SCORED

Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease – The SCORED Trial

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BWH

VE RI TAS

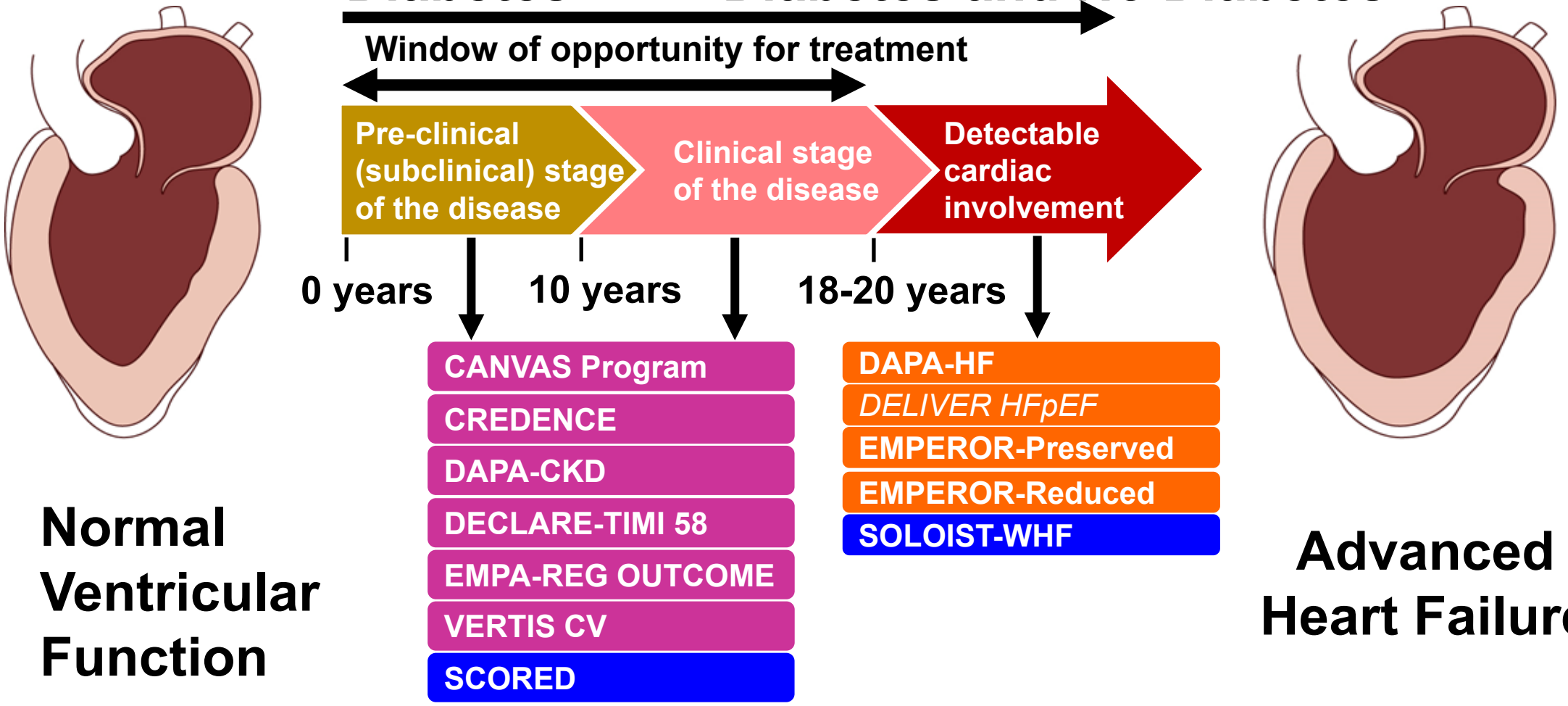
Disclosures

Dr. Bhatt discloses the following relationships - Advisory Board: Bayer, Boehringer Ingelheim, Cardax, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, Janssen, Level Ex, Medscape Cardiology, Merck, MyoKardia, NirvaMed, Novo Nordisk, PhaseBio, PLx Pharma, Regado Biosciences, Stasys; Board of Directors: Boston VA Research Institute, DRS.LINQ (stock options), Society of Cardiovascular Patient Care, TobeSoft; Chair: Inaugural Chair, American Heart Association Quality Oversight Committee; Data Monitoring Committees: Acesion Pharma, Assistance Publique-Hôpitaux de Paris, Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Boston Scientific (Chair, PEITHO trial), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Contego Medical (Chair, PERFORMANCE 2), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo; for the ABILITY-DM trial, funded by Concept Medical), Novartis, Population Health Research Institute; Rutgers University (for the NIH-funded MINT Trial); Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Chair, ACC Accreditation Oversight Committee), Arnold and Porter law firm (work related to Sanofi/Bristol-Myers Squibb clopidogrel litigation), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Canadian Medical and Surgical Knowledge Translation Research Group (clinical trial steering committees), Cowen and Company, Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), K2P (Co-Chair, interdisciplinary curriculum), Level Ex, Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Piper Sandler, Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Abbott, Afimmune, Aker Biomarine, Amarin, Amgen, **AstraZeneca**, Bayer, Beren, **Boehringer Ingelheim**, Bristol-Myers Squibb, Cardax, CellProthera, Cereno Scientific, Chiesi, CSL Behring, Eisai, Ethicon, Faraday Pharmaceuticals, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Garmin, HLS Therapeutics, Idorsia, Ironwood, Ischemix, Janssen, Javelin, **Lexicon**, **Lilly**, Medtronic, Merck, Moderna, MyoKardia, NirvaMed, Novartis, Novo Nordisk, Owkin, Pfizer, PhaseBio, PLx Pharma, Recardio, Regeneron, Reid Hoffman Foundation, Roche, **Sanofi**, Stasys, Synaptic, The Medicines Company, 89Bio; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Abbott, Biotronik, Boston Scientific, CSI, St. Jude Medical (now Abbott), Philips, Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Takeda.

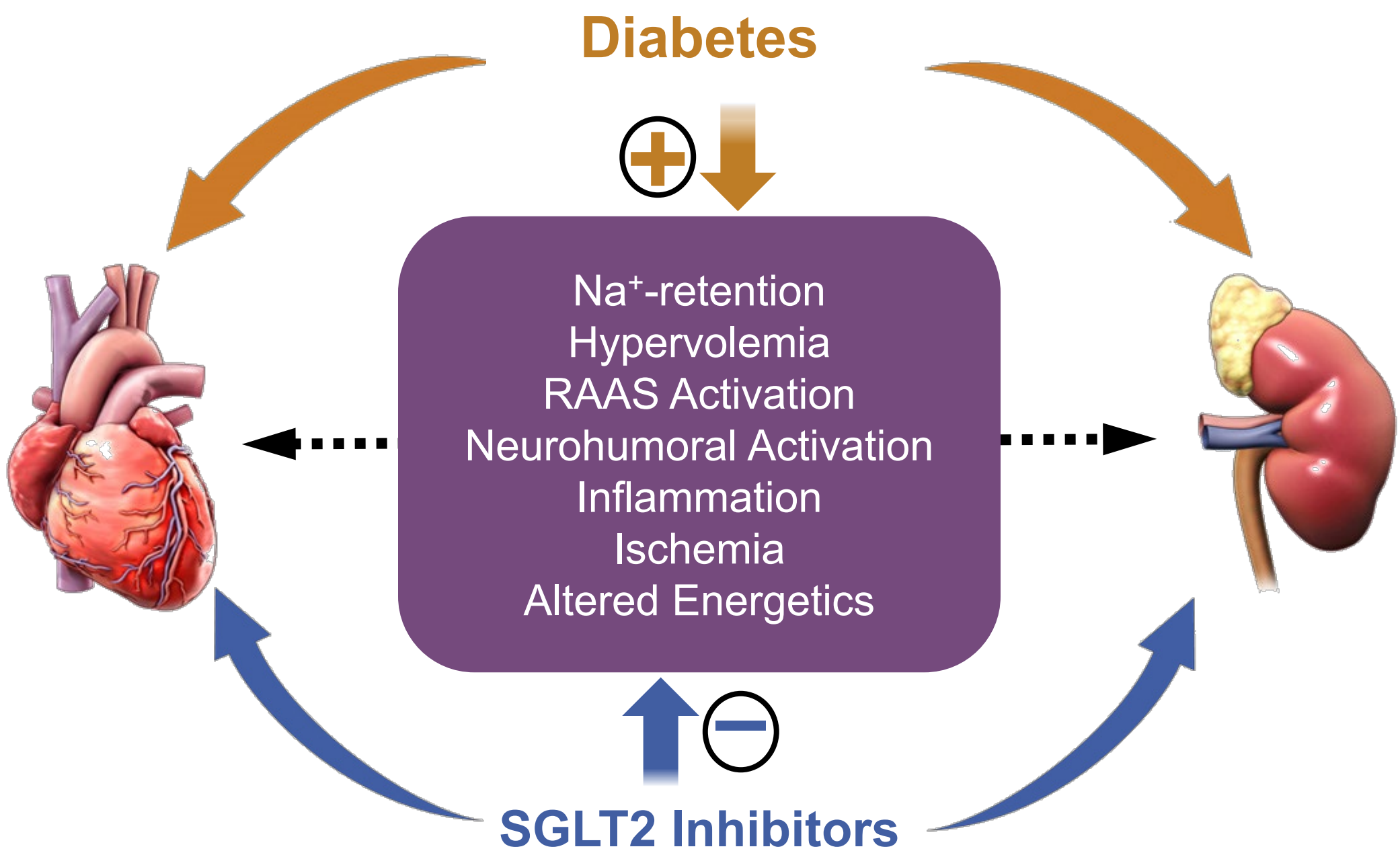
SCORED was initially sponsored by Sanofi and then by Lexicon.

This presentation includes off-label and investigational uses of drugs.

The Evolution of SGLT2i in Heart Failure Management

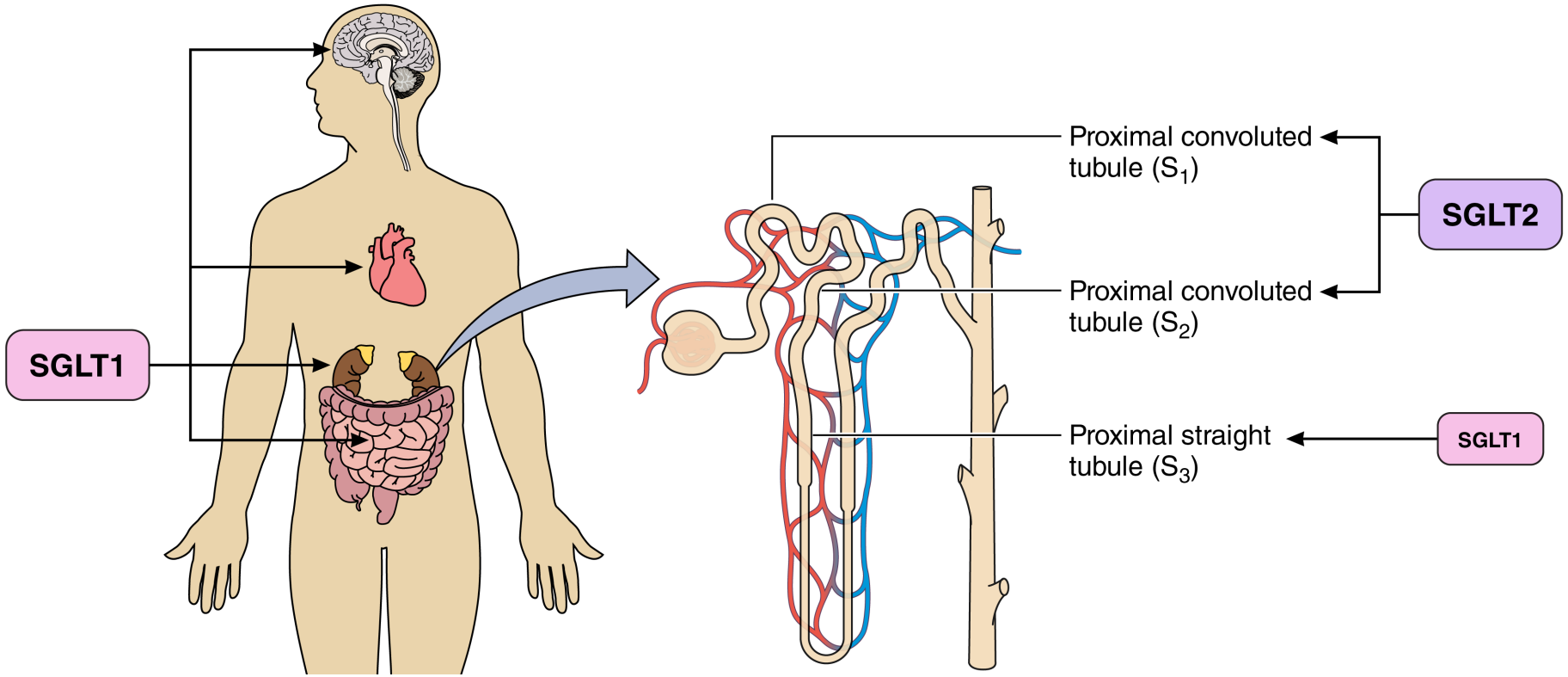


Adapted from Bhatt DL, Verma S, Braunwald E. *Cell Metabolism*. 2019;30:847-849.



Connelly KA, Bhatt DL, Verma S. *Cell Metabolism*. 2018;28:813-815.

Sotagliflozin: Dual SGLT1 and SGLT2 Inhibitor



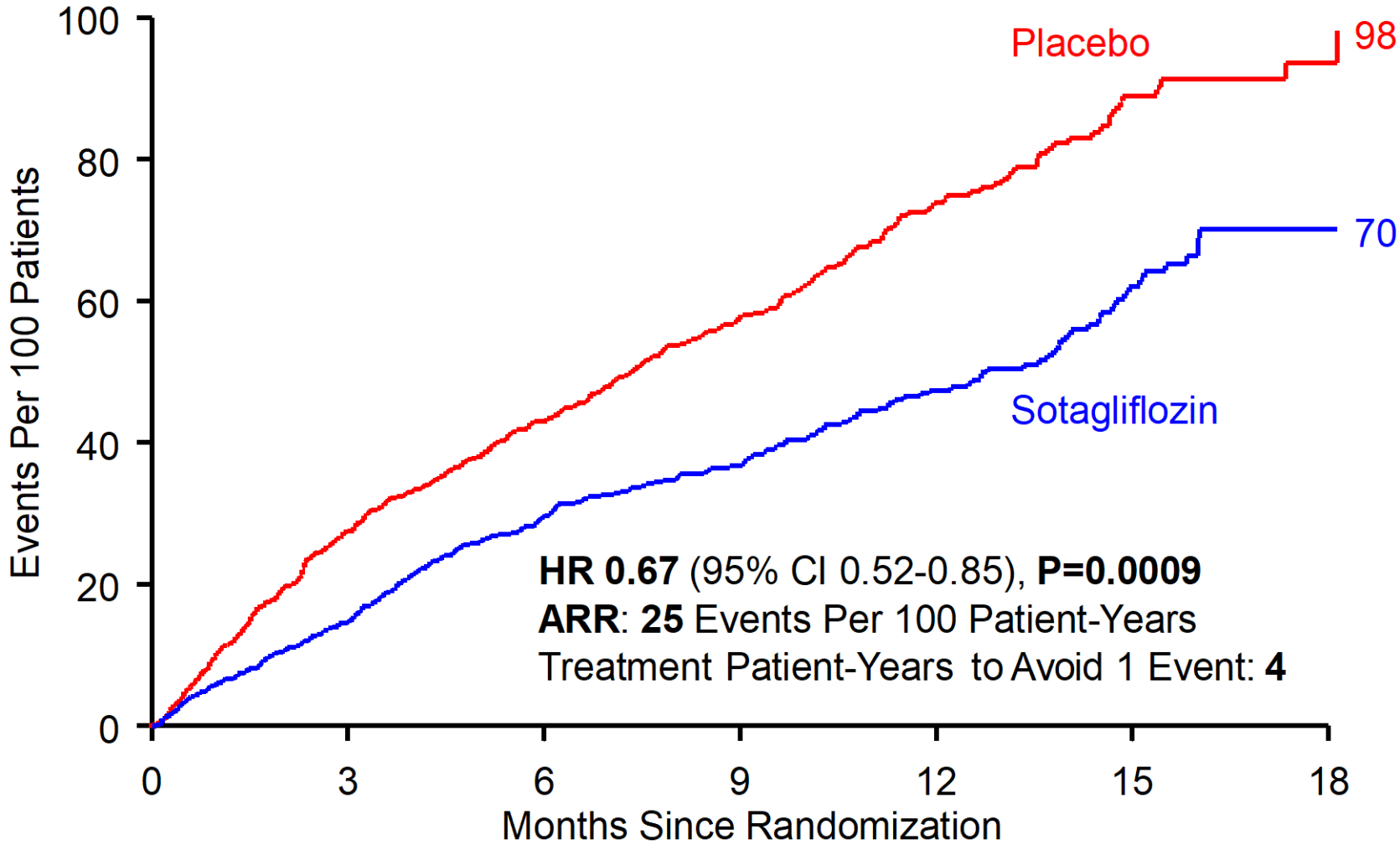
- **SGLT1** is the primary transporter for absorption of glucose and galactose in the GI tract
- Pharmacologic inhibition by sotagliflozin is independent of insulin and does not depend on kidney function
- Potential reduction in atherosclerotic risks

- **SGLT2** is expressed in the kidney, where it reabsorbs 90% of filtered glucose
- Pharmacologic inhibition by sotagliflozin is independent of insulin but requires kidney function

Pitt B, Bhatt DL. *Circulation*. 2021;144:4-6.

Primary Efficacy: Total CV Death, HHF, and Urgent HF Visit

SOLOIST

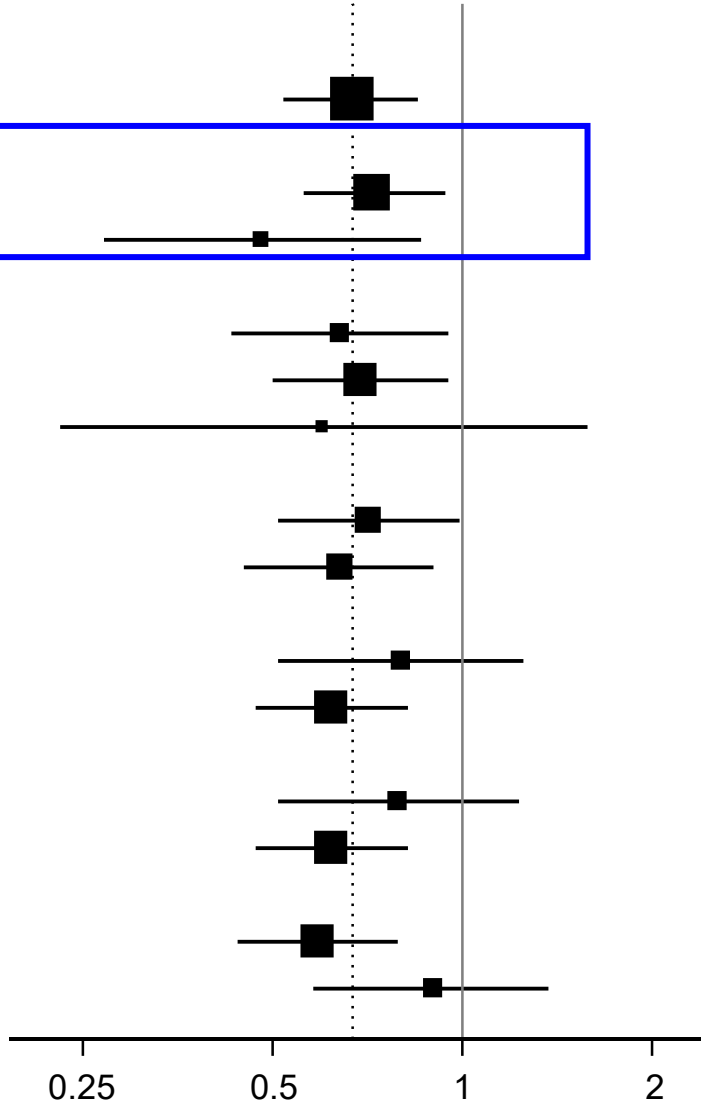


Bhatt DL, Szarek M, Steg PG, et al., and Pitt B. *N Engl J Med.* 2021;384:117-28. Bhatt DL. AHA 2020, virtual.

Primary Efficacy Subgroups

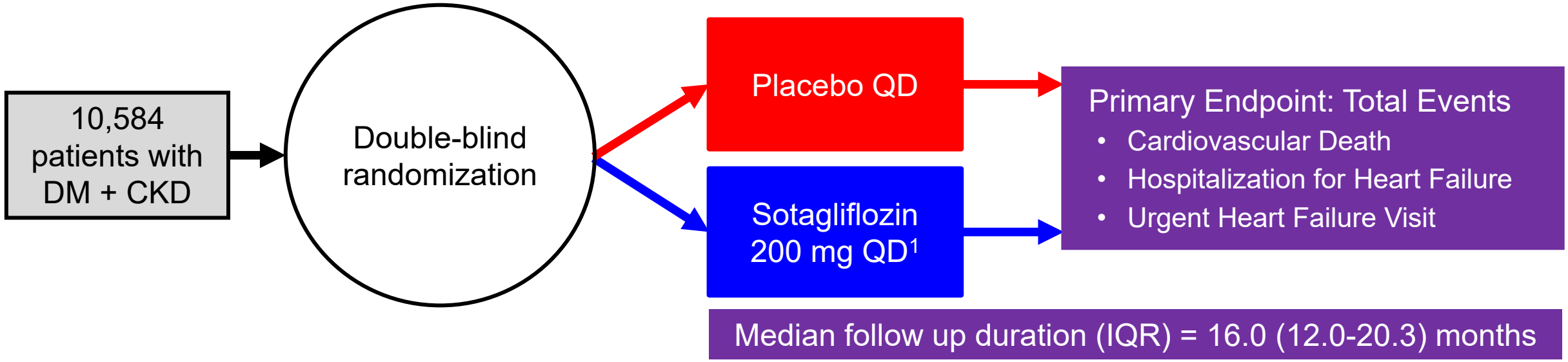
SOLOIST

Subgroup	Patients	Events Per 100 py: Sotagliflozin	Events Per 100 py: Placebo	HR (95% CI)
Overall	1222	51.0	76.3	0.67 (0.52, 0.85)
LVEF (%)				
< 50	966	56.9	79.9	0.72 (0.56, 0.94)
≥ 50	256	30.6	64.0	0.48 (0.27, 0.86)
Geographic Region				
Americas	346	68.3	103.0	0.64 (0.43, 0.95)
Europe	800	44.1	64.7	0.69 (0.50, 0.95)
Rest of World	76	48.4	78.3	0.60 (0.23, 1.58)
First Study Drug Dose				
Before Discharge	596	52.1	76.6	0.71 (0.51, 0.99)
After Discharge	626	50.0	76.1	0.64 (0.45, 0.90)
Sex				
Female	412	41.9	52.0	0.80 (0.51, 1.25)
Male	810	55.7	89.3	0.62 (0.47, 0.82)
Age (years)				
< 65	364	57.1	71.1	0.79 (0.51, 1.23)
≥ 65	858	48.0	78.5	0.62 (0.47, 0.82)
eGFR (ml/min/1.73m2)				
< 60	854	50.1	85.8	0.59 (0.44, 0.79)
≥ 60	368	53.1	58.1	0.90 (0.58, 1.37)



Bhatt DL, Szarek M, Steg PG, et al., and Pitt B. *N Engl J Med.* 2021. Bhatt DL. AHA 2020, virtual.

SCORED Trial Design



Key inclusion criteria:

- Type 2 diabetes with HbA1c ≥ 7%
- eGFR 25-60 mL/min/1.73m^2
  - with no requirement for macro- or micro-albuminuria
- CV risk factors

Key exclusion criteria:

- Planned start of SGLT2 inhibitor

Bhatt DL, Szarek M, Pitt B, et al., and Steg PG. *N Engl J Med.* 2021. Bhatt DL. AHA 2020, virtual.

[1]Goal of dose increase to 400 mg QD

Primary Efficacy: Total CV Death, HHF, and Urgent HF Visit

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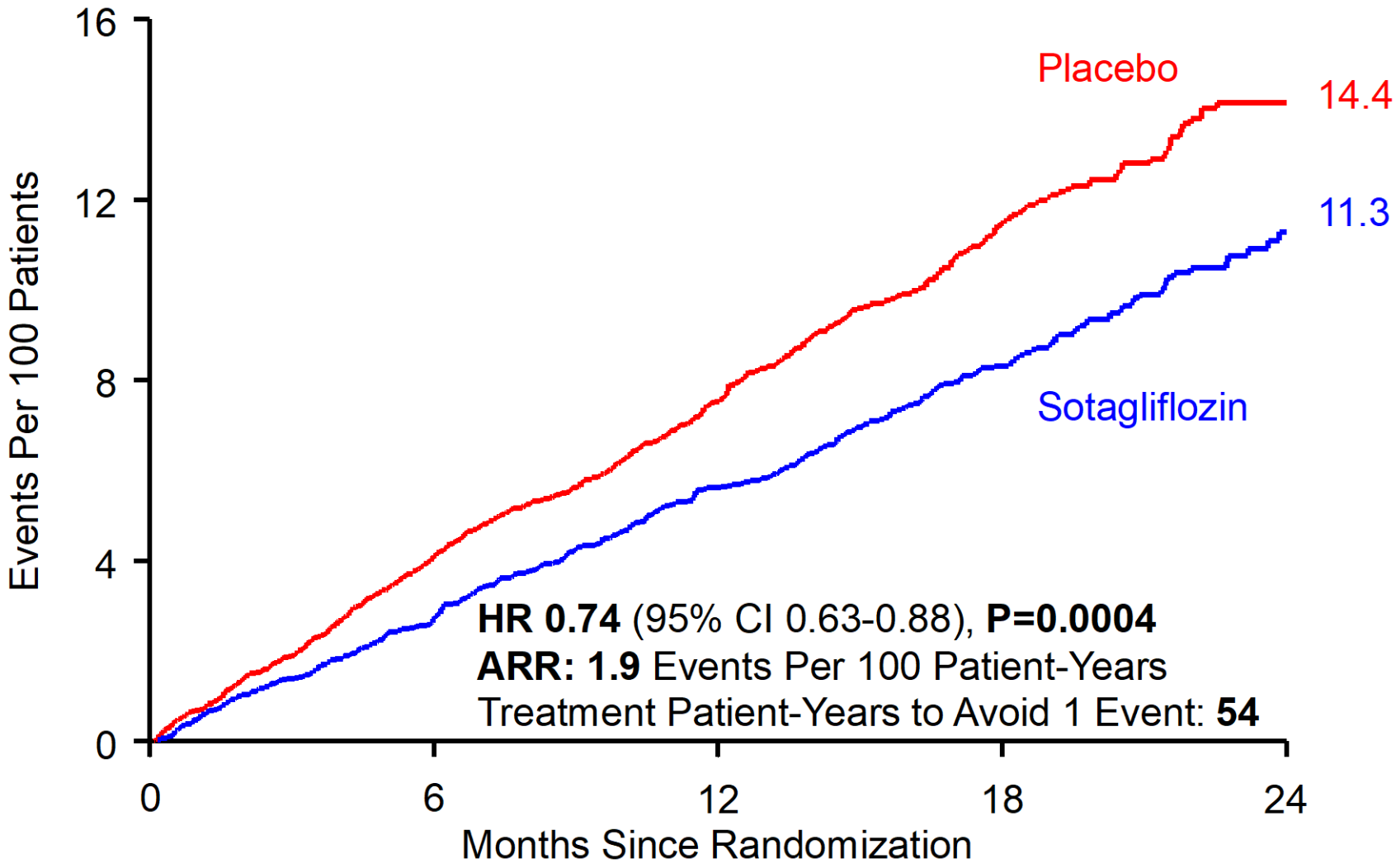

Bhatt DL, Szarek M, Steg PG, et al., and Pitt B. *N Engl J Med.* 2021;384:129-39. Bhatt DL. AHA 2020, virtual.

Total CV Death, Non-Fatal MI, or Non-Fatal Stroke

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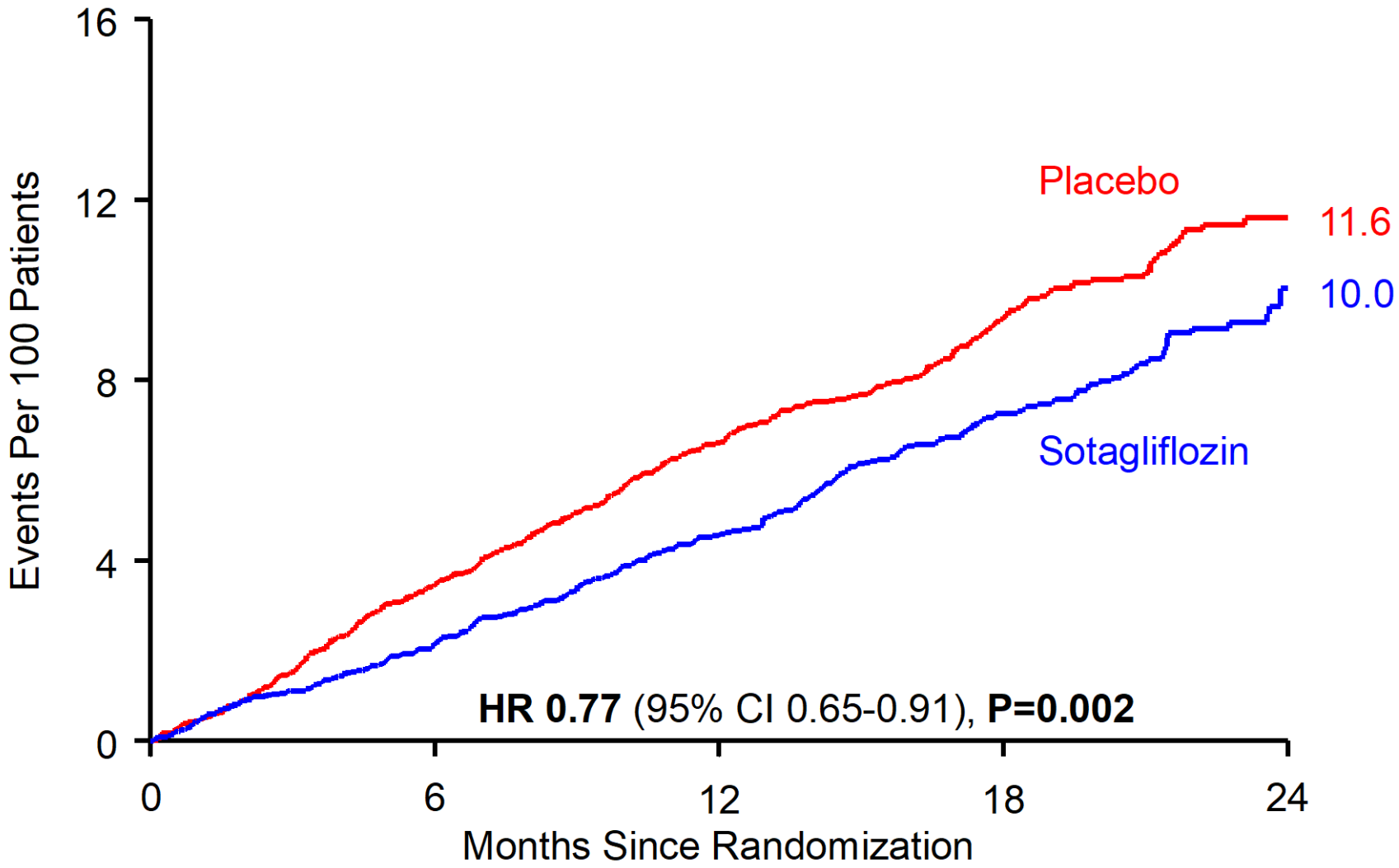

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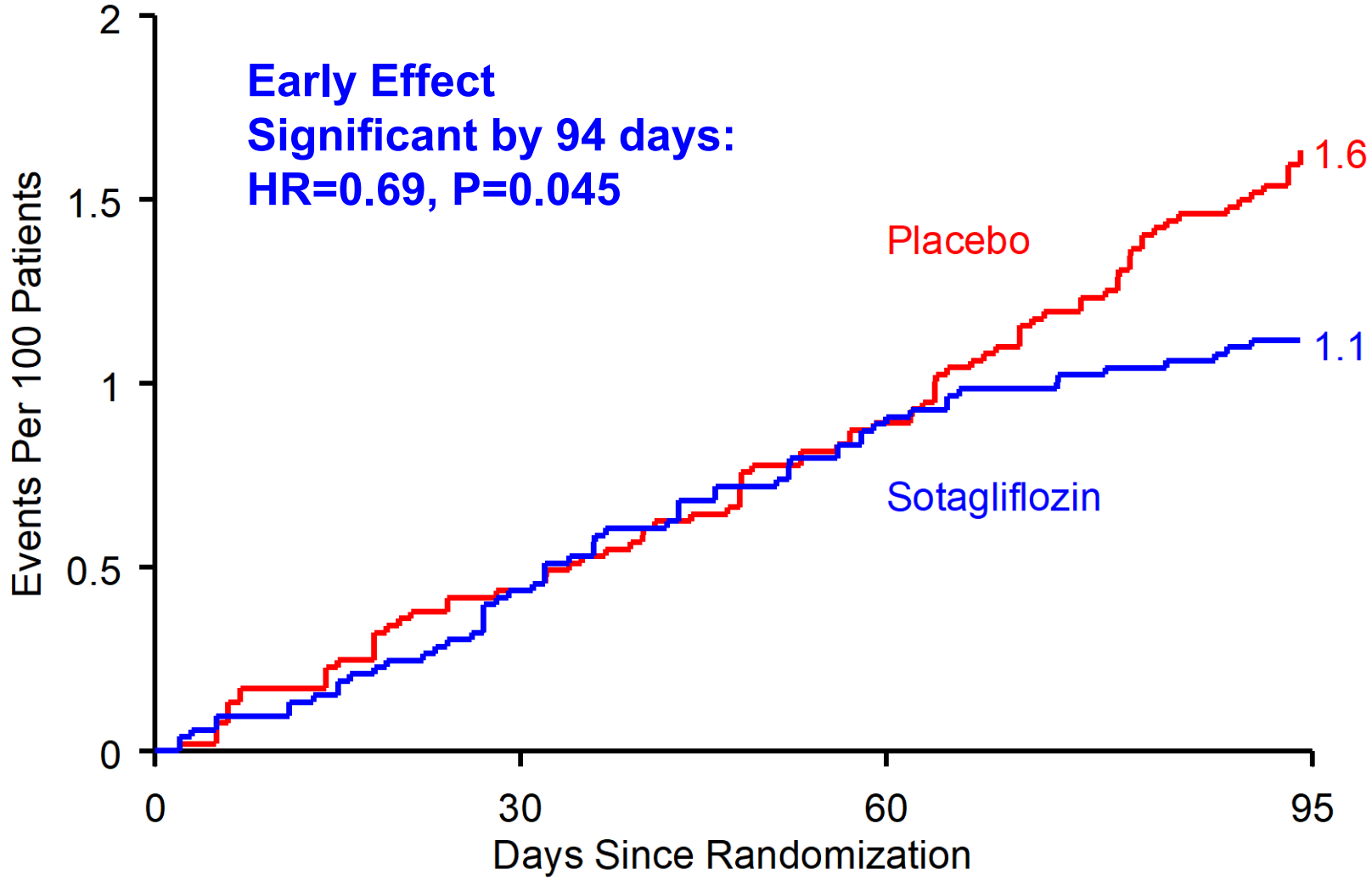

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Total CV Death, Non-Fatal MI, or Non-Fatal Stroke

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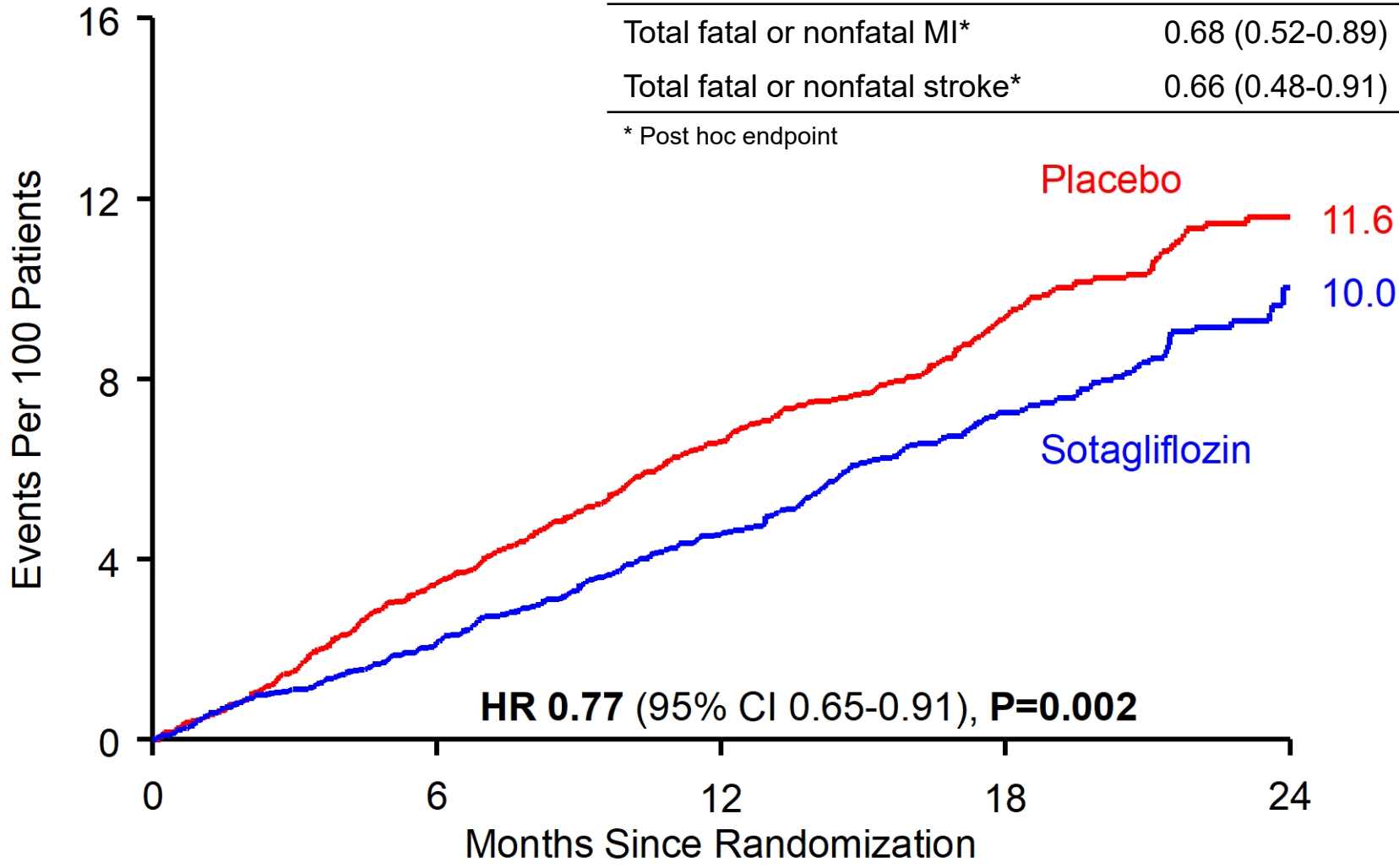
Endpoint	HR (95% CI)	P-value
Total fatal or nonfatal MI*	0.68 (0.52-0.89)	0.004
Total fatal or nonfatal stroke*	0.66 (0.48-0.91)	0.012

* Post hoc endpoint



Bhatt DL, Szarek M, Steg PG, et al., and Pitt B. *N Engl J Med.* 2021;384:129-39. Bhatt DL. AHA 2020, virtual.

History of Cardiovascular Disease (CVD) Subgroup Analyses

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Subgroups

1. History of cardiovascular disease at baseline (N=5144 patients)
2. No history of cardiovascular disease at baseline (N=5440 patients)

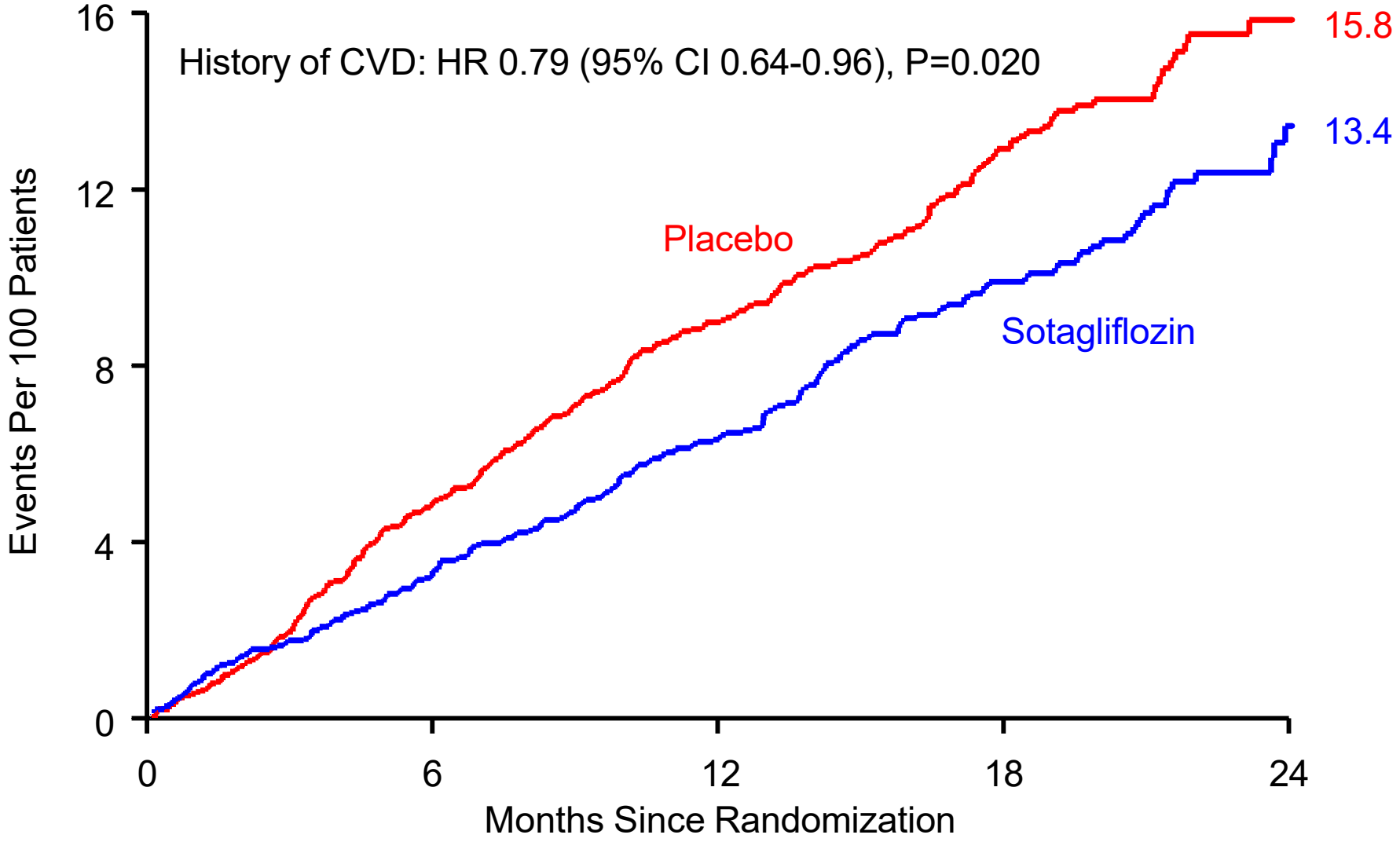
The prespecified definition of history of CVD included prior myocardial infarction, prior stroke, coronary revascularization, and peripheral vascular disease; (multiple *post hoc* sensitivity analyses yielded similar results)

Endpoints

1. Total MACE (first and recurrent events)
2. Total MI (fatal and non-fatal MI)
3. Total stroke (fatal and non-fatal stroke)

Bhatt DL, Szarek M, Pitt B, et al., and Steg PG. ACC 2022.

Total CV Death, Non-Fatal MI, or Non-Fatal Stroke by CVD Subgroup



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Total CV Death, Non-Fatal MI, or Non-Fatal Stroke by CVD Subgroup

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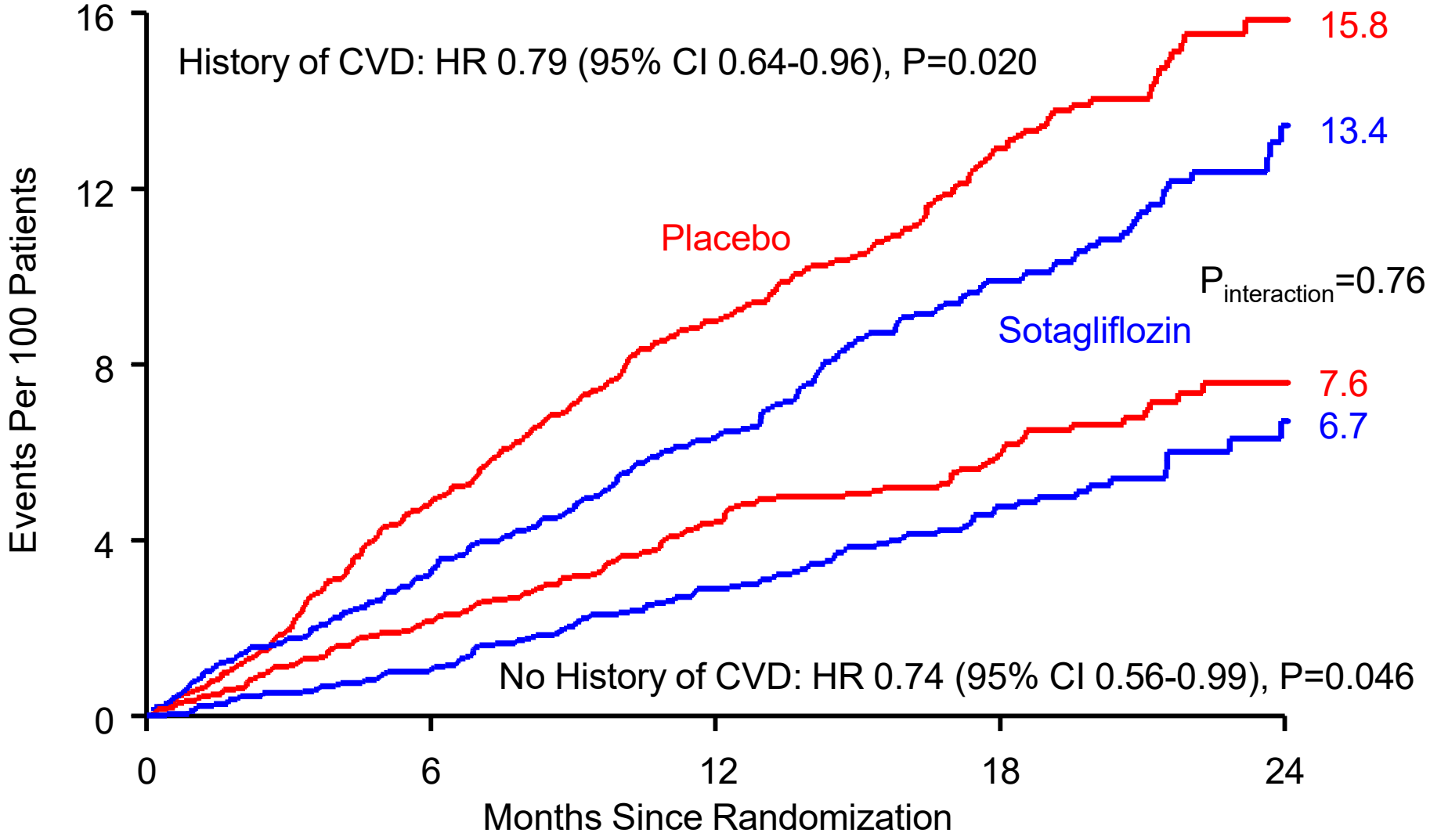

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Total MI by CVD Subgroup

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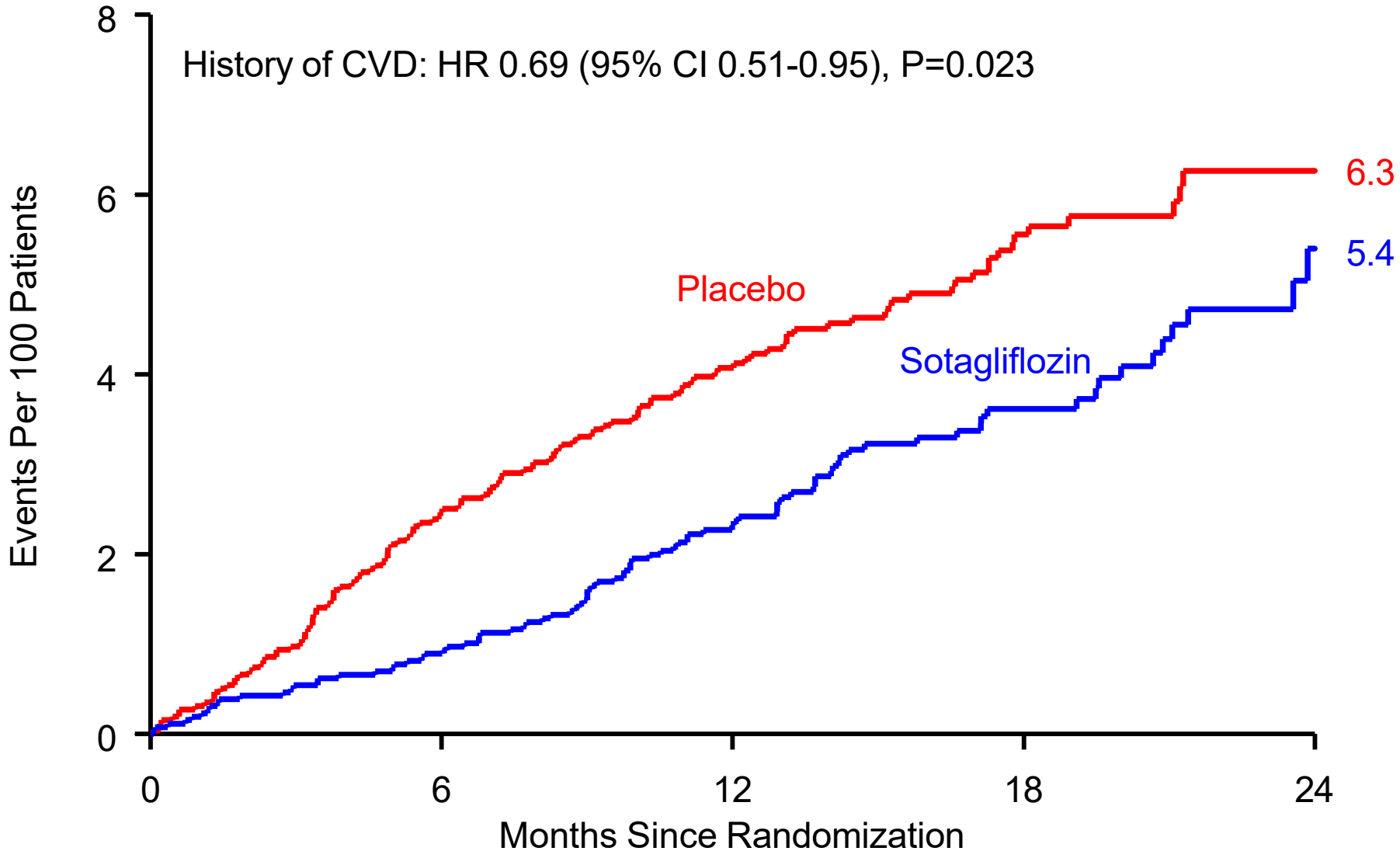

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Total MI by CVD Subgroup

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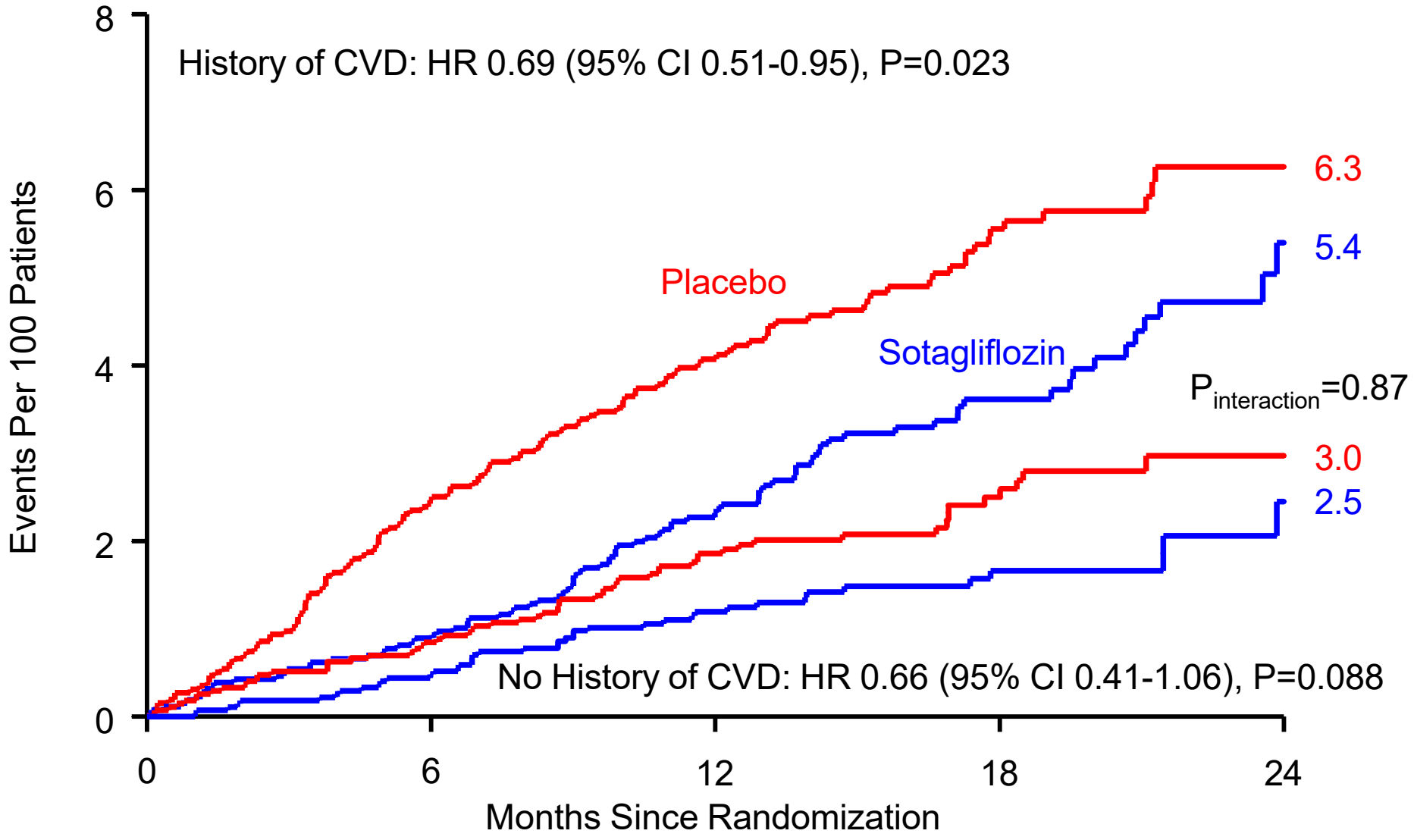

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Total Stroke by CVD Subgroup

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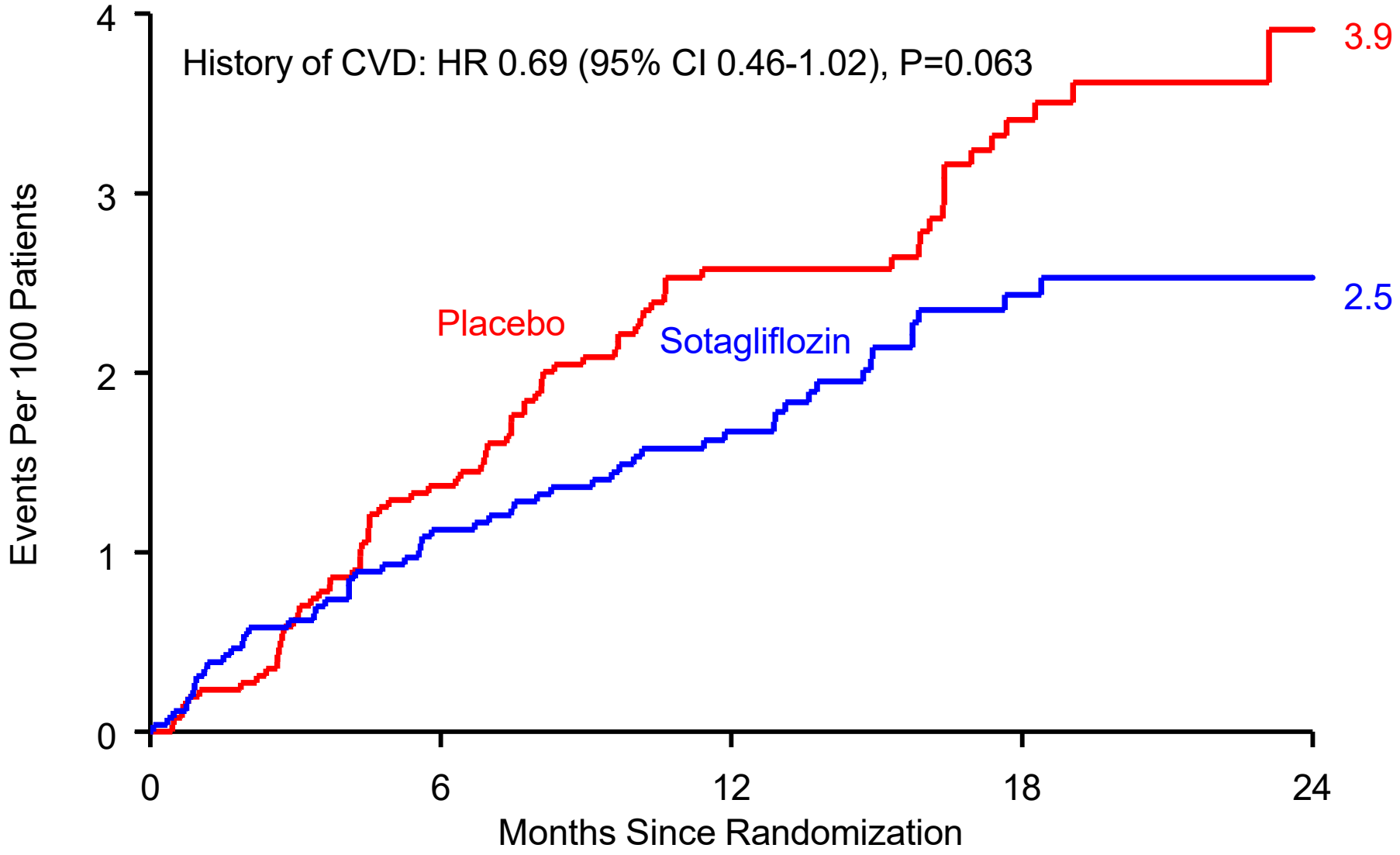

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Total Stroke by CVD Subgroup

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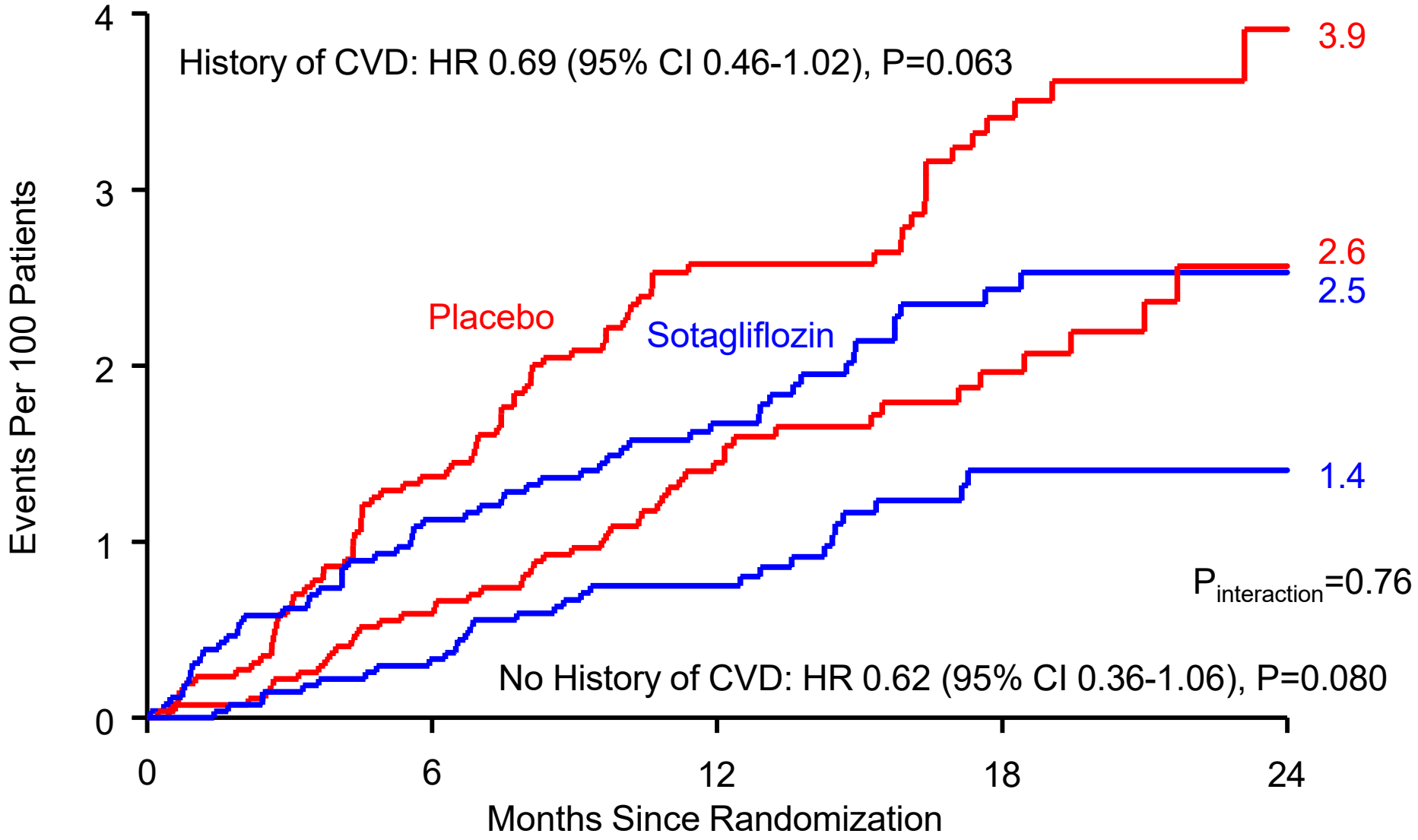

Bhatt DL, Szarek M, Pitt B, and Steg PG. ACC 2022.

Consistent Benefit on MACE Across Vascular Beds

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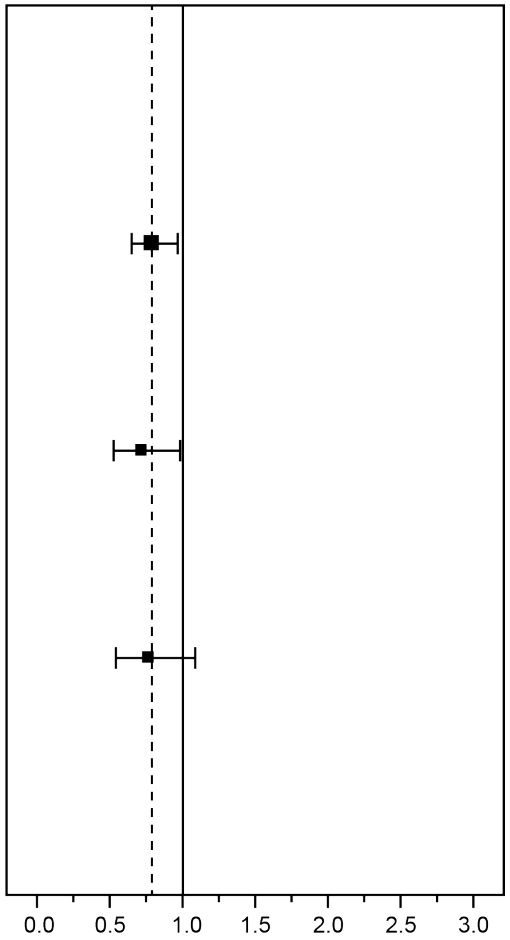
Subgroup	N	Events Per 100 py: Sotagliflozin	Events Per 100 py: Placebo	HR (95% CI)	p-value
Coronary Artery Disease	4943	6.13	7.77	0.79 (0.65, 0.97)	0.022
Cerebrovascular Disease	1777	7.03	9.54	0.72 (0.53, 0.99)	0.042
Peripheral Artery Disease	1393	6.76	9.50	0.77 (0.54, 1.09)	0.140

$P_{interaction}$=NS for all comparisons



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Adverse Events of Special Interest

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Composite Term	Sotagliflozin N=5291 n (%)	Placebo N=5286 n (%)	P-value
Urinary tract infections	610 (11.5)	585 (11.1)	0.45
Diarrhea	448 (8.5)	315 (6.0)	<0.0001*
Volume depletion	278 (5.3)	213 (4.0)	0.003*
Bone fractures	111 (2.1)	117 (2.2)	0.68
Genital mycotic infections	125 (2.4)	45 (0.9)	<0.0001*
Severe hypoglycemia	53 (1.0)	55 (1.0)	0.84
Malignancies	47 (0.9)	42 (0.8)	0.60
Venous thrombotic events	31 (0.6)	37 (0.7)	0.46
Adverse event leading to amputation	32 (0.6)	33 (0.6)	0.89
Diabetic ketoacidosis	30 (0.6)	14 (0.3)	0.022*
Pancreatitis	12 (0.2)	20 (0.4)	0.16

*Proportions considered serious were similar between groups, and adverse events generally did not lead to treatment discontinuation

Bhatt DL, et al. *N Engl J Med.* 2021;384:129-39.

Meta-analysis of MACE Across Sotagliflozin Trials (N>20,000)

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Study Cohort	Sotagliflozin	Placebo	HR (95% CI)
SCORED (N = 10,584) Total events (rate/100 PY)*	N = 5,292 343 (4.8)	N = 5,292 442 (6.3)	0.77 (0.65, 0.91)
SOLOIST (N = 1,222) Total events (rate/100 PY)*	N = 608 83 (17.4)	N = 614 80 (17.2)	0.99 (0.72, 1.37)
Core Phase 3 T2DM (N = 5,100) Total events (rate/100 PY)**	N = 2,904 55 (1.6)	N = 2,196 50 (2.1)	0.63 (0.42, 0.94)
Core Phase 3 T1DM, Phase 2 T2DM (N = 3,386) Total events (rate/100 PY)**	N = 1,998 9 (0.69)	N = 1,388 8 (0.87)	0.68 (0.25, 1.82)
Meta-analysis results (N=20,292)			**0.79 (0.68, 0.90)**

*Investigator-reported events; **Adjudicated events

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Limitations

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Trial was stopped early

- Shortened duration limited the statistical power to see significant reductions in CV death
- Limited the magnitude of absolute risk reductions in MACE

Investigator-reported events were used instead of adjudication

- Double-blind trial, with no reason to expect bias
- Results were generally concordant

Bhatt DL, Szarek M, Steg PG, et al., and Pitt B. *N Engl J Med.* 2021;384:129-39. Bhatt DL. AHA 2020, virtual.

Conclusions

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In patients with diabetes and chronic kidney disease, **sotagliflozin** significantly reduced the composite of total CV deaths, hospitalizations for HF, and urgent HF visits by **26%**

- With a very early benefit that was **significant by ~3 months**

Total CV deaths, MIs, and strokes were reduced by **23%**, potentially due to the SGLT1 effect of **sotagliflozin** **on MI and also stroke; this effect was significant by ~ 3 months**

MACE benefits were consistent across subgroups, including:

- **Prior coronary, cerebral, or peripheral artery disease**
- **And even without established cardiovascular disease**

Bhatt DL, Szarek M, Pitt B, et al., and Steg PG. ACC 2022.

BRIGHAM AND WOMEN'S HOSPITAL

Heart & Vascular Center

Thank You!

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