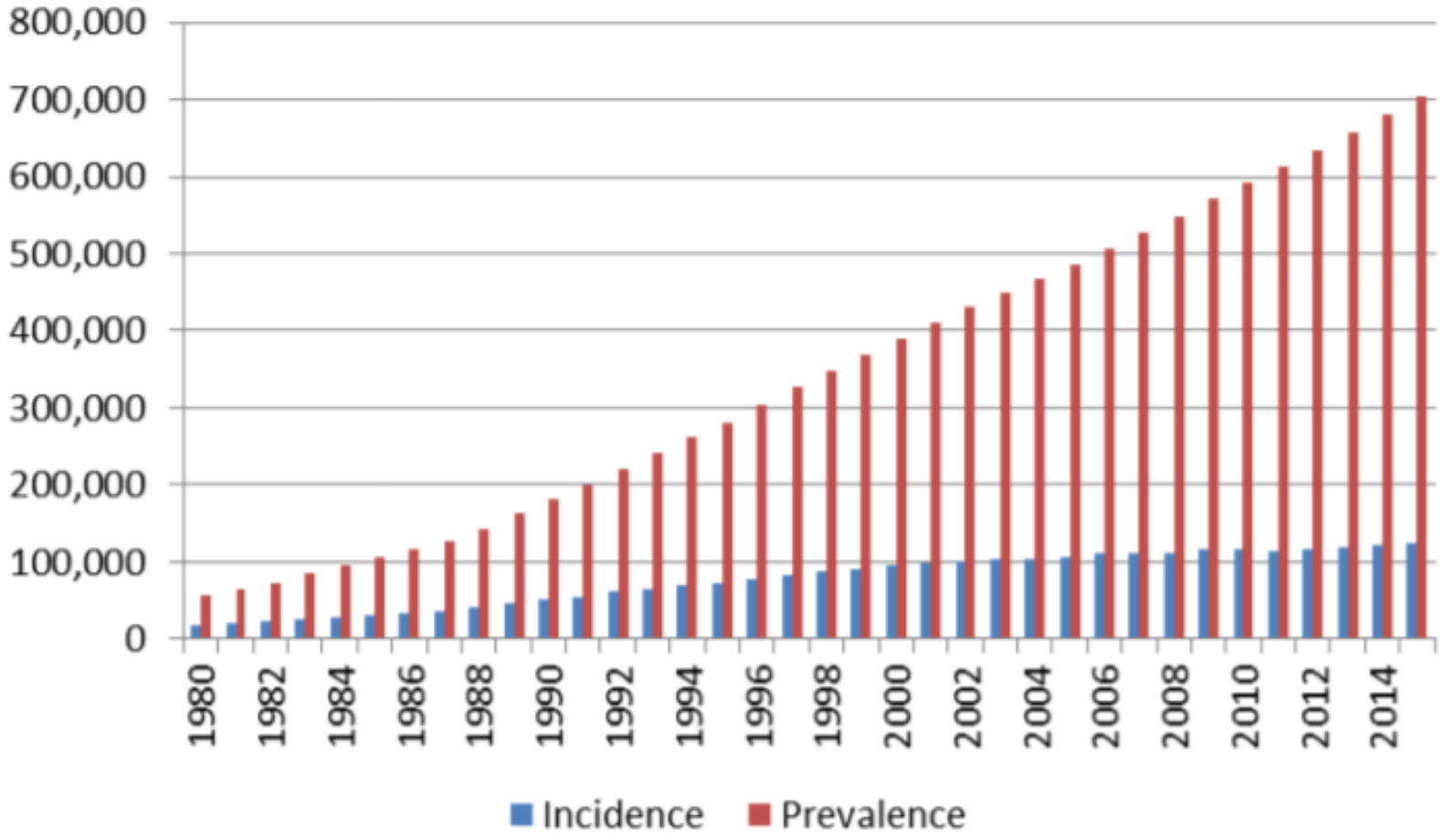
Redefining Diabetic Management Based on New Prospective Trial Results: Time for a Paradigm Shift

李美月 Mei-Yueh Lee , M.D., Ph.D.
Associate Professor, Kaohsiung Medical University
Endocrinology and Metabolism
Kaohsiung Medical University Hospital

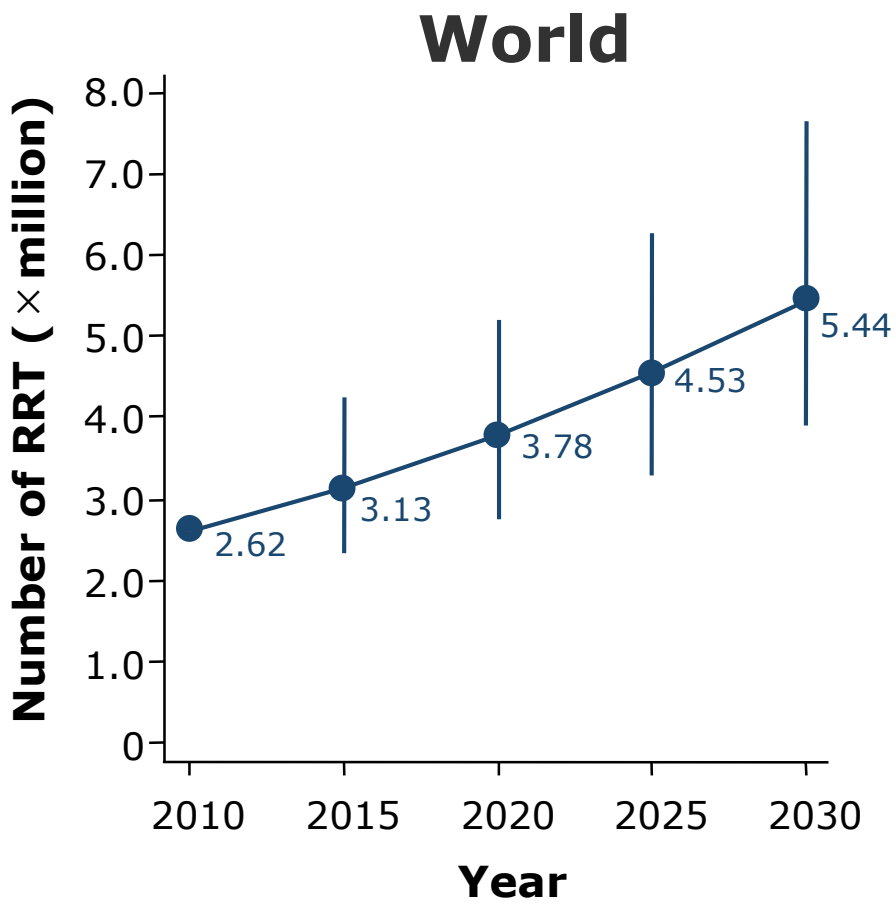
Increasing Incidence and Prevalence of ESKD: US Data

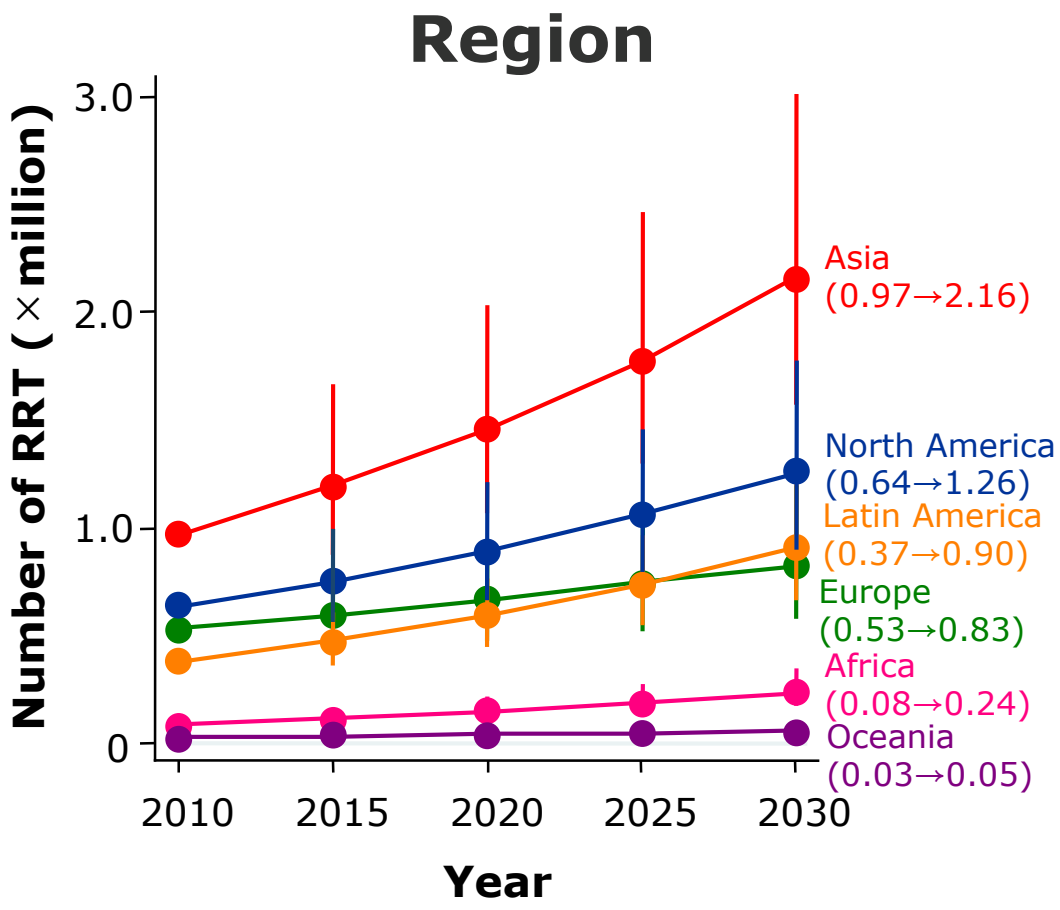


Kirchhoff S. Medicare coverage of end-stage renal disease (ESRD). https://fas.org/sgp/crs/misc/R45290.pdf. Accessed February 13, 2019.

CREDENCE

Number of People Receiving Renal Replacement Therapy Is Projected to Double

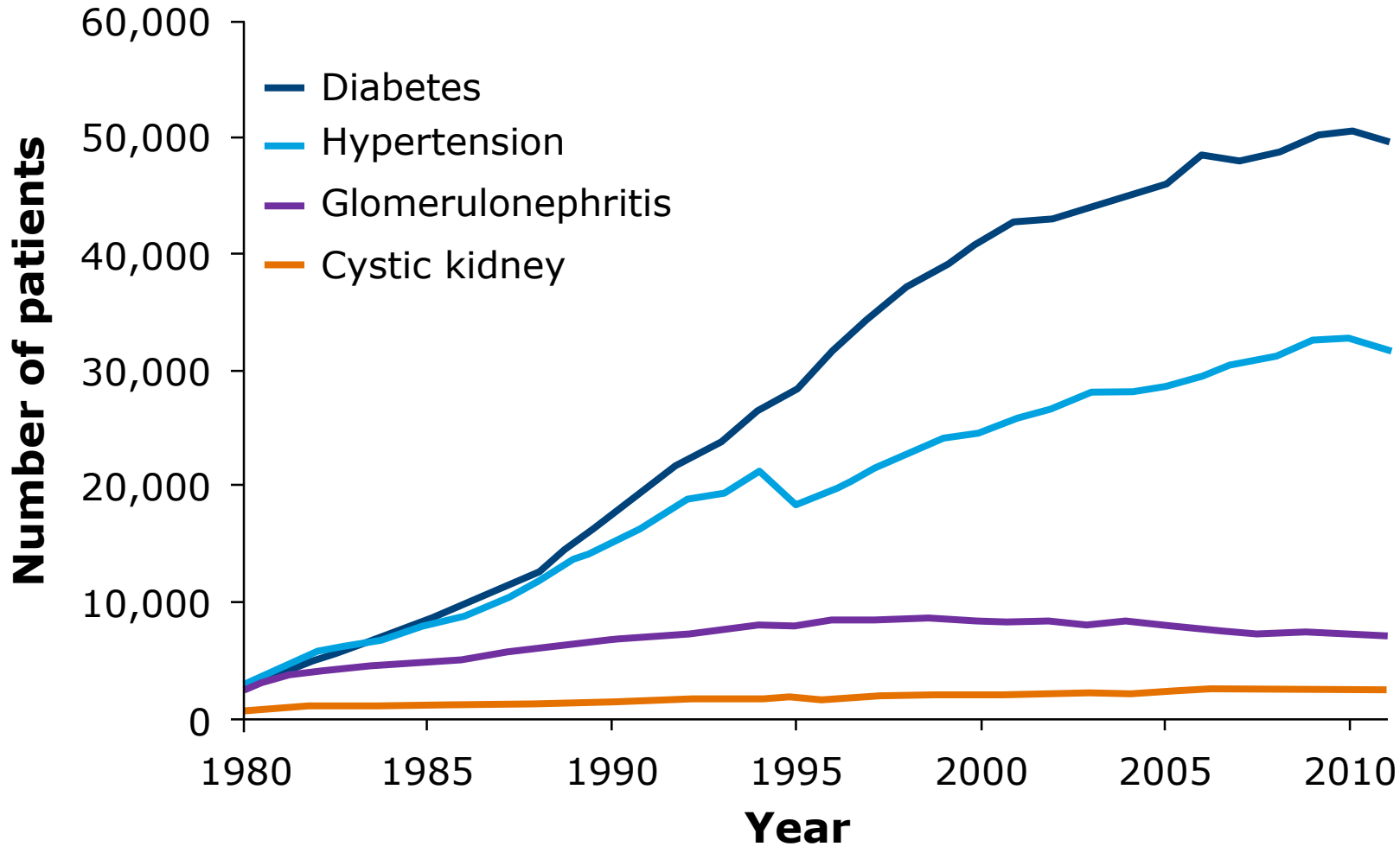




Liyanage T, et al. *Lancet*. 2015;385(9981):1975-1982.

CREDENCE

Diabetes Is the Leading Cause of Kidney Failure: US Data



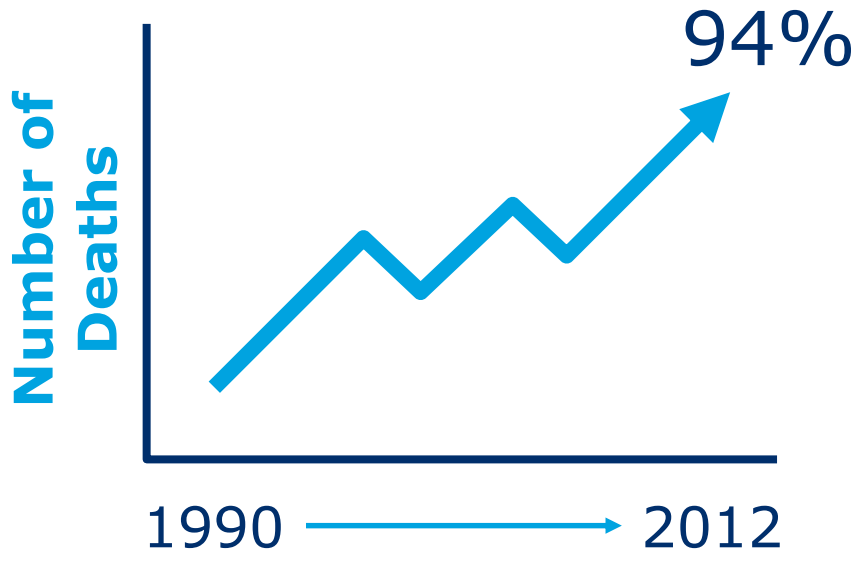
United States Renal Data System (USRDS). USRDS Annual Report, Chapter 1. https://www.usrds.org/2012/pdf/v2_ch1_12.pdf. Accessed March 15, 2019.

CREDENCE

Growing Problem of T2DM and CKD

~422 MILLION **adults** are living with diabetes

Deaths due to T2DM and CKD



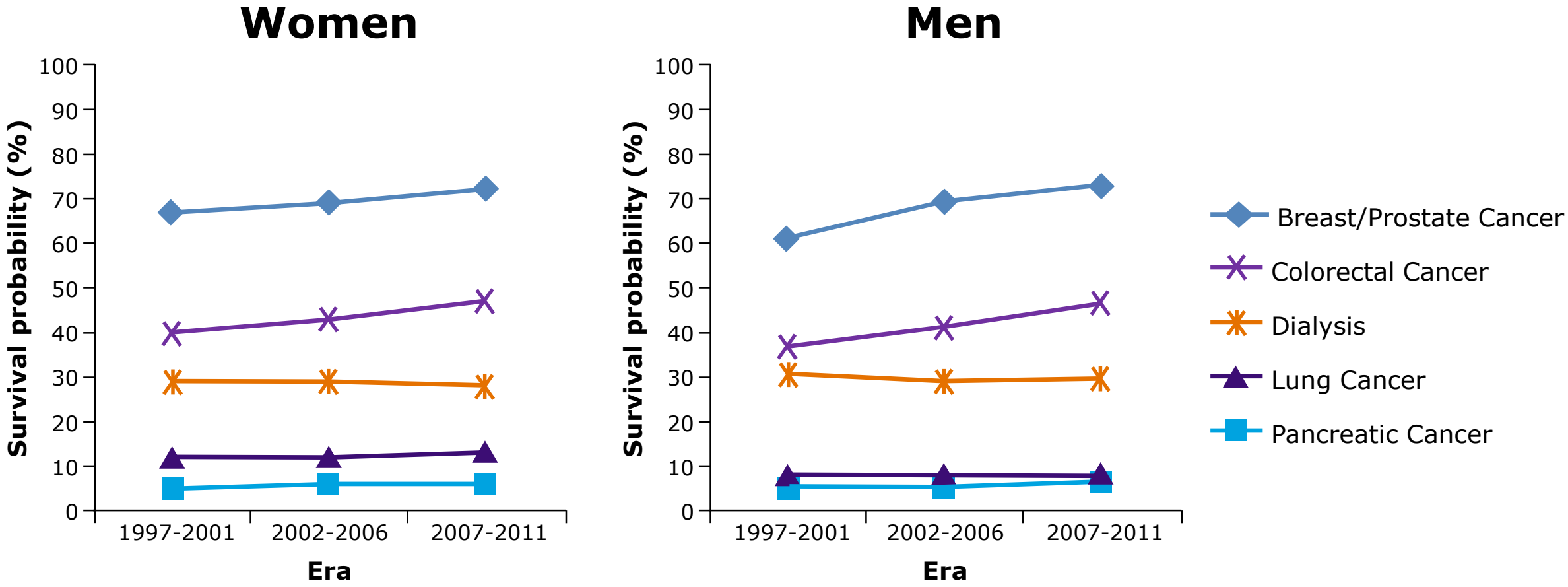
30 to 40%

of these patients will develop CKD

1. World Health Organization. Global Report on Diabetes. 2016.
2. Yee J. *Diabetes Spectr*. 2008;21(1):8-10.
3. Alicic RZ, et al. *Clin J Am Soc Nephrol*. 2017;12(12):2032-2045.

CREDENCE

Dialysis Survival Compared to Common Cancers



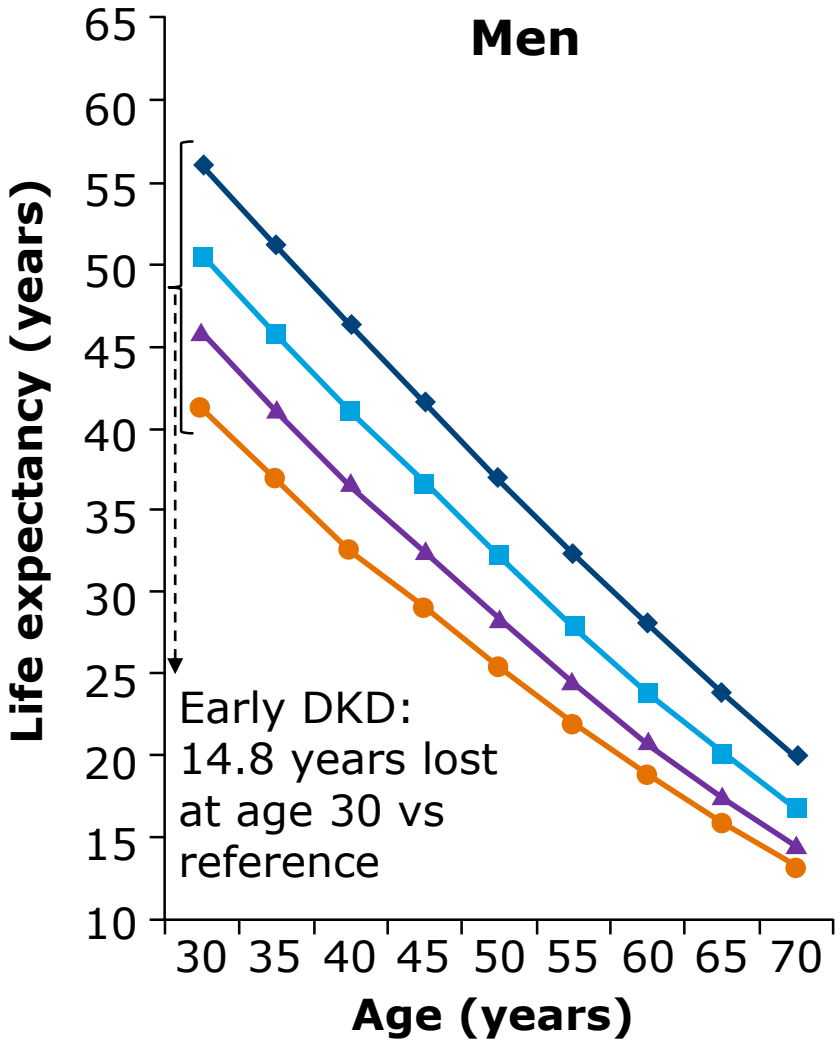
Unadjusted 10-year survival for all-cause mortality in Canada

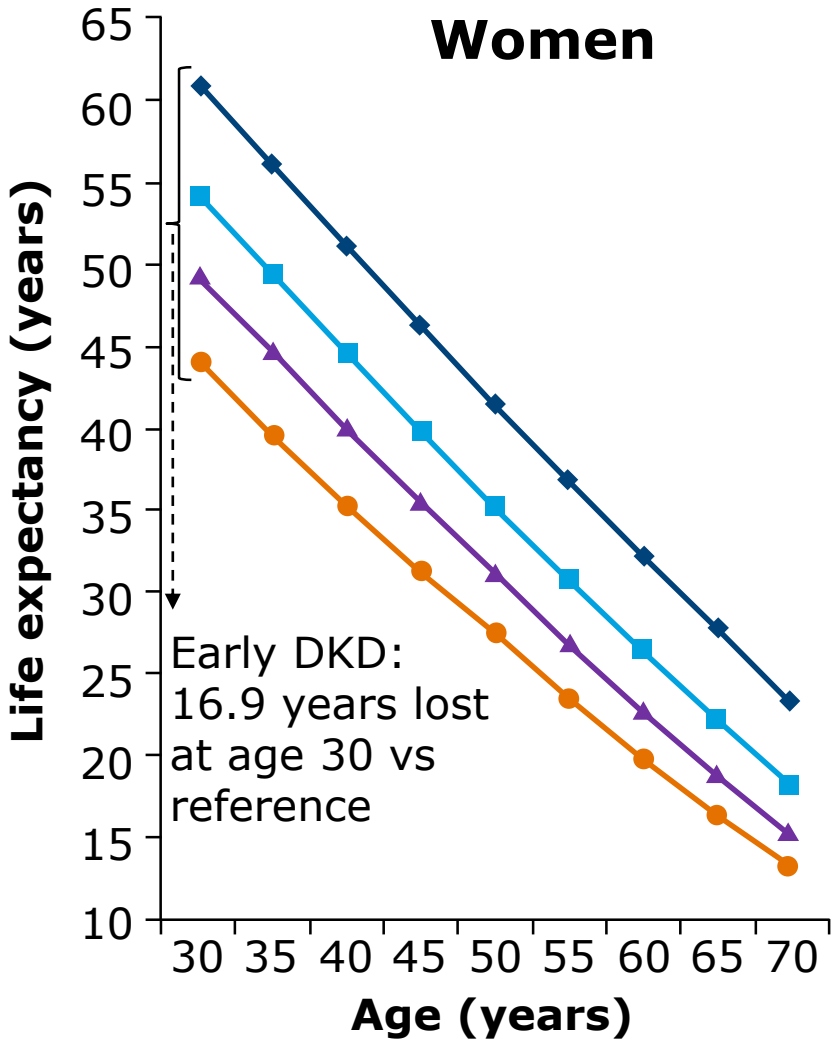
N = 33,500 incident maintenance dialysis patients; 532,452 incident cancer patients

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

CREDENCE

Diabetic Kidney Disease Shortens Life Span by 16 Years





Life span loss with:

- Early CKD: 6 years
- Diabetes: 10 years
- Early DKD: 16 years

Reference
Early CKD
Diabetes
Early DKD

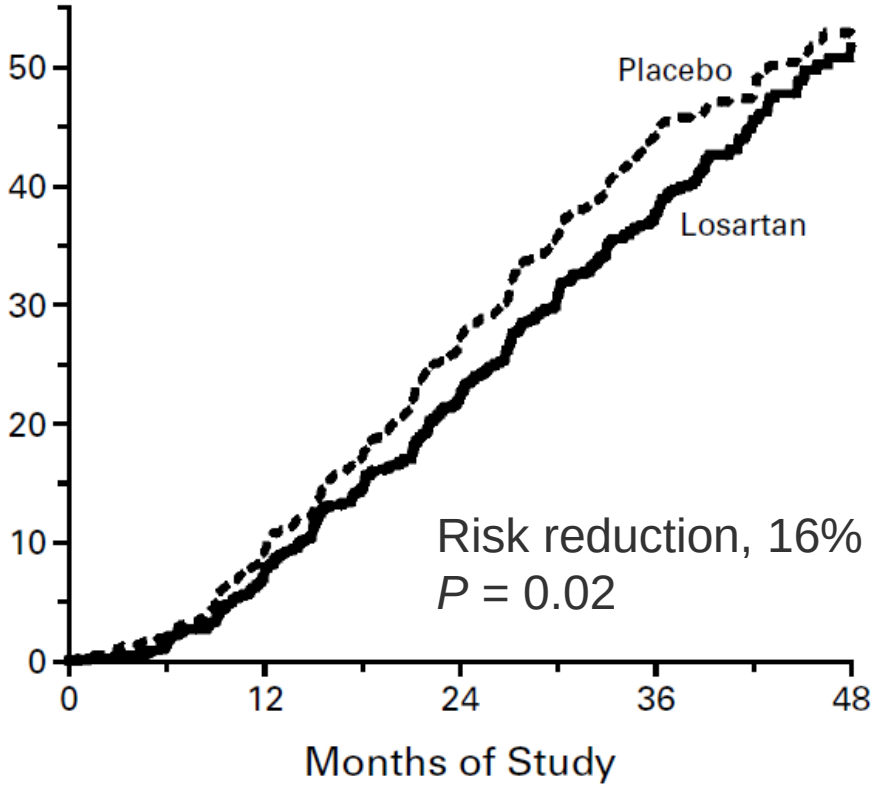
Wen CP, et al. *Kidney Int.* 2017;92(2):388-396.

CREDENCE

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

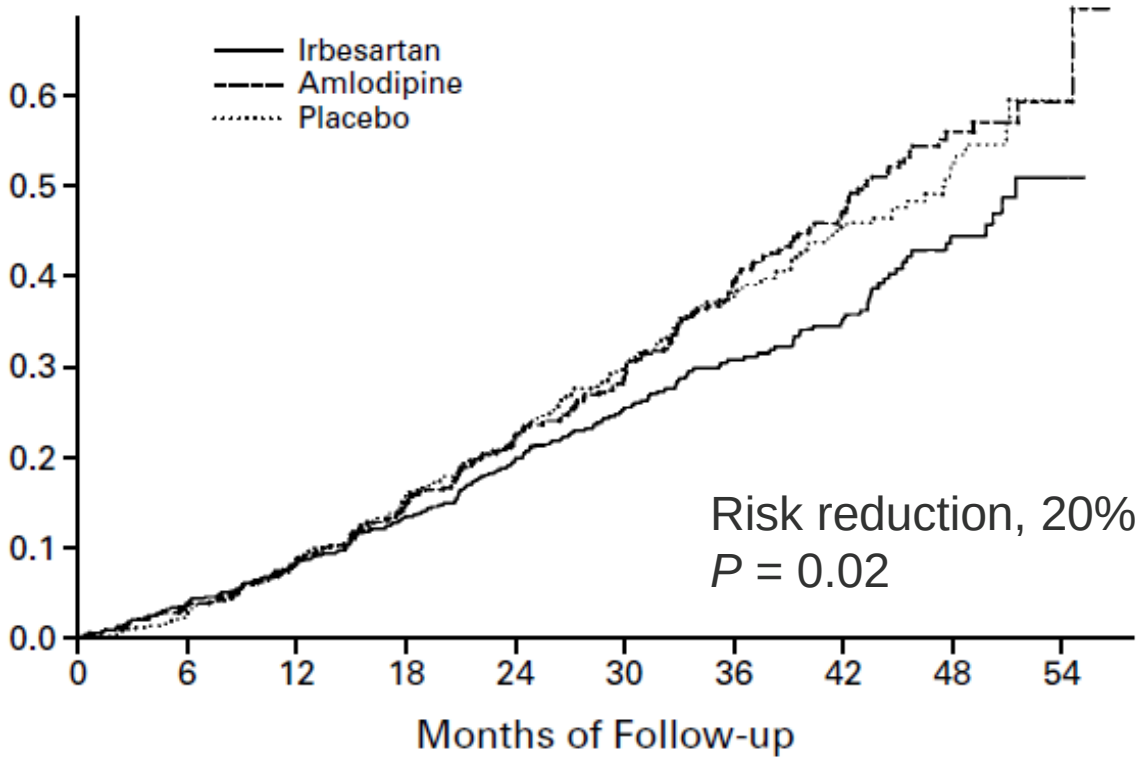
Doubling of serum creatinine, ESKD, or death

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.

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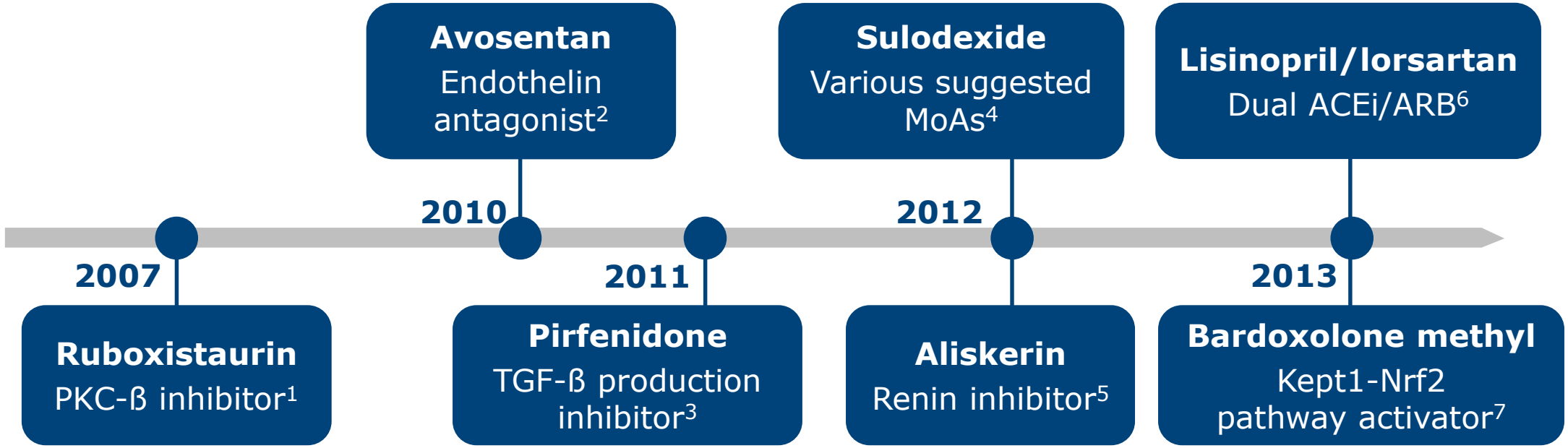
Since RENAAL and IDNT, New Therapeutic Strategies for Patients With T2DM and CKD Have Failed



1. Tuttle KR, et al. *Clin J Am Soc Nephrol.* 2007;2(4):631-636.
2. Mann JFE, et al. *J Am Soc Nephrol.* 2010;21(3):527-535.
3. Sharma K, et al. *J Am Soc Nephrol.* 2011;22(6):1144-1151.
4. Packham DK, et al. *J Am Soc Nephrol.* 2012;23(1);123-130.
5. Parving HH, et al. *N Engl J Med.* 2012;367(23):2204-2213.
6. Fried LF, et al. *N Engl J Med.* 2013;369(20):1892-1903.
7. de Zeeuw D, et al. *N Engl J Med.* 2013;369(26):2492-2503.

CREDENCE

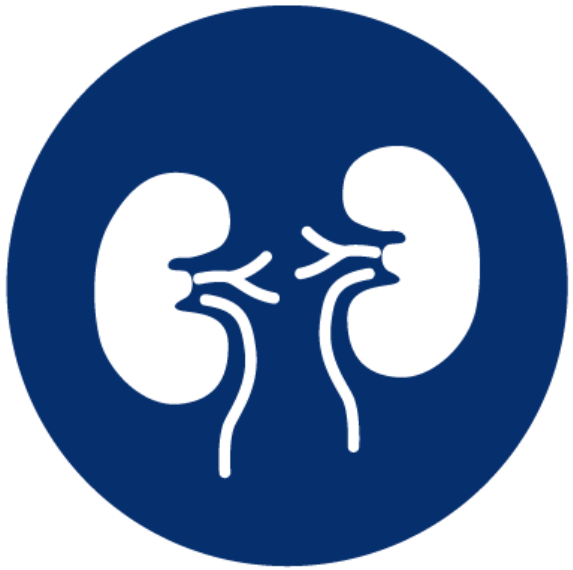
Many Renal Effects of SGLT2 Inhibition Have Been Proposed

↓ Intraglomerular pressure

↓ Glucose

↓ BP/arterial stiffness

↓ Volume



↓ Albuminuria

↓ Oxidant stress

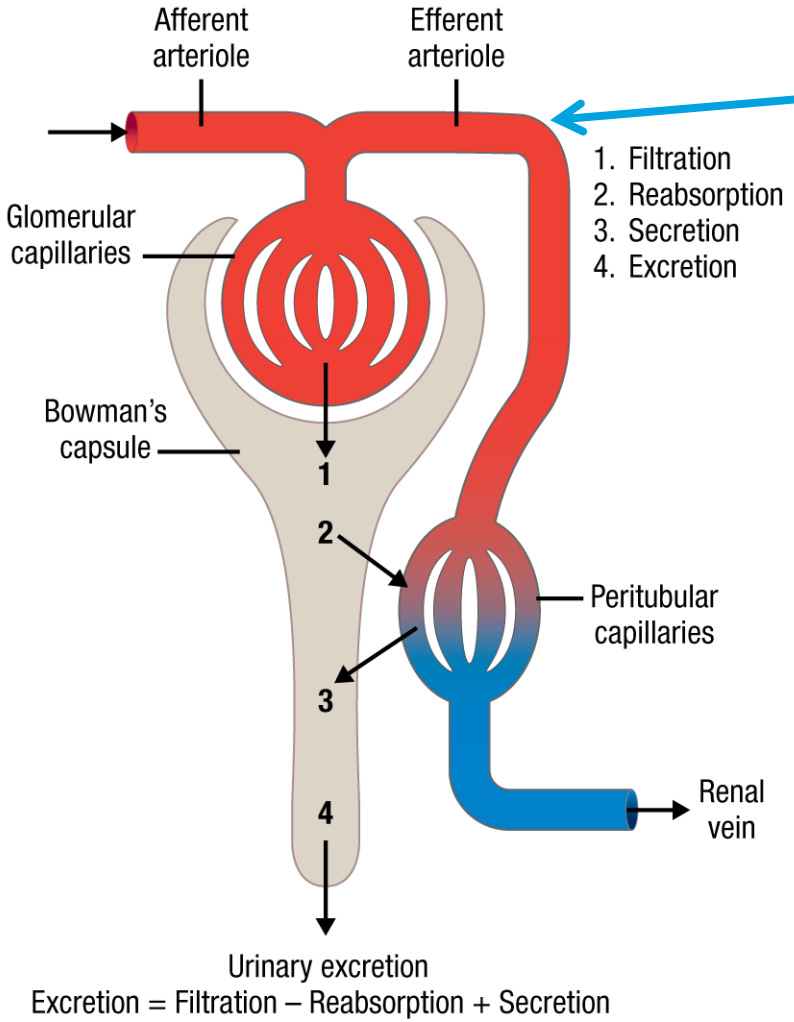
↓ Intrarenal angiotensinogen upregulation

↓ Inflammation/fibrosis

And many others…

CREDENCE

ACEi/ARB Reduce Intraglomerular Pressure: Mechanism for Renal Protection



ACEi and ARB
↓ efferent arteriole tone and
↓ intraglomerular pressure

↓

Initial ↓ in eGFR
followed by stabilization

↓ albuminuria

↓

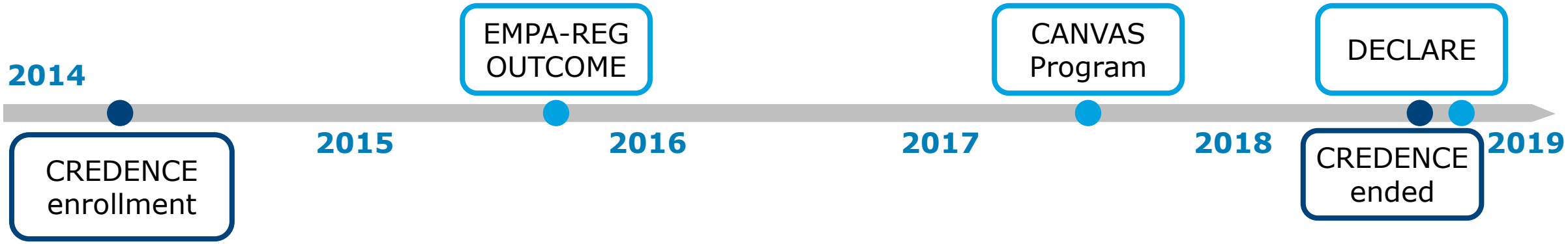
Renal protection

Sternlicht H, Bakris G. *Curr Hypertension Rep.* 2019;21(2):12-18.
Gilbert RE. *Kidney Int.* 2014;86(4):693-700.

CREDENCE

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

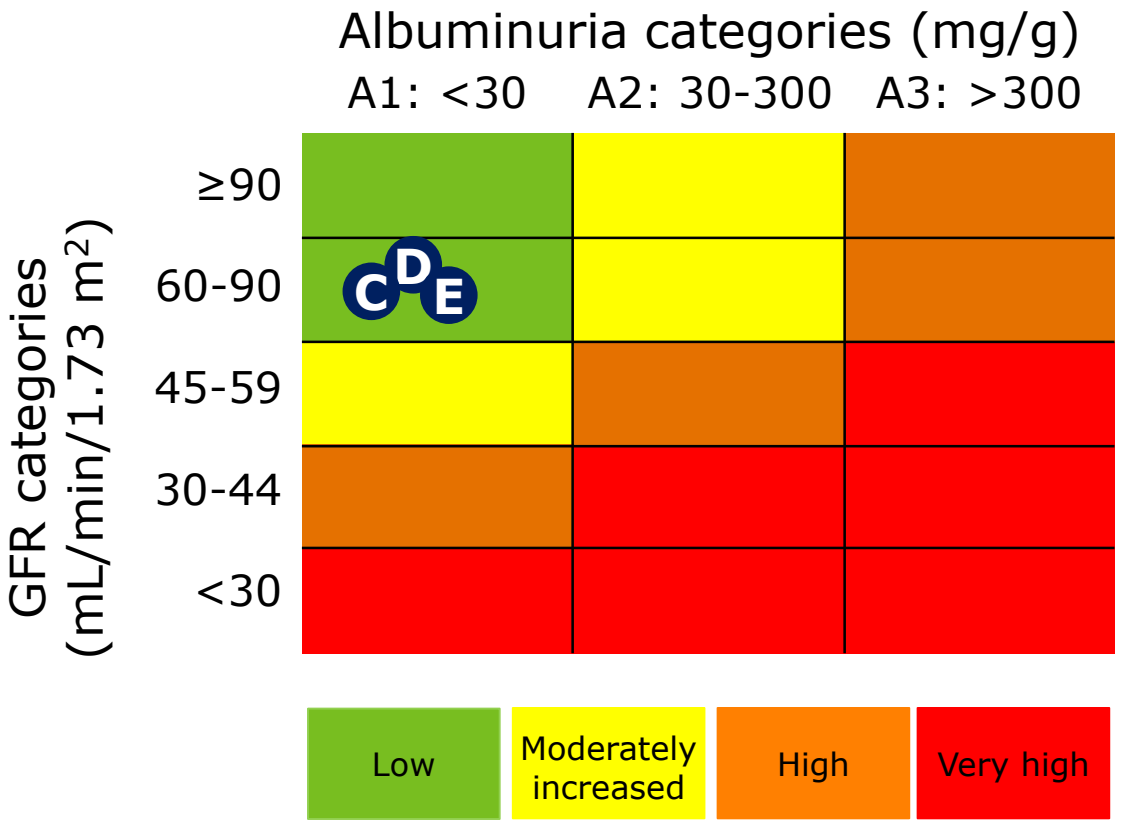
Study Quality Metrics: CREDENCE vs Other Long-term Outcome Trials in Diabetes

Trial	N	Median follow-up duration	Unknown final vital status, n (%)	Withdrawal of consent, n (%)	Study completion, n (%)	Discontinuation of study drug, n (%)
CREDENCE (canagliflozin)	**4401**	**2.6 years**	**6 (0.1)**	**16 (0.4)**	**4361 (99.1)**	**1201 (27.3)**
CANVAS Program (canagliflozin)[1]	10,142	2.4 years	34 (0.3)	140 (1.4)	9734 (96.0)	2990 (29.5)
EMPA-REG OUTCOME (empagliflozin)[2]	7020	3.1 years	53 (0.8)	102 (1.5)	6809 (97.0)	1780 (25.4)
DECLARE (dapagliflozin)[3]	17,160	4.2 years	NR	224 (1.3)	16,906 (98.5)	3962 (23.1)
TECOS (sitagliptin)[4]	14,671	3.0 years	368 (2.5)	662 (4.5)	13,877 (94.6)	3356 (22.9)
SAVOR-TIMI 53 (saxagliptin)[5]	16,492	2.1 years	147 (0.9)	388 (2.4)	16,076 (97.5)	3232 (19.6)
LEADER (liraglutide)[6]	9340	3.8 years	29 (0.3)	NR	9042 (96.8)	NR

1. Neal B, et al. *N Engl J Med.* 2017;377(7):644-657.
2. Zinman B, et al. *N Engl J Med.* 2015;373(22):2117-2128.
3. Wiviott SD, et al. *N Engl J Med.* 2019;380(4):347-357.
4. Green JB, et al. *N Engl J Med.* 2015;373(3):232-242.
5. Scirica BM, et al. *N Engl J Med.* 2013;369(14):1317-1326.
6. Marso SP, et al. *N Engl J Med.* 2016;375(4):311-322.

CREDENCE

Low Renal Risk Populations in 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

Sustained RRT Events

DECLARE	Not reported
CANVAS Program	18
EMPA-REG OUTCOME	11

Total of 29 sustained RRT events reported across trials

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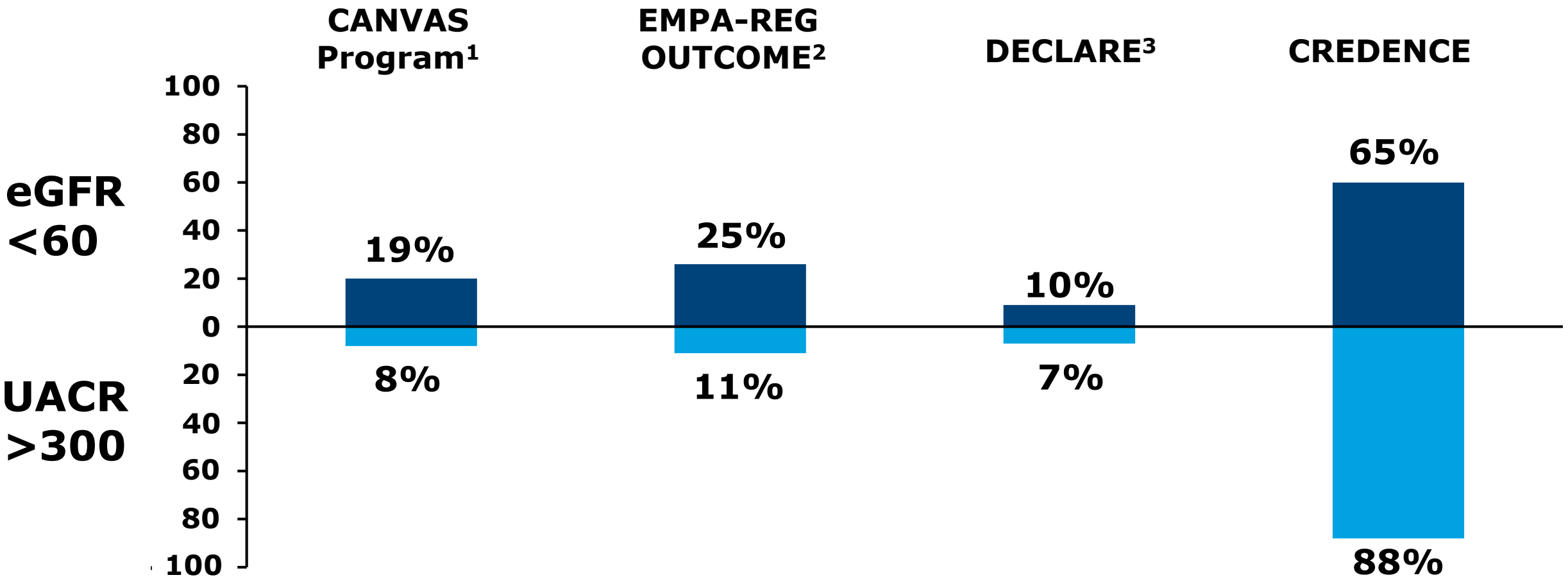
Lower Baseline Renal Function in CREDENCE Participants



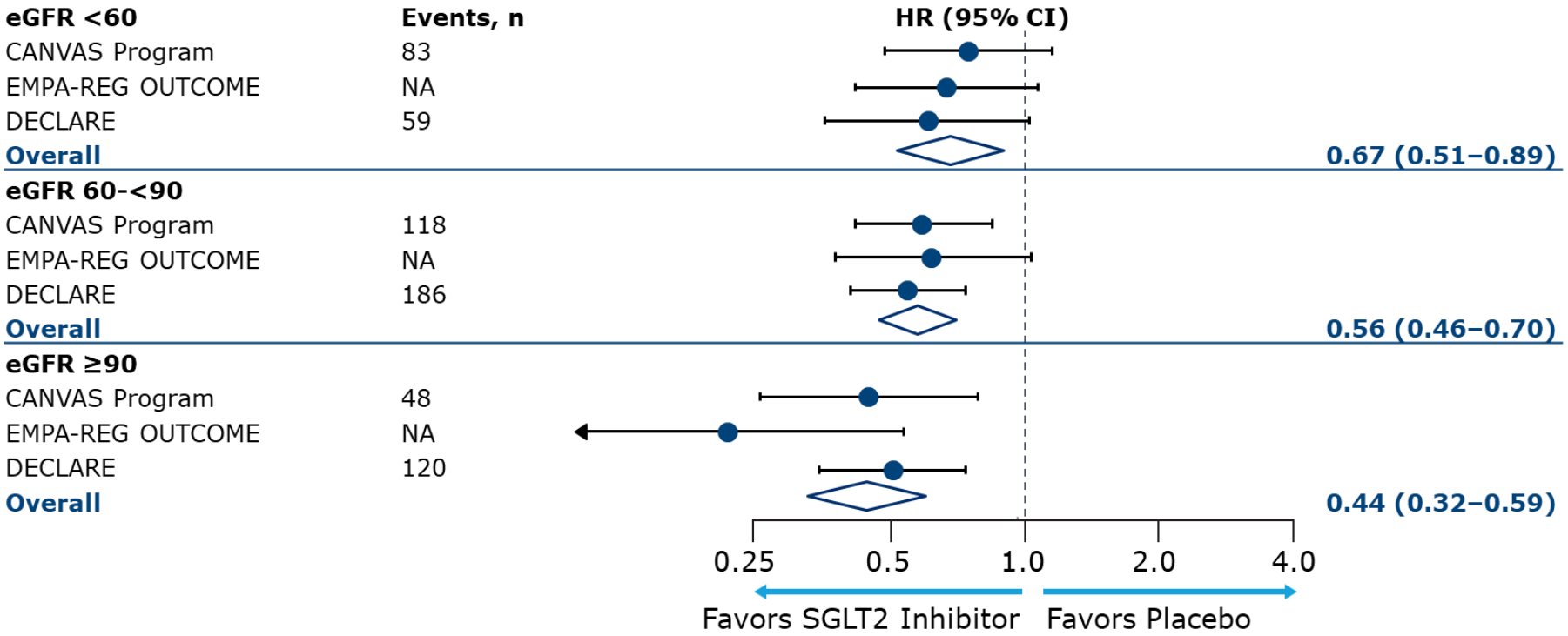
1. Neal B, et al. *N Engl J Med.* 2017;377(7):644-657.
2. Zinman B, et al. *N Engl J Med.* 2015;373(22):2117-2128.
3. Raz I, et al. *Diabetes Obes Metab.* 2018;20(5):1102-1110.

CREDENCE

Why Is CREDENCE Important?

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

Composite of worsening of renal function, ESKD, or renal death



Interaction
P value = 0.0258

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

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*

Slides available at www.georgeinstitute.org and http://med.stanford.edu/sccr.html

Paper and editorial available at www.nejm.org

CREDENCE

Objectives

In people with T2DM, eGFR 30 to 90 mL/min/1.73 m^2, and UACR 300 to 5000 mg/g who are receiving standard of care including a maximum tolerated dose of an ACEi or ARB, to assess whether canagliflozin compared with placebo reduces

Primary:

- Composite outcome of ESKD, doubling of serum creatinine, or renal or CV death

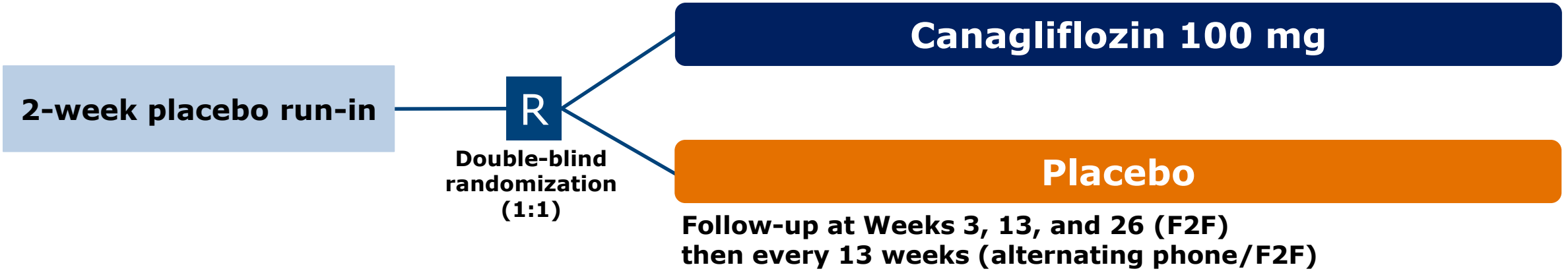
Secondary:

- CV death or hospitalization for heart failure
- Major cardiovascular events (3-point MACE: CV death, MI, or stroke)
- Hospitalization for heart failure
- ESKD, doubling of serum creatinine, or renal death
- CV death
- All-cause mortality
- CV death, MI, stroke, hospitalization for heart failure, or hospitalization for unstable angina

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.

Statistical Methods

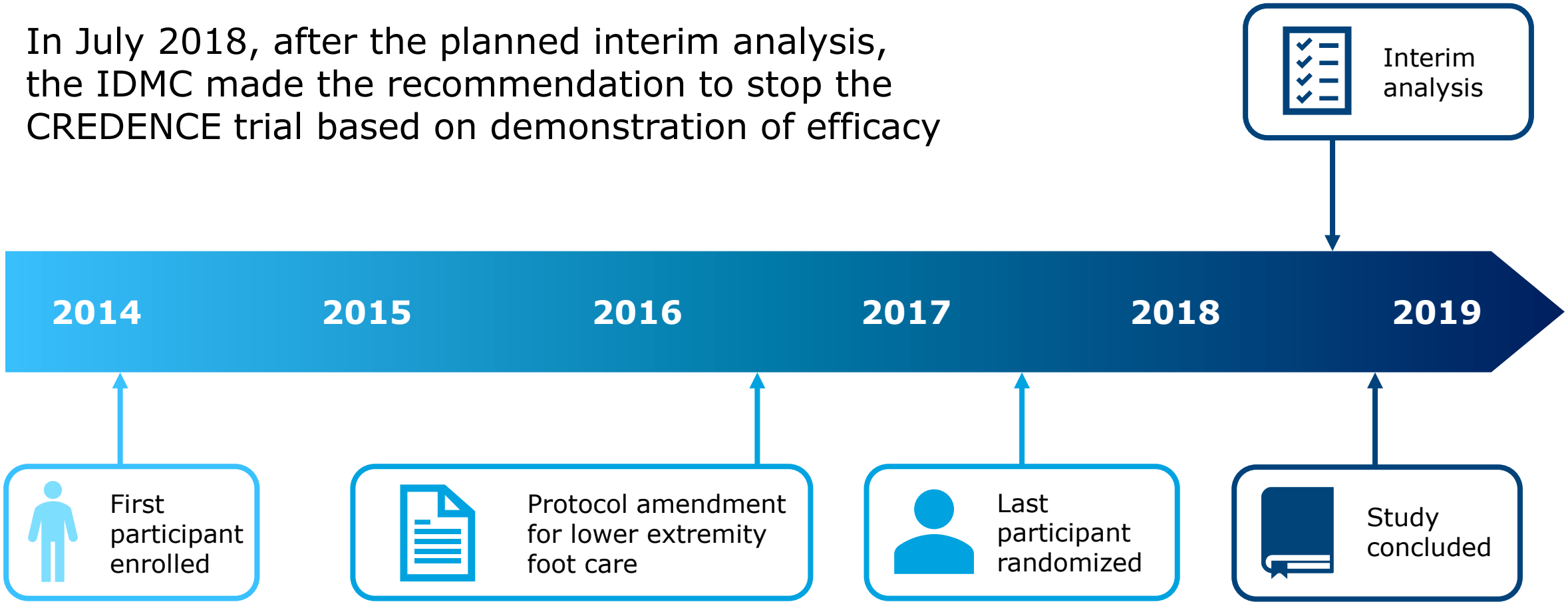
- Intent-to-treat (ITT) principle; event-driven duration
- Target of 844 events to provide 90% power to detect 20% relative risk reduction for the primary composite outcome
- Outcome analysis based on Cox proportional hazard model stratified by screening eGFR
- Sequential hypothesis testing prespecified to evaluate secondary outcomes
- Numbers needed to treat (NNT) to prevent 1 event over 2.5 years were calculated
- Subgroup analyses were also prespecified

Prespecified Hierarchical Testing

Primary
1. ESKD, doubling of serum creatinine, or renal or CV death
Secondary
2. CV death or hospitalization for heart failure
3. CV death, MI, or stroke
4. Hospitalization for heart failure
5. ESKD, doubling of serum creatinine, or renal death
6. CV death
7. All-cause mortality
8. CV death, MI, stroke, hospitalization for heart failure, or hospitalization for unstable angina

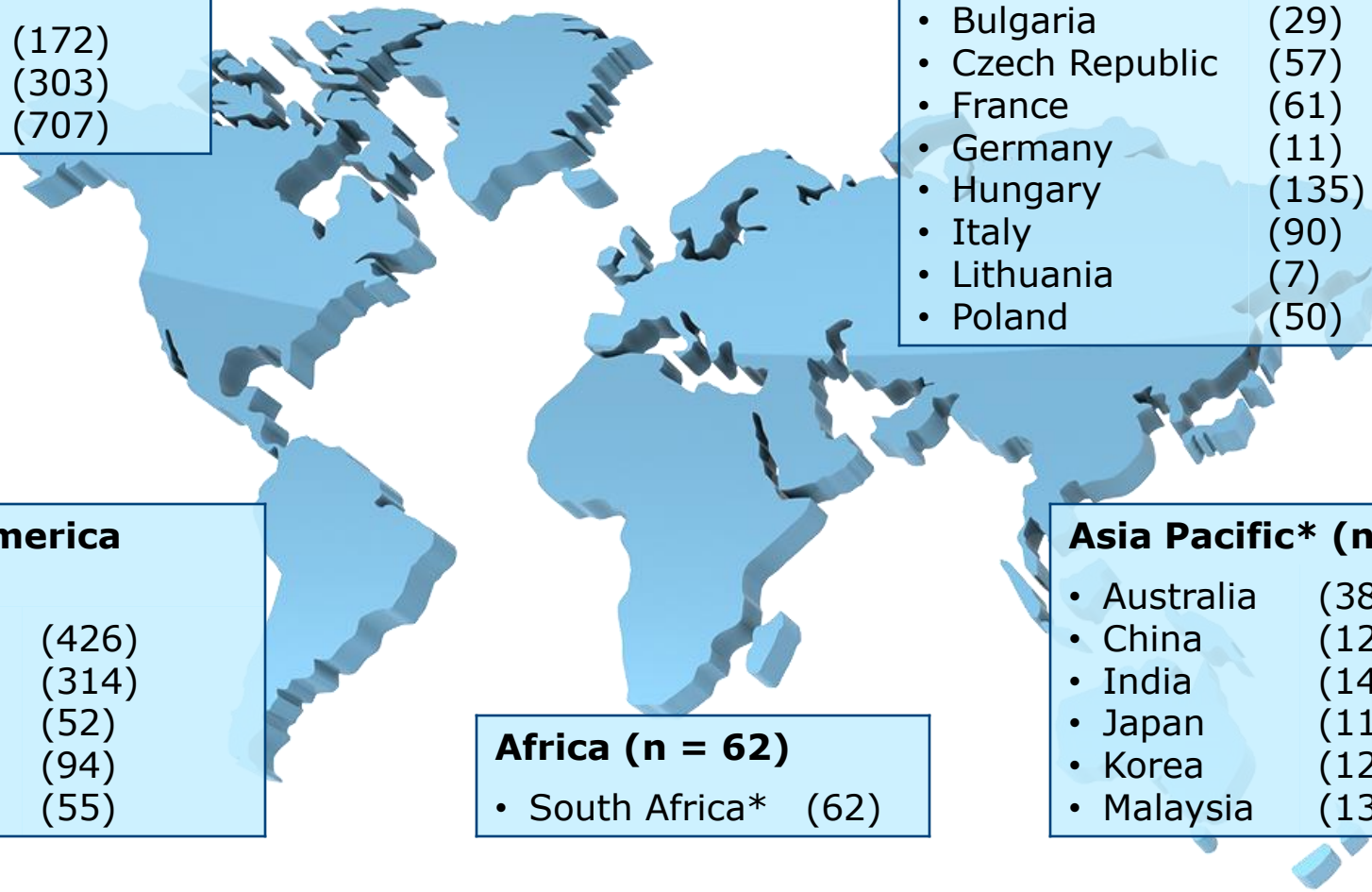
Study Timeline

In July 2018, after the planned interim analysis, the IDMC made the recommendation to stop the CREDENCE trial based on demonstration of efficacy



CREDENCE

34 Countries, 690 Sites, 4401 Participants



North America (n = 1182)

- Canada (172)
- Mexico (303)
- United States (707)

Europe (n = 1368)

- Bulgaria (29)
- Czech Republic (57)
- France (61)
- Germany (11)
- Hungary (135)
- Italy (90)
- Lithuania (7)
- Poland (50)
- Romania (59)
- Serbia (40)
- Slovakia (66)
- Spain (141)
- Russia* (133)
- Ukraine* (371)
- United Kingdom (118)

Central/South America (n = 941)

- Argentina (426)
- Brazil (314)
- Chile (52)
- Colombia (94)
- Guatemala (55)

Africa (n = 62)

- South Africa* (62)

Asia Pacific* (n = 848)

- Australia (38)
- China (129)
- India (144)
- Japan (110)
- Korea (122)
- Malaysia (135)
- New Zealand (61)
- Philippines (71)
- Taiwan (37)
- United Arab Emirates (1)

*Analyzed as part of rest of world (n = 1414) in prespecified subgroup analyses.

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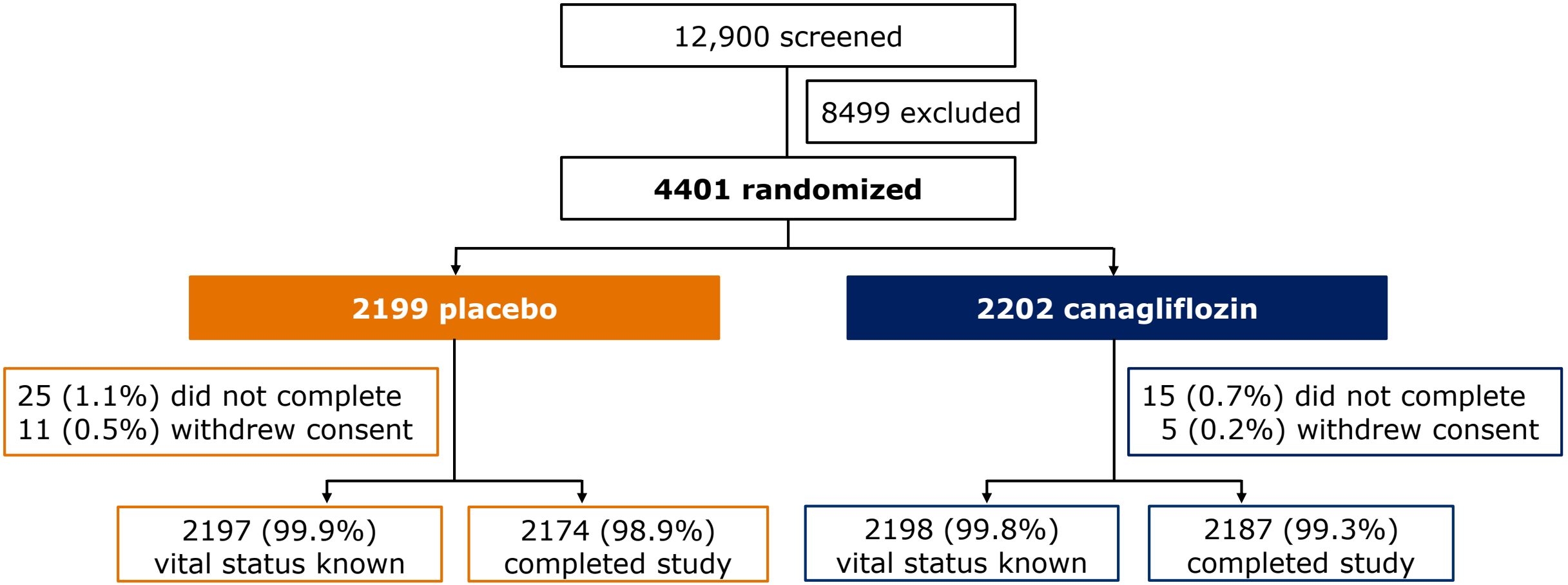
Enrollment and Follow-up



4395 (99.9%) vital status known; 4361 (99.1%) completed study*

*Patients who completed the study included those who were alive with follow-up at the end of the study or died before final follow-up.

CREDENCE

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**

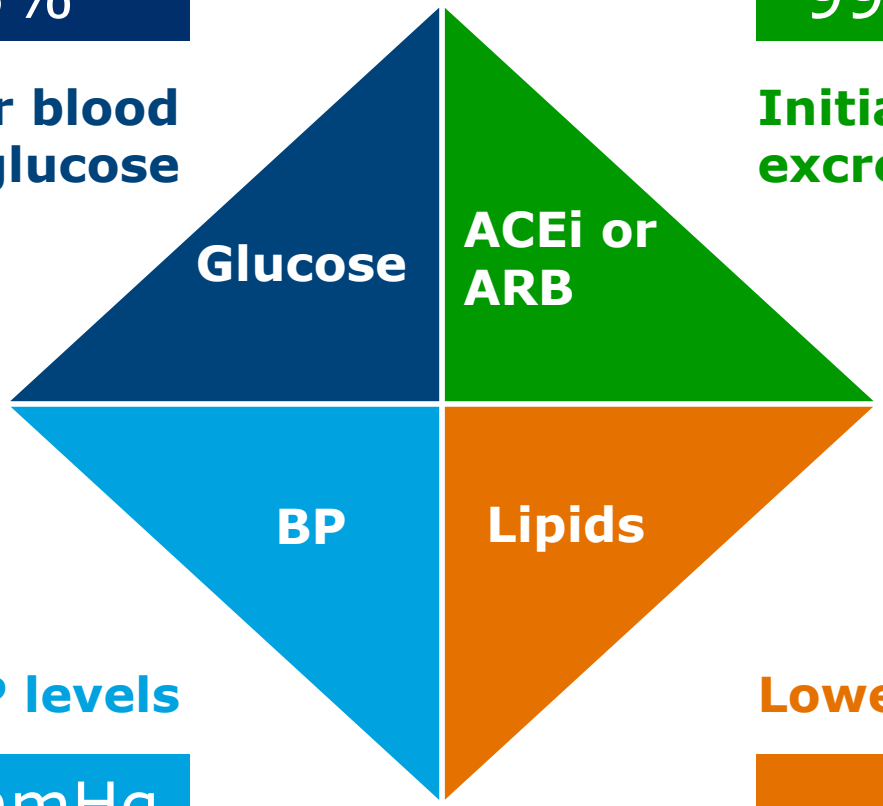
Baseline Renal Characteristics

	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

Risk Factor Management at Entry to CREDENCE

Mean HbA1c 8.3%

Lower blood glucose



99.9% on ACEi or ARB

Initiate when albumin excretion is ≥30 mg/g

Manage BP levels

Mean BP 140/78 mmHg

Lower LDL-C

~70% on statin

Baseline values from CREDENCE are shown.

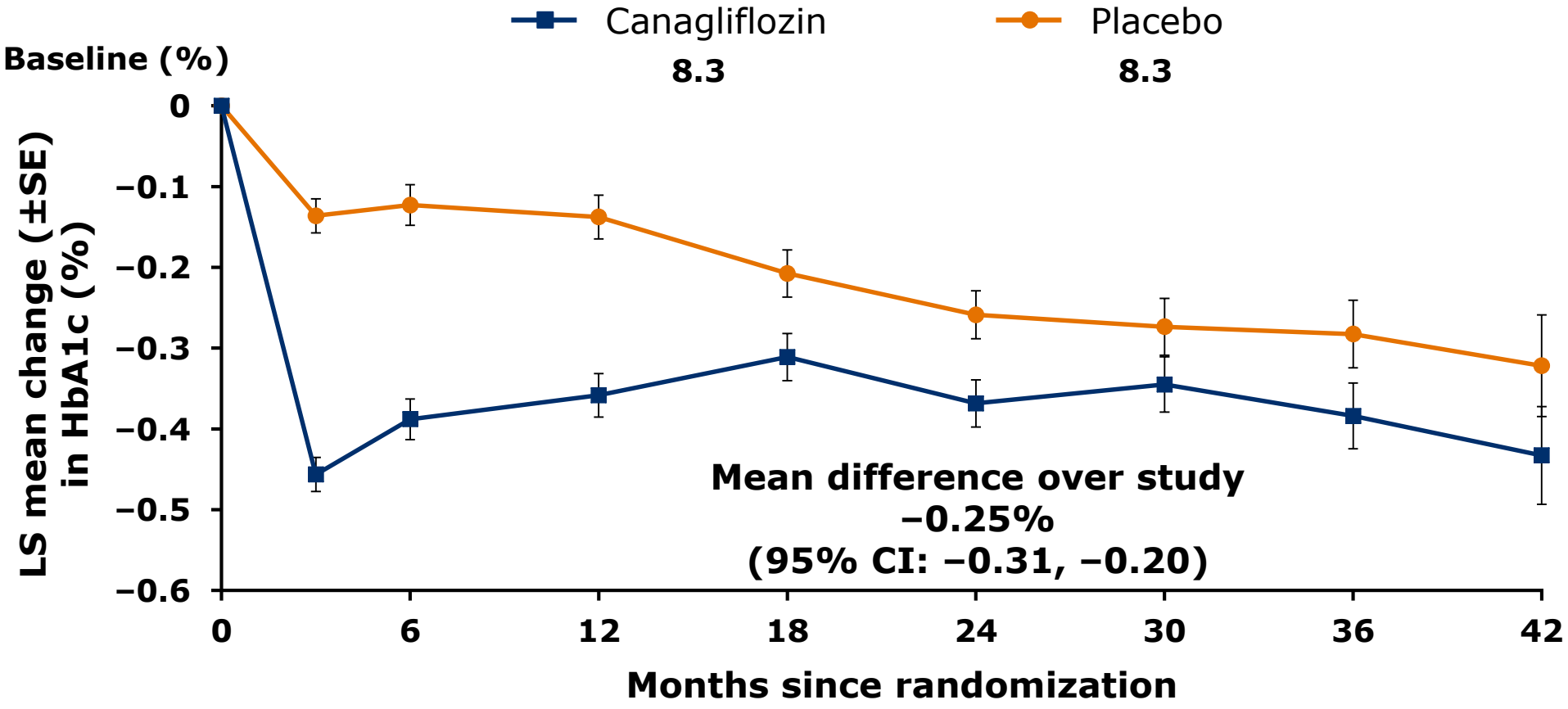
1. Molitch ME, et al. *Kidney Int.* 2015;87(1):20-30.
2. National Institute for Health and Care Excellence. NICE guideline (NG28). 2017. Accessed April 10, 2019.
3. American Diabetes Association. *Diabetes Care*. 2019;42(Suppl 1):S182-S183.

CREDENCE

Effects on Intermediate Outcomes

CREDENCE

Effects on HbA1c



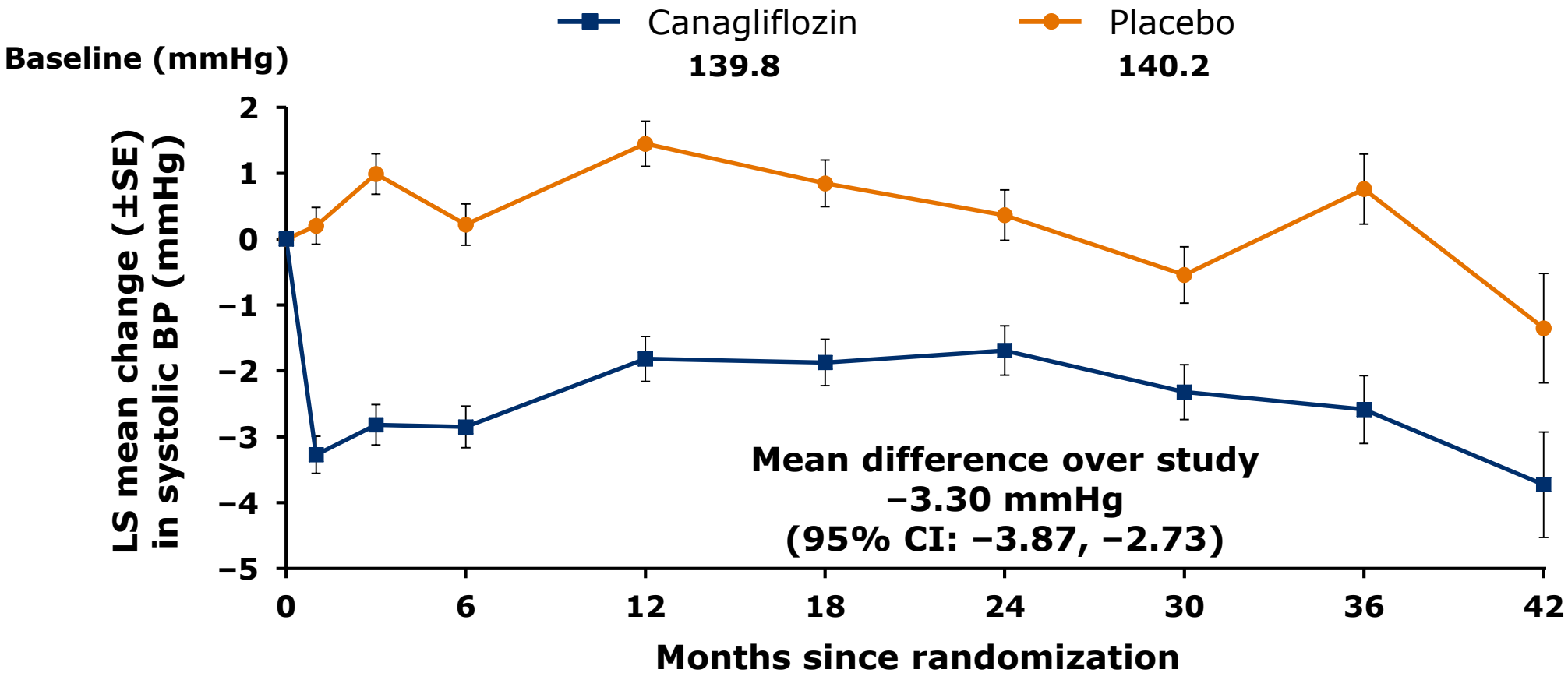
No. of participants

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

ITT analysis

CREDENCE

Effects on Systolic BP



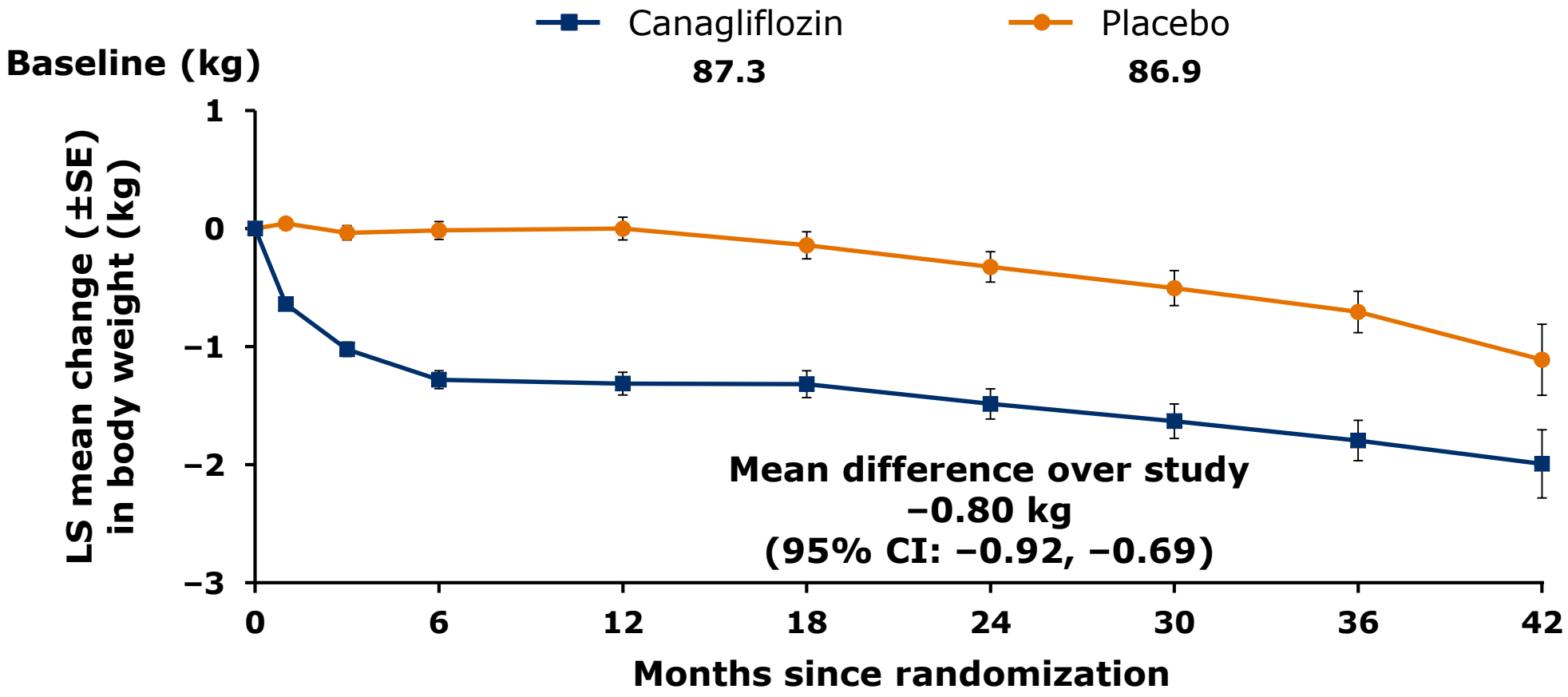
No. of participants

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

ITT analysis

CREDENCE

Effects on Body Weight



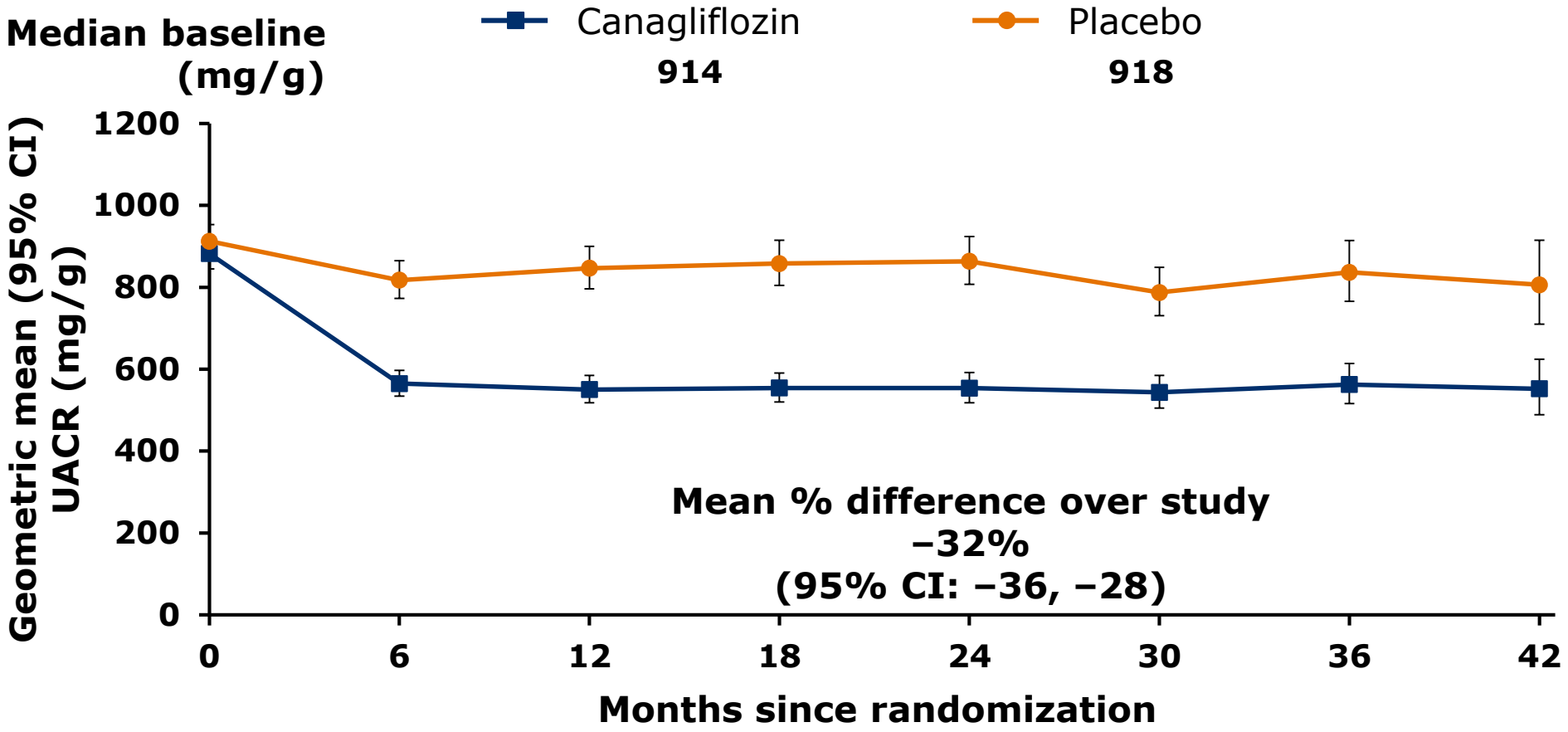
No. of participants

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

ITT analysis

CREDENCE

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

CREDENCE

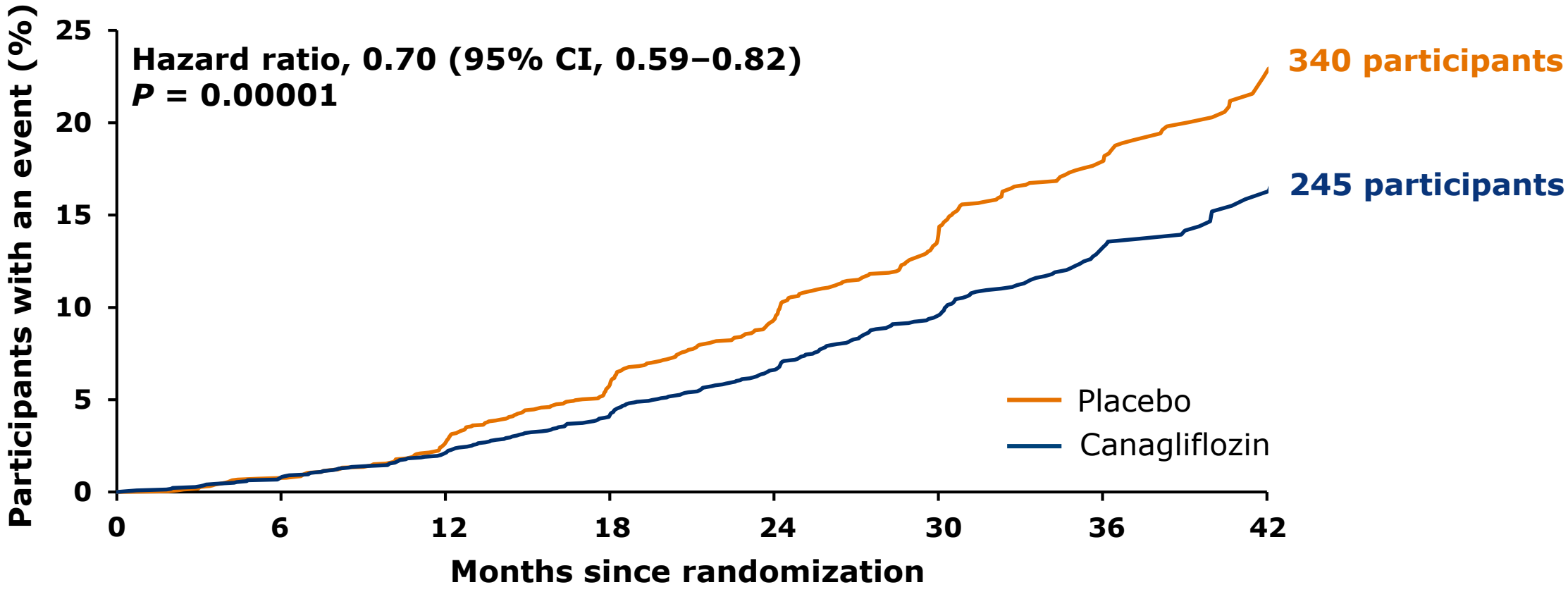
Primary and Renal Outcomes

CREDENCE

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

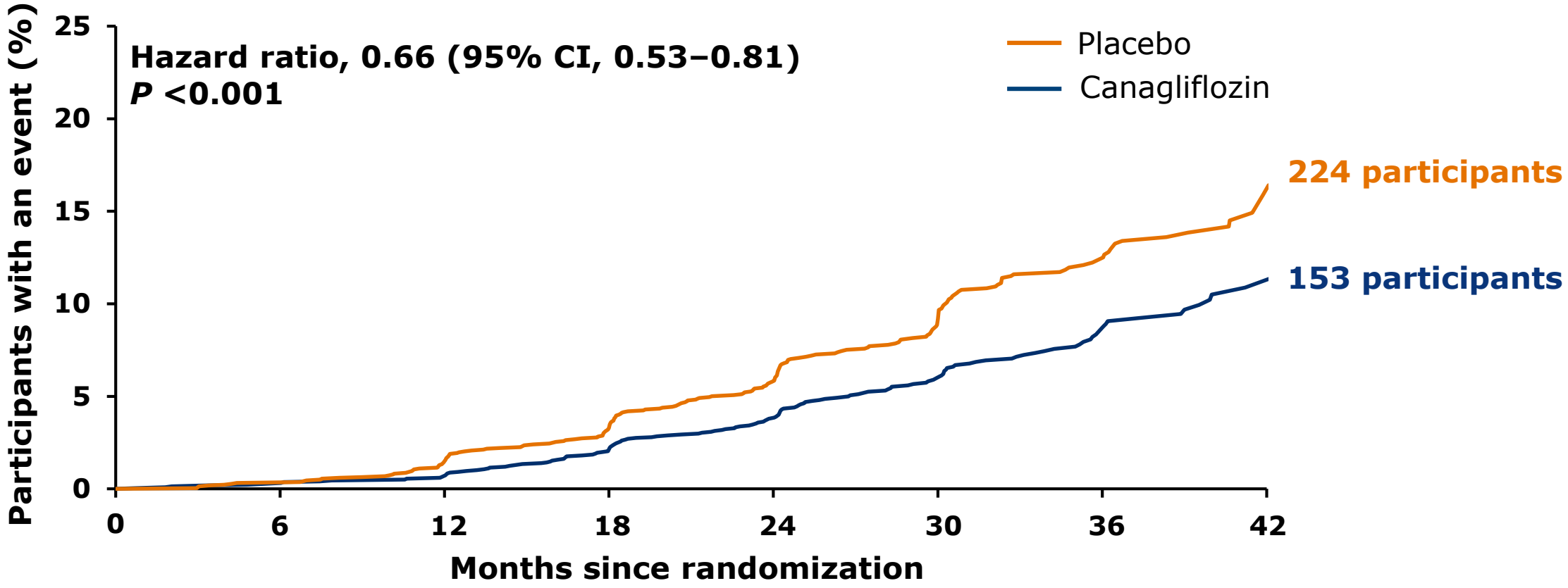
Primary Outcome:
ESKD, Doubling of Serum Creatinine, or Renal or CV Death



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

CREDENCE

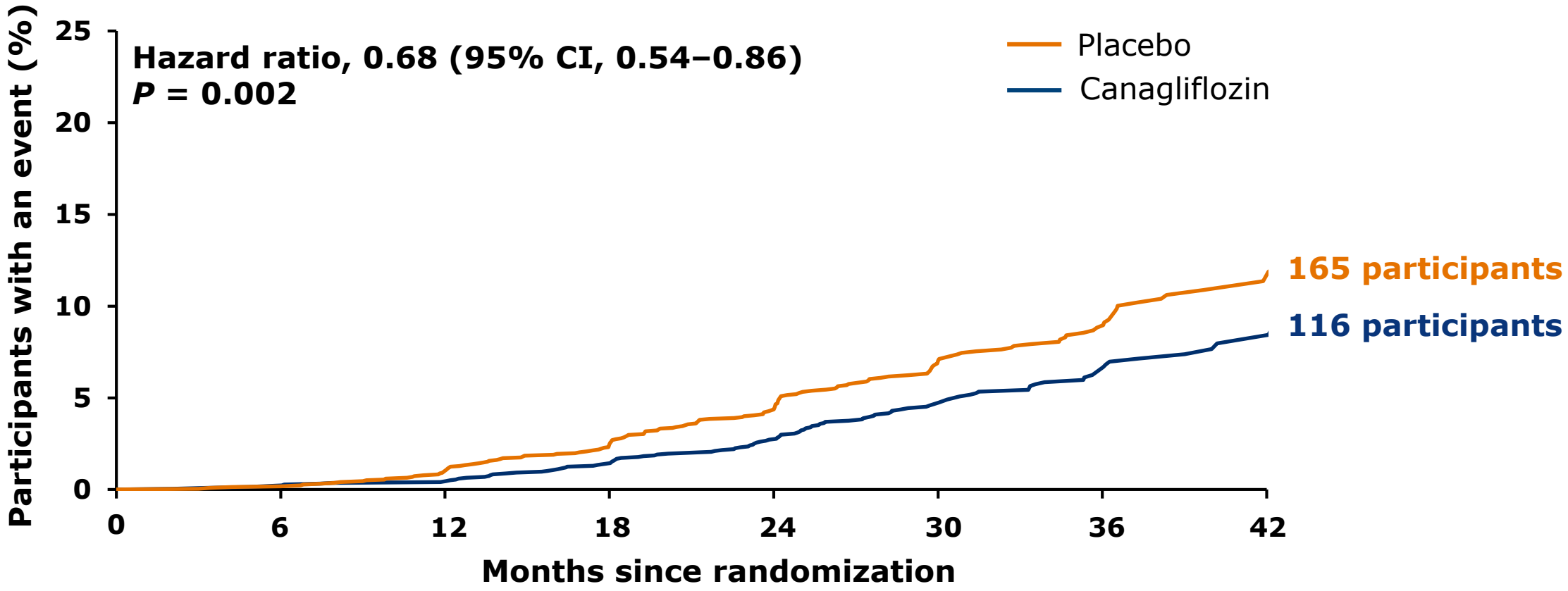
ESKD, Doubling of Serum Creatinine, or Renal Death



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

CREDENCE

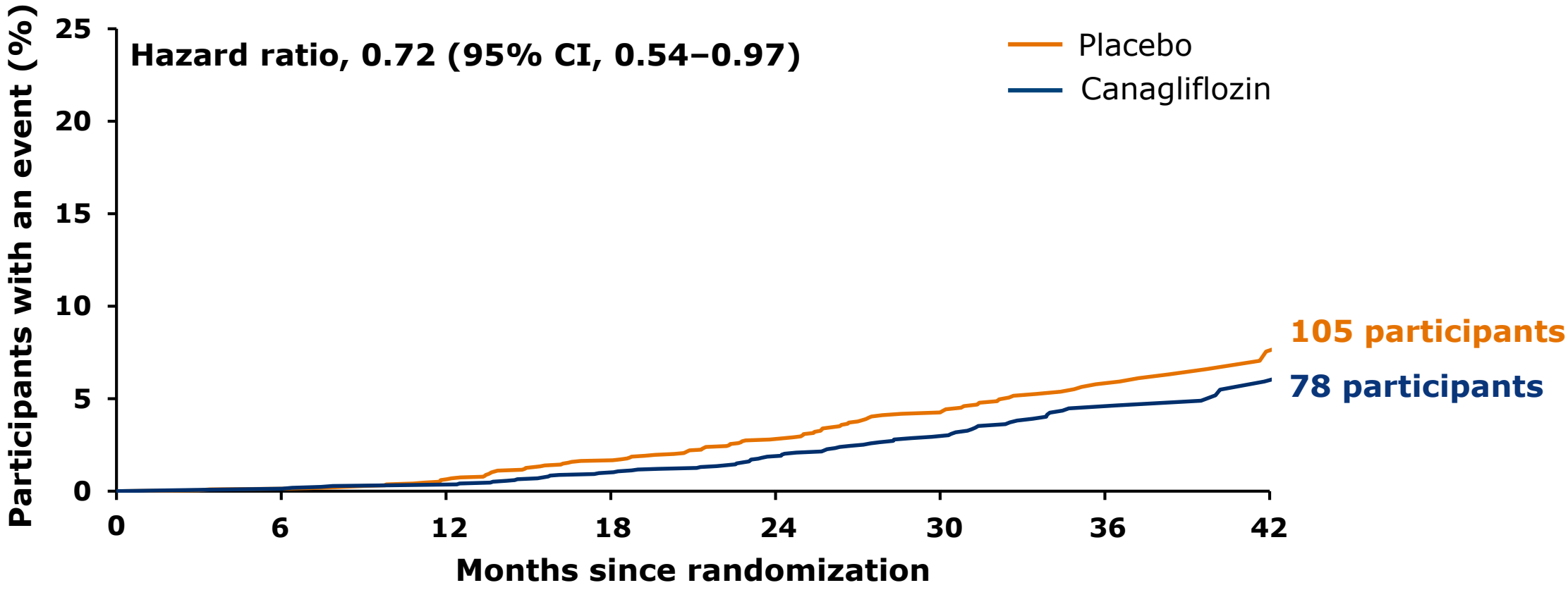
End-stage Kidney Disease



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

CREDENCE

Dialysis, Kidney Transplantation, or Renal Death*

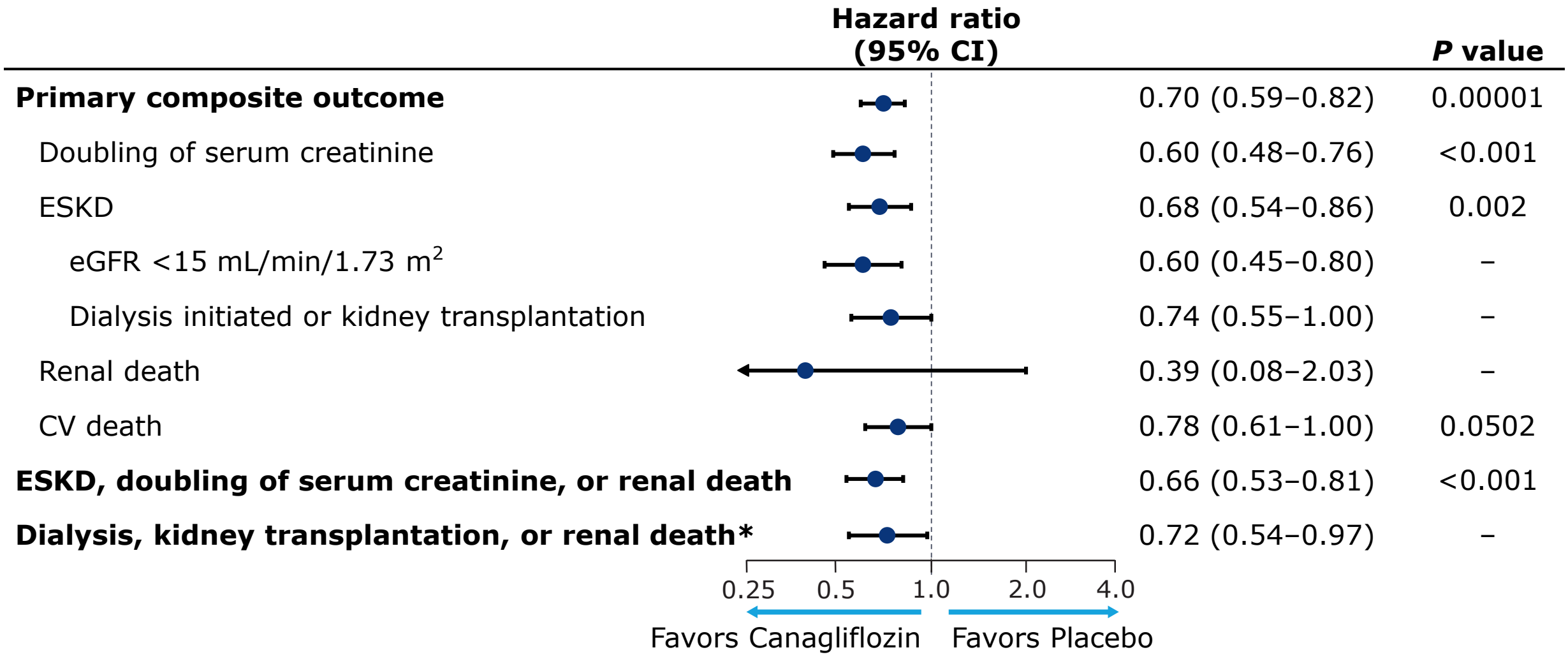


No. at risk								
Placebo	2199	2183	2147	2077	1776	1178	653	180
Canagliflozin	2202	2184	2148	2100	1811	1236	661	199

*Post hoc analysis.

CREDENCE

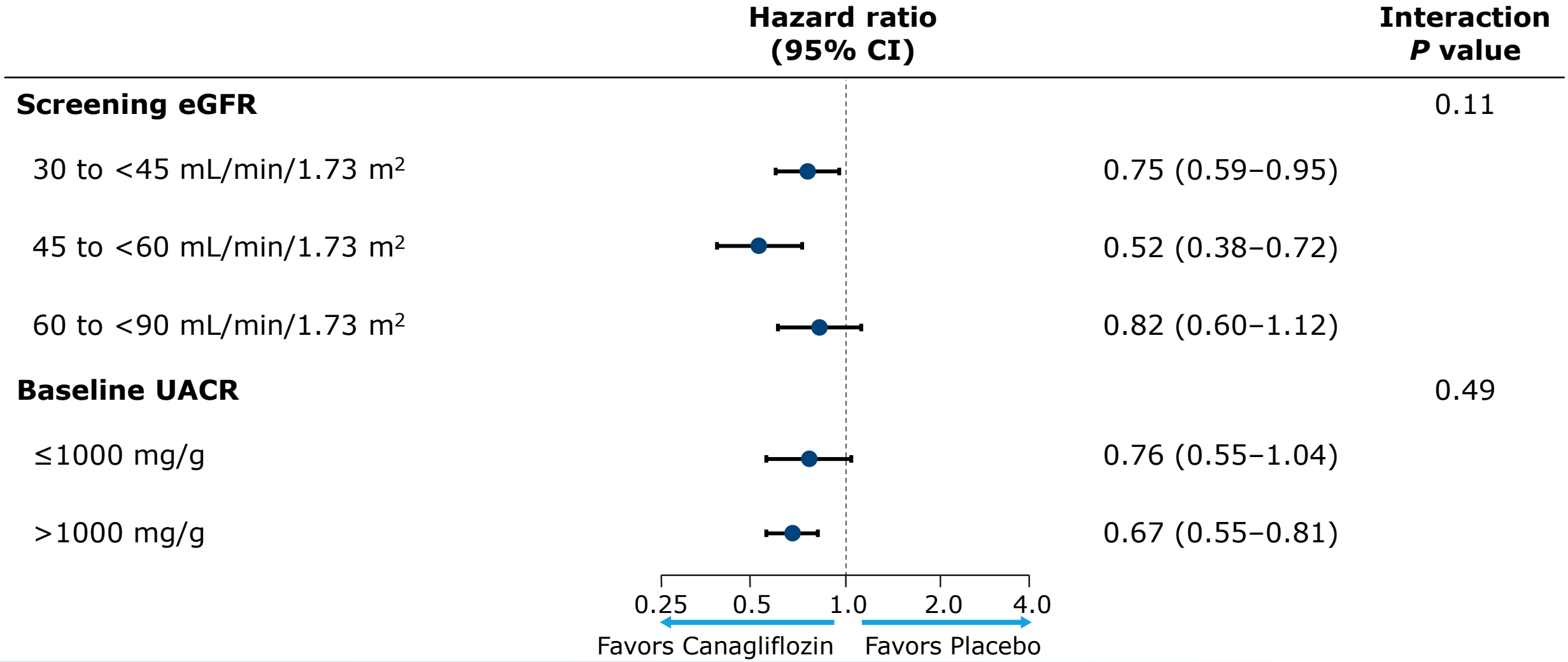
Summary Forest Plot



*Post hoc analysis.

CREDENCE

Primary Outcome by Screening eGFR and Albuminuria



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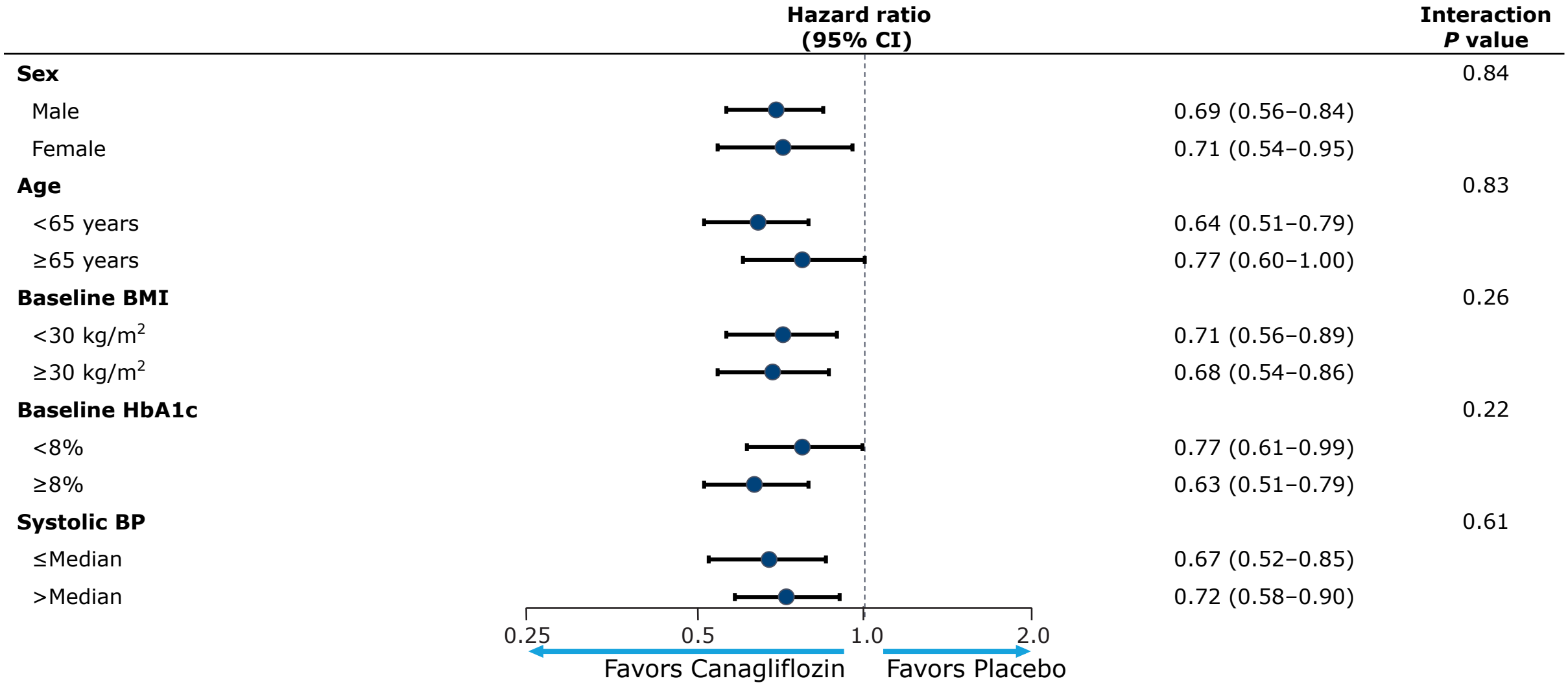
Primary Outcome: Demographic and Risk Factor Subgroups



CREDENCE

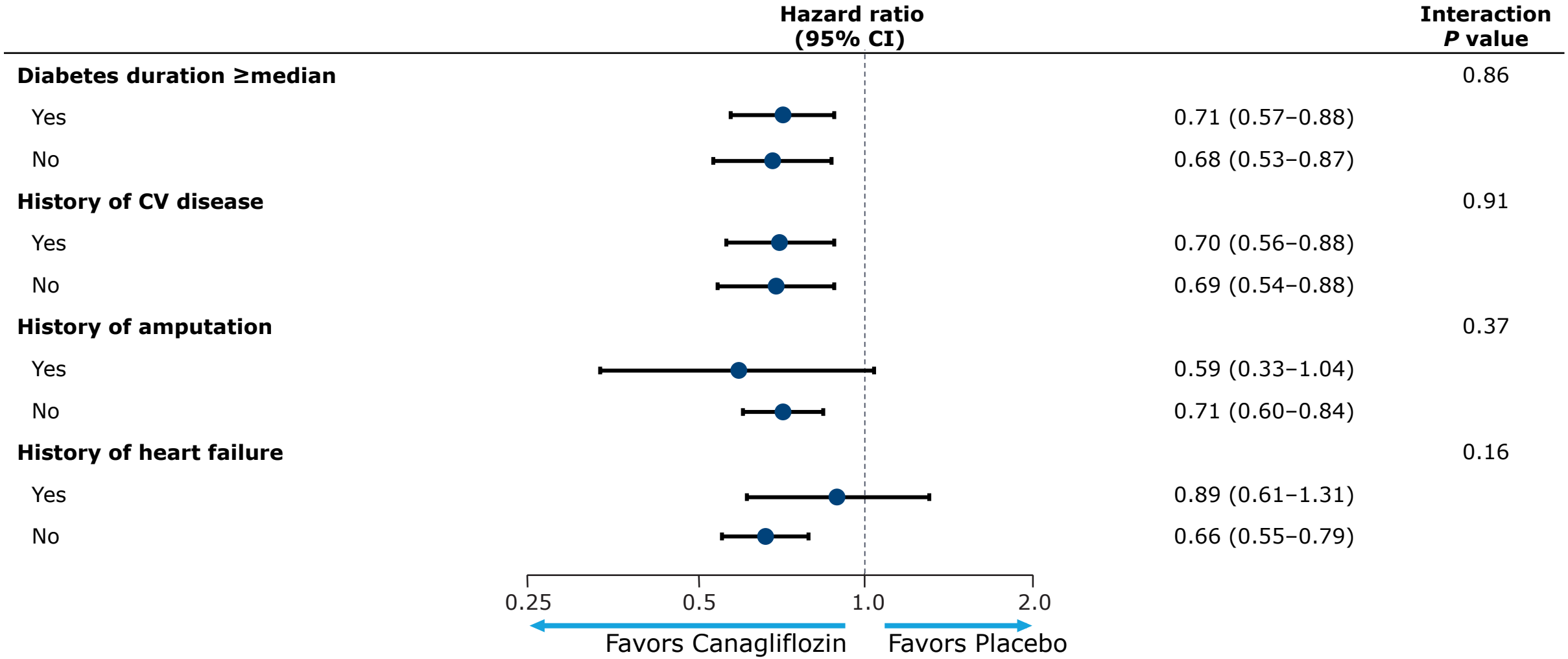
Primary Outcome: Demographic Subgroups

	Hazard ratio (95% CI)	Interaction *P* value
Race		0.91
White	0.70 (0.57–0.86)	
Black or African American	0.83 (0.43–1.60)	
Asian	0.66 (0.46–0.95)	
Other	0.71 (0.43–1.18)	
Ethnicity		0.55
Hispanic or Latino	0.62 (0.47–0.81)	
Not Hispanic or Latino	0.74 (0.60–0.91)	
Not reported/unknown	–*	
Region		0.18
North America	0.84 (0.63–1.13)	
Central/South America	0.61 (0.43–0.88)	
Europe	0.82 (0.54–1.24)	
Rest of world	0.58 (0.43–0.78)	

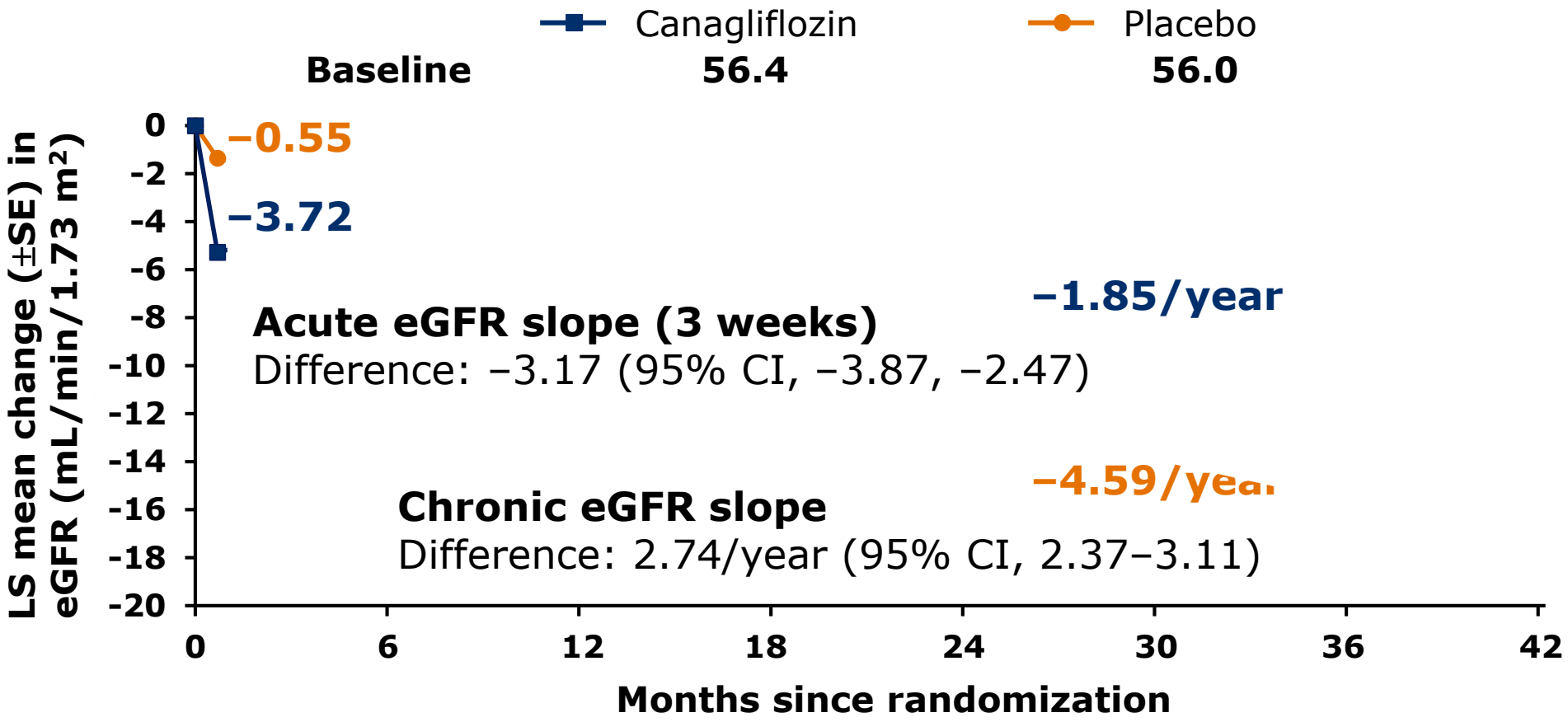
*Hazard ratios and 95% CIs were calculated for outcomes with >10 events.

CREDENCE

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

CREDENCE

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)

CREDENCE

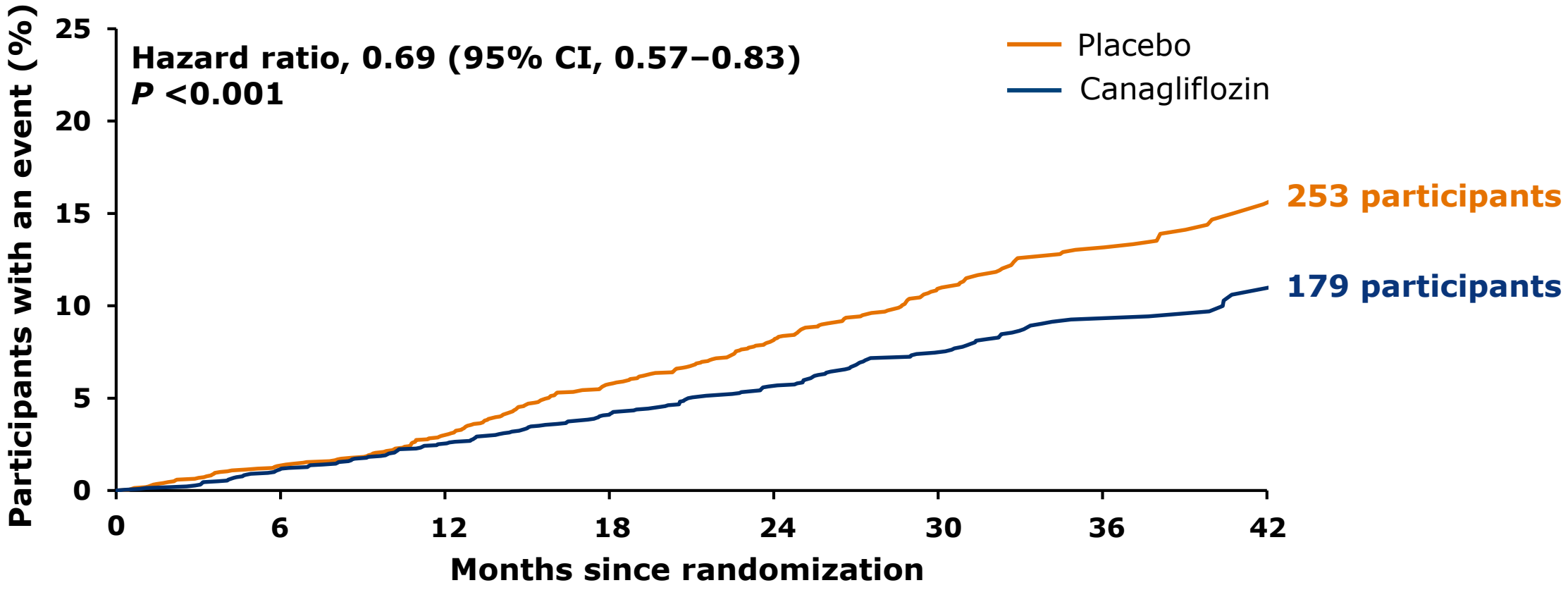
Secondary CV Outcomes

CREDENCE

CV-related Baseline Demographics

	Canagliflozin (n = 2202)	Placebo (n = 2199)	Total (N = 4401)
Hypertension, %	97	97	**97**
Heart failure (NYHA I-III), %	15	15	**15**
CV disease, %	51	50	**50**
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**

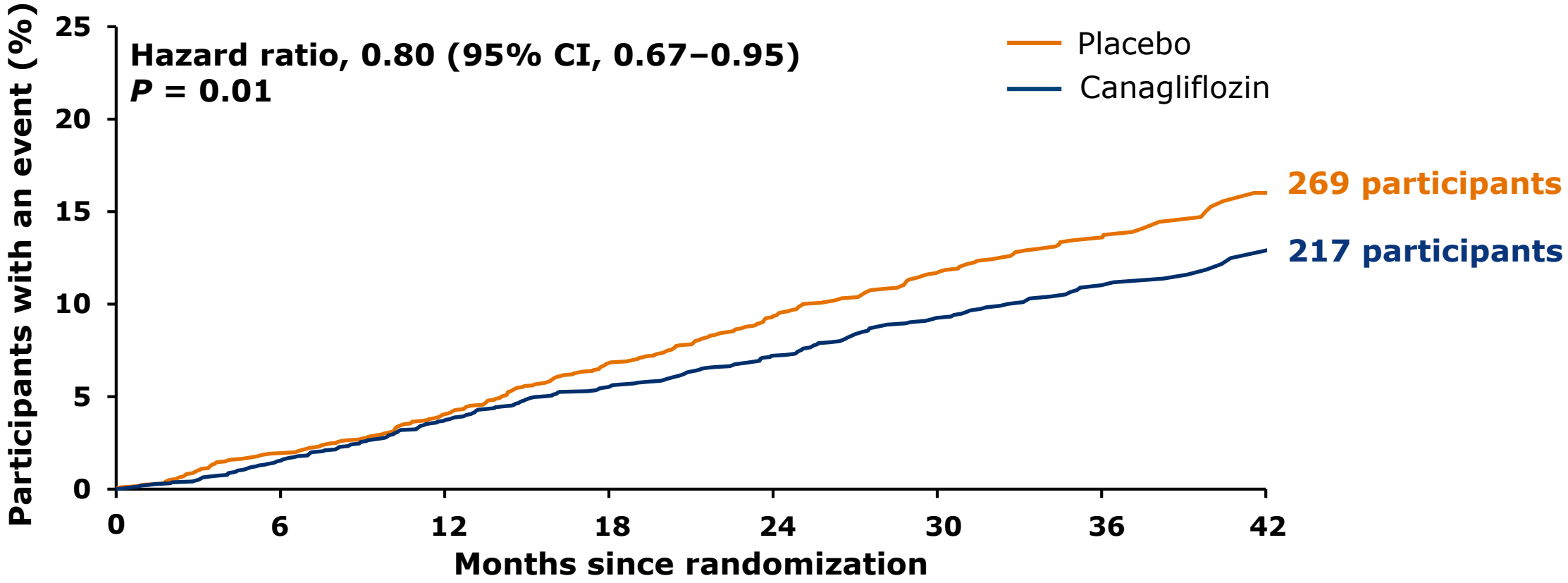
CV Death or Hospitalization for Heart Failure



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

CREDENCE

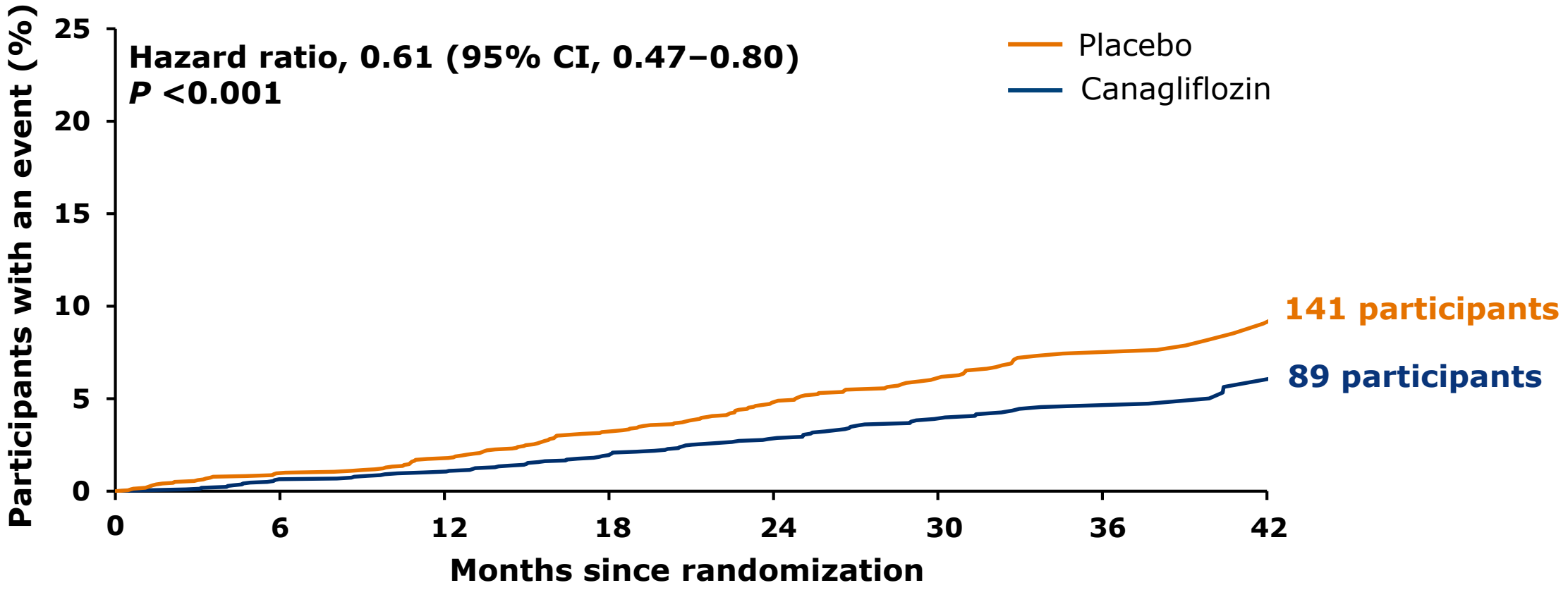
Major Cardiovascular Events: CV Death, MI, or Stroke



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

CREDENCE

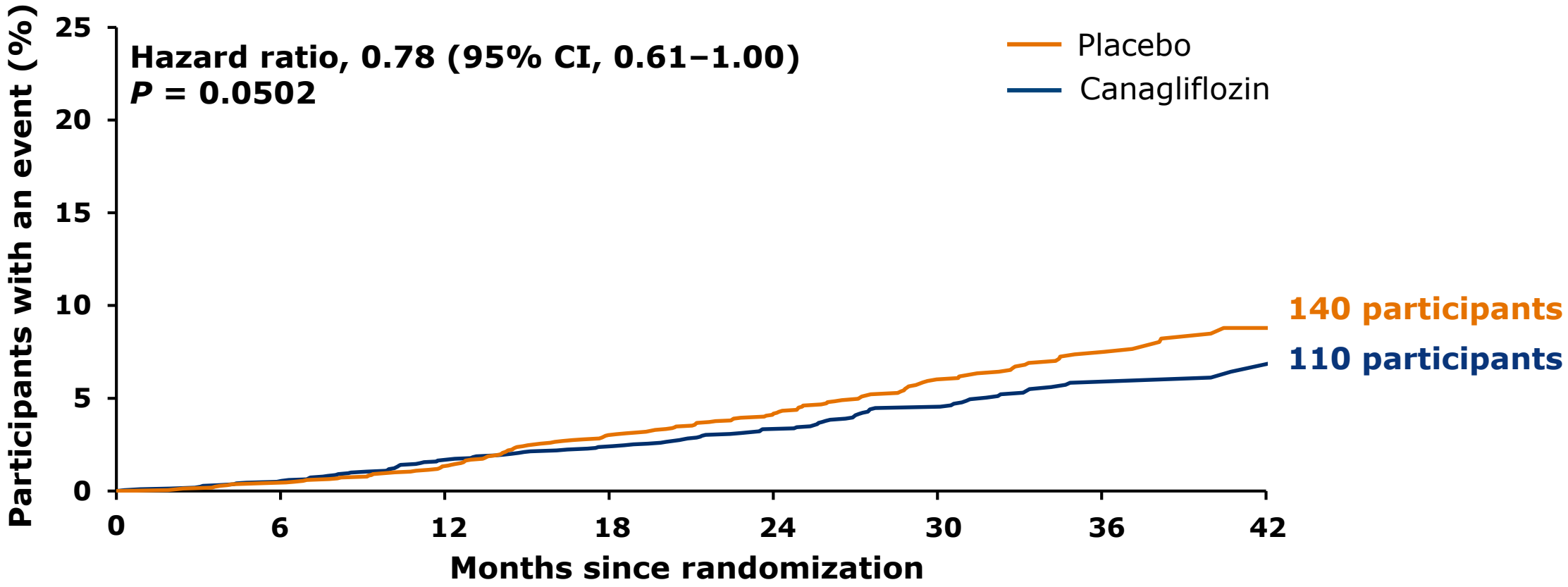
Hospitalization for Heart Failure



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

CREDENCE

CV Death

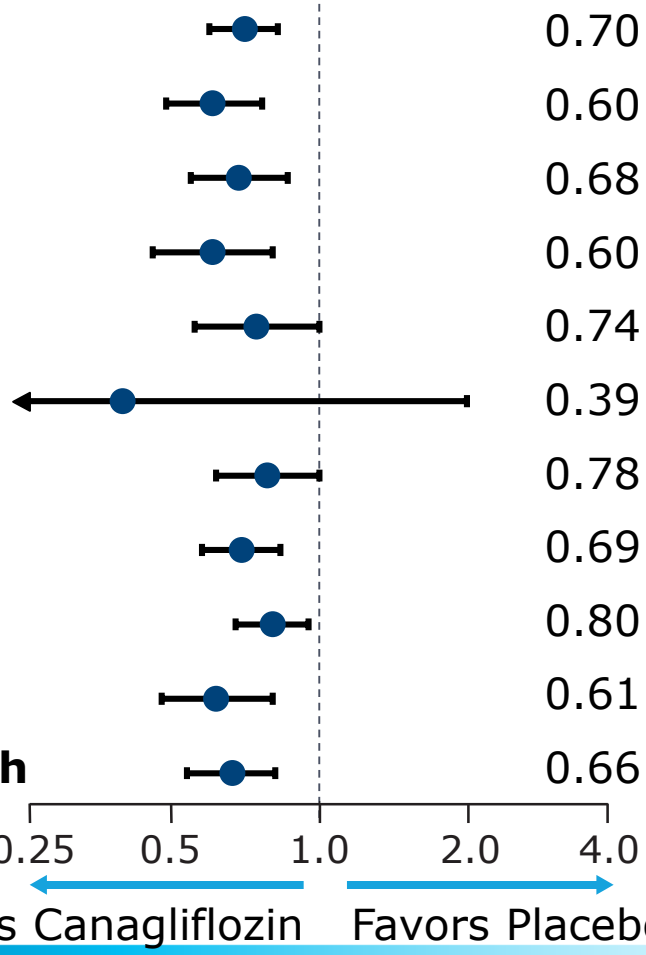


No. at risk								
Placebo	2199	2185	2160	2106	1818	1220	688	189
Canagliflozin	2202	2187	2155	2120	1835	1263	687	212

CREDENCE

Summary of Key Renal and CV Outcomes

	Hazard ratio (95% CI)	*P* value
Primary composite outcome	0.70 (0.59–0.82)	0.00001
Doubling of serum creatinine	0.60 (0.48–0.76)	<0.001
ESKD	0.68 (0.54–0.86)	0.002
eGFR <15 mL/min/1.73 m^2	0.60 (0.45–0.80)	–
Dialysis initiated or kidney transplantation	0.74 (0.55–1.00)	–
Renal death	0.39 (0.08–2.03)	–
CV death	0.78 (0.61–1.00)	0.0502
CV death or hospitalization for heart failure	0.69 (0.57–0.83)	<0.001
CV death, MI, or stroke	0.80 (0.67–0.95)	0.01
Hospitalization for heart failure	0.61 (0.47–0.80)	<0.001
ESKD, doubling of serum creatinine, or renal death	0.66 (0.53–0.81)	<0.001



CREDENCE

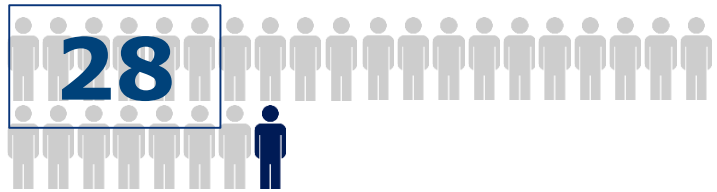
Summary

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

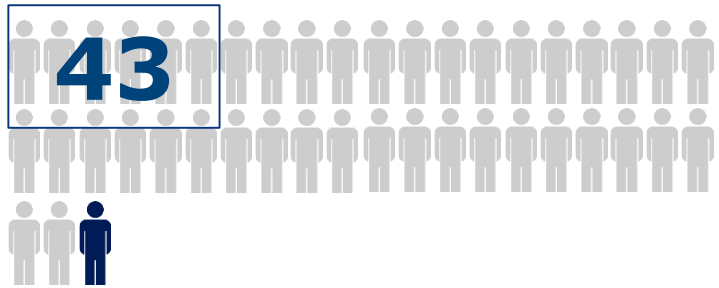
NNT for Renal and CV Outcomes Over 2.5 Years

Primary composite outcome

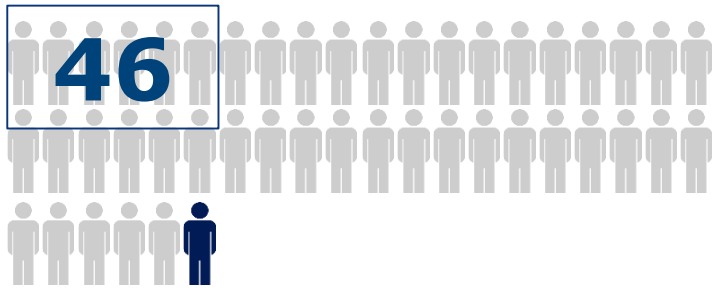
ESKD, doubling of serum creatinine, or renal death



ESKD



Hospitalization for heart failure



CV death, MI, or stroke

CREDENCE

Summary

Canagliflozin resulted in a clinically important and statistically significant reduction in kidney failure and major cardiovascular outcomes

CREDENCE

Safety Outcomes

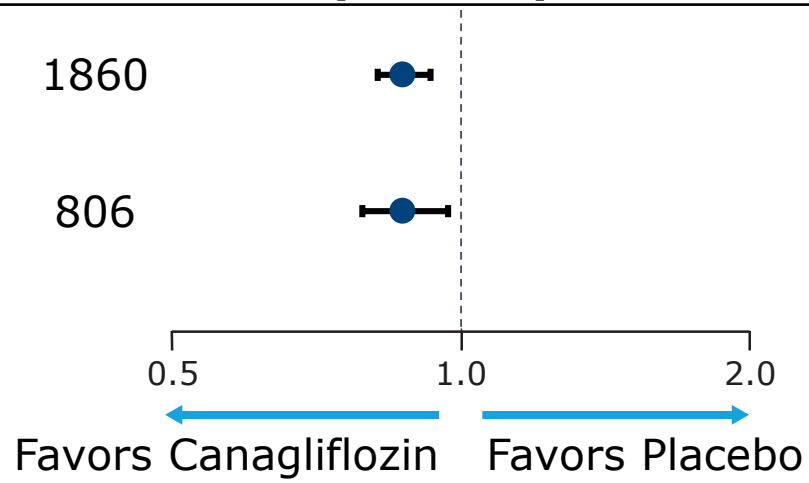
CREDENCE

Safety Analyses

- Independent blinded Endpoint Adjudication Committees adjudicated all suspected fractures, pancreatitis, diabetic ketoacidosis, and renal cell carcinoma events
- Other AEs of interest included
  - Renal-related AEs
  - Acute kidney injury
  - Hyperkalemia
  - Amputation
  - Male and female genital mycotic infections
  - Urinary tract infections
  - Volume depletion–related AEs

AEs and Serious AEs

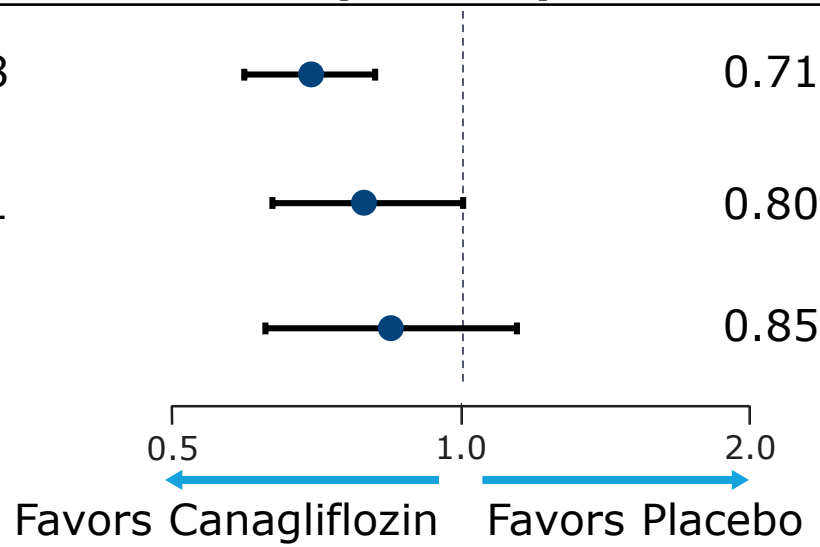
	Number of participants with an event, n		Hazard ratio (95% CI)
	Canagliflozin (N = 2200)	Placebo (N = 2197)	
All AEs	1784	1860	0.87 (0.82–0.93)
All serious AEs	737	806	0.87 (0.79–0.97)



Includes all treated participants through 30 days after last dose.

Renal Safety

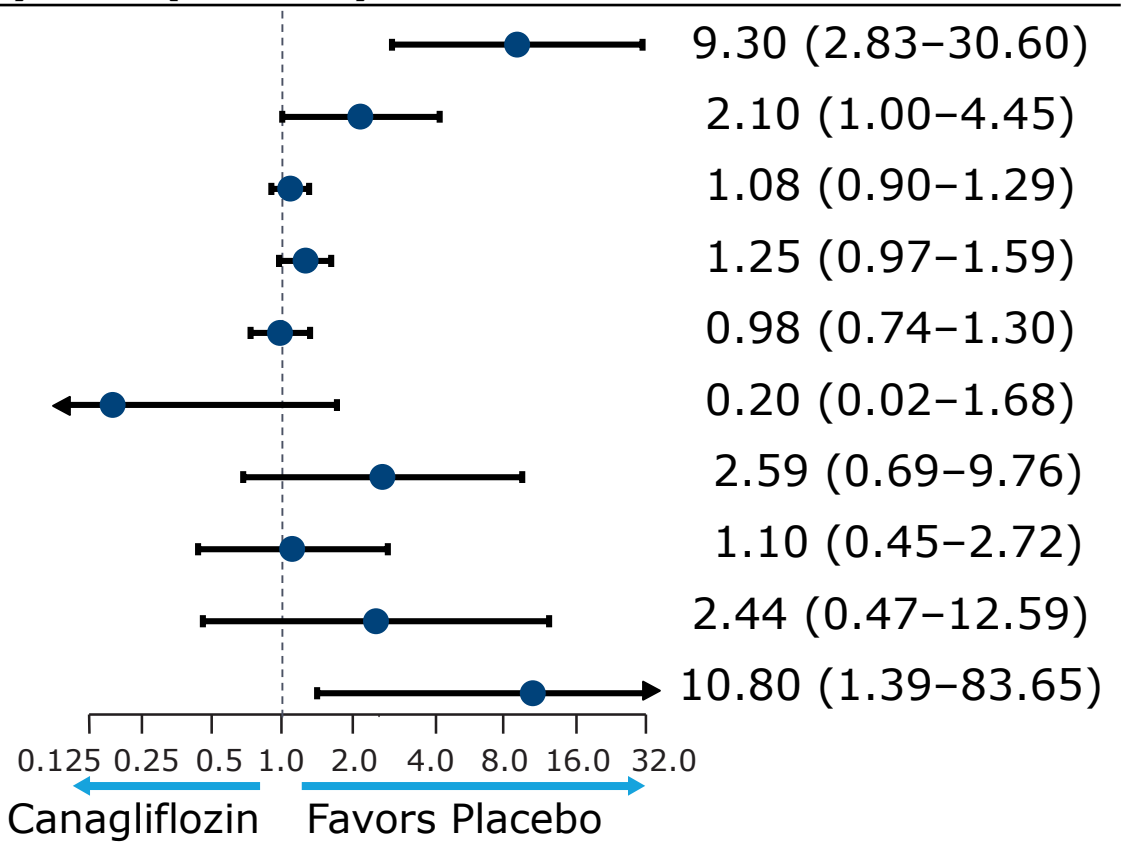
	Number of participants with an event, n		Hazard ratio (95% CI)
	Canagliflozin (N = 2200)	Placebo (N = 2197)	
All renal-related AEs	290	388	0.71 (0.61–0.82)
Hyperkalemia	151	181	0.80 (0.65–1.00)
Acute kidney injury	86	98	0.85 (0.64–1.13)



Includes all treated participants through 30 days after last dose.

Other AEs of Interest

	Number of participants with an event, n		Hazard ratio (95% CI)
	Canagliflozin (N = 2200)	Placebo (N = 2197)	
Male genital mycotic infections*	28	3	9.30 (2.83–30.60)
Female genital mycotic infections†	22	10	2.10 (1.00–4.45)
Urinary tract infections	245	221	1.08 (0.90–1.29)
Volume depletion–related AEs	144	115	1.25 (0.97–1.59)
Malignancies‡	98	99	0.98 (0.74–1.30)
Renal cell carcinoma	1	5	0.20 (0.02–1.68)
Breast†	8	3	2.59 (0.69–9.76)
Bladder	10	9	1.10 (0.45–2.72)
Acute pancreatitis	5	2	2.44 (0.47–12.59)
Diabetic ketoacidosis	11	1	10.80 (1.39–83.65)

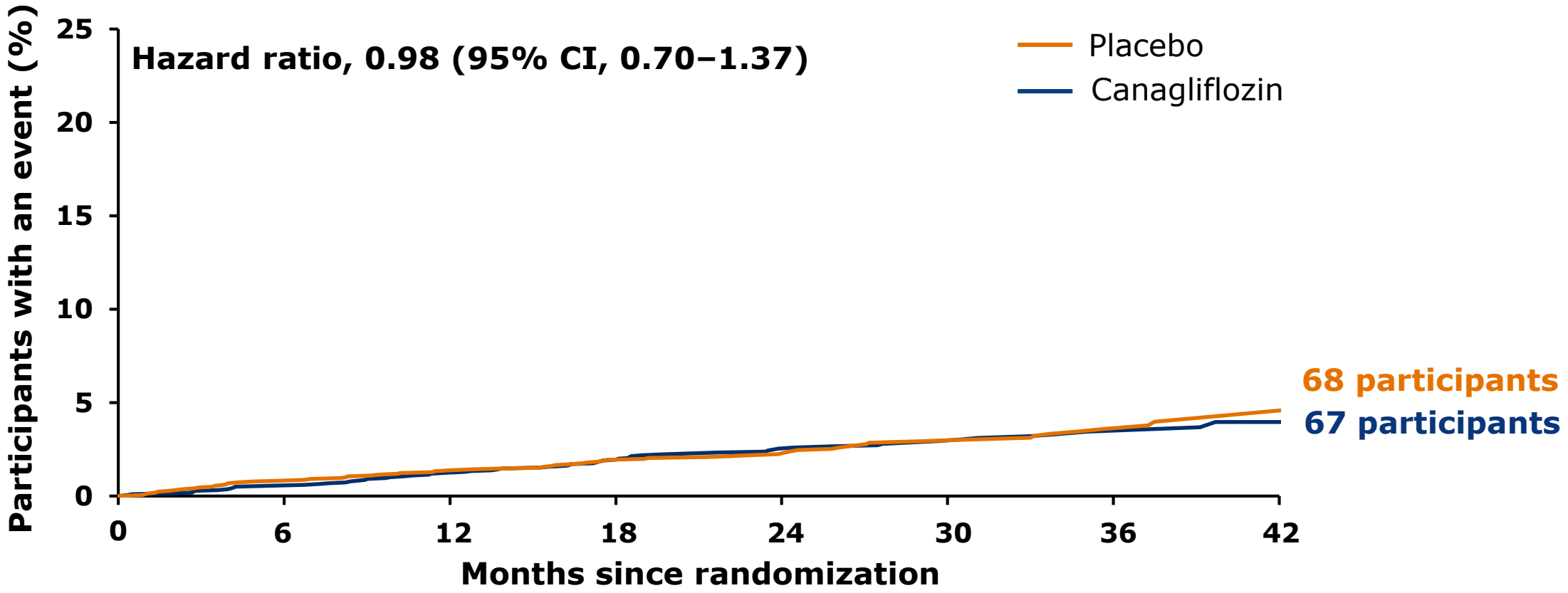


Includes all treated participants through 30 days after last dose except cancer, which includes all treated patients through the end of the trial.

*Includes male participants only (canagliflozin, n = 1439; placebo, n = 1466).
†Includes female participants only (canagliflozin, n = 761; placebo, n = 731).
‡Includes malignant tumors of unspecified type.

CREDENCE

Fracture

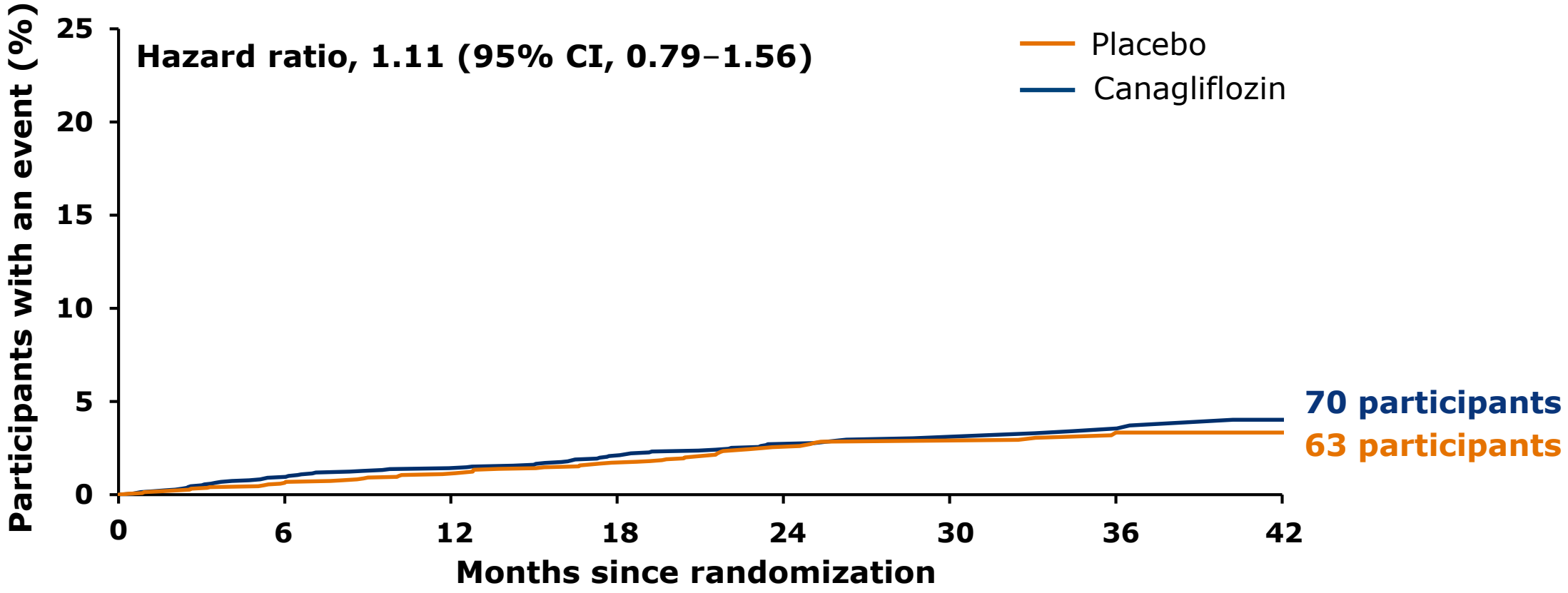


No. at risk								
Placebo	2197	2166	2128	2061	1769	1178	656	176
Canagliflozin	2200	2171	2121	2074	1785	1225	668	200

Includes all treated patients through the end of the trial.

CREDENCE

Lower Extremity Amputation



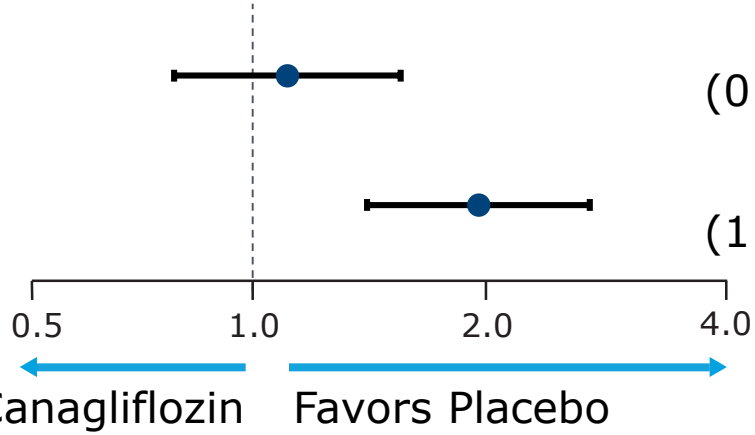
No. at risk								
Placebo	2197	2169	2131	2065	1766	1177	658	182
Canagliflozin	2200	2163	2118	2071	1788	1228	667	202

Includes all treated patients through the end of the trial.

CREDENCE

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.

CREDENCE

Summary

- No difference in risk was observed with canagliflozin compared with placebo for:
  - Fracture
  - Amputation
- Safety profile was otherwise consistent with previous canagliflozin studies

Conclusion

Canagliflozin safely reduced the risk of kidney failure and prevented CV events in people with T2DM and CKD