SOLOIST

Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure – The SOLOIST-WHF Trial

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

BWH

VE RI TAS

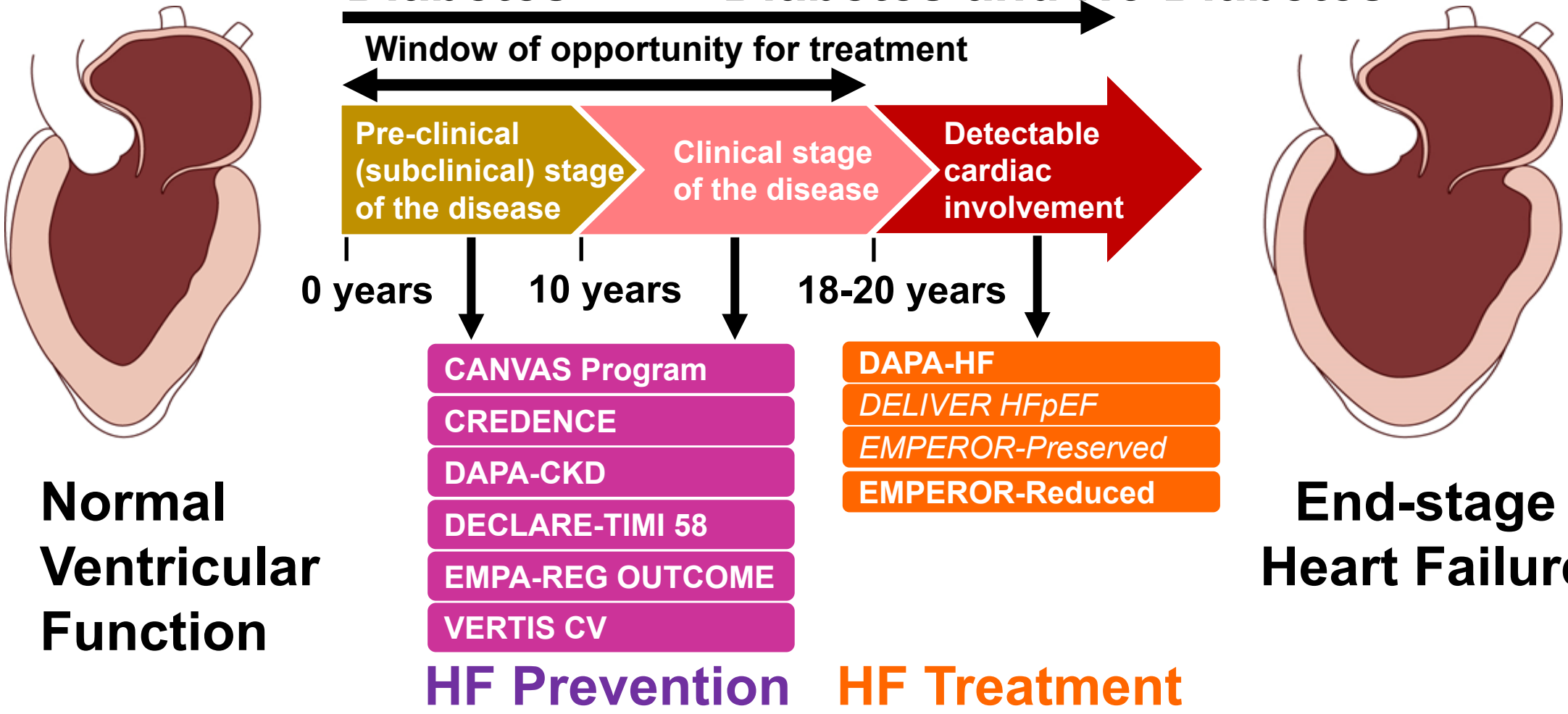
Disclosures

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.

SOLOIST-WHF was initially sponsored by Sanofi and then by Lexicon.

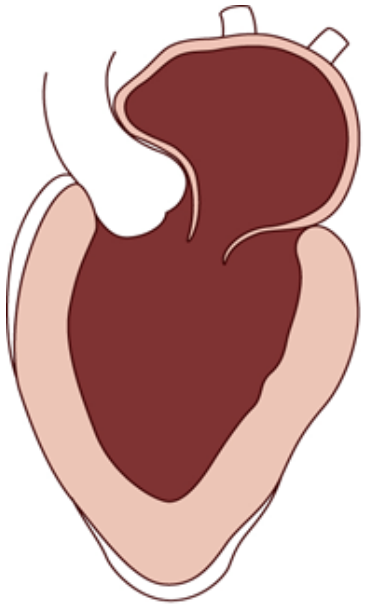
This presentation includes off-label and investigational uses of drugs.

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



Normal Ventricular Function

Diabetes

Diabetes and No Diabetes

Window of opportunity for treatment

Pre-clinical (subclinical) stage of the disease

Clinical stage of the disease

Detectable cardiac involvement

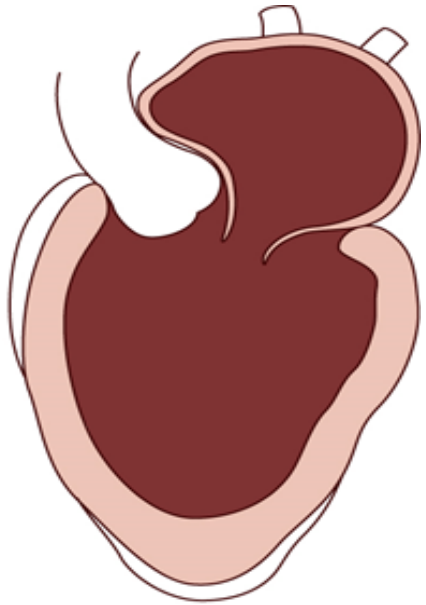
0 years

10 years

18-20 years

CANVAS Program
CREDENCE
DAPA-CKD
DECLARE-TIMI 58
EMPA-REG OUTCOME
VERTIS CV

DAPA-HF
DELIVER HFpEF
EMPEROR-Preserved
EMPEROR-Reduced
SOLOIST-WHF



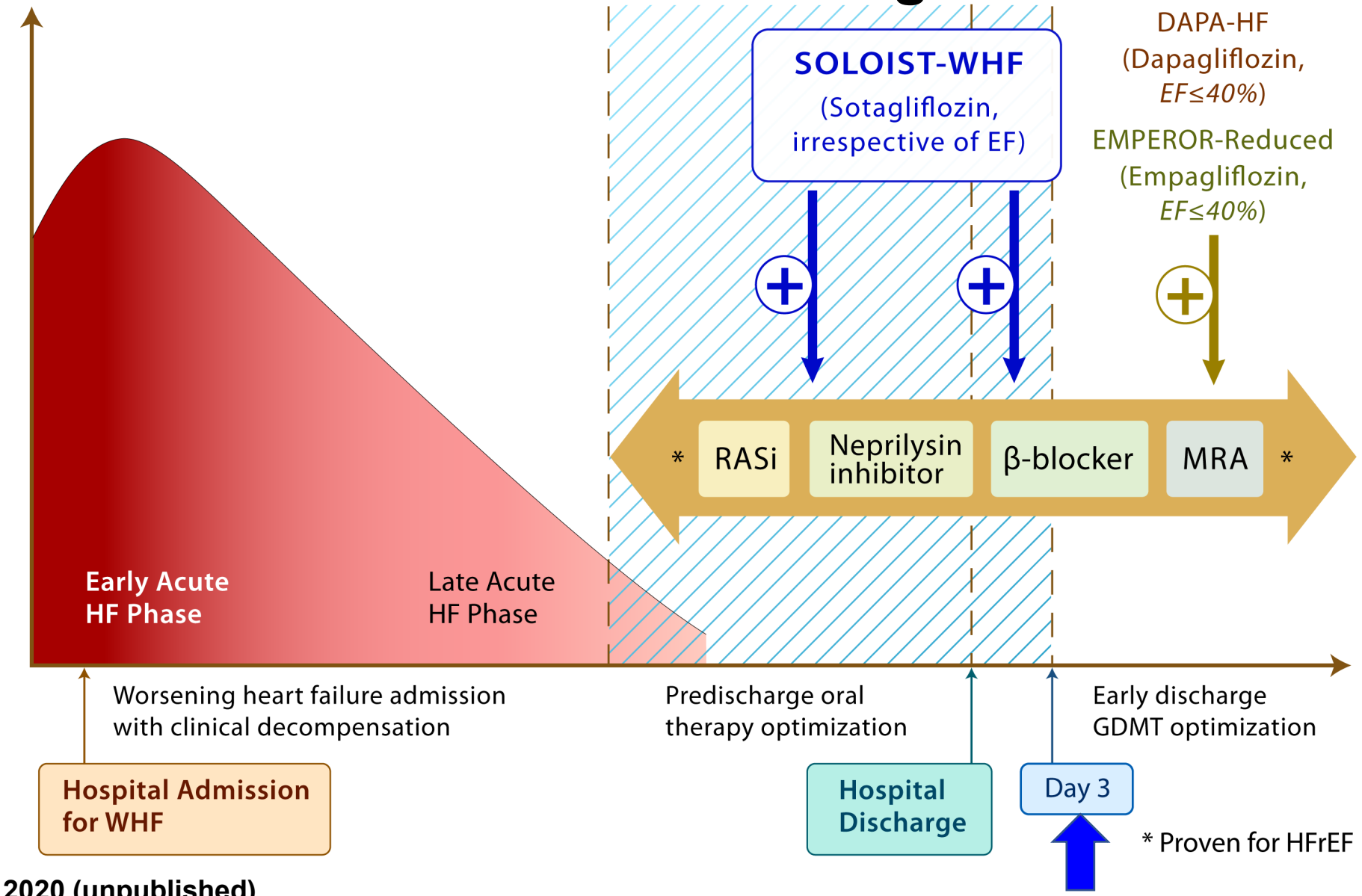
End-stage Heart Failure

HF Prevention

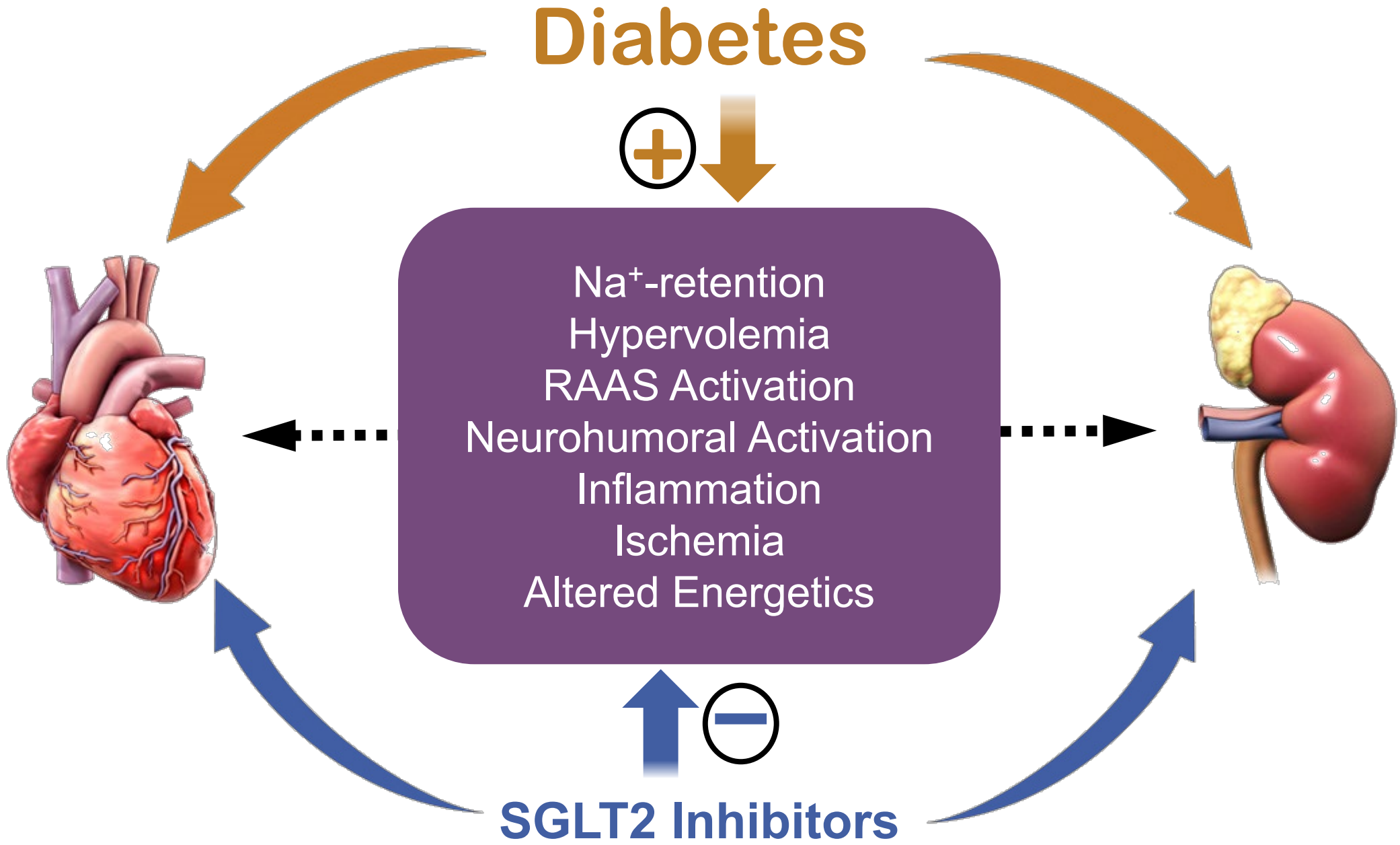
HF Treatment → Acute HF?

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

SOLOIST-WHF: Addressing the Vulnerable Period of an Admission for Worsening Heart Failure



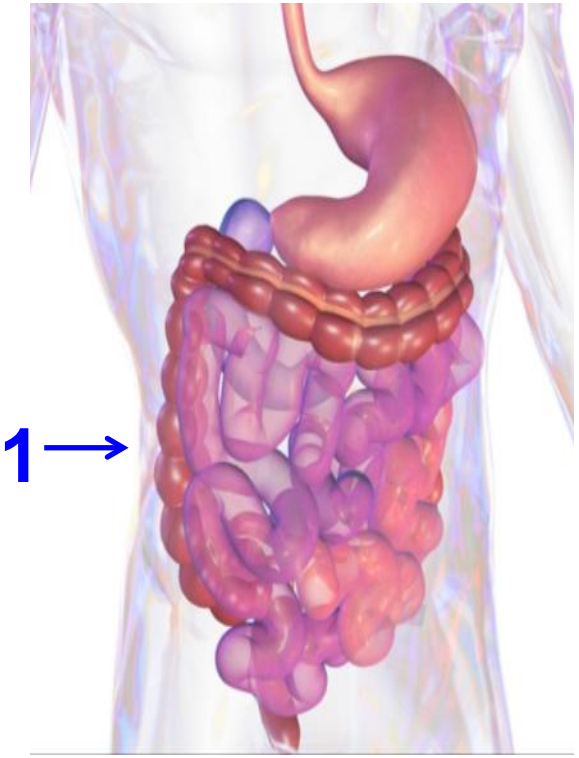
Verma S, Bhatt DL. 2020 (unpublished)



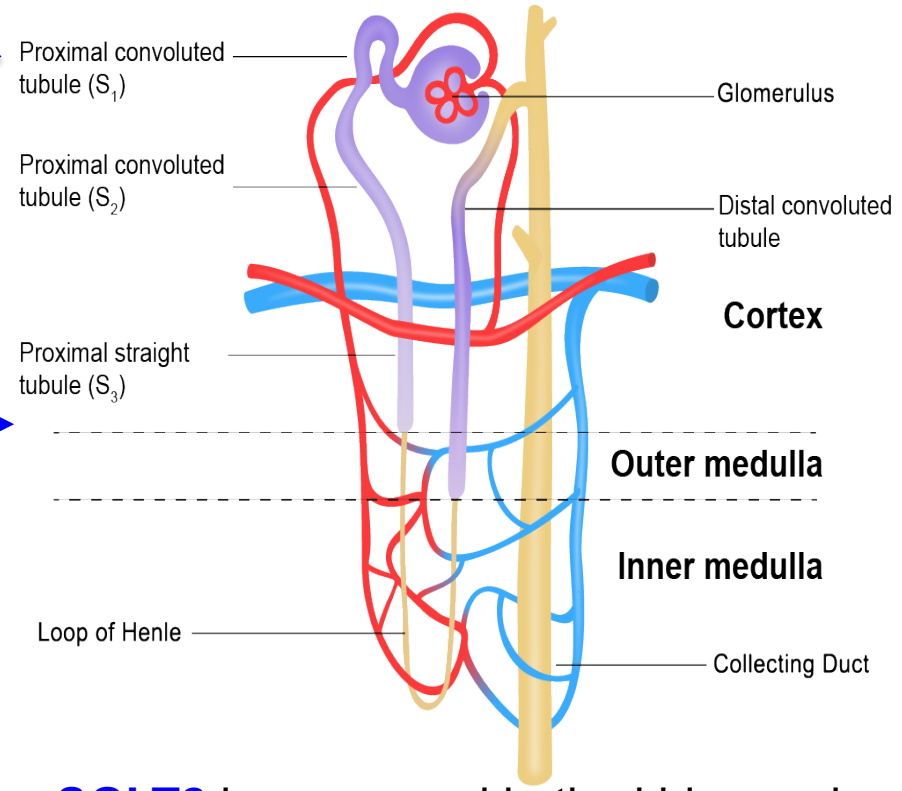
Connelly KA, Bhatt DL, Verma S. *Cell Metabolism*. 2018;28:813-815.

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.

SOLOIST-WHF Study Committees

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Executive Committee

Deepak L. Bhatt, MD, MPH (Chair), Christopher P. Cannon, MD, Lawrence A. Leiter, MD, Julia B. Lewis, MD, Darren K. McGuire, MD, MHSc, Bertram Pitt, MD, Matthew C. Riddle, MD, Ph. Gabriel Steg, MD

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Academic Statistician

Michael Szarek, PhD

SOLOIST-WHF Study Committees

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National Coordinators

Christopher P. Cannon, Robert Mentz, Frank Peacock, and Barry Greenberg (United States), Subodh Verma and Justin Ezekowitz (Canada), Stefan Janssens (Belgium), Jeroen Schaap (Netherlands), Andrew Lawrence Clark (United Kingdom), Morten Schou (Denmark), Veli-Pekka Harjola (Finland), Lars H. Lund (Sweden), Andrejs Erglis (Latvia), Jelena Celutkiene (Lithuania), Jindrich Spinar (Czech Republic), Jan Murin (Slovakia), Béla Peter Merkely (Hungary), Jadwiga Maria Nessler (Poland), Hans-Dirk Dungen (Germany), Kurt Huber (Austria), Christian Eugen Muller (Switzerland), Nicolas Lamblin (France), Piergiuseppe Agostoni and Maria Frigerio (Italy), John Parissis (Greece), Gheorghe Andrei Dan (Romania), Maria Generosa Crespo-Leiro (Spain), Tuvia Ben-Gal (Israel), Cândida Fonseca (Portugal), Mehmet Birhan Yilmaz (Turkey), Olga Barbarash (Russia), José Carlos Nicolau (Brazil), Eduardo Roque Perna (Argentina), Ramon Luis Corbalan Herreros (Chile), Kyu-Hyung Ryu (South Korea), Harvey D. White (Australia and New Zealand)

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

Key Inclusion Criteria

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- Admission with signs and symptoms of heart failure
- Treatment with intravenous diuretics
- Stabilized, off oxygen, transitioning to oral diuretics
- BNP ≥150 pg/mL (≥450 pg/mL if atrial fibrillation) or NT-proBNP ≥600 pg/mL (≥1800 pg/mL if atrial fibrillation)
- Type 2 diabetes

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

Key Exclusion Criteria

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- End-stage heart failure
- Recent ACS, stroke, PCI, or CABG
- eGFR <30 mL/min/1.73m^2

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

CONSORT Diagram

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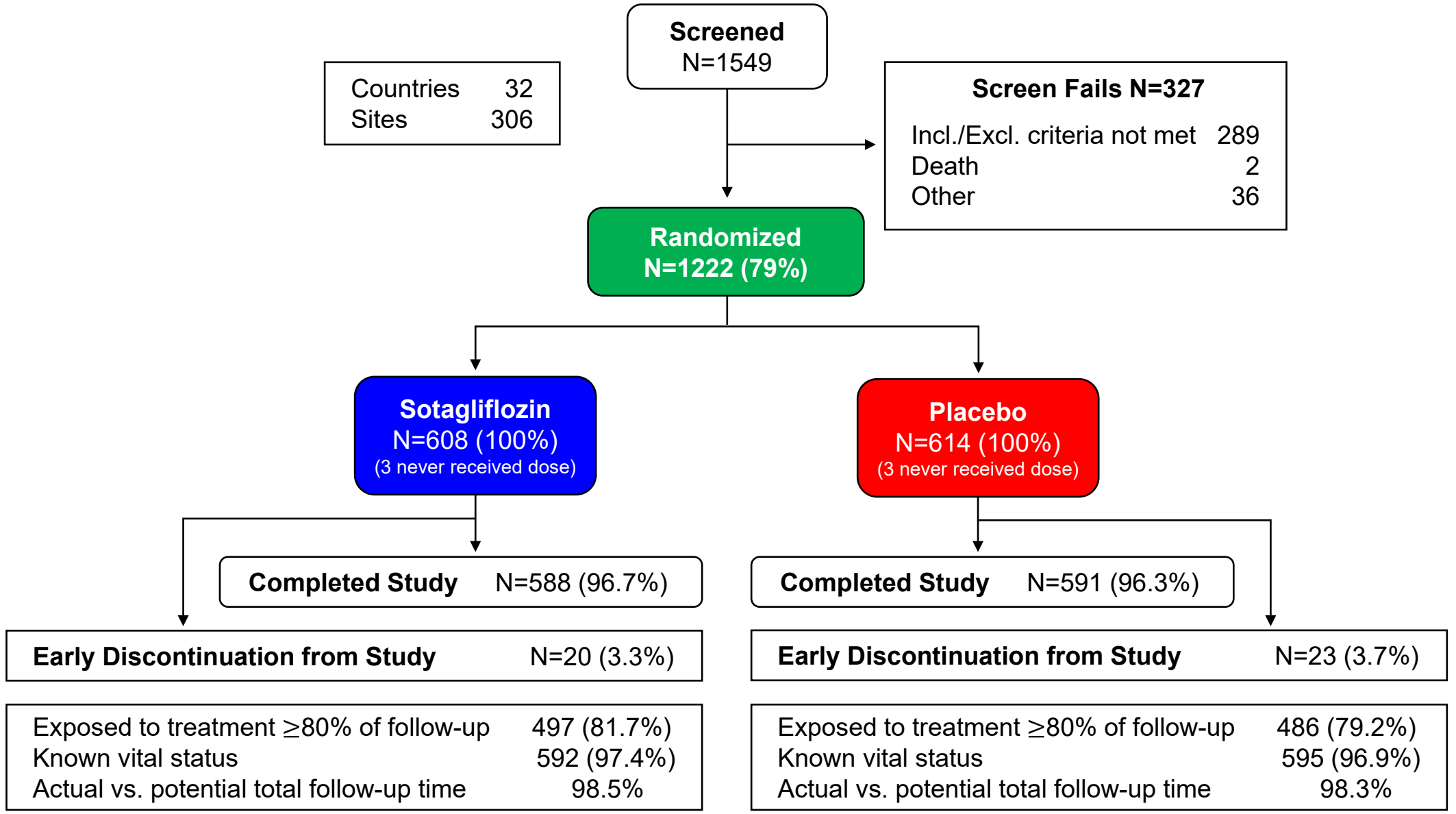

Median (Q1-Q3) **follow up duration = 9.0** (4.9-13.4) **months, maximum 22.3 months**

Bhatt DL, et al. *NEJM.* 2020.

Baseline Characteristics

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	Sotagliflozin (N=608)	Placebo (N=614)
Age, years	69 (63-76)	70 (64-76)
Female	198 (32.6)	214 (34.9)
Geographic Region		
Europe	399 (65.6)	401 (65.3)
Americas	171 (28.1)	175 (28.5)
Rest of World	38 (6.3)	38 (6.2)
LVEF, %	35 (28-47)	35 (28-45)
eGFR, mL/min/1.73m^2	49.2 (39.5-61.2)	50.5 (40.5-64.6)
NT-proBNP, pg/mL	1817 (855-3659)	1741 (843-3582)
Any RAAS Inhibitor	553 (91.0)	563 (91.7)
Any Glucose Lowering Medication	522 (85.9)	522 (85.0)
First Dose Prior to Index Hospitalization Discharge	290 (47.7)	306 (49.8)

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

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

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

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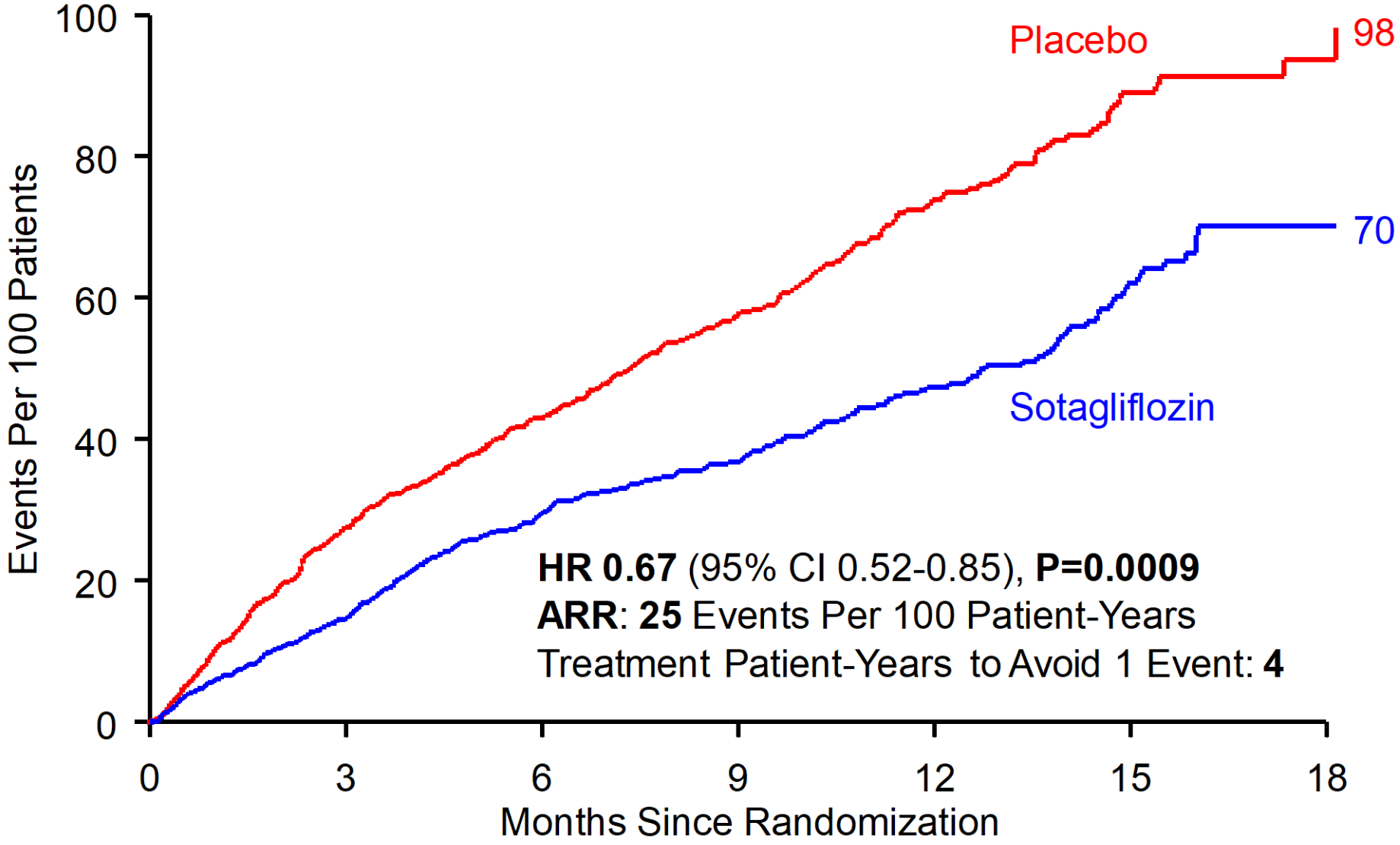

Bhatt DL, Szarek M, Steg PG, et al., and Pitt B. *N Engl J Med.* 2020. Bhatt DL. AHA 2020, virtual.

Primary Efficacy: Total CV Death, HHF, and Urgent HF Visit – Significant by 28 Days

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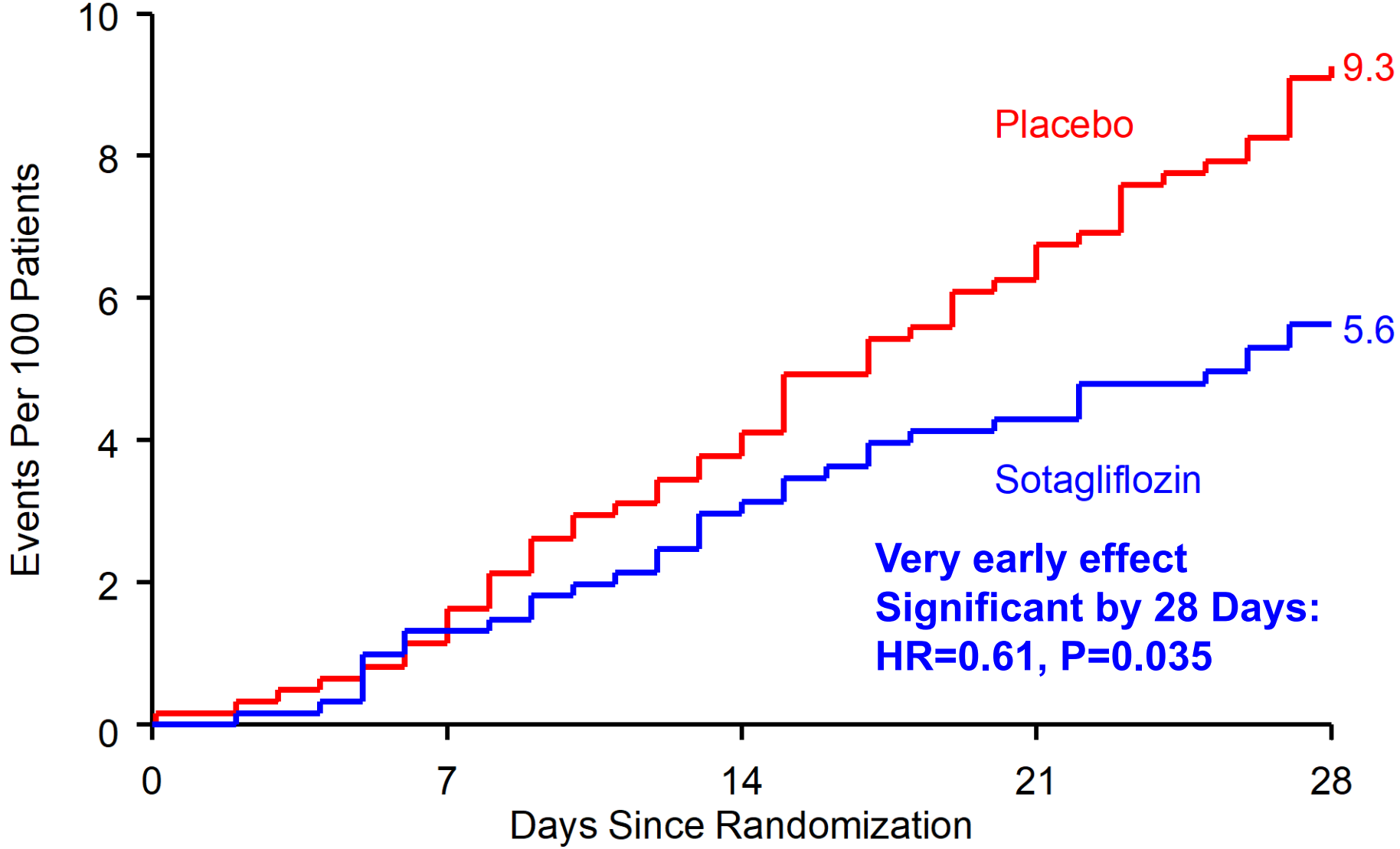

Bhatt DL, Szarek M, Steg PG, et al., and Pitt B. *N Engl J Med.* 2020. Bhatt DL. AHA 2020, virtual.

Total CV Death and HHF

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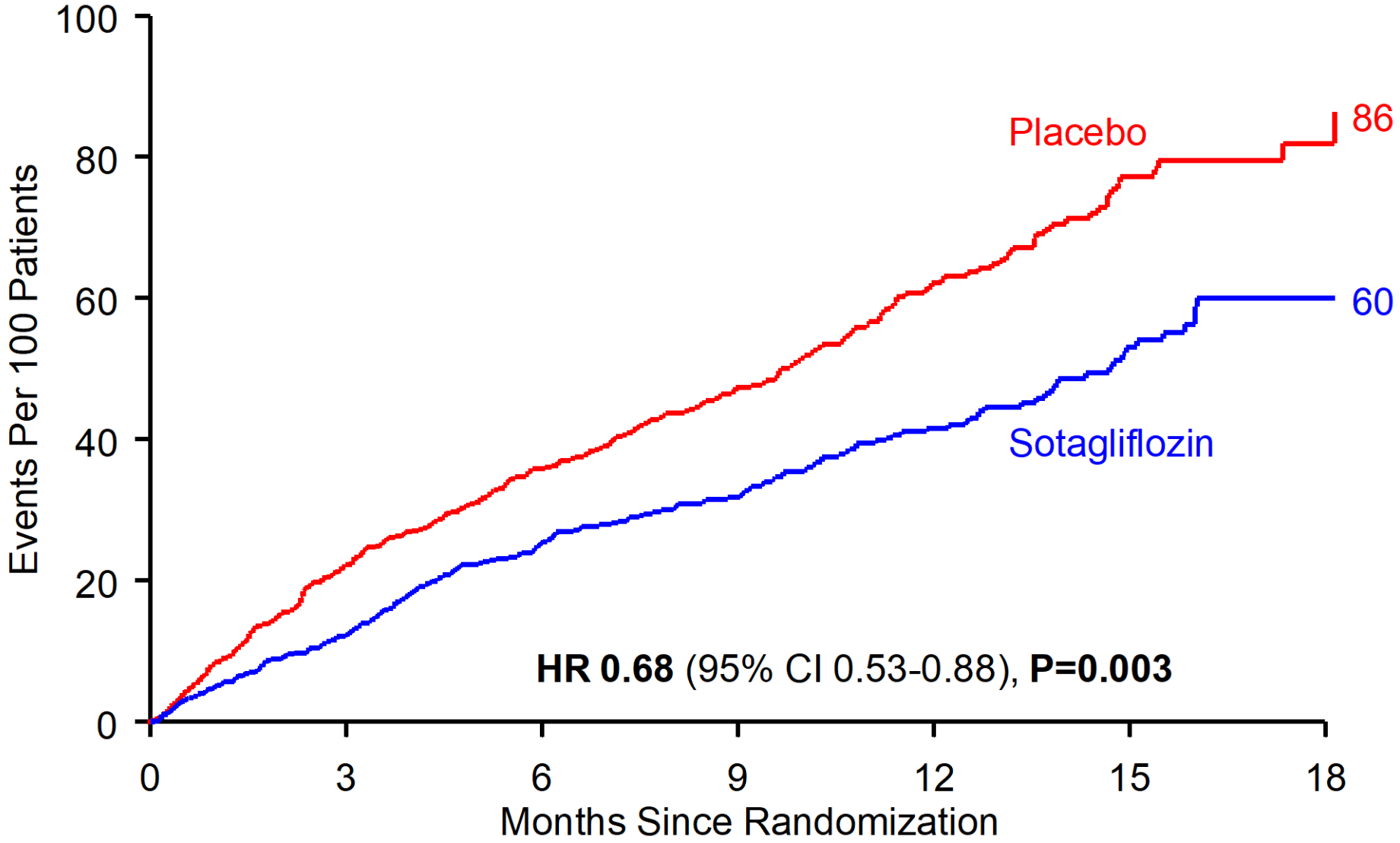

Bhatt DL, Szarek M, Steg PG, et al., and Pitt B. *N Engl J Med.* 2020. Bhatt DL. AHA 2020, virtual.

First of CV Death or HHF

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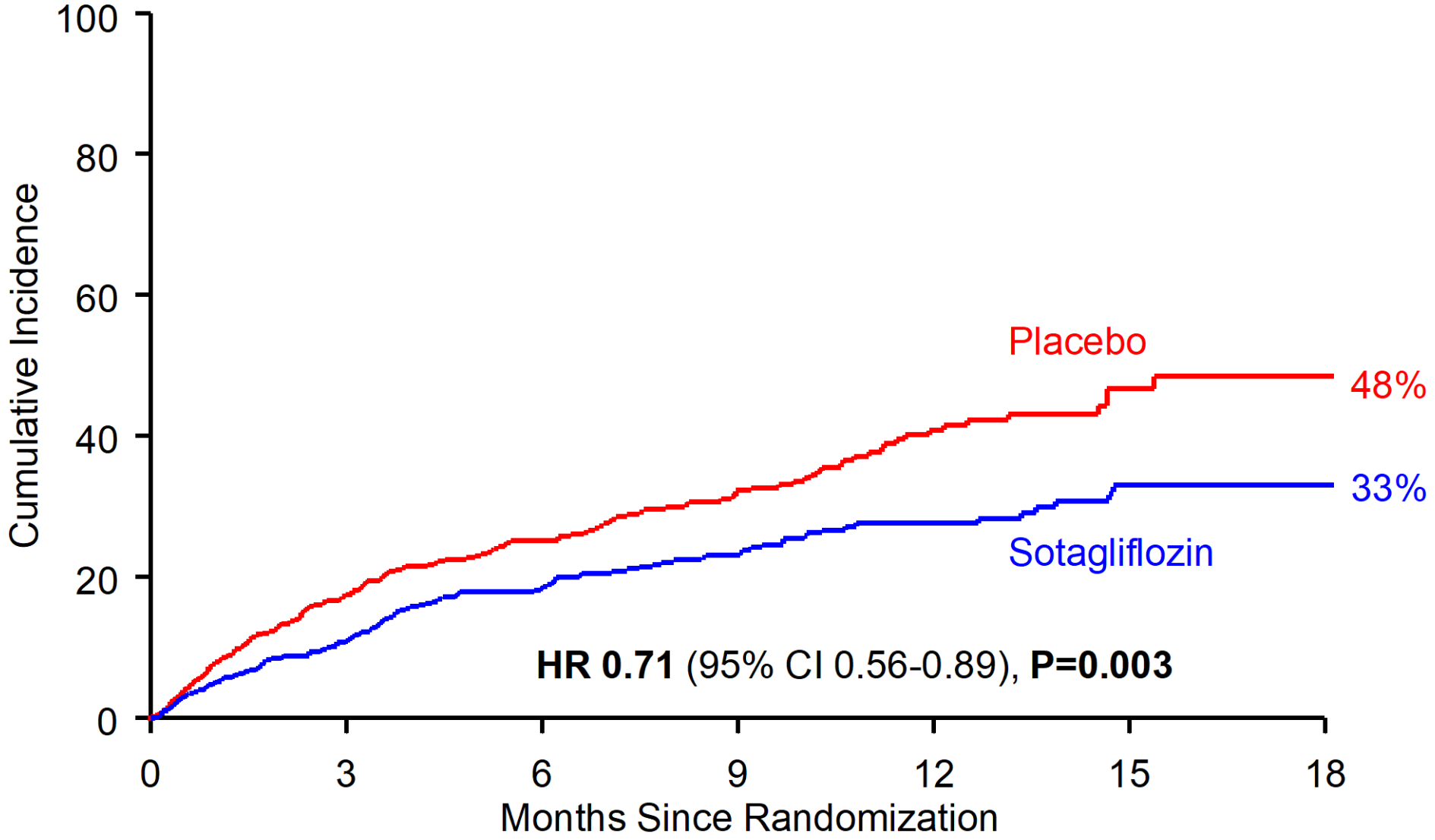

Bhatt DL, Szarek M, Steg PG, et al., and Pitt B. *N Engl J Med.* 2020. Bhatt DL. AHA 2020, virtual.

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	**51.0 [245]**	**76.3 [355]**	**0.67 (0.52-0.85)**	**0.0009**
Total HHF and urgent HF visit	40.4 [194]	63.9 [297]	0.64 (0.49-0.83)	0.0008
CV death	10.6 [51]	12.5 [58]	0.84 (0.58-1.22)	0.36
Total CV death, HHF, NFMI, and non-fatal stroke	51.4 [247]	71.0 [330]	0.72 (0.56-0.92)	0.008*
Total CV death, HHF, urgent HF visit, and HF while hospitalized	54.7 [263]	80.6 [375]	0.68 (0.54-0.86)	0.001*
All-cause death	13.5 [65]	16.3 [76]	0.82 (0.59-1.14)	0.23*
Change in KCCQ-12 score, points	17.7	13.6	4.1 (1.3-7.0)	0.005*
Change in eGFR, mL/min/1.73m^2	-0.34	-0.18	-0.16 (-1.30-0.98)	0.78*

*Nominal p-value. Rate = number of events per 100 patient-years. Values in table for change in KCCQ-12 score and change in eGFR are least squares means, difference in least squares means, and 95% CI for difference in least squares means

Adverse Events of Special Interest

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Composite Term	Sotagliflozin N=605 n (%)	Placebo N=611 n (%)	P-value
Bone fractures	12 (2.0)	9 (1.5)	0.52
Diabetic ketoacidosis	2 (0.3)	4 (0.7)	0.69
Genital mycotic infections	5 (0.8)	1 (0.2)	0.12
Urinary tract infections	52 (8.6)	44 (7.2)	0.40
Volume depletion	57 (9.4)	54 (8.8)	0.77
Diarrhea	42 (6.9)	25 (4.1)	0.032
Pancreatitis	0	3 (0.5)	0.25
Venous thrombotic events	0	7 (1.1)	0.015
Malignancies	4 (0.7)	4 (0.7)	1.00
Adverse event leading to amputation	4 (0.7)	1 (0.2)	0.22
Severe hypoglycemia	9 (1.5)	2 (0.3)	0.037

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

Improvement in KCCQ-12 to Month 4

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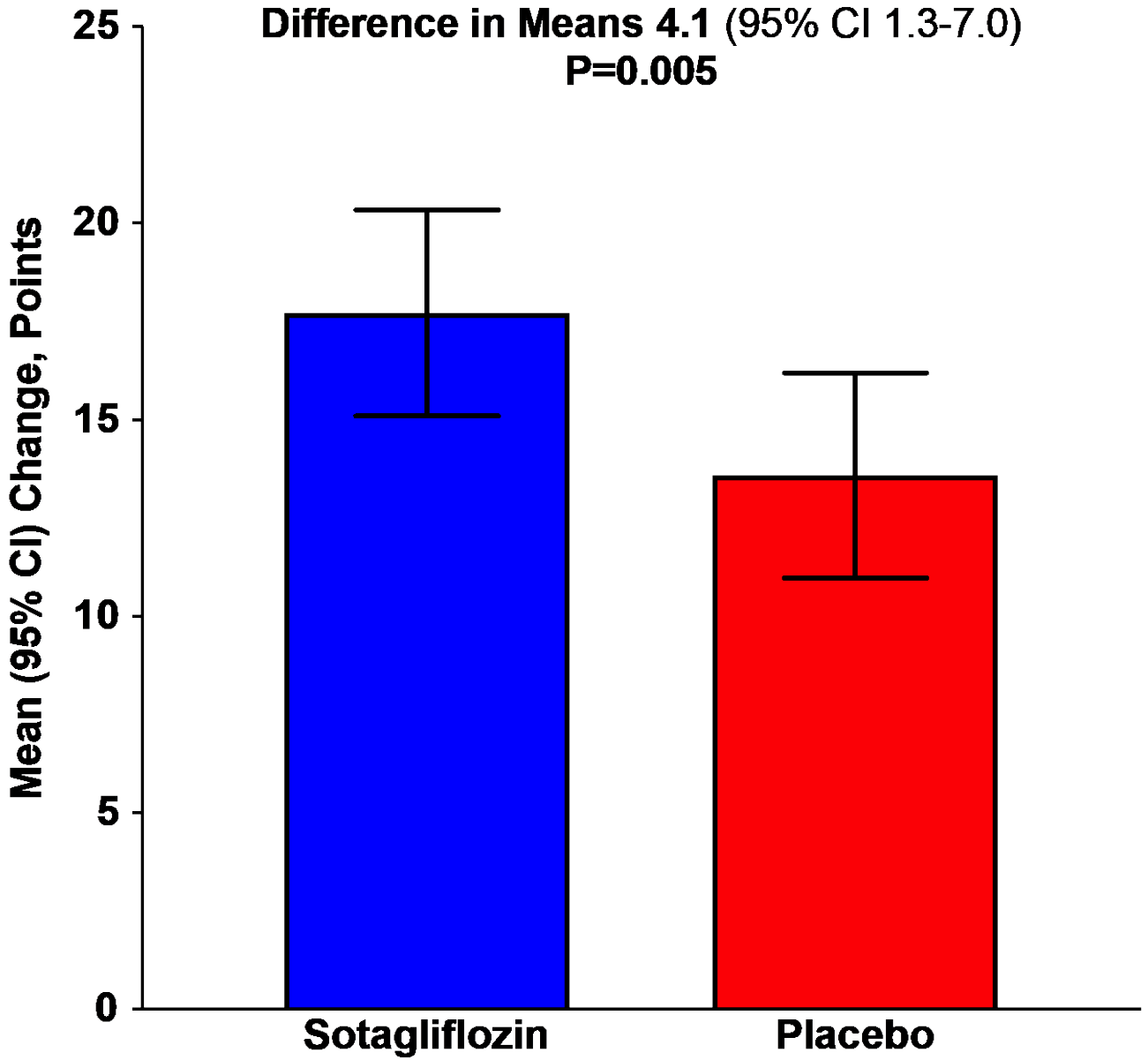

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Change in eGFR

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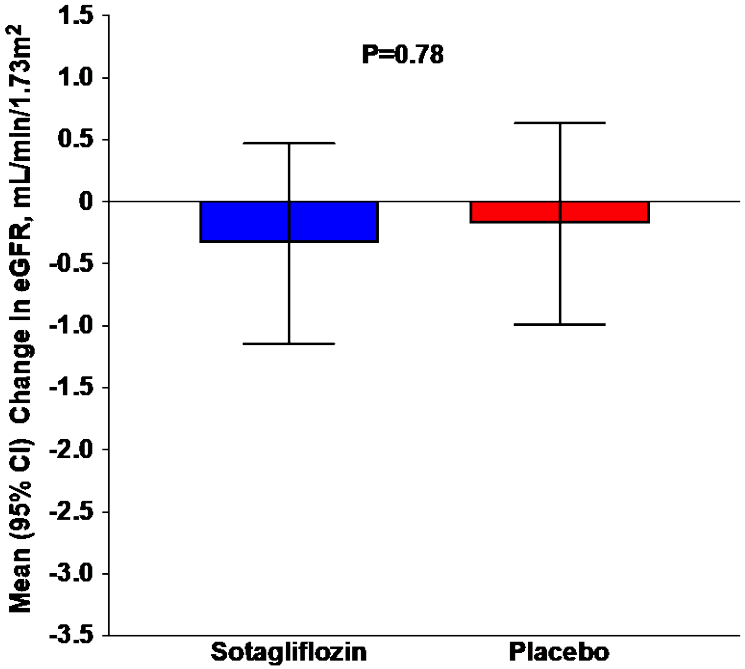
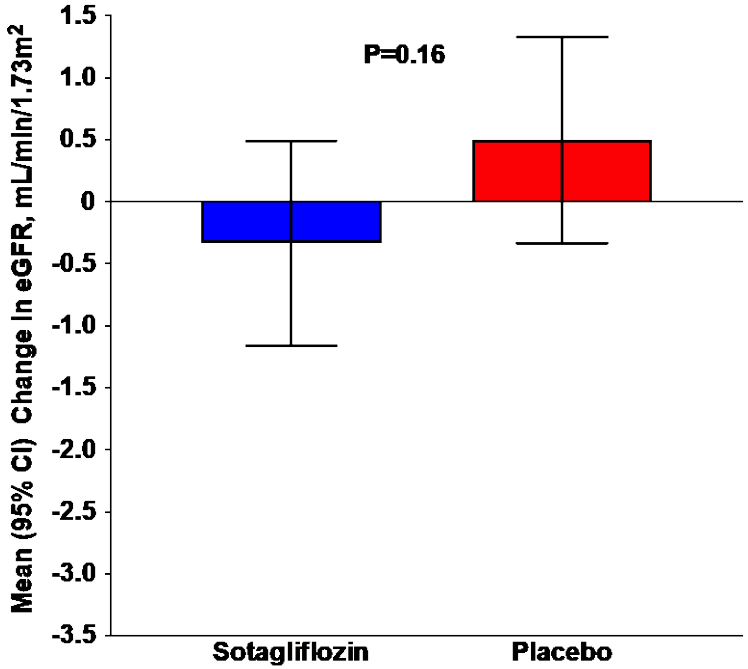
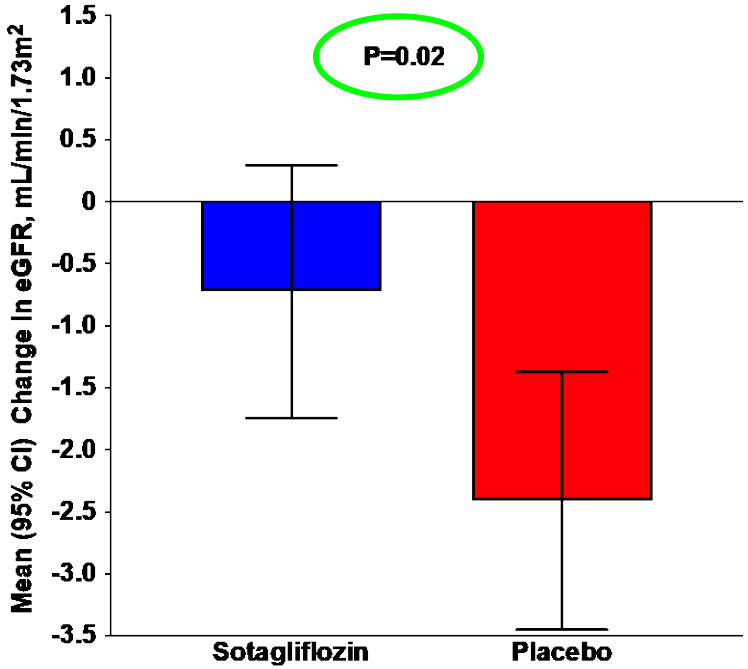
Overall



Prior to Week 4



After Week 4



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Primary Efficacy Subgroups

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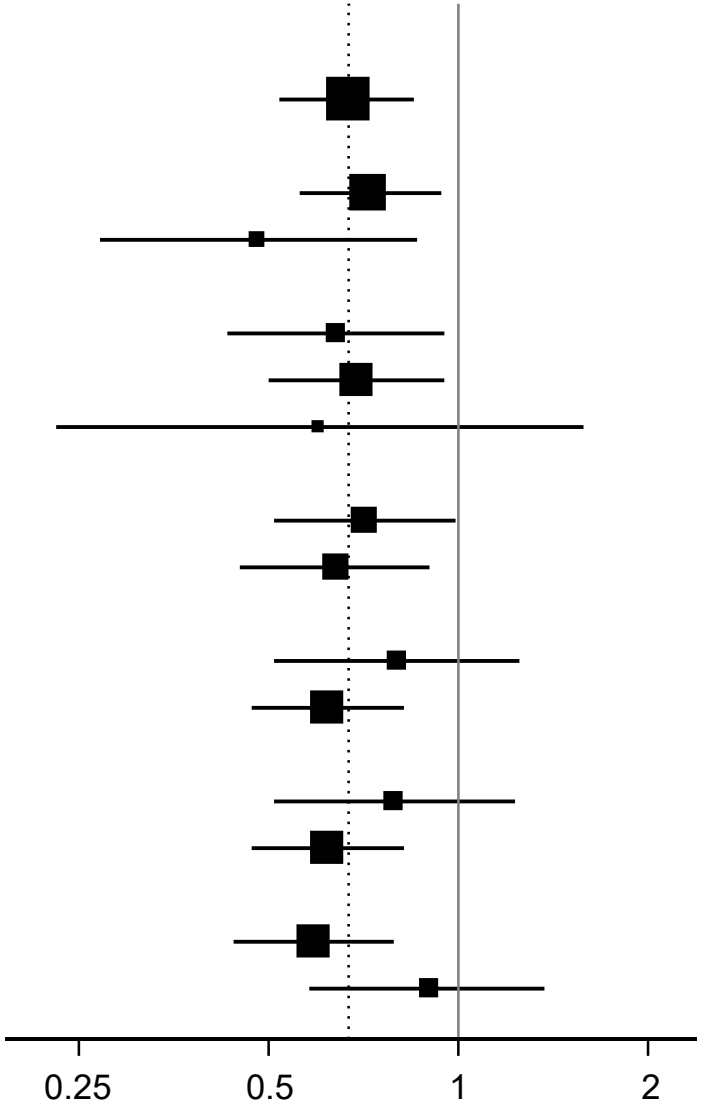
Subgroup	Patients	Events Per 100 py: Sotagliflozin	Events Per 100 py: Placebo	HR (95% CI)
Overall	1222	51.0	76.3	0.67 (0.52, 0.85)
LVEF (%)				
< 50	966	56.9	79.9	0.72 (0.56, 0.94)
≥ 50	256	30.6	64.0	0.48 (0.27, 0.86)
Geographic Region				
Americas	346	68.3	103.0	0.64 (0.43, 0.95)
Europe	800	44.1	64.7	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)



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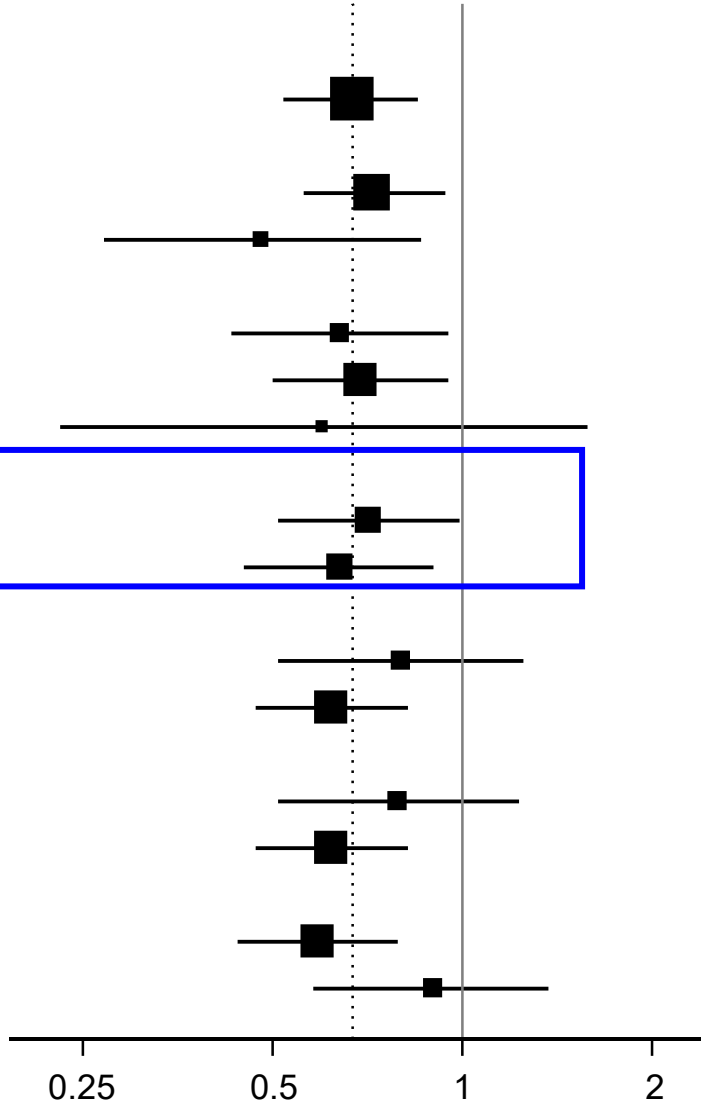

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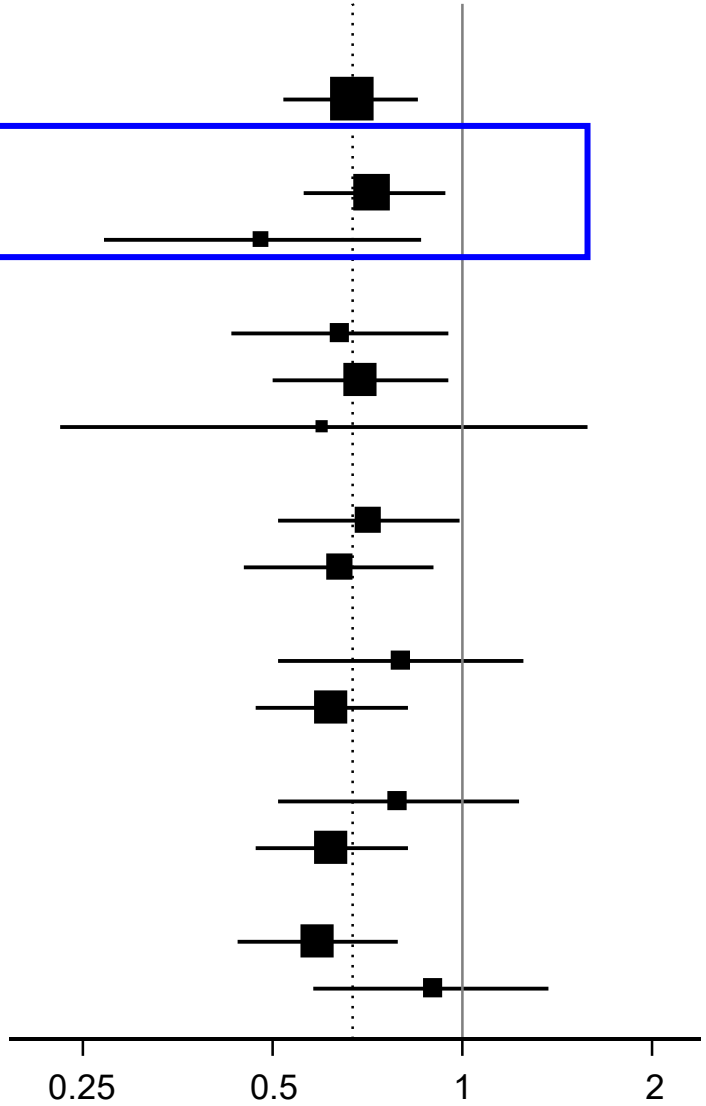

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Limitations

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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 primary endpoint was also strongly positive

Investigator-reported events were used instead of adjudication

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

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

Conclusions

SOLOIST

In patients with acute decompensated HF, **sotagliflozin** significantly reduced the composite of total CV deaths, hospitalizations for HF, and urgent HF visits by **33%**

- With an early benefit that was **significant by 1 month**
- A **Number Needed to Treat of only 4** patient-years

With careful patient selection and close monitoring, early initiation of **sotagliflozin** was generally well tolerated (similar to placebo) and safe

The benefits were consistent across subgroups, including:

- Initiation **prior to or soon after hospital discharge**
- In HF with **reduced or preserved ejection fraction**

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