Outcomes of SGLT2i in Diabetic Kidney Disease: Is it all diabetes?

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Standard of Care to Prevent Progression of CKD

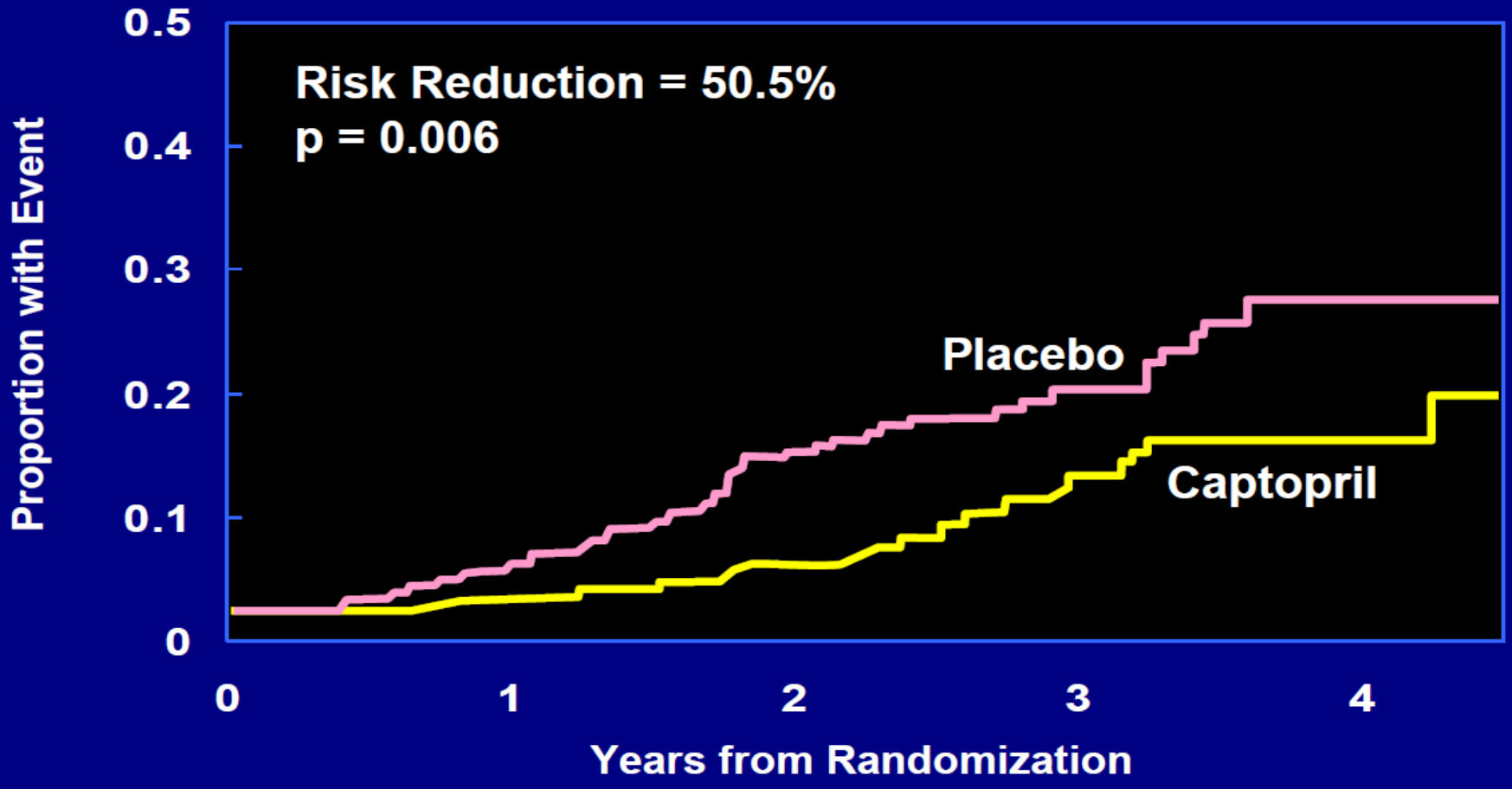
BP <130/80 mmHg[1-3]

RAAS inhibitors in patients with albumuinuria[4]

BP, blood pressure; RAAS, renin-angiotensin-aldosterone system.

1. Wright JT Jr et al. *JAMA*. 2002;288(19):2421-2431.
2. Wright JT Jr et al. *N Engl J Med*. 2015;373(22):2103-2116.
3. Hebert LA et al. *Hypertension*. 1997;30(3 Pt 1):428-435.
4. Kidney Disease Improving Global Outcomes (KDIGO). KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-Blood-Pressure-Guideline-English.pdf. Accessed May 7, 2019.

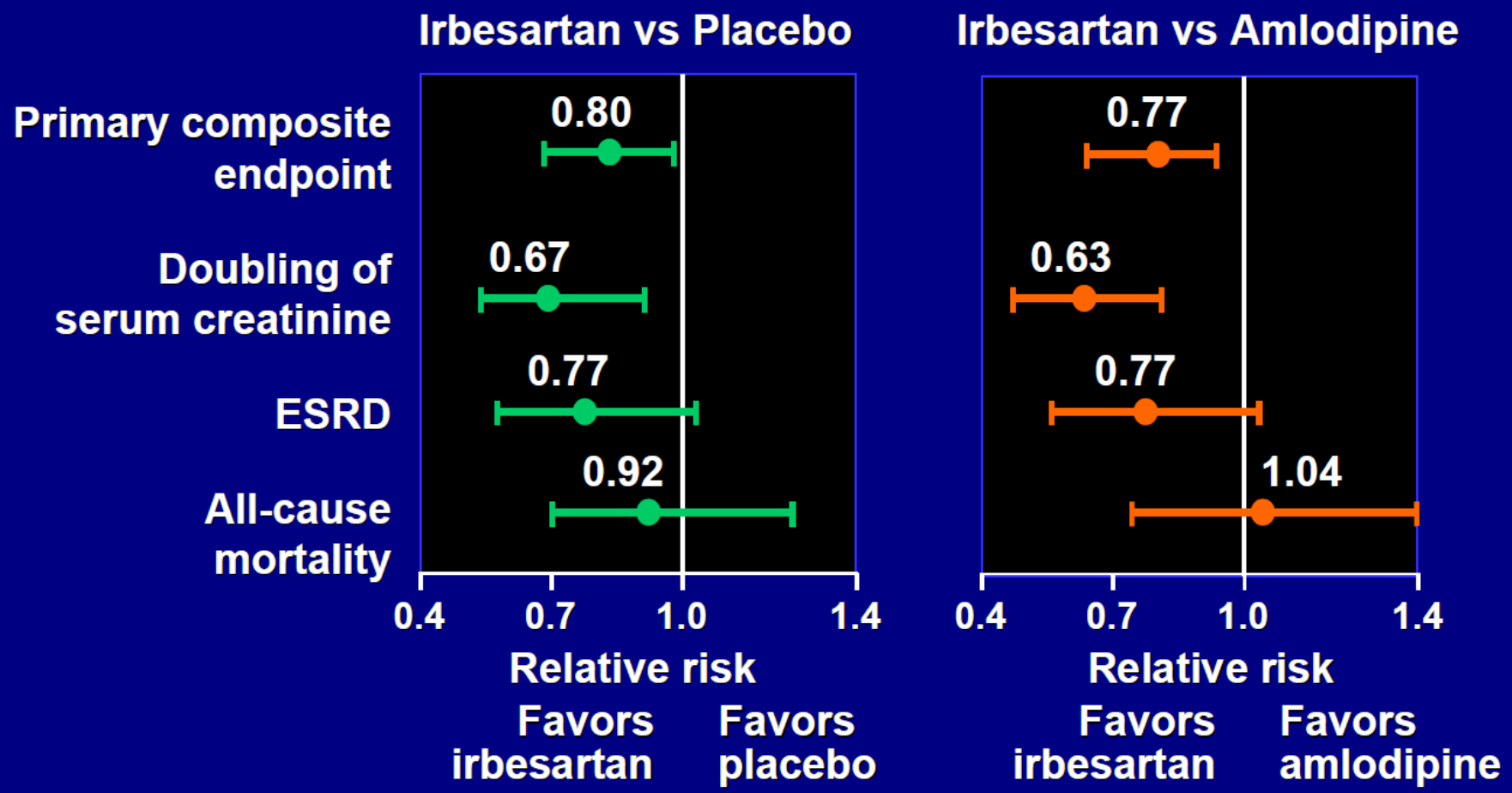
Effect of Captopril on End-Stage Renal Disease or Death in Type 1 Diabetic Nephropathy



No. at Risk

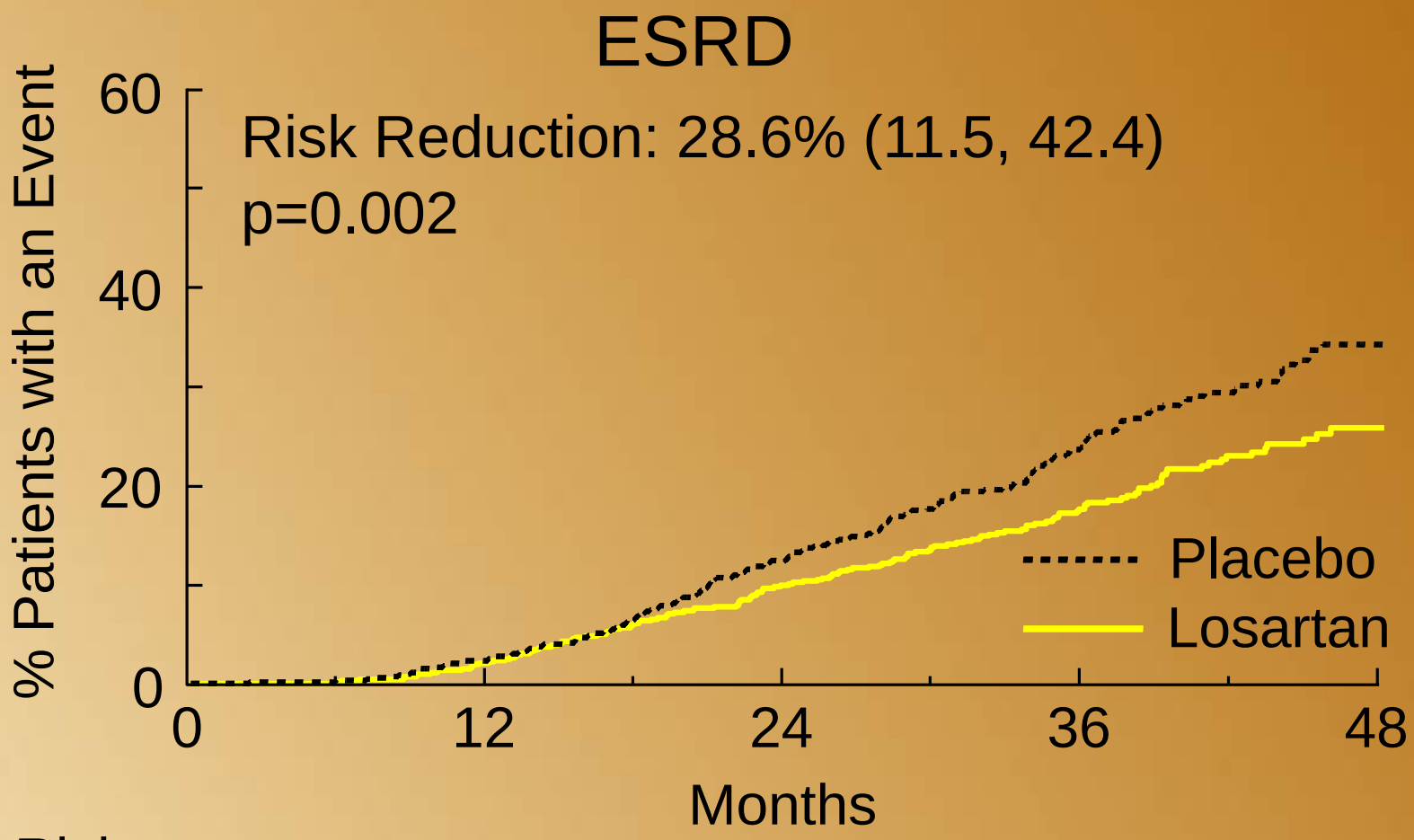
Placebo	202	192	172	101	28
Captopril	207	204	195	103	37

IDNT: Primary Endpoint Analysis – Composite and Components*



* Total incidence counts all occurrence of each individual components event.

RENAAL: Irreversible Clinical Endpoints



n at Risk

Pbo	762	715	610	348	43
Los	751	714	625	375	68

Outcome trials for CV safety in high-risk type 2 diabetes mellitus

- All these trials designed to assure cardiovascular safety of the drugs i.e. non-inferiority trials
- Not designed to test or demonstrate renal efficacy

Outcome trials for CV safety in high-risk type 2 diabetes mellitus

- SGLT-2 inhibitor trials
  - Empagliflozin EMPA-REG OUTCOME
  - Canagliflozin CANVAS
- SGLT-2 inhibitor trial designed to show renal protection
  - Canagliflozin CREDENCE

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EMPA REG OUTCOME

- Empagliflozin, 3 arms: 0, 10, 25 mg, n=7020
- All with CVD, none with eGFR <30
- Primary end-point: 3 point MACE
  - CV death
  - Non-fatal MI
  - Non-fatal stroke
- Primary end-point: HR 0.86 (0.74-0.99)
  - Non-inferiority p <0.001
  - Superiority p=0.04

Zinman B et al, NEJM 2015

Outcome trials for CV safety in high-risk type 2 diabetes mellitus

- SGLT-2 inhibitor trials
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  - Canagliflozin CANVAS
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CANVAS

- Canagliflozin, 3 arms: 0, 100, 300 mg, n=10142, 2 trials
  - Symptomatic ASCVD + age 30+ OR
  - 2 CV risk factors + age 50+, exclude eGFR <30
- Primary end-point: 3 point MACE
  - HR 0.86 (0.75-0.97)
  - Non-inferiority p <0.001, Superiority p=0.02
- Increased risk of leg amputation
  - HR 1.97, p<0.001

Neal B et al, NEJM 2017

Outcome trials for CV safety in high-risk type 2 diabetes mellitus

- SGLT-2 inhibitor trials
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CREDENCE

- Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy
- Inclusion
  - albuminuria (UACR 300-5000 mg/g)
  - eGFR 30-90
- Outcomes:
  - Primary outcome: time to first of end-stage kidney disease (ESKD), doubling of serum creatinine, renal or cardiovascular (CV) death.
  - Secondary outcome:
    - CV composite: CV death, MI, stroke, hosp-CHF, hosp-USAP
    - Individual components of renal composite: ESKD, doubling of serum creatinine, or renal death.
    - All cause mortality

NCT02065791

Phase 3 CREDENCE Renal Outcomes Trial of Canagliflozin is Being Stopped Early for Positive Efficacy Findings

RARITAN, N.J., July 16, 2018 – The Janssen Pharmaceutical Companies of Johnson & Johnson today announced that the Phase 3 CREDENCE (**C**anagliflozin and **R**enal **E**vents in **D**iabetes with **E**stablished **N**ephropathy **C**linical **E**valuation) clinical trial, evaluating the efficacy and safety of canagliflozin versus placebo when used in addition to standard of care for patients with chronic kidney disease (CKD) and type 2 diabetes (T2D), is being stopped early based on the achievement of pre-specified efficacy criteria.

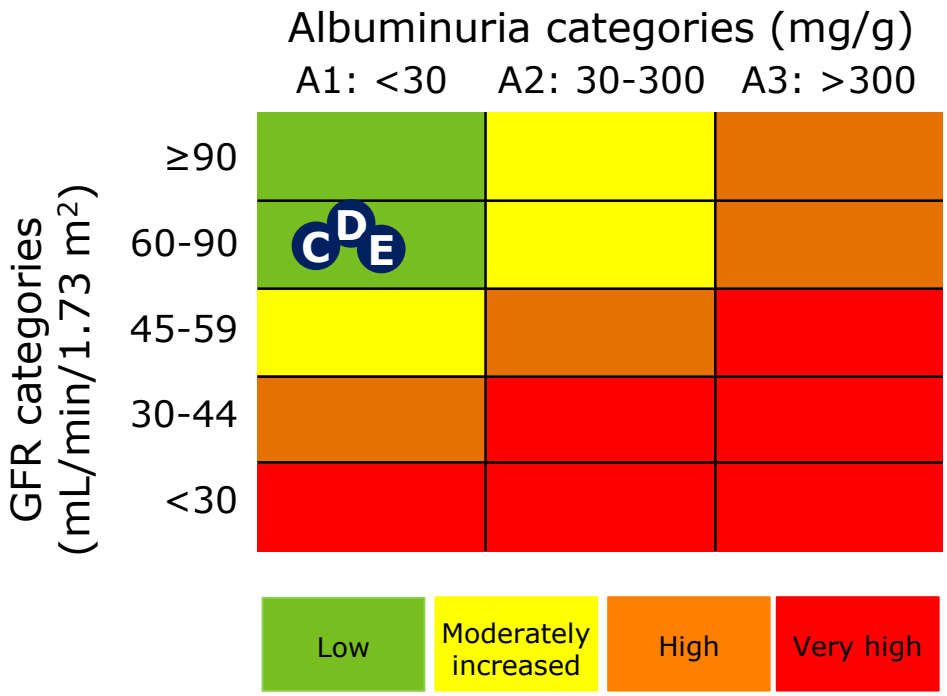
The decision is based on a recommendation from the study's Independent Data Monitoring Committee (IDMC) that met to review the data during a planned interim analysis. **This recommendation was based on demonstration of efficacy,** as the trial had achieved pre-specified criteria for the primary composite endpoint of end-stage kidney disease (time to dialysis or kidney transplantation), doubling of serum creatinine, and renal or cardiovascular (CV) death, when used in addition to standard of care.

https://www.jnj.com/phase-3-credence-renal-outcomes-trial-of-invokana-canagliflozin-is-being-stopped-early-for-positive-efficacy-findings

Renal outcomes SGLT-2 inhibitor trials

Trial	Definition	HR	p
EMPA-REG Secondary microvascular	Progression to macro, 2x creat + eGFR <45, RRT, renal death	0.61 0.53-0.70	<0.001
Post hoc	2x cr (+eGFR<45), RRT (n=27), renal death	0.54 0.40-0.75	<0.001
CANVAS: secondary	Albuminuria progression	0.73 0.76-0.79	<0.05
Post hoc	40% eGFR (n=239), RRT (n=18), renal death (n=3)	0.60 0.47-0.77	<0.05

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

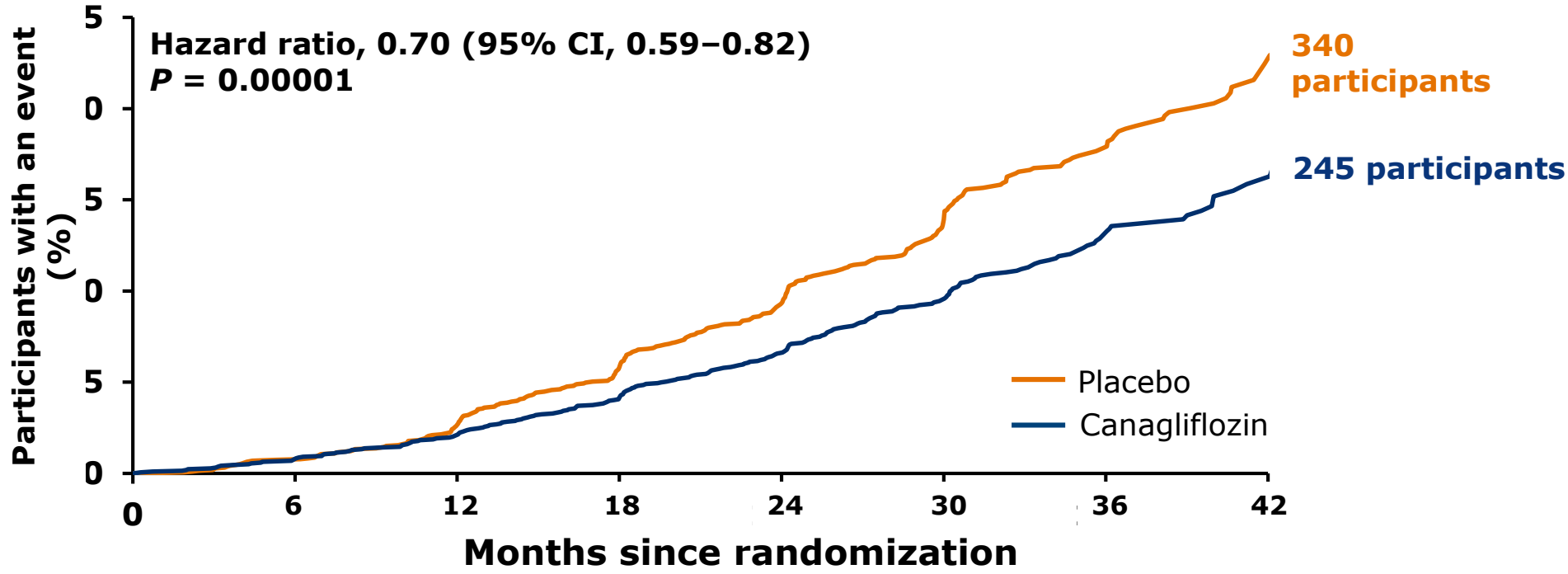
Sustained RRT Events

DECLARE	Not reported
CANVAS Program	18
EMPA-REG OUTCOME	11

Total of 29 sustained RRT events reported across trials

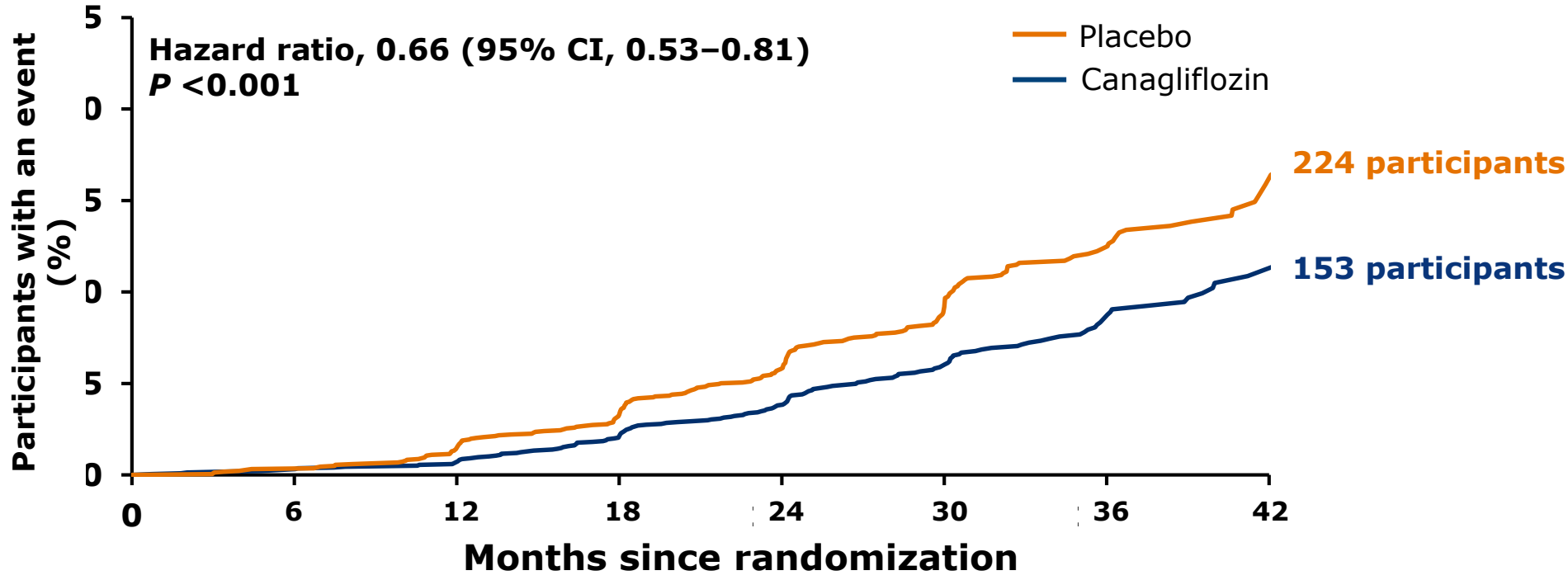
Effects on Renal Outcomes in CREDENCE

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



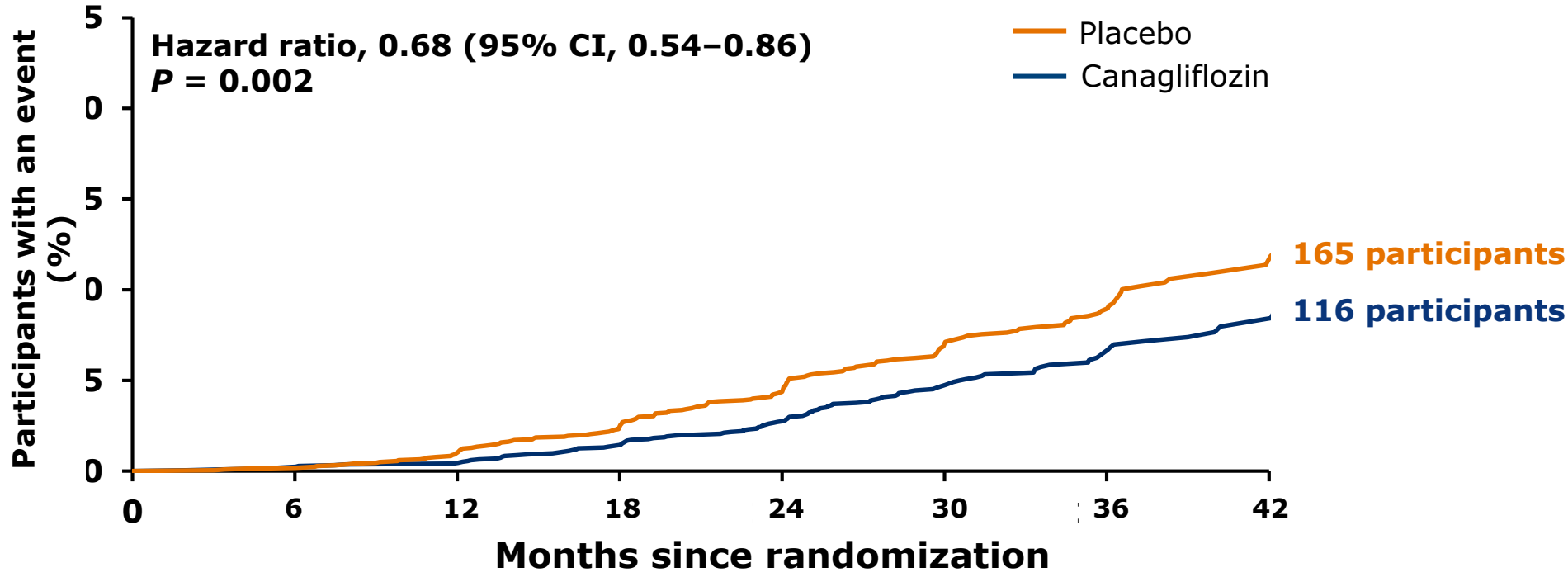
No. at risk								
Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

ESKD, Doubling of Serum Creatinine, or Renal Death



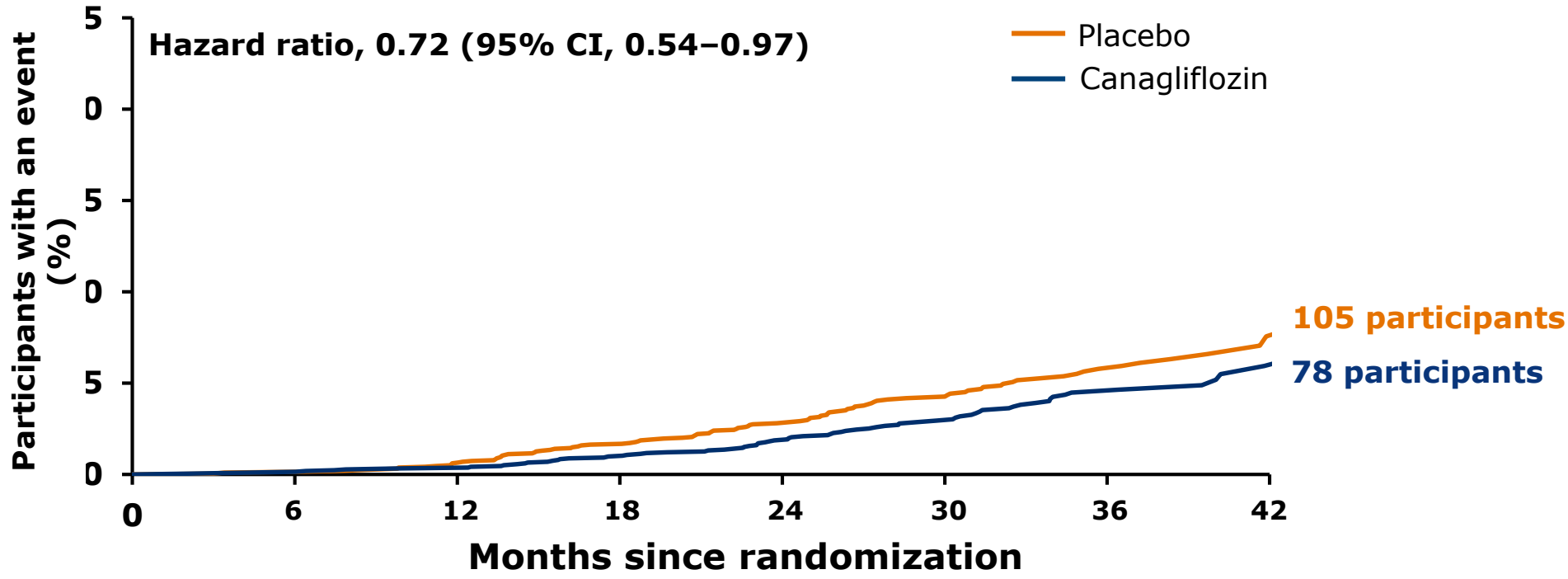
No. at risk								
Placebo	2199	2178	2131	2046	1724	1129	621	170
Canagliflozin	2202	2181	2144	2080	1786	1211	646	196

End-stage Kidney Disease



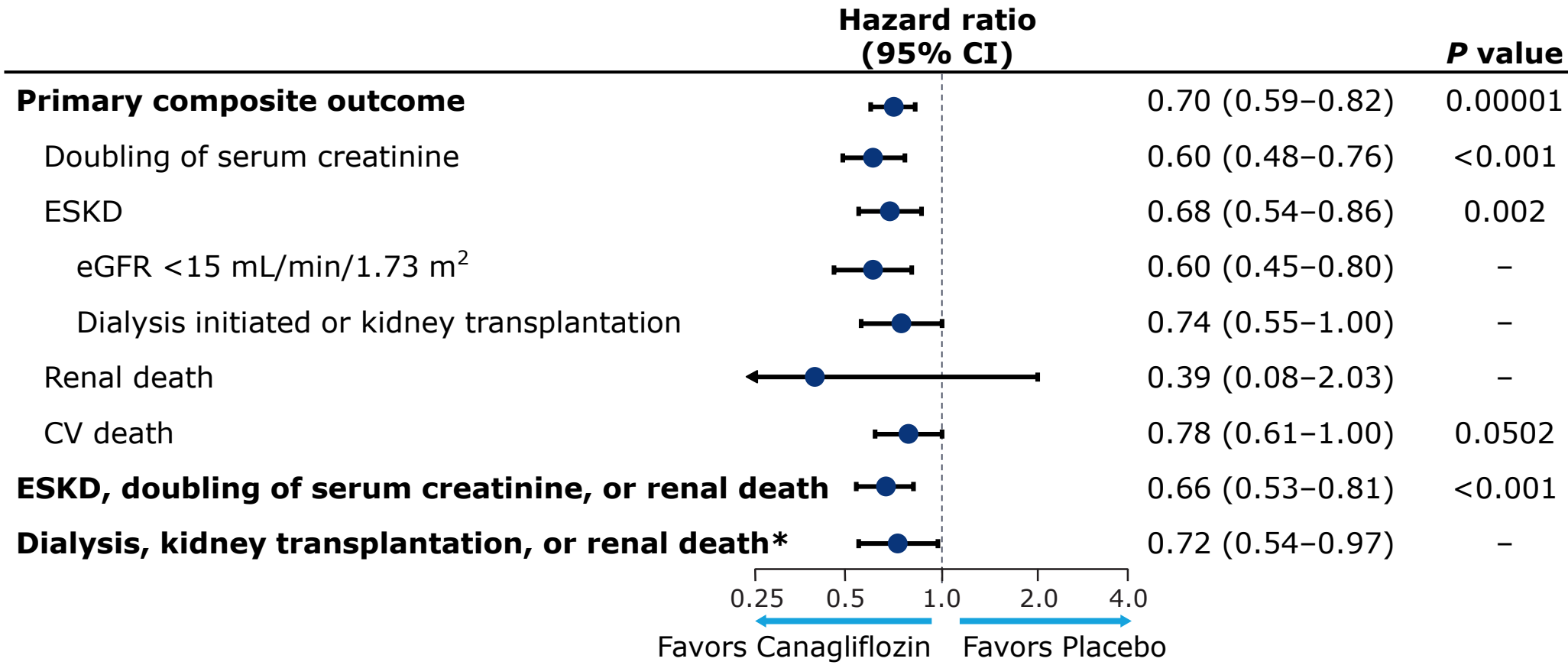
No. at risk								
Placebo	2199	2182	2141	2063	1752	1152	641	178
Canagliflozin	2202	2182	2146	2091	1798	1217	654	199

Dialysis, Kidney Transplantation, or Renal Death*



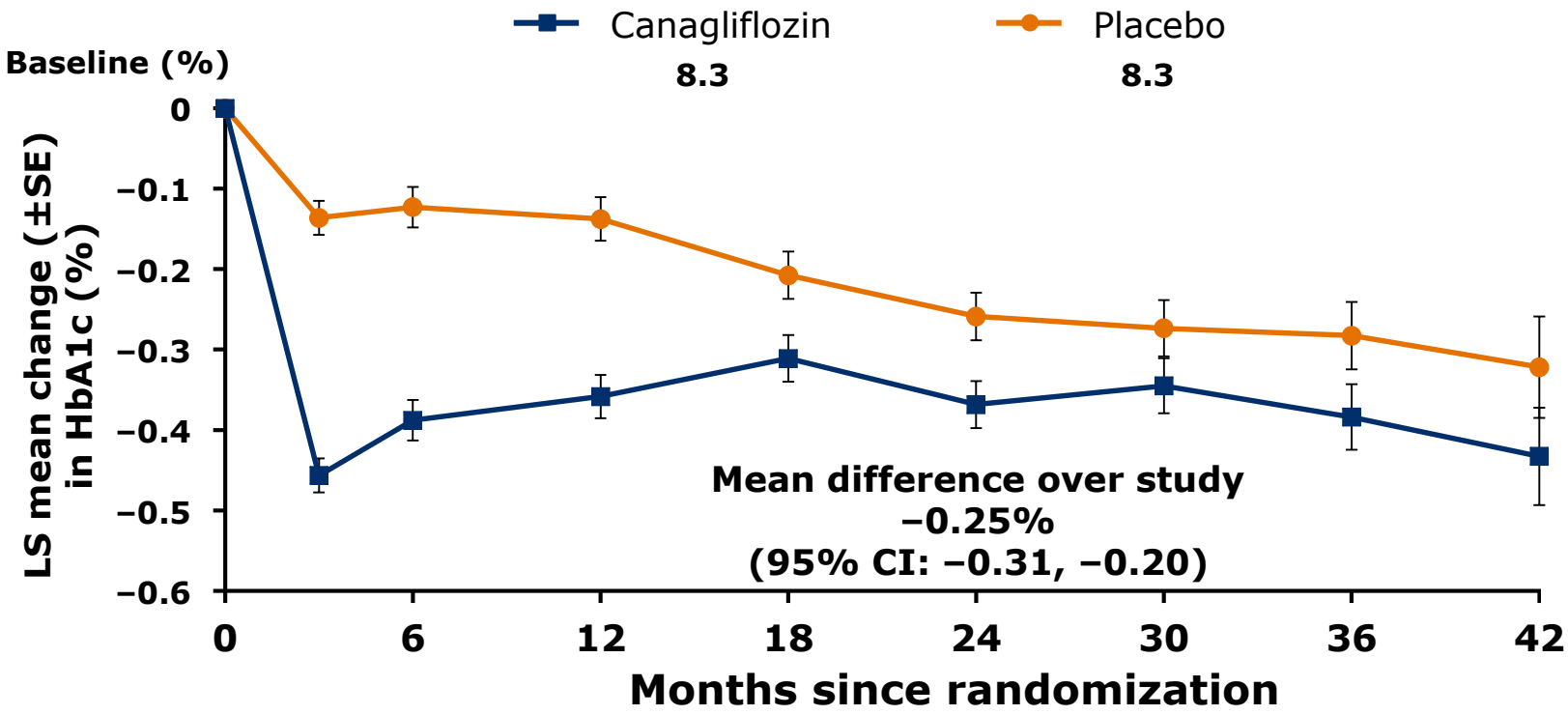
No. at risk								
Placebo	2199	2183	2147	2077	1776	1178	653	180
Canagliflozin	2202	2184	2148	2100	1811	1236	661	199

Summary Forest Plot



Effects on BP and glucose in CREDENCE

Effects on HbA1c

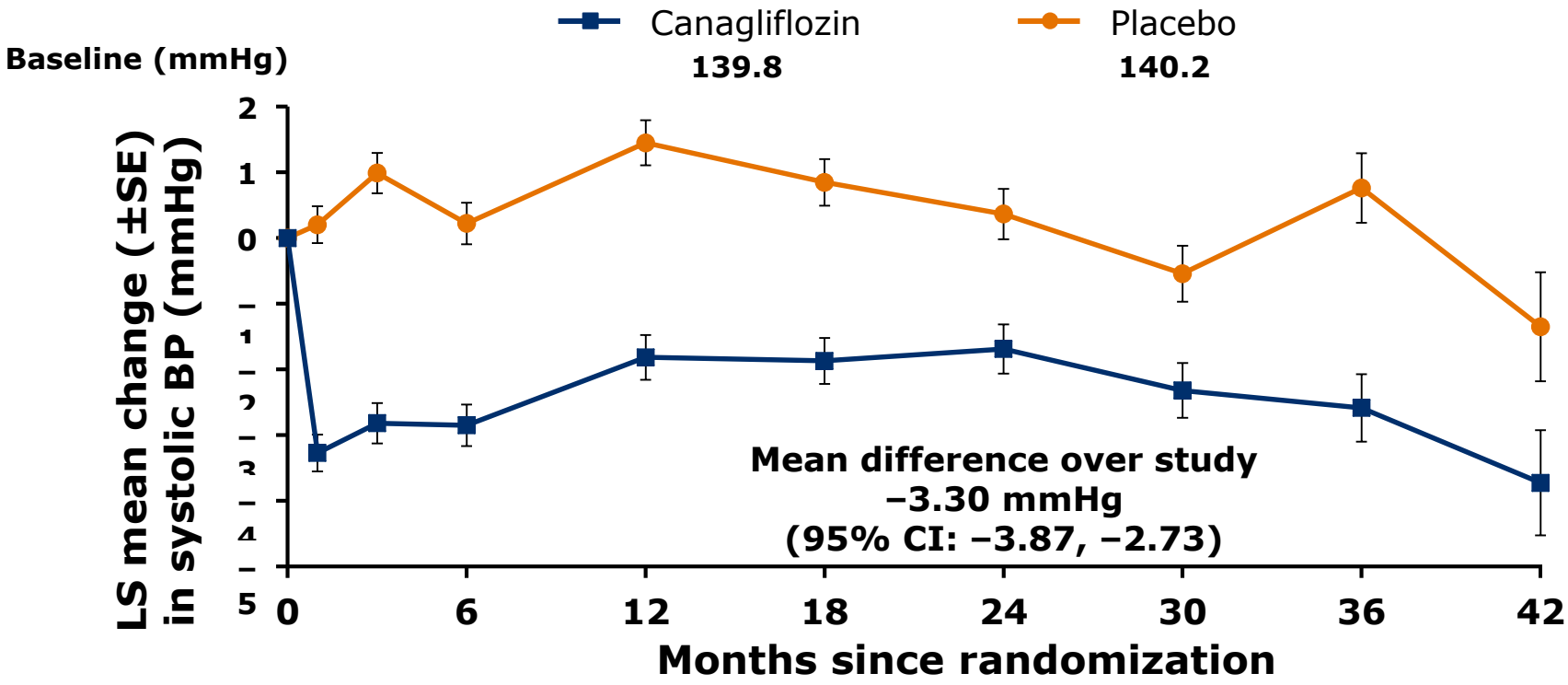


No. of participants

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

ITT analysis

Effects on Systolic BP

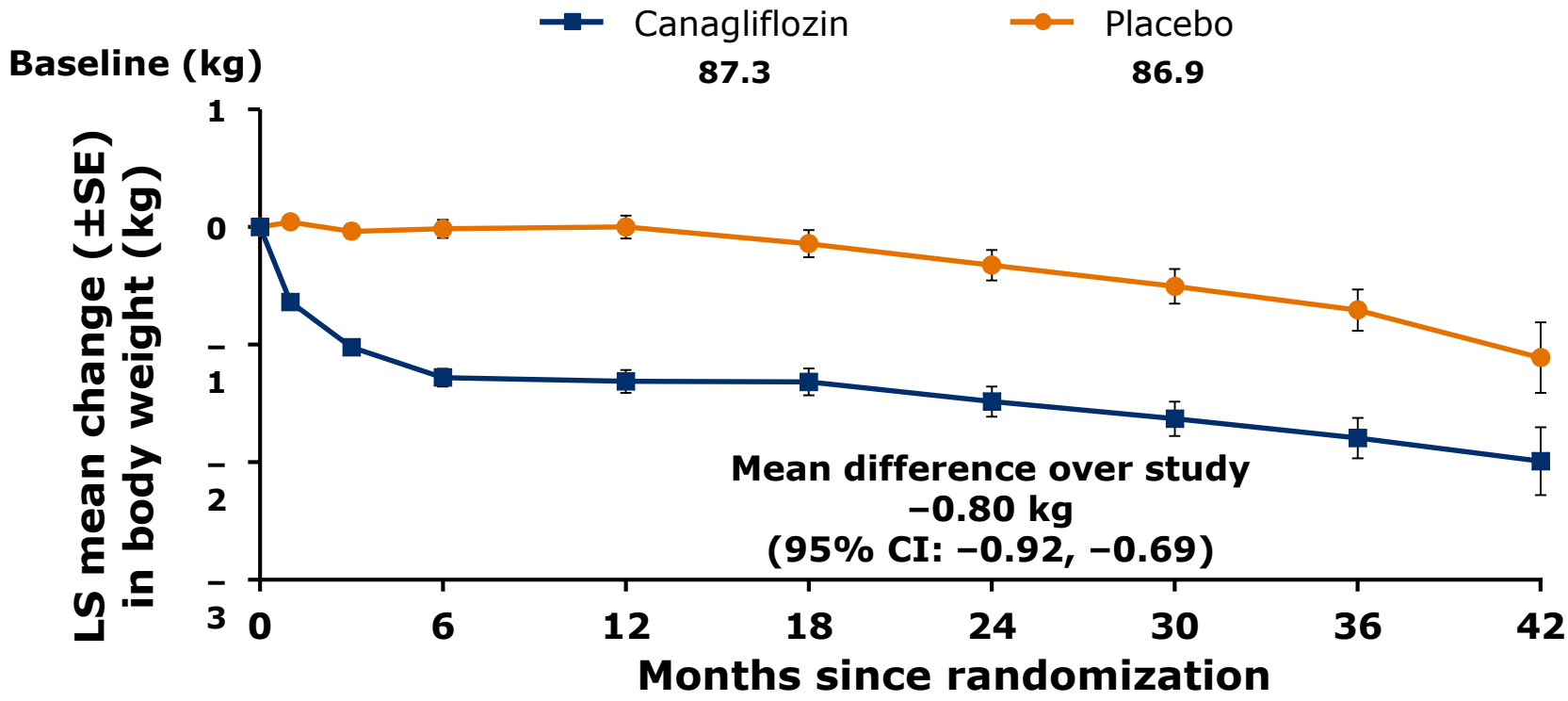


No. of participants

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

Summary

- Na restriction, diet, smoking cessation, BP control, glycemic control, statins and RAAS inhibition are the current standards of care in DKD.
- SGLT-2 inhibitor protects the kidney in DKD.
- The effects on glycemic control, systolic BP, and body weight are relatively small. Thus, the benefit of SGLT-2 inhibition appears to be independent of diabetes and BP.

ADA has revised its guidelines

- 11.3 For patients with type 2 diabetes and diabetic kidney disease, consider use of an SGLT2 inhibitor in patients with an eGFR $\geq$ 30 mL/min/1.73m^2 and particularly in those with > 300 mg/g albuminuria to reduce risk of CKD progression, cardiovascular events, or both. *Grade of evidence: A*