SOLOIST SCORED

Benefits of SGLT1/2 Inhibition with Sotagliflozin in Heart Failure With Preserved Ejection Fraction

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, Phillip Banks, MS, Adriaan A. Voors, MD, PhD, Marco Metra, MD, Lars H. Lund, MD, PhD, Mikhail N. Kosiborod, MD, Subodh Verma, MD, PhD, Jacob A. Udell, MD, Justin A. Ezekowitz, MBBch, Renato D. Lopes, MD, PhD, Harvey D. White, D.Sc, Rafael Díaz, MD, **Bertram Pitt, MD**, on Behalf of the **SOLOIST-WHF** and **SCORED** Investigators

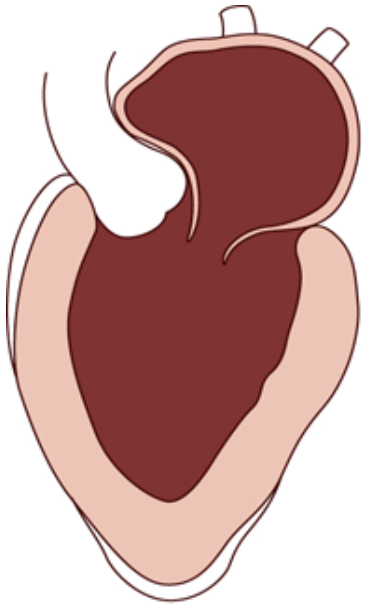
Disclosures

Dr. Deepak L. Bhatt discloses the following relationships - Advisory Board: Cardax, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, Janssen, Level Ex, Medscape Cardiology, MyoKardia, Novo Nordisk, 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, HLS Therapeutics, Idorsia, Ironwood, Ischemix, Janssen, **Lexicon**, Lilly, Medtronic, MyoKardia, Novo Nordisk, Owkin, 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: Abbott, Biotronik, Boston Scientific, CSI, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, Takeda.

SOLOIST-WHF and SCORED were 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



Diabetes **Diabetes and No Diabetes**

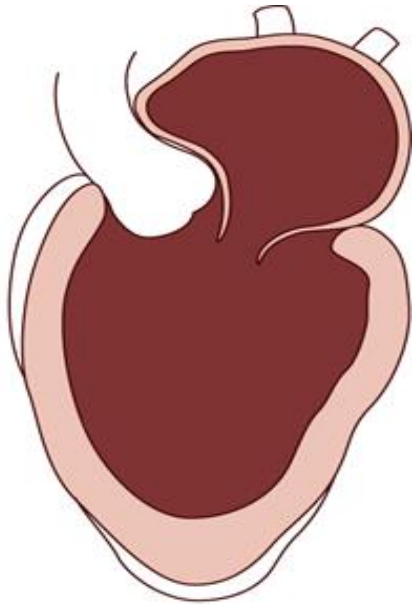
Window of opportunity for treatment

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**

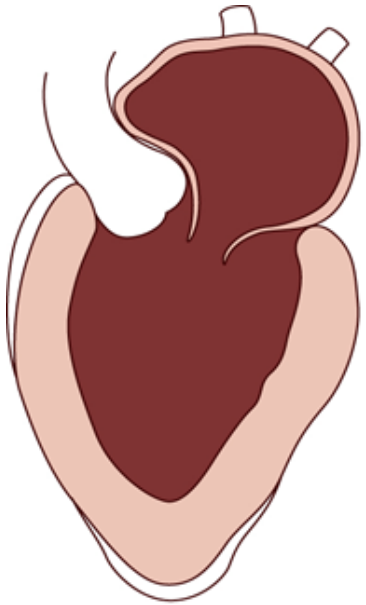


Normal Ventricular Function

Advanced Heart Failure

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

The Evolution of SGLT2i in HF Management



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

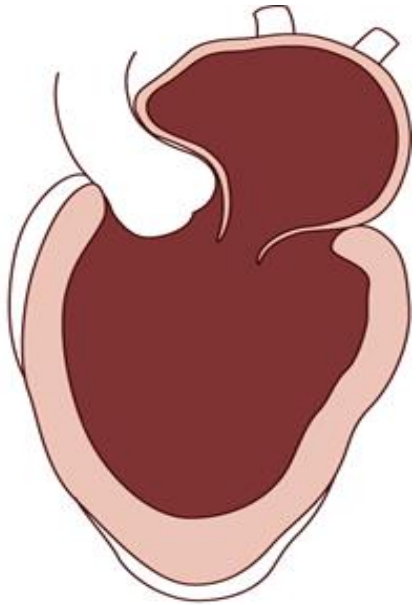
0 years

10 years

18-20 years

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

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

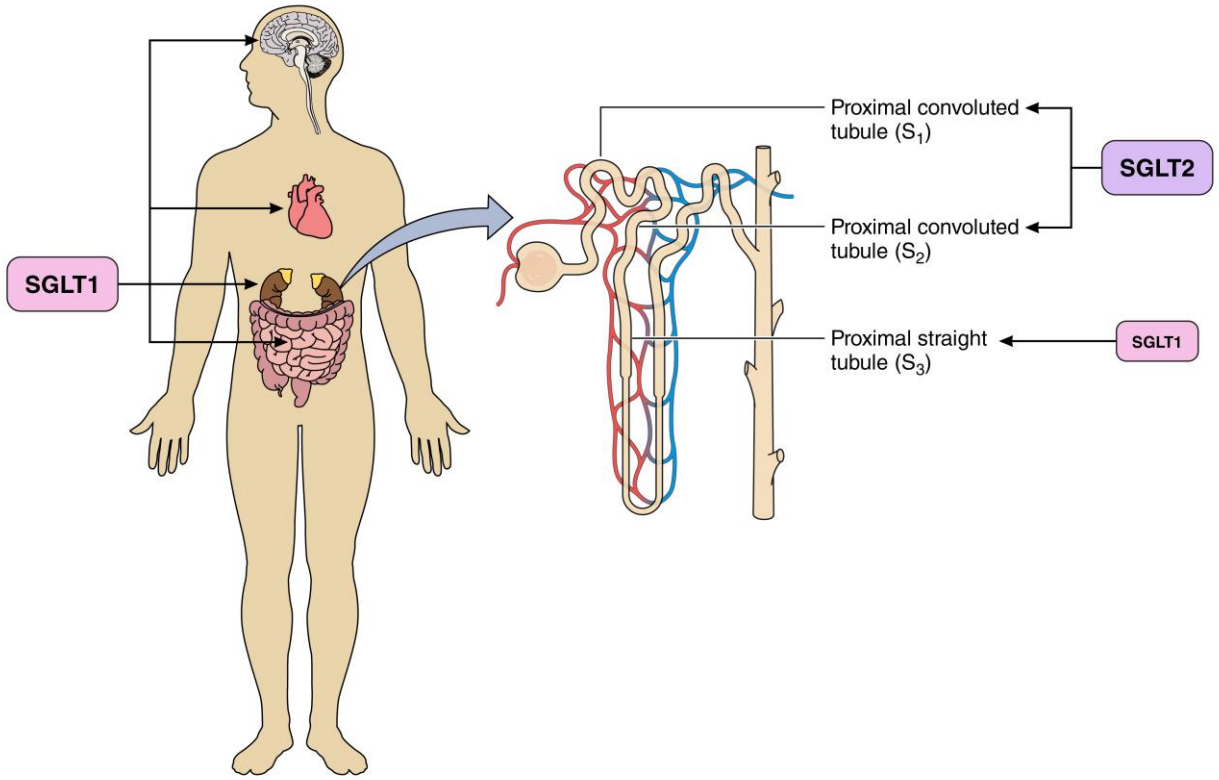


Normal Ventricular Function

Advanced Heart Failure

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

Sotagliflozin: Dual SGLT1 and SGLT2 Inhibitor

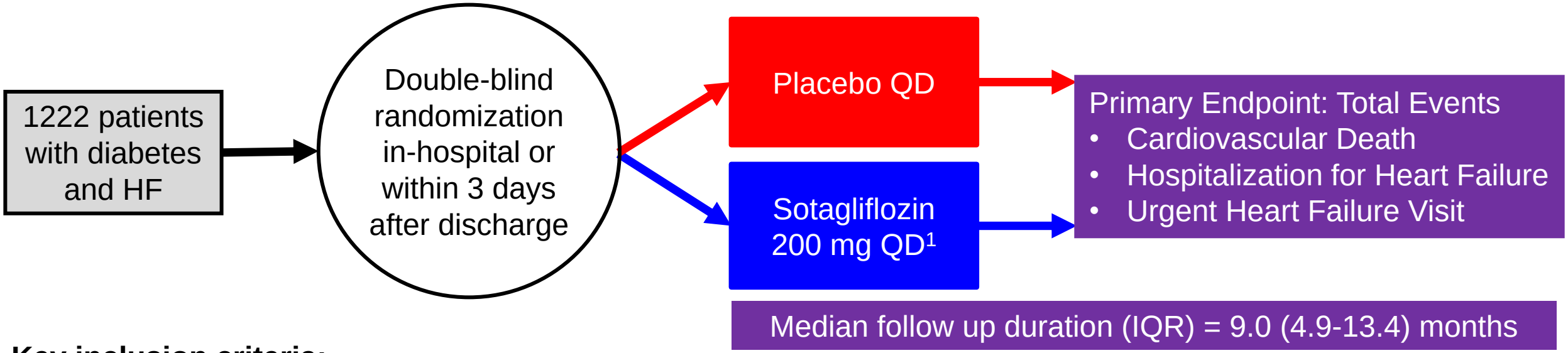


- **SGLT1** is the primary transporter for absorption of glucose and galactose in the GI tract
- Pharmacologic inhibition by sotagliflozin is independent of insulin and does not depend on kidney function
- Potential reduction in atherosclerotic risks

- **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.

SOLOIST-WHF Trial Design



Key inclusion criteria:

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

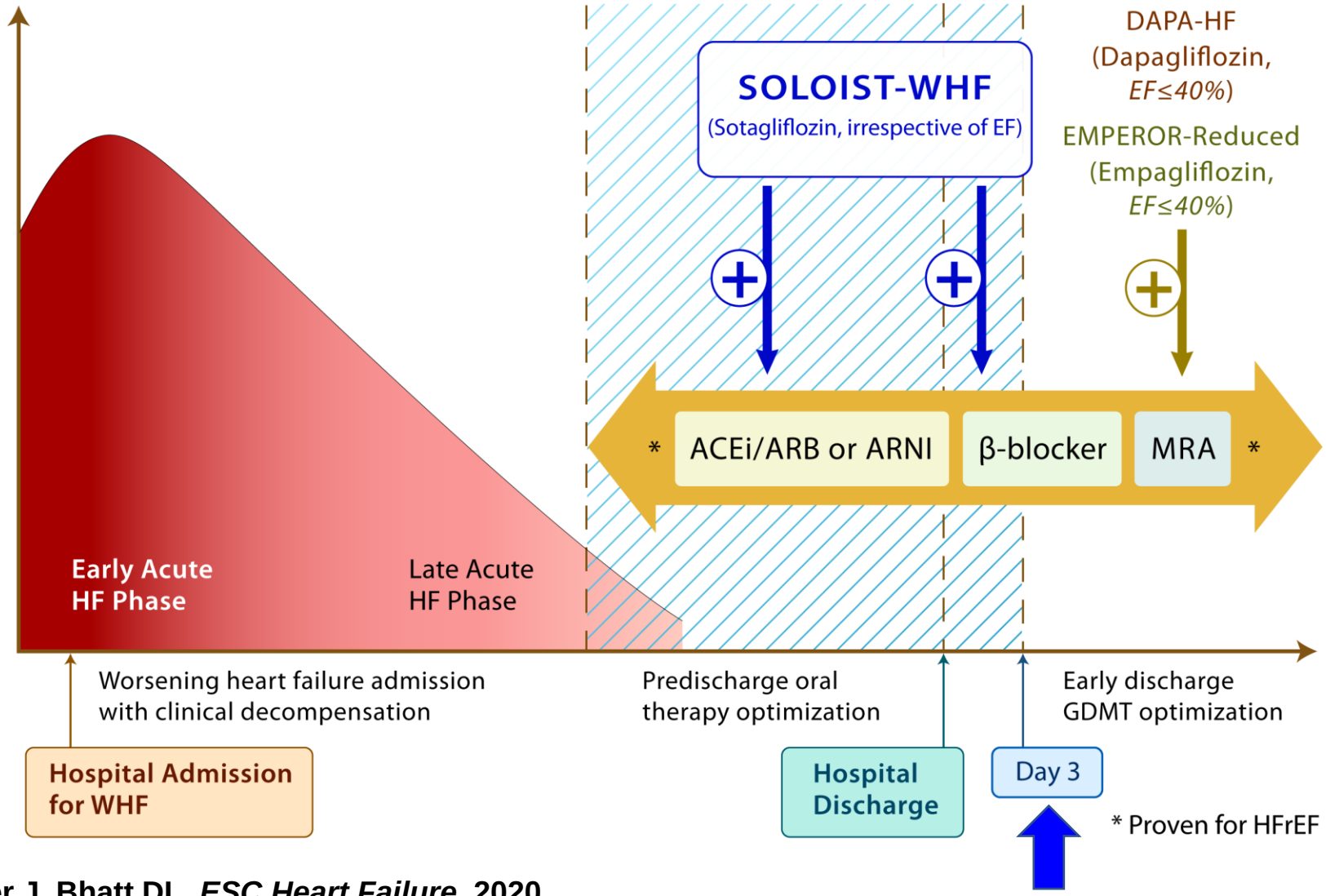
Key exclusion criteria:

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

[1]Goal of dose increase to 400 mg QD

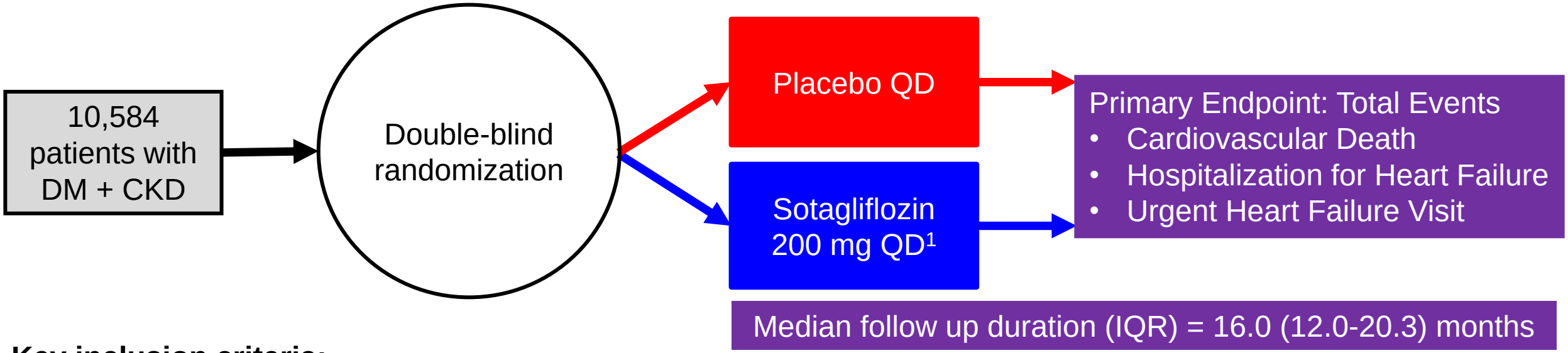
Bhatt DL, Szarek M, Steg PG, et al., and Pitt B. *N Engl J Med.* 2020. Bhatt DL. AHA 2020, virtual.

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



Verma S, Anker SD, Butler J, Bhatt DL. *ESC Heart Failure.* 2020.

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:

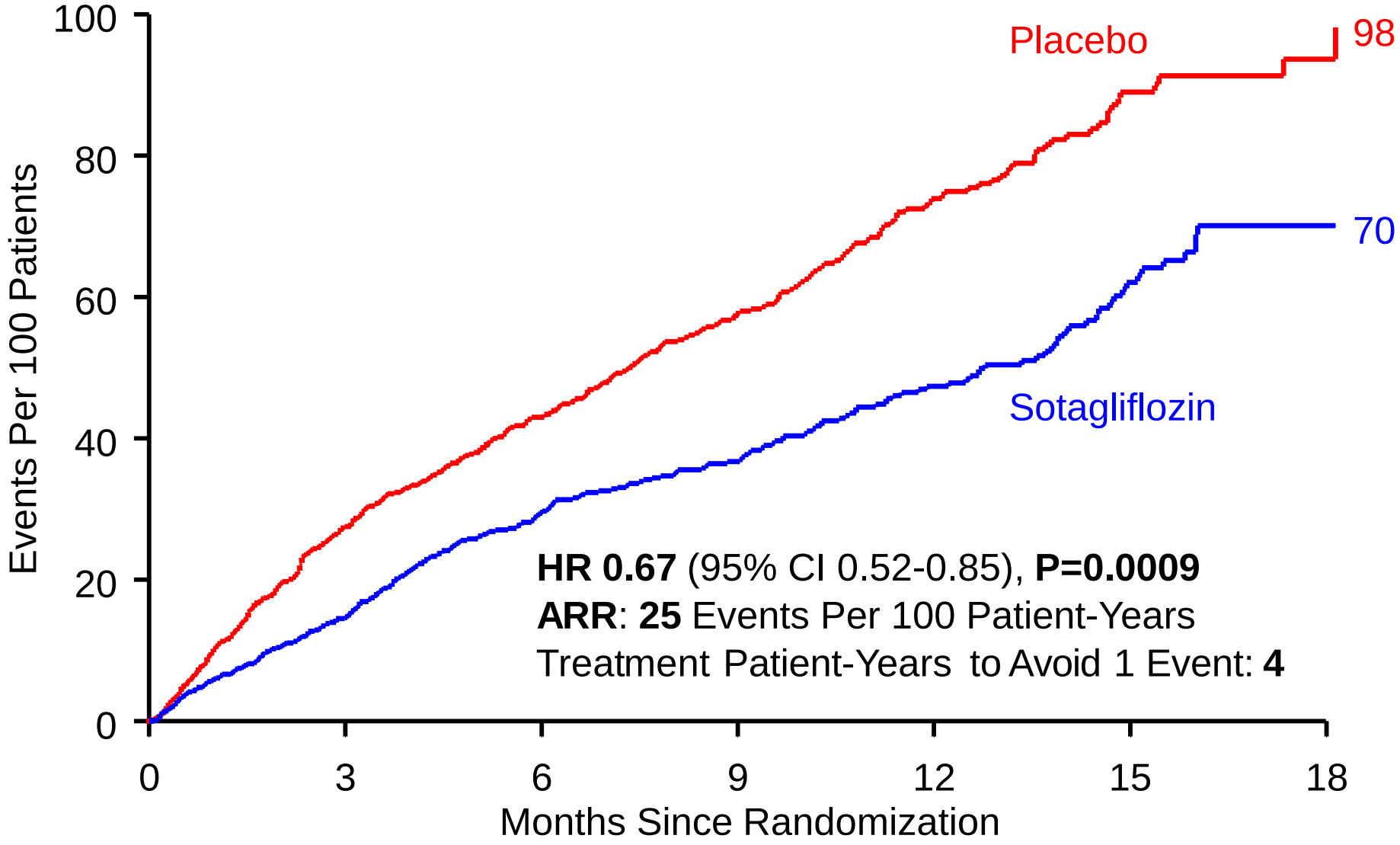
- Planned start of SGLT2 inhibitor

[1]Goal of dose increase to 400 mg QD

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

SOLOIST



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

Days Alive Out of Hospital (DAOH)
(Poisson regression)

SOLOIST

	Sotagliflozin (N=608)	Placebo (N=614)		
	Rate per 100 p-y		RR (95% CI)	P value
DAOH	91.8 years	88.9 years	1.03 (1.00, 1.06)	0.027
Days dead	6.3 years	8.9 years	0.71 (0.52, 0.99)	0.041
Days in hospital	1.9 years	2.2 years	0.86 (0.69, 1.08)	0.21

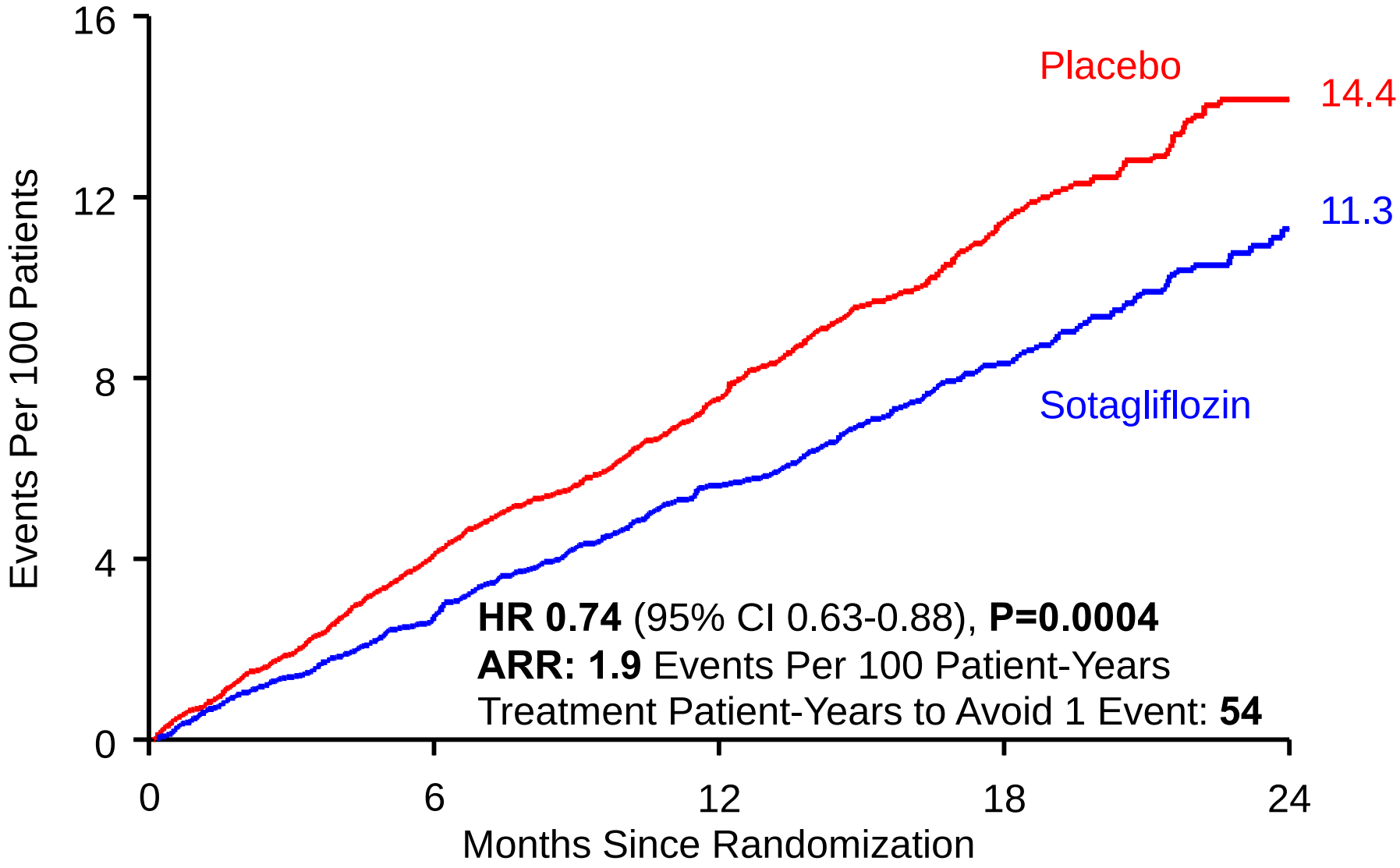
CI, confidence interval; DAOH, days alive and out of hospital; p-y, patient-years; RR, rate ratio; SD, standard deviation.

For every 100 patient-years of follow-up, patients in the **sotagliflozin** group were alive and out of the hospital for 2.9 years more in absolute terms and 3% in relative terms.

Szarek M, Bhatt DL, Steg PG, et al., and Pitt B. *Under Review.* 2021. Szarek M. ACC 2021, virtual.

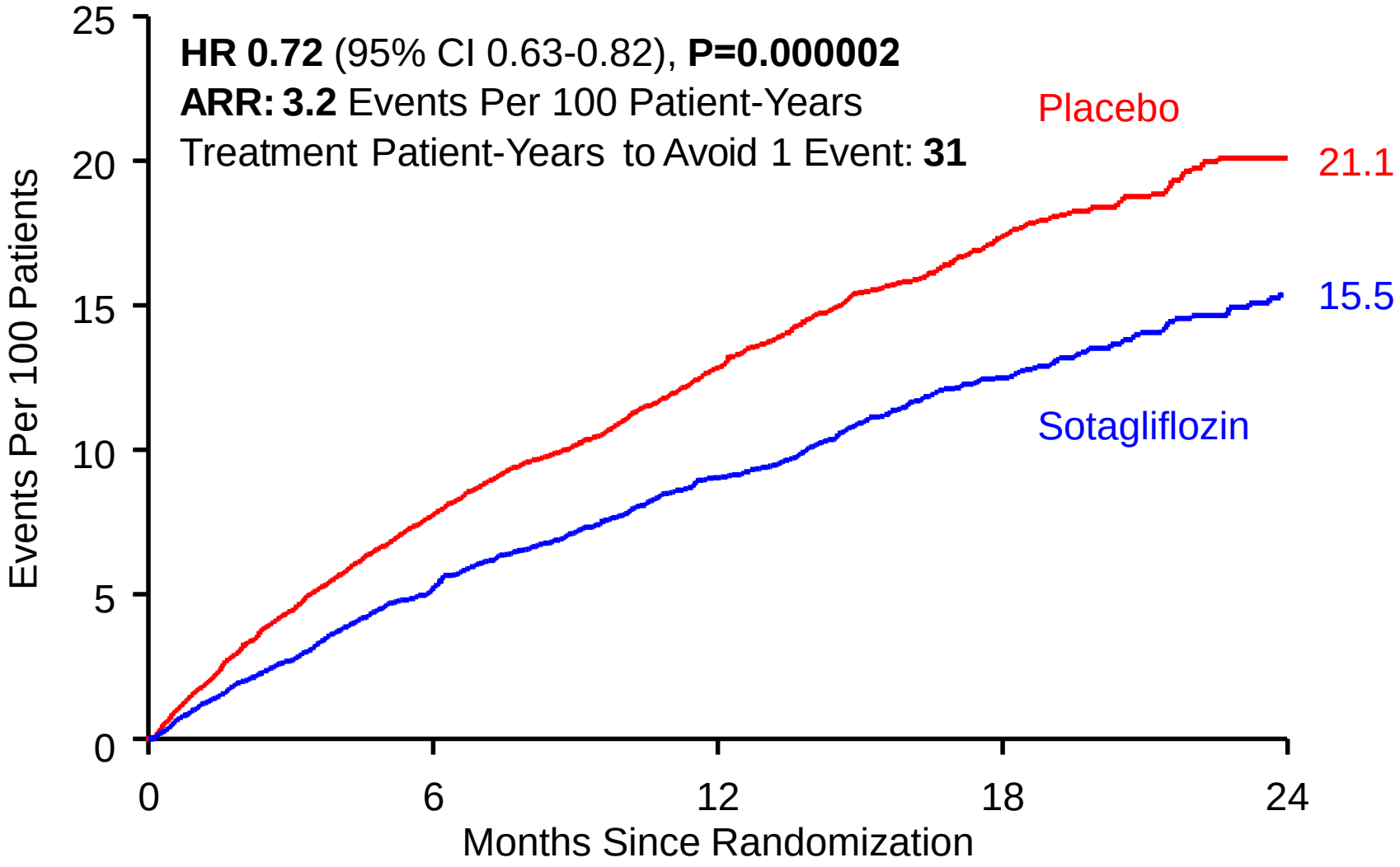
Primary Efficacy: Total CV Death, HHF, and Urgent HF Visit

SCORED



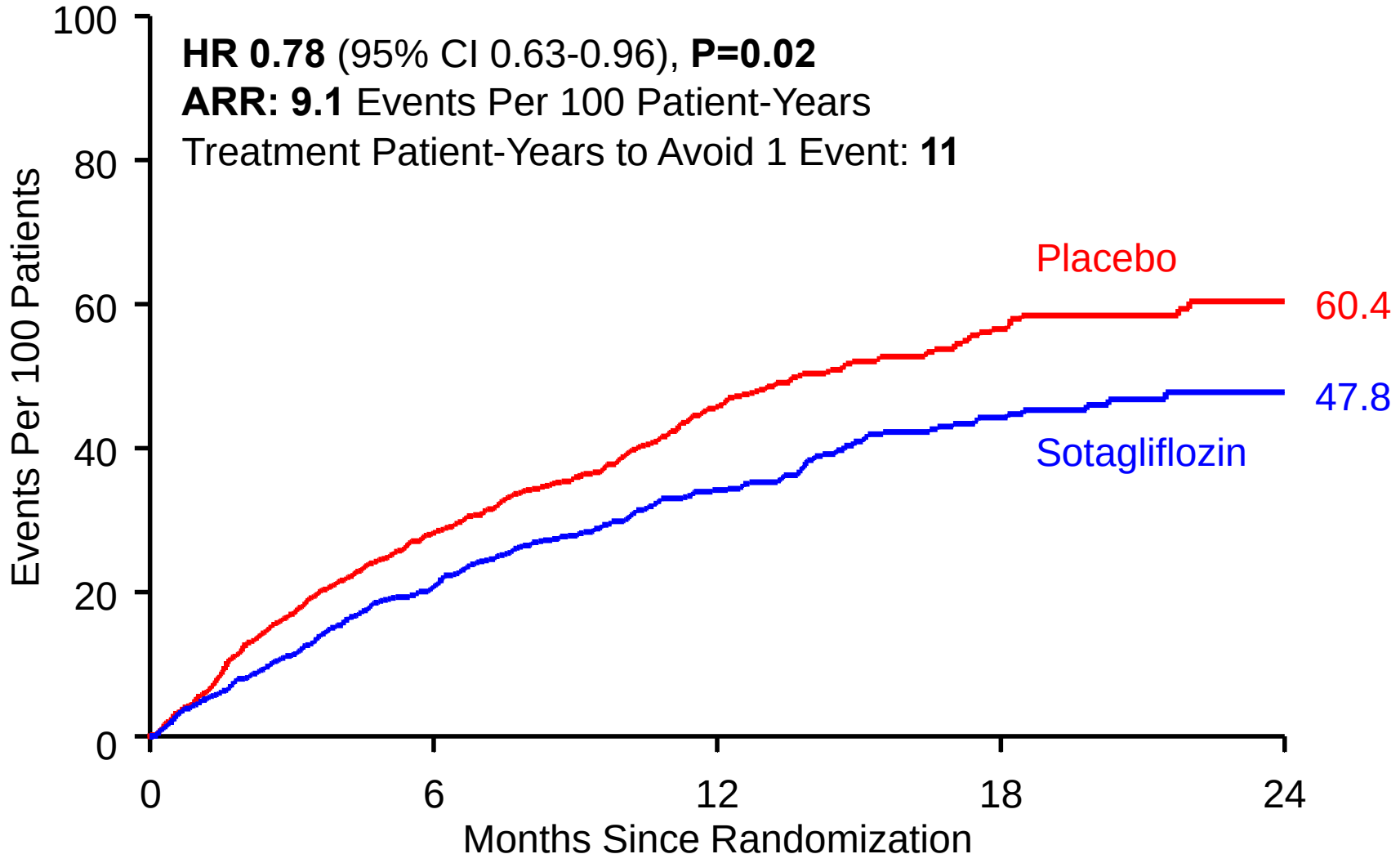
Bhatt DL, Szarek M, Pitt B, et al., and Steg PG. *N Engl J Med.* 2020. Bhatt DL. AHA 2020, virtual.

Pooled Data: SOLOIST and SCORED Total CV Death, HHF, and Urgent HF Visit in 11,784 Patients



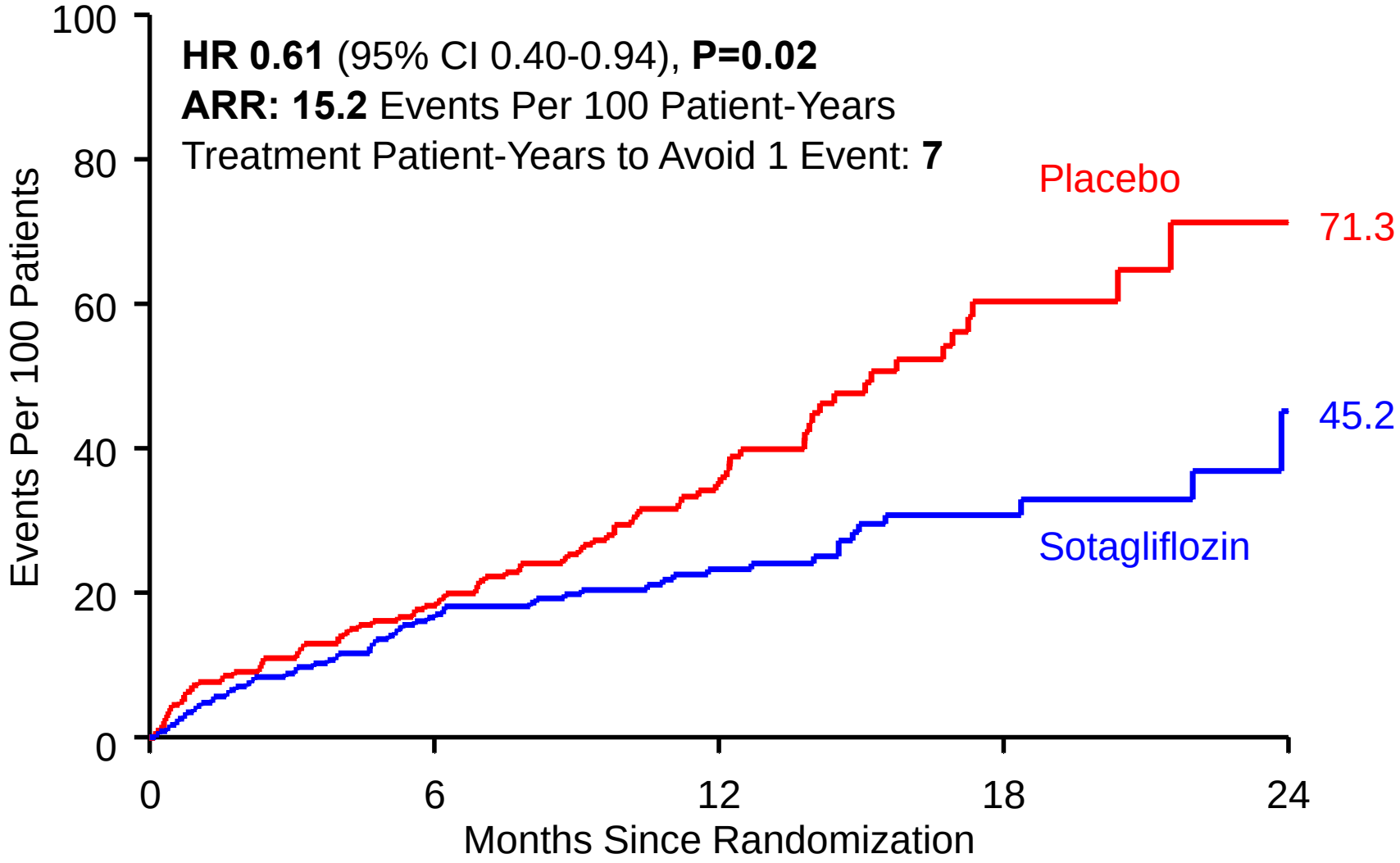
Bhatt DL. ACC 2021, virtual.

Pooled Data: SOLOIST and SCORED Total CV Death, HHF, and Urgent HF Visit in 1758 Patients with HFrEF (<40%)



Bhatt DL. ACC 2021, virtual.

Pooled Data: SOLOIST and SCORED Total CV Death, HHF, and Urgent HF Visit in 456 Patients with HFmrEF (40% - <50%)*

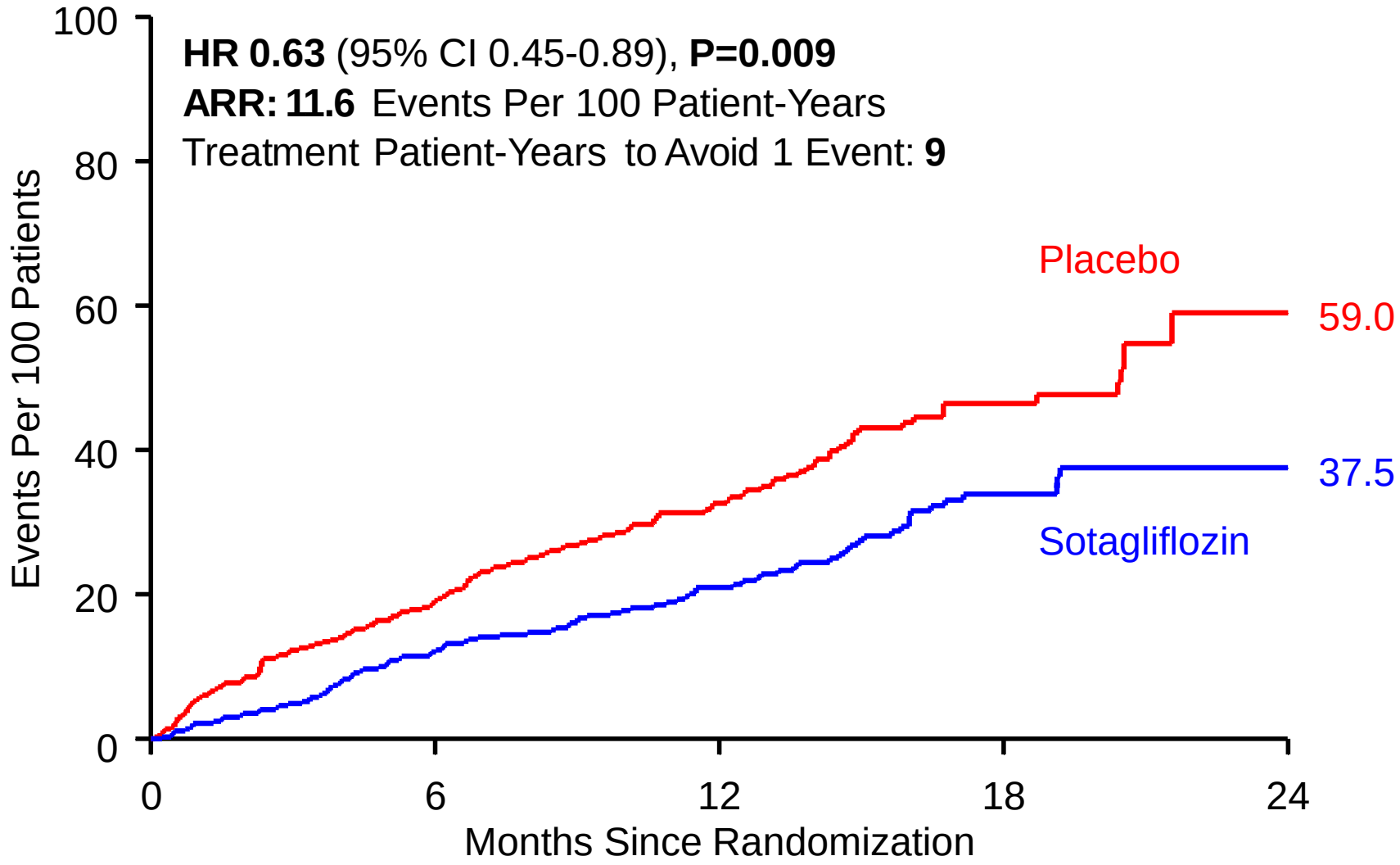


Bhatt DL. ACC 2021, virtual.

For this analysis, patients from SCORED needed to have a history of HF within 2 years.

*post hoc

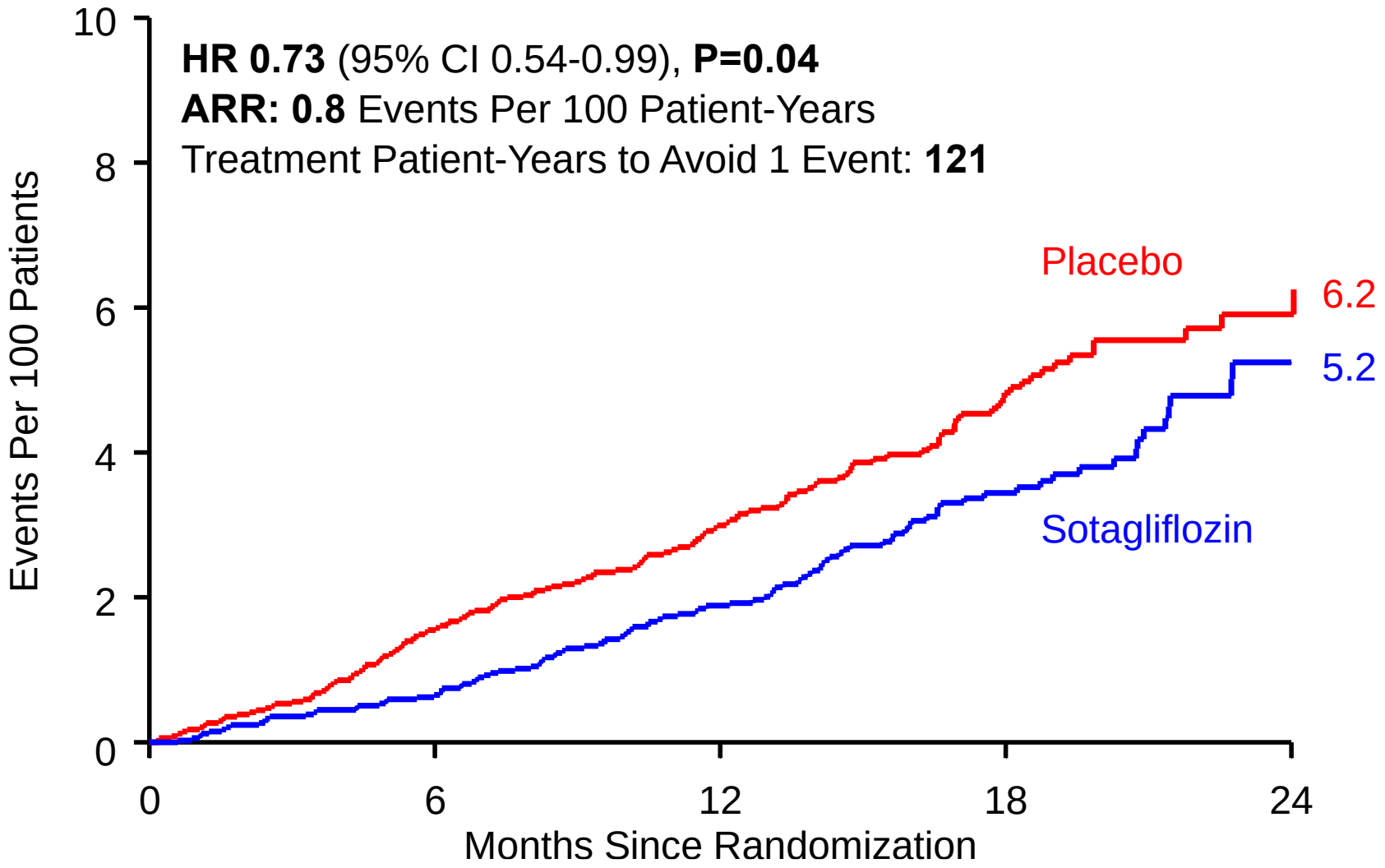
Pooled Data: SOLOIST and SCORED Total CV Death, HHF, and Urgent HF Visit in 739 Patients with HFpEF (≥50%)



For this analysis, patients from SCORED needed to have a history of HF within 2 years.

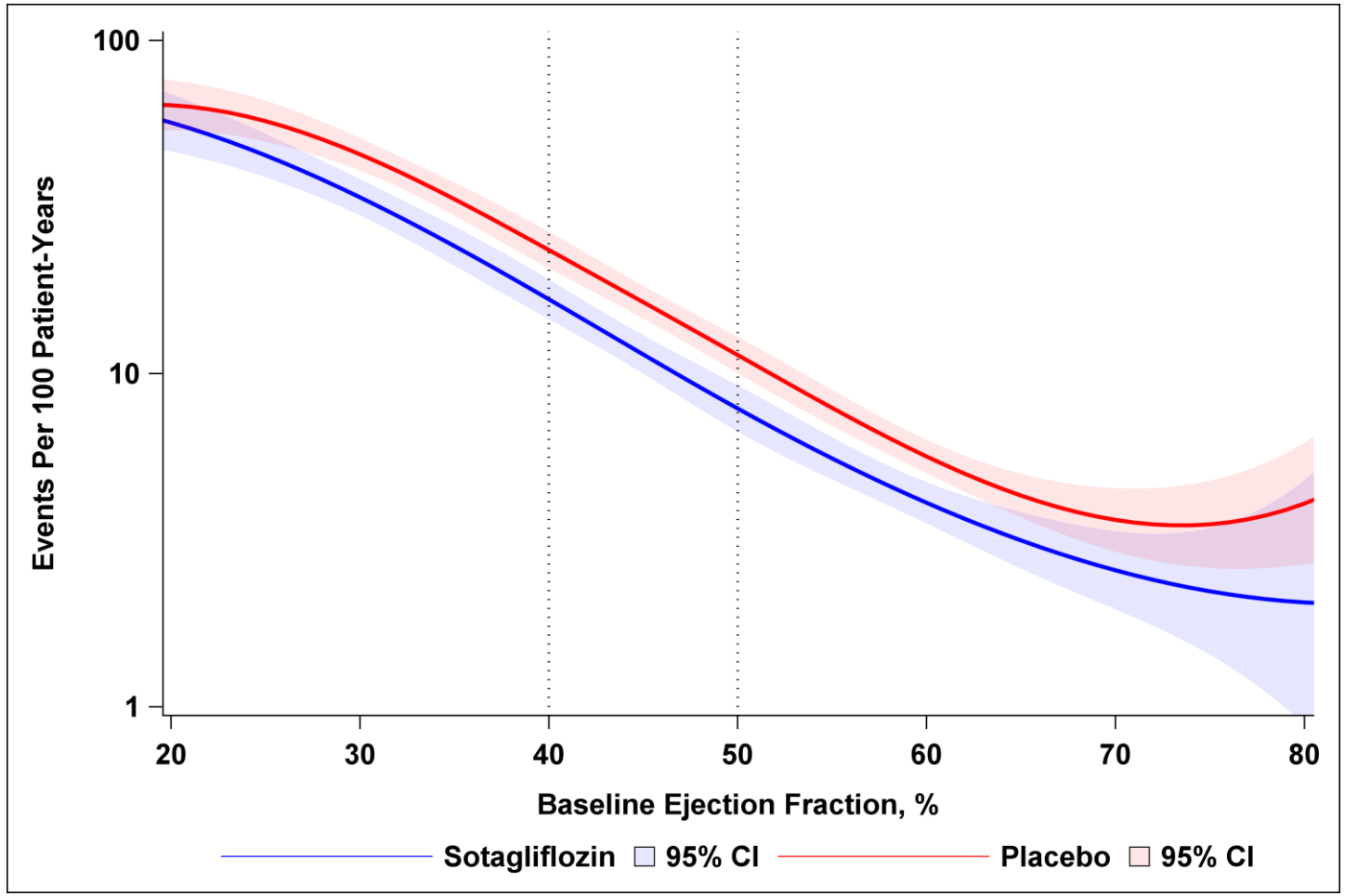
Bhatt DL. ACC 2021, virtual.

SCORED Total CV Death, HHF, and Urgent HF Visit in 6738 Patients with no History of HF (EF≥50%)



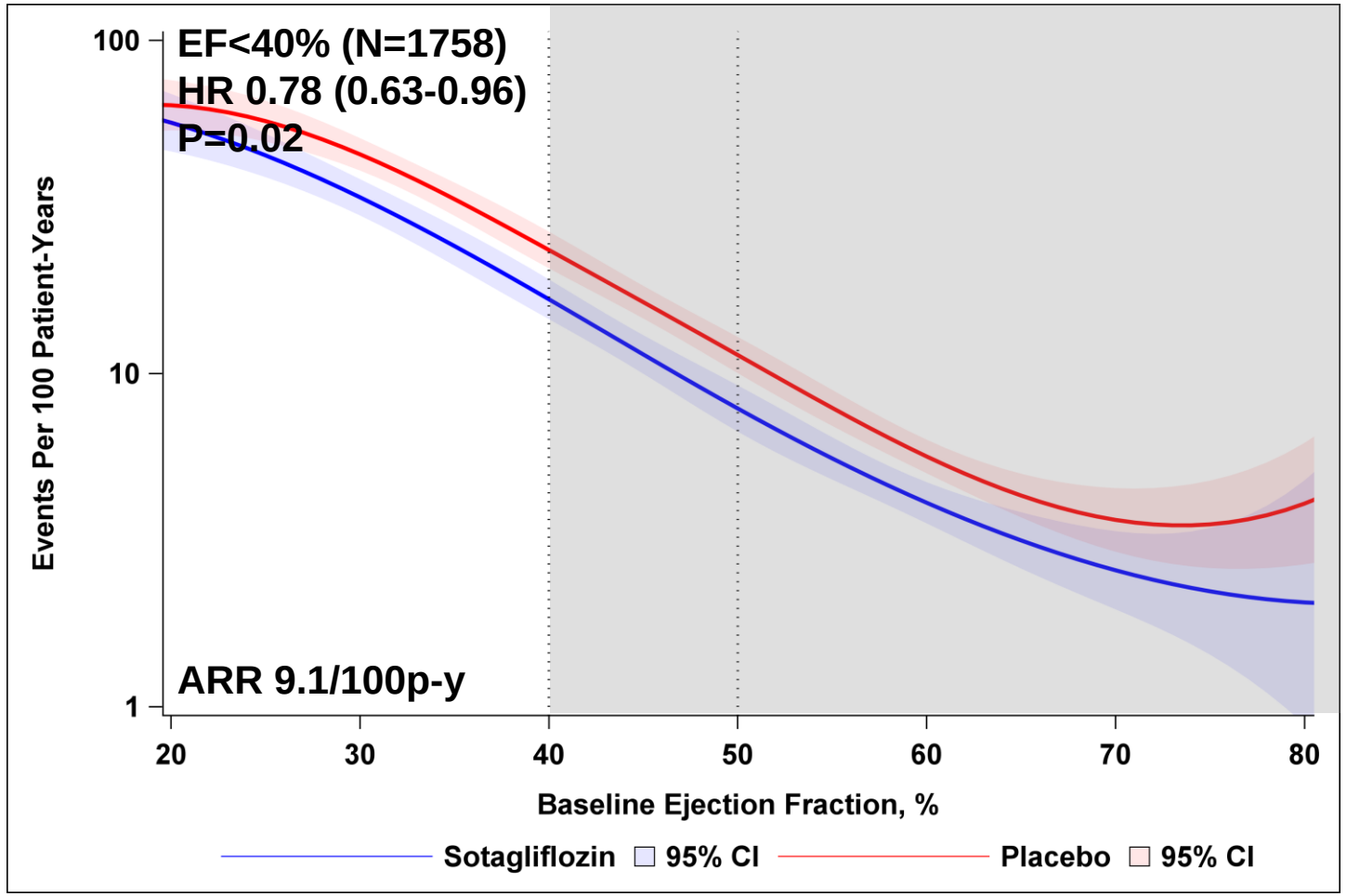
Bhatt DL. ACC 2021, virtual.

Pooled Data: SOLOIST and SCORED Total CV Death, HHF, and Urgent HF Visit in 11,784 Patients



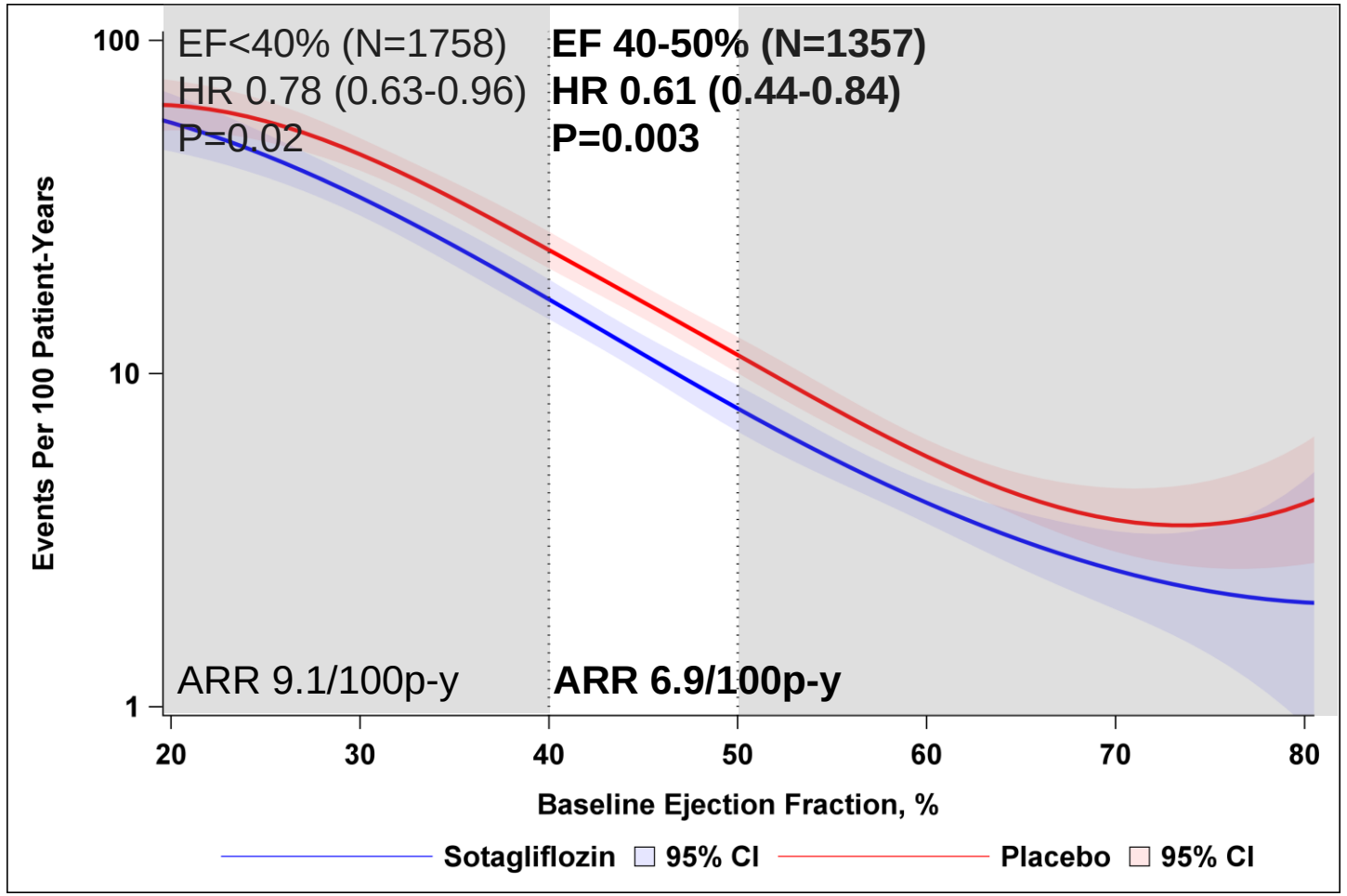
Bhatt DL. ACC 2021, virtual.

Pooled Data: SOLOIST and SCORED Total CV Death, HHF, and Urgent HF Visit in 11,784 Patients



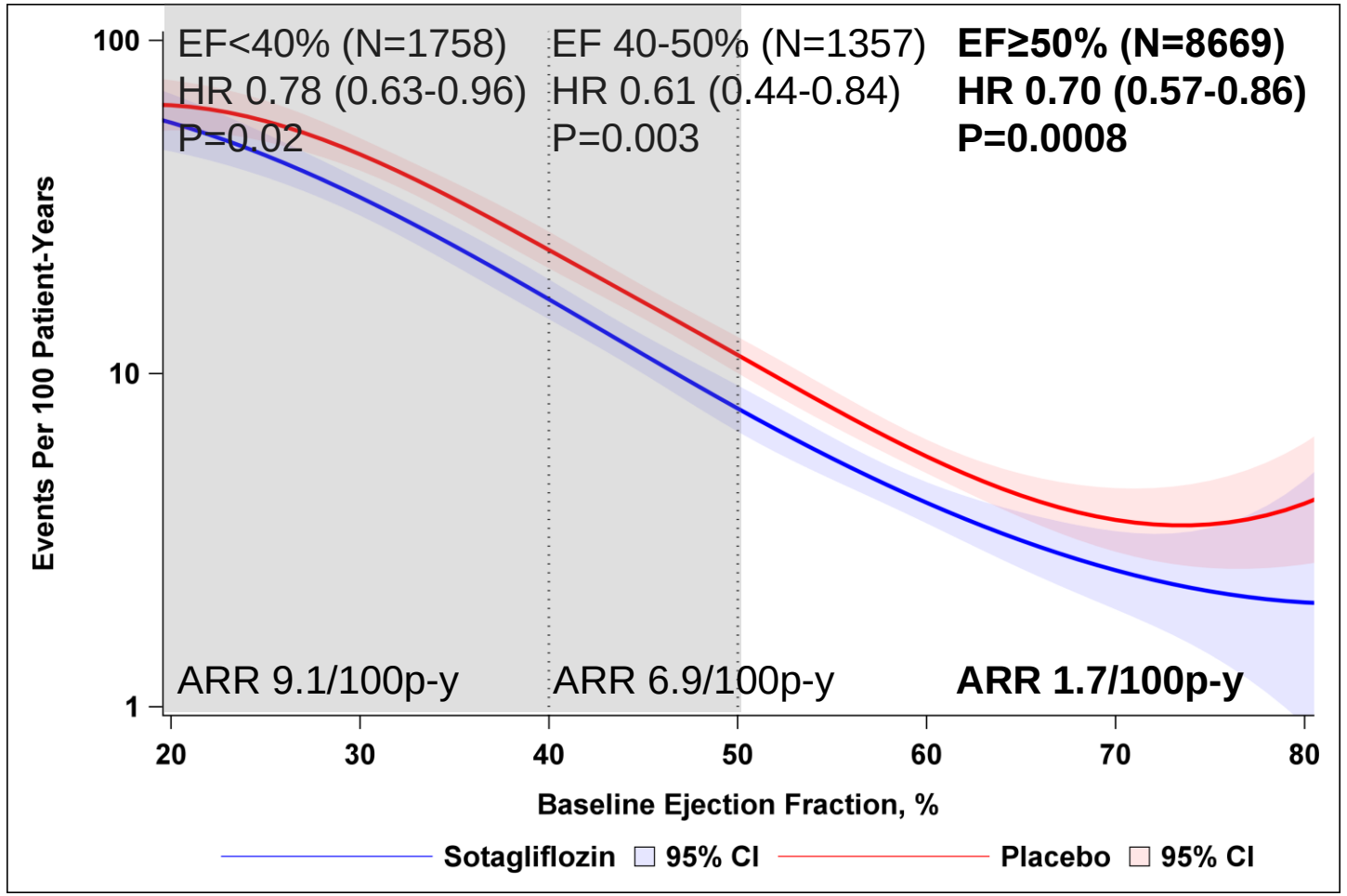
Bhatt DL. ACC 2021, virtual.

Pooled Data: SOLOIST and SCORED Total CV Death, HHF, and Urgent HF Visit in 11,784 Patients



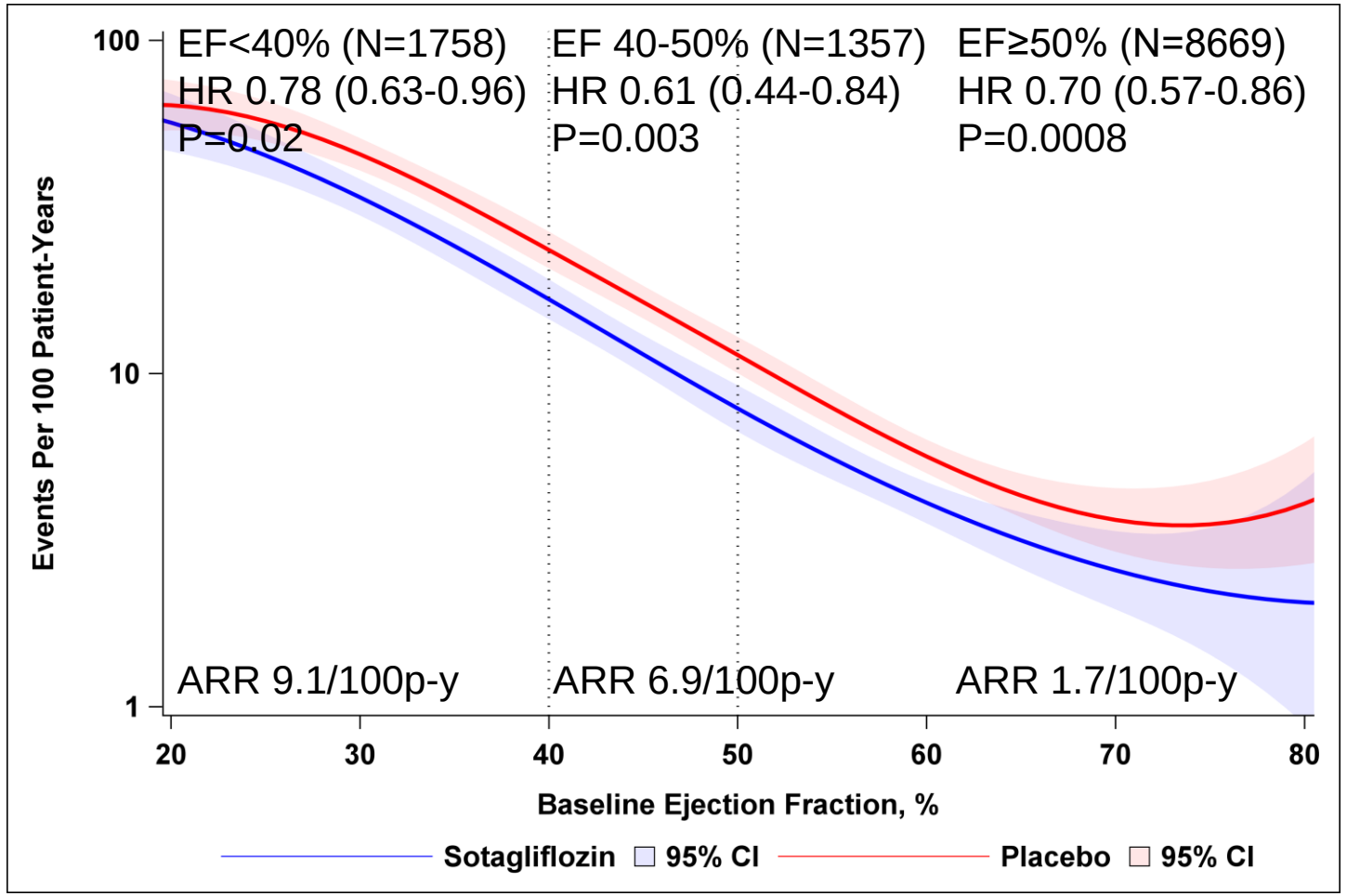
Bhatt DL. ACC 2021, virtual.

Pooled Data: SOLOIST and SCORED Total CV Death, HHF, and Urgent HF Visit in 11,784 Patients



Bhatt DL. ACC 2021, virtual.

Pooled Data: SOLOIST and SCORED Total CV Death, HHF, and Urgent HF Visit in 11,784 Patients

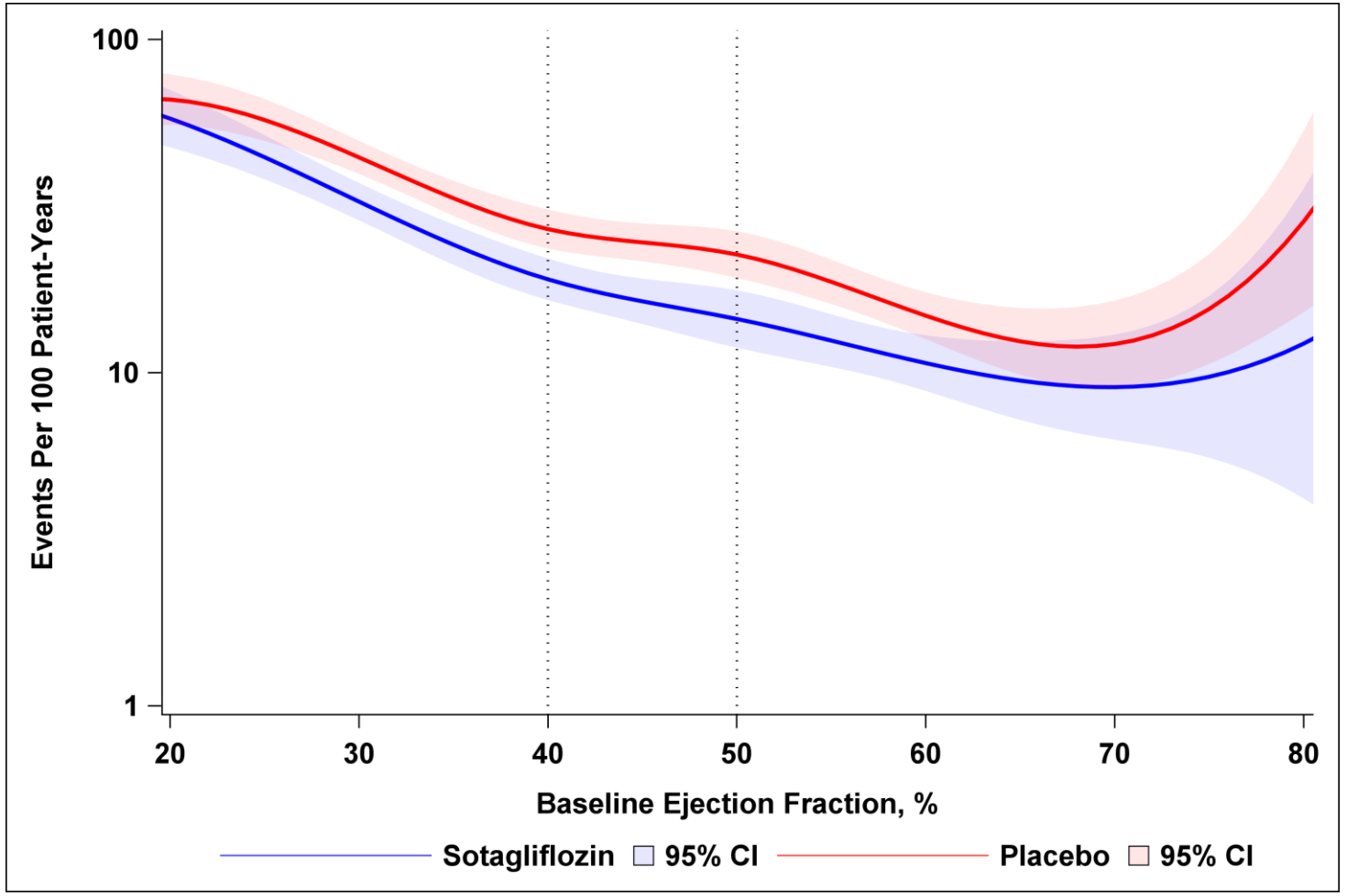


HR $P_{interaction}$=0.46 (by EF category)

RR $P_{interaction}$ =0.49 (by continuous EF)

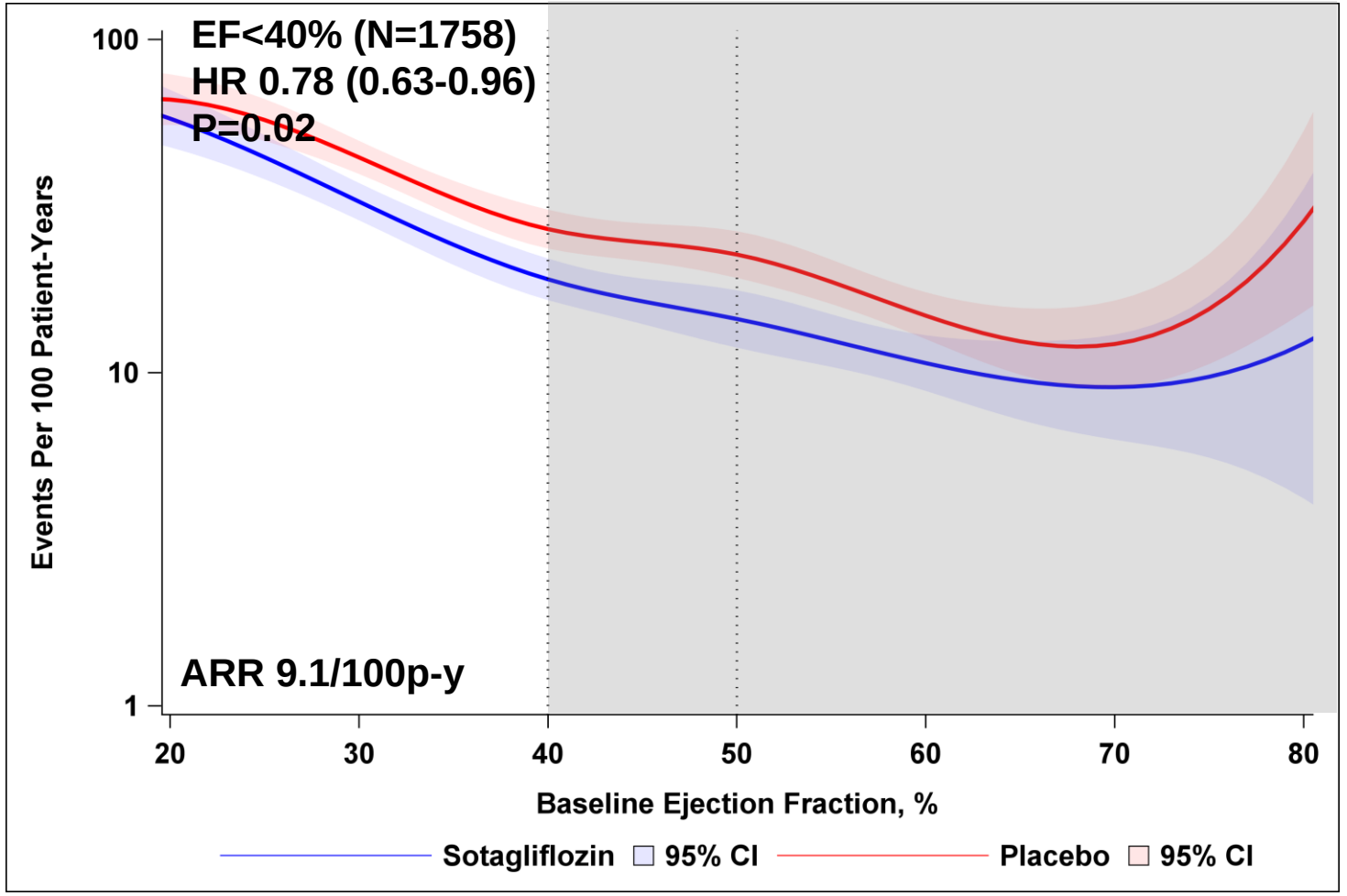
HR, hazard ratio; RR, rate ratio

Pooled Data: SOLOIST and SCORED Total CV Death, HHF, and Urgent HF Visit in 4500 Patients with History of HF



For this analysis, patients from SCORED with any history of HF are included.

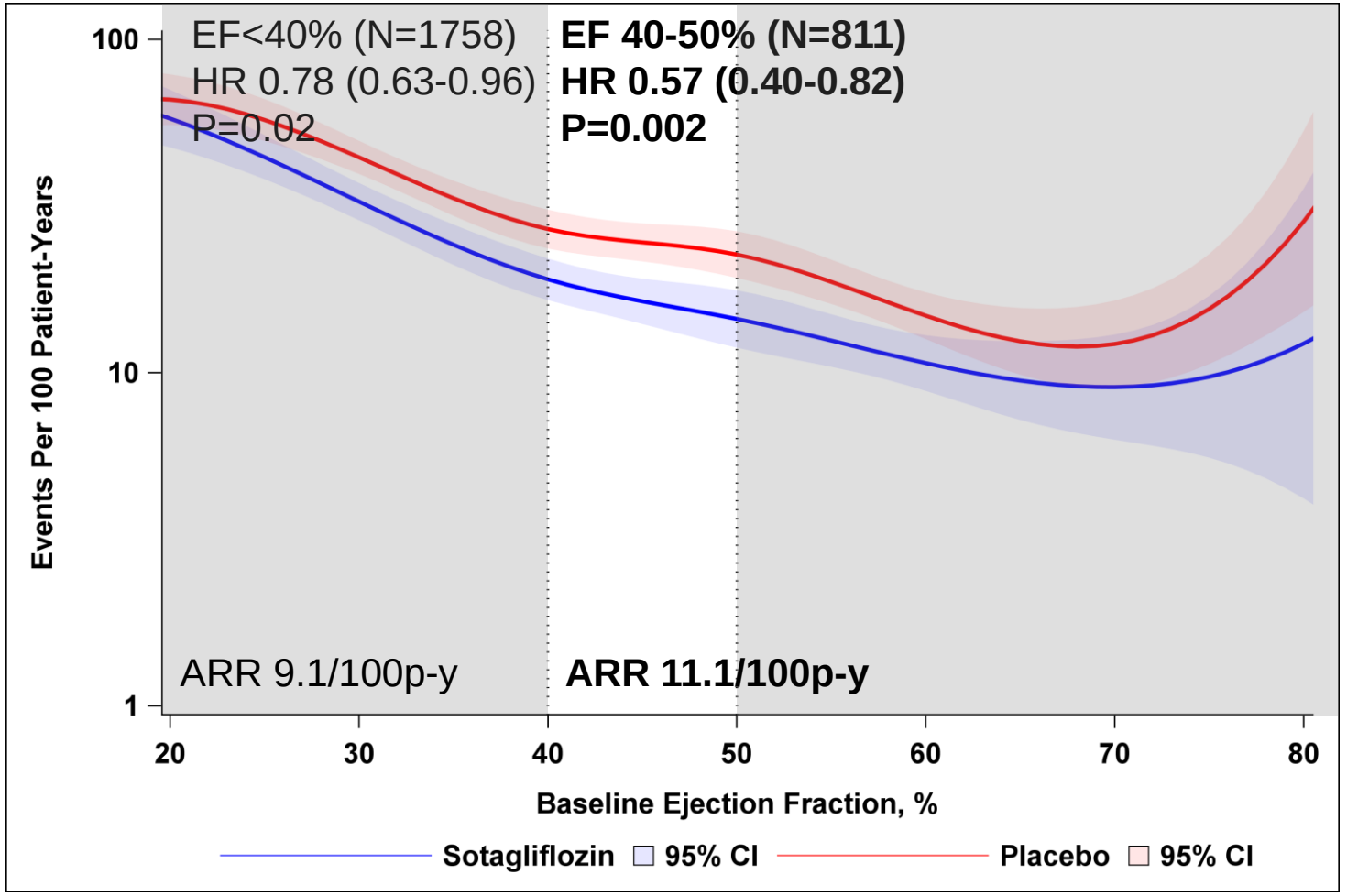
Pooled Data: SOLOIST and SCORED Total CV Death, HHF, and Urgent HF Visit in 4500 Patients with History of HF



Bhatt DL. ACC 2021, virtual.

For this analysis, patients from SCORED with any history of HF are included.

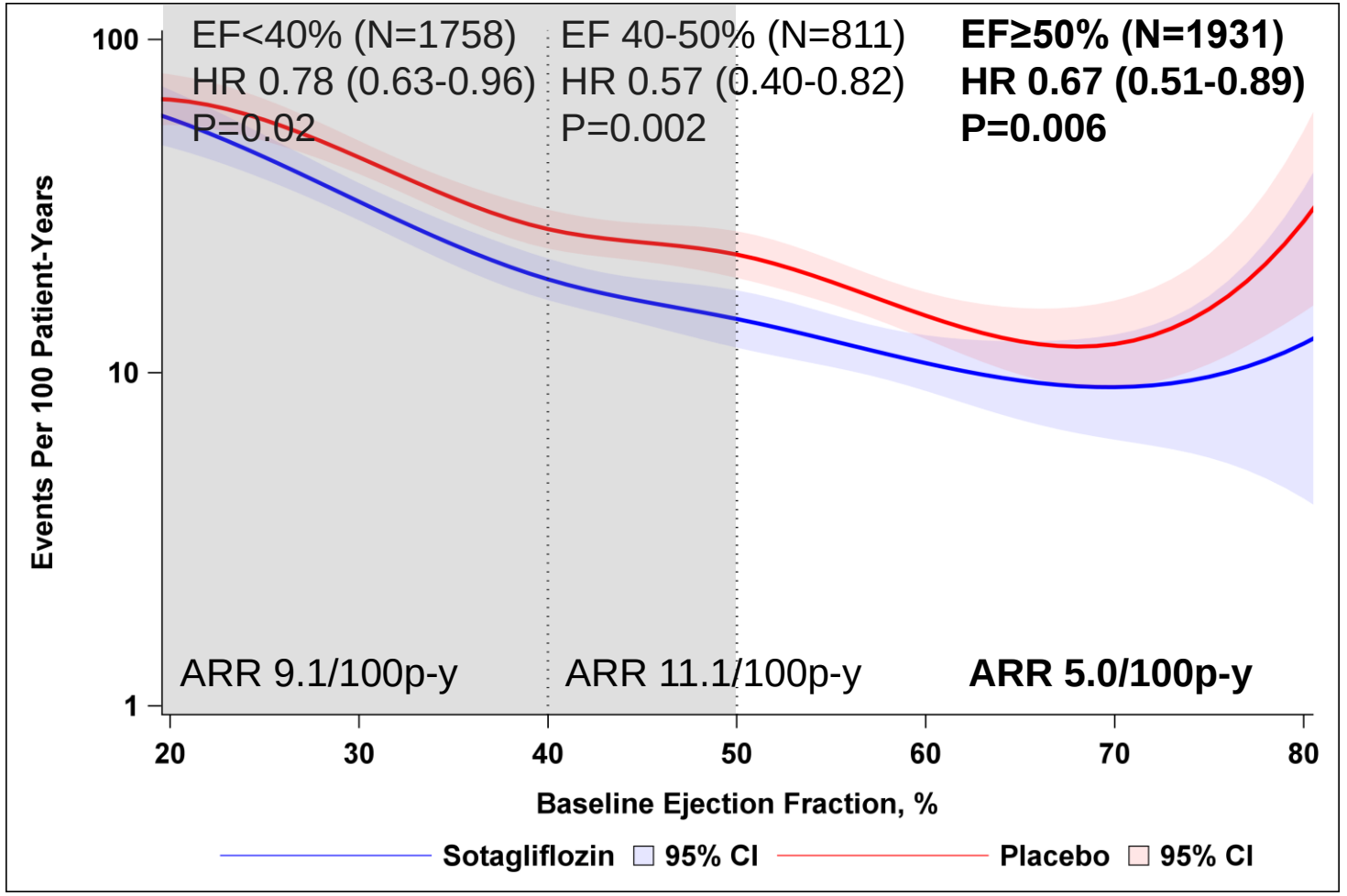
Pooled Data: SOLOIST and SCORED Total CV Death, HHF, and Urgent HF Visit in 4500 Patients with History of HF



Bhatt DL. ACC 2021, virtual.

For this analysis, patients from SCORED with any history of HF are included.

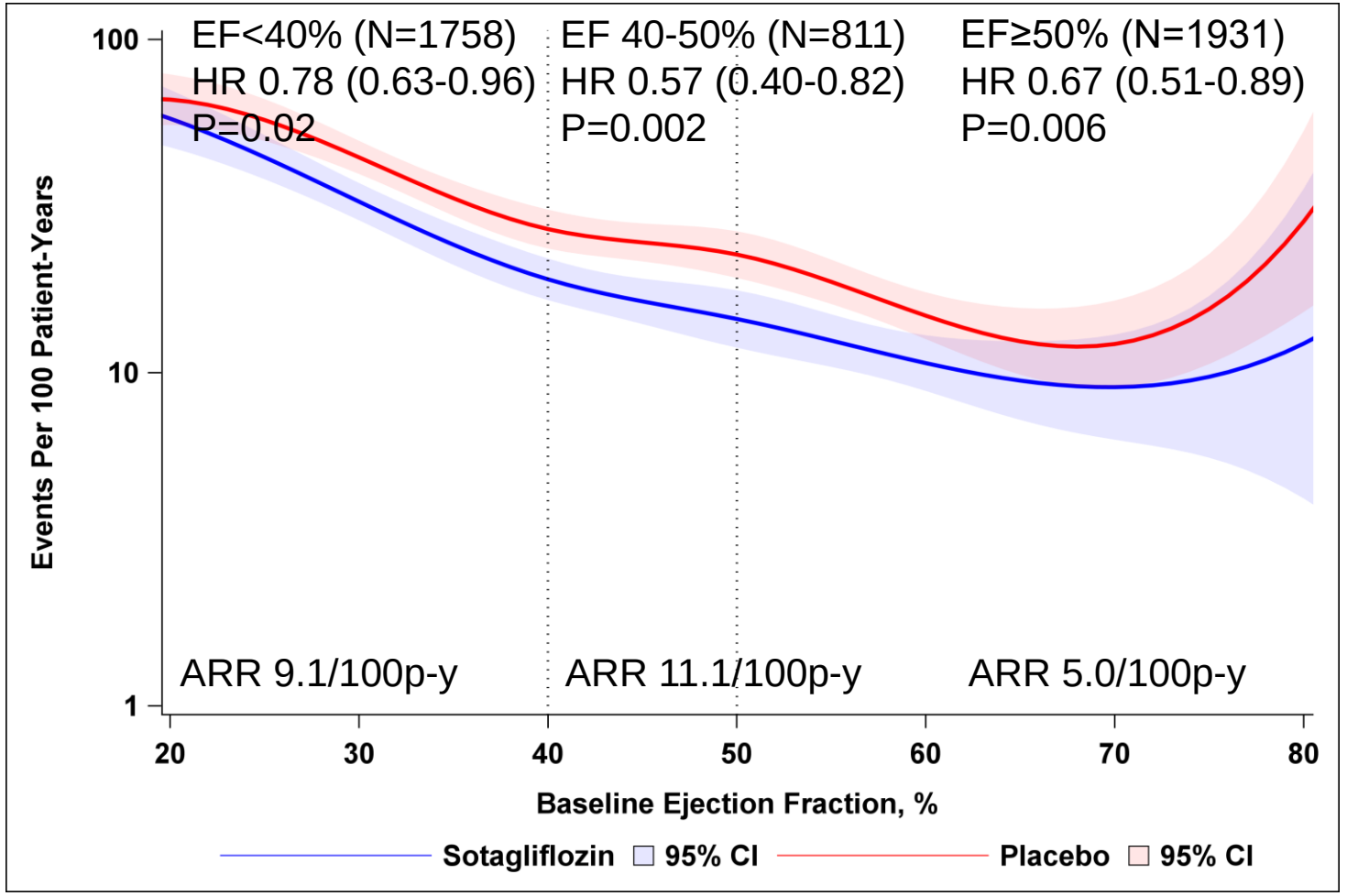
Pooled Data: SOLOIST and SCORED Total CV Death, HHF, and Urgent HF Visit in 4500 Patients with History of HF



Bhatt DL. ACC 2021, virtual.

For this analysis, patients from SCORED with any history of HF are included.

Pooled Data: SOLOIST and SCORED Total CV Death, HHF, and Urgent HF Visit in 4500 Patients with History of HF



HR $P_{interaction}$ =0.35 (by EF category)

RR $P_{interaction}$ =0.33 (by continuous EF)

Bhatt DL. ACC 2021, virtual.

For this analysis, patients from SCORED with any history of HF are included.

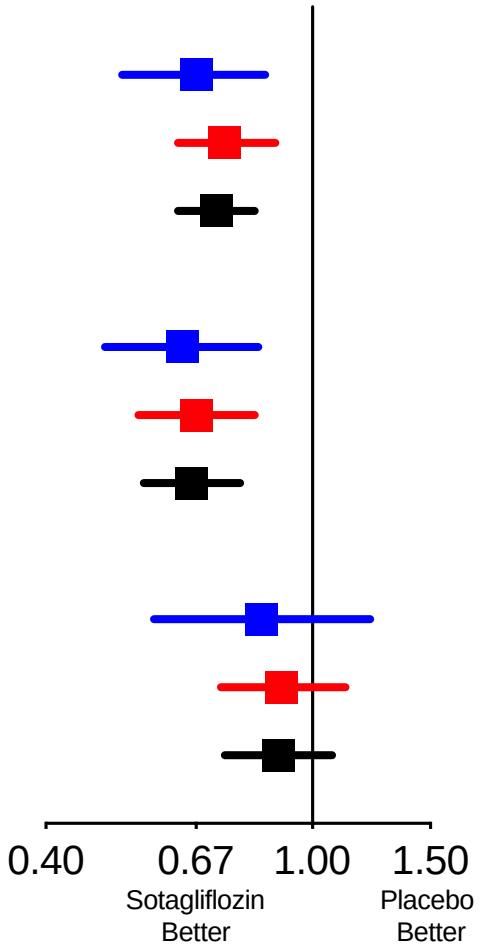
HR, hazard ratio; RR, rate ratio

Pooled Data: SOLOIST and SCORED Total CV Death, HHF, and Urgent HF Visit in 11,784 Patients

SOLOIST
SCORED

Intention-to-Treat Analysis

	HR (95% CI)
Total CV Death, HHF, and Urgent HF Visit	
SOLOIST	0.67 (0.52, 0.85)
SCORED	0.74 (0.63, 0.88)
Pooled	0.72 (0.63, 0.82)
Total HHF and Urgent HF Visit	
SOLOIST	0.64 (0.49, 0.83)
SCORED	0.67 (0.55, 0.82)
Pooled	0.66 (0.56, 0.78)
CV Death	
SOLOIST	0.84 (0.58, 1.22)
SCORED	0.90 (0.73, 1.12)
Pooled	0.89 (0.74, 1.07)

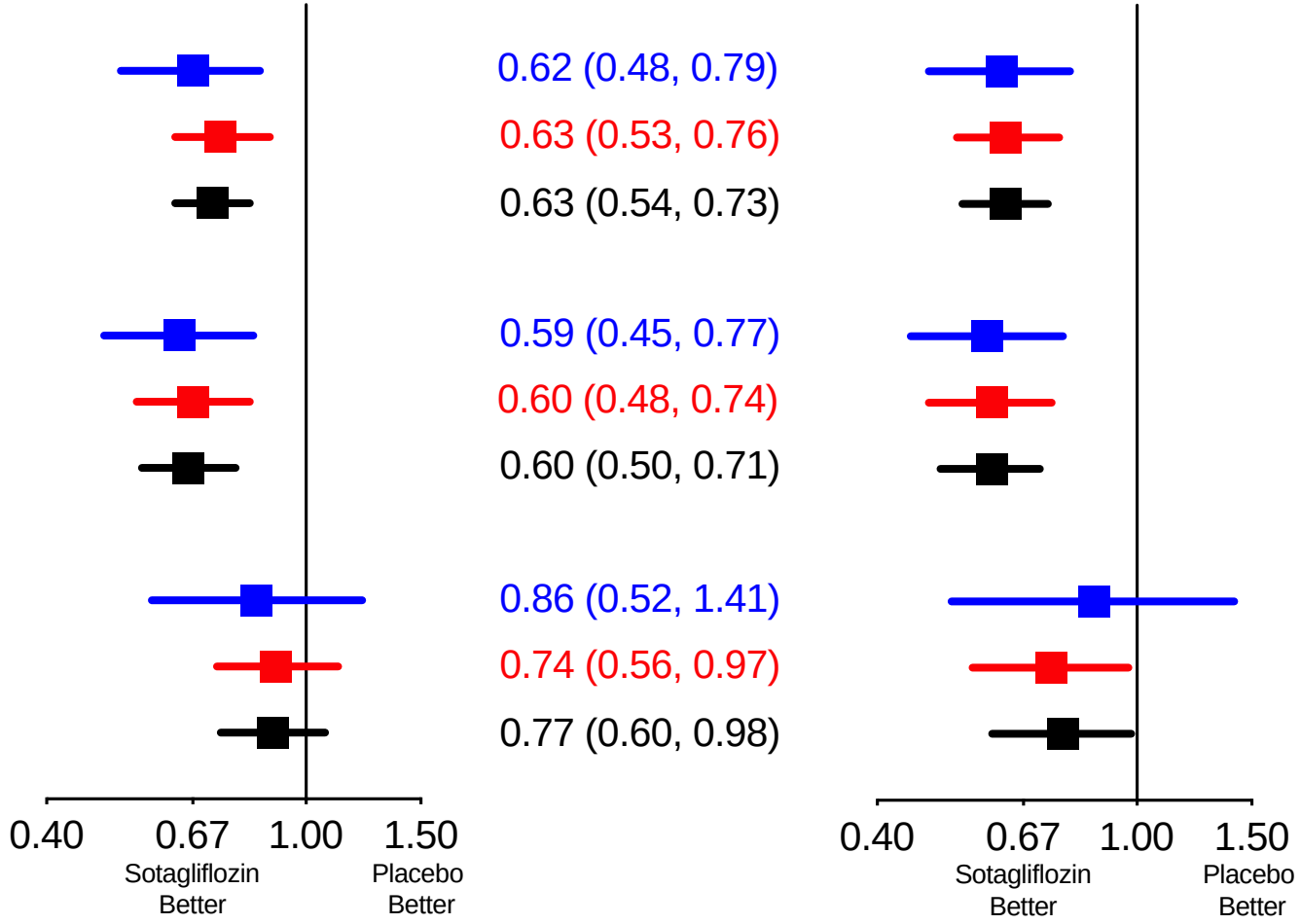


Bhatt DL. ACC 2021, virtual.

Pooled Data: SOLOIST and SCORED Total CV Death, HHF, and Urgent HF Visit in 11,784 Patients

SOLOIST
SCORED

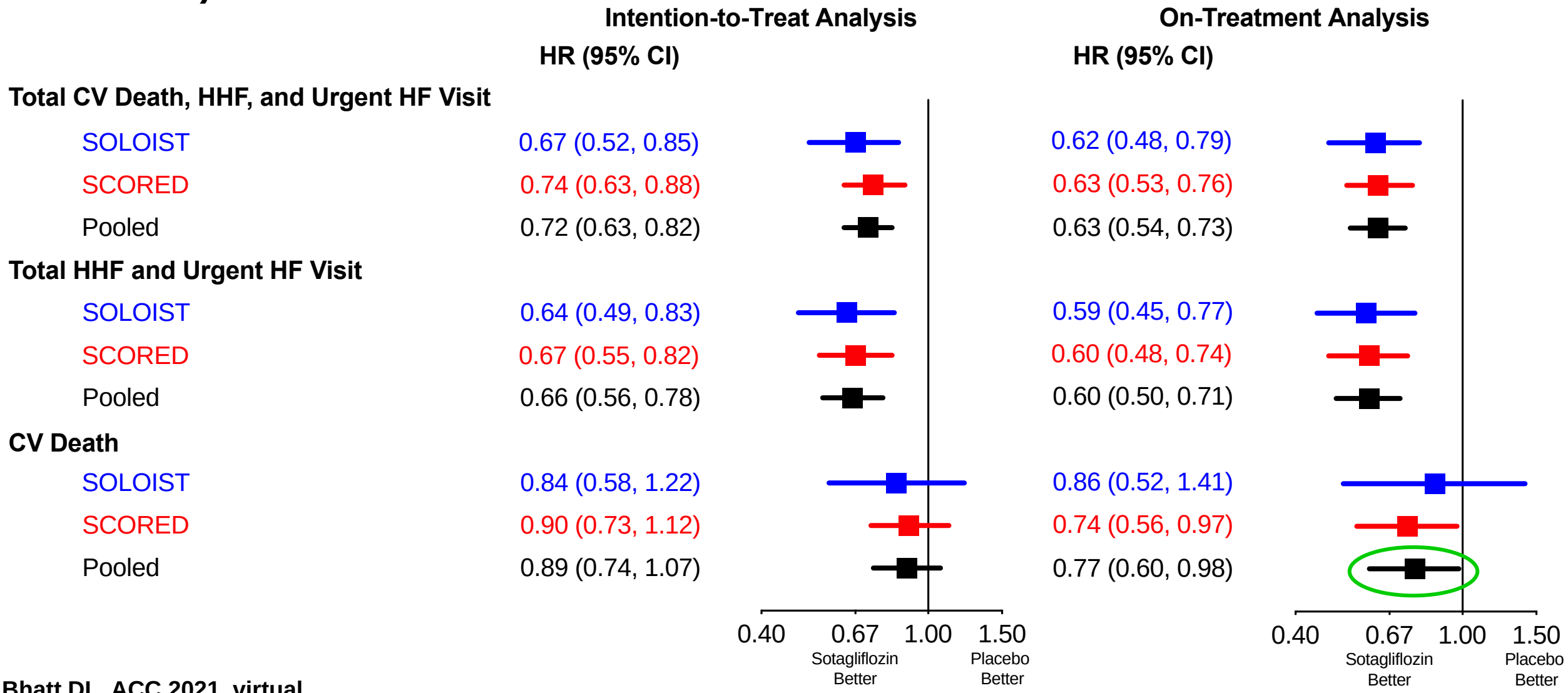
	Intention-to-Treat Analysis HR (95% CI)	On-Treatment Analysis HR (95% CI)
Total CV Death, HHF, and Urgent HF Visit		
SOLOIST	0.67 (0.52, 0.85)	0.62 (0.48, 0.79)
SCORED	0.74 (0.63, 0.88)	0.63 (0.53, 0.76)
Pooled	0.72 (0.63, 0.82)	0.63 (0.54, 0.73)
Total HHF and Urgent HF Visit		
SOLOIST	0.64 (0.49, 0.83)	0.59 (0.45, 0.77)
SCORED	0.67 (0.55, 0.82)	0.60 (0.48, 0.74)
Pooled	0.66 (0.56, 0.78)	0.60 (0.50, 0.71)
CV Death		
SOLOIST	0.84 (0.58, 1.22)	0.86 (0.52, 1.41)
SCORED	0.90 (0.73, 1.12)	0.74 (0.56, 0.97)
Pooled	0.89 (0.74, 1.07)	0.77 (0.60, 0.98)



Bhatt DL. ACC 2021, virtual.

Pooled Data: SOLOIST and SCORED Total CV Death, HHF, and Urgent HF Visit in 11,784 Patients

SOLOIST
SCORED



Bhatt DL. ACC 2021, virtual.

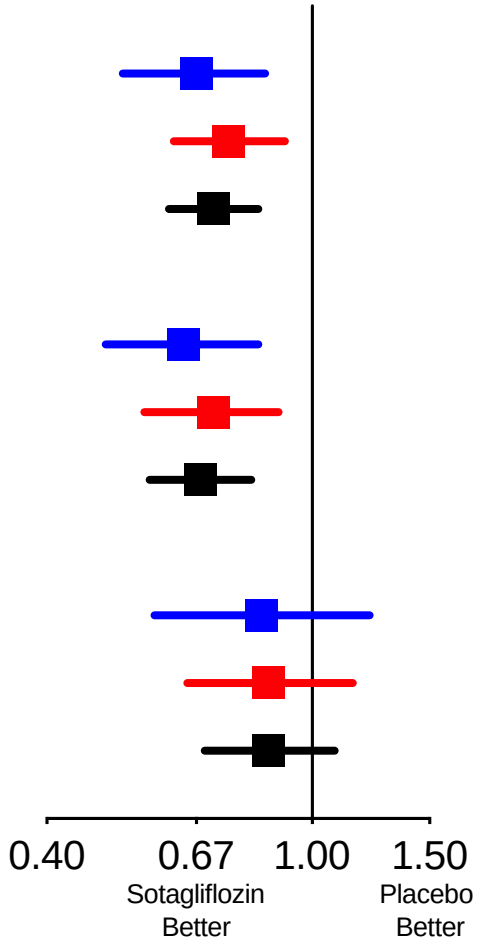
Pooled Data: SOLOIST and SCORED Total CV Death, HHF, and Urgent HF Visit in 4500 Patients with History of HF

SOLOIST

SCORED

Intention-to-Treat Analysis

	HR (95% CI)
Total CV Death, HHF, and Urgent HF Visit	
SOLOIST	0.67 (0.52, 0.85)
SCORED	0.75 (0.62, 0.91)
Pooled	0.71 (0.61, 0.83)
Total HHF and Urgent HF Visit	
SOLOIST	0.64 (0.49, 0.83)
SCORED	0.71 (0.56, 0.89)
Pooled	0.68 (0.57, 0.81)
CV Death	
SOLOIST	0.84 (0.58, 1.22)
SCORED	0.86 (0.65, 1.15)
Pooled	0.86 (0.69, 1.08)

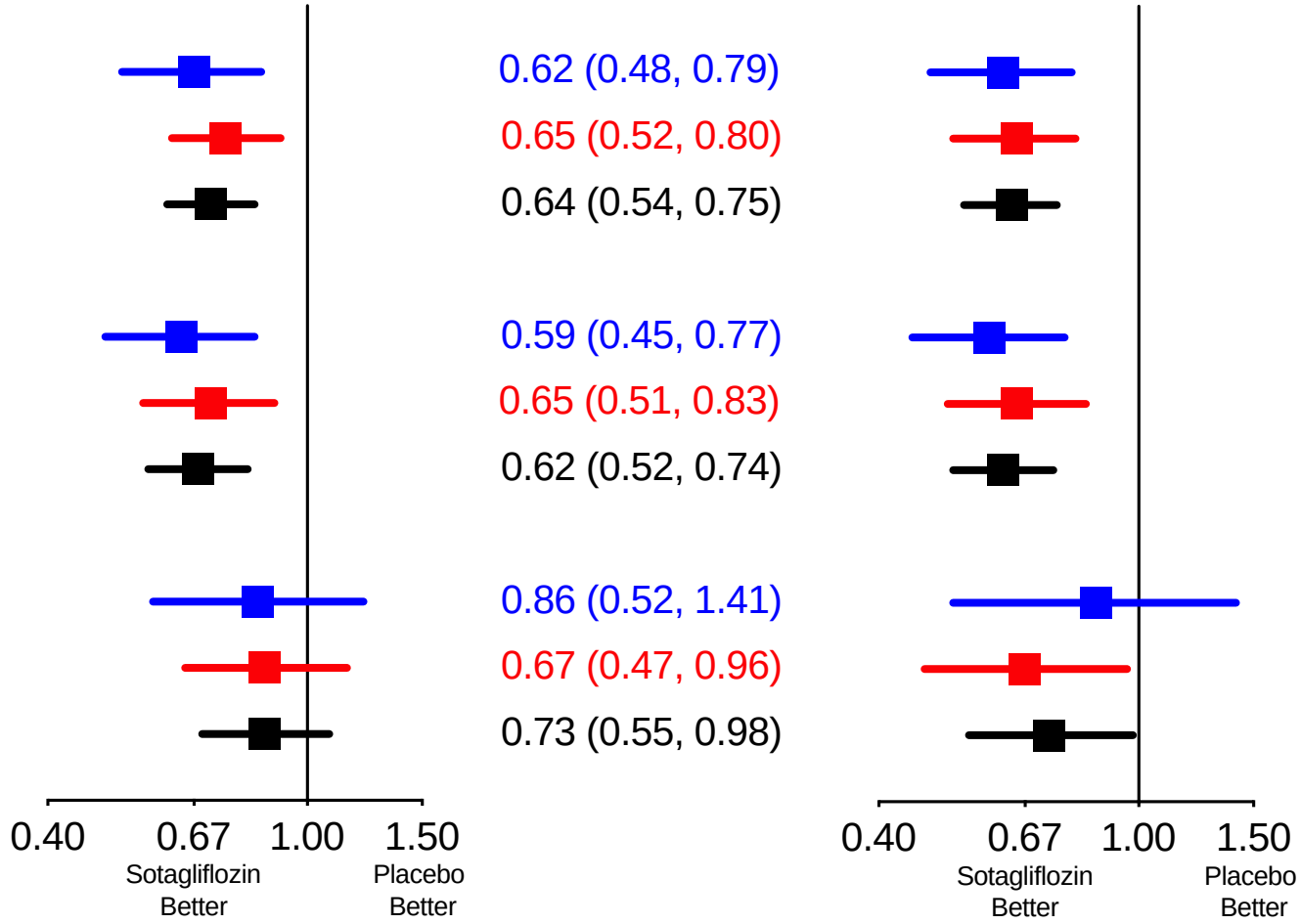


Bhatt DL. ACC 2021, virtual.

Pooled Data: SOLOIST and SCORED Total CV Death, HHF, and Urgent HF Visit in 4500 Patients with History of HF

SOLOIST
SCORED

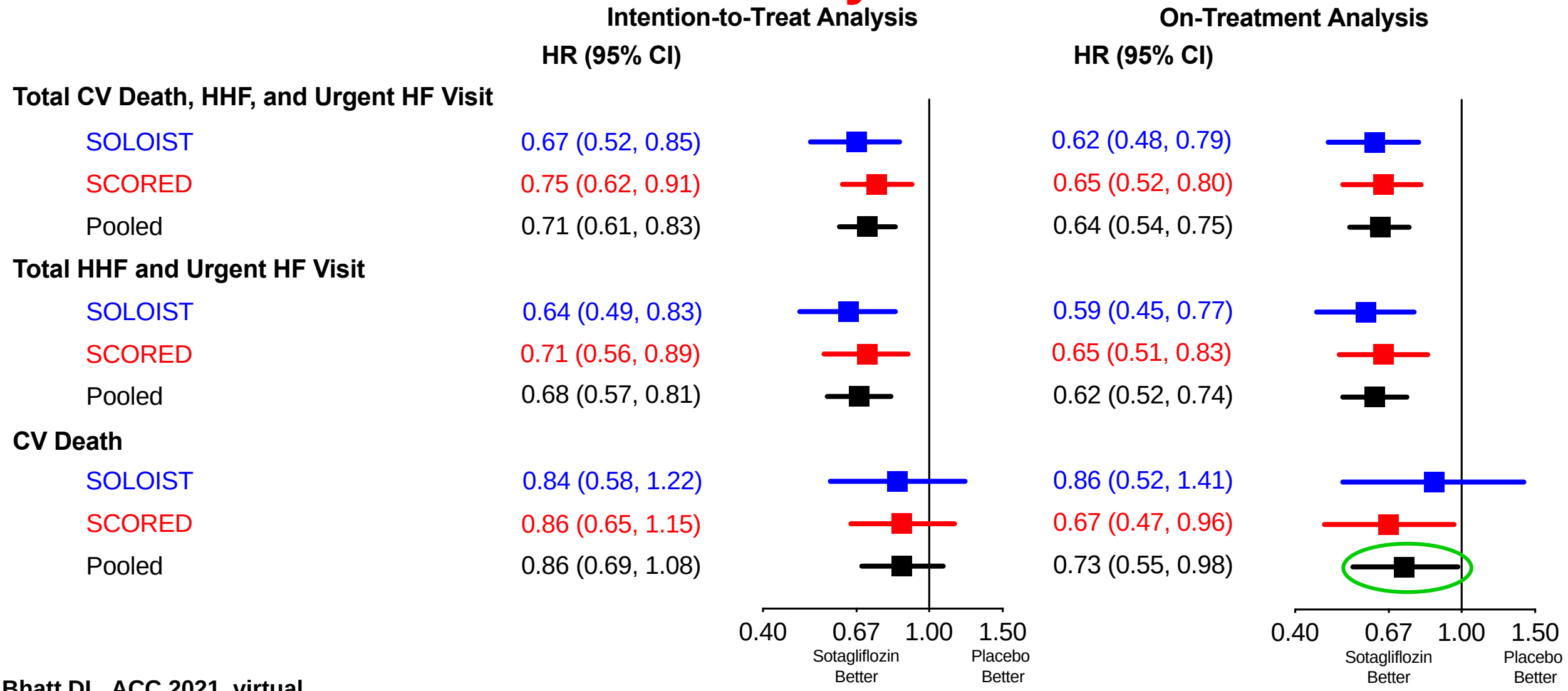
	Intention-to-Treat Analysis HR (95% CI)	On-Treatment Analysis HR (95% CI)
Total CV Death, HHF, and Urgent HF Visit		
SOLOIST	0.67 (0.52, 0.85)	0.62 (0.48, 0.79)
SCORED	0.75 (0.62, 0.91)	0.65 (0.52, 0.80)
Pooled	0.71 (0.61, 0.83)	0.64 (0.54, 0.75)
Total HHF and Urgent HF Visit		
SOLOIST	0.64 (0.49, 0.83)	0.59 (0.45, 0.77)
SCORED	0.71 (0.56, 0.89)	0.65 (0.51, 0.83)
Pooled	0.68 (0.57, 0.81)	0.62 (0.52, 0.74)
CV Death		
SOLOIST	0.84 (0.58, 1.22)	0.86 (0.52, 1.41)
SCORED	0.86 (0.65, 1.15)	0.67 (0.47, 0.96)
Pooled	0.86 (0.69, 1.08)	0.73 (0.55, 0.98)



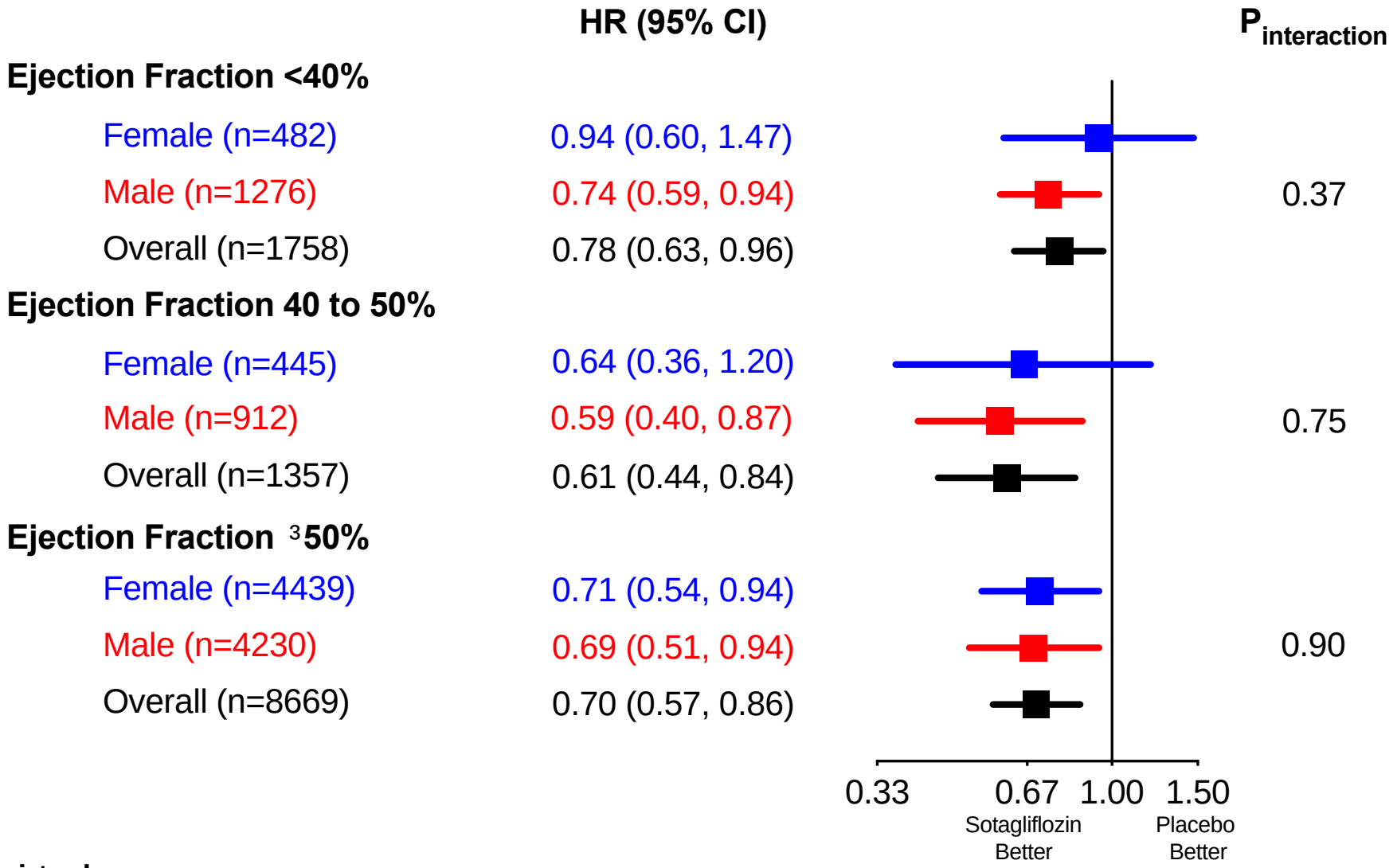
Bhatt DL. ACC 2021, virtual.

Pooled Data: SOLOIST and SCORED Total CV Death, HHF, and Urgent HF Visit in 4500 Patients with History of HF

SOLOIST
SCORED



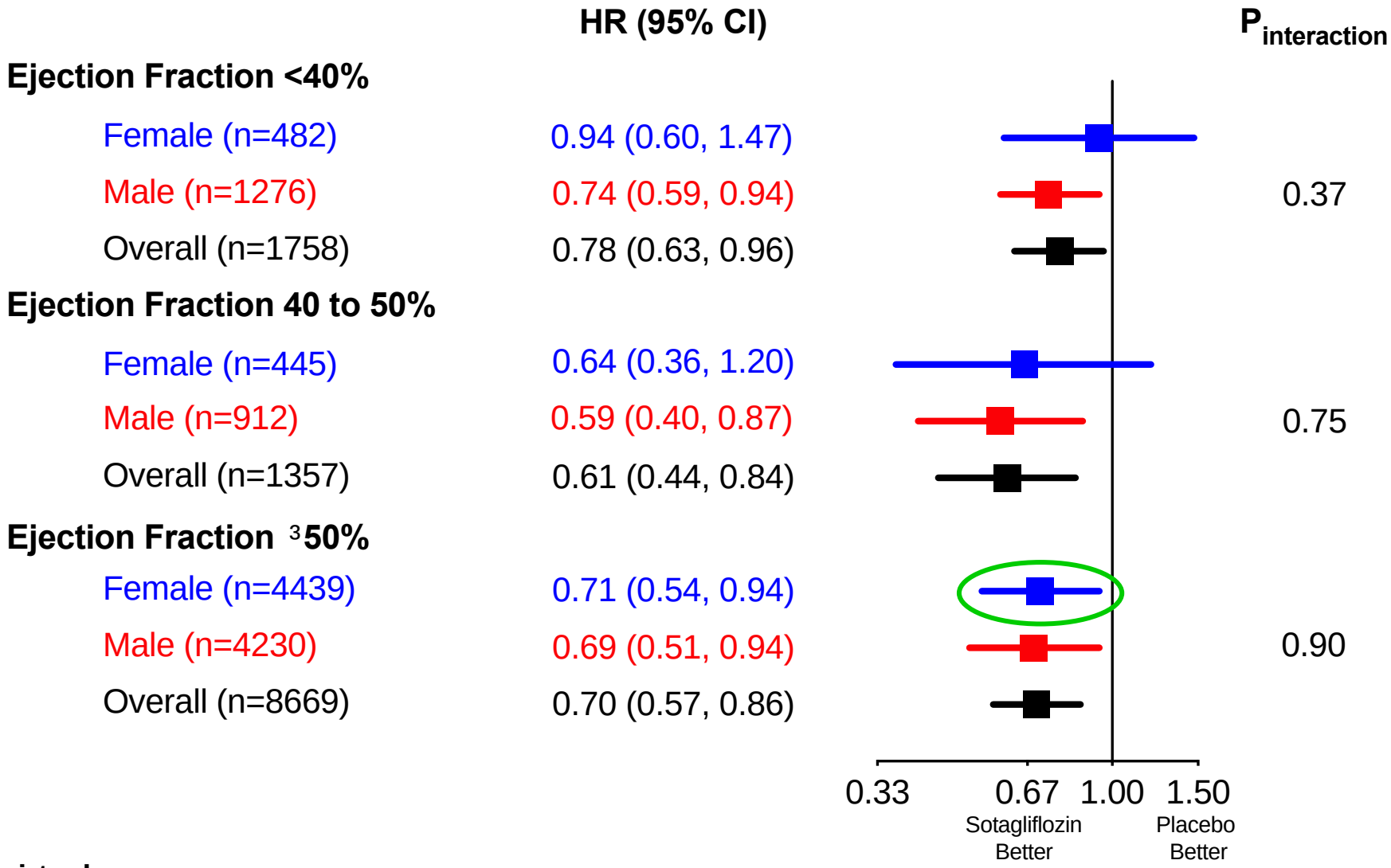
Pooled Data: SOLOIST and SCORED Total CV Death, HHF, and Urgent HF Visit in 11,784 Patients



Bhatt DL. ACC 2021, virtual.

Pooled Data: SOLOIST and SCORED Total CV Death, HHF, and Urgent HF Visit in 11,784 Patients

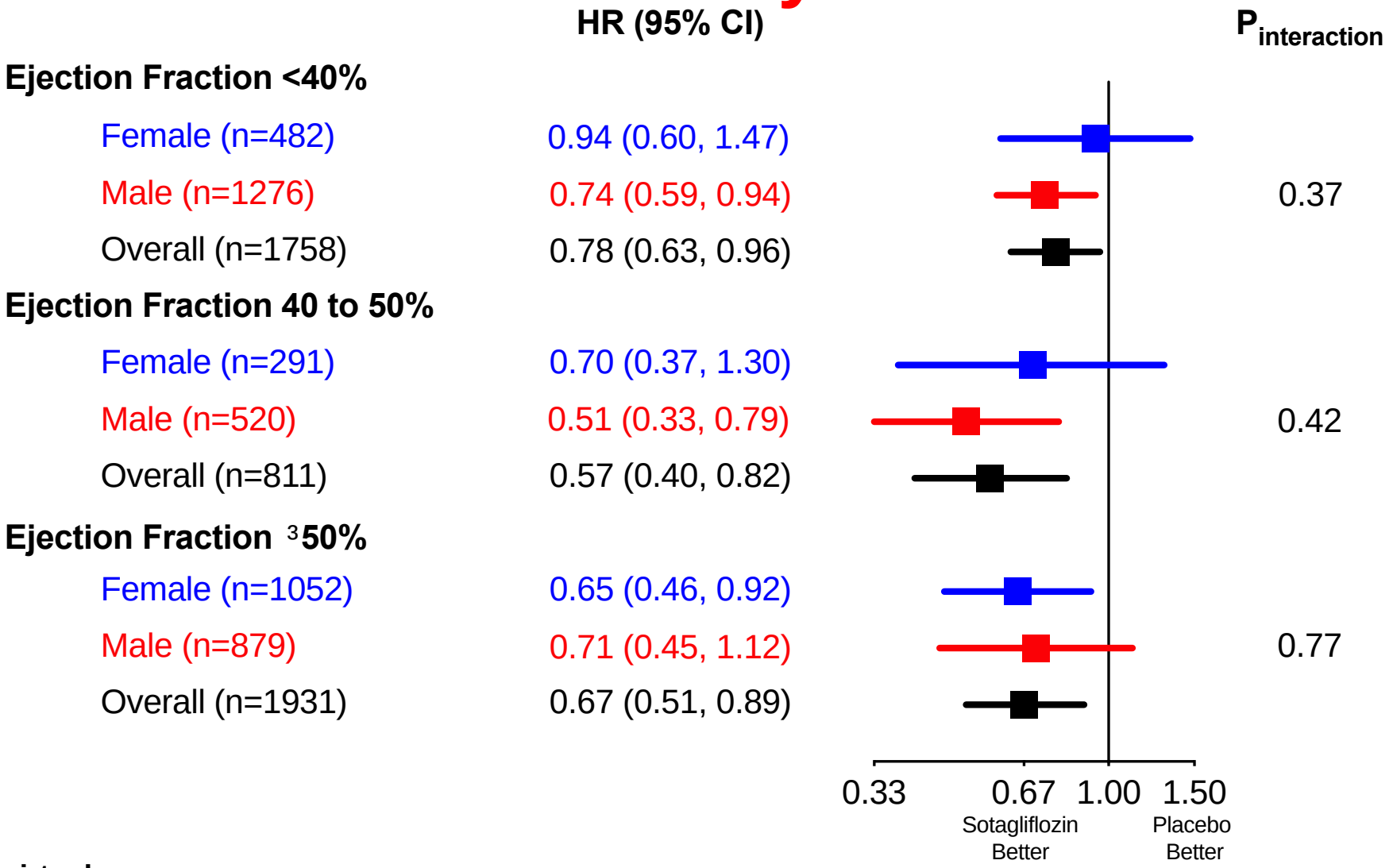
SOLOIST
SCORED



Bhatt DL. ACC 2021, virtual.

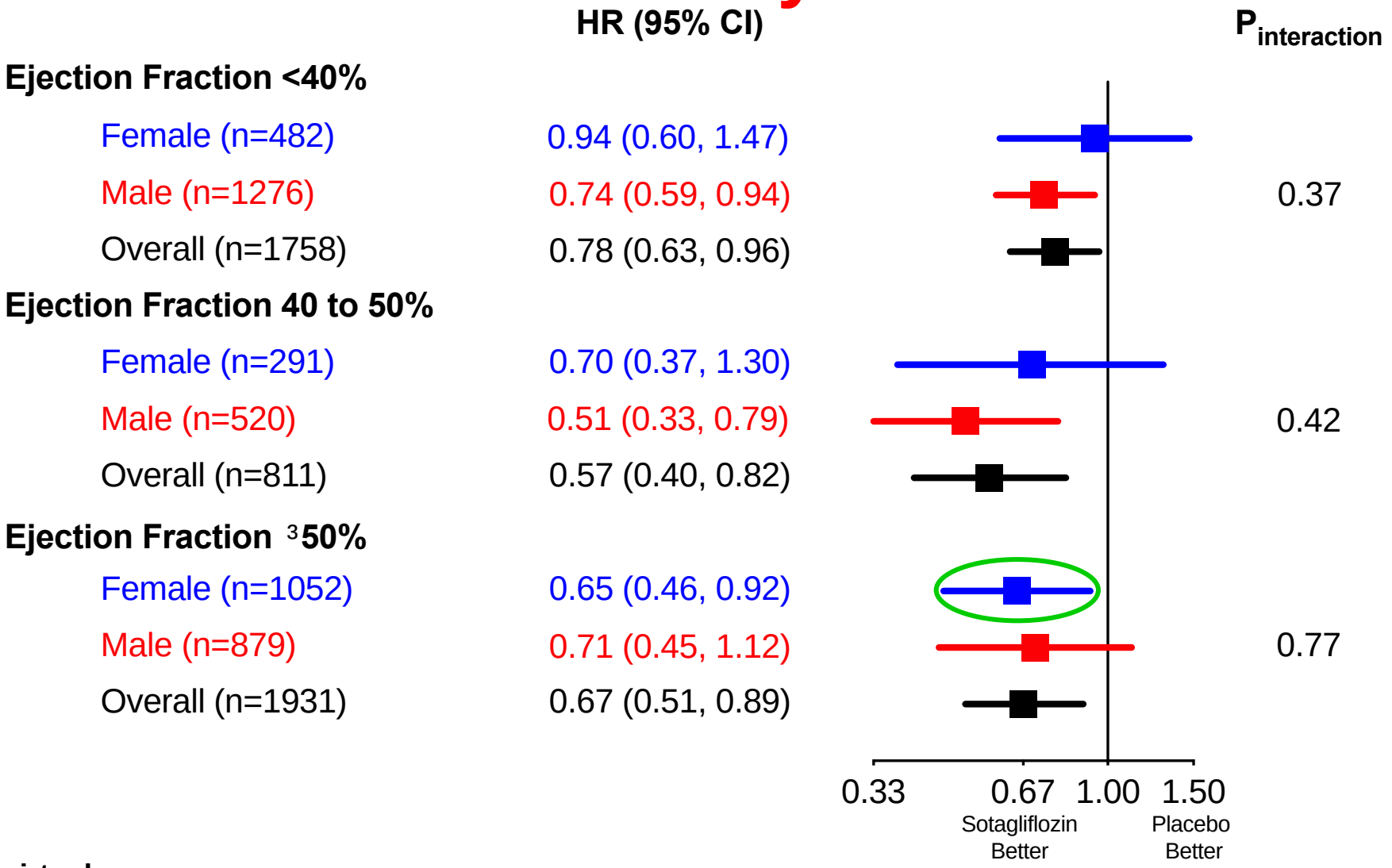
Pooled Data: SOLOIST and SCORED Total CV Death, HHF, and Urgent HF Visit in 4500 Patients with History of HF

SOLOIST
SCORED



Bhatt DL. ACC 2021, virtual.

Pooled Data: SOLOIST and SCORED Total CV Death, HHF, and Urgent HF Visit in 4500 Patients with History of HF



Bhatt DL. ACC 2021, virtual.

Limitations

SOLOIST SCORED

Trials were stopped early during the onset of the pandemic

- Nevertheless, robust reduction in primary endpoint

Shortened duration limited the statistical power to see significant reductions in certain endpoints

- Though on-treatment analyses show a significant reduction in CV death

Some of the present analyses were prespecified, others were *post hoc*

- Both types of analyses were consistent in terms of demonstrating significant benefits

Bhatt DL. ACC 2021, virtual.

Conclusions

SOLOIST SCORED

Sotagliflozin robustly and significantly reduced the composite of total cardiovascular deaths, hospitalizations for heart failure, and urgent visits for heart failure across the full range of ejection fraction, including in patients with heart failure with preserved ejection fraction.

As well, in on-treatment analyses, **sotagliflozin** demonstrated a significant reduction in cardiovascular death.

These are the first randomized data from a prespecified analysis of clinical trials to show a significant effect of a therapy on heart failure with preserved ejection fraction, additionally demonstrating a consistent and significant benefit in women.

Bhatt DL. ACC 2021, virtual.

BRIGHAM AND WOMEN'S HOSPITAL

Heart & Vascular Center

Thank You!

Deepak L. Bhatt, MD, MPH
Executive Director,
Interventional Cardiovascular Programs,
BWH Heart & Vascular Center;
Professor of Medicine,
Harvard Medical School
Email: DLBhattMD@post.Harvard.edu
Twitter: @DLBhattMD

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL