

Heart Failure Risk Stratification and Efficacy of SGLT2 Inhibitors in Patients with Type 2 Diabetes Mellitus

David D. Berg, MD
TIMI Study Group
Brigham and Women's Hospital

David D. Berg, Stephen D. Wiviott, Benjamin M. Scirica, Yared Gurmu, Ofri Mosenzon, Sabina A. Murphy, Deepak L. Bhatt, Lawrence A. Leiter, Darren K. McGuire, John Wilding, Per Johanson, Peter A. Johansson, Anna Maria Langkilde, Itamar Raz, Eugene Braunwald, & Marc S. Sabatine

Declaration of Interest

- I have no personal conflicts to declare
- The SAVOR-TIMI 53 and DECLARE-TIMI 58 studies were sponsored by AstraZeneca, including research grants to the TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital

Diabetes and Heart Failure

Risk of Congestive Heart Failure According to Sex and Diabetic Status at Each Biennial Examination: 18 Year Follow-Up Study

Diabetic Status	Person Years At Risk	Incidence		Relative Risk
		Crude Annual per 10,000	Age- Adjusted* per 10,000	
Men Aged 45 to 74 years				
Nondiabetic	26,988	31.87	32.14	2.36†
Diabetic	1,226	89.72	75.98	
Women Aged 45 to 74 years				
Nondiabetic	35,322	19.53	19.75	5.14‡
Diabetic	1,190	142.85	101.60	

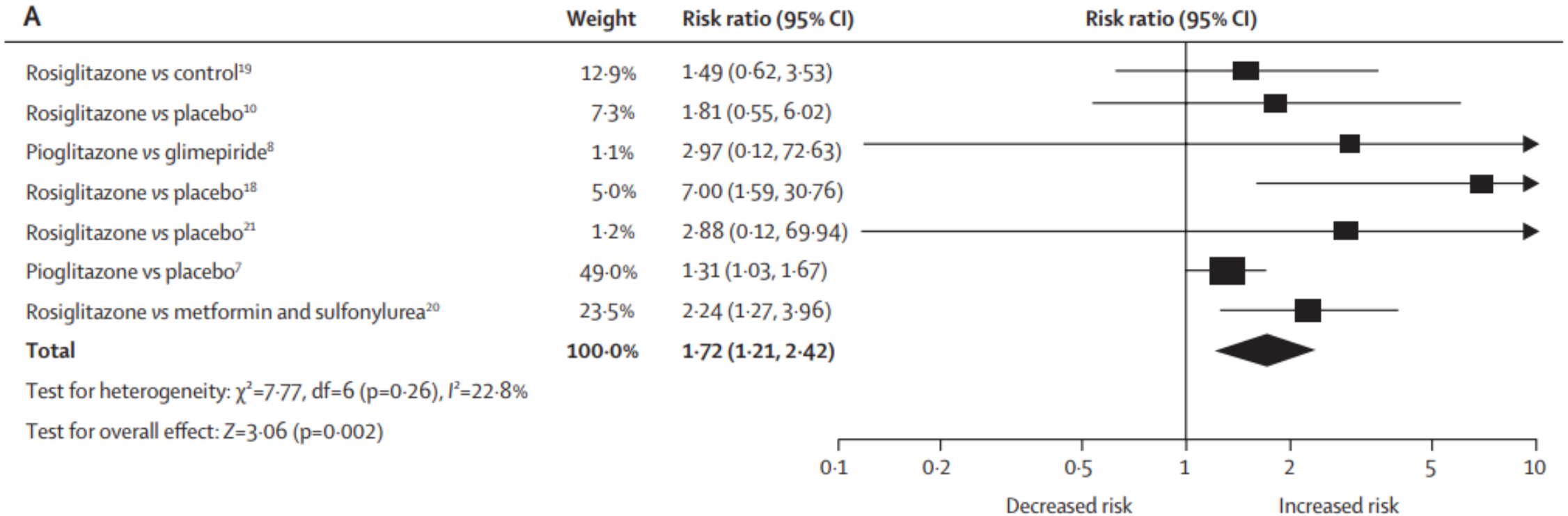
* Indirect method.

† Significant at $P < 0.05$ (chi square = 6.50).

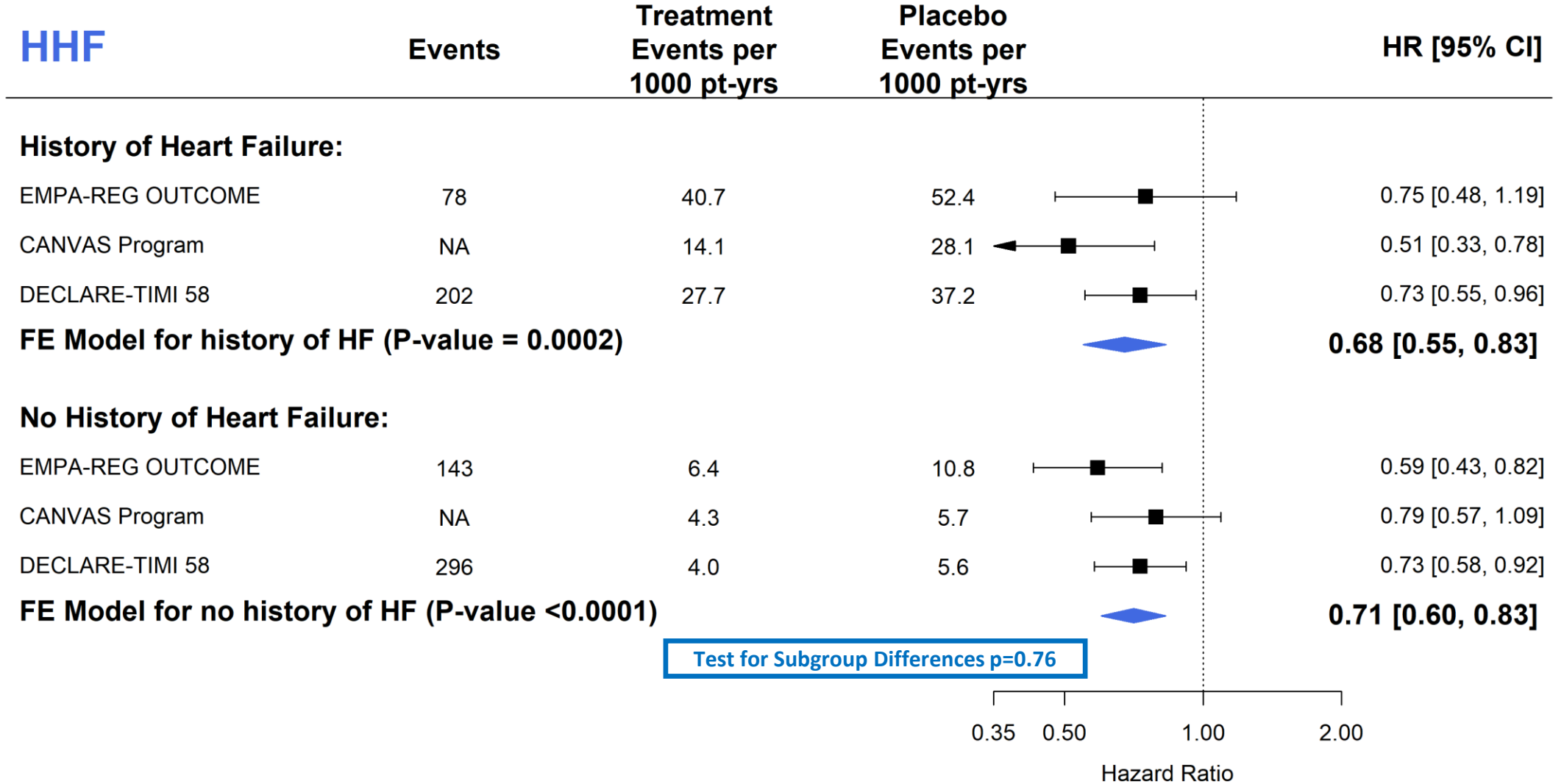
‡ Significant at $P < 0.01$ (chi square = 12.53).

Some Therapies Increase HF Risk

Thiazolidinediones and HF Risk



SGLT2 Inhibitors Reduce HF Risk



Objectives

- To develop and validate a practical **clinical risk score** for predicting hospitalization for HF in patients with T2DM
- To assess whether this score can identify high-risk diabetic patients who have the greatest reduction in risk for HHF with **SGLT2 inhibitors**

Study Population

- Placebo Arm of **SAVOR-TIMI 53** (Derivation Cohort)
 - N=8212
 - Trial Inclusion: T2DM (A1c 6.5-12.0) + h/o ASCVD or multiple CV risk factors
 - Trial Exclusion: ESRD (on HD), s/p renal tx, sCr >6.0 mg/dl

- Placebo Arm of **DECLARE-TIMI 58** (Validation Cohort)
 - N=8578
 - Trial Inclusion: T2DM (A1c 6.5-12.0) + h/o ASCVD or multiple CV risk factors
 - Trial Exclusion: CrCl <60 ml/min

Hospitalization for Heart Failure

- Admission to inpatient unit or ED visit for heart failure that results in >12-hour stay (SAVOR-TIMI 53) or >24-hour stay (DECLARE-TIMI 58)
- Objective evidence of new or worsening HF (e.g., orthopnea, JVD, pulmonary basilar crackles, elevated natriuretic peptides, etc.)
- Intensification of HF therapy (e.g., IV diuretics or inotropes)

Candidate Risk Indicators

- Age
- Sex
- Race
- BMI
- Duration of T2DM
- Hemoglobin A1c
- Baseline Insulin Use
- H/o Retinopathy
- H/o Nephropathy
- Estimated GFR
- Urine Albumin/Creatinine Ratio
- H/o Coronary Artery Disease
- H/o Prior Myocardial Infarction
- H/o Peripheral Arterial Disease
- H/o Ischemic Stroke
- H/o Heart Failure
- H/o Atrial Fibrillation
- H/o PCI
- H/o CABG
- H/o Dyslipidemia
- H/o Hypertension
- Current Tobacco Use
- Heart Rate
- Systolic Blood Pressure
- Systolic Blood Pressure

Statistical Analysis

- Identified **univariate predictors** using Cox regression
 - All individual risk indicators achieving significance level of **$p < 0.10$** on univariate screen were included in multivariable model
- Selected **independent** clinical risk indicators using AIC criterion based on consistency of forward, backward, and stepwise selection
- Narrowed model by applying stringent statistical threshold of **$p < 0.001$**

Statistical Analysis

- Assessed discriminatory performance using **Harrell's C-index**
- **Internally validated** the model using a bootstrap technique with 1000 replications in the placebo population of SAVOR-TIMI 53
- **Externally validated** the model by assessing discrimination and calibration (using Nam-D'Agostino statistic) in DECLARE-TIMI 58

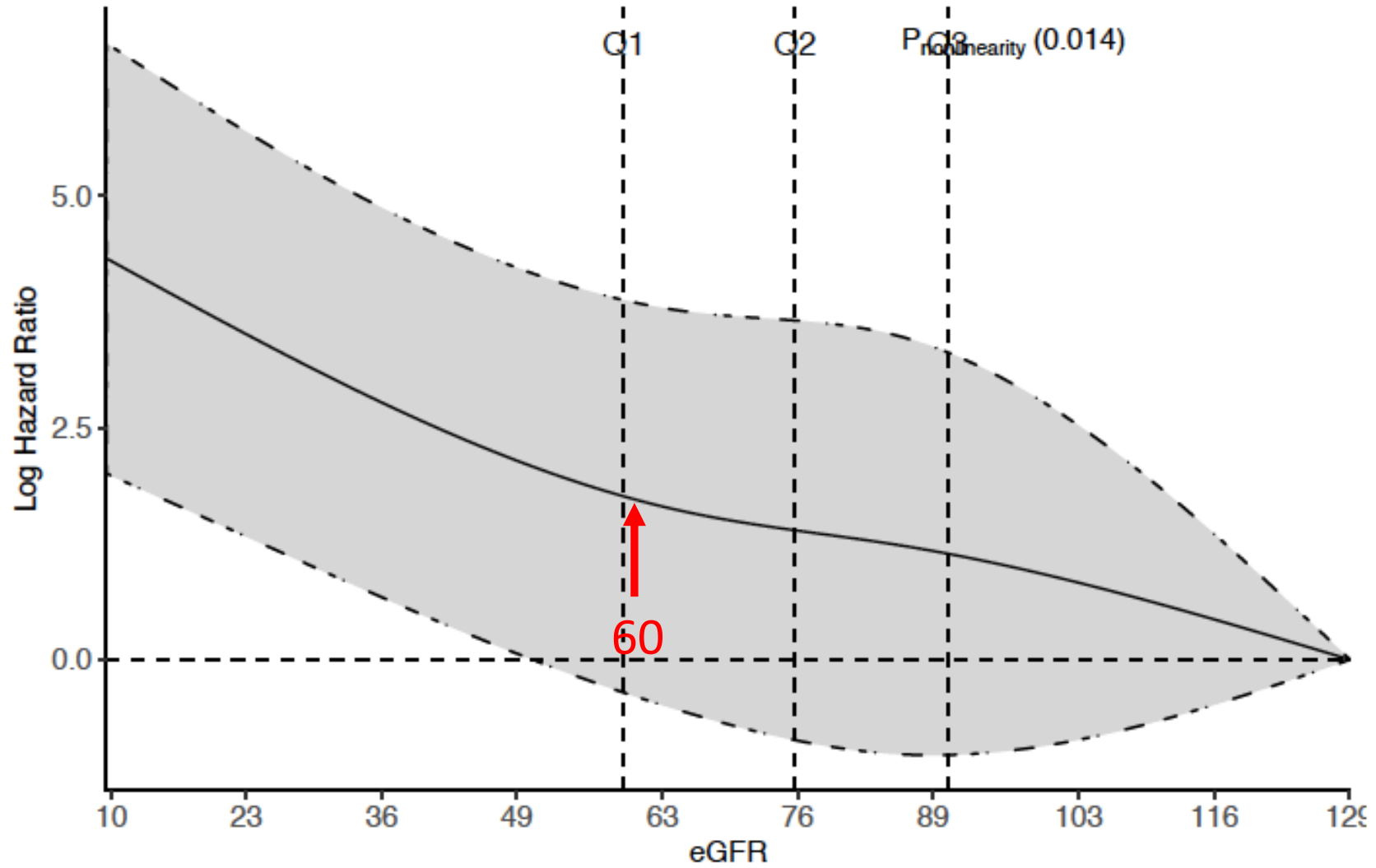
Candidate Risk Indicators

- Age
- Sex
- Race
- BMI
- Duration of T2DM
- Hemoglobin A1c
- Baseline Insulin Use
- H/o Retinopathy
- H/o Nephropathy
- Estimated GFR
- Urine Albumin/Creatinine Ratio
- H/o Coronary Artery Disease
- H/o Prior Myocardial Infarction
- H/o Peripheral Arterial Disease
- H/o Ischemic Stroke
- H/o Heart Failure
- H/o Atrial Fibrillation
- H/o PCI
- H/o CABG
- H/o Dyslipidemia
- H/o Hypertension
- Current Tobacco Use
- Heart Rate
- Systolic Blood Pressure
- Systolic Blood Pressure

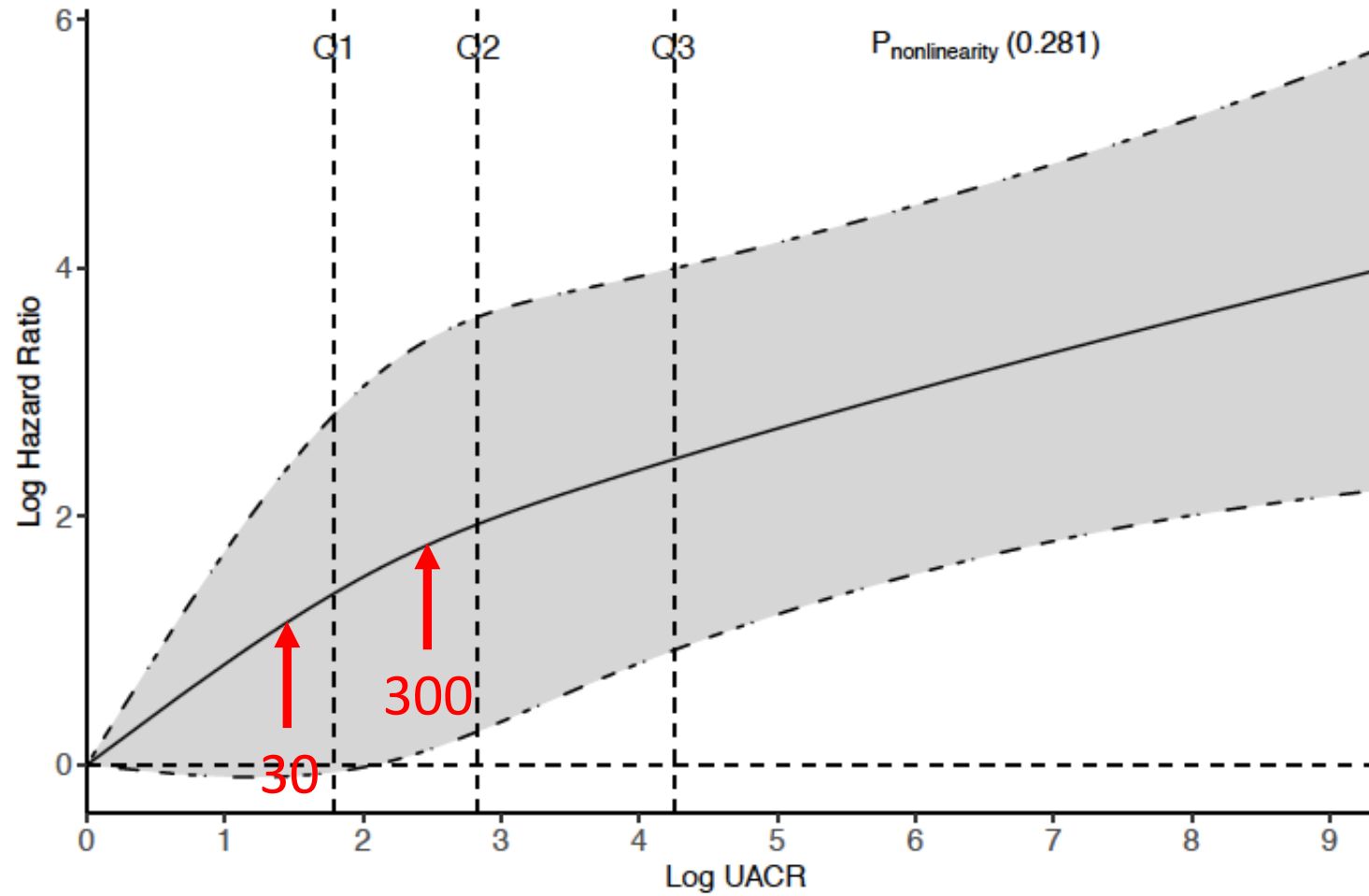
Candidate Risk Indicators

- ~~• Age~~
- ~~• Sex~~
- ~~• Race~~
- ~~• BMI~~
- ~~• Duration of T2DM~~
- ~~• Hemoglobin A1c~~
- ~~• Baseline Insulin Use~~
- ~~• H/o Retinopathy~~
- ~~• H/o Nephropathy~~
- ~~• Estimated GFR~~
- ~~• Urine Albumin/Creatinine Ratio~~
- ~~• H/o Coronary Artery Disease~~
- ~~• H/o Prior Myocardial Infarction~~
- ~~• H/o Peripheral Arterial Disease~~
- ~~• H/o Ischemic Stroke~~
- ~~• H/o Heart Failure~~
- ~~• H/o Atrial Fibrillation~~
- ~~• H/o PCI~~
- ~~• H/o CABG~~
- ~~• H/o Dyslipidemia~~
- ~~• H/o Hypertension~~
- ~~• Current Tobacco Use~~
- ~~• Heart Rate~~
- ~~• Systolic Blood Pressure~~
- ~~• Systolic Blood Pressure~~

eGFR



UACR



TIMI Risk Score for HF in Diabetes

Variable	Adj-HR (95% CI)	P-value	Points
Prior Heart Failure	4.22 (3.18-5.59)	<0.001	2
Atrial Fibrillation	2.26 (1.62-3.14)	<0.001	1
CAD	2.06 (1.45-2.93)	<0.001	1
eGFR <60	1.85 (1.40-2.46)	<0.001	1
Urine ACR >300 mg/g	4.50 (3.18-6.36)	<0.001	2
30-300 mg/g	2.08 (1.50-2.87)	<0.001	1

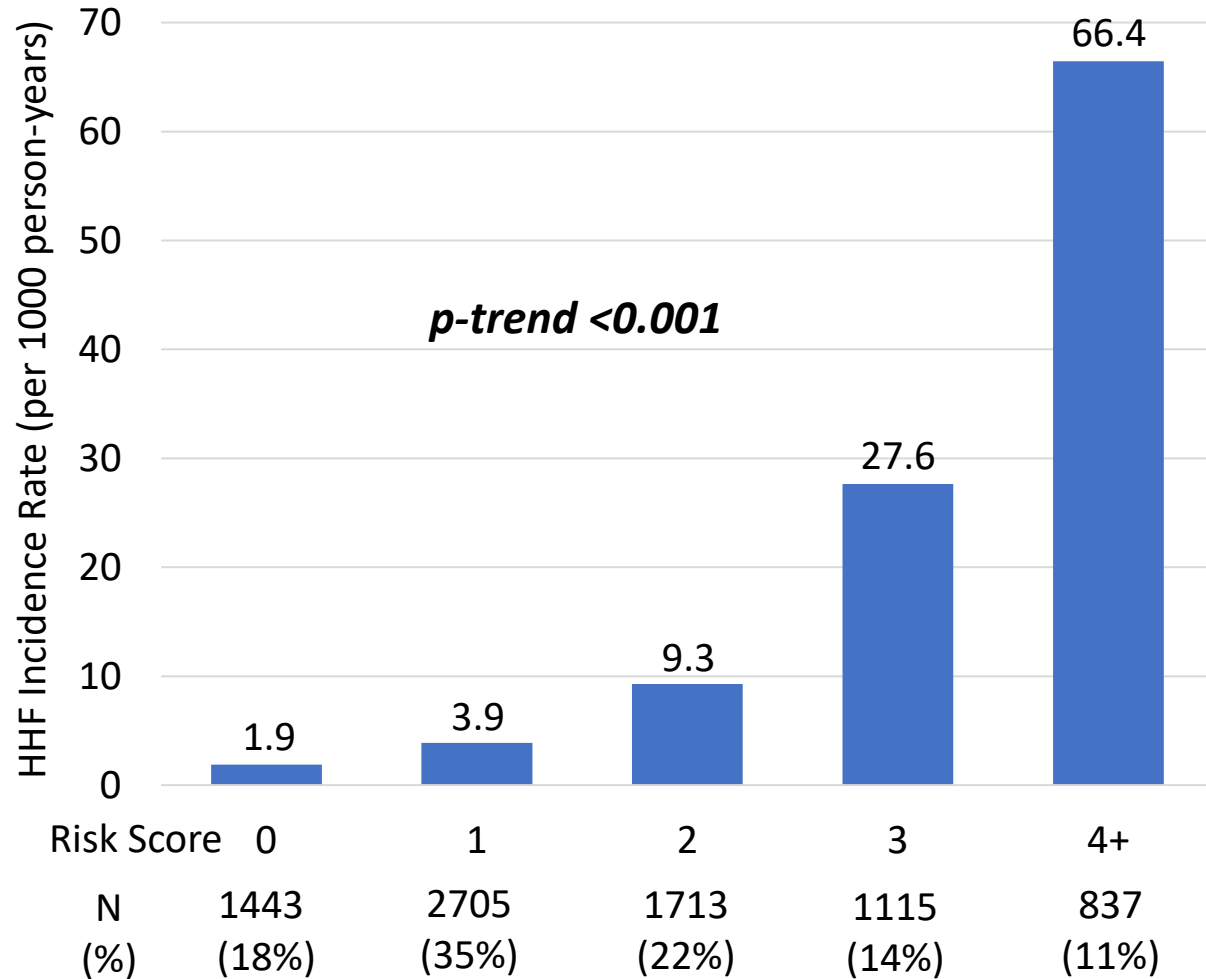
C-index (naïve) = 0.81

C-index (bootstrap) = 0.81

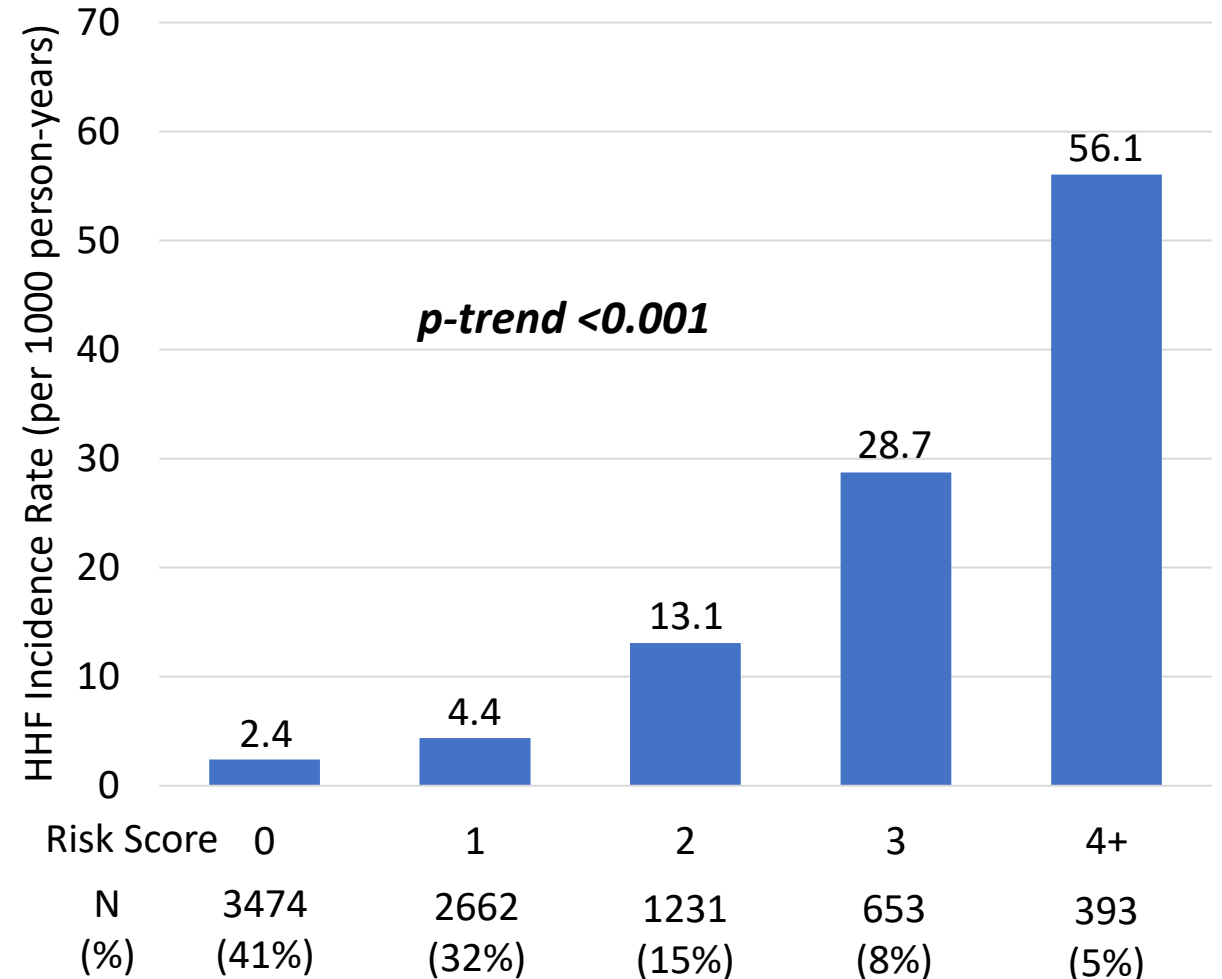
C-index (external) = 0.78

HHF Incidence Rates by Risk Score

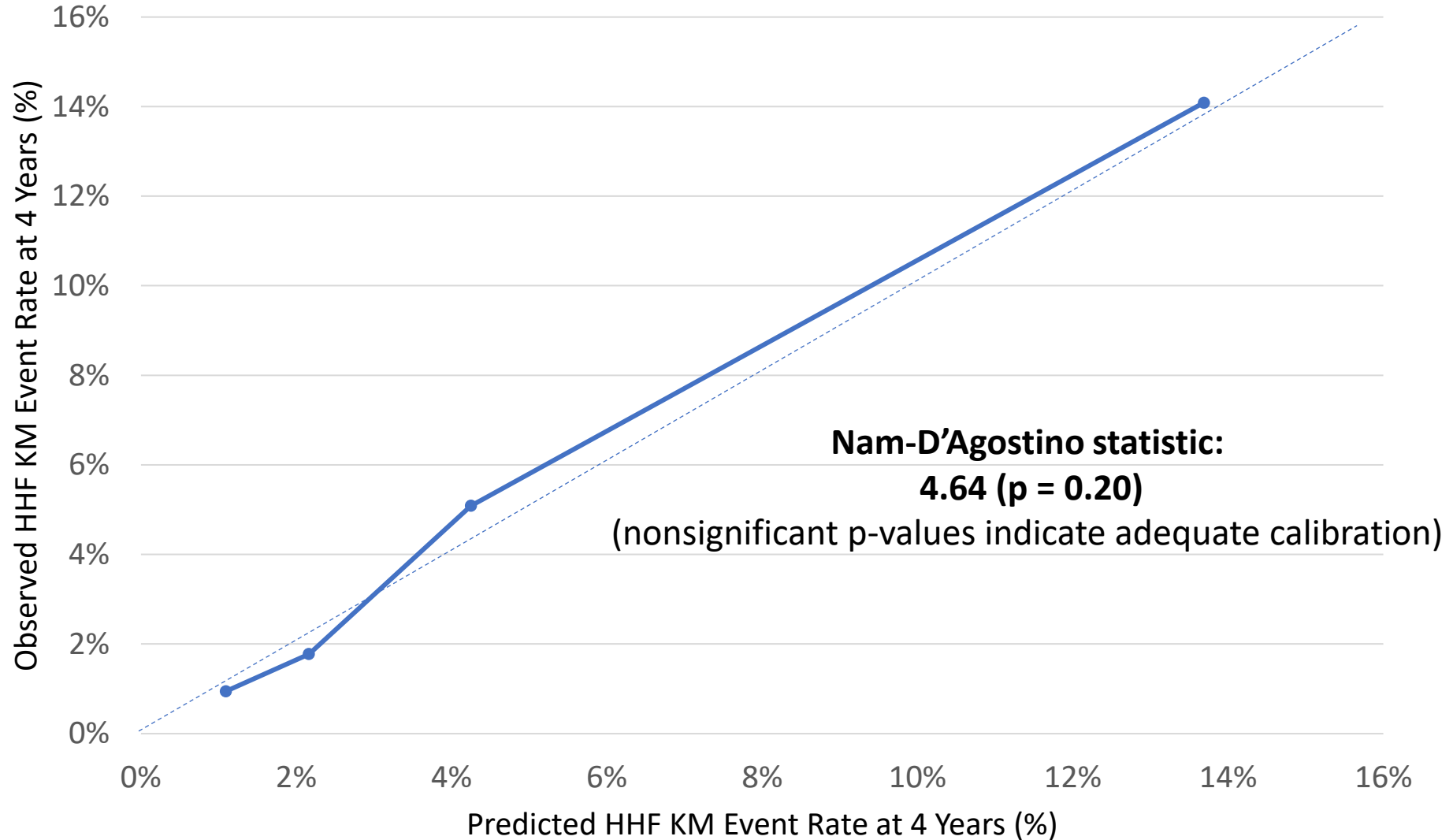
Derivation Cohort (SAVOR-TIMI 53)



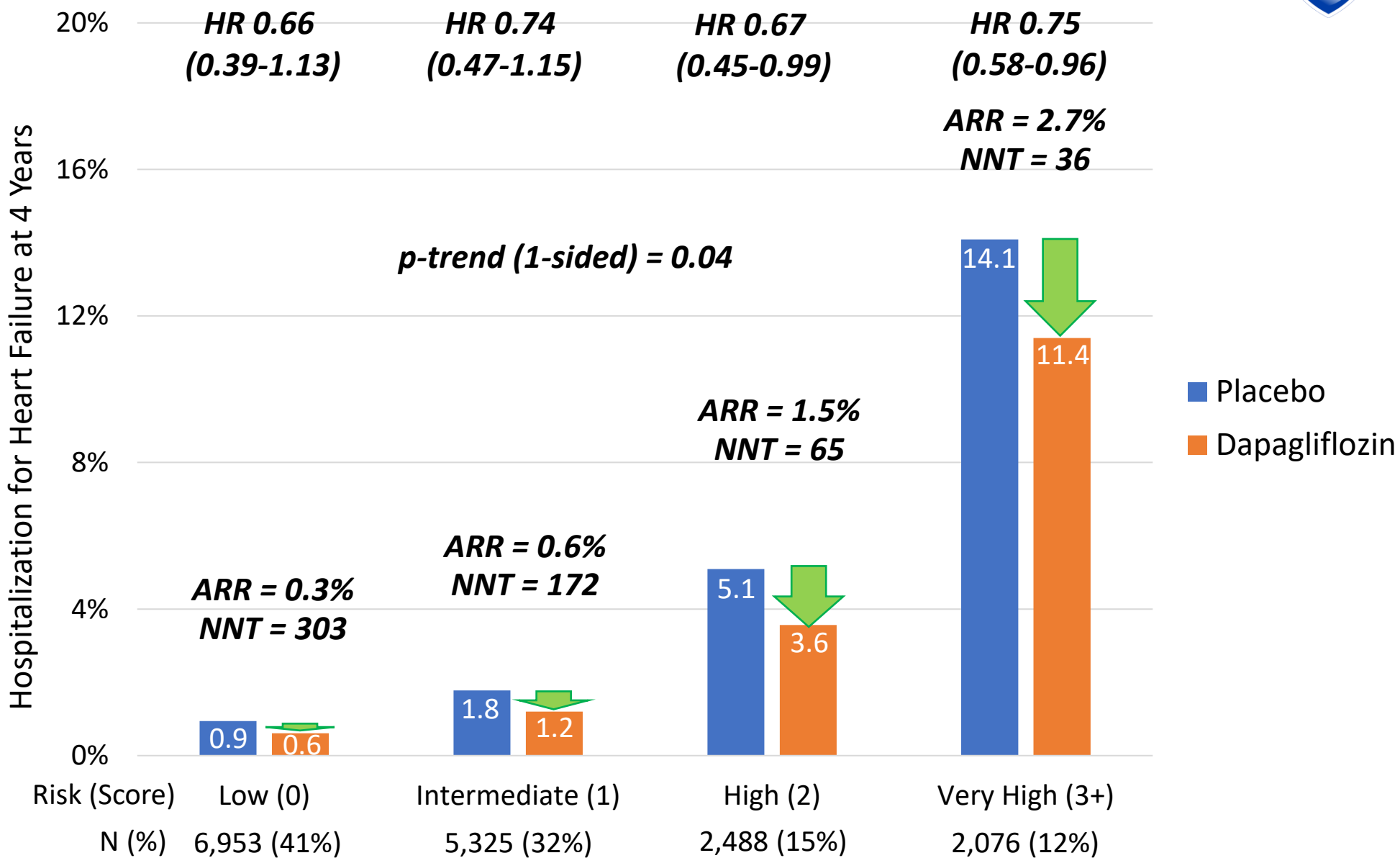
Validation Cohort (DECLARE-TIMI 58)



TRS-HF_{DM} Calibration in Validation Cohort



Treatment Effect of Dapagliflozin by Risk Score



Summary

- We developed and externally validated the **TIMI Risk Score for Heart Failure in Diabetes (TRS-HF_{DM})**, a novel, integer-based clinical risk score for predicting HHF in patients with T2DM
- The score has **excellent discrimination** (c-index 0.78-0.81) and was **well-calibrated** in the external validation cohort
- The score identifies a gradient of increasing **absolute** reduction in HHF risk in patients treated with an SGLT2 inhibitor

Circulation

ORIGINAL RESEARCH ARTICLE

Heart Failure Risk Stratification and Efficacy of Sodium-Glucose Cotransporter-2 Inhibitors in Patients With Type 2 Diabetes Mellitus

<http://www.timi.org/index.php?page=calculators>