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

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BWH

VE RI TAS

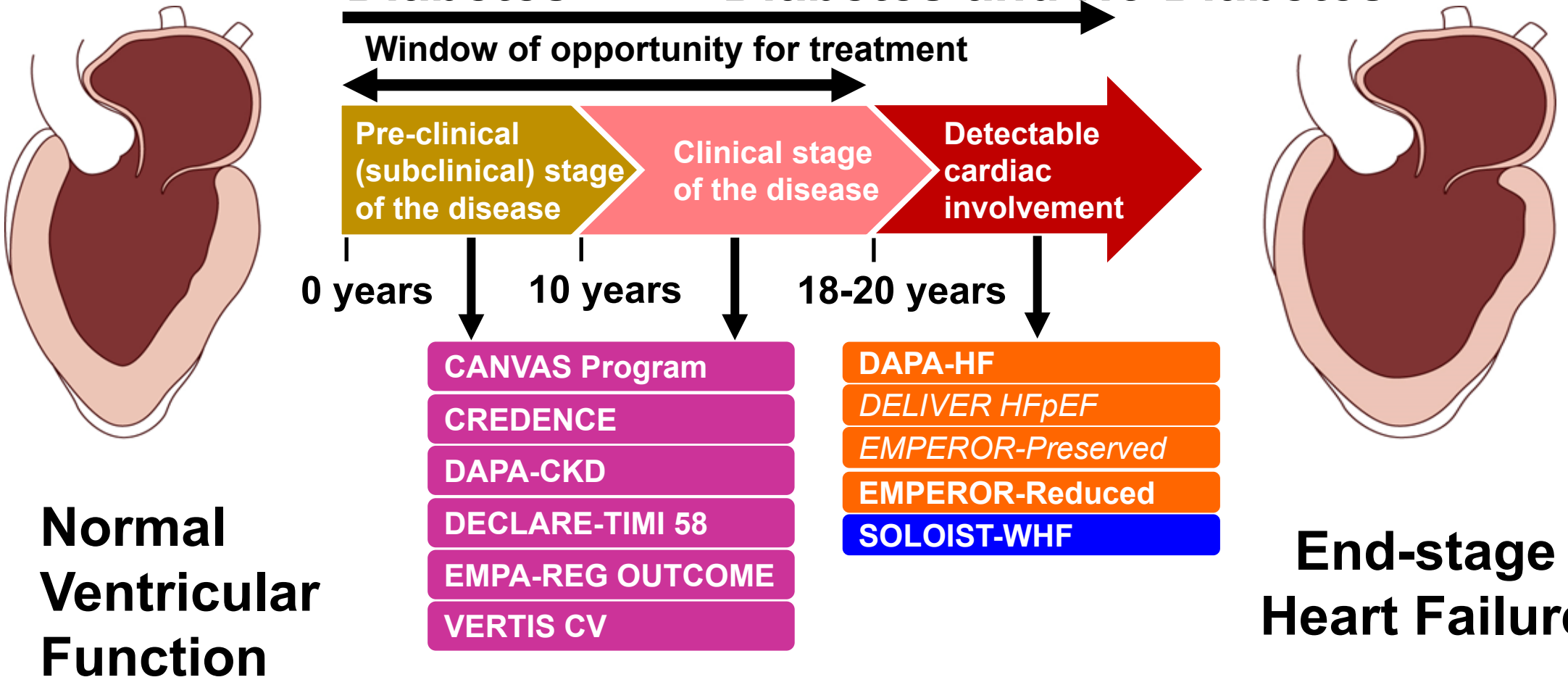
Disclosures

Dr. Deepak L. Bhatt discloses the following relationships - Advisory Board: Cardax, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, Level Ex, Medscape Cardiology, MyoKardia, PhaseBio, PLx Pharma, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), 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), Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), 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), 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, 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, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Cardax, Chiesi, CSL Behring, Eisai, Ethicon, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Idorsia, Ironwood, Ischemix, **Lexicon**, Lilly, Medtronic, MyoKardia, Pfizer, PhaseBio, PLx Pharma, Regeneron, Roche, **Sanofi**, Synaptic, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, CSI, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, Novo Nordisk, Takeda.

SCORED was initially sponsored by Sanofi and then by Lexicon.

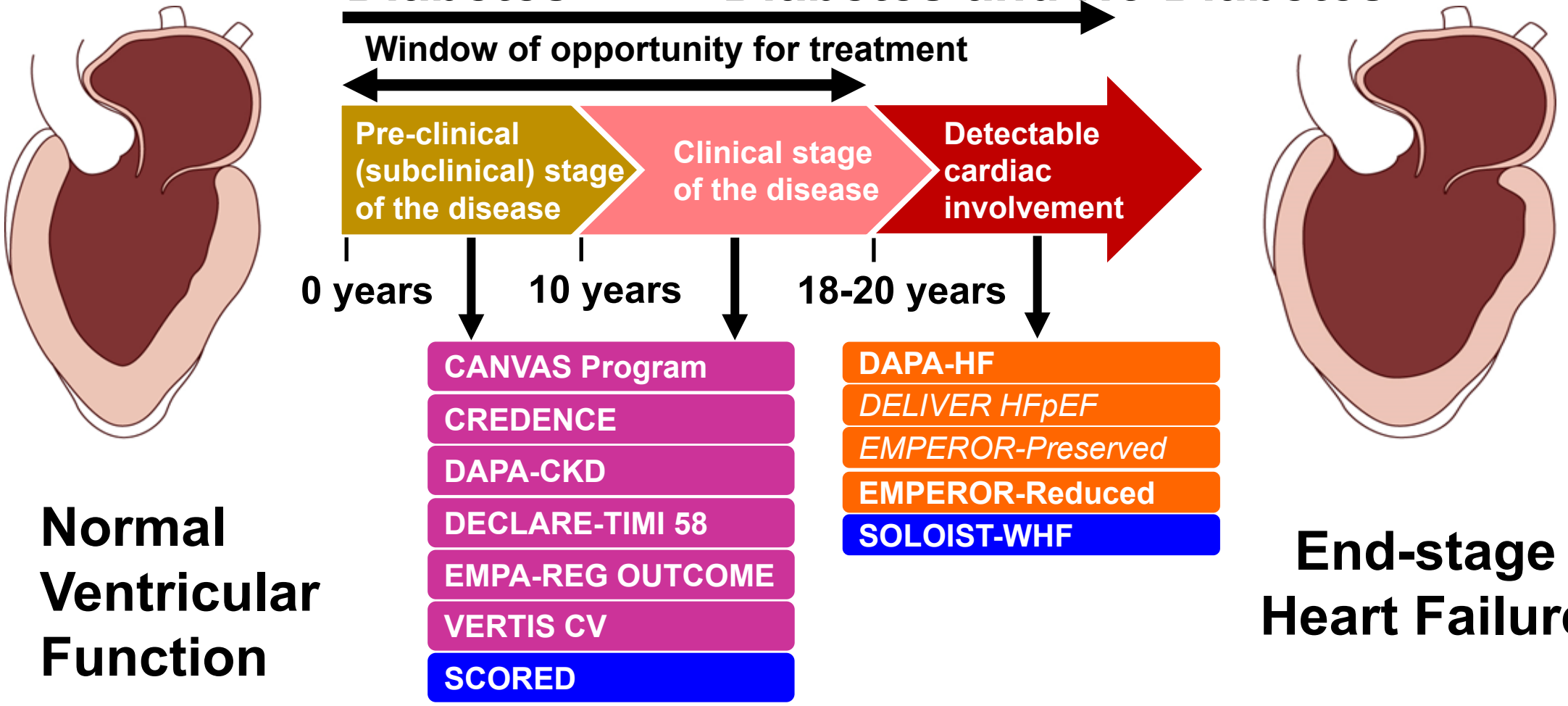
This presentation includes off-label and investigational uses of drugs.

The Evolution of SGLT2i in HF Management

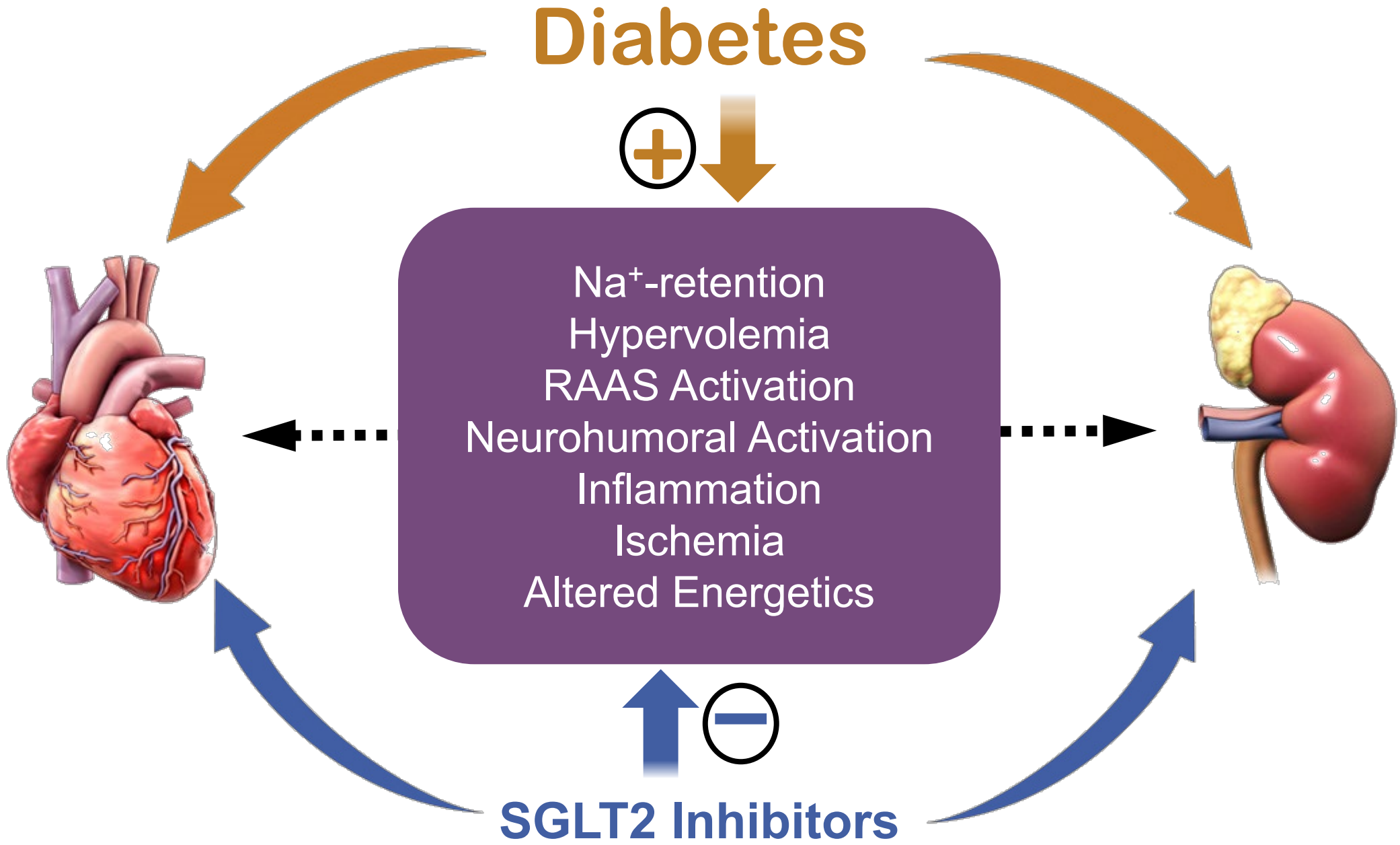


Adapted from Bhatt DL, Verma S, Braunwald E. *Cell Metabolism.* 2019;30:847-849.

The Evolution of SGLT2i in HF Management



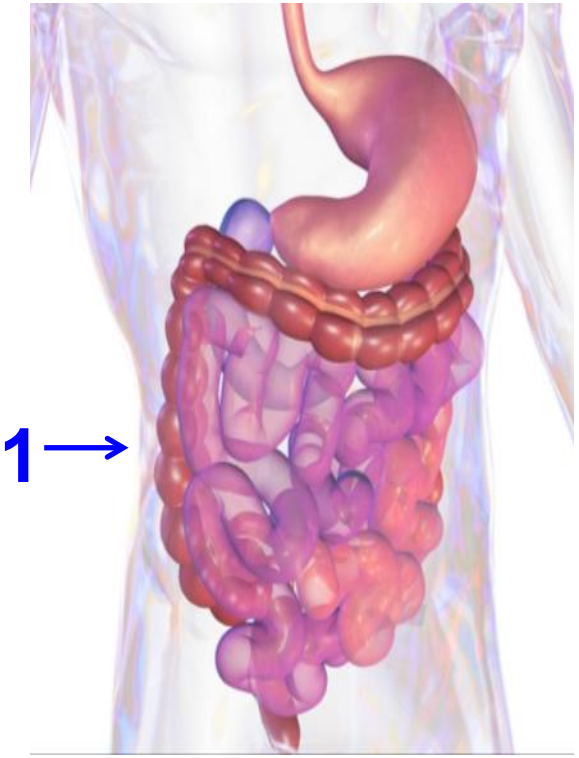
Adapted from Bhatt DL, Verma S, Braunwald E. *Cell Metabolism*. 2019;30:847-849.



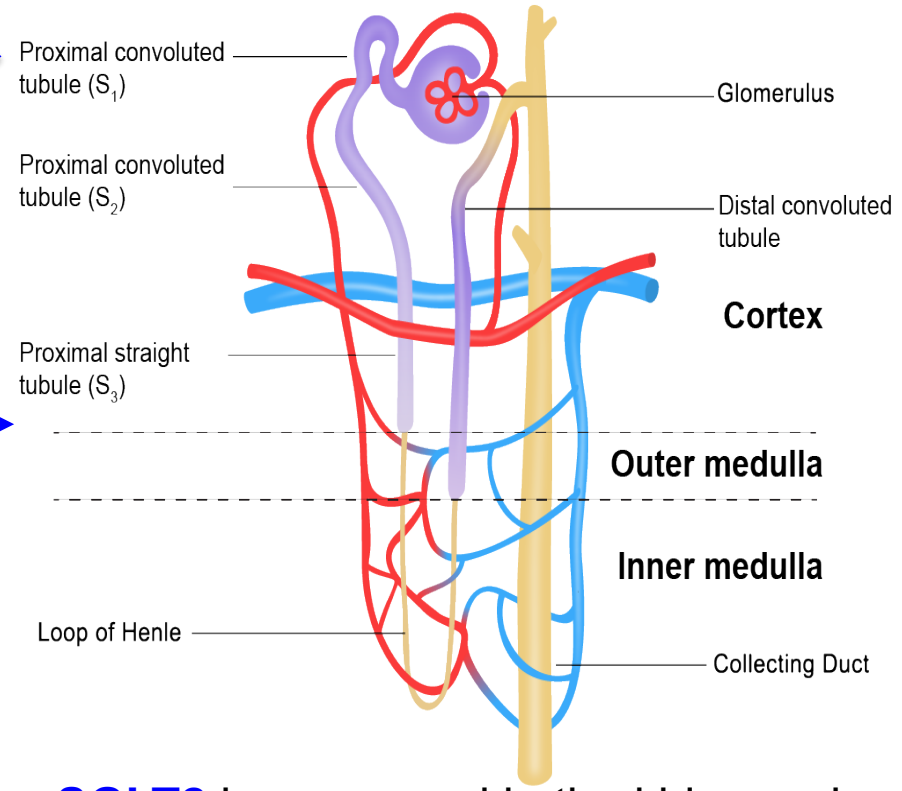
Connelly KA, Bhatt DL, Verma S. *Cell Metabolism*. 2018;28:813-815.

Sotagliflozin: Dual SGLT1 and SGLT2 Inhibitor

SGLT1 →



SGLT2 →



- **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 effects on 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

CARDIOVASCULAR MEDICINE AND SOCIETY

The Consequences of the COVID-19 Pandemic on Non-COVID-19 Clinical Trials

Emilia Bagiella, PhD,[a] Deepak L. Bhatt, MD, MPH,[b] Mario Gaudino, MD[c]

- Loss of funding during the onset of the COVID-19 pandemic
- Academic leadership did everything to ensure patient safety and to honor the scientific contribution of the patients

Bagiella E, Bhatt DL, Gaudino M. *JACC* 2020;76:342-345.

SCORED Study Committees

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Academic Statistician

Michael Szarek, PhD

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Key Inclusion and Exclusion Criteria

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Inclusion:

- 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

Exclusion:

- Planned start of SGLT2 inhibitor

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

CONSORT Diagram

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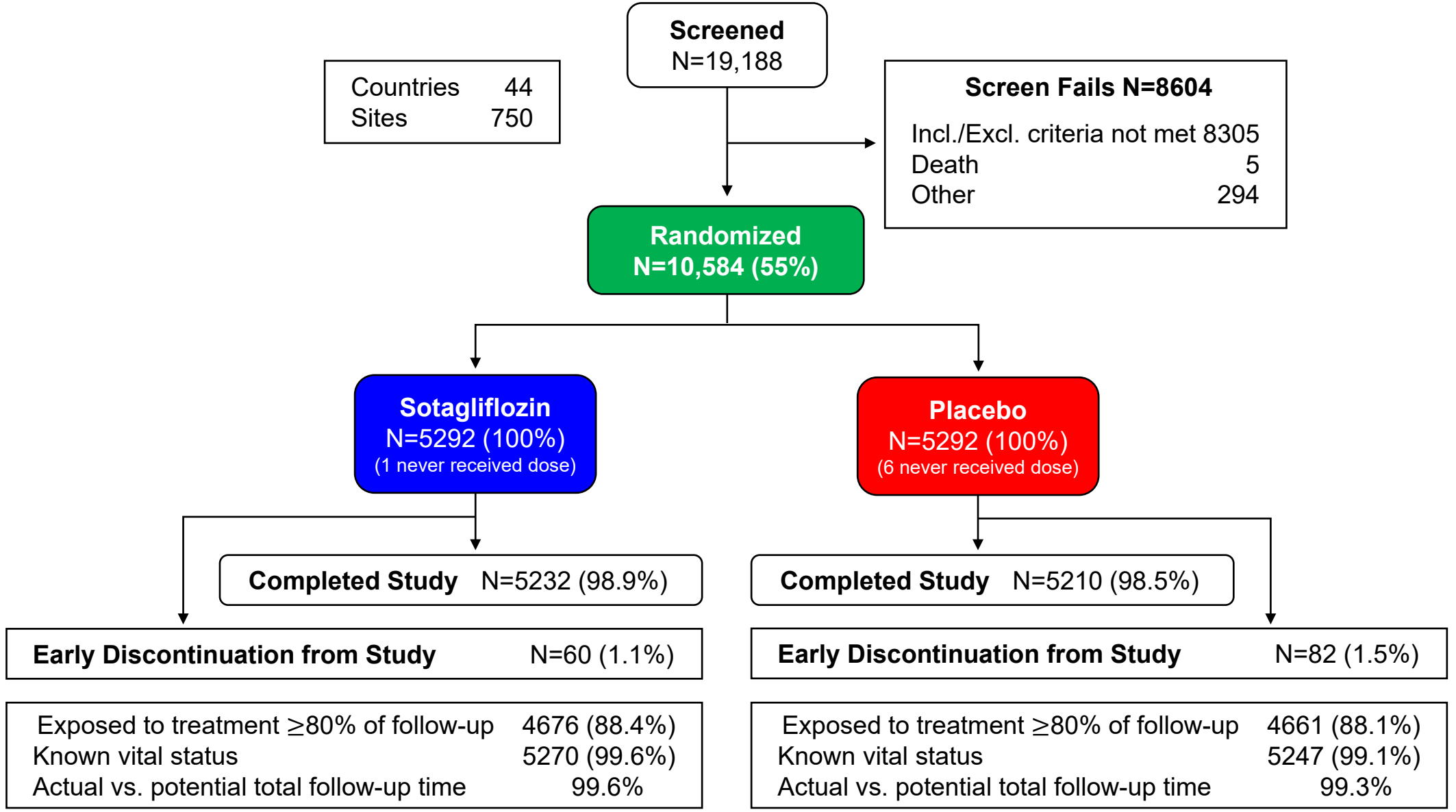

Median (Q1-Q3) **follow up duration = 15.9** (12.0-20.3**) months, maximum 30.0 months**

Bhatt DL et al. *NEJM.* 2020.

Baseline Characteristics

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	Sotagliflozin (N=5292)	Placebo (N=5292)
Age, years	69 (63-74)	69 (63-74)
Female	2347 (44.3)	2407 (45.5)
Geographic Region		
Europe	2324 (43.9)	2322 (43.9)
Americas	2332 (44.1)	2333 (44.1)
Rest of World	636 (12.0)	637 (12.0)
LVEF, %	60 (51-64)	60 (51-65)
eGFR, mL/min/1.73m^2	44.4 (37.0-51.3)	44.7 (37.0-51.5)
Urine Albumin/Creatinine Ratio, mg/g	74 (18-486)	75 (17-477)
History of Heart Failure	1640 (31.0)	1643 (31.0)
Any RAAS Inhibitor	4705 (88.9)	4660 (88.1)
Any Glucose Lowering Medication	5111 (96.6)	5136 (97.1)

Numbers in table are n (%) or median (Q1, Q3).

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

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

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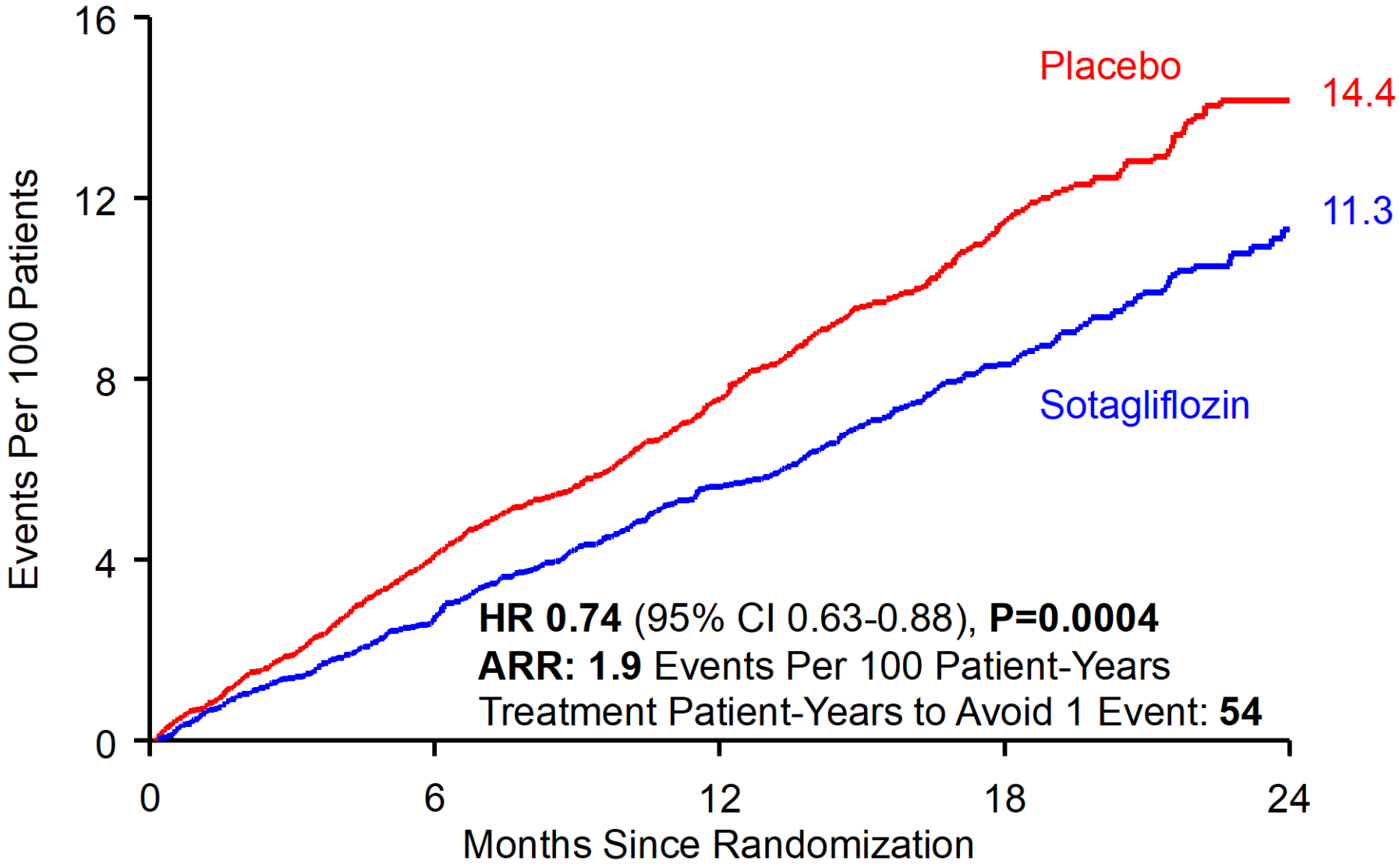

Bhatt DL, Szarek M, Pitt B, et al., and Steg PG. *N Engl J Med.* 2020. Bhatt DL. AHA 2020, virtual.

Primary Efficacy: Total CV Death, HHF, and Urgent HF Visit – Significant by 95 Days

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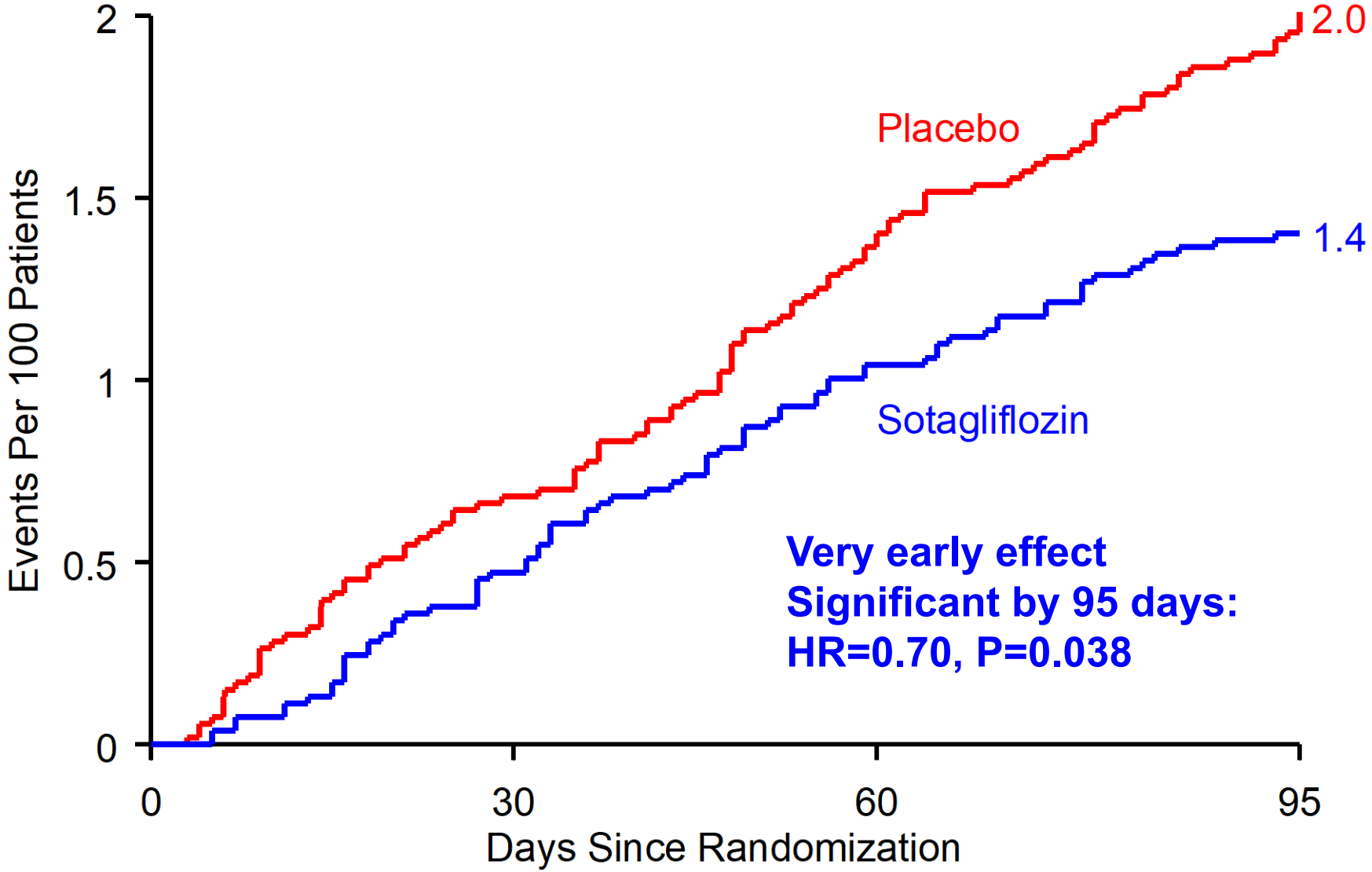

Bhatt DL, Szarek M, Pitt B, et al., and Steg PG. *N Engl J Med.* 2020. Bhatt DL. AHA 2020, virtual.

First of CV Death, Non-Fatal MI, or Non-Fatal Stroke

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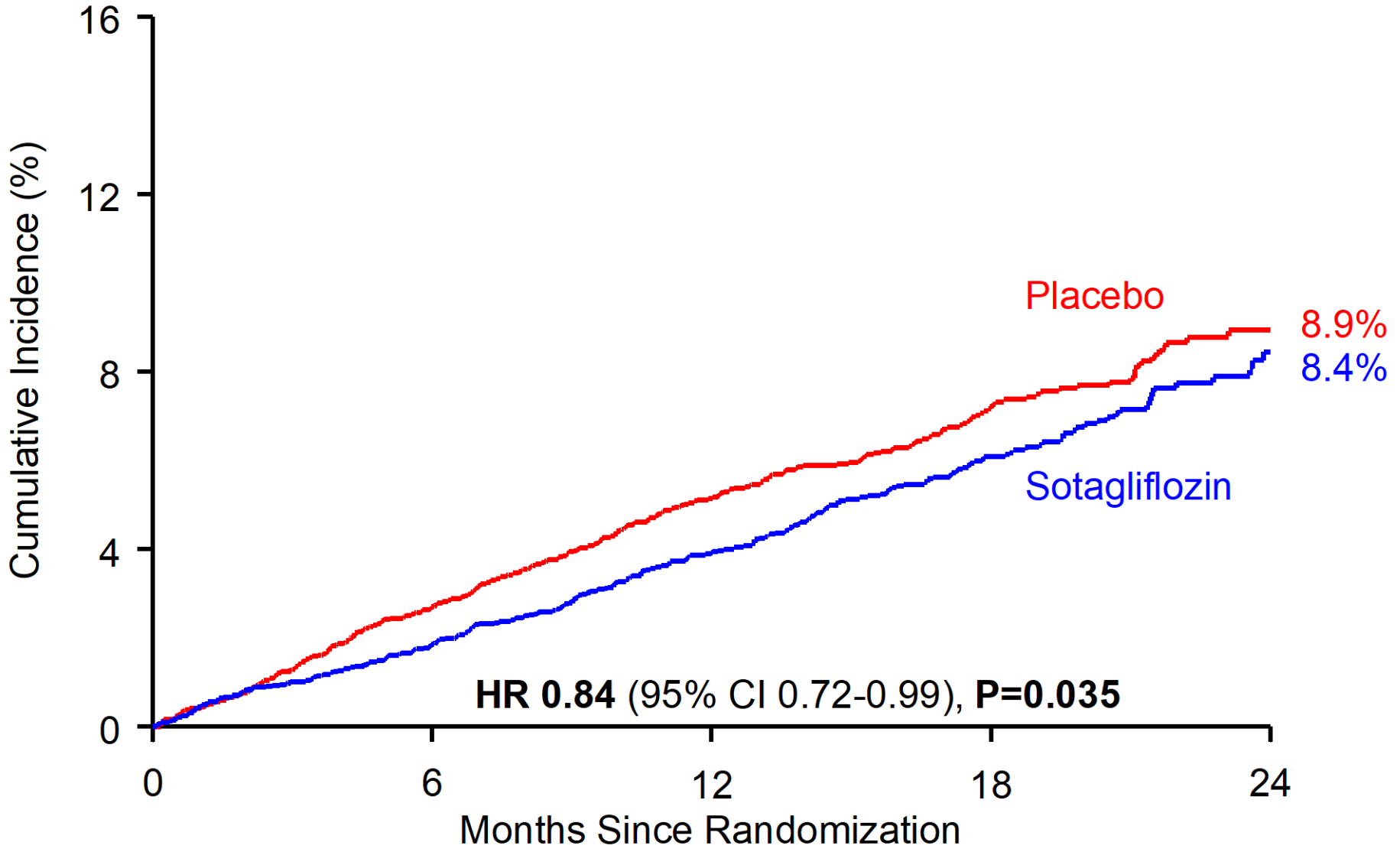

Bhatt DL, Szarek M, Pitt B, et al., and Steg PG. *N Engl J Med.* 2020. Bhatt DL. AHA 2020, virtual.

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

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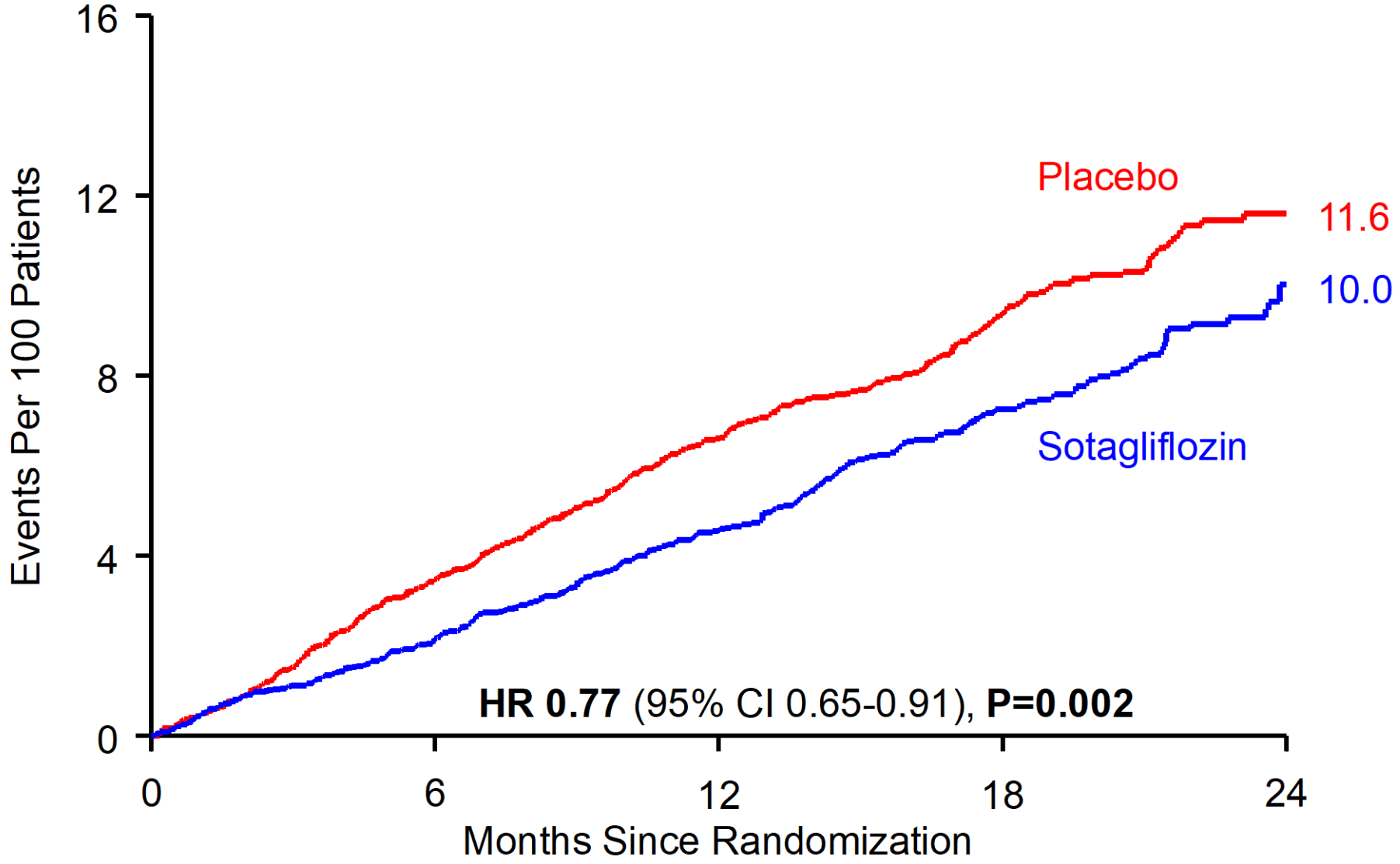

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Total CV Death, Non-Fatal MI, or Non-Fatal Stroke

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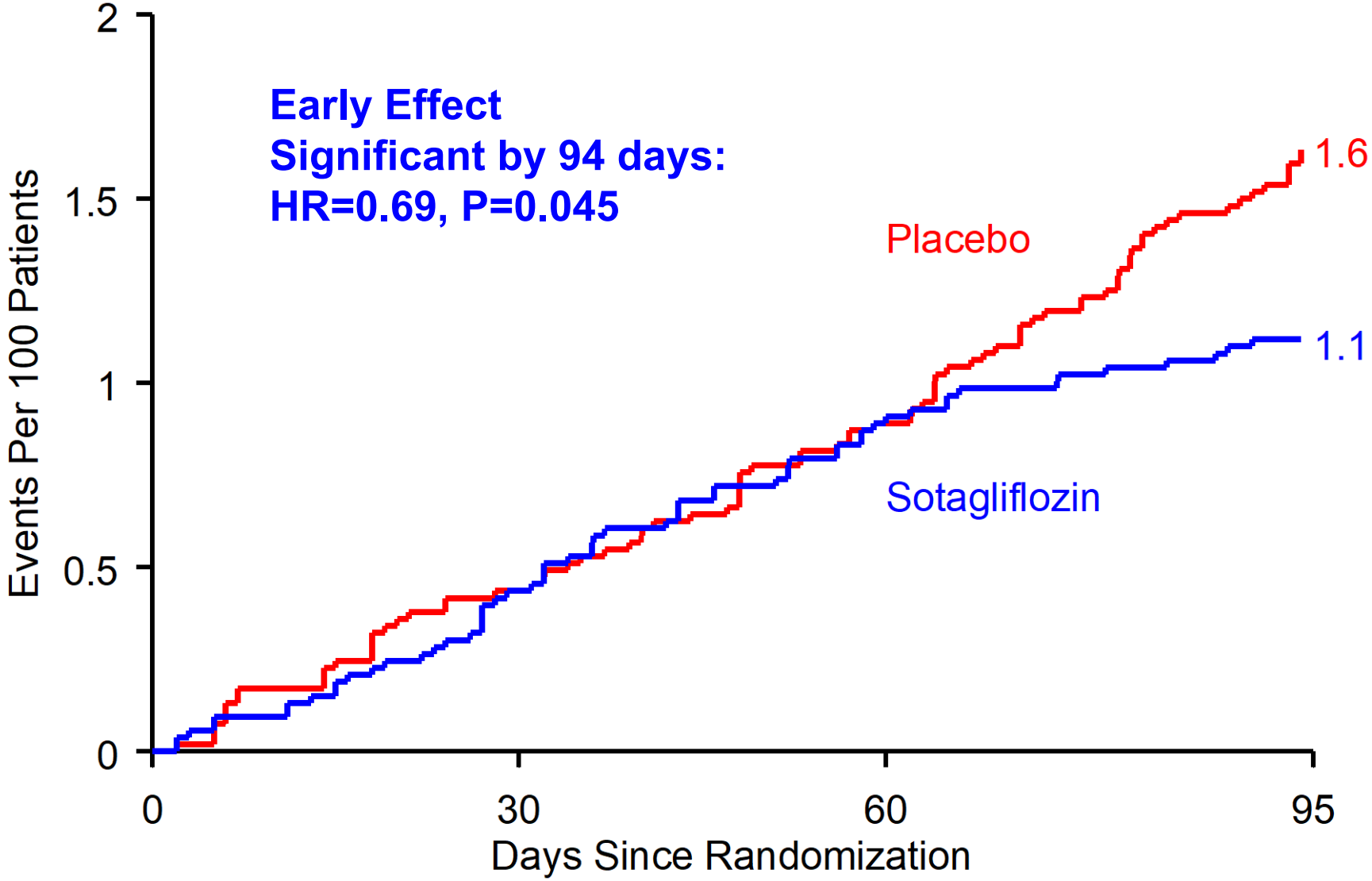

Bhatt DL, Szarek M, Pitt B, et al., and Steg PG. *N Engl J Med.* 2020. Bhatt DL. AHA 2020, virtual.

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

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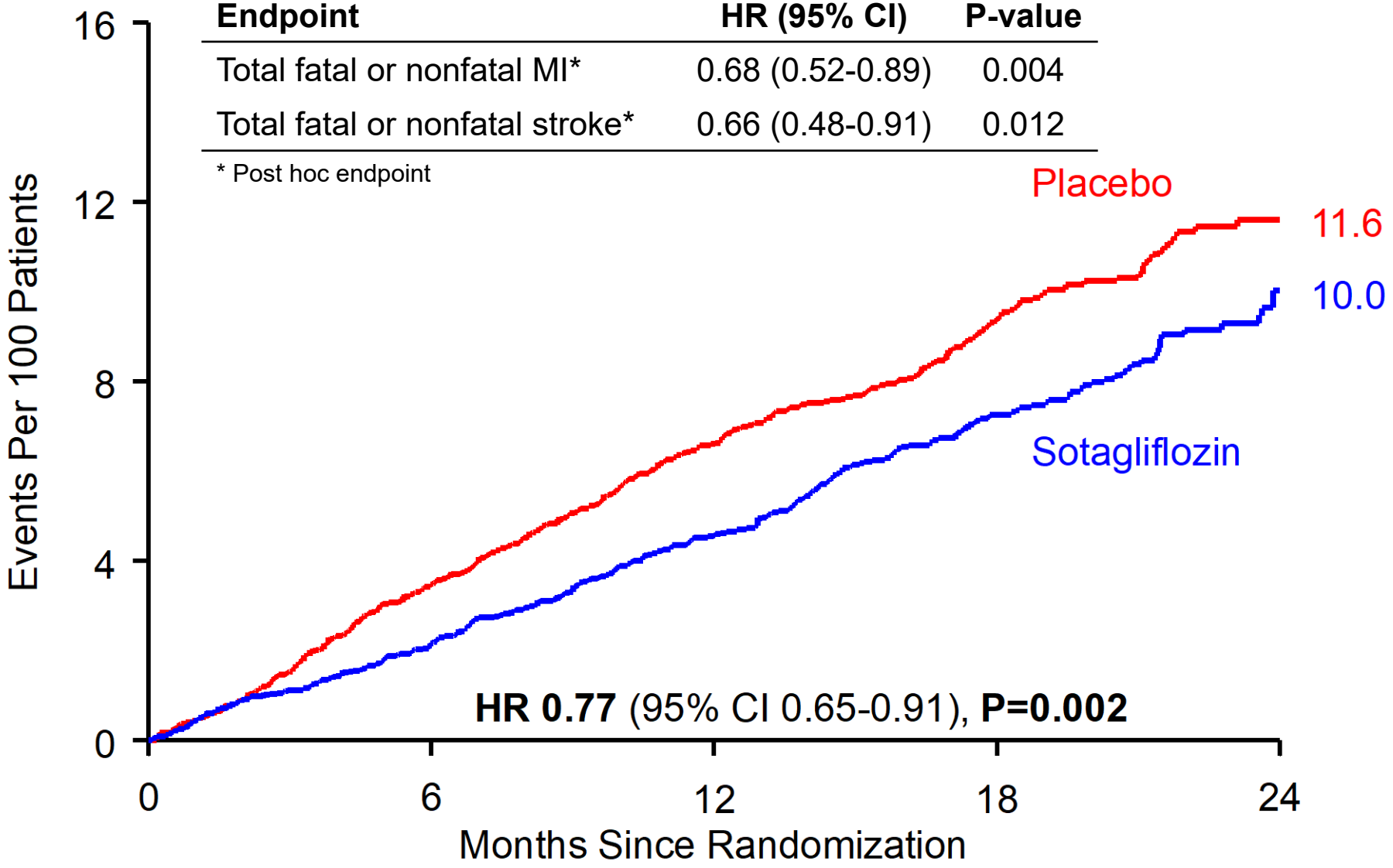
Endpoint	HR (95% CI)	P-value
Total fatal or nonfatal MI*	0.68 (0.52-0.89)	0.004
Total fatal or nonfatal stroke*	0.66 (0.48-0.91)	0.012

* Post hoc endpoint



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

First of CV Death or HHF

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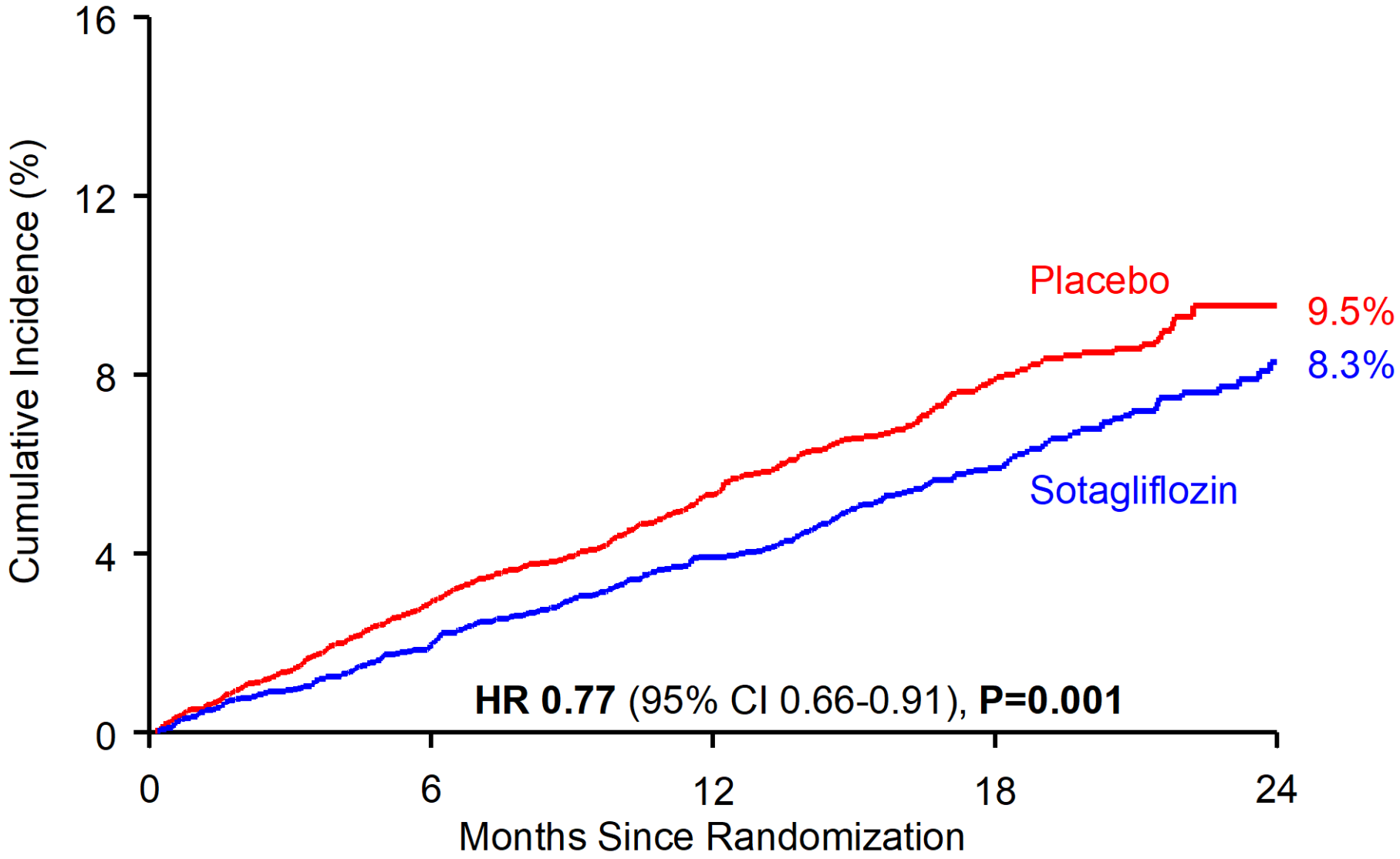

Bhatt DL, Szarek M, Pitt B, et al., and Steg PG. *N Engl J Med.* 2020. Bhatt DL. AHA 2020, virtual.

Efficacy Testing Hierarchy

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Endpoint	Sotagliflozin Rate [Events]	Placebo Rate [Events]	HR (95% CI)	P-value
Total CV death, HHF, and urgent HF visit	**5.6 [400]**	**7.5 [530]**	**0.74 (0.63-0.88)**	**0.0004**
Total HHF and urgent HF visit	3.5 [245]	5.1 [360]	0.67 (0.55-0.82)	0.0001
CV death	2.2 [155]	2.4 [170]	0.90 (0.73-1.12)	0.35
Total CV death, HHF, non-fatal MI, and non-fatal stroke	7.6 [541]	10.4 [738]	0.72 (0.63-0.83)	0.000008*
Total CV death, HHF, urgent HF visit, and HF while hospitalized	6.4 [453]	8.3 [589]	0.76 (0.65-0.89)	0.0005*
First sustained** ≥50% decrease in eGFR, chronic dialysis, renal transplant or sustained* eGFR <15 mL/min/1.73m^2	0.5 [37]	0.7 [52]	0.71 (0.46-1.08)	0.11*
All-cause death	3.5 [246]	3.5 [246]	0.99 (0.83-1.18)	0.93*
Total CV death, non-fatal MI, and non-fatal stroke	4.8 [343]	6.3 [442]	0.77 (0.65-0.91)	0.002*

**For ≥30 days. *Nominal p-value. Rate = number of events per 100 patient-years.

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

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

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

Primary Efficacy Subgroups

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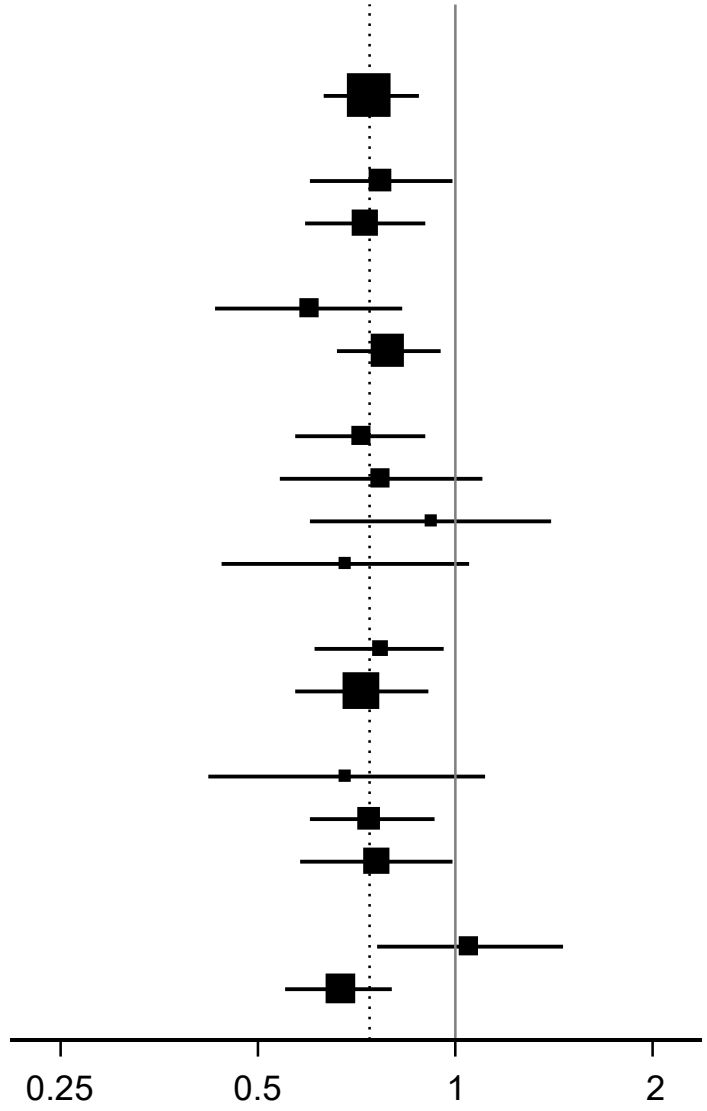
Subgroup	Patients	Events Per 100 py Sotagliflozin	Placebo	HR (95% CI)
Overall	10584	5.6	7.5	0.74 (0.63, 0.88)
Sex				
Female	4754	5.1	6.5	0.77 (0.60, 0.99)
Male	5830	6.1	8.3	0.73 (0.59, 0.90)
Age (years)				
< 65	3224	3.8	6.4	0.60 (0.43, 0.83)
≥ 65	7360	6.4	8.0	0.79 (0.66, 0.95)
Geographic Region				
Europe	3226	6.5	9.0	0.72 (0.57, 0.90)
Latin America	3172	3.9	5.0	0.77 (0.54, 1.10)
North America	1493	5.6	6.0	0.92 (0.60, 1.40)
Rest of World	1273	6.7	9.8	0.68 (0.44, 1.05)
HF-Related Criteria				
Yes	2108	15.9	20.6	0.77 (0.61, 0.96)
No	8476	3.2	4.4	0.72 (0.57, 0.91)
eGFR (ml/min/1.73m2)				
< 30	813	9.3	14.1	0.68 (0.42, 1.11)
30 to <45	4655	6.9	9.1	0.74 (0.60, 0.93)
≥ 45	5116	3.9	5.1	0.76 (0.58, 0.99)
Urine ACR (mg/g)				
<30	3709	4.4	4.2	1.05 (0.76, 1.46)
≥30	6875	6.3	9.4	0.67 (0.55, 0.80)



Change in eGFR

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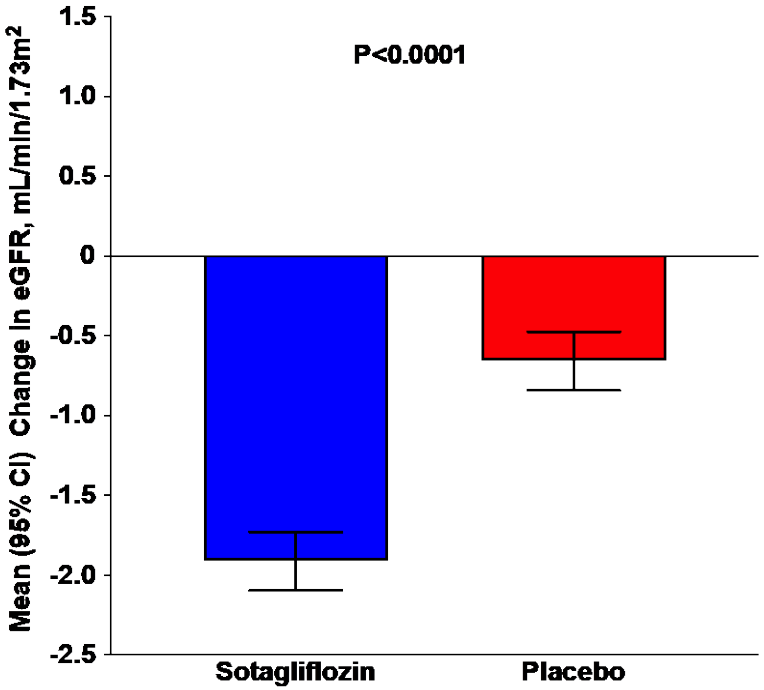
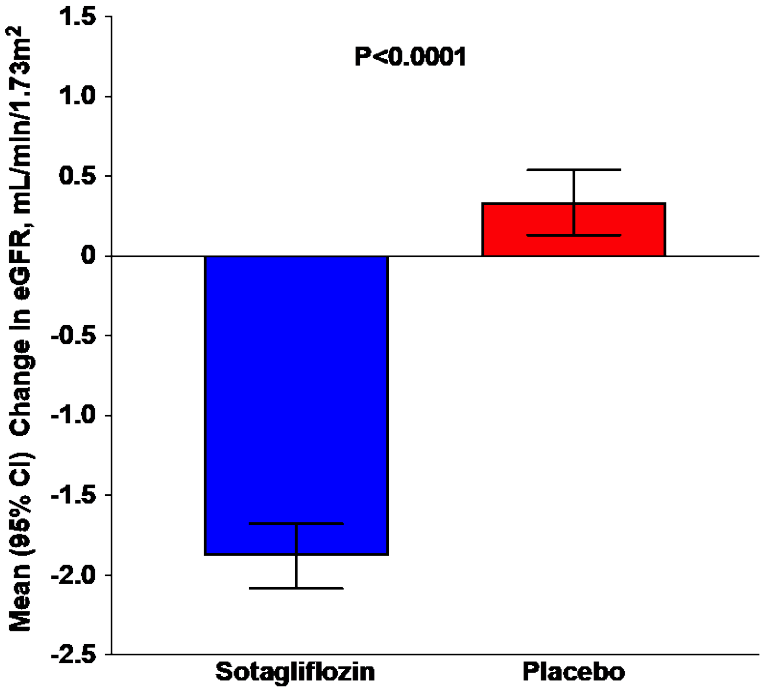
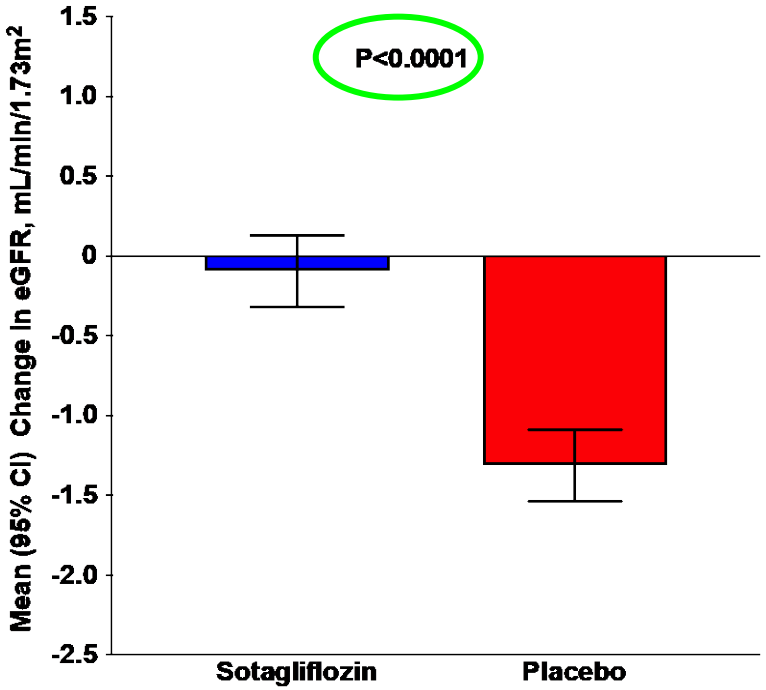
Overall



Prior to Week 4



After Week 4



- After the initial 4 weeks, sotagliflozin slowed the decline in kidney function

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

Reductions in HbA1c, Systolic Blood Pressure, and Weight with Sotagliflozin

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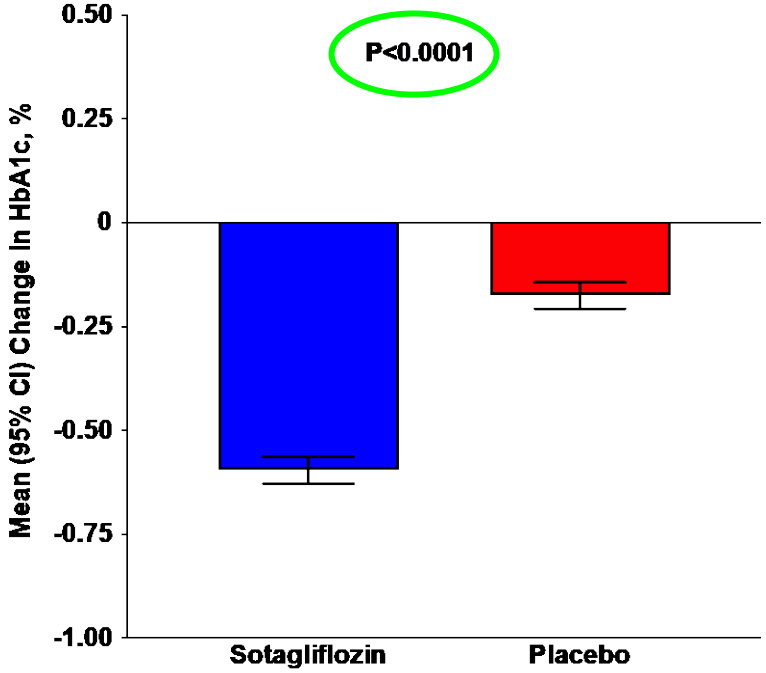
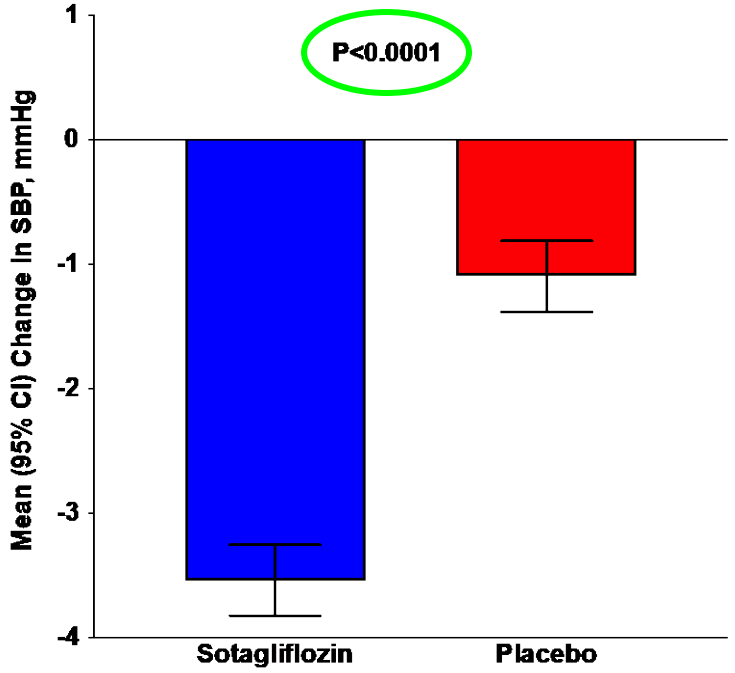
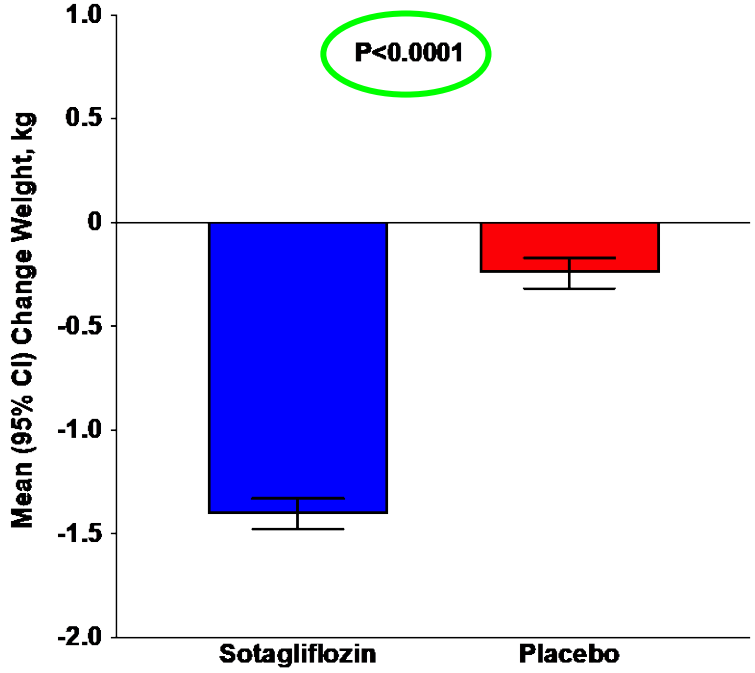
HbA1c



SBP



Weight



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

Reduction in HbA1c Across Moderate and Severe eGFR Categories with Sotagliflozin

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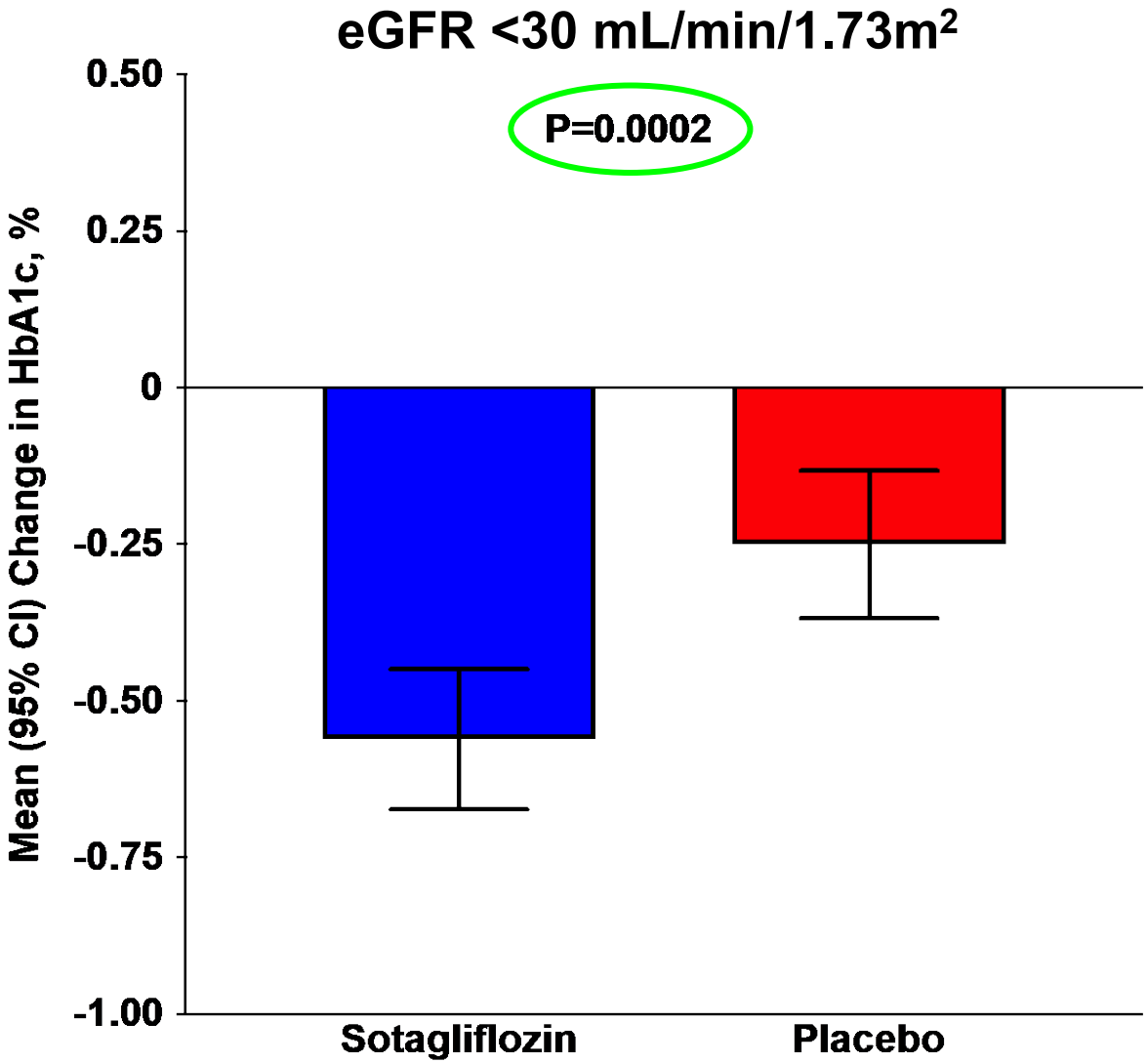

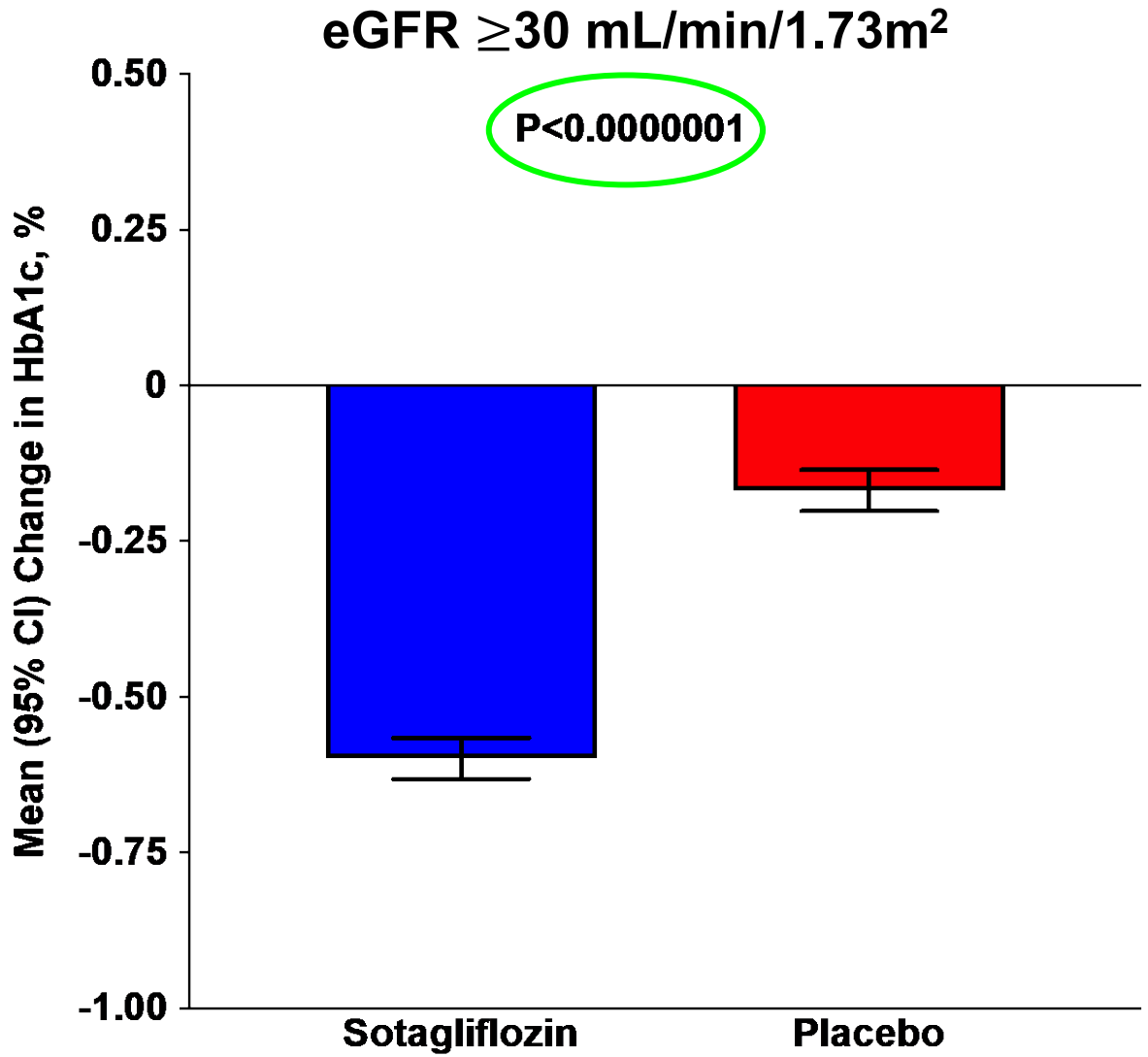

Bhatt DL, Szarek M, Pitt B, et al., and Steg PG. *N Engl J Med.* 2020. Bhatt DL. AHA 2020, virtual.

Limitations

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Trial was stopped early

- Nevertheless, robust reduction in primary endpoint
- Shortened duration limited the statistical power to see significant reductions in CV death or in kidney endpoints

Primary endpoint was changed while blinded to results

- However, original co-primary endpoints were also positive

Investigator-reported events were used instead of adjudication

- Double-blind trial, with no reason to expect bias

Bhatt DL, Szarek M, Pitt B, et al., and Steg PG. *N Engl J Med.* 2020. 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%**, likely due to the SGLT1 effect of **sotagliflozin** **on MI and also stroke**

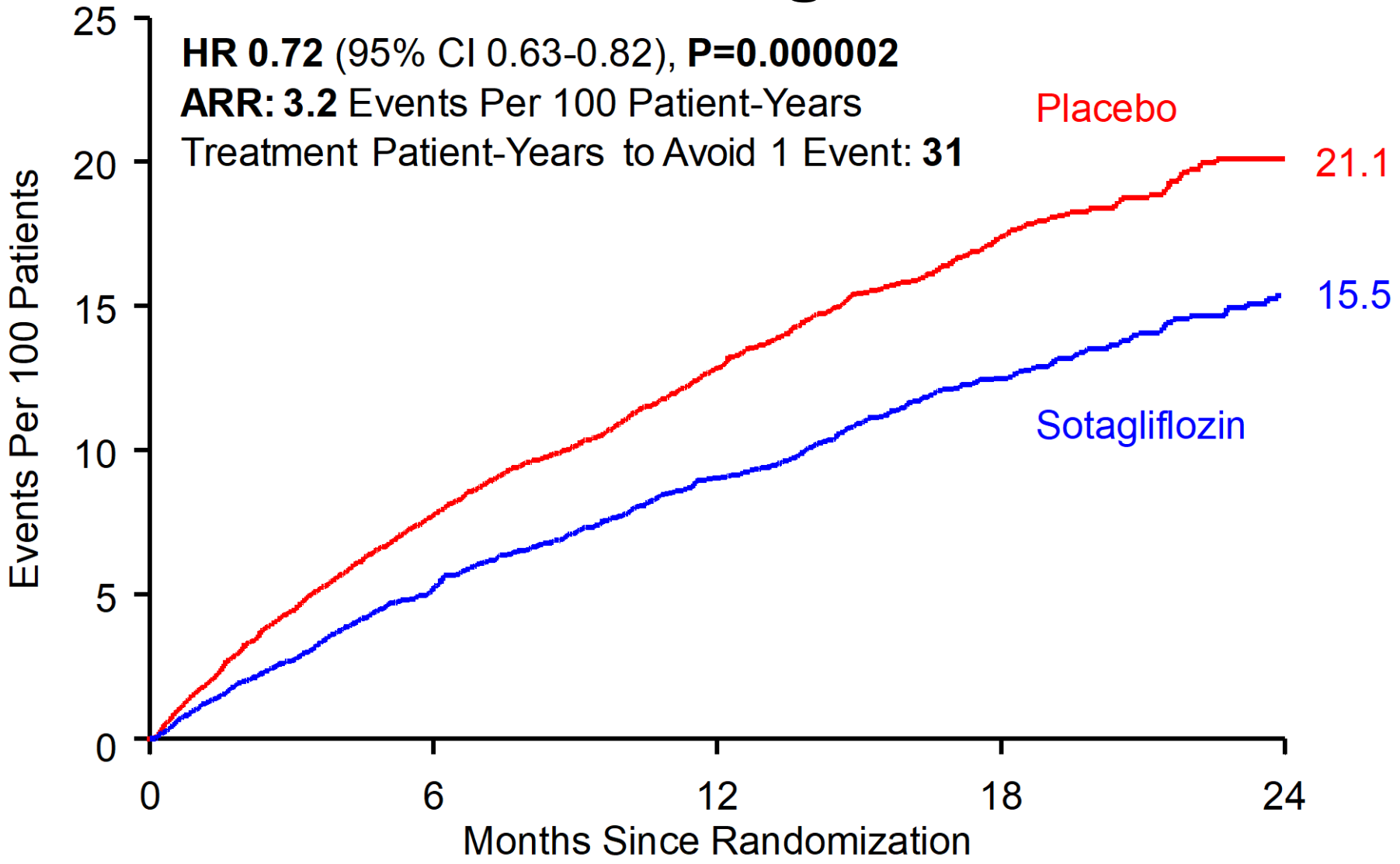
With careful patient selection, **sotagliflozin** was generally well tolerated (similar to placebo) and safe

The benefits were consistent across subgroups, including:

- Not only **macro- but also micro-albuminuria**
- In HF with **reduced or preserved ejection fraction**

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

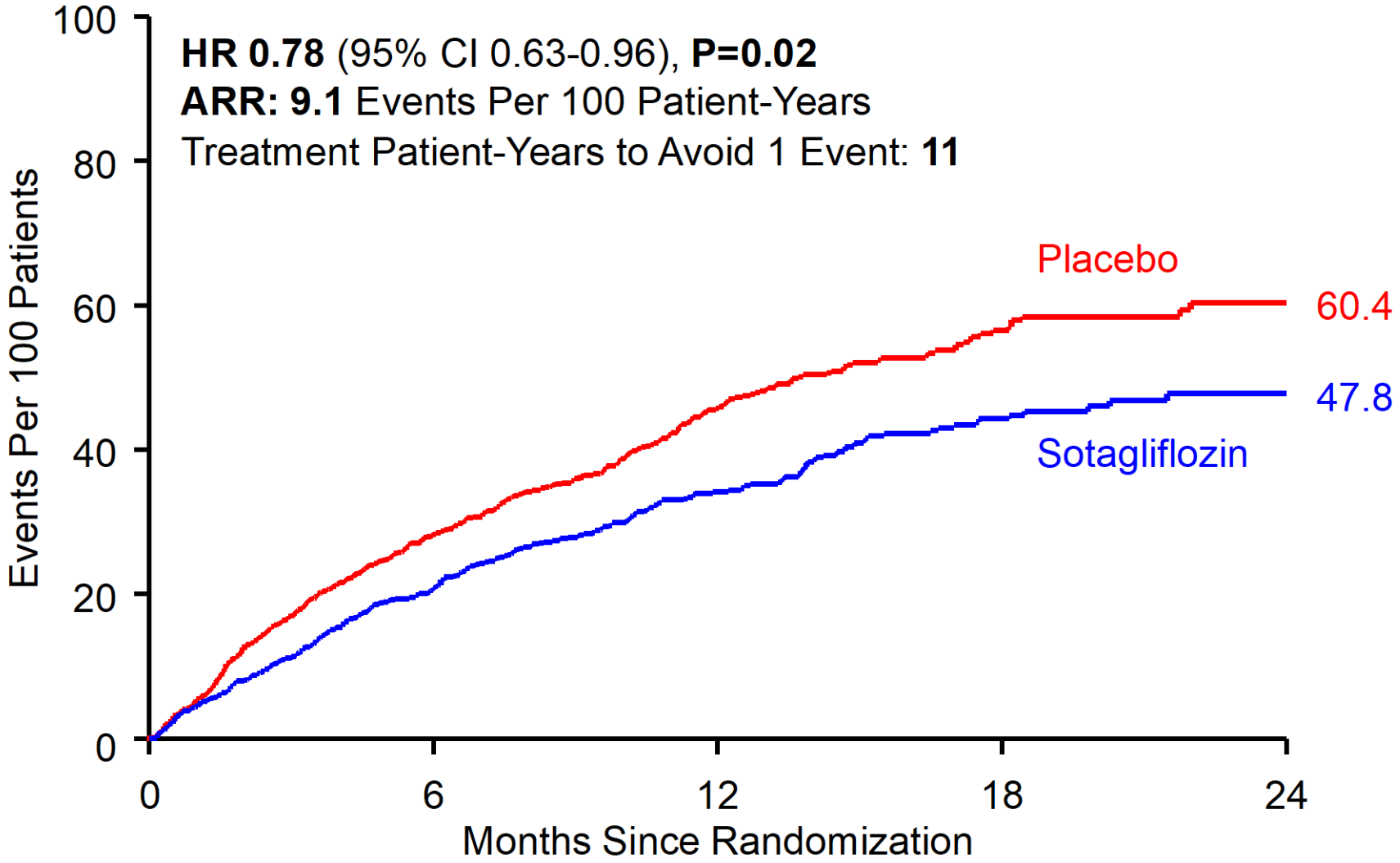
Pooled Data: SOLOIST and SCORED
Total CV Death, HHF, and Urgent HF Visit



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

Pooled Data: SOLOIST and SCORED Total CV Death, HHF, and Urgent HF Visit Among 1758 Patients with HFrEF

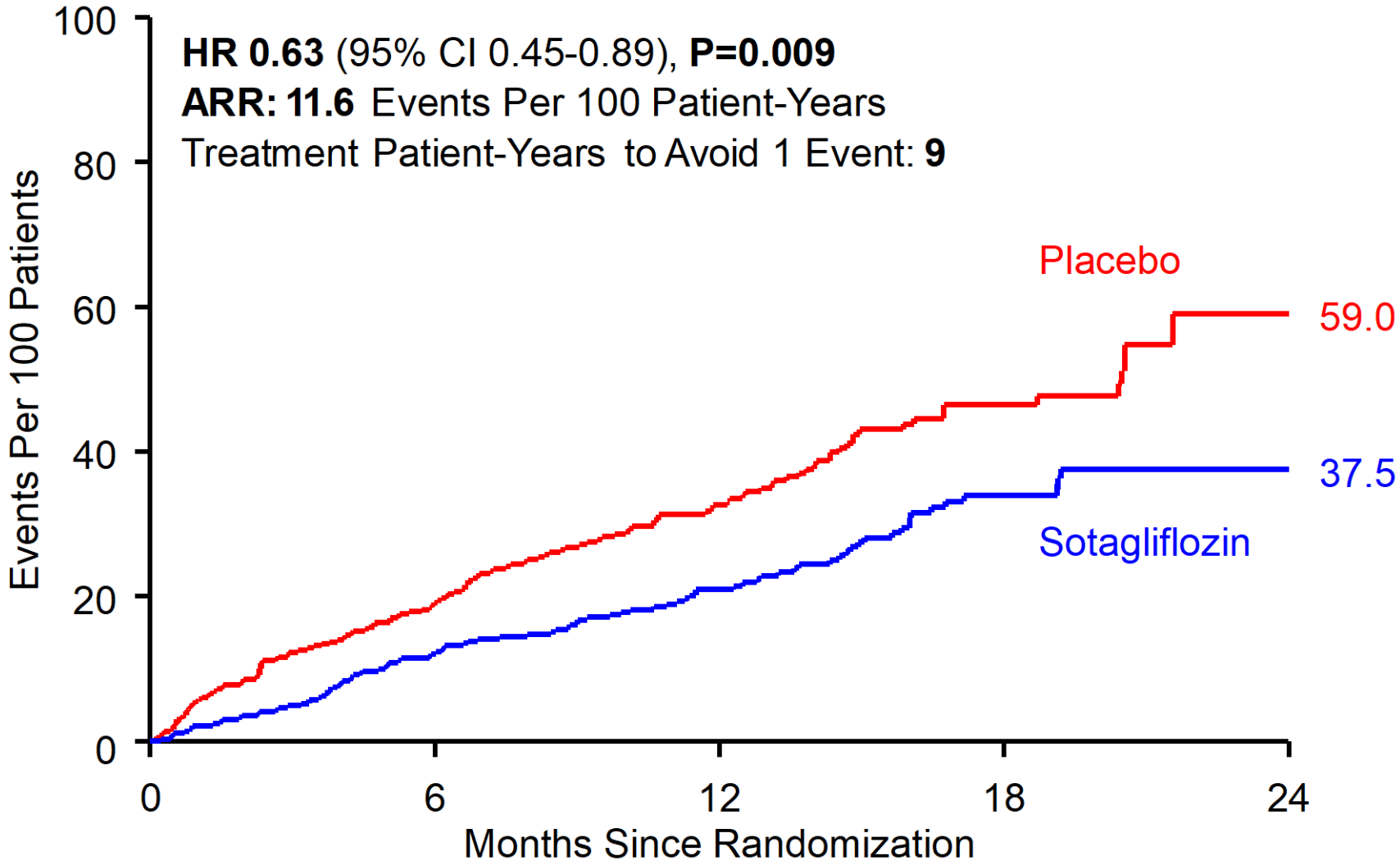
SCORED
SOLOIST



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

Pooled Data: SOLOIST and SCORED Total CV Death, HHF, and Urgent HF Visit Among 739 Patients with HFpEF

SCORED
SOLOIST



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

Implications of SOLOIST and SCORED

SCORED

SOLOIST

With careful patient selection and monitoring, **as a class, SGLT2 inhibitors should be strongly considered in the majority of patients with type 2 diabetes** including those:

- Admitted with **acute decompensated heart failure**
- With heart failure with **either reduced or preserved EF**
- With **CKD across the full range of proteinuria**

Unlike with pure SGLT2, the SGLT1 inhibition from **sotagliflozin** provided **glycemic control even at the lower range of eGFR**

The lower rate of MI and stroke with **sotagliflozin** suggests an additional relatively **early anti-ischemic effect of SGLT1** inhibition which should be explored further

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

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

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SOLOIST

ORIGINAL ARTICLE

Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure

Deepak L. Bhatt, M.D., M.P.H., Michael Szarek, Ph.D., P. Gabriel Steg, M.D., Christopher P. Cannon, M.D., Lawrence A. Leiter, M.D., Darren K. McGuire, M.D. , Julia B. Lewis, M.D., Matthew C. Riddle, M.D., Adriaan A. Voors, M.D., Ph.D., Marco Metra, M.D., Lars H. Lund, M.D., Ph.D., Michel Komajda, M.D., Jeffrey M. Testani, M.D., M.T.R., Christopher S. Wilcox, M.D., Piotr Ponikowski, M.D., Renato D. Lopes, M.D., Ph.D., Subodh Verma, M.D., Ph.D., Pablo Lapuerta, M.D., and Bertram Pitt, M.D., for the SOLOIST-WHF Trial Investigators*

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ORIGINAL ARTICLE

Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease

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