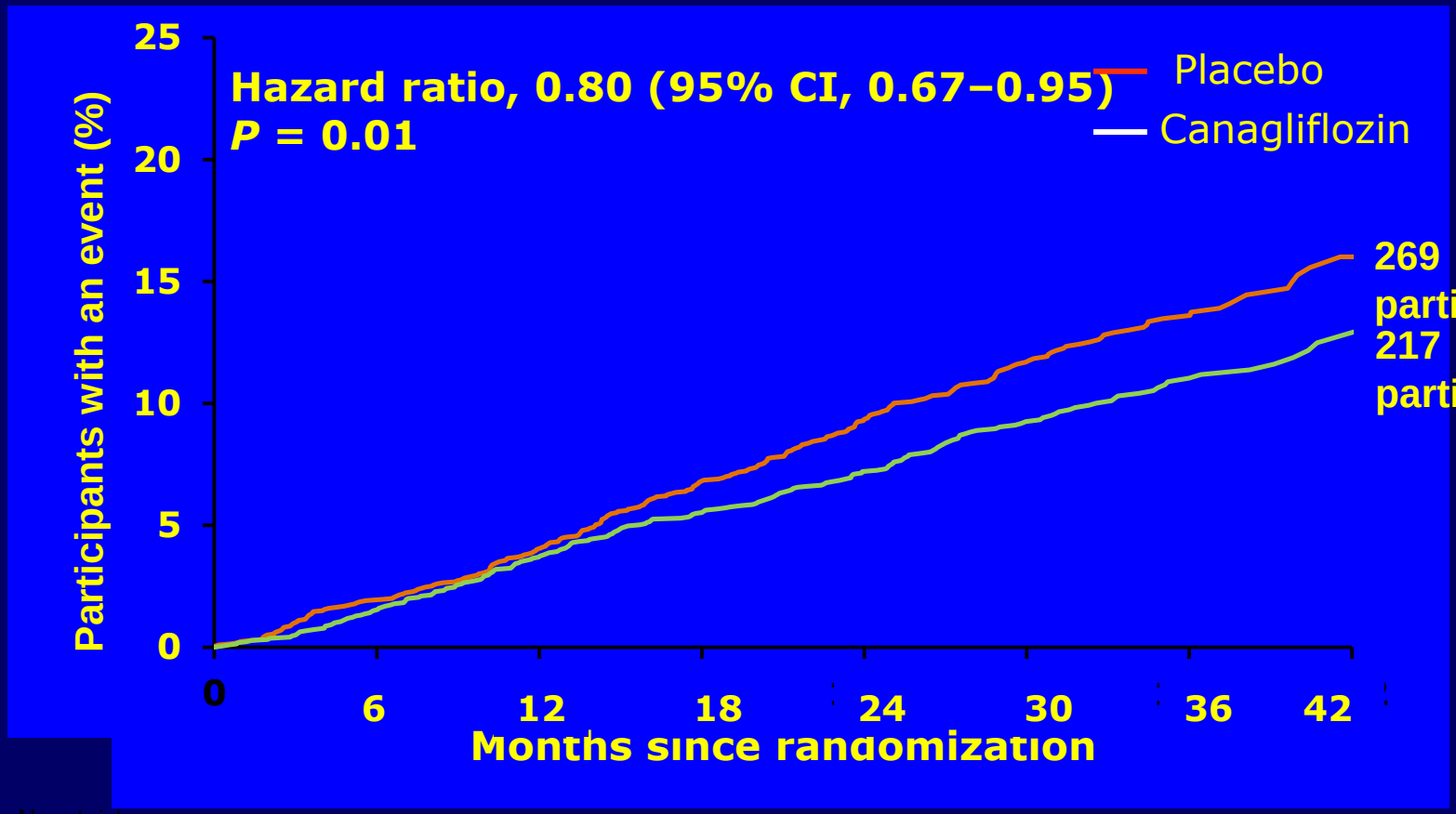
On treatment

CV Death or Hospitalization for Heart Failure



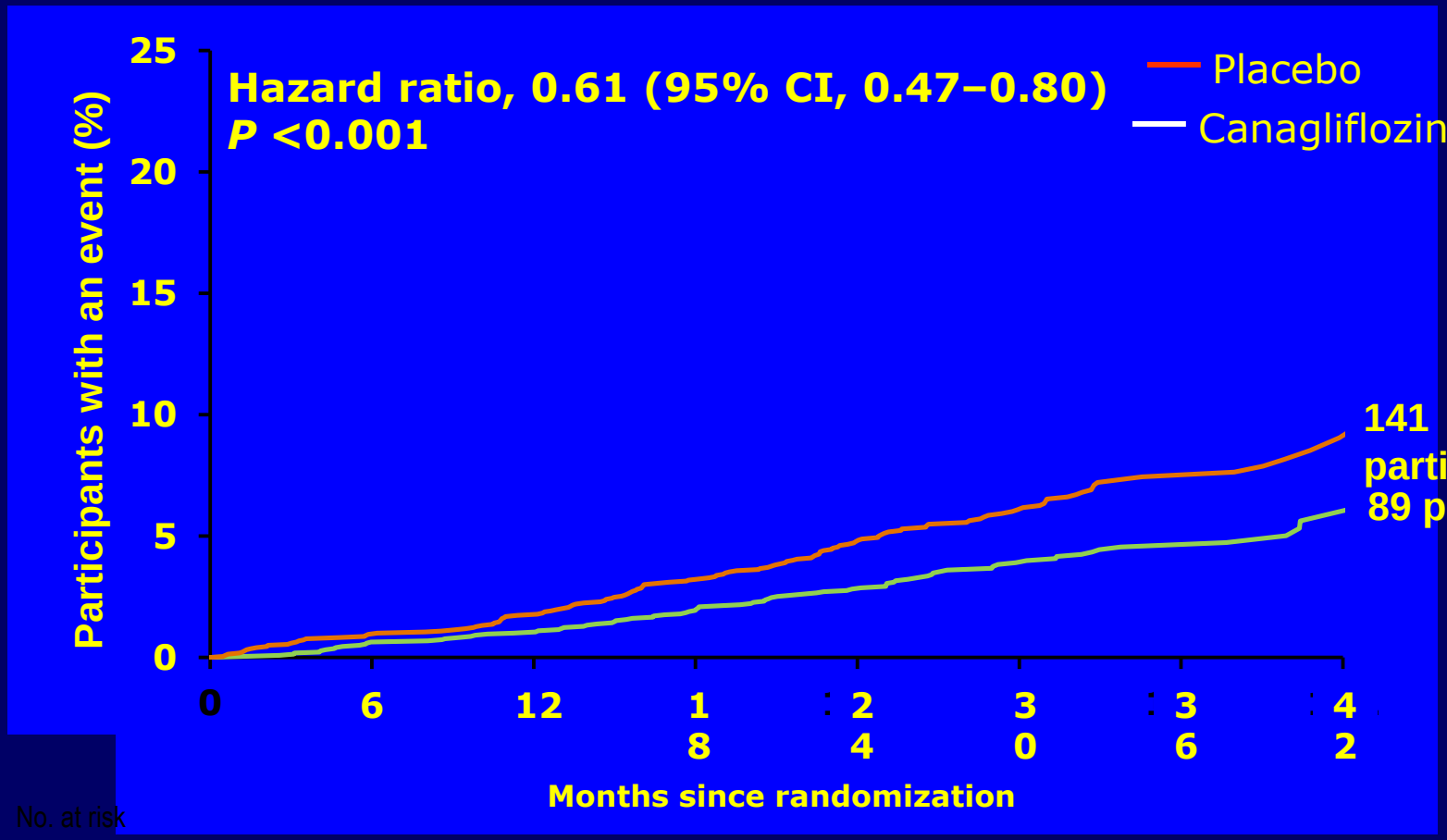
No. at risk								
Placebo	2199	2165	2123	2044	1736	1147	638	170
Canagliflozin	2202	2171	2132	2077	1789	1226	668	199

Major Cardiovascular Events: CV Death, MI, or Stroke



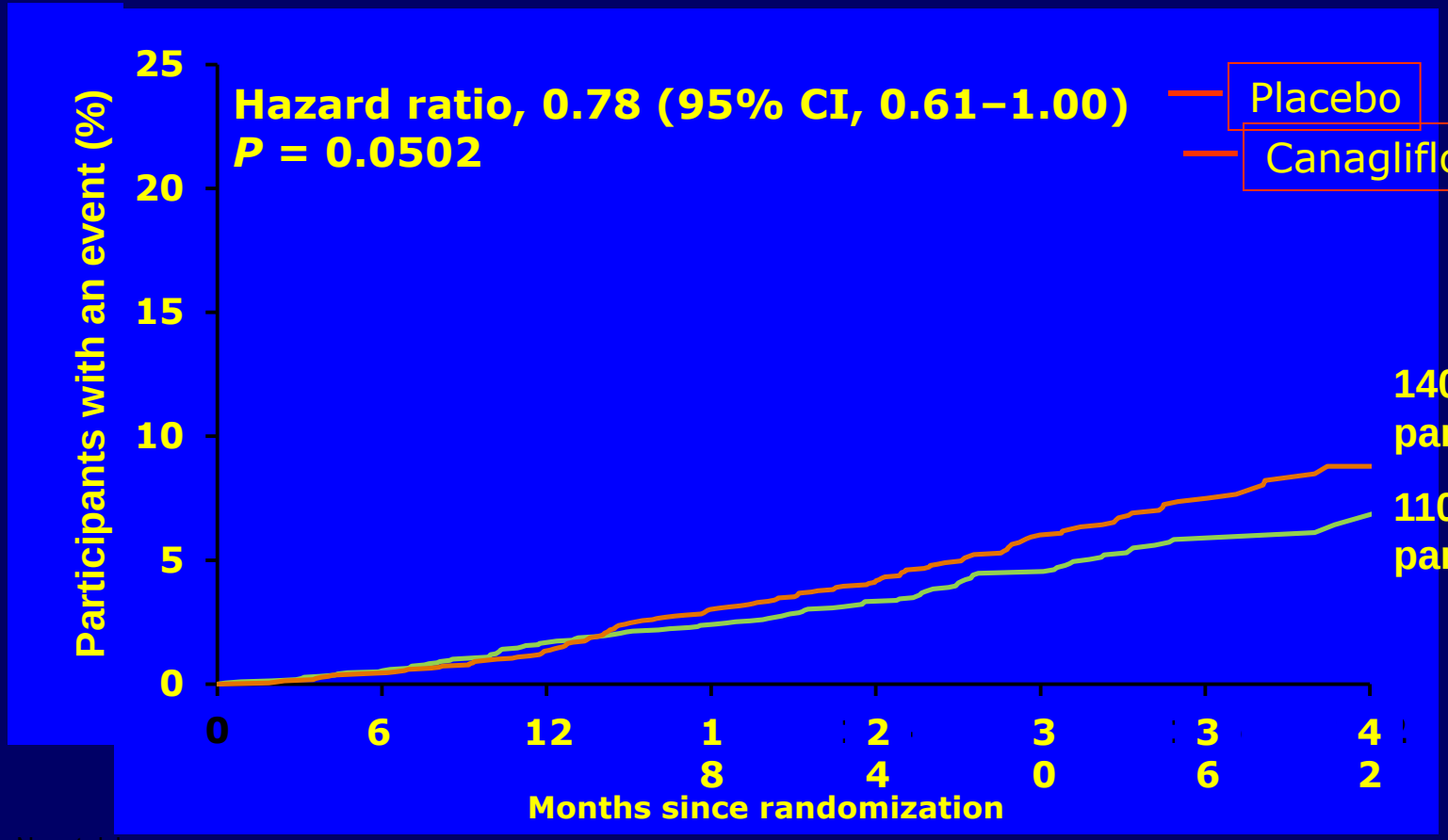
No. at risk								
Placebo	2199	2152	2100	2022	1717	1143	635	168
Canagliflozin	2202	2163	2106	2047	1756	1196	642	198

Hospitalization for Heart Failure



No. at risk								
Placebo	2199	2165	2122	2043	1735	1147	638	170
Canagliflozin	2202	2171	2131	2076	1789	1226	668	199

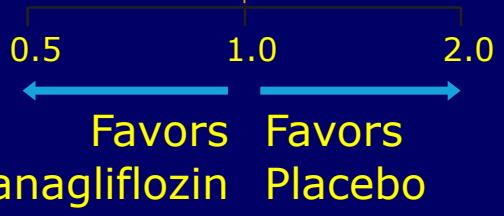
CV Death



No. at risk								
Placebo	2199	2185	2160	2106	1818	1220	688	189
Canagliflozin	2202	2187	2155	2120	1835	1263	687	212

AEs and Serious AEs

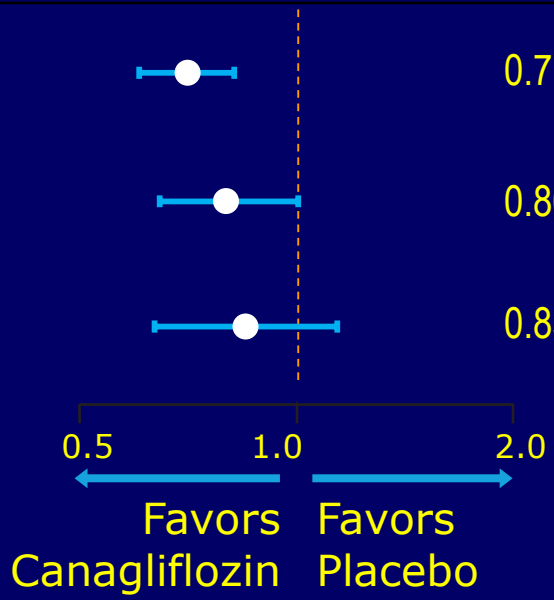
	Number of participants with an event, n		
	Canagliflozin (N = 2200)	Placebo (N = 2197)	Hazard ratio (95% CI)
All AEs	1784	1860	0.87 (0.82–0.93)
All serious AEs	737	806	0.87 (0.79–0.97)



Includes all treated participants through 30 days after last dose.

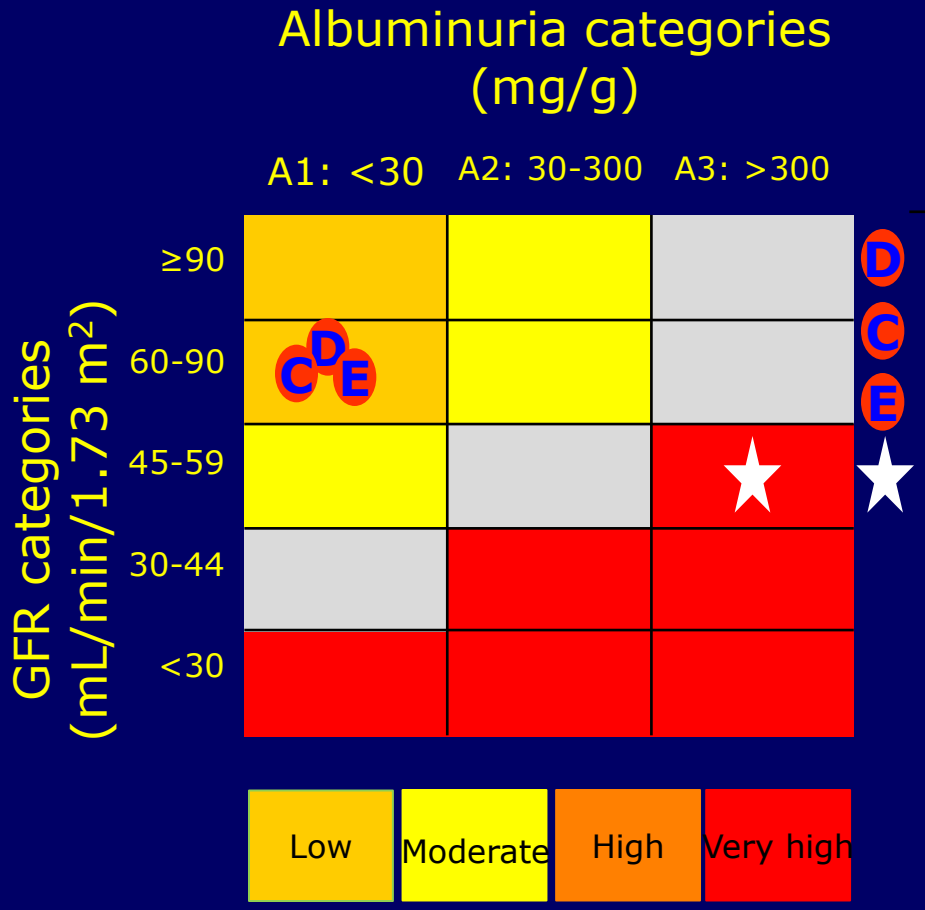
Renal Safety

	Number of participants with an event, n		Hazard ratio (95% CI)
	Canagliflozin (N = 2200)	Placebo (N = 2197)	
All renal-related AEs	290	388	0.71 (0.61–0.82)
Hyperkalemia	151	181	0.80 (0.65–1.00)
Acute kidney injury	86	98	0.85 (0.64–1.13)



Includes all treated participants through 30 days after last dose.

Higher Renal Risk Population in CREDENCE

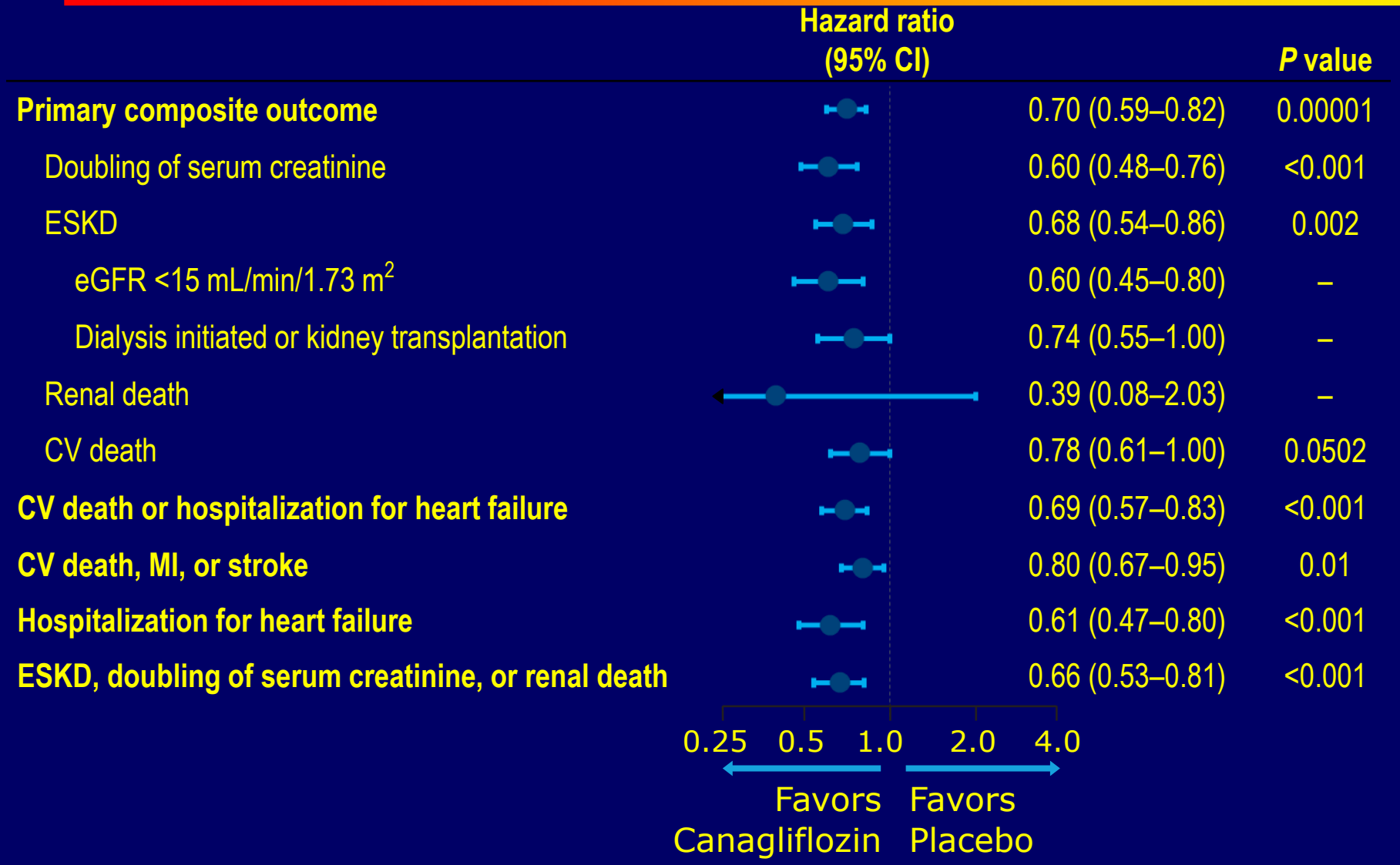


	Mean eGFR (mL/min/1.73 m²)	Median UACR (mg/g)
D DECLARE	85	13
C CANVAS Program	76	12
E EMPA-REG OUTCOME	74	18

Sustained RRT Events

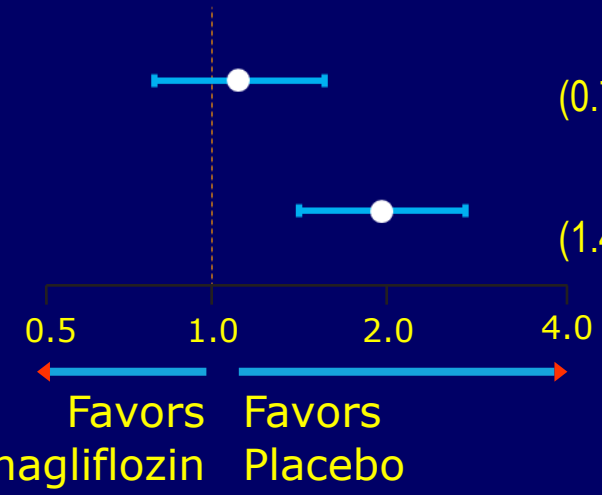
DECLARE	Not reported
CANVAS Program	18
CREDENCE	**176**

CREDENCE: Summary of Key Renal and CV Outcomes



Lower Extremity Amputation

	Participants with an event per 1000 patient-years (n/N)		IRD per 1000 patient-years (95% CI)	Hazard ratio (95% CI)
	Canagliflozin	Placebo		
CREDENCE	12.3 (70/2200)	11.2 (63/2197)	1.16 (–2.87, 5.18)	1.11 (0.79–1.56)
CANVAS Program[1]	6.3 (140/5790)	3.4 (47/4344)	2.93 (1.50, 4.36)	1.97 (1.41–2.75)



Whether the increased risk of lower limb amputation in the CANVAS Program was due to differing trial populations or protocols, or to chance remains unclear

IRD, incidence rate difference.

1. Neal B, et al. *N Engl J Med*. 2017;377(7):644-657.

Still Awake?

“Mannekin Pis” in Brussels—? first SGLT2 user

DECLARE
TIMI-58 TIM STUDY GROUP/MASSIAH MEDICAL ORG
Dapagliflozin Effect on Cardiovascular Events

TIMI

DECLARE – TIMI 58

Stephen D. Wiviott, MD

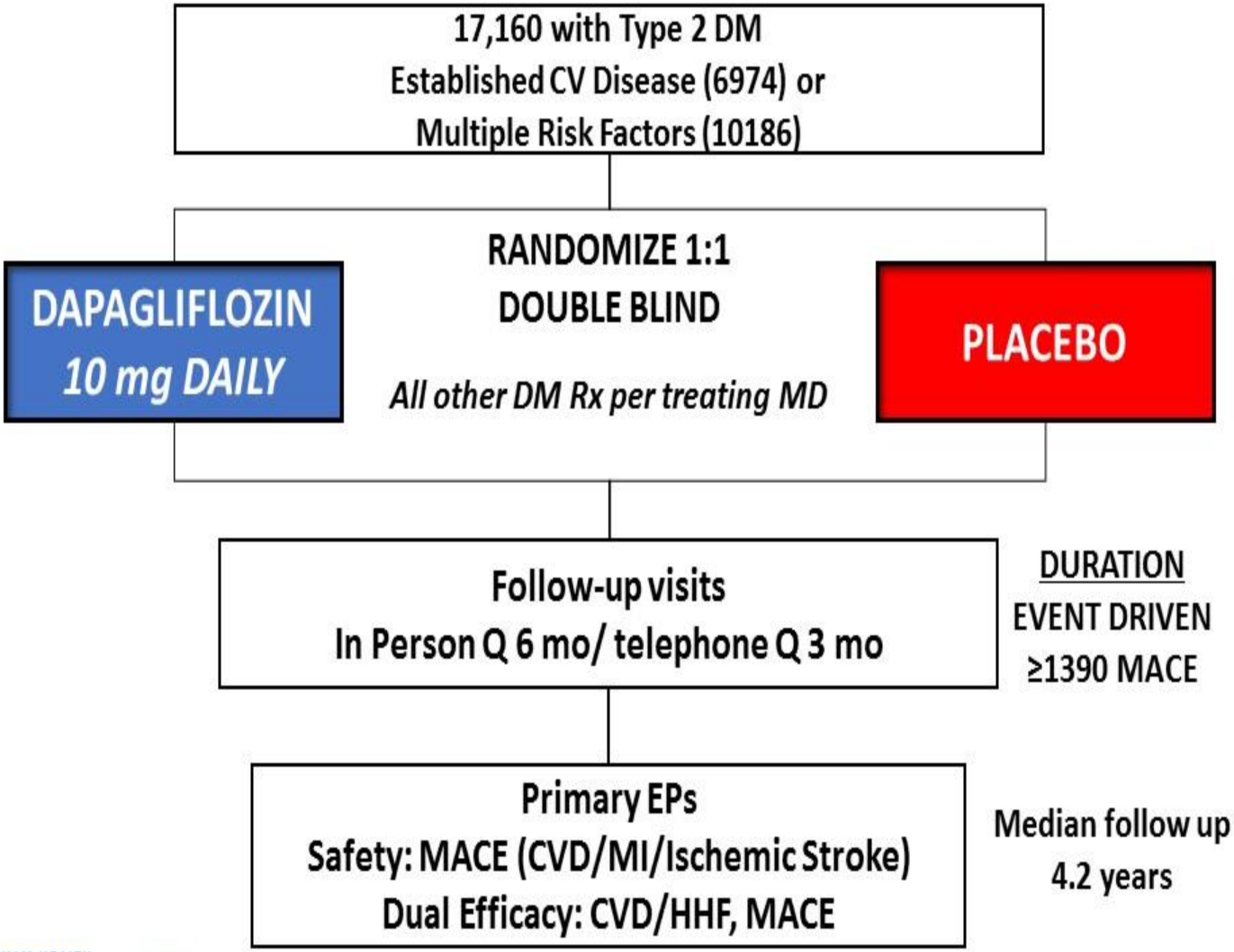
for the DECLARE – TIMI 58 Investigators

American Heart Association, Scientific Sessions

November 10, 2018

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

Trial Design



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

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

Enrollment Criteria

Diagnosis of T2DM, HbA1c 6.5-12%, CrCl ≥60 ml/min

AND

Established ASCVD (Secondary prevention)

- Ischemic heart disease
- Cerebrovascular disease
- Peripheral Artery Disease

Or

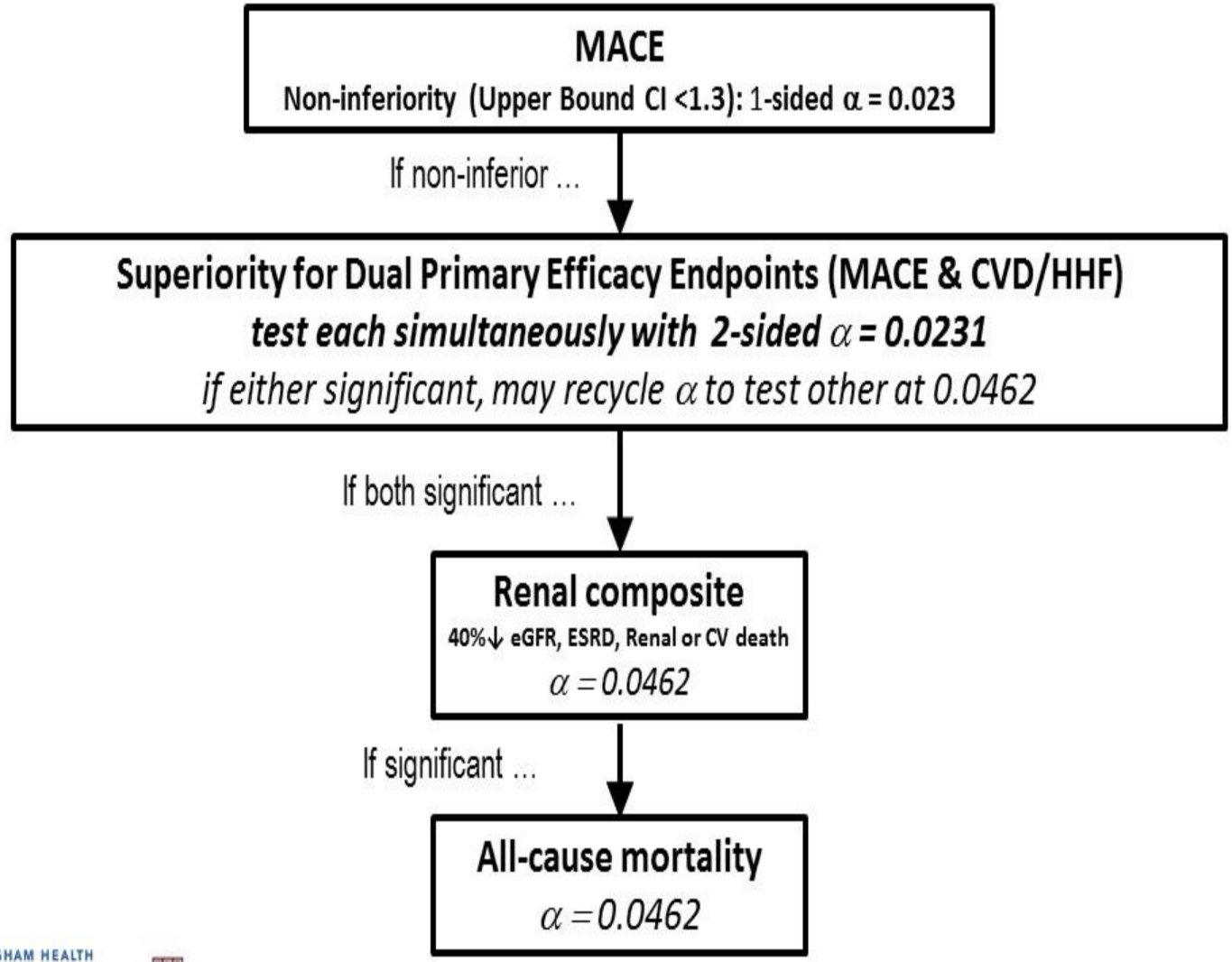
Multiple risk factors for ASCVD (Primary prevention)

Men ≥ 55 yrs and women ≥ 60 yrs with at least one additional risk factor:

- Dyslipidemia
- Hypertension
- Current Tobacco use

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

Analytic Plan



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

Baseline Characteristics

	Full Trial Cohort N = 17160
Age, yrs, Mean (SD)	64 (7)
Female Sex (%)	37
BMI, Mean (SD)	32 (6)
Duration of T2DM, yrs, Median (IQR)	11 (6, 16)
HbA1c (%), Mean (SD)	8.3 (1.2)
eGFR (CKD-EPI), Mean (SD)	85 (16)
Region (%): North America	32
Europe	44
Latin America	11
Asia Pacific	13
Established CV Disease (%)	41
History of Heart Failure (%)	10

P=NS for all between treatment arm comparisons

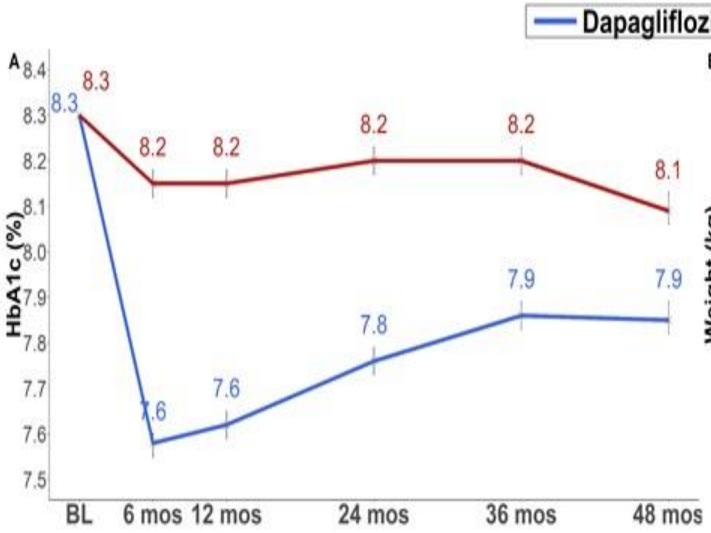
	VERTIS-CV (N = 8,237)	EMPA-REG (N = 7,034)	CANVAS (N = 10,142)	DECLARE (N = 17,160)
	Ertugliflozin	Empagliflozin	Canagliflozin	Dapagliflozin
Age (years)	64.4 ± 8.1	63.1 ± 8.6	63.3 ± 8.3	63.8 ± 6.8
Men, n (%)	5,763 (70.0)	5,026 (72)	6,509 (64.2)	10,738 (62.6)
Race				
White	7,231 (87.8)	5,089 (72)	7,944 (78.3)	79.6%
Black	235 (2.9)	357 (5)	336 (3.3)	3.5%
Asian	497 (6.0)	1,518 (22)	1,284 (12.7)	13.4%
Other	274 (3.3)	70 (1)	578 (5.7)	3.5%
Diabetes duration (years)	12.9 ± 8.3	NA	13.5 ± 7.8	NA
A1C (%)	8.3 ± 0.9[a]	8.1 ± 0.8	8.2 ± 0.9	8.3 ± 1.2
BMI (kg/m^2)	32.0 ± 5.4	30.6 ± 5.3	32.0 ± 5.9	32.1 ± 6.0
eGFR (mL/min/1.73 m^2)	76.0 ± 20.9	74 ± 21	76.5 ± 20.5	86.1 ± 21.8
≥90	2,044 (24.8)	1,534 (22)	2,474 (24.4)	6,855 (39.9)
60 to <90	4,385 (53.2)	3,671 (52)	5,620 (55.5)	8739 (50.9)
30 to <60	1,776 (21.6)	1,796 (26)	2,010 (19.8)	1566 (9.1)[e]
Established CV Disease (%)	99	99	65.6	40.6
Myocardial Infarction	3,940 (47.8)	3,275 (47)		3,580 (20.9)
Coronary Revascularization				
CABG	1,808 (21.9)	1,738 (25)	5721 (56.4)[c]	1,678 (9.8)
PCI	3,402 (41.3)	NA		3,655 (21.3)
Stroke	1,723 (20.9)	1,631 (23)	1,958 (19.3)[d]	1,107 (6.5)[f]
Peripheral arterial disease	1,546 (18.8)	1449 (21)	2,113 (20.8)	1,025 (6.0)
History of Heart Failure	1,777 (21.6)	706 (10.1)[b]	1,461 (14.4)	1,698 (9.9)

Data are n (%) or mean ± SD, unless otherwise shown. NA = data not available. [a]A1C data from screening visit; [b]Percentage based on 7,020 patients; [c]Coronary atherosclerotic disease; [d]Cerebrovascular disease; [e]<60 mL/min/1.73m^2; [f]Ischemic stroke.
A1C = glycosylated hemoglobin. BMI = body-mass index. CABG = coronary artery bypass graft. eGFR = estimated glomerular filtration rate by MDRD. PCI = Percutaneous Coronary Intervention.

Cardiovascular Risk Factors

HbA1c

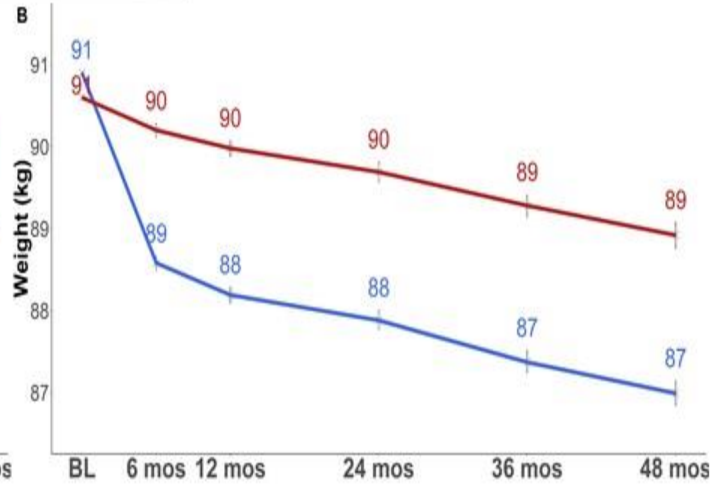
LSM Difference 0.42% (95% CI 0.40-0.45)



All P-values (except BL) <0.001

Weight

LSM Difference 1.8 kg (95% CI 1.7-2.0)

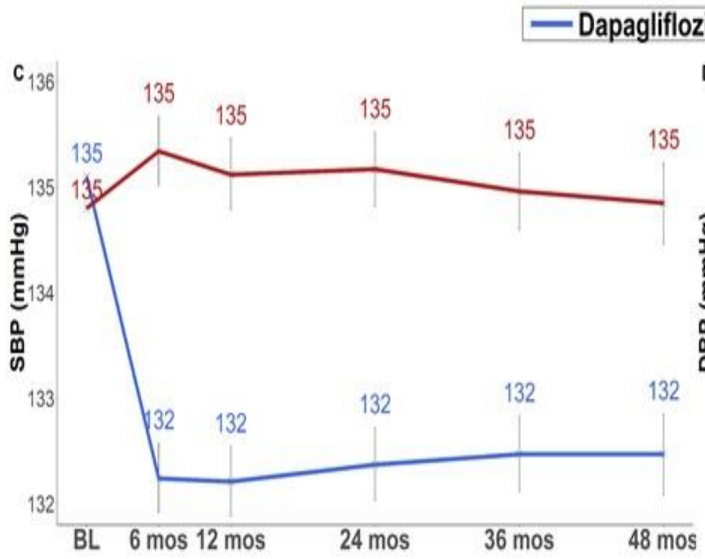


All P-values (except BL) <0.001

Cardiovascular Risk Factors

SBP

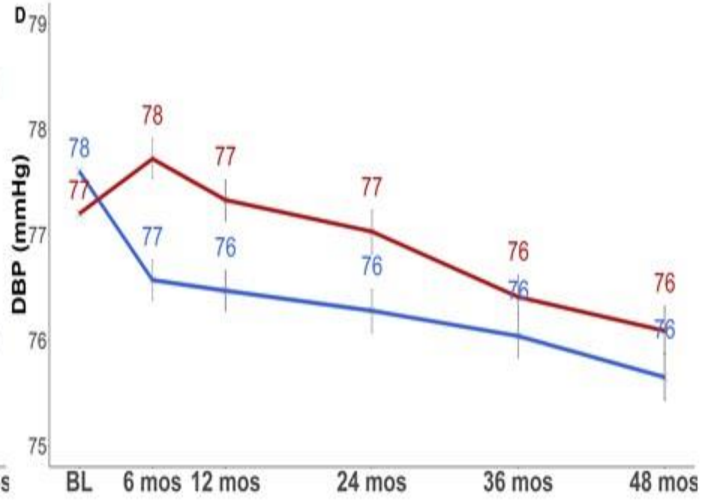
LSM Difference 2.7 mmHg (95% CI 2.4-3.0)



All P-values (except BL) <0.001

DBP

LSM Difference 0.7mmHg (95% CI 0.6-0.9)



All P-values (except BL) <0.001

Primary Endpoints

DECLARE
TIMI-58 TIM STUDY GROUP-HADASSAH MEDICAL ORG
Dapagliflozin Effect on Cardiovascular Events

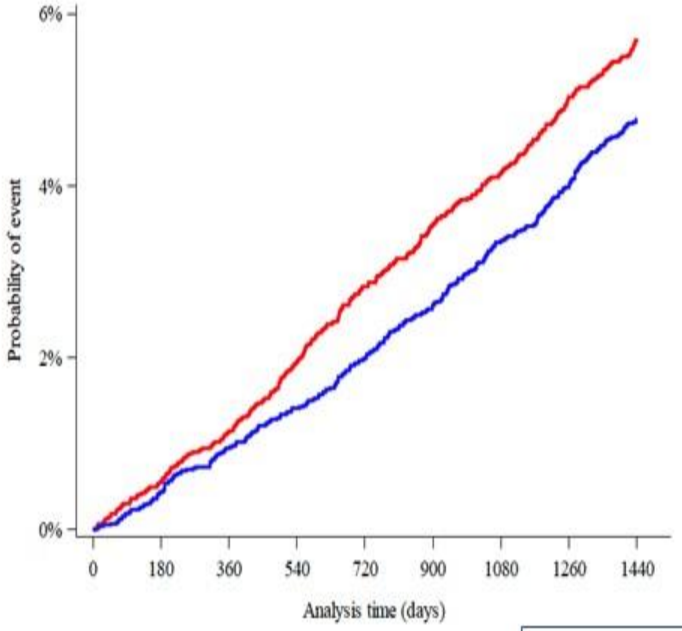
TIMI

CVD/HHF

4.9% vs 5.8%

HR 0.83 (0.73-0.95)

P(Superiority) 0.005



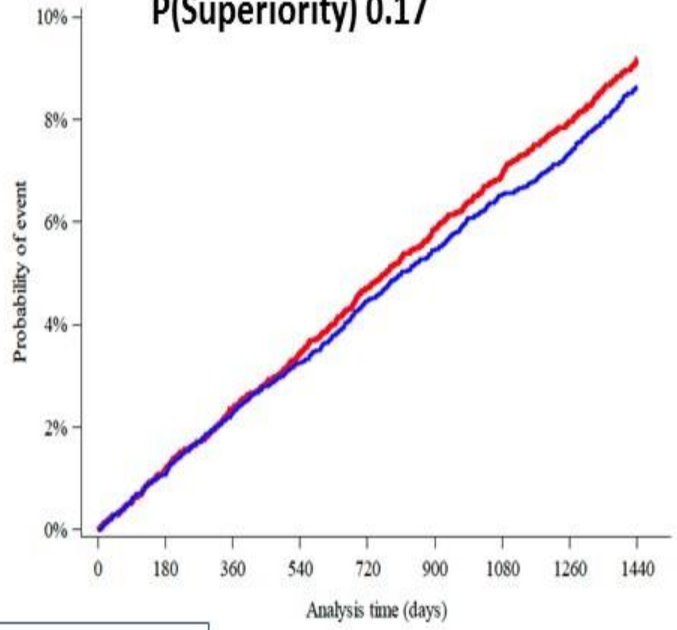
MACE

8.8% vs 9.4%

HR 0.93 (0.84-1.03)

P(Noninferiority) <0.001

P(Superiority) 0.17



Dapagliflozin

Placebo

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Secondary Endpoints

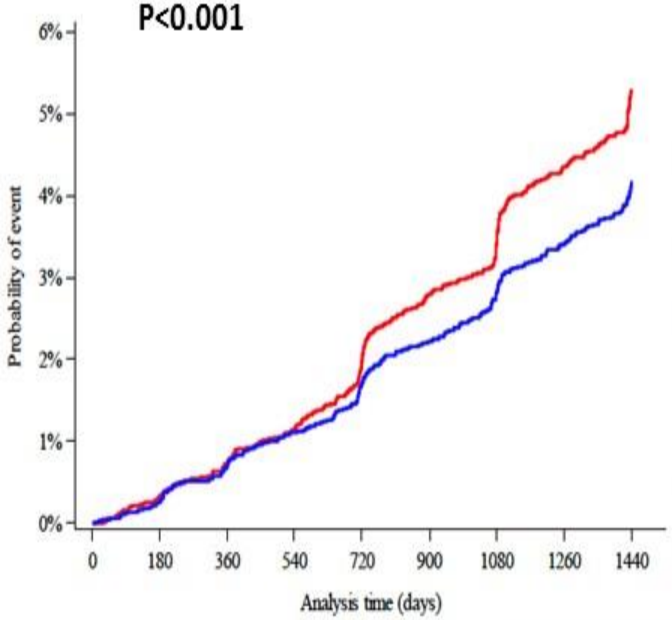
Renal Composite EP

40%↓ eGFR, ESRD, Renal or CV death

4.3% vs. 5.6%

HR 0.76 (0.67-0.87)

P<0.001

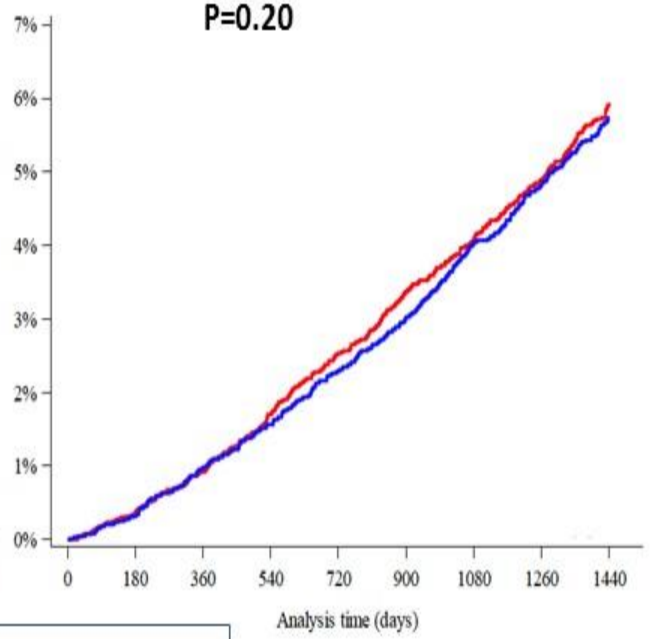


All-Cause Mortality

6.2% vs 6.6%

HR 0.93 (0.82-1.04)

P=0.20



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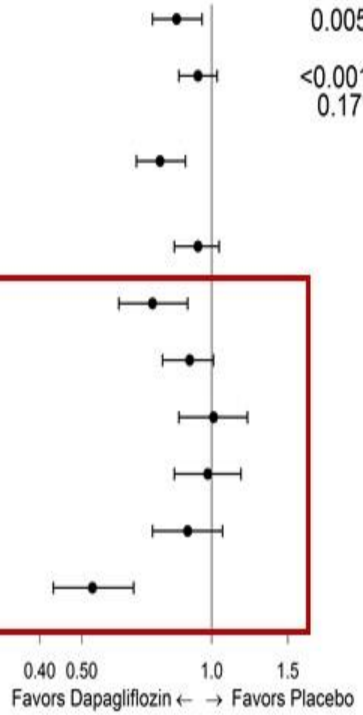
Endpoints and Components

	Dapagliflozin rate/1000 patient-yr	Placebo rate/1000 patient-yr	Hazard Ratio (95% CI)	P value
CV death/HHF	12.2	14.7	0.83 (0.73-0.95)	0.005*
MACE	22.6	24.2	0.93 (0.84-1.03)	<0.001** 0.17*
40% decrease in eGFR to <60 ml/min/m2, ESRD, or renal or CV death	10.8	14.1	0.76 (0.67-0.87)	
All-cause death	15.1	16.4	0.93 (0.82-1.04)	
HHF	6.2	8.5	0.73 (0.61-0.88)	
Myocardial infarction	11.7	13.2	0.89 (0.77-1.01)	
Ischemic Stroke	6.9	6.8	1.01 (0.84-1.21)	
CV death	7.0	7.1	0.98 (0.82-1.17)	
Non-CV death	6.0	6.8	0.88 (0.73-1.06)	
40% decrease in eGFR to <60 ml/min/m2, ESRD, or renal death	3.7	7.0	0.53 (0.43-0.66)	



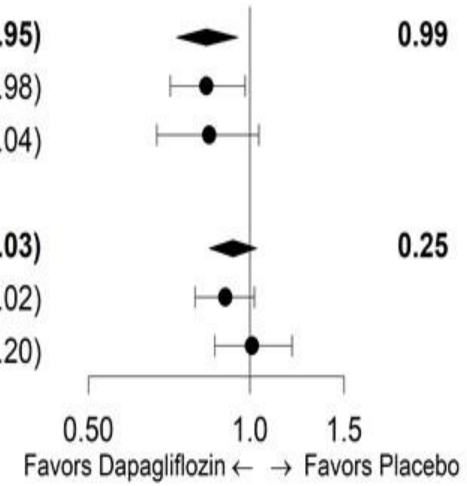
*P for superiority, **P for non-inferiority

Primary Efficacy Endpoints by Presence of ASCVD vs MRF

DECLARE TIMI-58 Dapagliflozin Effect on Cardiovascular Events

TIMI

Outcomes	Dapagliflozin Events per 1000 pt years	Placebo Events per 1000 pt years	Hazard Ratio (95% CI)	P value for interaction
CV death/HHF	**12.2**	**14.7**	**0.83 (0.73-0.95)**	**0.99**
ASCVD	19.9	23.9	0.83 (0.71-0.98)	
MRF	7.0	8.4	0.84 (0.67-1.04)	
MACE	**22.6**	**24.2**	**0.93 (0.84-1.03)**	**0.25**
ASCVD	36.8	41.0	0.90 (0.79-1.02)	
MRF	13.4	13.3	1.01 (0.86-1.20)	



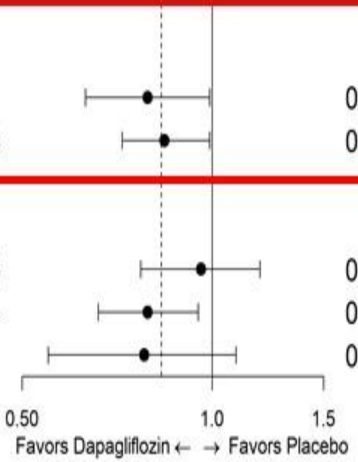
Effect on CVD/HHF in Key Subgroups

DECLARE TIMI-58 Dapagliflozin Effect on Cardiovascular Events

TIMI

CVD/HHF

	Dapagliflozin n\N	Placebo n\N	Hazard Ratio (95% CI)	HR (95%-CI)	P Value for Interaction
Total Cohort	**417/8582**	**496/8578**		**0.83 (0.73-0.95)**	
Risk Group					**0.99**
ASCVD	272/3474	325/3500		0.83 (0.71-0.98)	
MRF	145/5108	171/5078		0.84 (0.67-1.04)	
History of HF					**0.60**
Yes	142/852	172/872		0.79 (0.63-0.99)	
No	275/7730	324/7706		0.84 (0.72-0.99)	
eGFR					**0.37**
>=90 mL/min/1.73m2	163/4137	163/4025		0.96 (0.77-1.19)	
60 - <90 mL/min/1.73m2	199/3838	252/3894		0.79 (0.66-0.95)	
<60 mL/min/1.73m2	55/606	81/659		0.78 (0.55-1.09)	



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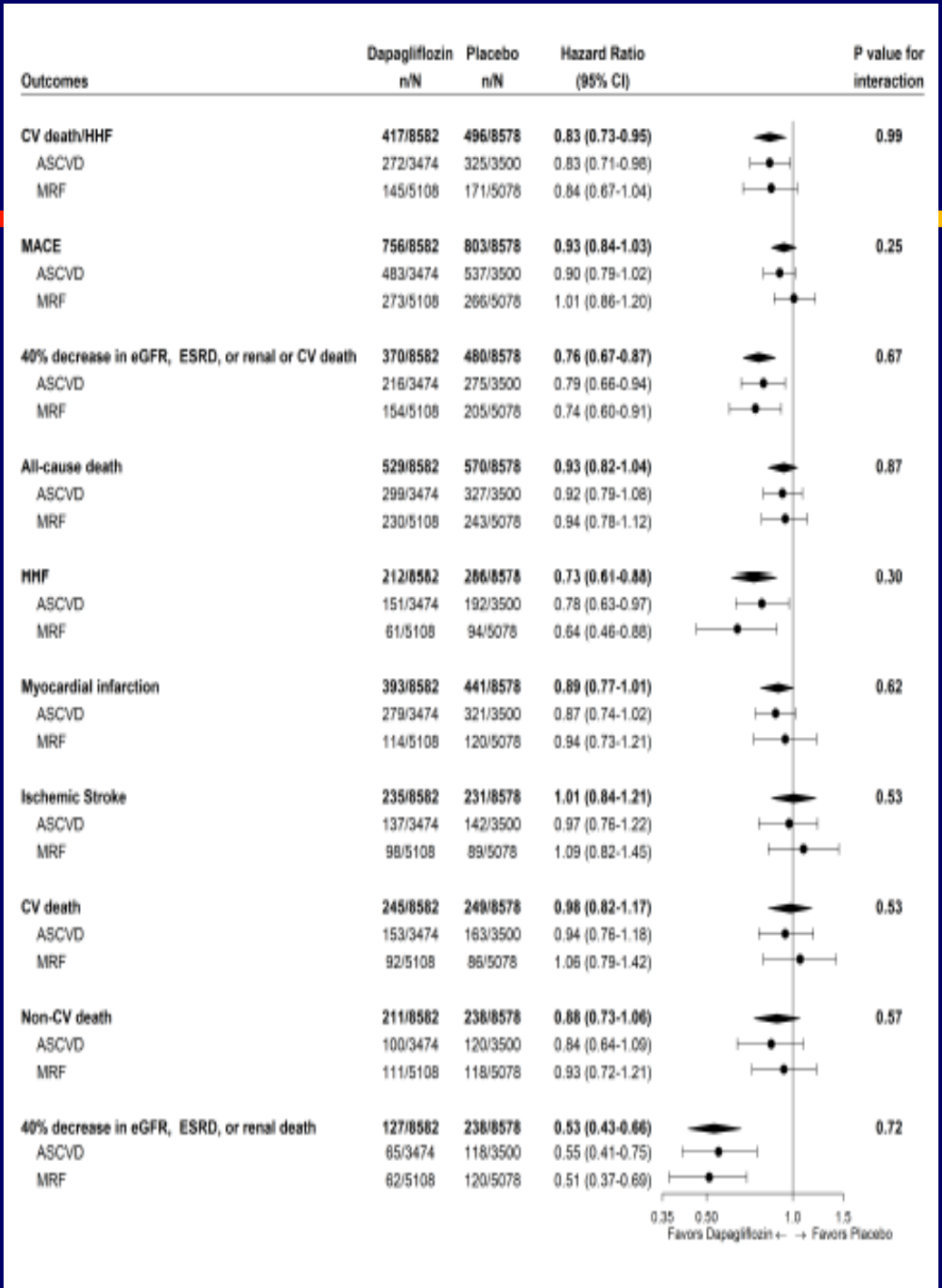
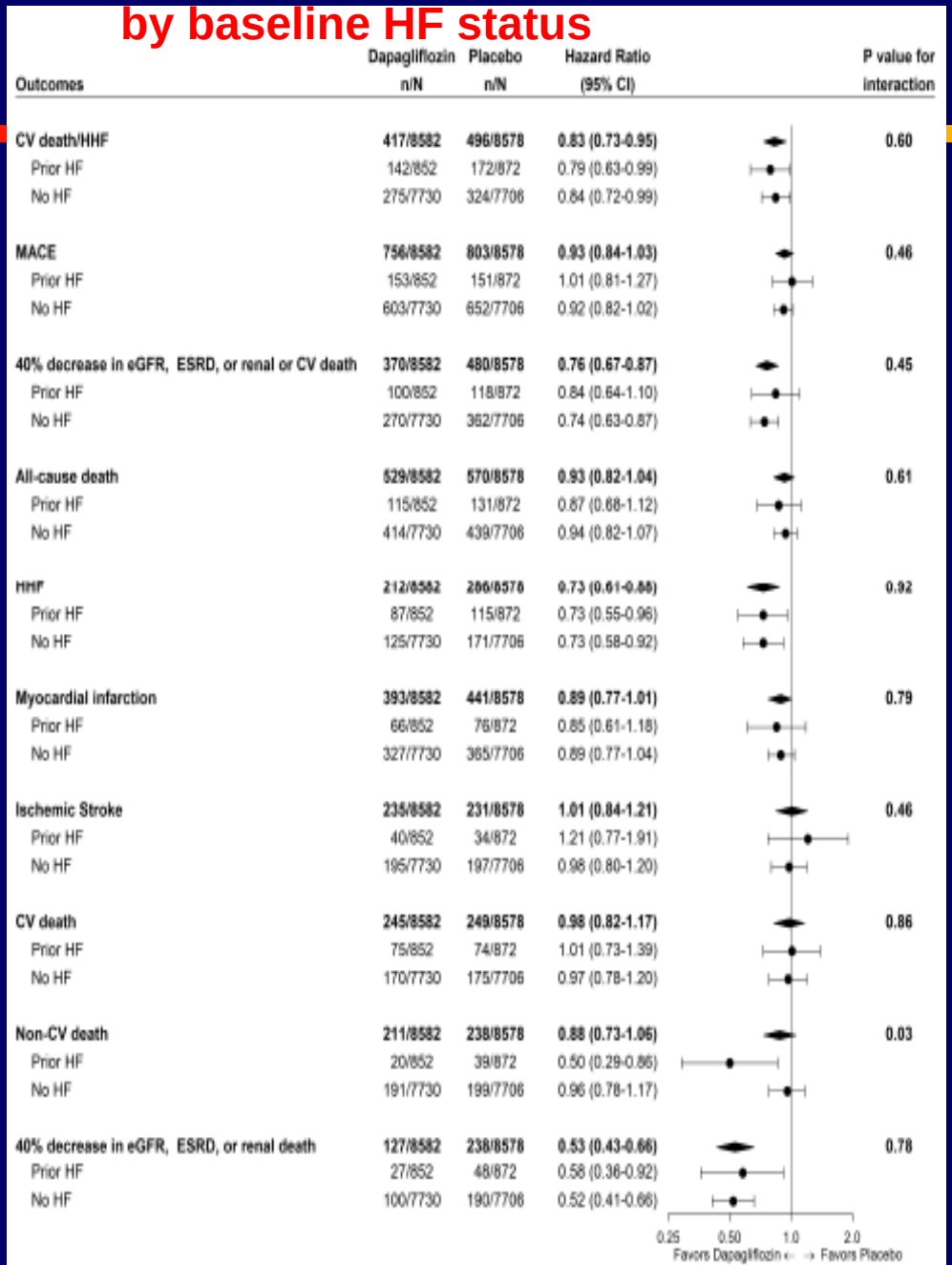
Supplemental Figure 4: Key Outcomes by Enrollment Stratum (Composites and Components)



Supplemental Figure 5: Key outcomes by baseline HF status



Key Safety Events

	Dapagliflozin (%)	Placebo (%)	Between Group Comparison
Treatment emergent SAE	34.1	36.2	P<0.001
Treatment emergent AE leading to drug D/C	8.1	6.9	P=0.01
Major Hypoglycemia	0.7	1.0	P=0.02
Diabetic Ketoacidosis* (DKA)	0.3	0.1	P=0.02
Amputation	1.4	1.3	NS
Fracture	5.3	5.1	NS
Acute Kidney Injury	1.5	2.0	P=0.002
Symptoms of volume depletion	2.5	2.4	NS
Genital infection (SAE, DAE)	0.9	0.1	P<0.001
Urinary tract infection (SAE, DAE)	1.5	1.6	NS
Fournier's Gangrene	0.01	0.08	NS
Cancer of Bladder*	0.3	0.5	P=0.02

*CEC Adjudicated

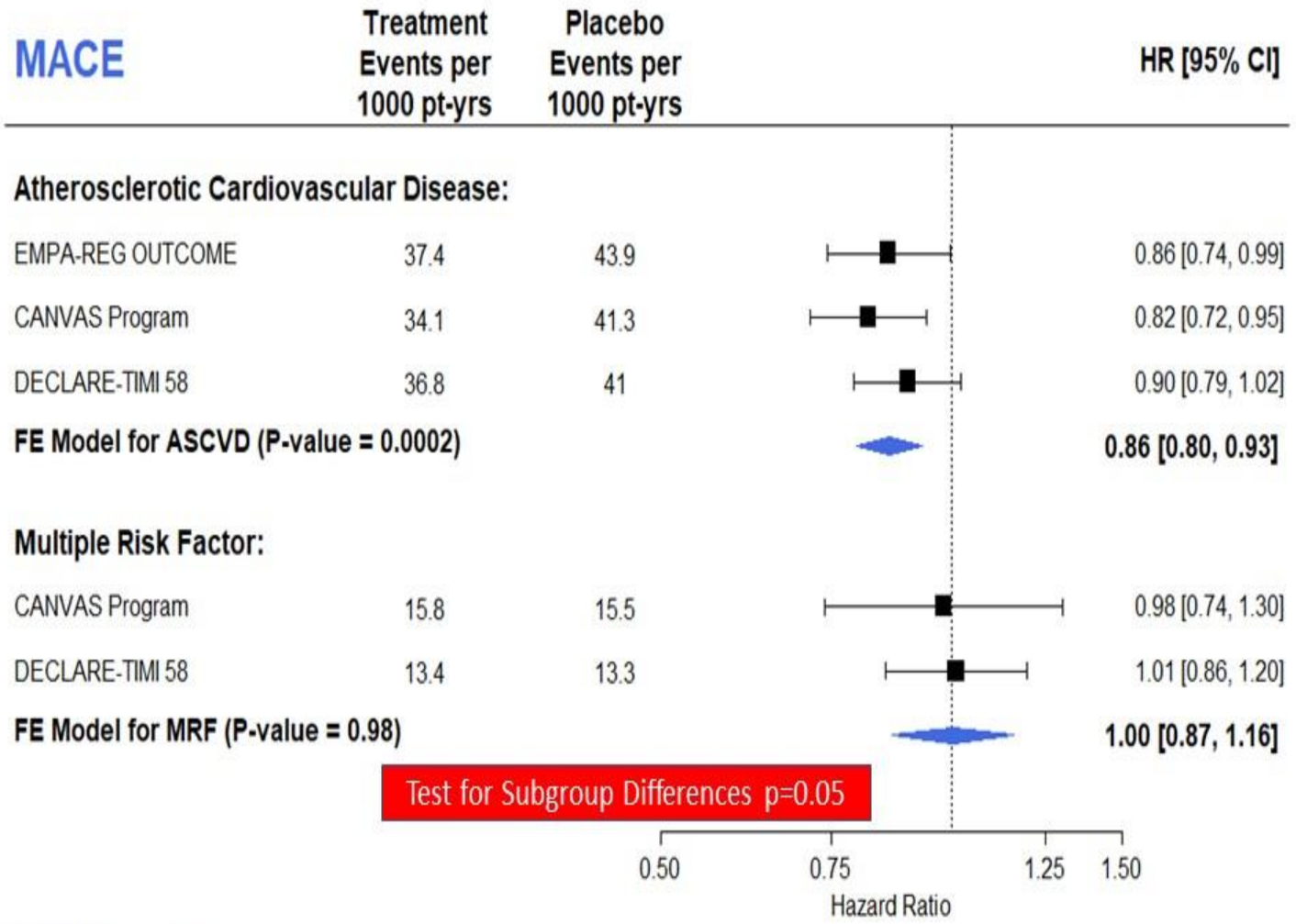
Due to external events during the trial, both amputations and events of potential diabetic ketoacidosis were collected retro- and prospectively with specific case record forms introduced during the study to collect additional relevant information. Study sites were asked to review all subjects for events occurring prior to initiation of the collection forms and report those events.

Summary

In DECLARE – TIMI 58, the largest SGLT2i trial, which included a broad representation of 1° and 2° prevention patients:

- Dapagliflozin reduced CVD/HHF, was safe with regard to MACE and appeared to reduce renal events
  - ↓ CVD/HHF was consistent regardless of baseline ASCVD or HF
- Dapagliflozin was safe and generally well-tolerated
  - ↑ Genital infections & DKA
  - No difference in: amputation, fracture, or stroke
  - ↓ Hypoglycemia, AKI, bladder Ca

Meta-Analysis of CVOTs: MACE by Presence of ASCVD



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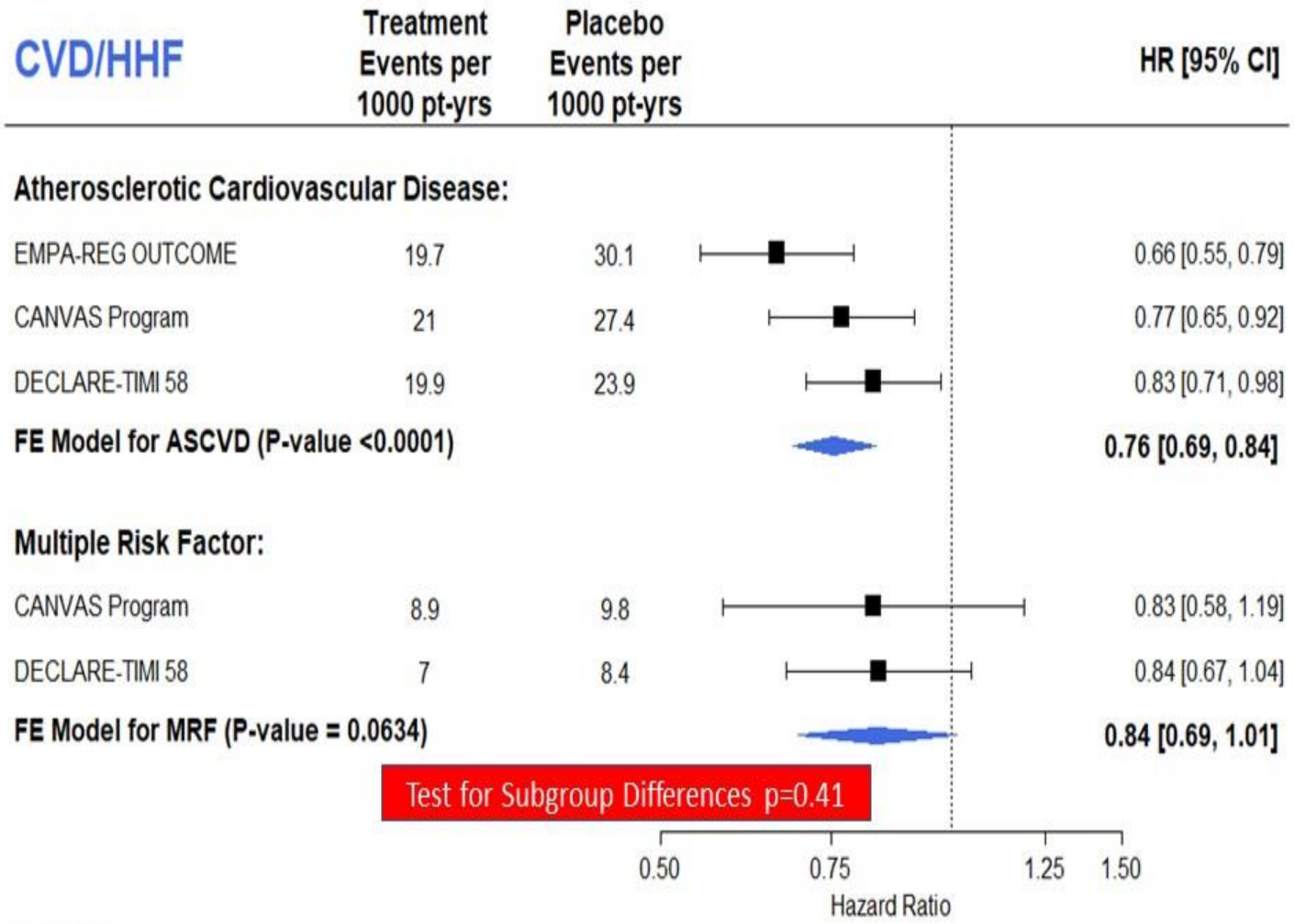
Zelniker TA, Wiviott SD...Sabatine MA, Lancet 2018

Meta-Analysis of CVOTs: CVD/HHF by Presence of ASCVD



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Zelniker TA, Wiviott SD...Sabatine MA, Lancet 2018

SGLT2 Pros

- Inhibit renal reabsorption of glucose leading to:
- Osmotic diuresis
- NO increase in heart rate
- HgbA1c reduction similar to other oral agents
- No intrinsic hypoglycemia (unless used with hypoglycemic agent/s)
- Approx 5# weight loss
- 3-5 mmHg SBP drop: consider reducing diuretics/BP meds
- Reduced 3 point MACE in most (powered) studies
- Reduced risk of Heart Failure: secondary and possibly primary prevention
- Reduced progression of Nephropathy: albuminuria and GFR decline

SGLT2 Cons

- “Normoglycemic DKA”
- Increase in UTI and Fournier’s Gangrene (perineum)
- May worsen orthostasis
- Slight increase in LDL-C
- Increased risk LE amputations in CANVAS trial (had preexisting dz)
- Not approved for GFR <45 ml/min (60)
- Increased fracture risk in some trials
- Increased bladder cancer risk in some trials
- Cost (in Medicare Patients)

- Caviats:
- discuss above with patients prior to Rx
- document absence of PAD prior to use
- Not approved for Type 1 DM (yet)
- Canagliflozin raises Digoxin levels – use alternative

Freedom to Choose

Caviats:

- **Use antihyperglycemics instead of hypoglycemics**
- **Consider non-glycemic benefits**