



American Heart Association

Scientific Sessions



# Development of A Novel Biomarker-Based Risk Score for Heart Failure in Patients with Diabetes

David D. Berg,<sup>1</sup> Stephen D. Wiviott,<sup>1</sup> Benjamin M. Scirica,<sup>1</sup> Erica L. Goodrich,<sup>1</sup> Deepak L. Bhatt,<sup>2</sup> Lawrence A. Leiter,<sup>3</sup> Darren K. McGuire,<sup>4</sup> John P.H. Wilding,<sup>5</sup> Per Johanson,<sup>6</sup> Anna Maria Langkilde,<sup>6</sup> Eugene Braunwald,<sup>1</sup> Marc S. Sabatine,<sup>1</sup> David A. Morrow<sup>1</sup>

<sup>1</sup>TIMI Study Group, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; <sup>2</sup>Brigham and Women's Hospital, Harvard Medical School, Boston, MA;

<sup>3</sup>Li Ka Shing Knowledge Institute, St. Michael's Hospital, University of Toronto, Toronto, Canada; <sup>4</sup>University of Texas Southwestern Medical Center and Parkland Health and Hospital System, Dallas, TX; <sup>5</sup>University of Liverpool, Liverpool, United Kingdom; <sup>6</sup>AstraZeneca, Goteborg, Sweden



# Disclosures

**DDB** is supported by Harvard Catalyst KL2/CMerIT (NIH/NCATS UL 1TR002541), and has received research grant support to his institution from AstraZeneca. **SDW** reports grants from Amgen, Arena, AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, Eisai, Eli Lilly, Janssen, Merck and Sanofi-Aventis, consulting fees from ARENA, AstraZeneca, Aegerion, Allergan, Angelmed, Boehringer-Ingelheim, Boston Clinical Research Institute, Bristol Myers Squibb, Daiichi Sankyo, Eisai, Eli Lilly, Icon Clinical, Janssen, Lexicon, Merck, Servier, St Jude Medical, Xoma; his spouse, Dr. Caroline Fox is an employee of Merck; and is a member of the TIMI Study Group, which has received institutional research grant support through Brigham and Women's Hospital from: Abbott, Amgen, Aralez, AstraZeneca, Bayer HealthCare Pharmaceuticals, Inc., BRAHMS, Daiichi-Sankyo, Eisai, GlaxoSmithKline, Intarcia, Janssen, MedImmune, Merck, Novartis, Pfizer, Poxel, Quark Pharmaceuticals, Roche, Takeda, The Medicines Company, Zora Biosciences. **BMS** reports research grants via Brigham and Women's Hospital from AstraZeneca, Eisai, Novartis, and Merck. Consulting fees from AstraZeneca, Biogen Idec, Boehringer Ingelheim, Covance, Dr. Reddy's Laboratory, Eisai, Elsevier Practice Update Cardiology, GlaxoSmithKline, Lexicon, Merck, NovoNordisk, Sanofi, St. Jude's Medical, and equity in Health [at] Scale. **EG** reports grants from AstraZeneca, during the conduct of the study; and is a member of the TIMI Study Group which has received institutional research grant support through Brigham and Women's from: Abbott, Amgen, Anthos Therapeutics, Aralez, AstraZeneca, Bayer HealthCare Pharmaceuticals, Inc., Daiichi-Sankyo, Eisai, Intarcia, MedImmune, Merck, Novartis, Pfizer, Quark Pharmaceuticals, Regeneron Pharmaceuticals, Inc., Roche, Siemens Healthcare Diagnostics, Inc., Takeda, The Medicines Company, Zora Biosciences. **DLB** discloses research funding from 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 Aventis, Synaptic, The Medicines Company. **LAL** reports speakers bureau/honoraria from AstraZeneca, Boehringer-Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, Sanofi, Servier; consulting Fees from AstraZeneca, Boehringer-Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, Sanofi, Servier; participation in clinical trials funded by AstraZeneca, Boehringer-Ingelheim, Eli Lilly, GSK, Janssen, Novo Nordisk, Sanofi. **DKM** has received personal fees from AstraZeneca, Boehringer Ingelheim, Janssen, Lexicon, Merck, Merck Sharp & Dohme, Novo Nordisk, Sanofi, Eisai, Esperion, GlaxoSmithKline, Eli Lilly, Pfizer, Metavant, Applied Therapeutics, and Afimmune, CSL Behring. **JPHW** reports grants, consultancy fees (paid to his institution), and personal fees for lectures and trial steering committee participation from AstraZeneca; grants, consultancy fees (paid to his institution), and personal fees for lectures from Novo Nordisk; consultancy fees (paid to his institution) and personal fees for lectures from Boehringer Ingelheim, Janssen, Napp, Mundipharma, Lilly, Takeda, and Sanofi; and consultancy fees (paid to his institution) from Wilmington Healthcare. **PJ** and **AML** are employees and shareholders of AstraZeneca. **EB** reports grants to his institution from AstraZeneca, Daiichi Sankyo, Merck, and Novartis; personal fees for consultancies with Amgen, Cardurion, MyoKardia, NovoNordisk, and Verve. **MSS** reports Research grant support through Brigham and Women's Hospital from: Amgen; Anthos Therapeutics; AstraZeneca; Bayer; Daiichi-Sankyo; Eisai; Intarcia; Medicines Company; MedImmune; Merck; Novartis; Pfizer; Quark Pharmaceuticals; Takeda; Consulting for: Althera; Amgen; Anthos Therapeutics; AstraZeneca; Bristol-Myers Squibb; CVS Caremark; DalCor; Dr. Reddy's Laboratories; Dyrnamix; Esperion; IFM Therapeutics; Intarcia; Janssen Research and Development; Medicines Company; MedImmune; Merck; Novartis. **DAM** reports grants to the TIMI Study Group from Abbott Laboratories, Amgen, Astra Zeneca, BRAHMS, Eisai, Glaxosmithkline, Medicines Co, Merck, Novartis, Pfizer, Roche Diagnostics, Quark, Takeda and consultant fees from Abbott Laboratories, Aralez, Astra Zeneca, Bayer Pharma, InCardia, Pfizer, and Roche Diagnostics. **SAVOR-TIMI 53 and DECLARE-TIMI 58 were supported by institutional research grants to Brigham and Women's Hospital from AstraZeneca. The present analysis was supported by a grant from Roche Diagnostics (reagent only).**

## Background & Objective

- Heart failure is a frequent and prognostically important complication of type 2 diabetes mellitus (T2DM), the risk of which can be reduced by treatment with sodium-glucose cotransporter-2 (SGLT2) inhibitors
- The TIMI Risk Score for Heart Failure in Diabetes (TRS-HF<sub>DM</sub>) predicts risk of hospitalization for HF in patients with T2DM
- We aimed to integrate circulating biomarkers of myocardial injury and hemodynamic stress into a clinical/biomarker-based risk score for HHF in T2DM

**TIMI Risk Score for Heart Failure in Diabetes (TRS-HF<sub>DM</sub>)**

Risk Indicator	Adjusted 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
Coronary artery disease	2.06 (1.45–2.93)	<0.001	1
eGFR <60 mL·min <sup>-1</sup> ·1.73 m <sup>-2</sup>	1.85 (1.40–2.46)	<0.001	1
Urine albumin-to-creatinine ratio			
>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

# Methods

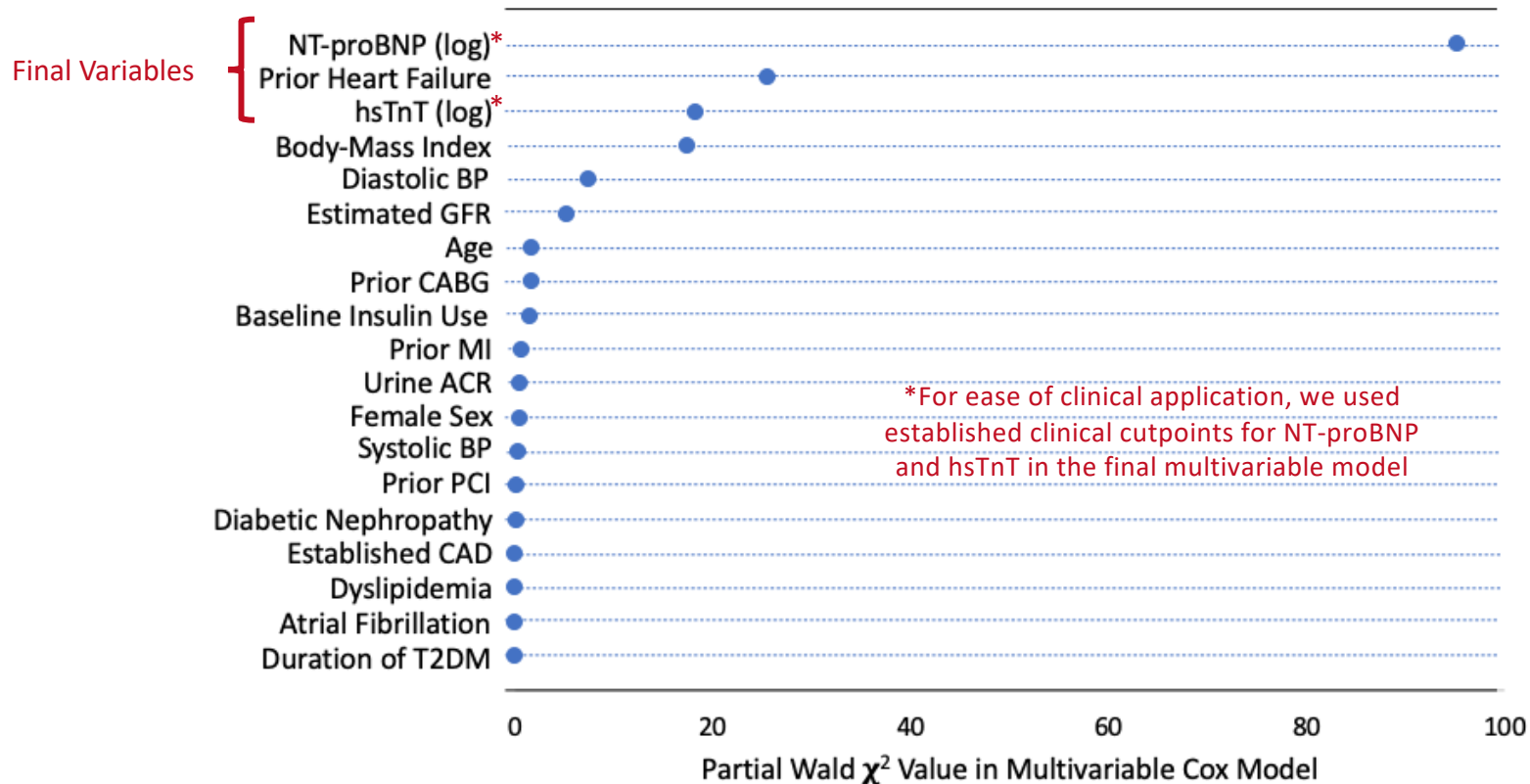
- Study Population
  - CV outcomes trials of patients with T2DM and either established ASCVD or multiple CV risk factors
  - Derivation cohort → **6,106 pts** in placebo arm of **SAVOR-TIMI 53**
  - Validation cohort → **7,251 pts** in placebo arm of **DECLARE-TIMI 58**
- Biomarkers
  - Blood samples prospectively collected at time of randomization
  - High-sensitivity troponin T (hsTnT) and N-terminal B-type natriuretic peptide (NT-proBNP) concentrations measured (Roche Diagnostics)
- Clinical Outcome
  - Hospitalization for heart failure (HHF) → centrally adjudicated by TIMI Clinical Events Committee (CEC) using standard definitions

# Methods

- Candidate variables (n=19) assessed using Cox regression analysis
- Selected **independent** risk indicators using Akaike Information Criterion (AIC) model selection procedure
  - Looked for consistency of forward, backward, and stepwise procedures
- Narrowed model to strongest risk indicators (based on partial Wald  $\chi^2$  values) → then modeled biomarkers using established cutpoints
- Assigned **integer weights** proportional to magnitude of regression coefficients in the final multivariable model
- Discrimination assessed using **Harrell's C-index**
- **Absolute risk reductions** in HHF in patients treated with dapagliflozin (SGLT2i) vs. placebo assessed by risk category

# Results

## Relative Strength of Each Variable in Multivariable Risk Model for HHF



ACR = albumin/creatinine ratio; BP = blood pressure; CABG = coronary artery bypass grafting; CAD = coronary artery disease; GFR = glomerular filtration rate; hsTnT = high-sensitivity troponin T; MI = myocardial infarction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PCI = percutaneous coronary intervention; T2DM = type 2 diabetes mellitus.

# Results

## TIMI Biomarker Score for Heart Failure in Diabetes

### Risk Score

• <b>History of HF</b>	3 points
• <b>hsTnT</b>	
<6 ng/L	0 points
6-10 ng/L	2 points
10-14 ng/L	3 points
≥14 ng/L	5 points
• <b>NT-proBNP</b>	
<50 ng/L	0 points
50-125 ng/L	3 points
125-450 ng/L	6 points
≥450 ng/L	10 points



### Risk Category

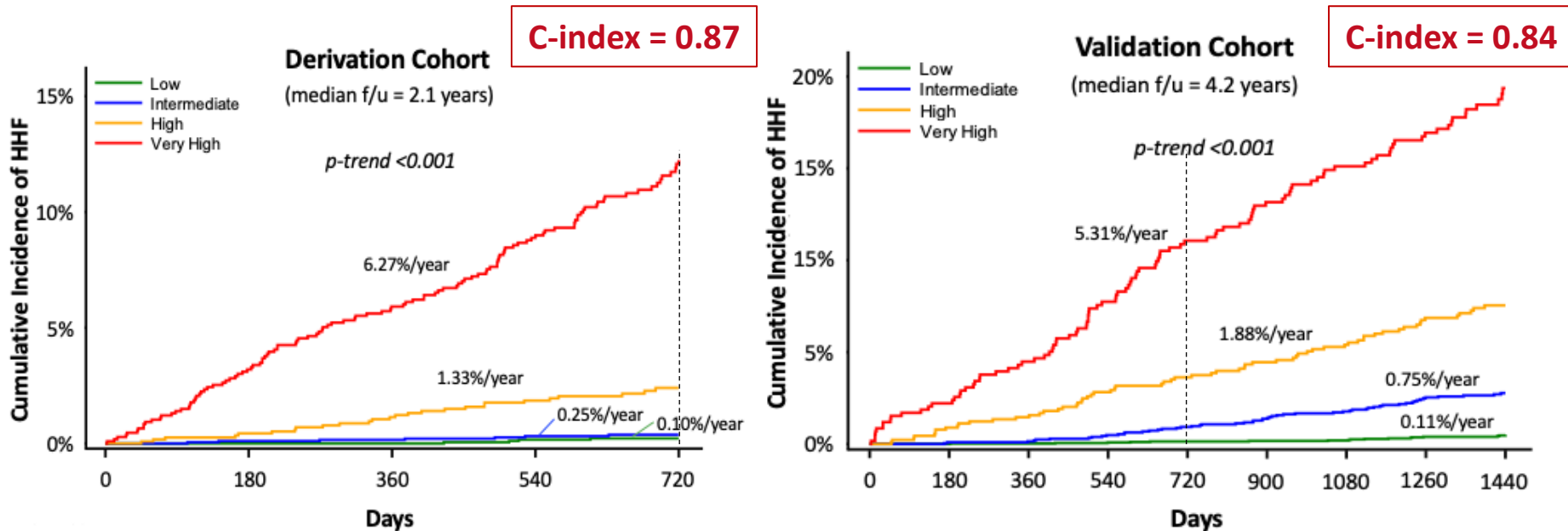
• <b>Low</b> 31%	0-5 points
• <b>Intermediate</b> 32%	6-9 points
• <b>High</b> 19%	10-13 points
• <b>Very High</b> 18%	14+ points

Proportion of patients in each risk category in the derivation cohort indicated in red

Integer weights were proportional to the magnitude of the regression coefficients in the multivariable model. Simple risk categories (low, intermediate, high, and very high) were defined. HF = heart failure; hsTnT = high-sensitivity troponin T; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

# Results

## Cumulative Risk of HHF by Risk Category in Derivation and Validation Cohorts



Annualized rates of HHF are shown for each risk category. The biomarker-based risk score identified a gradient of HHF risk with comparable annualized event rates in each cohort. f/u = follow-up; HHF = hospitalization for heart failure.

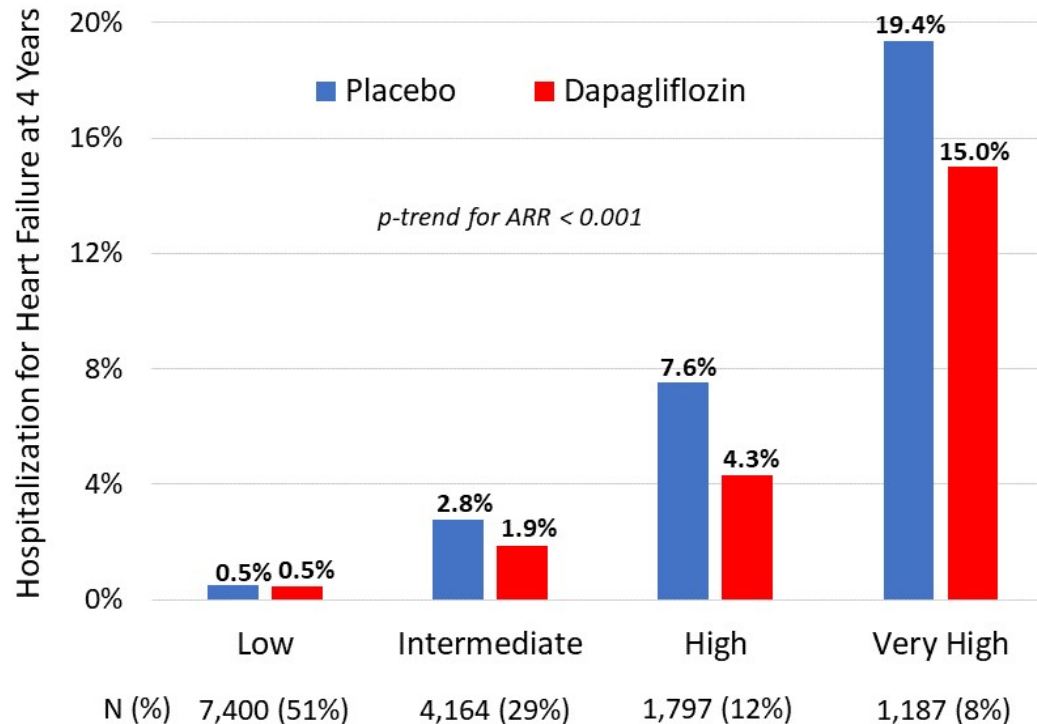
Greenwood-Nam-D'Agostino statistic:  $p=0.50$  (non-significant  $p$ -values indicate adequate calibration)



# Results

## Treatment Effect of Dapagliflozin by Risk Category

<b>HR (95% CI)</b>	0.98 (0.50, 1.91)	0.65 (0.44, 0.97)	0.61 (0.41, 0.90)	0.73 (0.55, 0.98)
<b>ARR (95% CI)</b>	0.0% (-0.3%, 0.4%)	0.9% (-0.1%, 1.8%)	3.2% (1.0%, 5.5%)	4.4% (-0.2, 8.9%)



Absolute risk reduction (ARR) was calculated by subtracting the Kaplan-Meier event rates for HHF at 4 years in patients treated with dapagliflozin from the Kaplan-Meier event rates for HHF at 4 years in patients treated with placebo across each risk score category. There was a significant gradient of increasing ARR with increasing risk category. ARR = absolute risk reduction; HR = hazard ratio.



## Conclusions

- We developed and externally validated a novel and highly parsimonious risk score for HHF in patients with T2DM incorporating NT-proBNP, hsTnT, and prior history of HF
- The risk score has excellent discrimination, is well-calibrated, and identifies patients with T2DM at higher risk of HHF who derive greater absolute benefit from SGLT2 inhibitors