The CANVAS Program (CANagliflozin cardioVascular Assessment Study)

CANVAS Program

The CANVAS Program

Introduction

David R. Matthews, FRCP, DPhil

CANVAS Program

Photography Prohibited

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- Slides will be available upon conclusion of this presentation at www.georgeinstitute.org

Support

- The CANVAS Program was supported by Janssen Research & Development, LLC

Presentation Outline

• Background	Greg Fulcher
• Design and Methods	Kenneth W. Mahaffey
• Effects on CV Outcomes	Bruce Neal
• Effects on Renal Outcomes	Dick de Zeeuw
• Effects on Safety Outcomes	Vlado Perkovic
• Implications for Clinical Practice	David R. Matthews
• Independent Commentary	Clifford J. Bailey

The CANVAS Program

Background

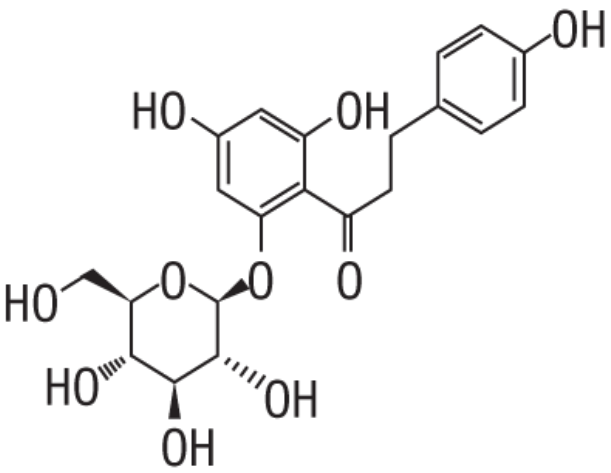
Greg Fulcher, MD

CANVAS Program

Presenter Disclosures: Greg Fulcher, MD

- Research support
  - Novo Nordisk
- Advisory boards
  - Janssen, Novo Nordisk, Boehringer Ingelheim, MSD
- Consultant
  - Janssen, Novo Nordisk, Boehringer Ingelheim, MSD

In 1835, French Chemists Isolated Phlorizin From the Bark of the Apple Tree

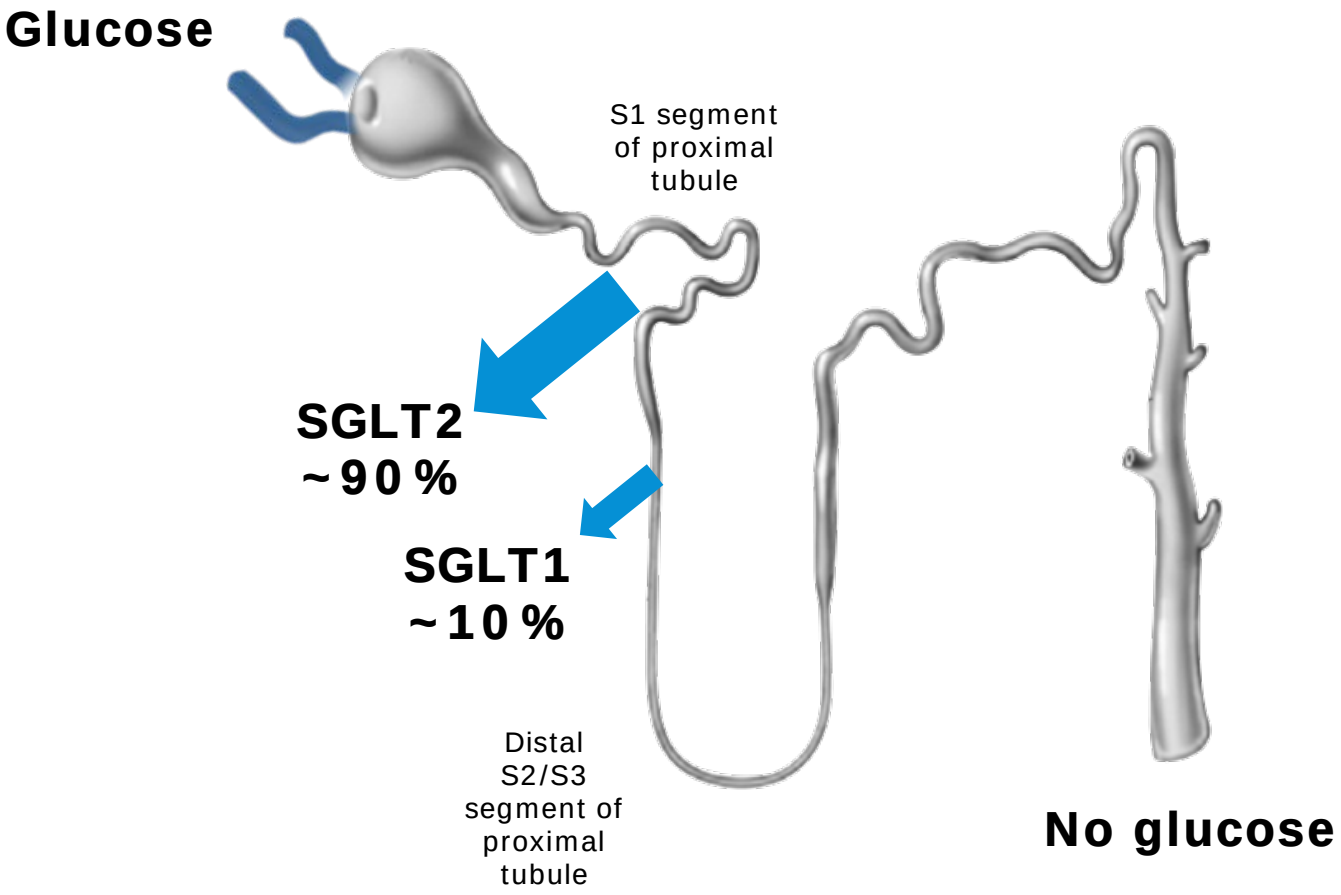


Phlorizin

"Few can foresee whither their road will lead them, till they come to its end" J.R.R. Tolkien

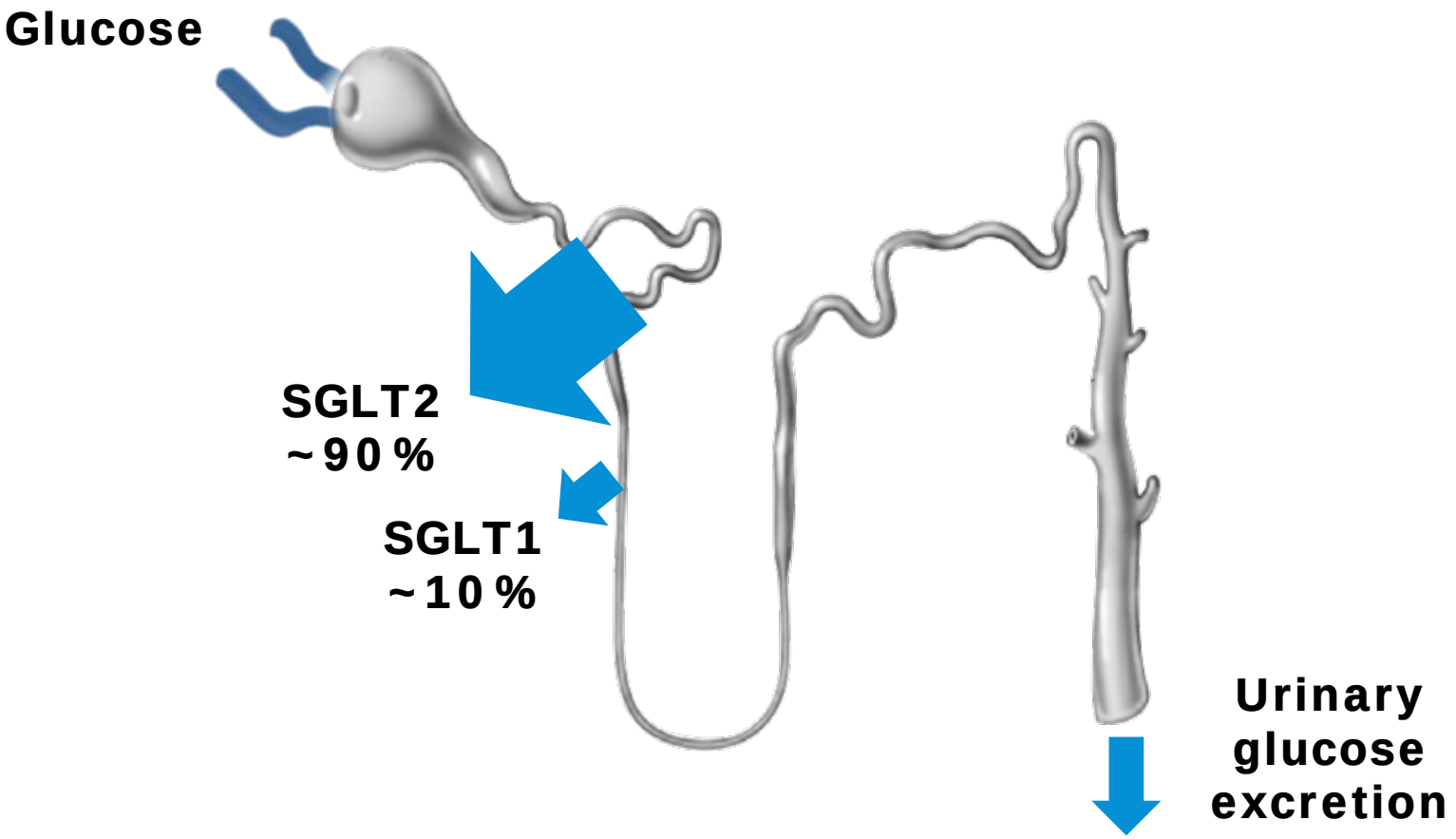
Petersen C. *Annales Academie Science Francaise.* 1835;15:178.

Normal Renal Glucose Metabolism



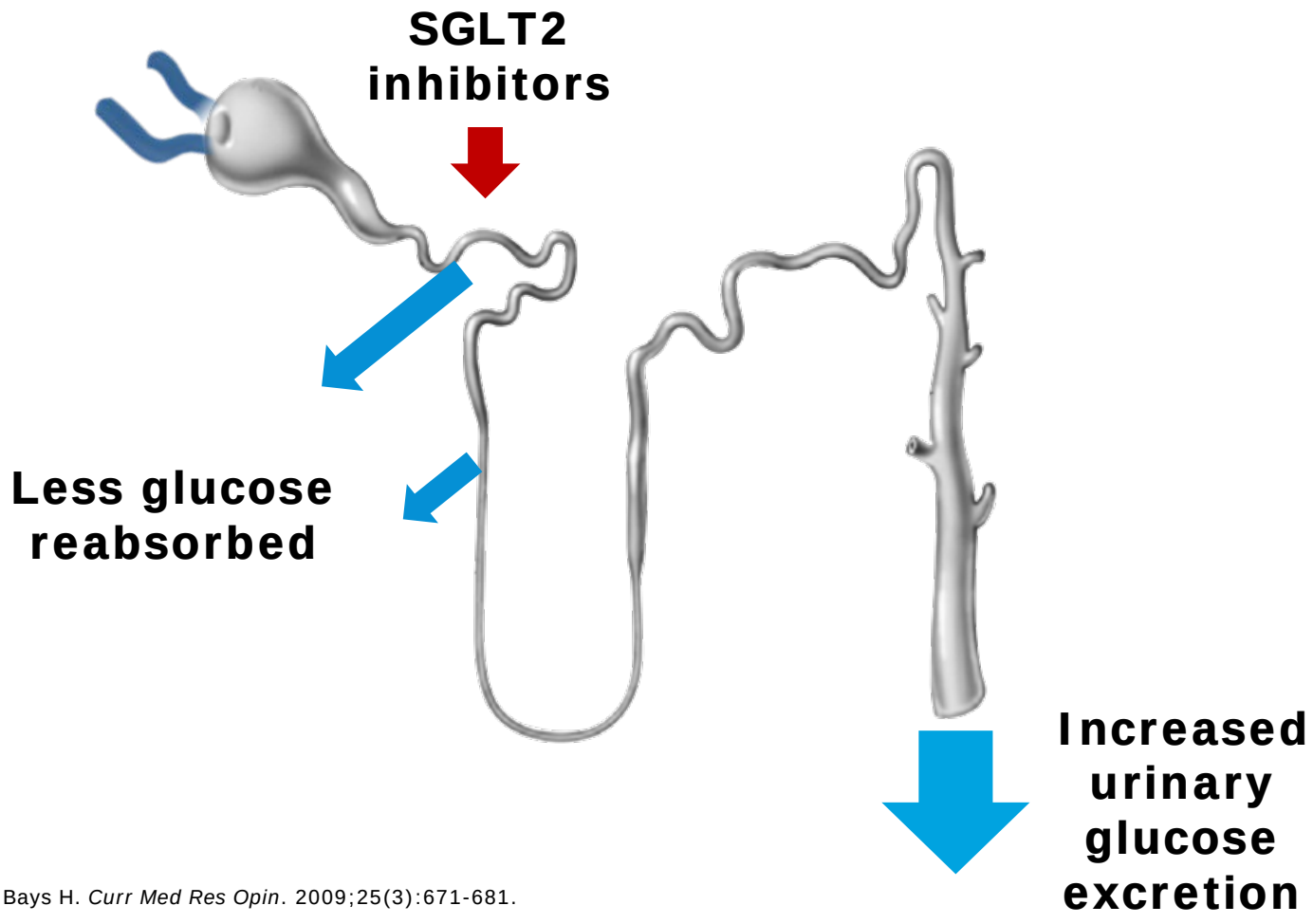
Adapted from Bays H. *Curr Med Res Opin*. 2009;25(3):671-681.

Glucose Metabolism in Diabetes



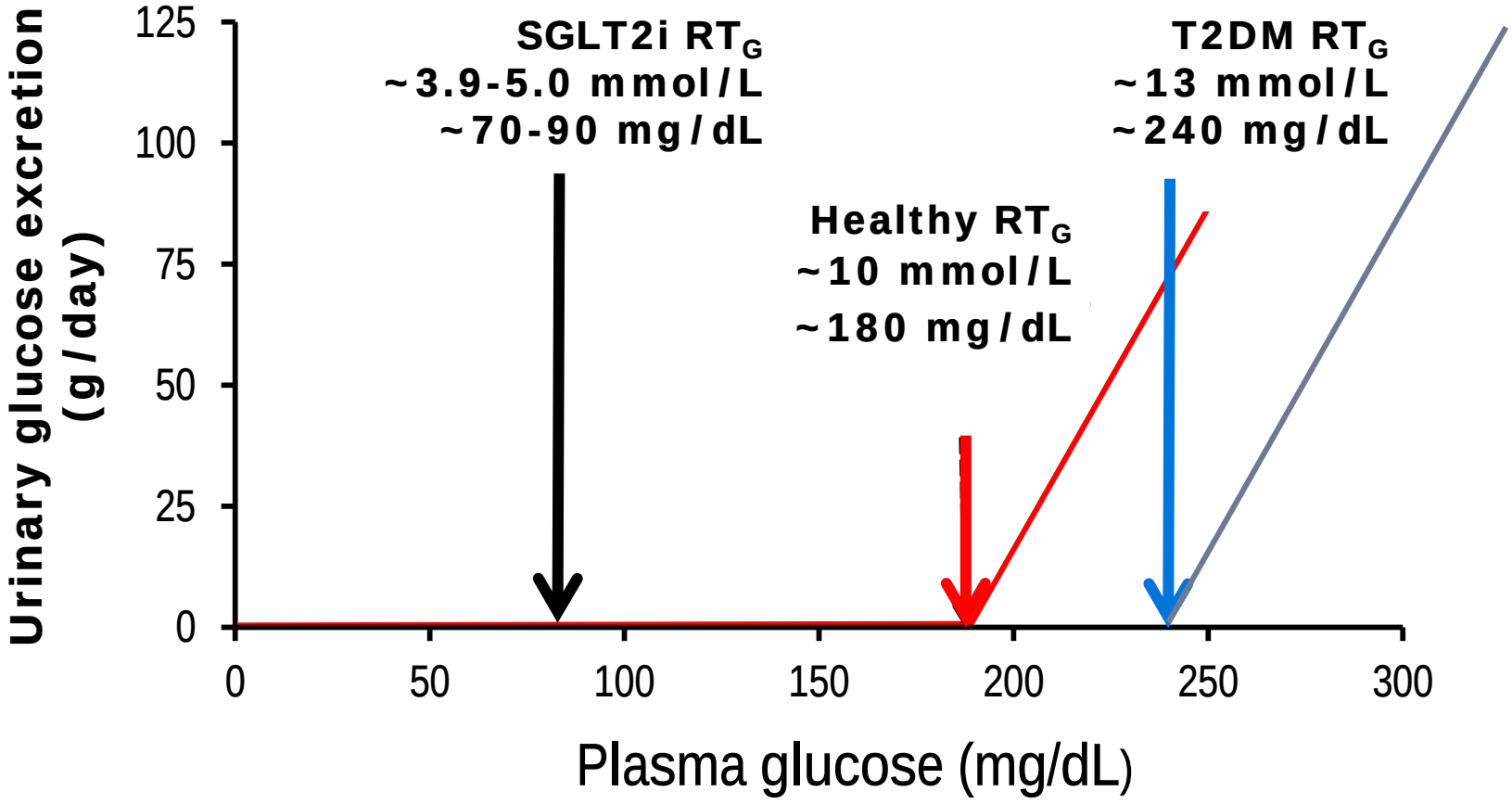
Adapted from Bays H. *Curr Med Res Opin*. 2009;25(3):671-681.

Inhibition of Renal Glucose Reabsorption

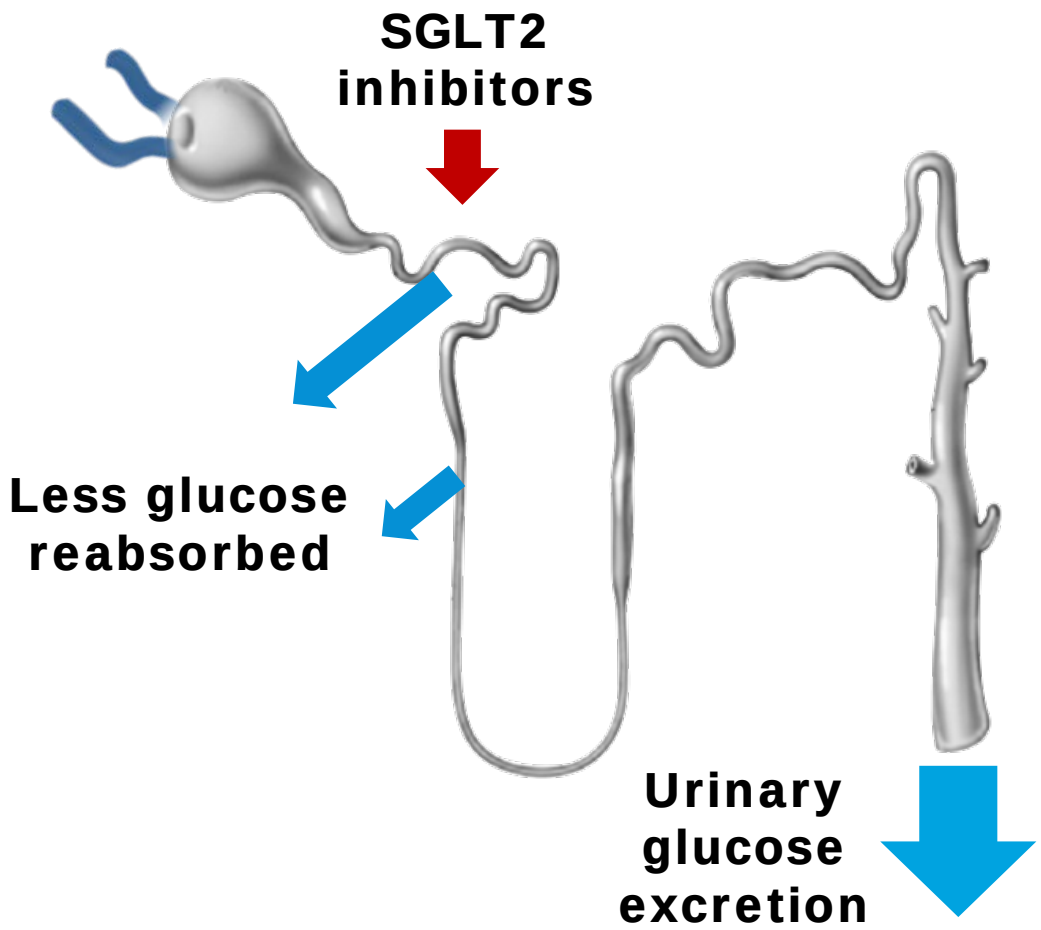


Adapted from Bays H. *Curr Med Res Opin*. 2009;25(3):671-681.

Renal Glucose Reabsorption



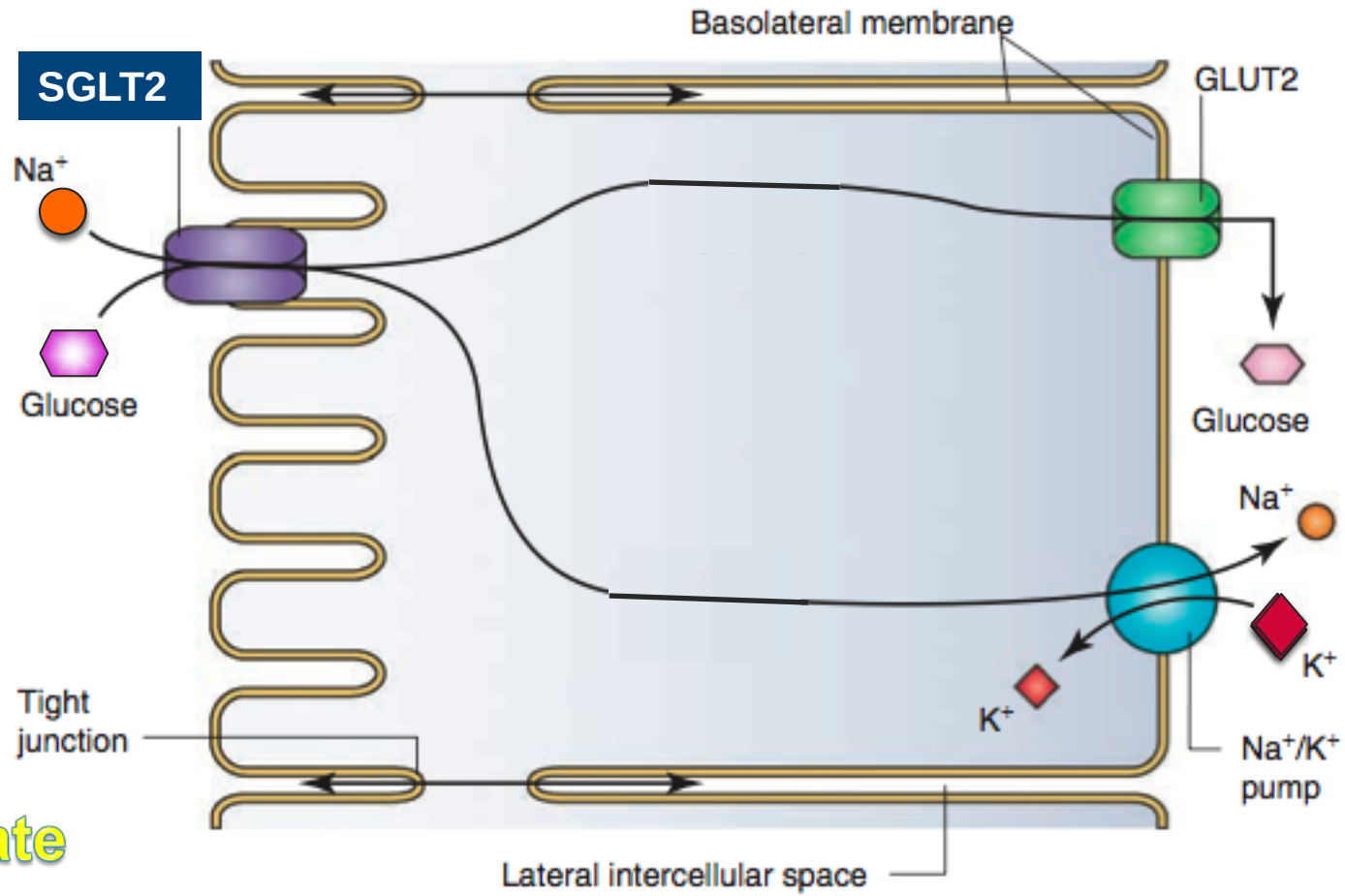
SGLT2 Inhibition



CV Risk Factor Reduction

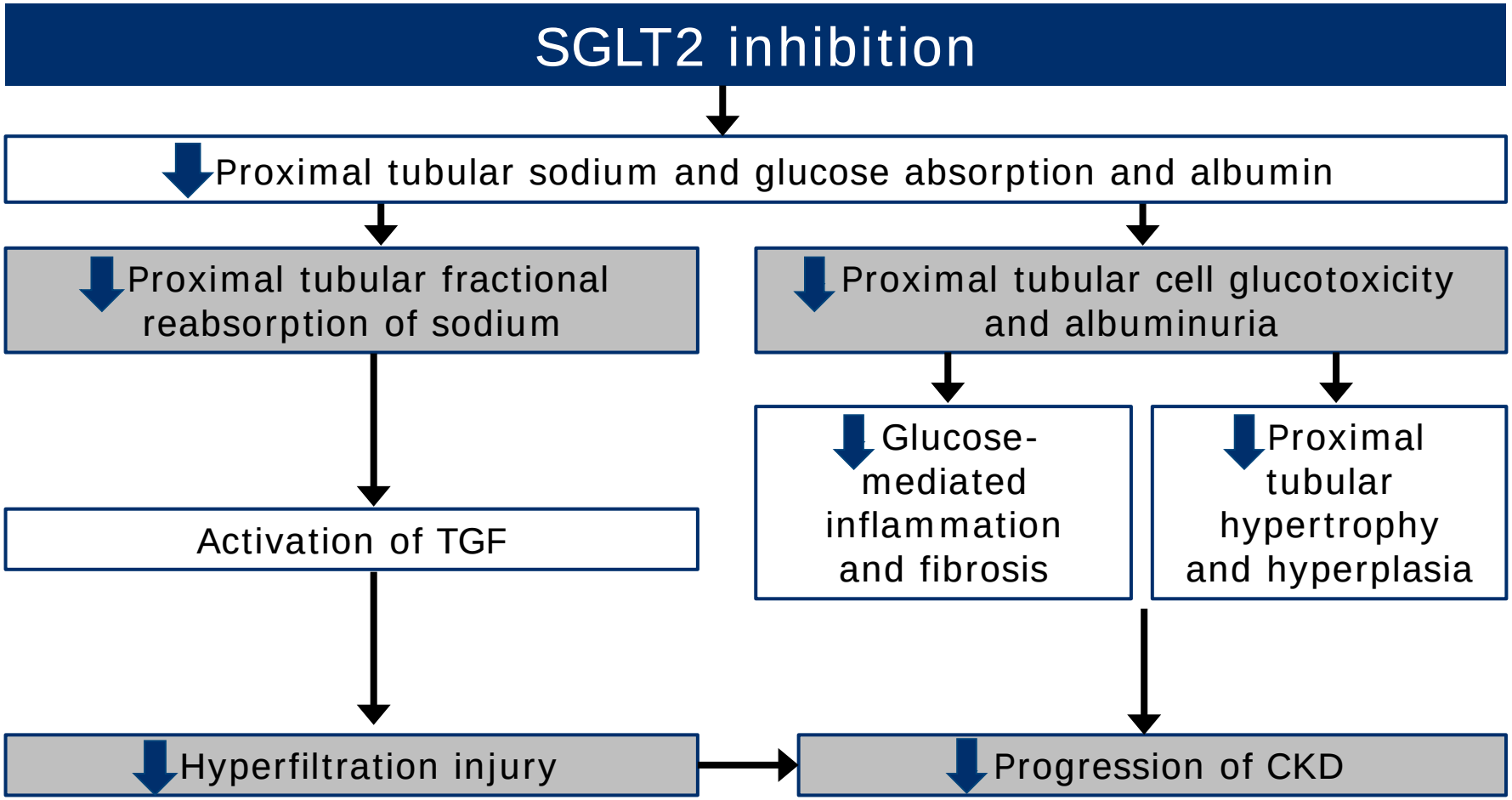
- Lowers blood glucose levels
- Lowers BP via osmotic diuresis
- Increases urinary caloric loss with reductions in body weight
- Reduces albuminuria possibly due to alterations in tubuloglomerular feedback

Glucose Reabsorption From the Glomerular Filtrate Through a Proximal Tubule Epithelial Cell Into the Blood



Bakris GI, et al. *Kidney Int*. 2009;75(12):1272-1277.

Potential Role of SGLT2 Inhibition in Renoprotection

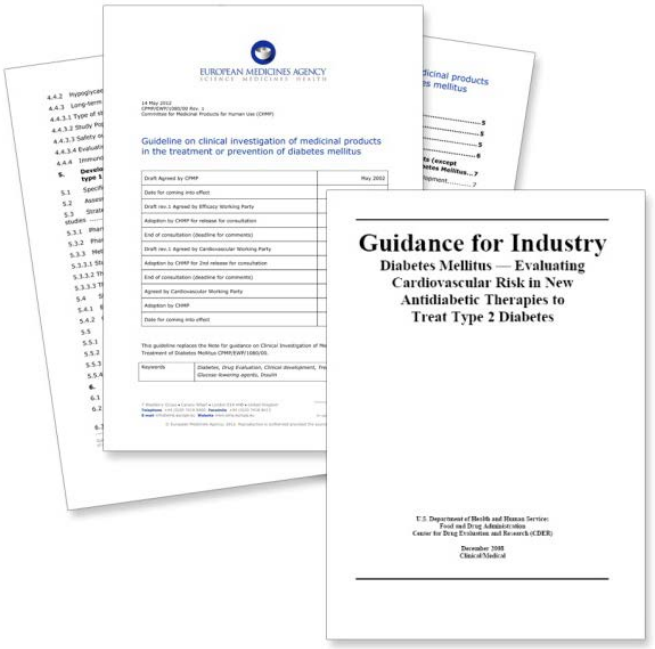


Adapted from Komala MG, et al. *Curr Opin Nephrol Hypertens* 2013;22:113–119.

Regulatory Requirements

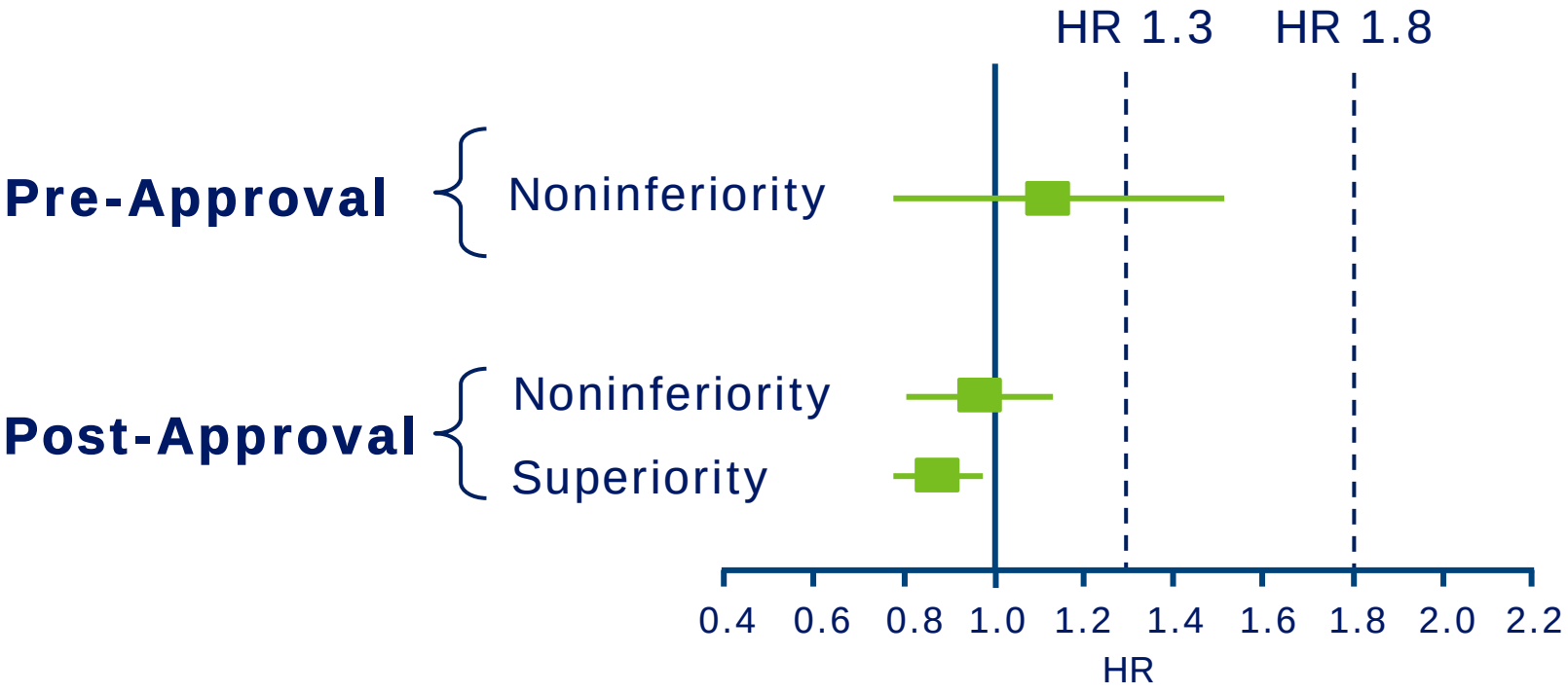
European Medicines Agency (EMA) and US Food and Drug Administration (FDA): Need for CV Outcomes Studies

- 'Demonstrate that a new anti-diabetic therapy is not associated with **unacceptable increase** in cardiovascular risk'



EMA. 2012. http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500129256&mid=WC0b01ac058009a3dc.
FDA. 2008. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf

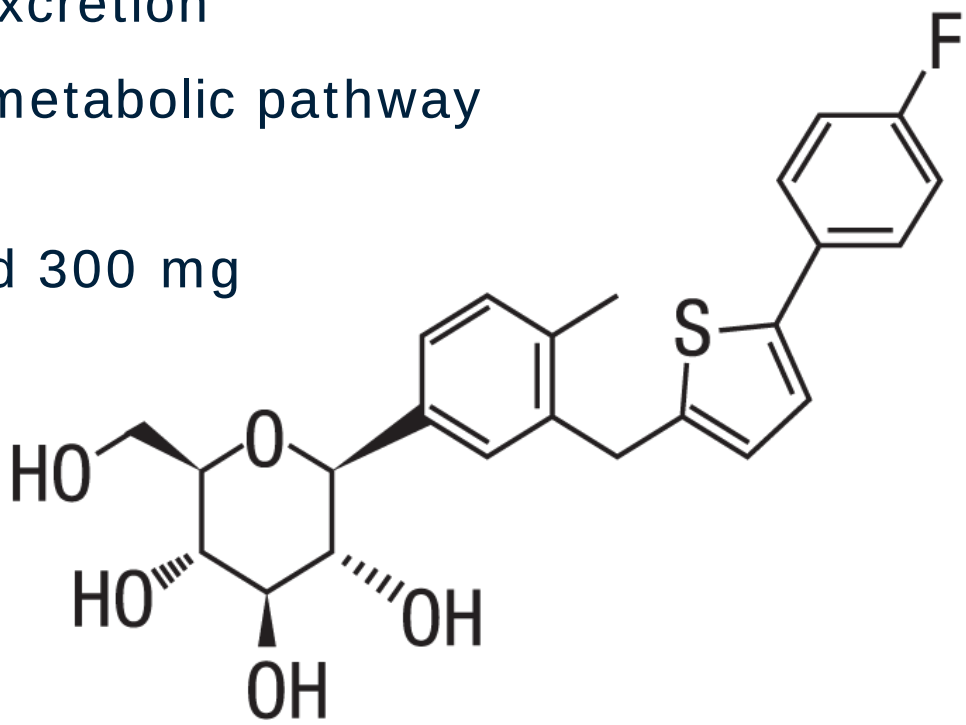
FDA Criteria for Assessing CV Risk



Adequately powered for noninferiority

Canagliflozin

- Orally-active, selective SGLT2 inhibitor
- Half-life of 11 to 13 hours (once-daily dosing)
- Balanced renal and biliary excretion
- Glucuronidation is a major metabolic pathway
  - No active metabolites
- Approved doses 100 mg and 300 mg



The CANVAS Program

Design and Methods

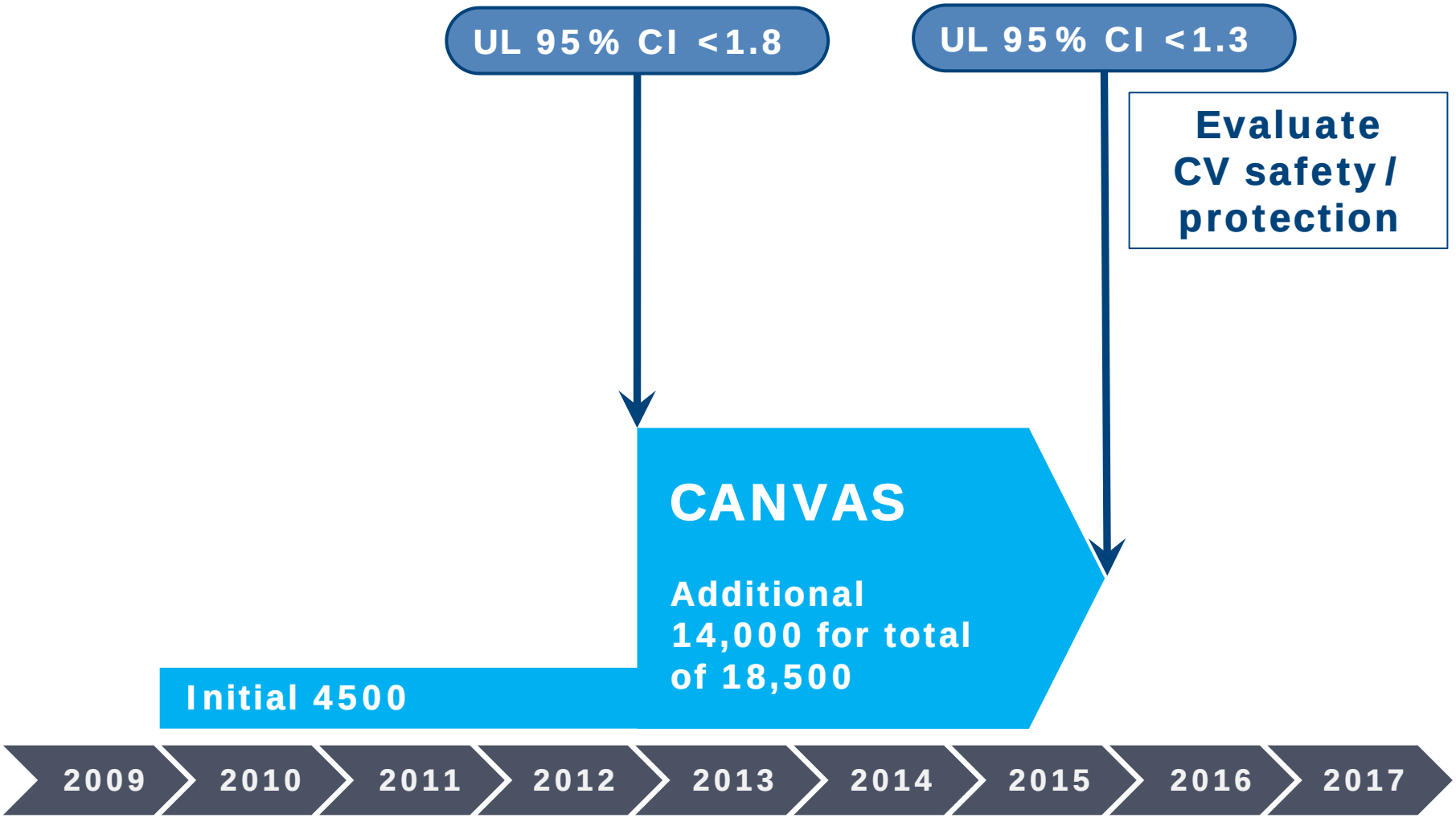
Kenneth W. Mahaffey, MD

CANVAS Program

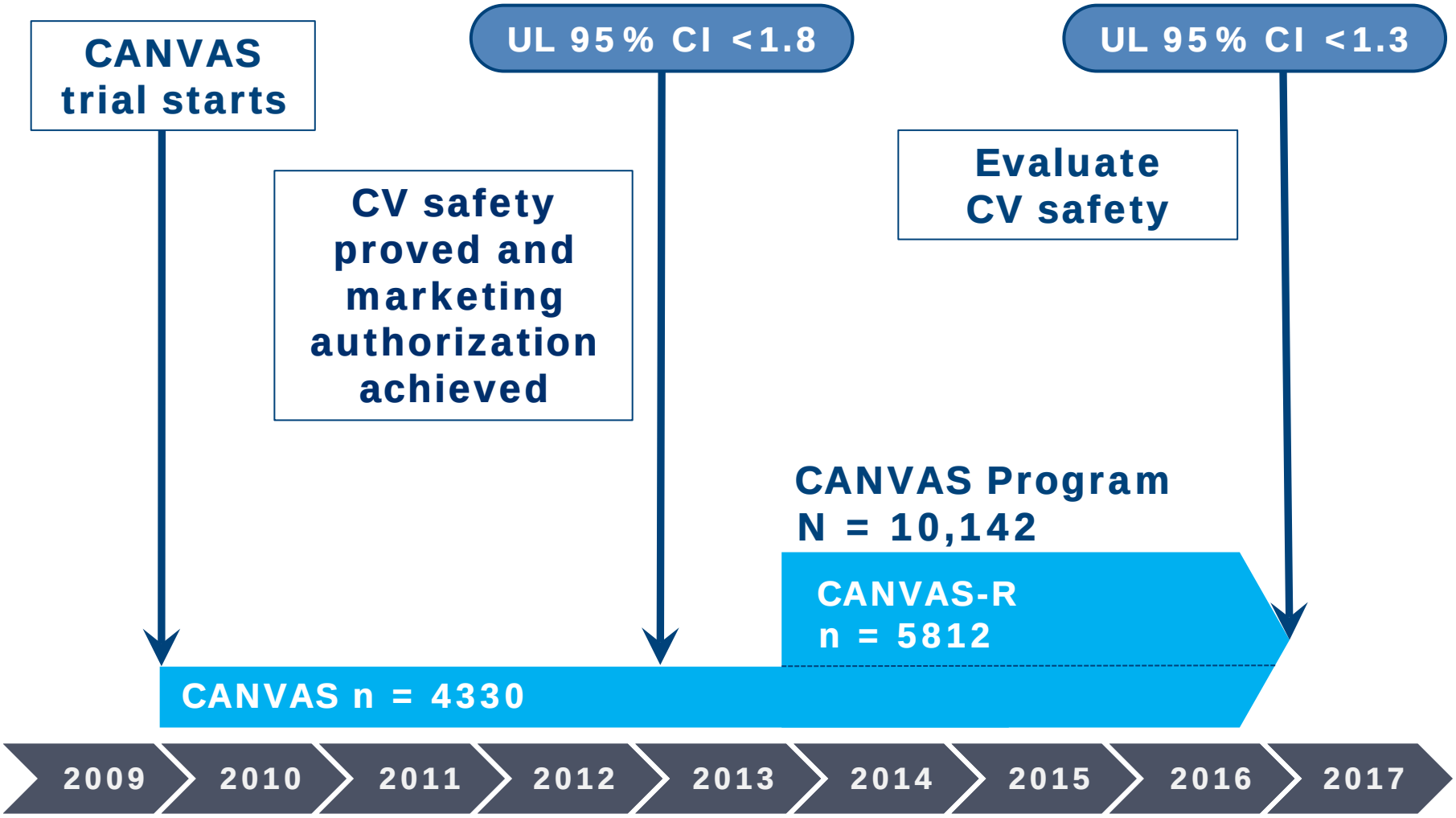
Presenter Disclosures: Kenneth W. Mahaffey, MD

- Research support
  - Afferent, Amgen, AstraZeneca, Daiichi, Ferring, Google (Verily), Janssen, Medtronic, Merck, Novartis, Sanofi, St. Jude
- Consultant (including CME)
  - Ablynx, AstraZeneca, BAROnova, Bio2 Medical, Boehringer Ingelheim, Bristol Myers Squibb, Cardiometabolic Health Congress, Cubist, Eli Lilly, Elsevier, Epson, GlaxoSmithKline, Janssen, Merck, Mt. Sinai, Myokardia, Novartis, Oculeve, Portola, Radiometer, Springer Publishing, The Medicines Company, Theravance, Vindico, WebMD
- Equity
  - BioPrint Fitness

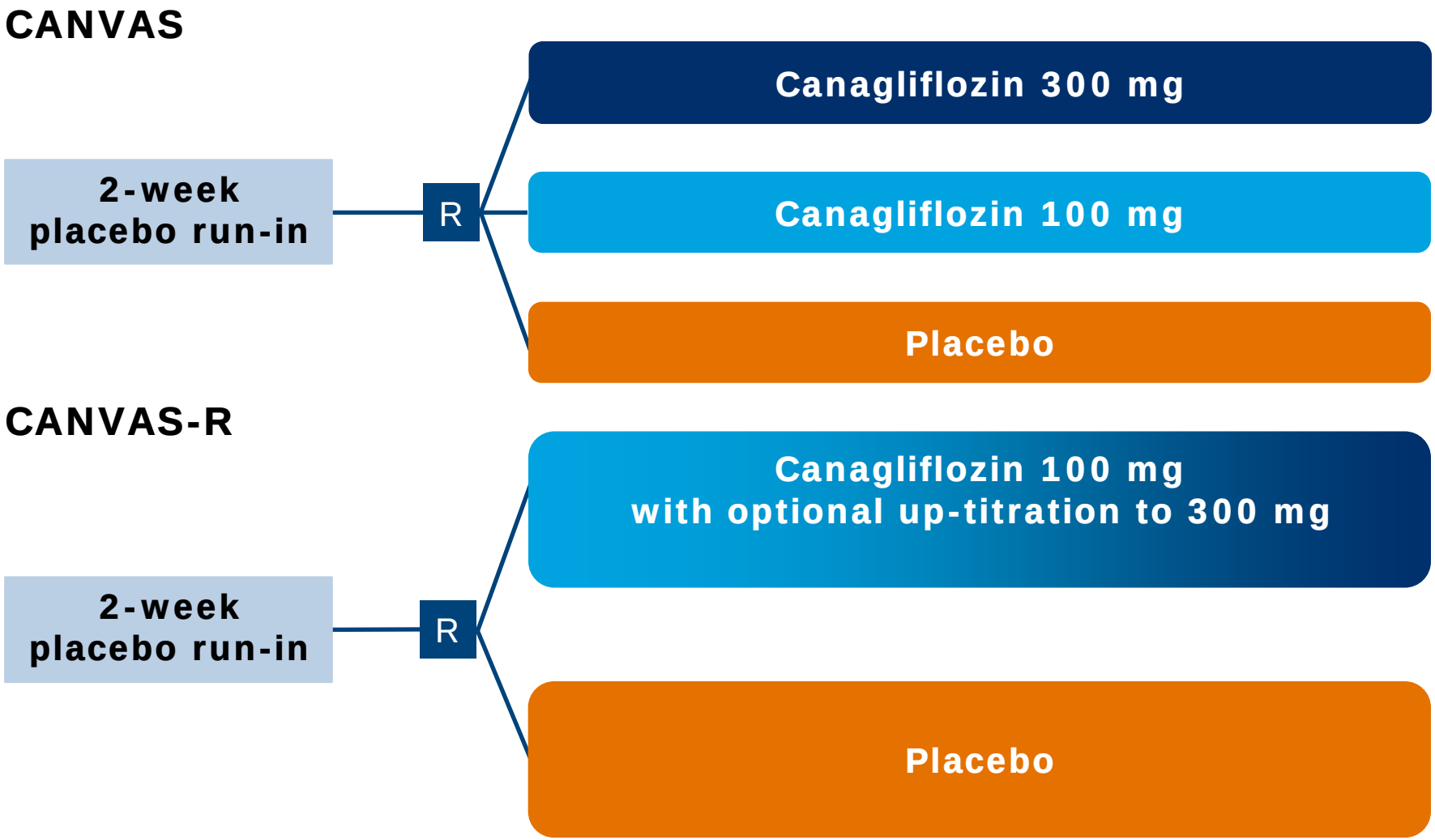
Initial Design



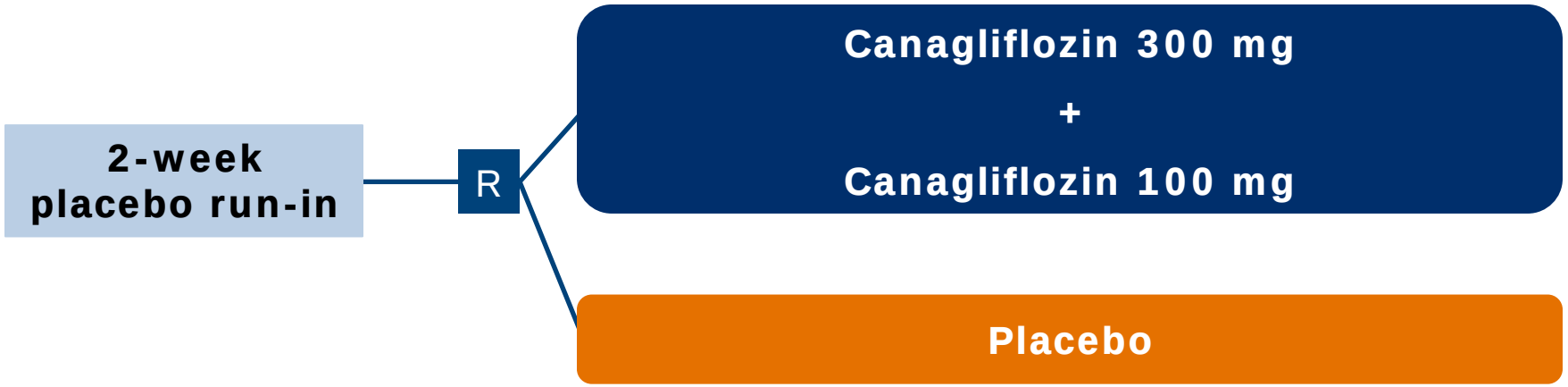
Final Design



Randomization



Analytic Approach



Organizational Structure

Steering Committee

D. Matthews (Co-chair), B. Neal (Co-chair), G. Fulcher, K. Mahaffey, V. Perkovic, M. Desai (Sponsor), D. de Zeeuw

Independent Data Monitoring Committee

P. Home (Chair), J. Anderson, I. Campbell, J. Lachin (withdrew in September 2015), D. Scharfstein, S. Solomon, R. Uzzo

Cardiovascular Adjudication Committee

G. Fulcher (Chair), J. Amerena, C. Chow, G. Figtree, J. French, G. Hillis, M. Hlatky, B. Jenkins, N. Leeper, R. Lindley, B. McGrath, A. Street, J. Watson

Renal Adjudication Committee

G. Fulcher (Chair), S. Shahinfar, T. Chang, A. Sinha, P. August

Safety Adjudication Committees

Fracture Adjudication: Bioclinica
Diabetic Ketoacidosis Adjudication: Baim Institute for Clinical Research
Pancreatitis Adjudication: A. Cheifetz (Chair), S. Sheth, J. Feuerstein

Data Management

Similar electronic case report forms and same endpoint definitions

Participant Inclusion Criteria

Patients with type 2 diabetes

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

  OR

  Age ≥50 years with ≥2 CV risk factors*

*Diabetes duration ≥10 years, SBP >140 mmHg on ≥1 medication, current smoker, micro- or macroalbuminuria, or HDL cholesterol <1 mmol/L.

Statistical Methods - Efficacy

- Integrated data set and intent-to-treat (ITT) principle
- Primary endpoint analysis based on Cox regression model with stratification by trial and CV disease history
- Pooled data from canagliflozin doses compared with placebo
- CV event (90% power) and time (>78 weeks) driven study
- Homogeneity of treatment effects across the two trials was evaluated
- Sequential testing prespecified

Objectives

PRIMARY

CV death, nonfatal MI, or nonfatal stroke

SECONDARY

All-cause mortality

CV death

EXPLORATORY

Nonfatal MI

Nonfatal stroke

Hospitalization for HF

Hospitalization for HF or CV death

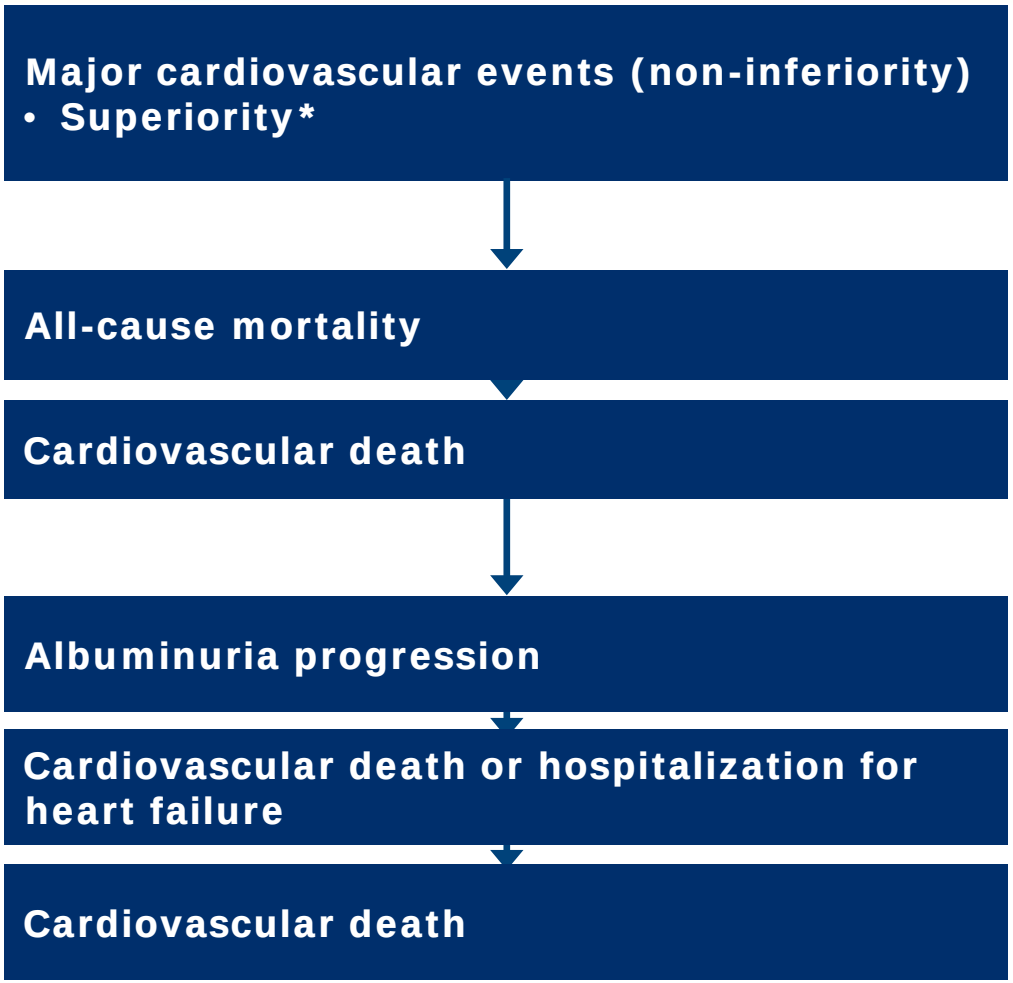
Total hospitalizations

Albuminuria progression

Albuminuria regression

Renal composite: 40% reduction in eGFR, end-stage renal disease, or renal death

Hypothesis Testing Plan



CANVAS Program

(CANVAS and CANVAS-R)

CANVAS-R alone

*Superiority testing was included in the Statistical Analysis Plan.

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The CANVAS Program

Effects on Cardiovascular Outcomes

Bruce Neal, MB, ChB, PhD

CANVAS Program

Presenter Disclosures: Bruce Neal, MB ChB, PhD

- Research support
  - Australian National Health and Medical Research Council Principal Research Fellowship
  - Janssen, Roche, Servier, Merck Schering Plough
- Advisory boards and/or continuing medical education
  - Abbott, Janssen, Novartis, Pfizer, Roche, Servier
  - Consultancy, honoraria, or travel support paid to his institution

Global Participation

North America
- Canada
- USA

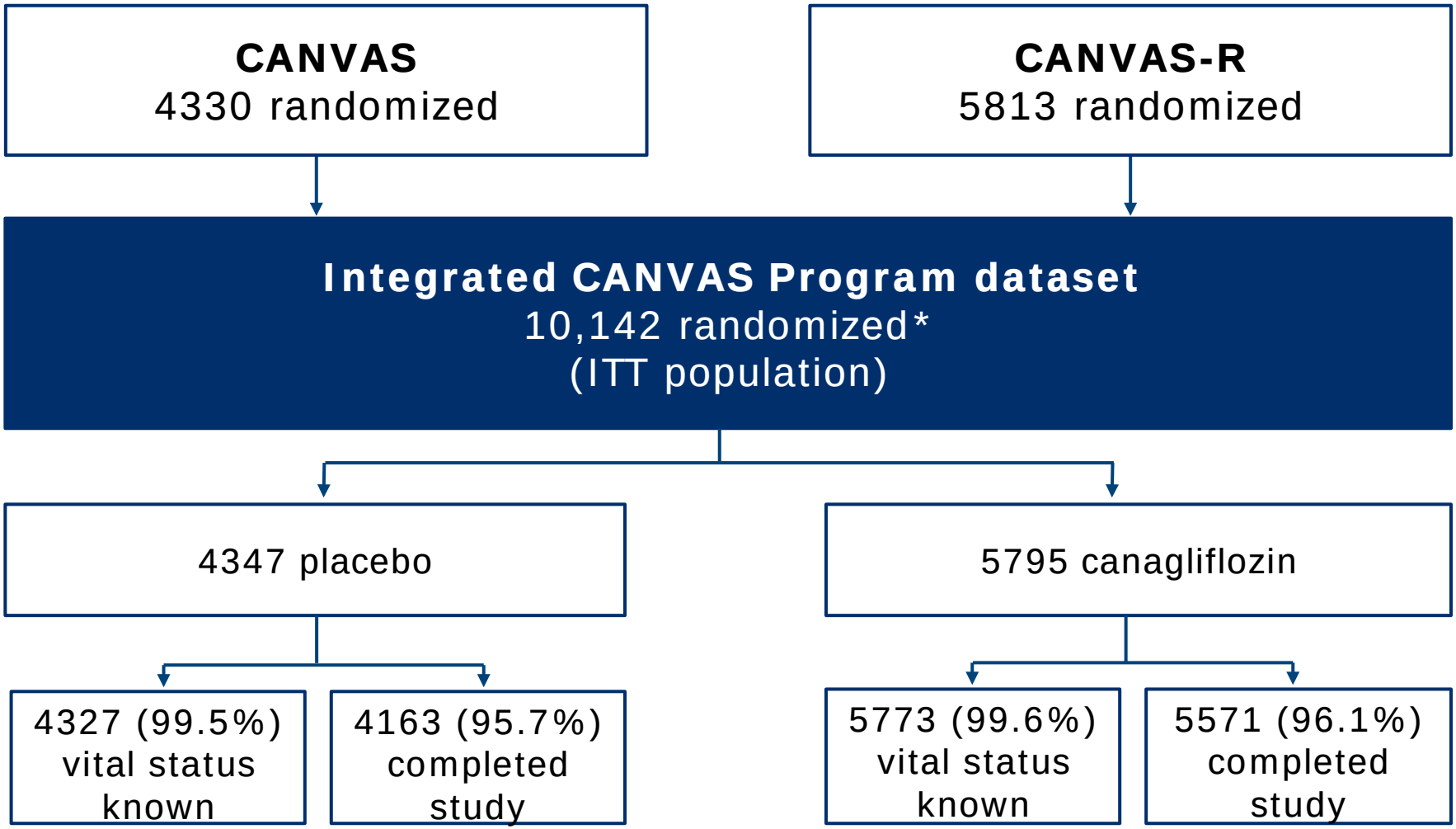
Europe
- Belgium
- Czech Republic
- Estonia
- France
- Germany
- Great Britain
- Hungary
- Israel
- Italy
- Luxembourg
- Netherlands
- Spain
- Sweden
- Norway
- Poland
- Russia
- Ukraine

30 Countries
667 sites

Latin America
- Argentina
- Brazil
- Colombia
- Mexico

Asia Pacific
- Australia
- China
- India
- Korea
- Malaysia
- New Zealand
- Taiwan

Enrollment and Follow-up



*One participant was randomized at 2 different sites and only the first randomization is included in the ITT analysis set.

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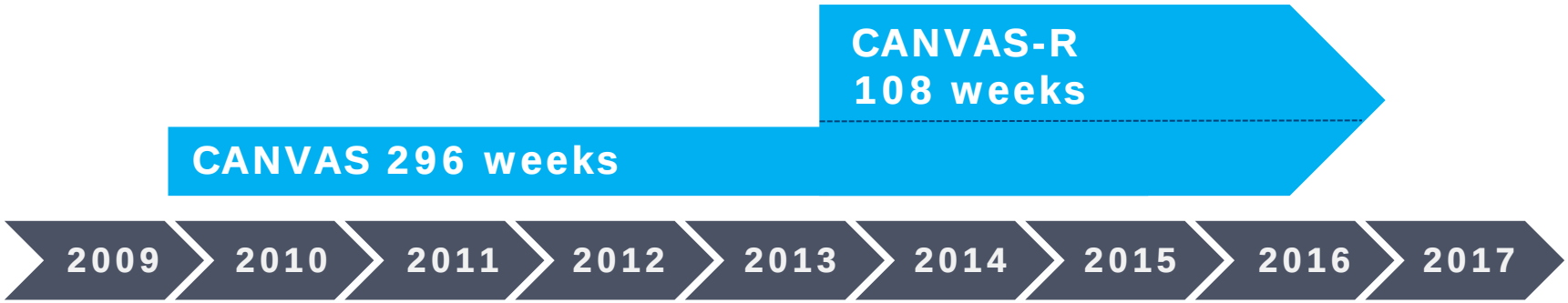
Follow-up



CANVAS Program mean follow-up 188 weeks

Patients remaining on randomized treatment:

- Canagliflozin 71%
- Placebo 70%

Demographics and Disease History

	Canagliflozin (n = 5795)	Placebo (n = 4347)
Mean age, y	63	63
Female, %	35	37
Mean duration of diabetes, y	14	14
Hypertension, %	90	91
Heart failure (NYHA I-III), %	14	15
Cardiovascular disease, %	65	67

Demographics (cont)

	Canagliflozin (n = 5795)	Placebo (n = 4347)
	%	%
Race		
White	78	79
Asian	13	12
Black or African American	3	4
Other	6	6
Geographic region		
North America	25	23
Central/South America	9	11
Europe	35	36
Rest of world	31	30

Baseline Therapies

	Canagliflozin (n = 5795)	Placebo (n = 4347)
	%	%
Antihyperglycemic agents		
Metformin	77	78
Insulin	50	51
Sulfonylurea	44	42
DPP-4 inhibitor	12	13
GLP-1 receptor agonist	4	4
Cardioprotective agents		
RAAS inhibitor	80	80
Statin	75	75
Antithrombotic	73	74
Beta blocker	52	55
Diuretic	44	45

Baseline Risk Factors

	Canagliflozin (n = 5795)	Placebo (n = 4347)
HbA1c, %	8.2	8.2
Body mass index, kg/m^2	31.9	32.0
Systolic BP, mmHg	136	137
Diastolic BP, mmHg	78	78
Total cholesterol, mmol/L	4.4	4.4
HDL-C, mmol/L	1.2	1.2
LDL-C, mmol/L	2.3	2.3
Triglycerides, mmol/L	2.0	2.0

Results

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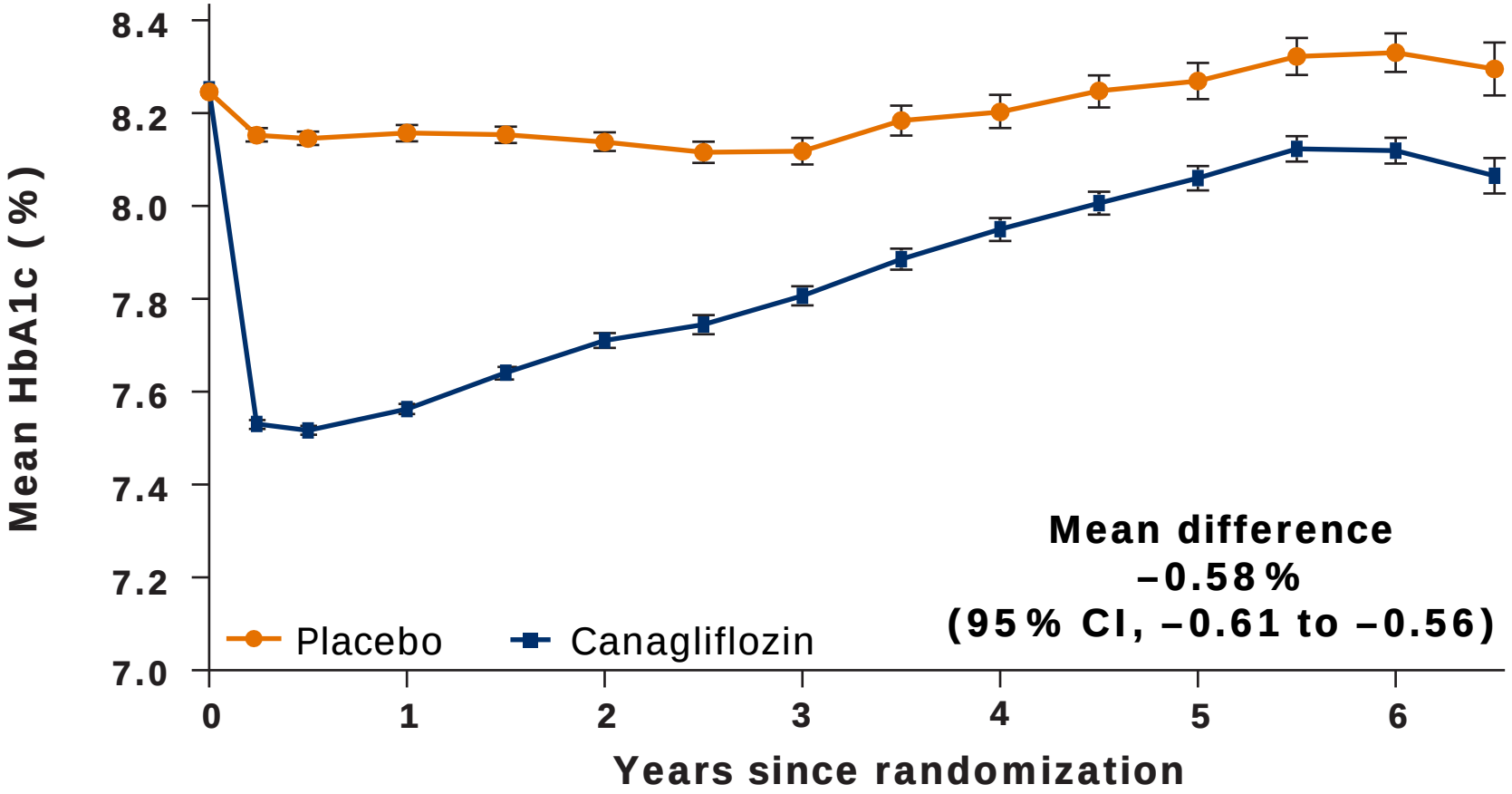
Effects on HbA1c

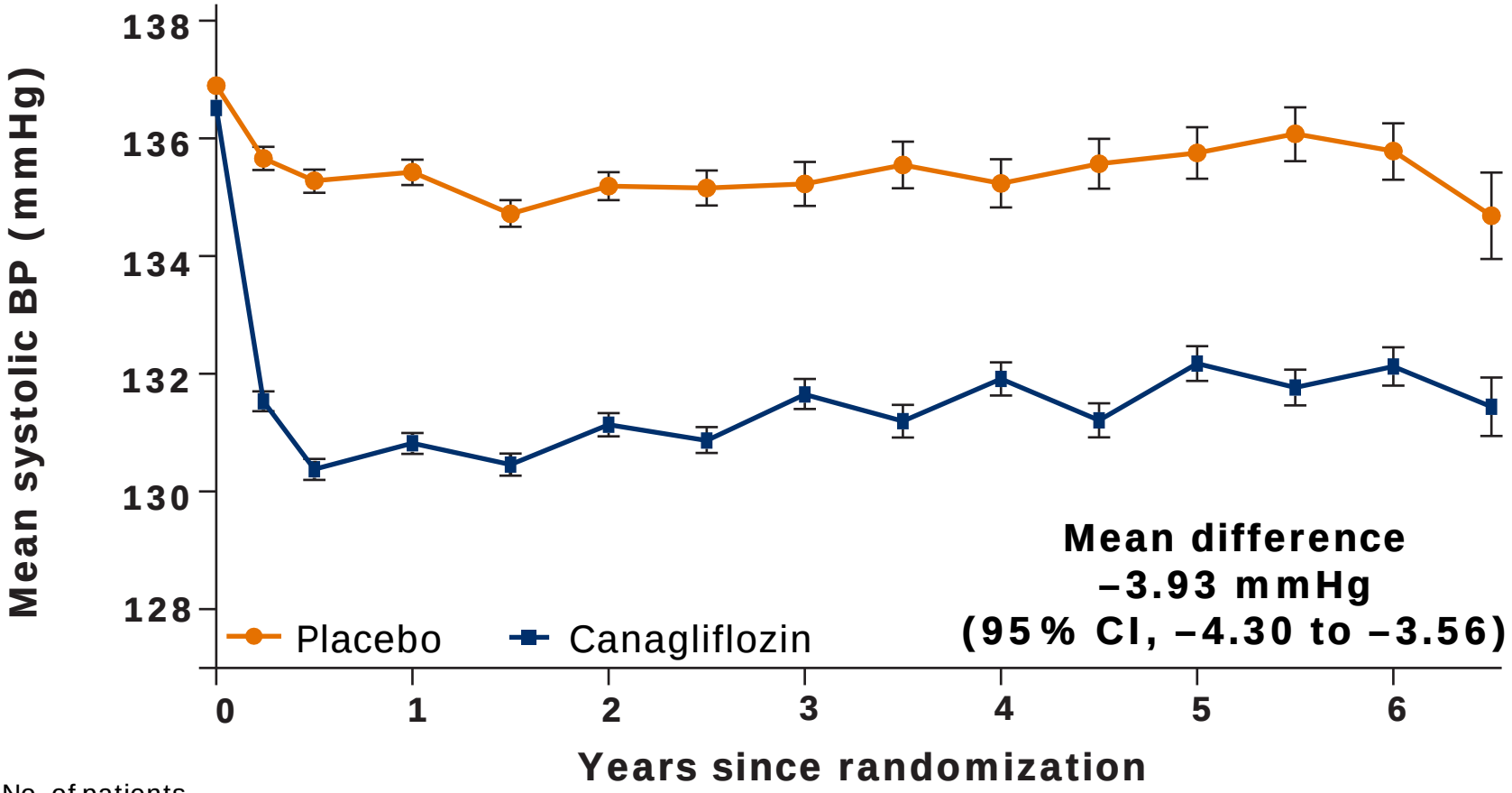


No. of patients

Placebo	4231	3854	2891	1014	899	805	695
Canagliflozin	5644	5211	4228	2206	2042	1889	1661

Mixed model for repeated measures (MMRM) analysis

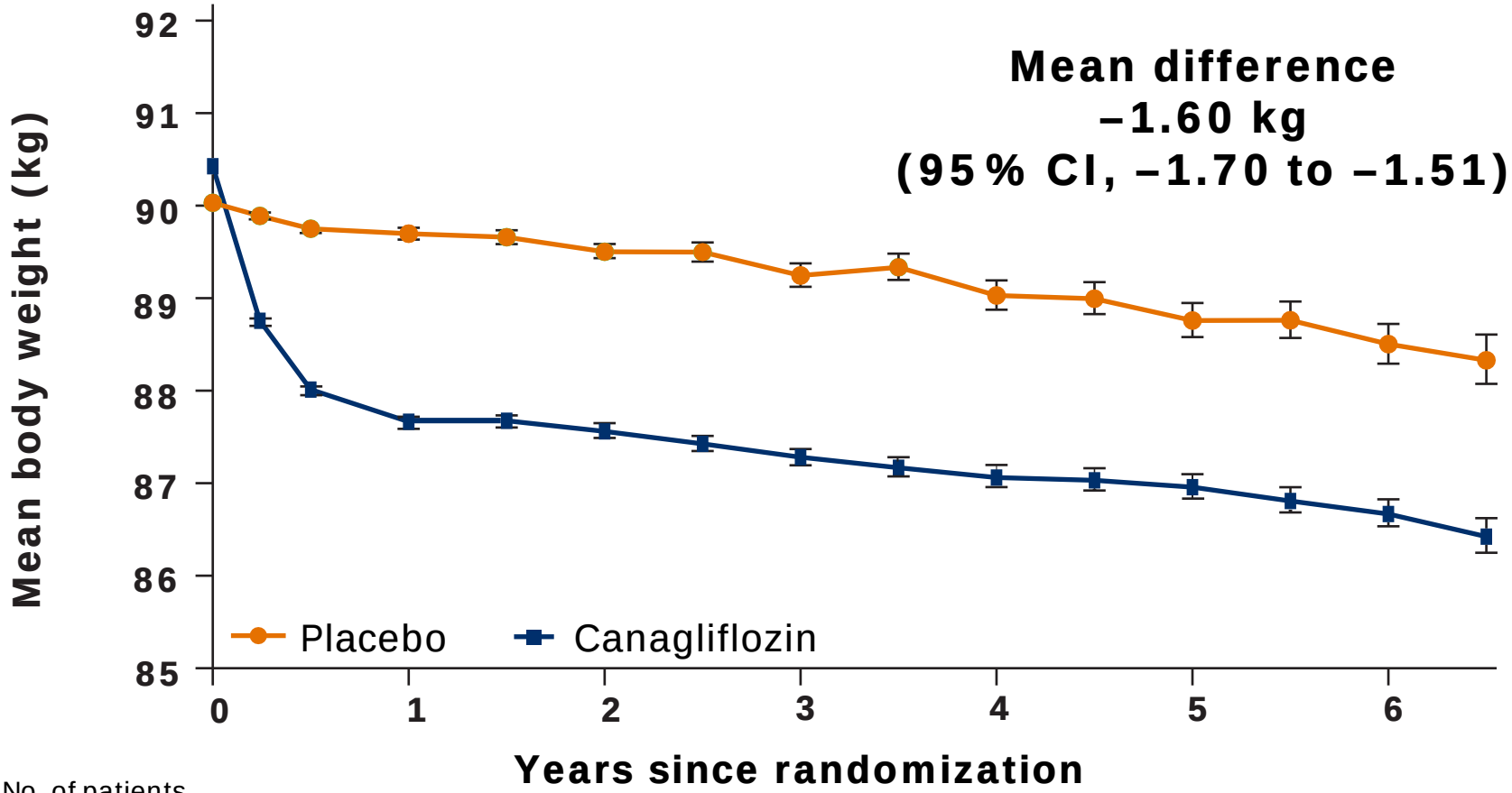
Effects on Systolic BP



No. of patients							
Placebo	4247	3945	2979	1038	922	828	713
Canagliflozin	5652	5293	4338	2255	2092	1936	1675

Mixed model for repeated measures (MMRM) analysis

Effects on Body Weight



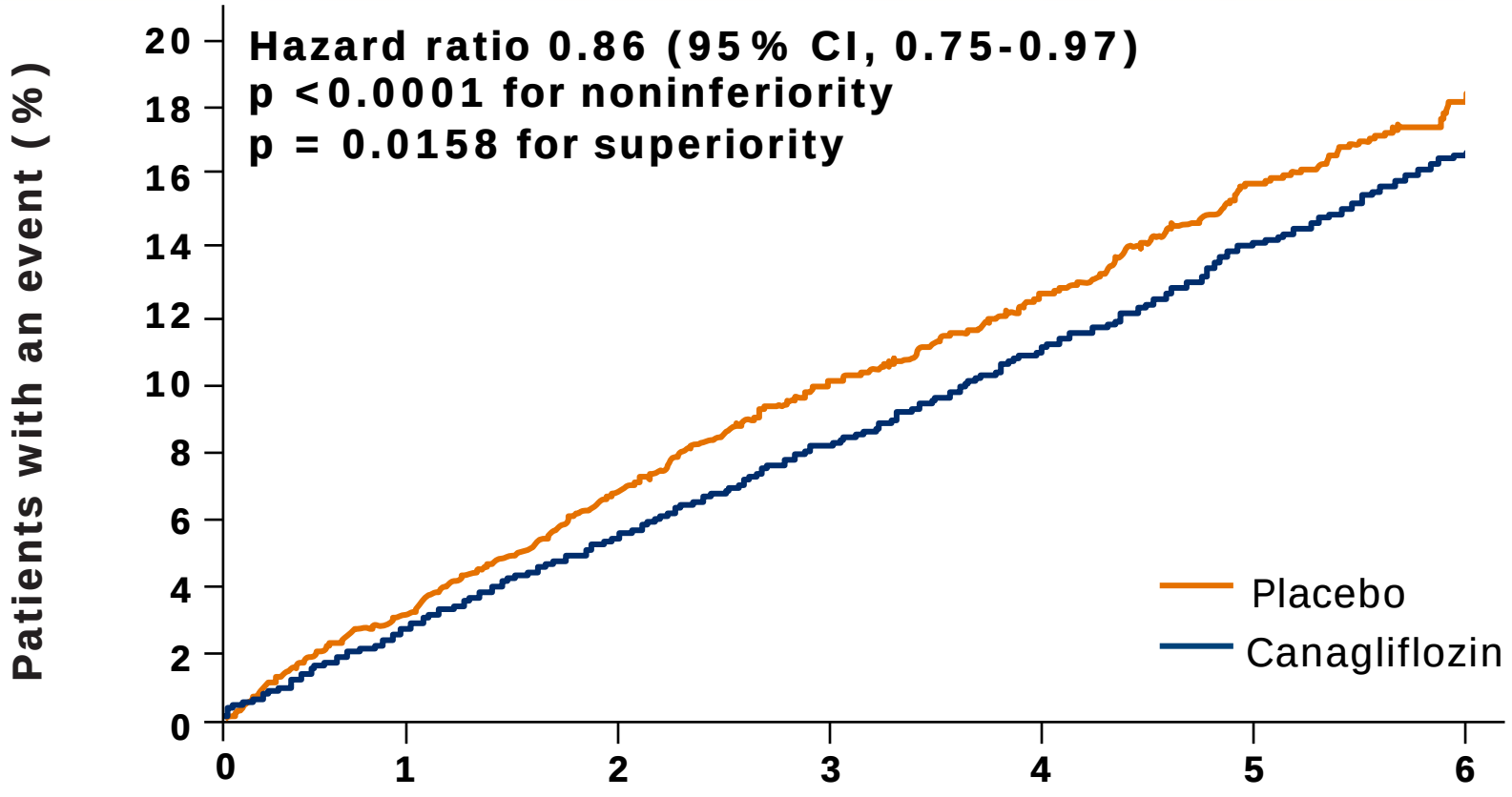
No. of patients

Placebo	4245	3931	2977	1036	920	826	714
Canagliflozin	5651	5277	4331	2247	2086	1928	1669

Mixed model for repeated measures (MMRM) analysis

Primary MACE Outcome

CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke

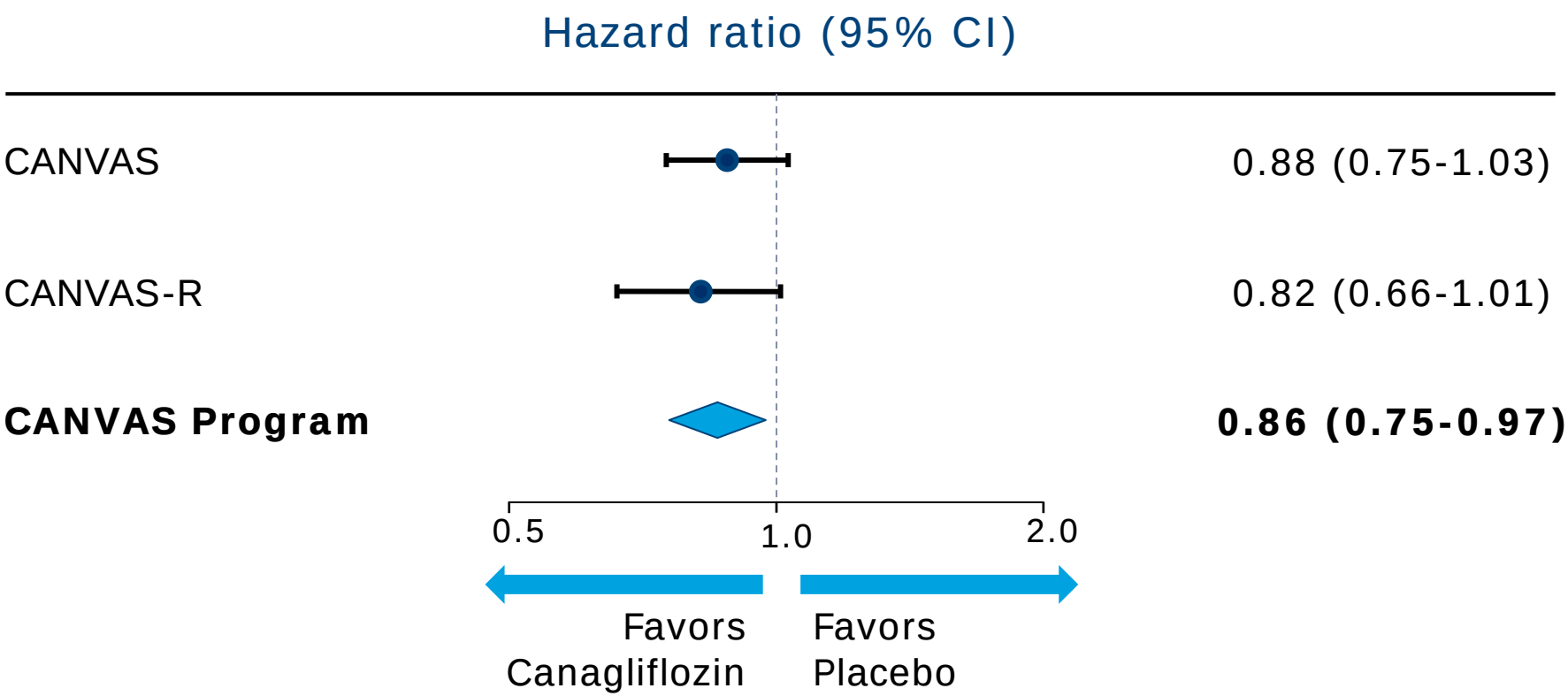


No. of patients							
Placebo	4347	4153	2942	1240	1187	1120	789
Canagliflozin	5795	5566	4343	2555	2460	2363	1661

Intent-to-treat analysis

CANVAS Program

Primary Cardiovascular Outcome by Study



Intent-to-treat analysis

CANVAS Program

Hypothesis Testing Outcome

Major cardiovascular events (non-inferiority) • Superiority*	p <0.001 p = 0.0158
All-cause mortality	p = 0.24
Cardiovascular death	Exploratory Nominal effect estimates
Albuminuria progression	
Cardiovascular death or hospitalization for heart failure	
Cardiovascular death	

*Superiority testing was included in the Statistical Analysis Plan.

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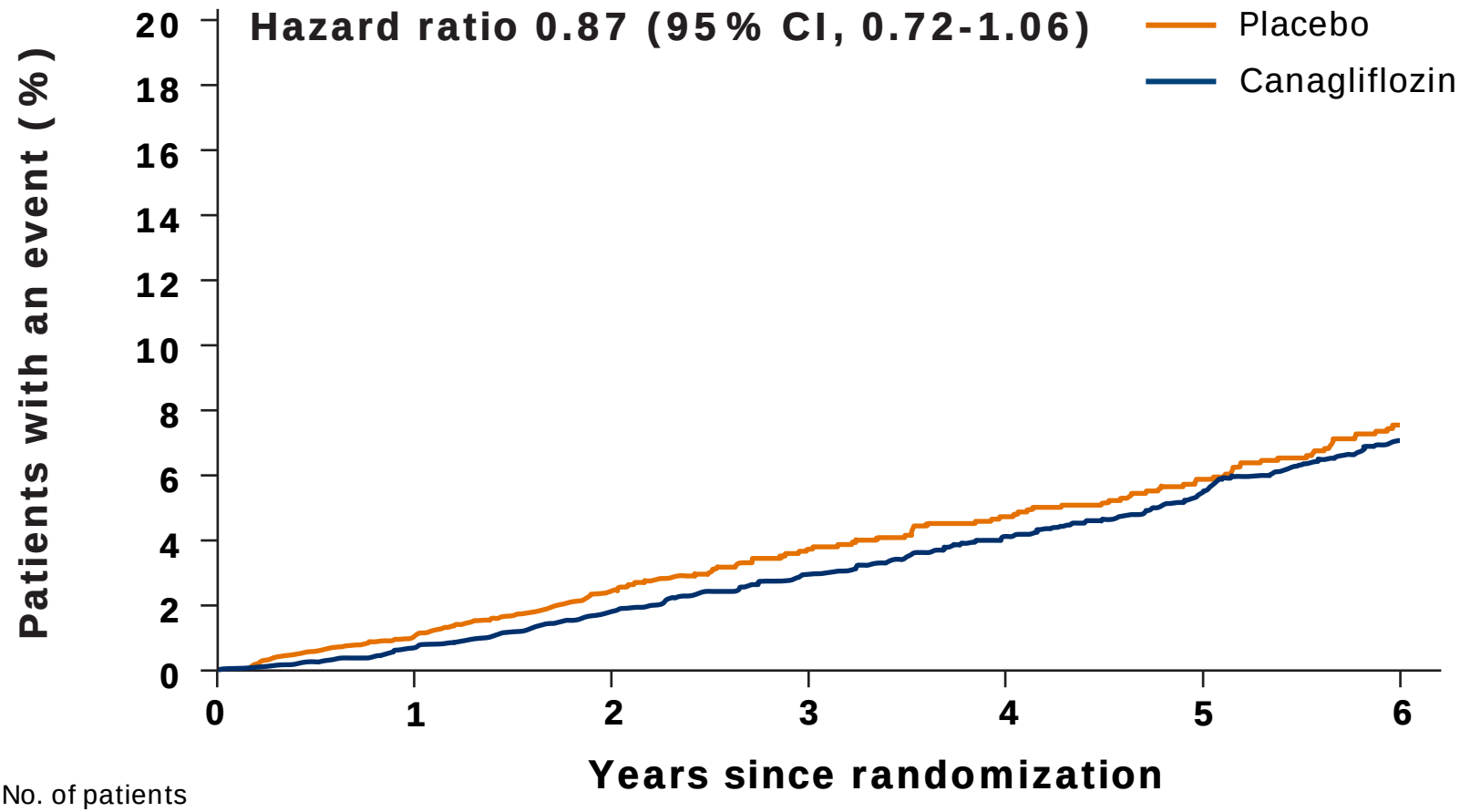
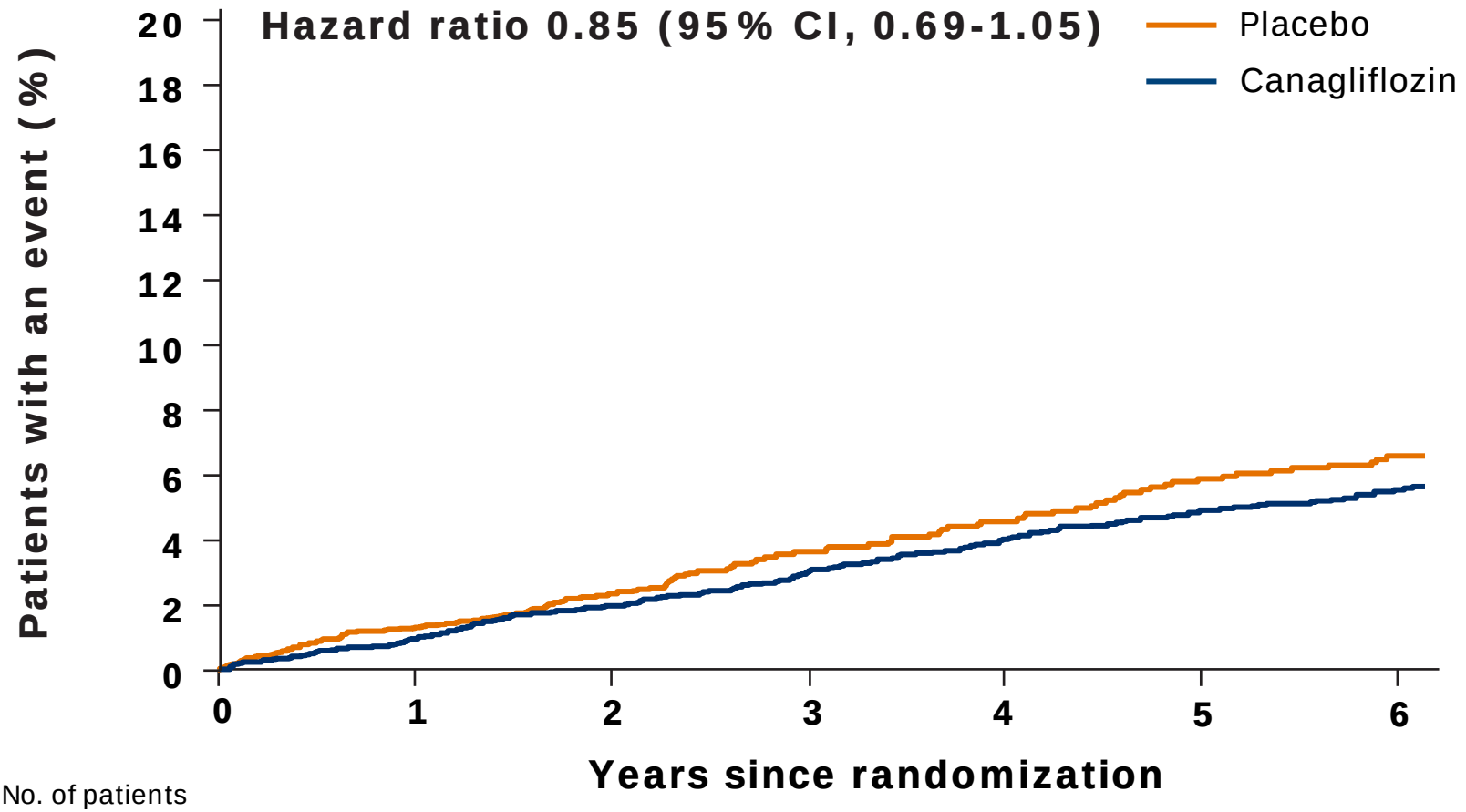
CV Death Component of Primary Outcome



No. of patients							
Placebo	4347	4279	3119	1356	1328	1292	924
Canagliflozin	5795	5723	4576	2761	2710	2651	1904

Intent-to-treat analysis

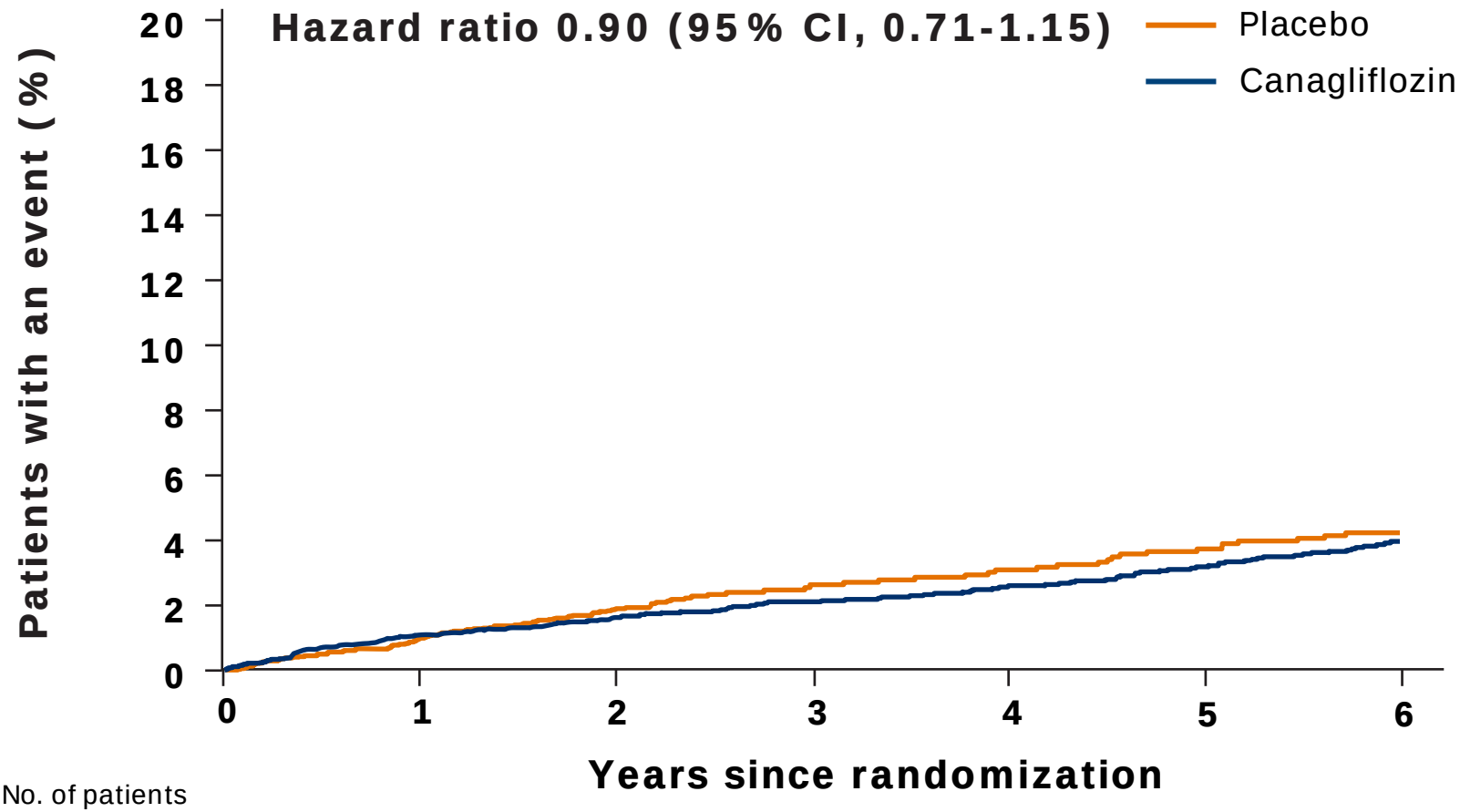
MI Component of Primary Outcome



No. of patients							
Placebo	4347	4187	2986	1255	1207	1146	812
Canagliflozin	5795	5625	4405	2602	2516	2425	1728

Intent-to-treat analysis

Stroke Component of Primary Outcome



No. of patients							
Placebo	4347	4197	3004	1274	1232	1177	829
Canagliflozin	5795	5615	4414	2621	2543	2464	1751

Intent-to-treat analysis

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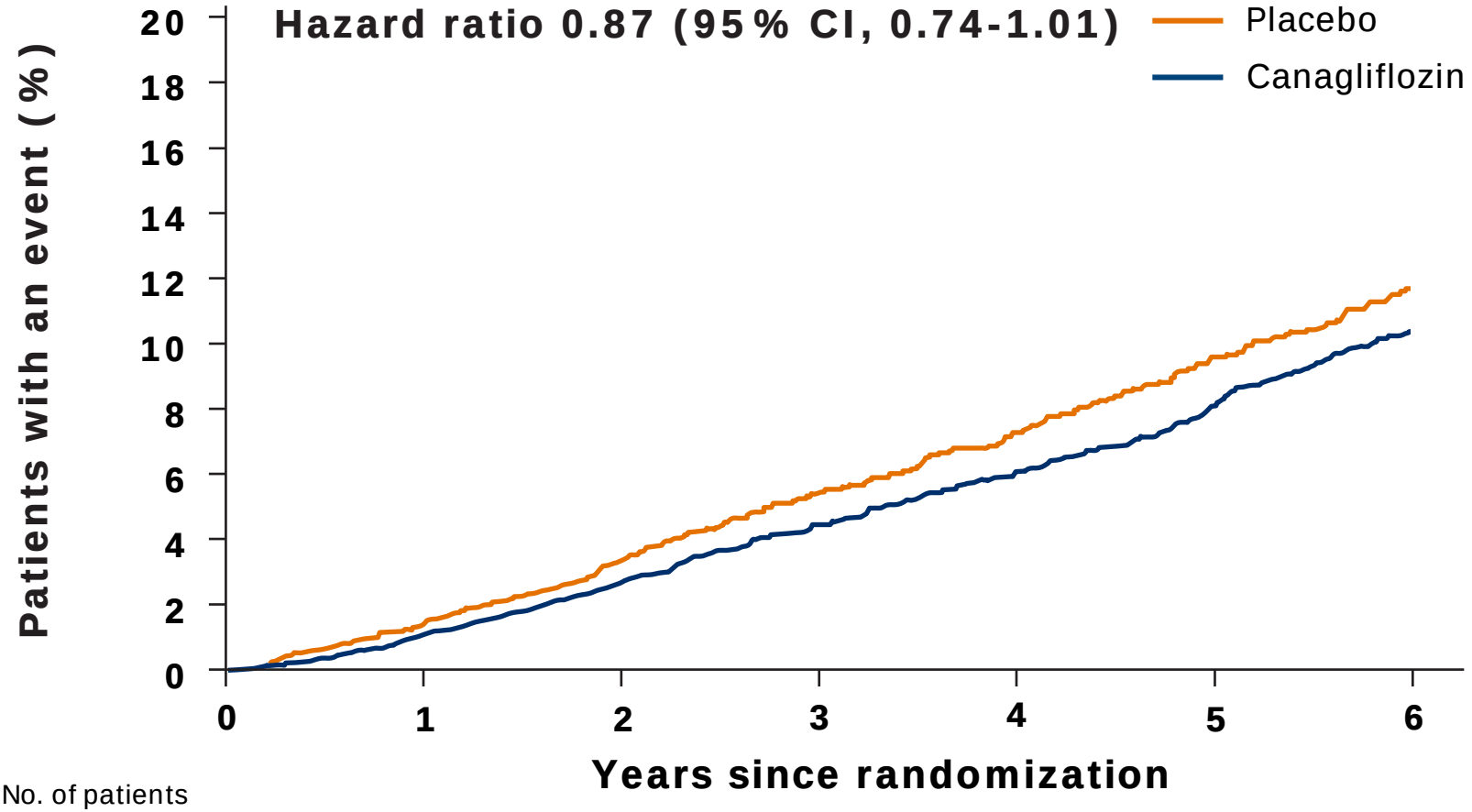
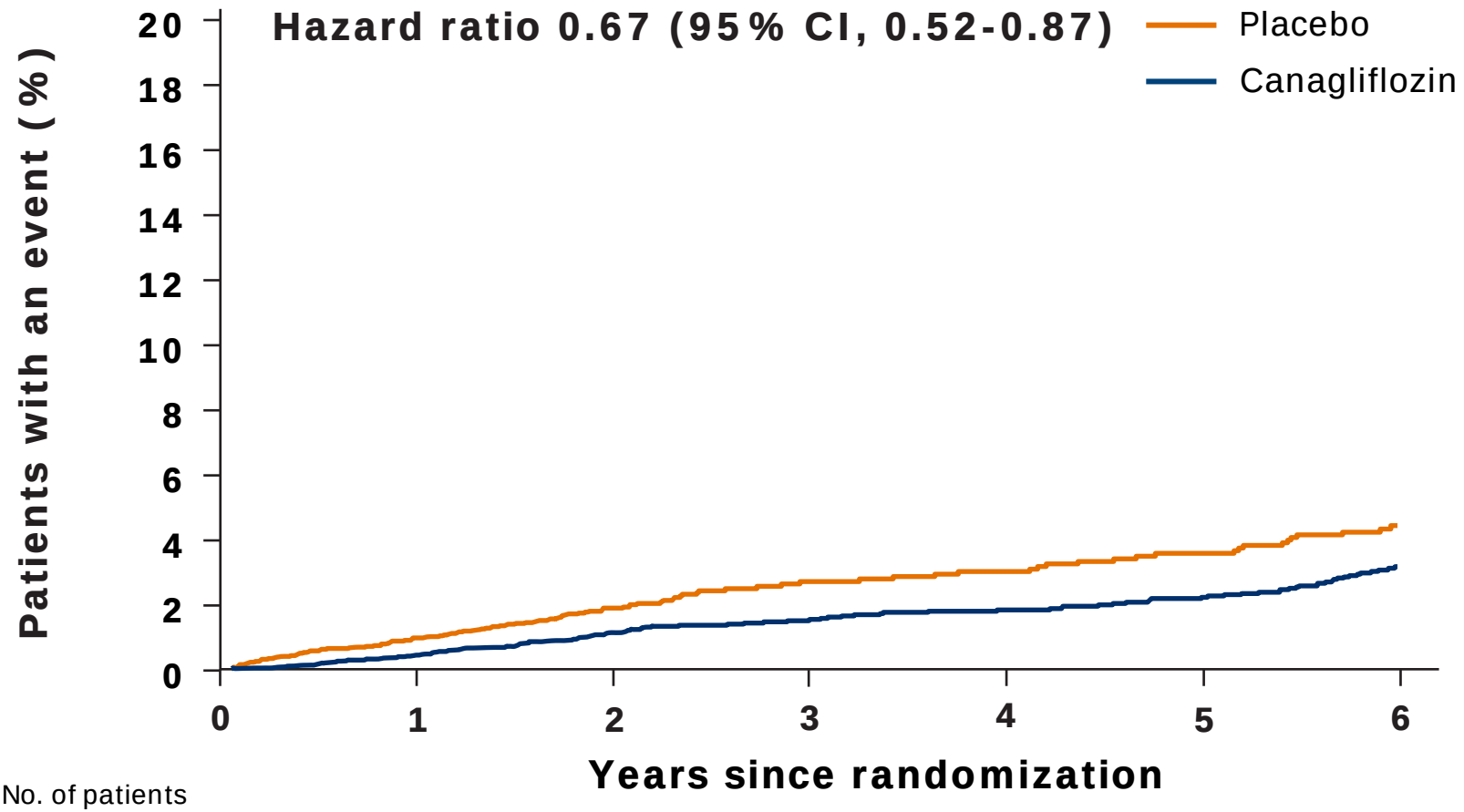
All-Cause Mortality



No. of patients							
Placebo	4347	4279	3119	1356	1328	1292	924
Canagliflozin	5795	5723	4576	2761	2710	2651	1904

Intent-to-treat analysis

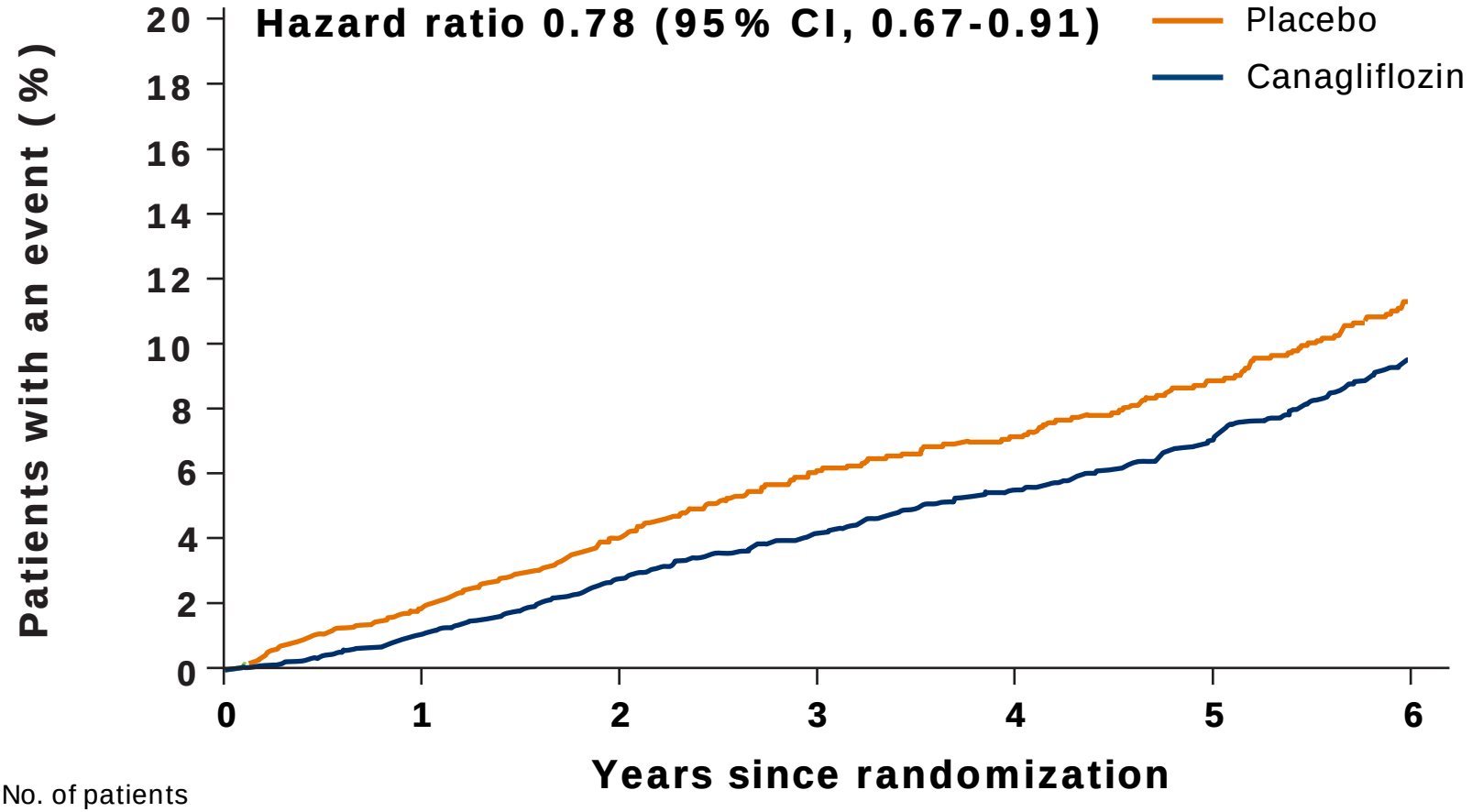
Hospitalization for Heart Failure



No. of patients							
Placebo	4347	4198	3011	1274	1236	1180	829
Canagliflozin	5795	5653	4437	2643	2572	2498	1782

Intent-to-treat analysis

CV Death or Hospitalization for Heart Failure

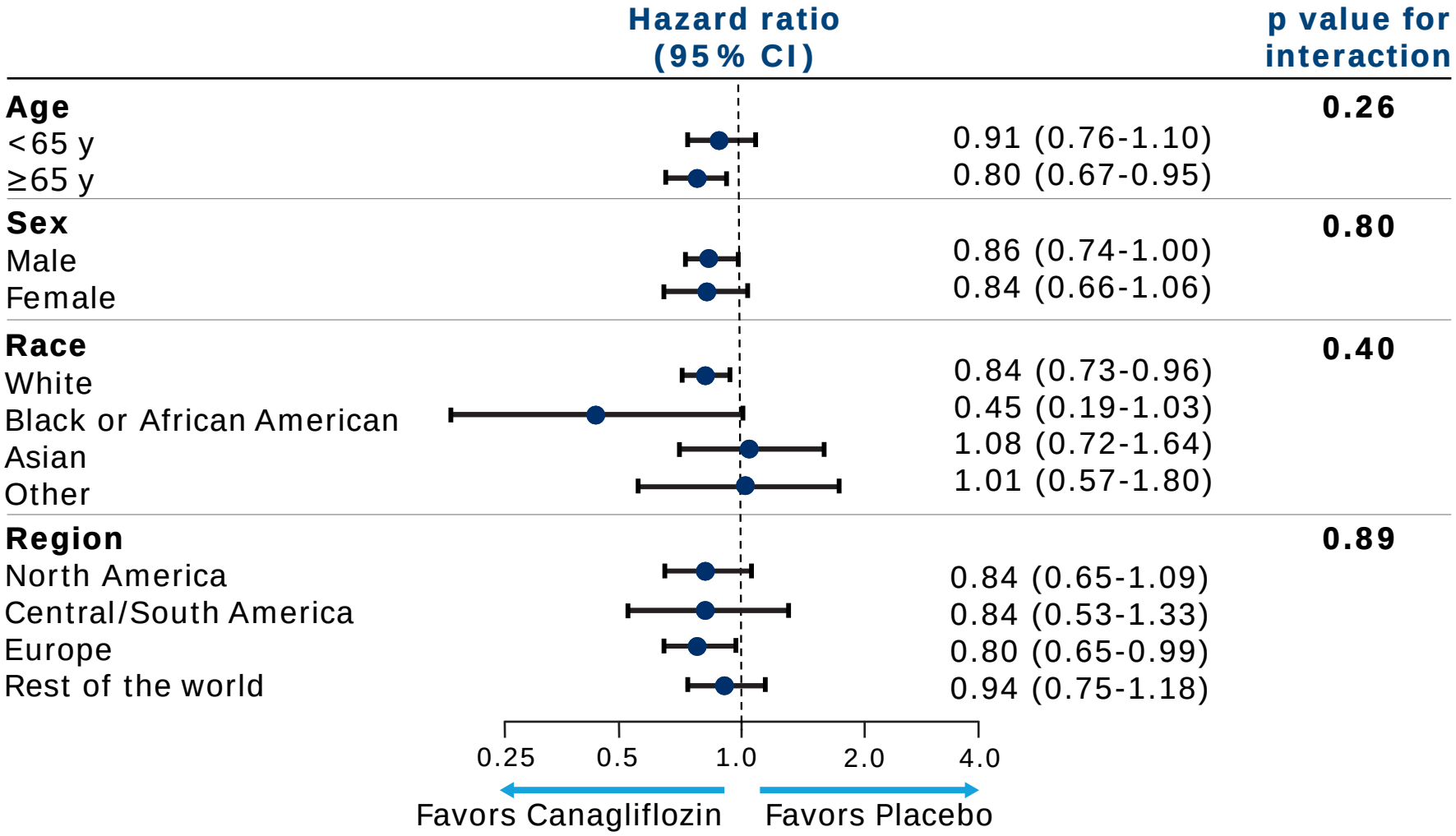


No. of patients							
Placebo	4347	4202	3015	1281	1242	1184	831
Canagliflozin	5795	5655	4442	2647	2577	2503	1782

Intent-to-treat analysis

CANVAS Program

Demographic Subgroups (Primary outcome)



Intent-to-treat analysis

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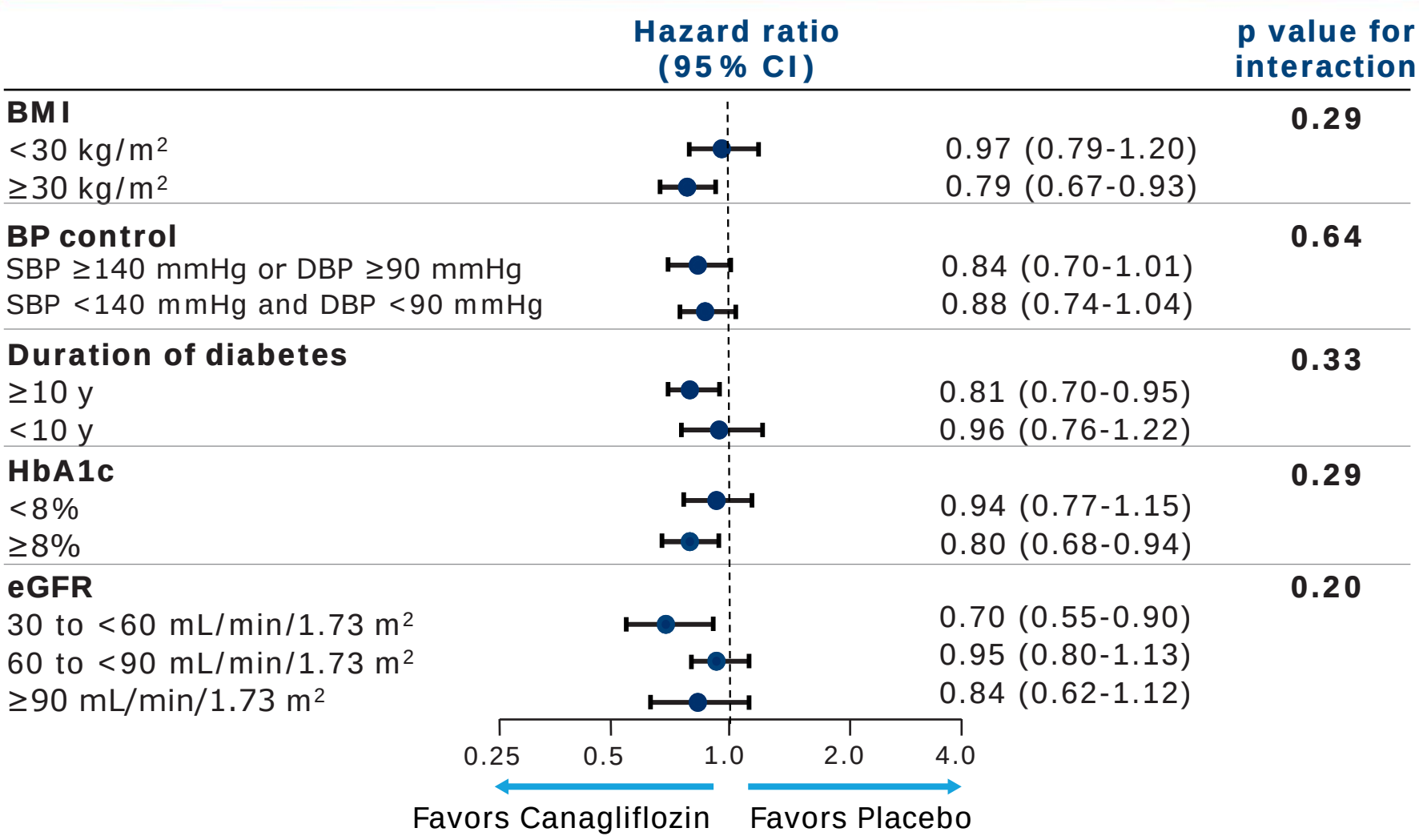
Risk Factor Subgroups (Primary Outcome)



Intent-to-treat analysis

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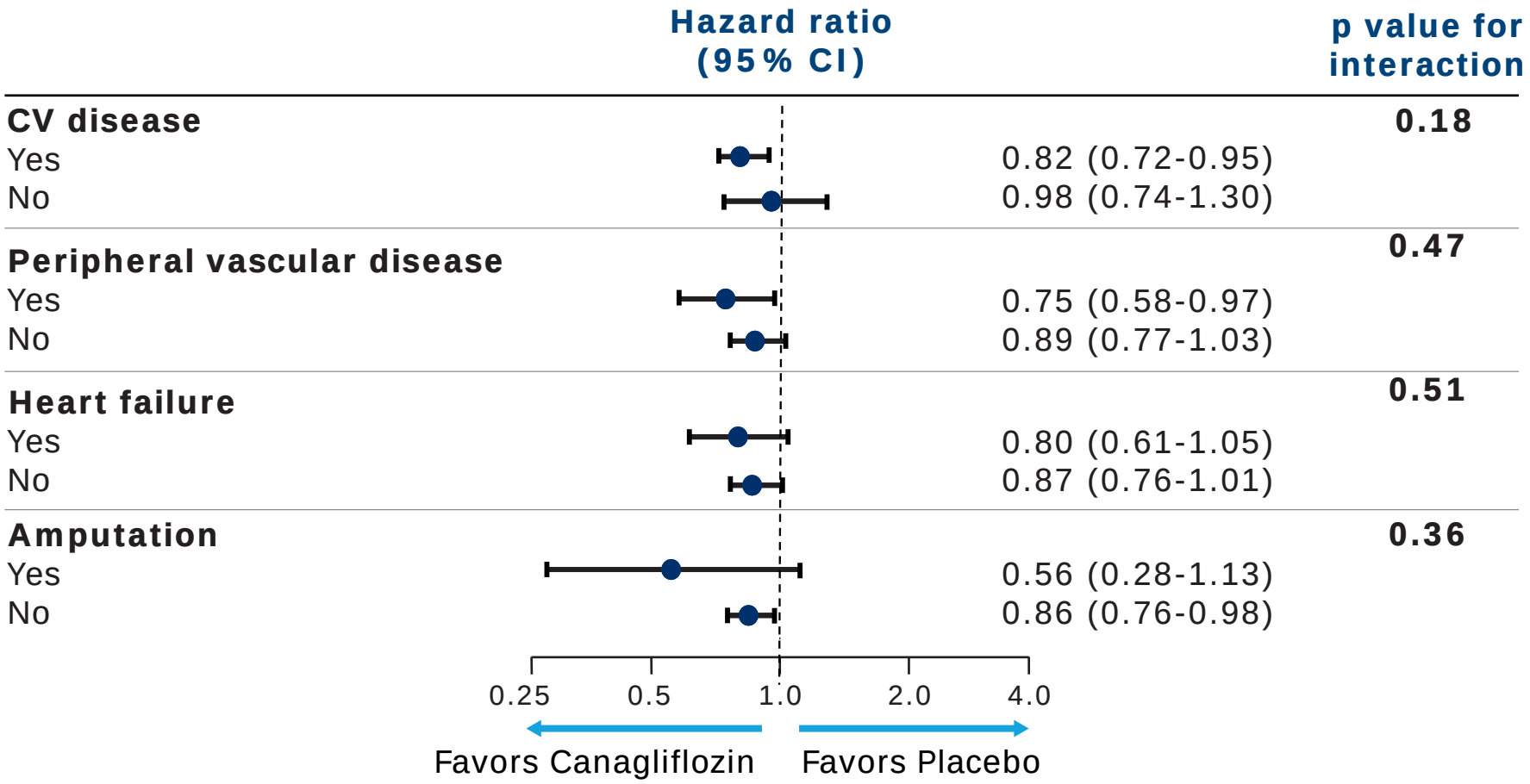
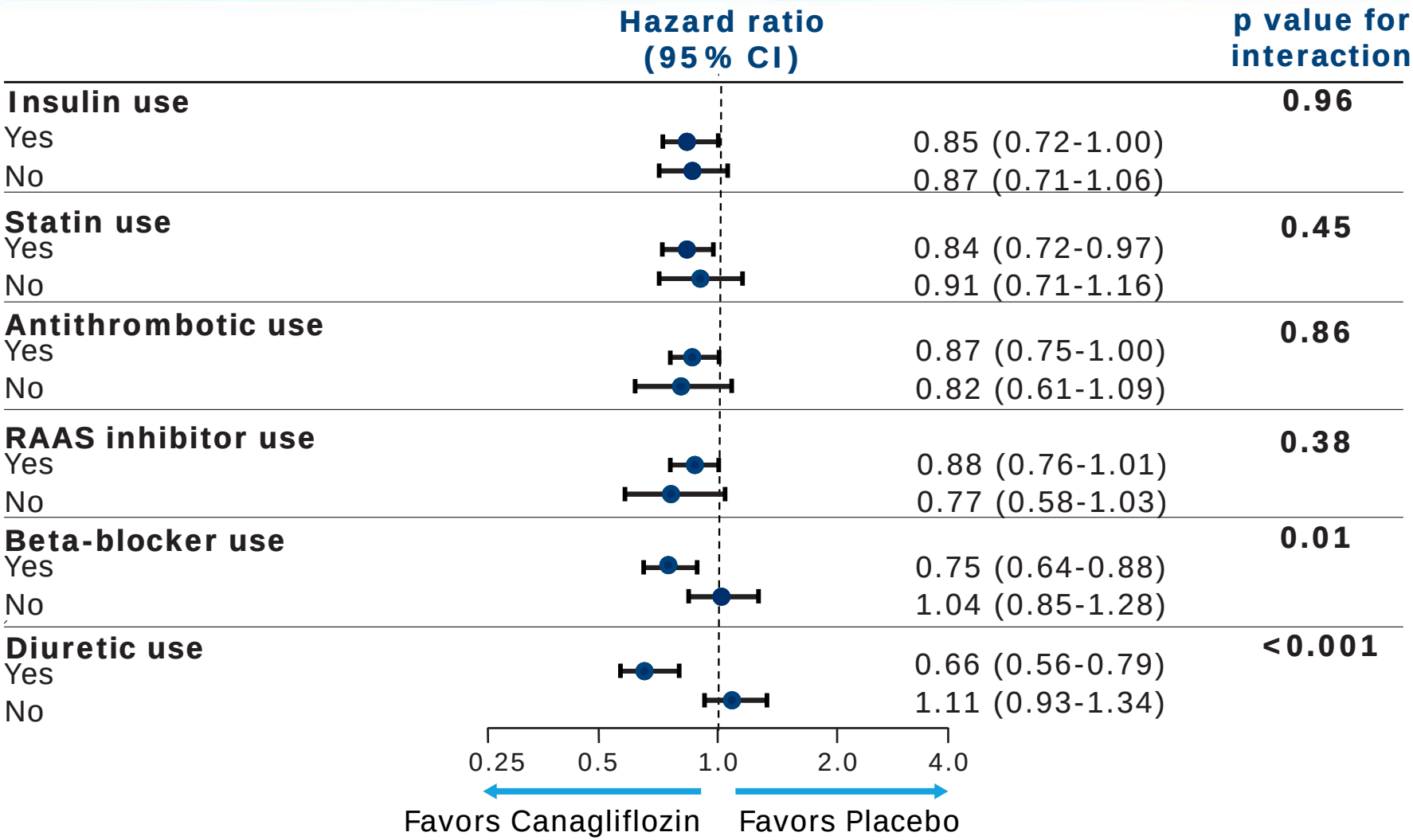
Disease History Subgroups (Primary Outcome)



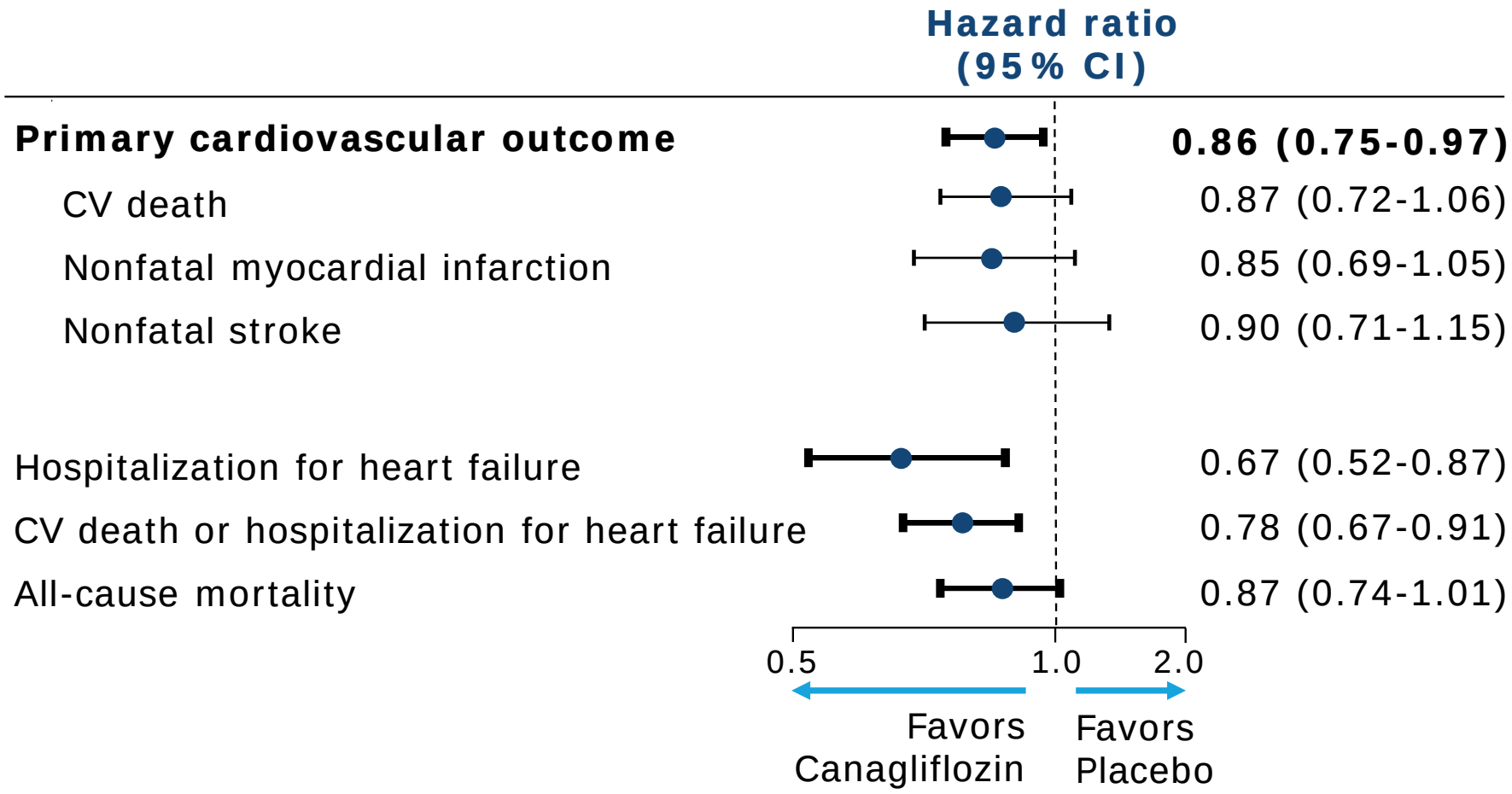
Background Therapy Subgroups (Primary Outcome)



Intent-to-treat analysis

CANVAS Program

Summary


Hazard ratio
(95% CI)
Primary cardiovascular outcome
0.86 (0.75-0.97)
CV death
0.87 (0.72-1.06)
Nonfatal myocardial infarction
0.85 (0.69-1.05)
Nonfatal stroke
0.90 (0.71-1.15)
Hospitalization for heart failure
0.67 (0.52-0.87)
CV death or hospitalization for heart failure
0.78 (0.67-0.91)
All-cause mortality
0.87 (0.74-1.01)
0.5
1.0
2.0
Favors Canagliflozin
Favors Placebo

The CANVAS Program

Effects on Renal Outcomes

Dick de Zeeuw, MD, PhD

CANVAS Program

Presenter Disclosures: Dick de Zeeuw, MD, PhD

- Advisory boards and/or speaker for:
  - AbbVie, Astellas, Eli Lilly, Fresenius, Janssen, Boehringer Ingelheim, Bayer, Mitsubishi-Tanabe
  - All consultancy honoraria are paid to his institution

Renal Outcomes

Biomarker outcome
- Change in albuminuria

Renal intermediate outcomes
- Progression of albuminuria
- Regression of albuminuria

Composite renal outcome [confirmed and adjudicated]
- 40% decrease in glomerular filtration rate (GFR)
- End-stage renal disease
- Renal death

Measurement of Renal Outcomes

Albuminuria
- Urine albumin:creatinine ratio (UACR)

Progression/Regression of albuminuria
- Change in albuminuria class (normo-, micro-, macroalbuminuria) plus >30% UACR change from baseline

40% decrease in GFR
- Sustained more than 40% decrease in estimated GFR (eGFR)

End-stage renal disease
- Reaching dialysis or transplantation or sustained eGFR <15 mL/min/1.73 m^2

Renal death
- Death due to kidney disease

Renal Baseline Characteristics

Similar for Canagliflozin and Placebo

	Canagliflozin (n = 5795)	Placebo (n = 4347)
Mean eGFR, mL/min/1.73 m²	77	76
Median albumin:creatinine ratio, mg/g	12.4	12.1
ACE inhibitor/ARB use, %	80	80

Low Renal Risk Population

High Percentage of "Normal" eGFR and Albuminuria

	Canagliflozin (n = 5795)	Placebo (n = 4347)
Mean eGFR, mL/min/1.73 m²	**77**	**76**
≥90 mL/min/1.73 m², %	*25*	*24*
60 to <90 mL/min/1.73 m², %	*56*	*54*
45 to <60 mL/min/1.73 m², %	*14*	*16*
<45 mL/min/1.73 m², %	*5*	*6*
Median albumin:creatinine ratio, mg/g	**12.4**	**12.1**
Normoalbuminuria (<30 mg/g), %	*70*	*70*
Microalbuminuria (30 to 300 mg/g), %	*23*	*22*
Macroalbuminuria (>300 mg/g), %	*7*	*8*

Results

Biomarker outcome

- Change in albuminuria

Renal intermediate outcomes

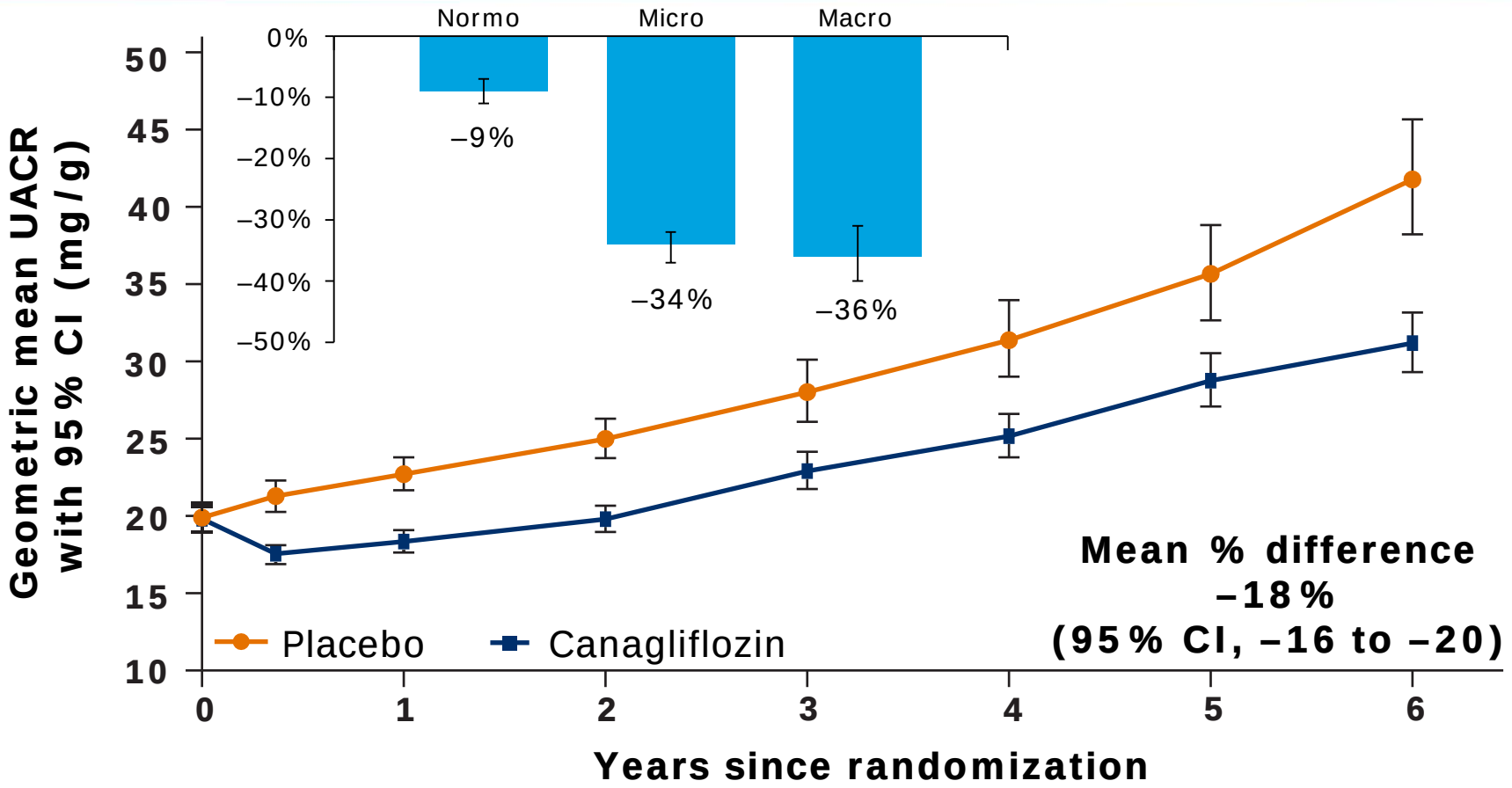
- Progression of albuminuria
- Regression of albuminuria

Composite renal outcome [confirmed and adjudicated]

- 40% decrease in glomerular filtration rate (GFR)
- End-stage renal disease
- Renal death

Change in Albumin:Creatinine Ratio (UACR)

Percent Change in UACR per Albuminuria Class (inset)



No. of patients							
Placebo	4084	3775	2556	753	652	594	618
Canagliflozin	5500	5103	3565	1689	1541	1408	1534

Mixed model for repeated measures (MMRM) analysis
Excluding those below detection level

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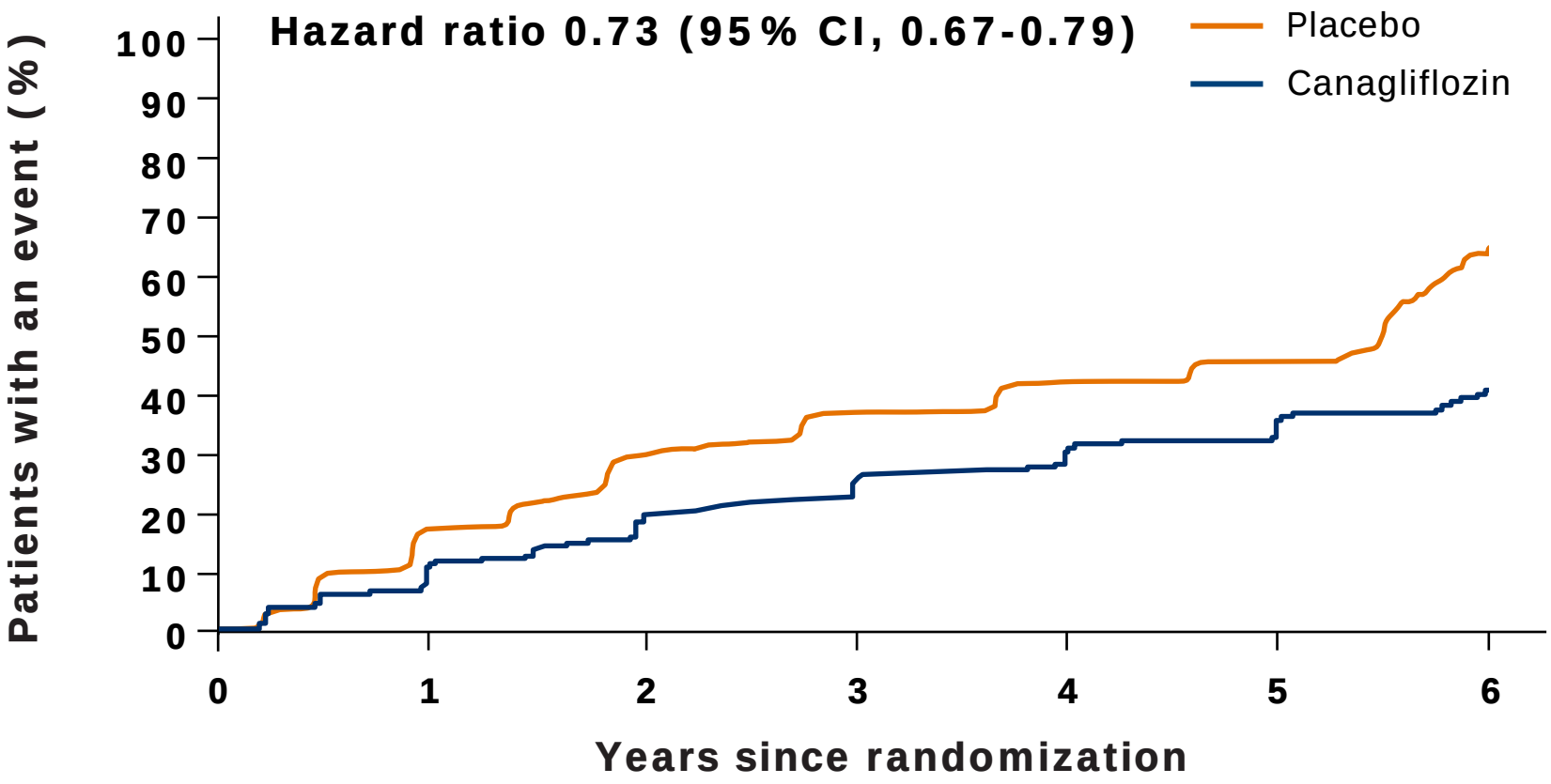
Results

Biomarker outcome
- Change in albuminuria

Renal intermediate outcomes
- Progression of albuminuria
- Regression of albuminuria

Composite renal outcome [confirmed and adjudicated]
- 40% decrease in glomerular filtration rate (GFR)
- End-stage renal disease
- Renal death

Progression of Albuminuria

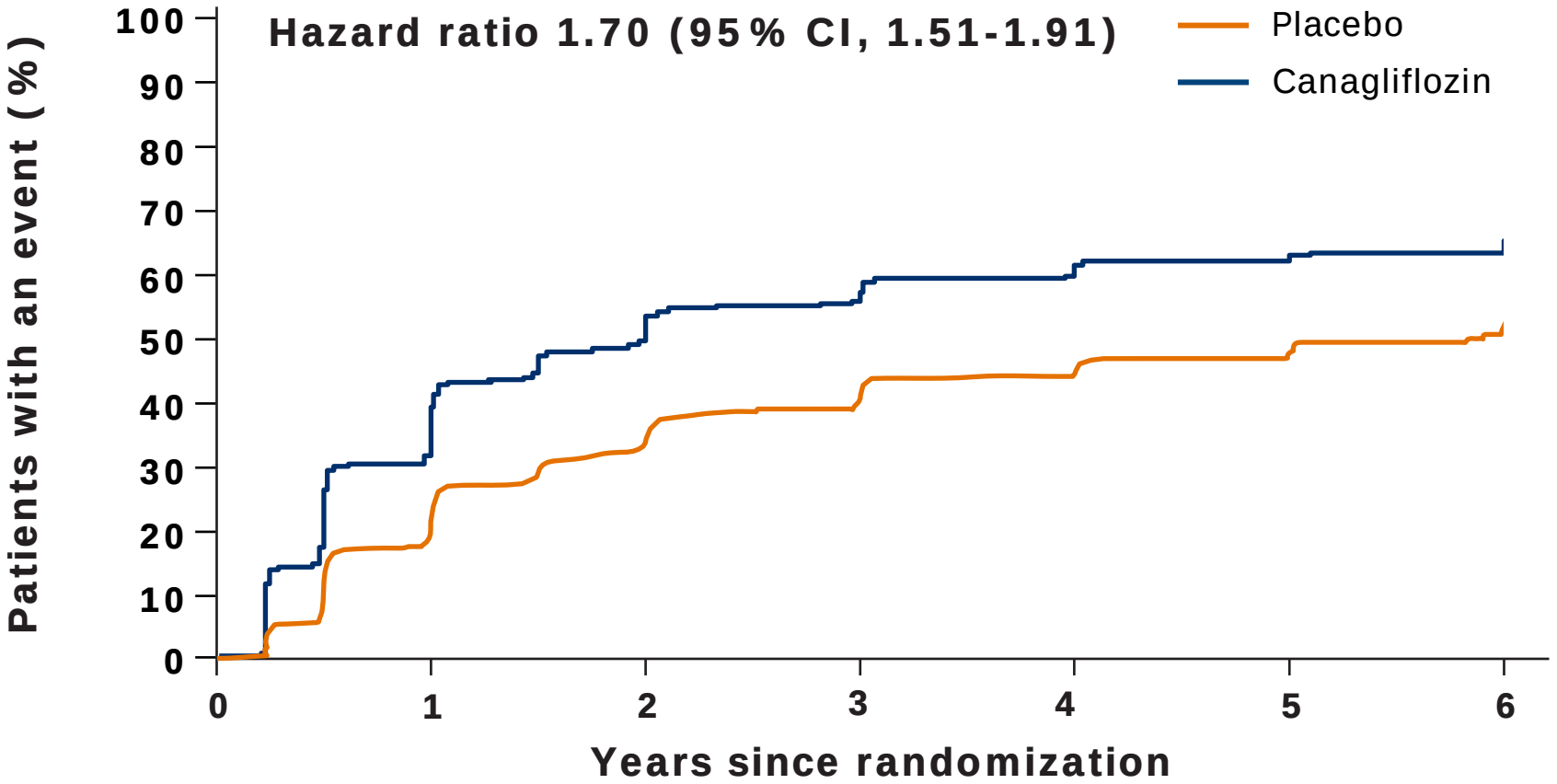


No. of patients							
Placebo	3819	3096	1690	724	626	548	303
Canagliflozin	5196	4475	2968	1730	1528	1354	775

Intent-to-treat analysis

CANVAS Program

Regression of Albuminuria



No. of patients

Placebo	1257	913	426	163	144	123	59
Canagliflozin	1679	1009	518	276	227	198	112

Intent-to-treat analysis

CANVAS Program

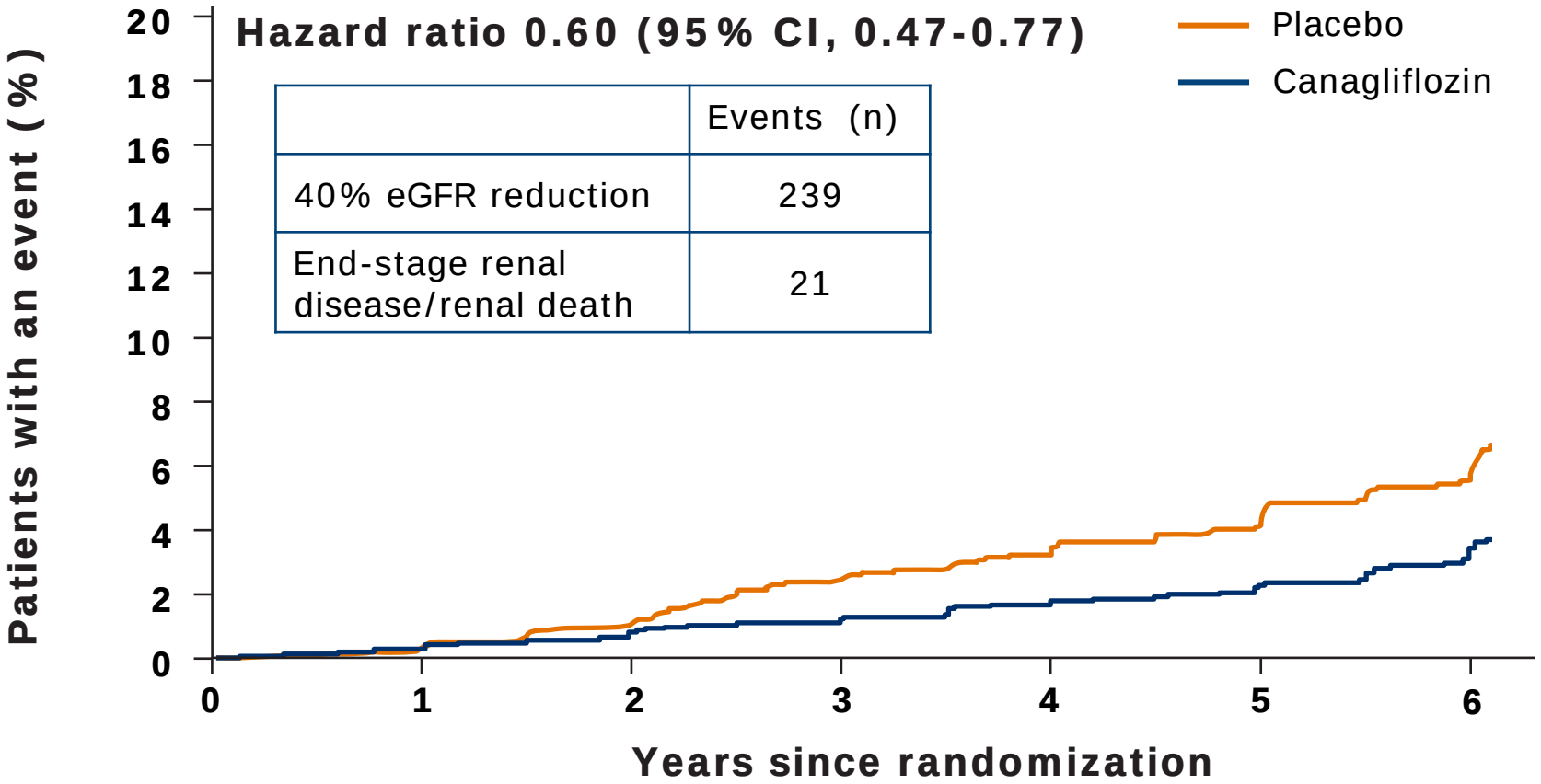
Results

Biomarker outcome
- Change in albuminuria

Renal intermediate outcomes
- Progression of albuminuria
- Regression of albuminuria

Composite renal outcome [confirmed and adjudicated]
- 40% decrease in glomerular filtration rate (GFR)
- End-stage renal disease
- Renal death

Composite of 40% Reduction in eGFR, End-stage Renal Disease, or Renal Death



	Events (n)
40% eGFR reduction	239
End-stage renal disease/renal death	21

No. of patients

Placebo	4347	4227	3029	1274	1229	1173	819
Canagliflozin	5795	5664	4454	2654	2576	2495	1781

Intent-to-treat analysis

CANVAS Program

Renal Outcomes Summary

- Canagliflozin compared to placebo
  - Induced sustained lowering of albuminuria
  - Prevented progression in albuminuria
  - Induced regression in albuminuria
  - Reduced renal function loss events
- Conclusion
  - These data suggest a potential renoprotective effect of canagliflozin treatment in patients with type 2 diabetes at high CV risk on top of ACE/ARBs

The CANVAS Program

Effects on Safety Outcomes

Vlado Perkovic, MBBS, PhD

CANVAS Program

Presenter Disclosures: Vlado Perkovic, MBBS, PhD

- Research support
  - Senior Research Fellowship and Program Grant from the Australian National Health and Medical Research Council
- Steering Committees
  - Abbvie, Boehringer Ingelheim, GSK, Janssen, Pfizer
- Advisory boards and/or speaker at scientific meetings
  - Abbvie, Astellas, Astra Zeneca, Bayer, Baxter, BMS, Boehringer Ingelheim, Durect, Eli Lilly, Gilead, GSK, Janssen, Merck, Novartis, Novo Nordisk, Pfizer, Pharmalink, Relypsa, Roche, Sanofi, Servier, Vitae
- All honoraria are paid to employer

Adverse Event Collection in CANVAS Program

Pre-registration

- All adverse events

Post-registration streamlined approach

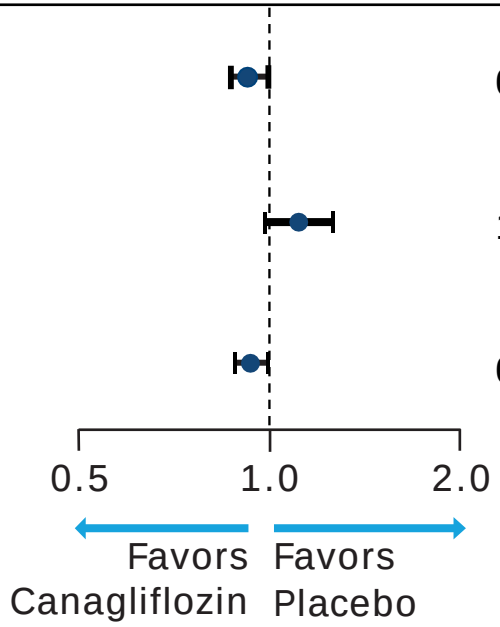
- All serious adverse events
- Adverse events leading to discontinuation
- Adverse events of interest

Adverse Events of Interest

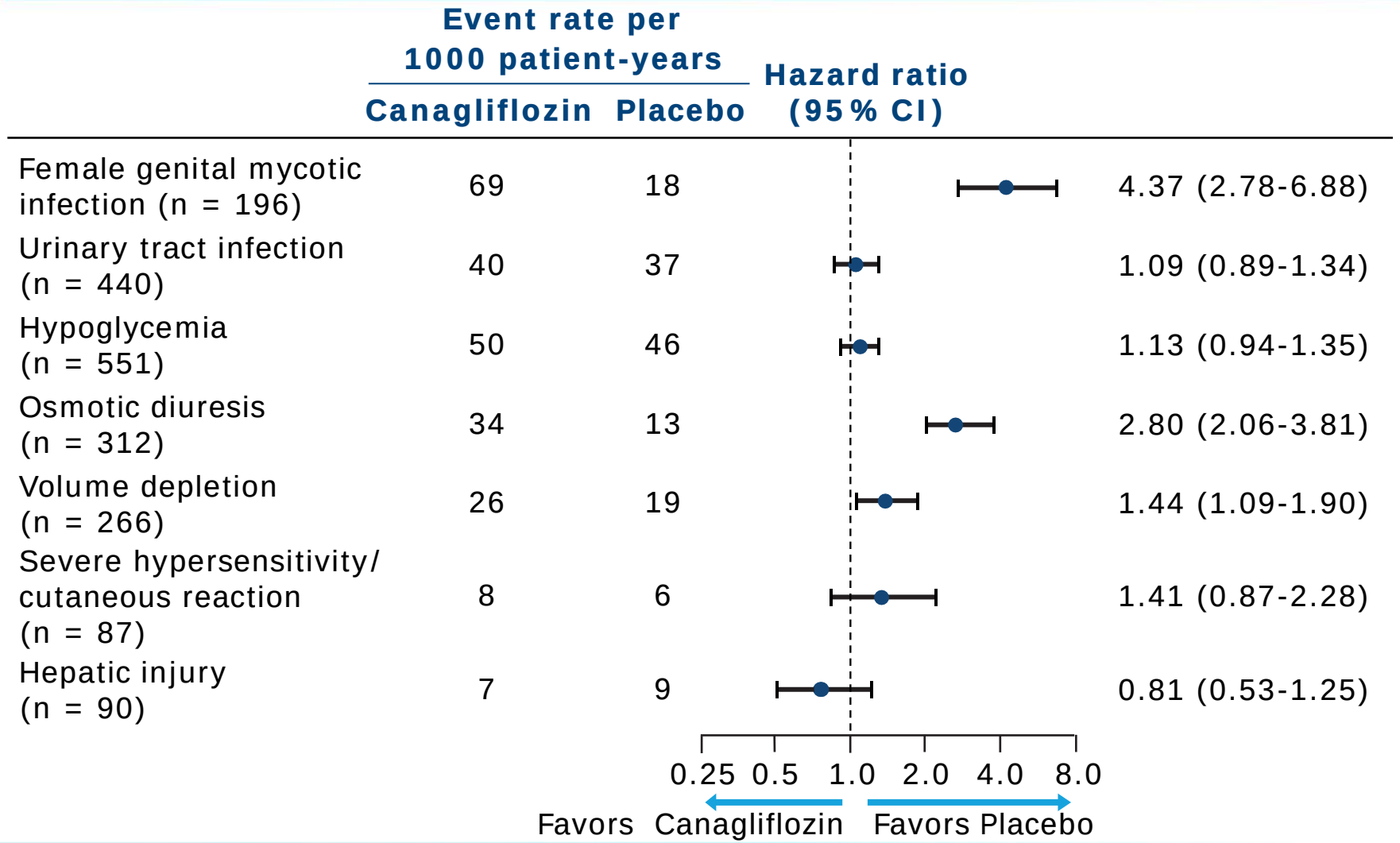
- Prespecified
  - Male genital mycotic infections
  - Malignancies
  - Photosensitivity
  - Venous thromboembolism
  - Fracture
- Added during trials
  - Diabetic ketoacidosis (health authority surveillance for class)
  - Acute pancreatitis (health authority surveillance for class)
  - Amputation (data monitoring committee advice)

Serious Adverse Events, Adverse Events Leading to Discontinuation & Hospitalizations

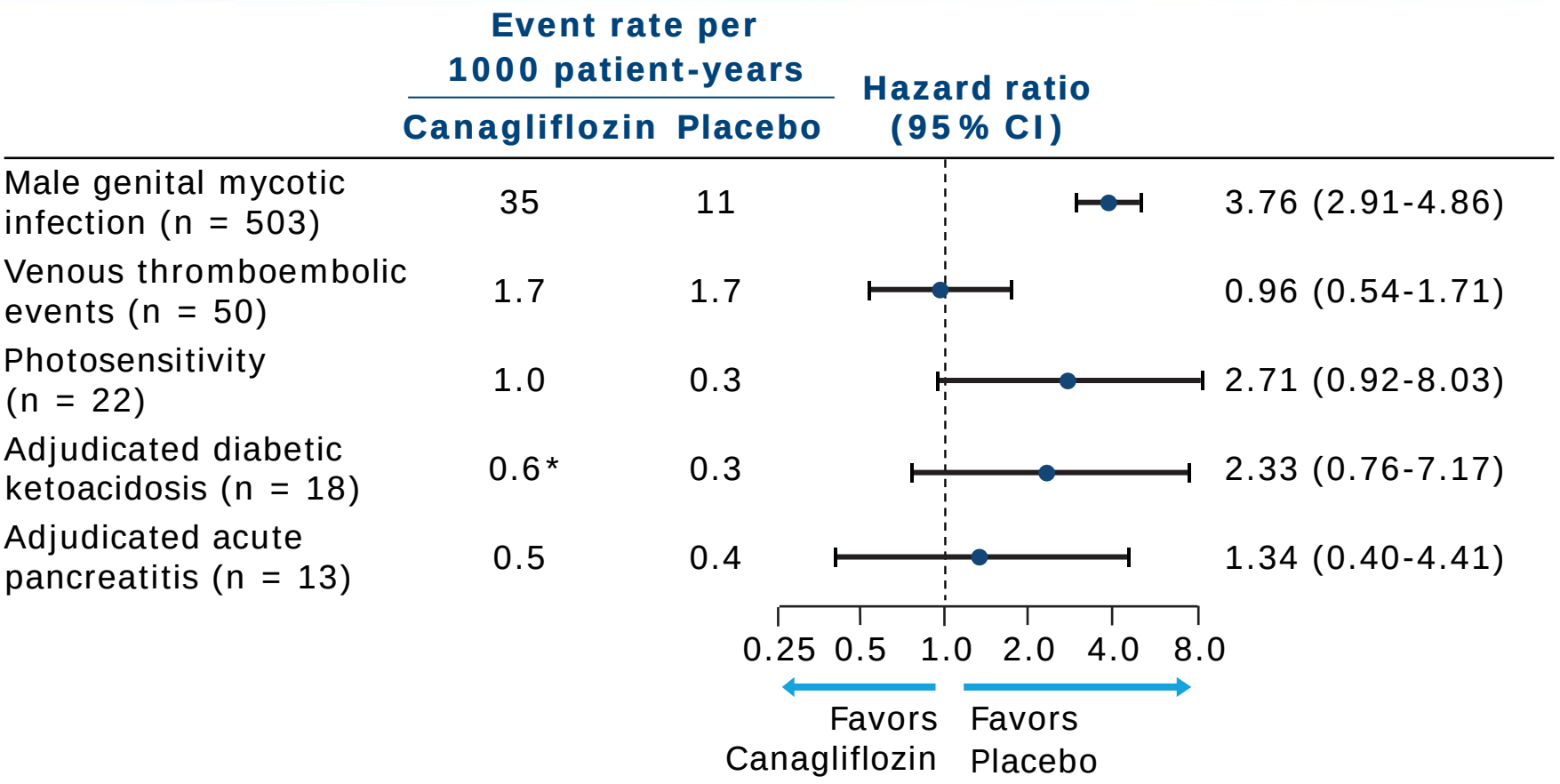
	Event rate per 1000 patient-years		Hazard ratio (95% CI)
	Canagliflozin	Placebo	
All serious adverse events (n = 3280)	104	120	0.93 (0.87-1.00)
Adverse events leading to discontinuation (n = 1025)	35	33	1.13 (0.99-1.28)
All-cause hospitalization (n = 3486)	119	131	0.94 (0.88-1.00)



Adverse Events (CANVAS)

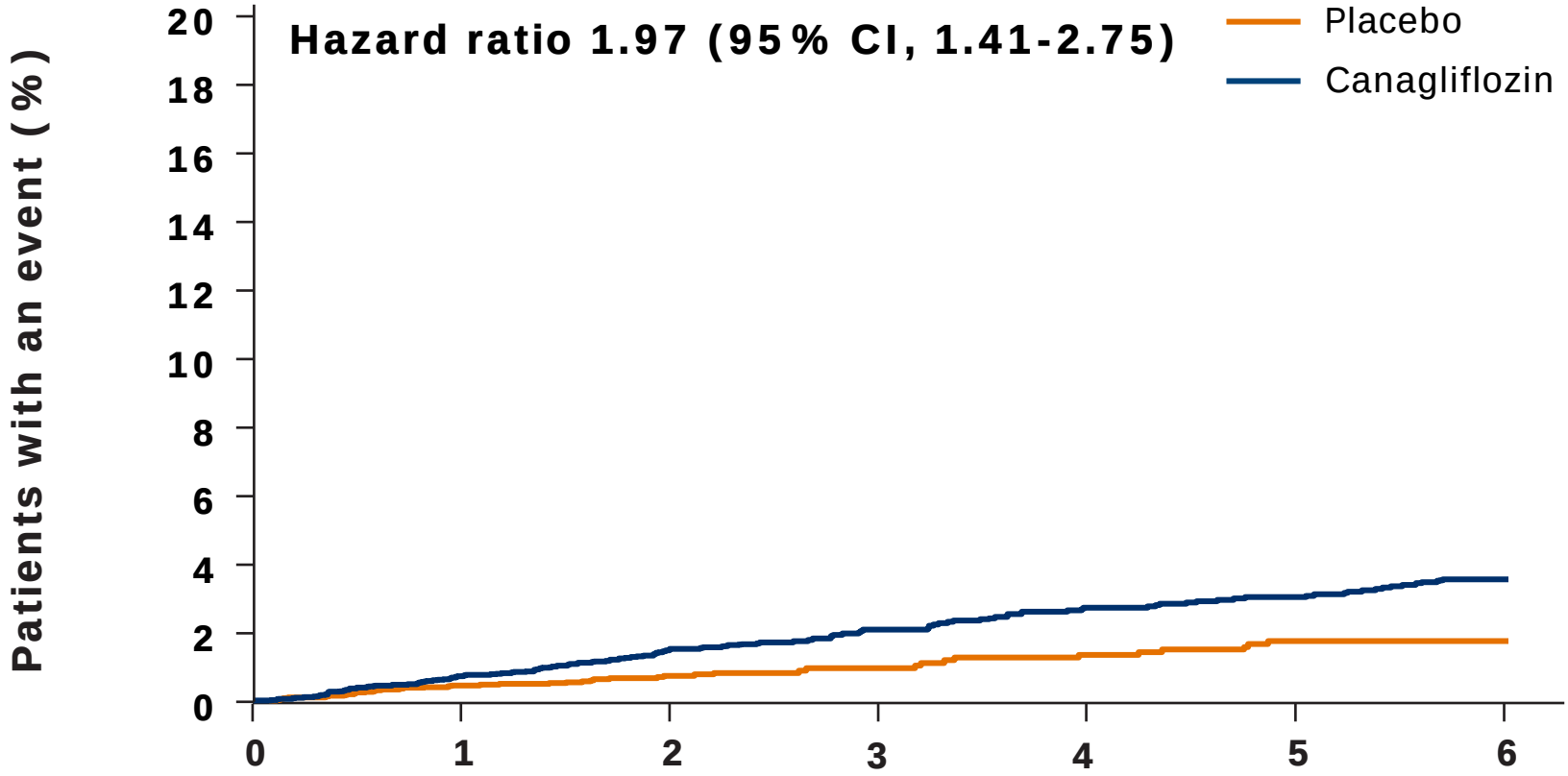


Adverse Events of Interest Across Program



*5 patients reporting diabetic ketoacidosis (all on canagliflozin) identified as having autoimmune diabetes (positive GADA and mIAA or a reported history of T1DM).

Lower-extremity Amputations



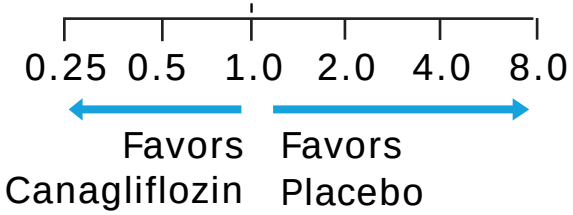
No. at risk							
Placebo	4344	4217	3037	1289	1247	1194	844
Canagliflozin	5790	5634	4420	2618	2536	2460	1765

Increased risk communicated to health authorities, investigators, and providers in 2016 based on IDMC letter.

CANVAS Program

Highest Level of Amputation

	Event rate per 1000 patient-years		Hazard ratio (95% CI)
	Canagliflozin	Placebo	
All amputations (n = 187)	6.3	3.4	1.97 (1.41-2.75)
Minor amputation (71%)	4.5	2.4	1.94 (1.31-2.88)
Toe	3.4	2.2	
Transmetatarsal	1.0	0.3	
Major amputation (29%)	1.8	0.9	2.03 (1.08-3.82)
Ankle	0.04	0.07	
Below-knee	1.2	0.6	
Above-knee	0.6	0.2	



Amputation Risk Factors - Multivariate Analysis

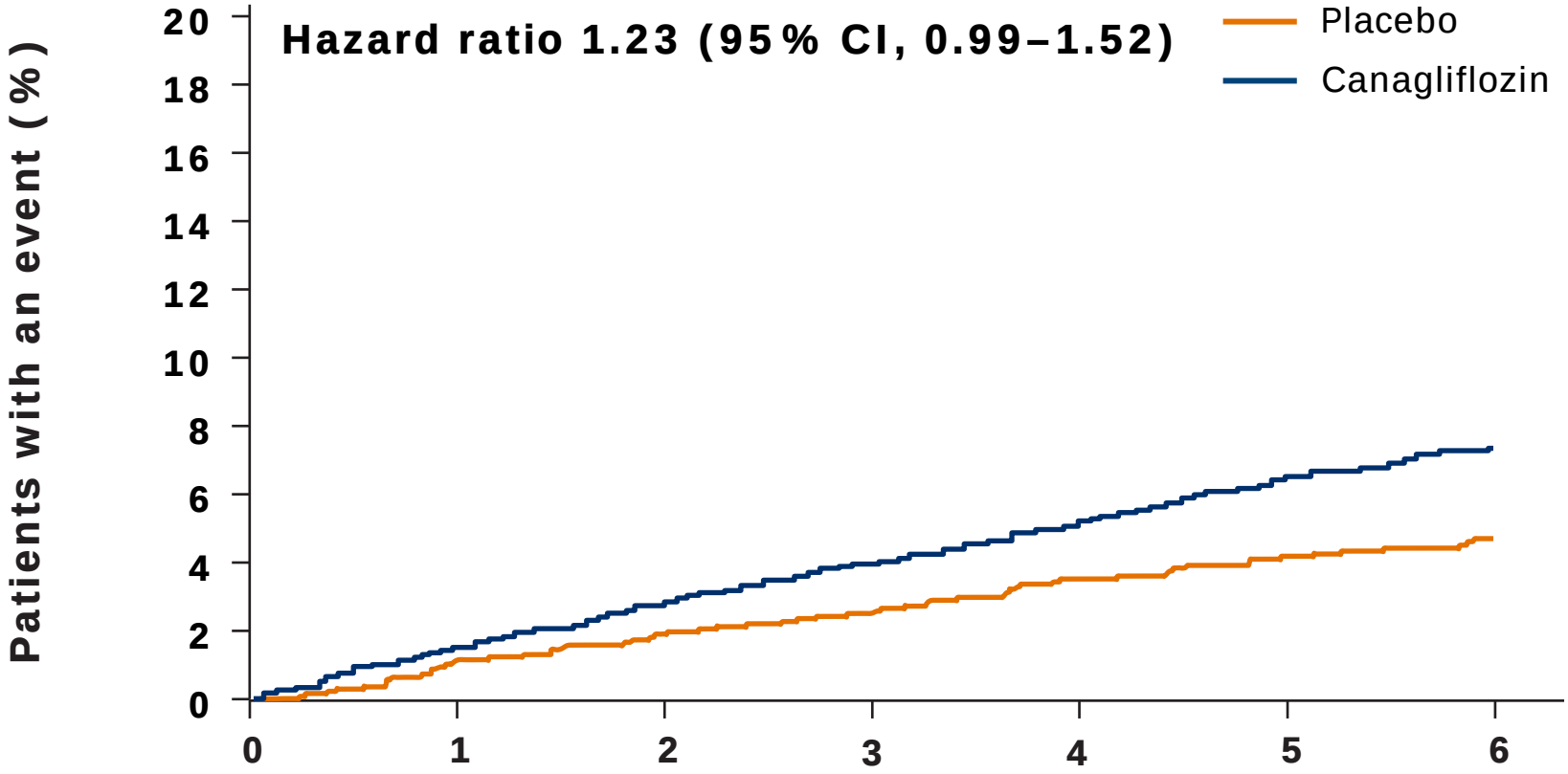
Risk Factor at Baseline	Hazard Ratio	95% CI
Amputation	20.9	(14.2-30.8)
Peripheral vascular disease*	3.1	(2.2-4.5)
Male	2.4	(1.6-3.5)
Neuropathy	2.1	(1.6-2.9)
HbA1c >8%	1.9	(1.4-2.6)
Canagliflozin treatment	1.8	(1.3-2.5)
Presence of CV disease	1.5	(1.0-2.3)

- Predictors of amputation risk are similar in both arms
- Canagliflozin treatment, independent of the risk factors, increased amputation risk

Predictive on univariate analysis: nephropathy, insulin use, retinopathy, loop diuretic, eGFR, diabetes duration
Factors assessed but not significantly predictive: non-loop diuretic, smoking, SBP, hemoglobin, age

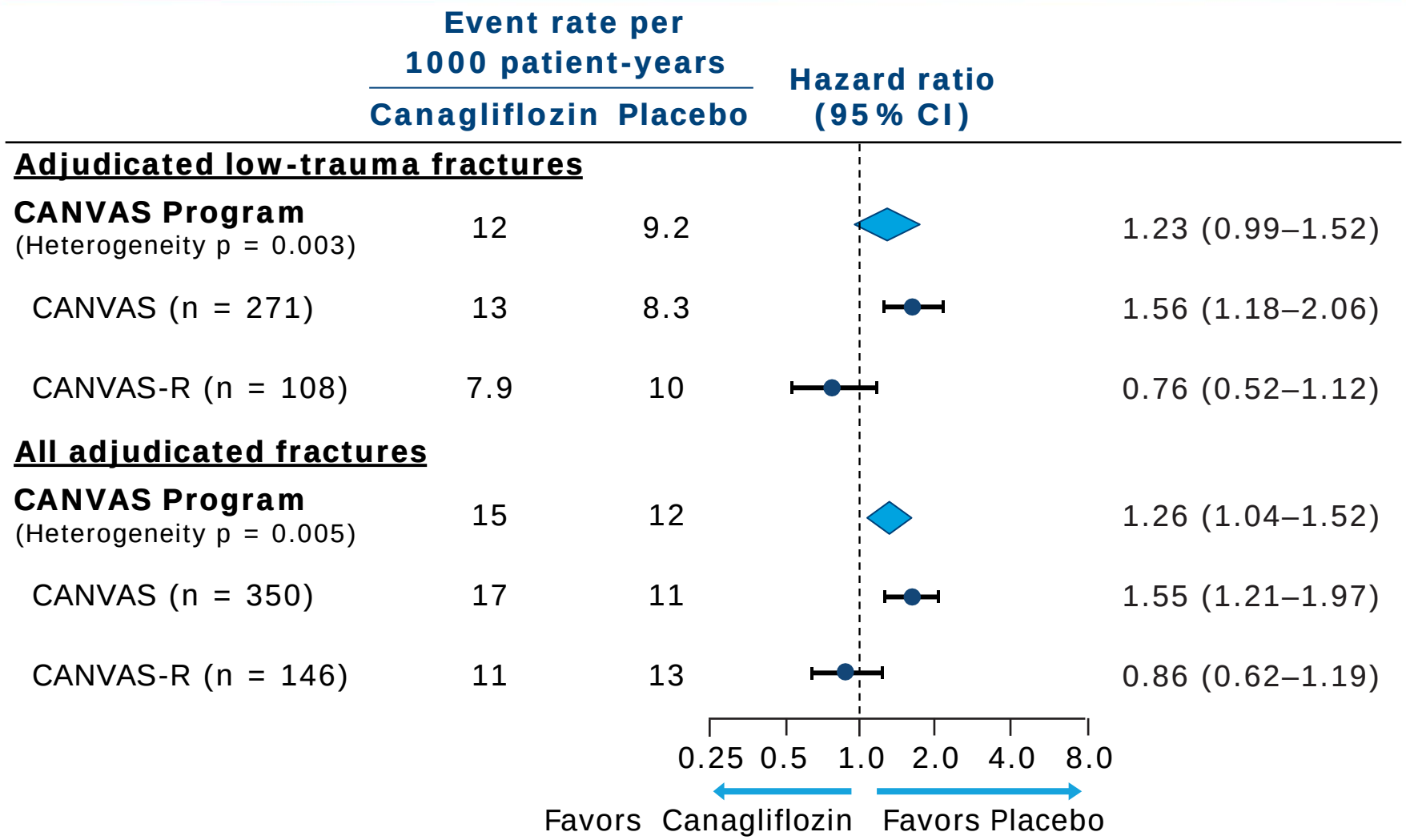
* Excludes amputations

Low-trauma Fracture



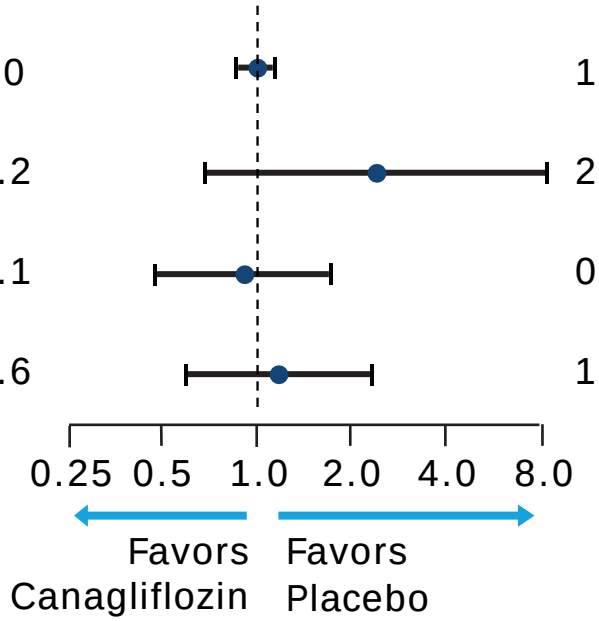
No. of patients							
Placebo	4344	4182	2987	1263	1217	1162	817
Canagliflozin	5790	5606	4376	2566	2467	2373	1692

Fractures


Event rate per 1000 patient-years
Canagliflozin
Placebo
Hazard ratio (95% CI)
Adjudicated low-trauma fractures
CANVAS Program
(Heterogeneity p = 0.003)
12
9.2
1.23 (0.99–1.52)
CANVAS (n = 271)
13
8.3
1.56 (1.18–2.06)
CANVAS-R (n = 108)
7.9
10
0.76 (0.52–1.12)
All adjudicated fractures
CANVAS Program
(Heterogeneity p = 0.005)
15
12
1.26 (1.04–1.52)
CANVAS (n = 350)
17
11
1.55 (1.21–1.97)
CANVAS-R (n = 146)
11
13
0.86 (0.62–1.19)
0.25
0.5
1.0
2.0
4.0
8.0
Favors Canagliflozin
Favors Placebo

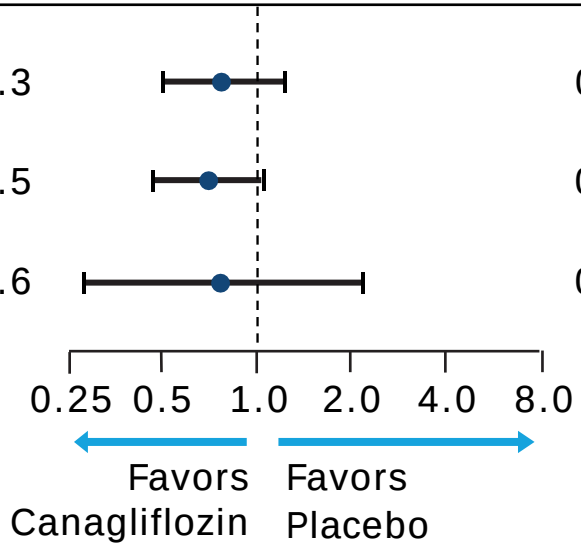
Malignancy

	Event rate per 1000 patient-years		Hazard ratio (95% CI)
	Canagliflozin	Placebo	
Neoplasms (n = 741)	21	20	1.00 (0.86-1.16)
Renal cancer (n = 17)	0.6	0.2	2.39 (0.68-8.34)
Bladder cancer (n = 38)	1.0	1.1	0.90 (0.47-1.72)
Breast cancer (n = 37)	3.1	2.6	1.17 (0.59-2.32)



Renal Safety

	Event rate per 1000 patient-years		Hazard ratio (95% CI)
	Canagliflozin	Placebo	
Serious renal-related (n = 83)	2.5	3.3	0.76 (0.49-1.19)
Serious acute kidney injury (n = 58)	1.6	2.5	0.68 (0.45-1.02)
Serious hyperkalemia (n = 15)	0.4	0.6	0.75 (0.27-2.11)



Safety Summary

Canagliflozin use was associated with:

- Newly identified increase in risk of amputation
- Possible increase in fracture risk
- Adverse event profile otherwise consistent with known effects of canagliflozin

The CANVAS Program

Implications for Clinical Practice

David R. Matthews, FRCP, DPhil

CANVAS Program

Presenter Disclosures: David R. Matthews, FRCP, DPhil

- Research support
  - Janssen
- Advisory boards
  - Novo Nordisk, GlaxoSmithKline, Novartis, Eli Lilly, Sanofi-Aventis, Janssen, Servier
- Consultant
  - Novo Nordisk, GlaxoSmithKline, Novartis, Eli Lilly, Sanofi-Aventis, Janssen, Servier
- Lectures
  - Novo Nordisk, Servier, Sanofi-Aventis, Eli Lilly, Novartis, Janssen, Aché Laboratories

What Was the Population Studied?

- T2DM ~14 years
- High CV risk
- Hypertensive
- Overweight
- Multiple comorbidities
- 2/3 with prior CV disease
- 1/3 primary prevention

What Did the Trial Assess?

- **Hard outcomes**
  - CV disease
  - Renal protection

  Trial powered for events and time

  Pre-specified
- **Biomarkers**
  - HbA_{1c}
  - Blood pressure

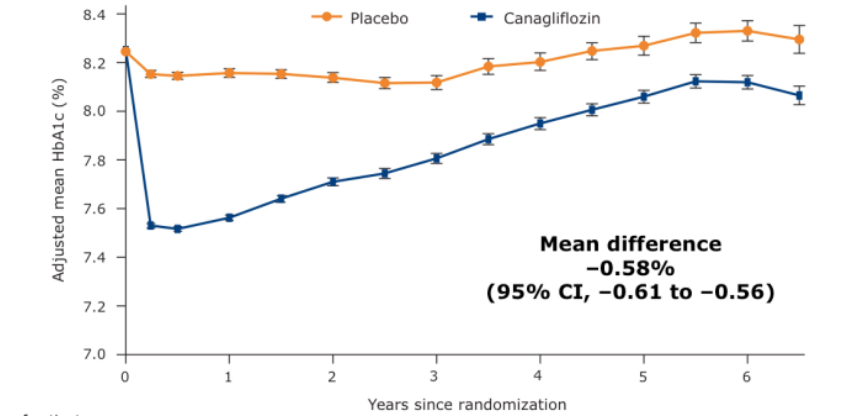
  Measures of microvascular and macrovascular risk
  - Weight

    A measure of multiple health and social risks
  - Albuminuria

    A measure of renal and CV risk
- **Safety and side effects**

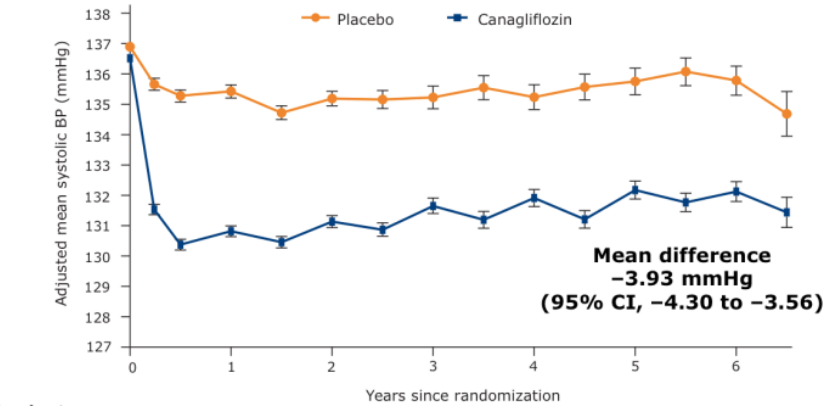
Biomarkers

Effects on HbA1c



- The CANVAS Program was not designed to maintain a glycemic difference. Even so the difference in average glycemia was -0.58%

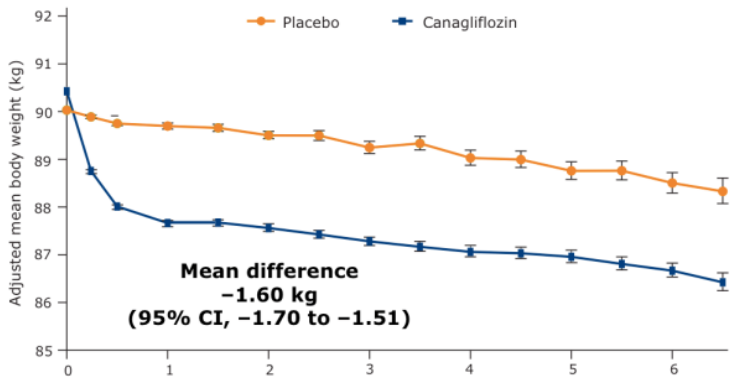
Effects on Systolic BP



- Blood pressure was 3.9 mmHg lower than in the placebo group

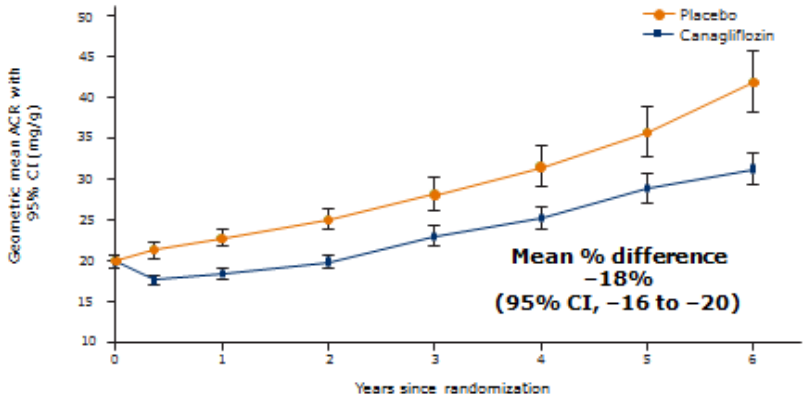
Biomarkers (cont)

Effects on Body Weight



- Body weight was 1.6 kg lower than in the placebo group

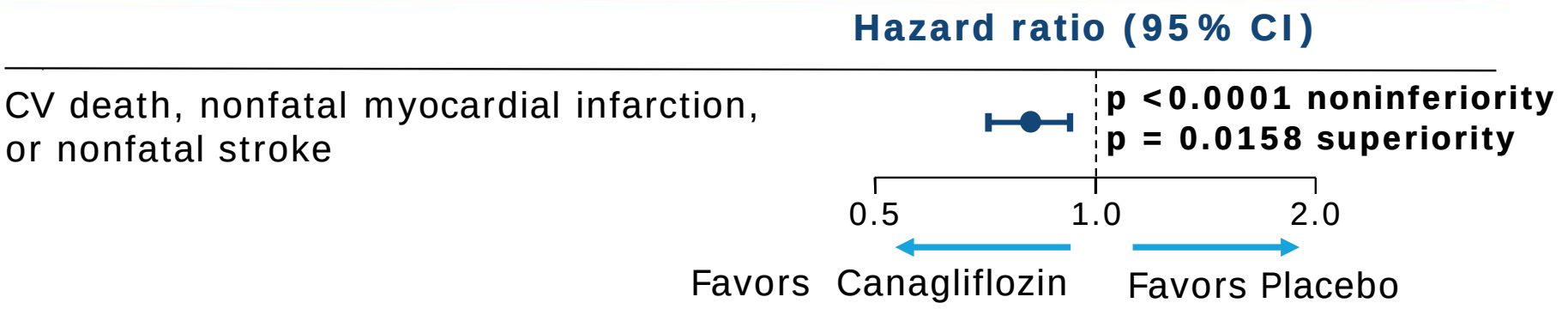
Change in Albumin:Creatinine Ratio (UACR)



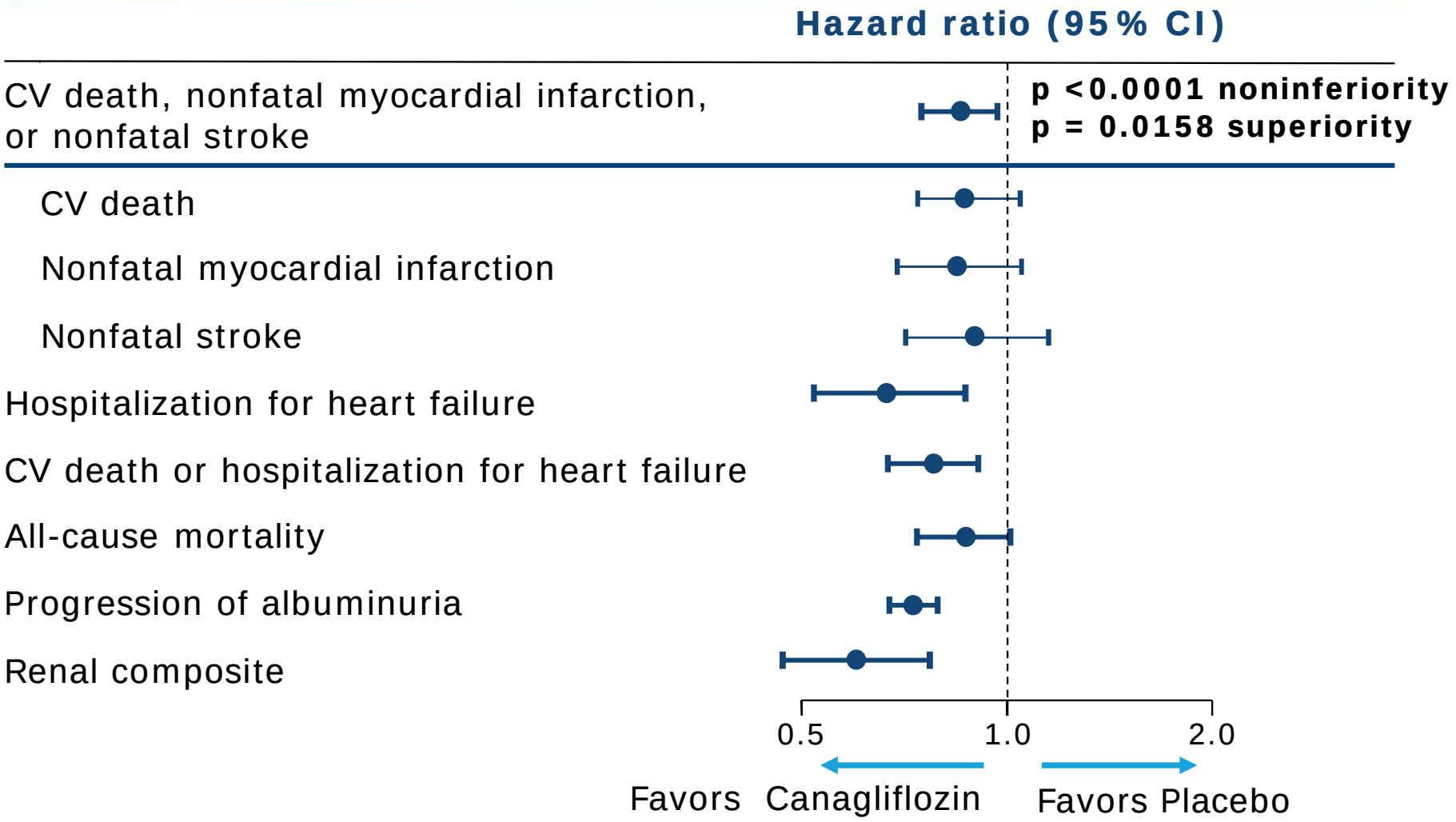
- Urinary albumin:creatinine ratio was 18% lower than in the placebo group

CANVAS Program

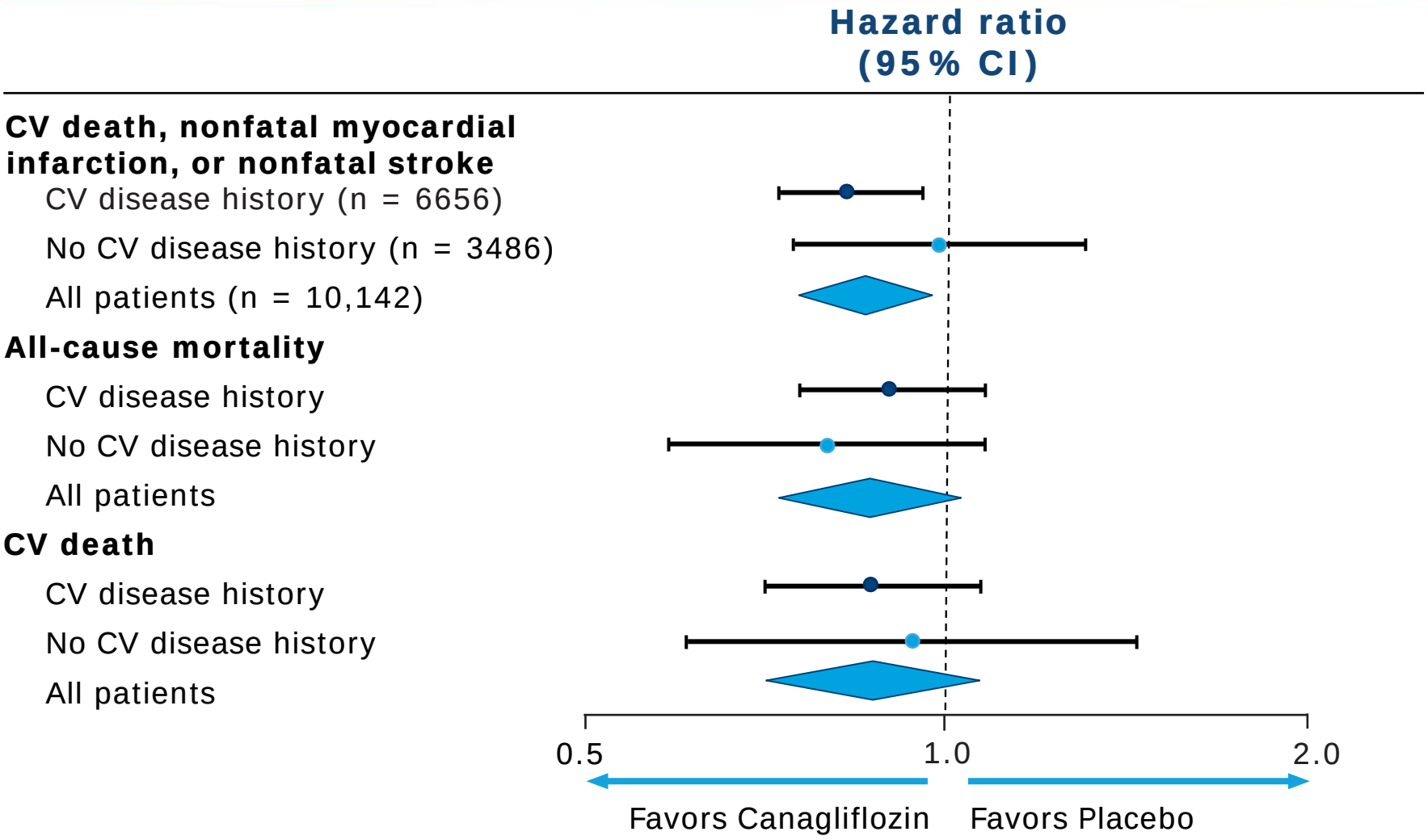
Key Efficacy Outcomes in the CANVAS Program



Key Efficacy Outcomes in the CANVAS Program



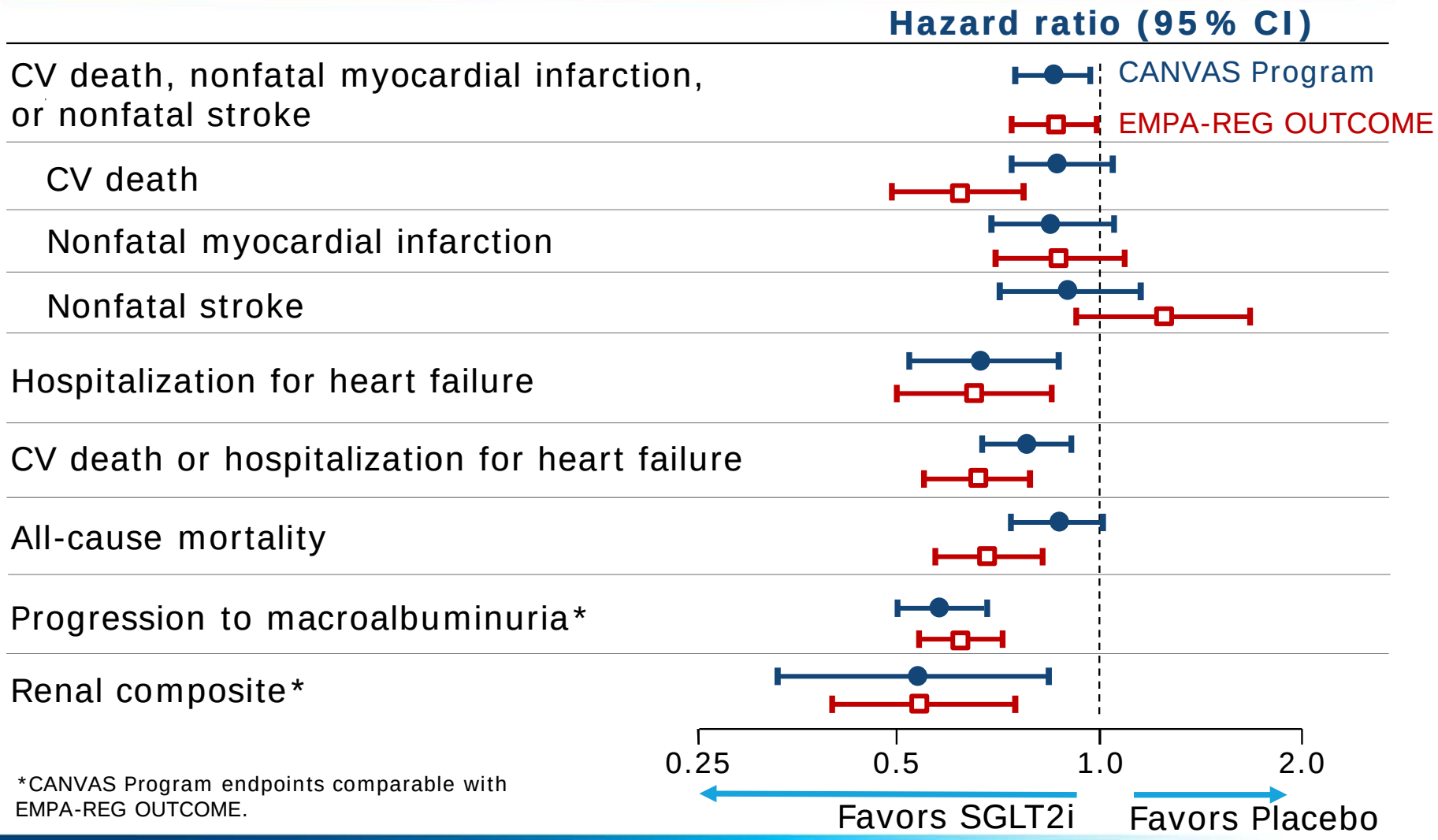
Primary and Secondary Prevention?



Comparisons Between Trials

- There is interest in interpreting these data in the context of EMPA-REG OUTCOME
- Comparisons between trials are complicated by differences in:
  - Populations
  - Trial designs
  - Analytic approaches
  - Drug effects
- Comparisons are therefore hazardous, subject to bias, and may be confounded by multiple uncontrolled factors

Key Outcomes in the CANVAS Program and EMPA-REG OUTCOME



*CANVAS Program endpoints comparable with EMPA-REG OUTCOME.

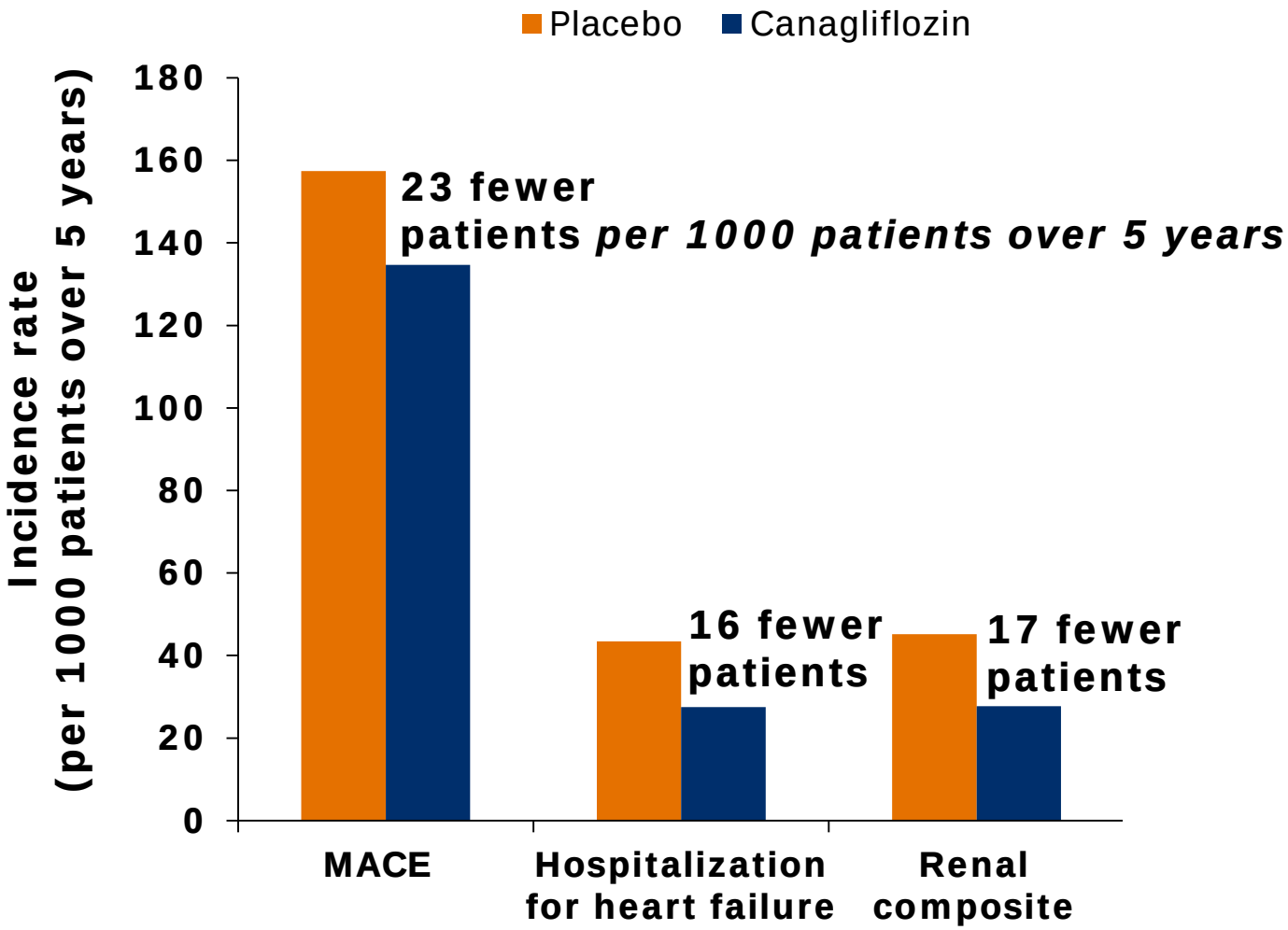
Zinman Bet al. N Engl J Med. 2015 ;373(22):2117-2128.
Wanner K et al. N Engl J Med. 2016;375(4):323-334.

CANVAS Program

Who Might Benefit?
Patients With High CV Risk

CV death, nonfatal myocardial infarction, or nonfatal stroke

Who Might Benefit?



Newly Identified Risk - Amputation

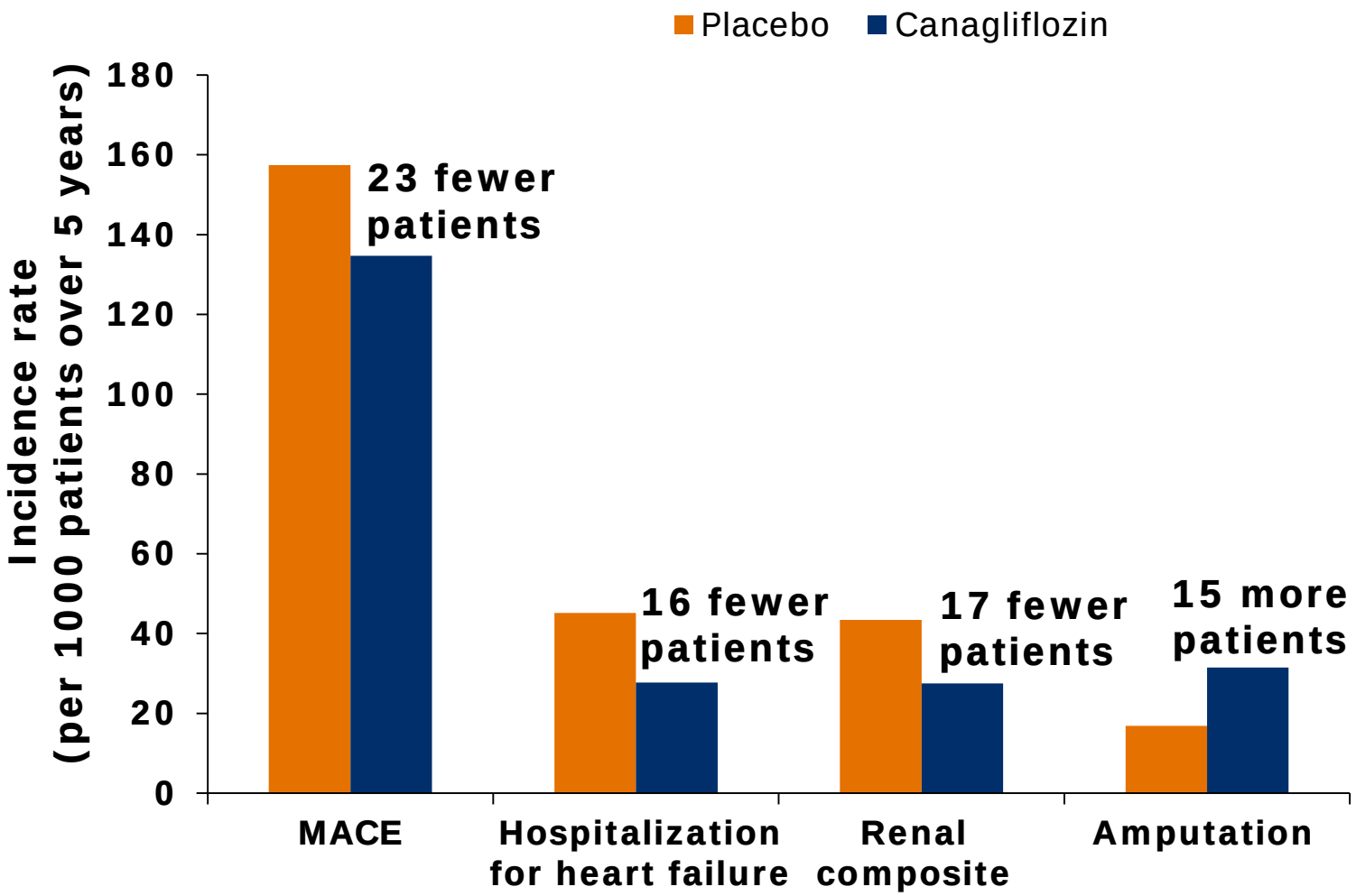
- The mechanism of increased amputation risk is unknown
- The US FDA issued a drug safety communication regarding increased risk of amputation with canagliflozin
- The European regulatory pharmacovigilance risk assessment committee (PRAC) noted that:
  - 'An *increased amputation risk has only become apparent with canagliflozin so far*
  - *One large cardiovascular outcome study (DECLARE) is still on-going for dapagliflozin*
  - *Amputation events were not been [sic] systematically captured within the completed large cardiovascular outcome study conducted with empagliflozin (EMPA-REG)*
  - *Hence, it is currently not possible to establish whether the increased amputation risk is a class effect or not'*

EMA PRAC assessment report. 9 February 2017.
http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/SGLT2_inhibitors_Canagliflozin_20/European_Commission_final_decision/WC500227102.pdf

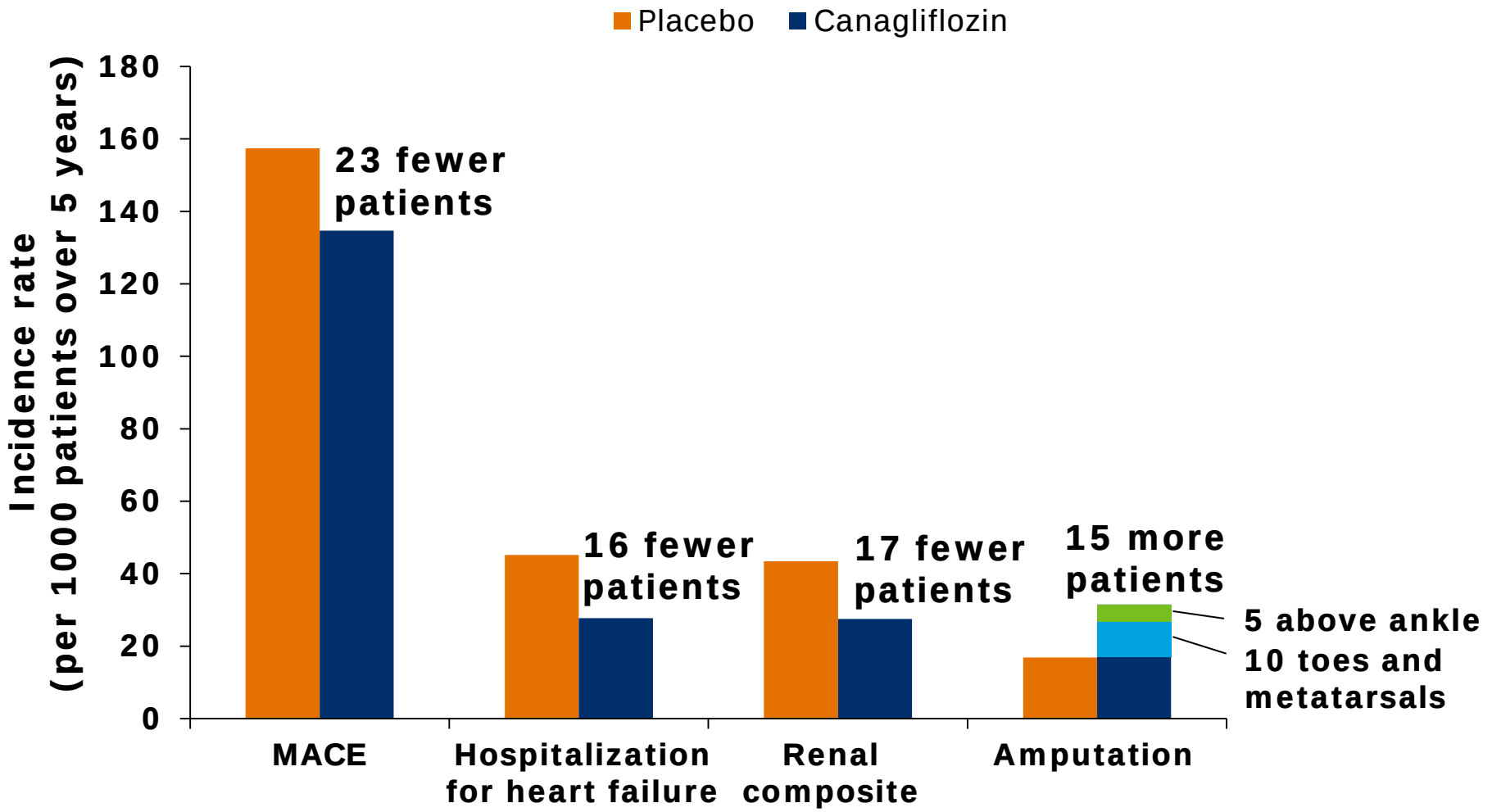
Clinical Considerations - Amputation

- Caution in patients at high risk
- Canagliflozin EU Summary of Product Characteristics (product label)
  - *'As an underlying mechanism has not been established, risk factors, apart from general risk factors, for amputation are unknown*
  - *However, as precautionary measures, consideration should be given to carefully monitoring patients with a higher risk for amputation events and counselling patients about the importance of routine preventative foot care and maintaining adequate hydration*
  - *Consideration may also be given to stopping treatment in patients that develop events preceding amputation such as lower-extremity skin ulcer, infection, osteomyelitis or gangrene'*

Benefits and Risk



Benefits and Risk



Conclusion

- The CANVAS Program met its primary objective of demonstrating the cardiovascular safety and efficacy of canagliflozin
- Canagliflozin use was associated with an increased risk of amputation which should be taken into consideration when prescribing this agent
- These data suggest a favorable benefit/risk profile with canagliflozin treatment in many patients with type 2 diabetes and high cardiovascular risk

The NEW ENGLAND JOURNAL of MEDICINE

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., and David R. Matthews, D.Phil., B.M., B.Ch., for the CANVAS Program Collaborative Group*

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International Centers – Patients and PIs

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