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A Targeted Proteomic Approach to Identify Circulating Biomarkers of Heart Failure Risk in Patients with Type 2 Diabetes Mellitus in DECLARE-TIMI 58

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Background & Objective

- Patients with type 2 diabetes mellitus (T2DM) are at increased risk of developing heart failure (HF)
- The underlying mechanisms by which T2DM contributes to HF are incompletely understood
- ***We aimed to identify biological pathways associated with risk of hospitalization for HF in a well-characterized cohort of patients with T2DM***

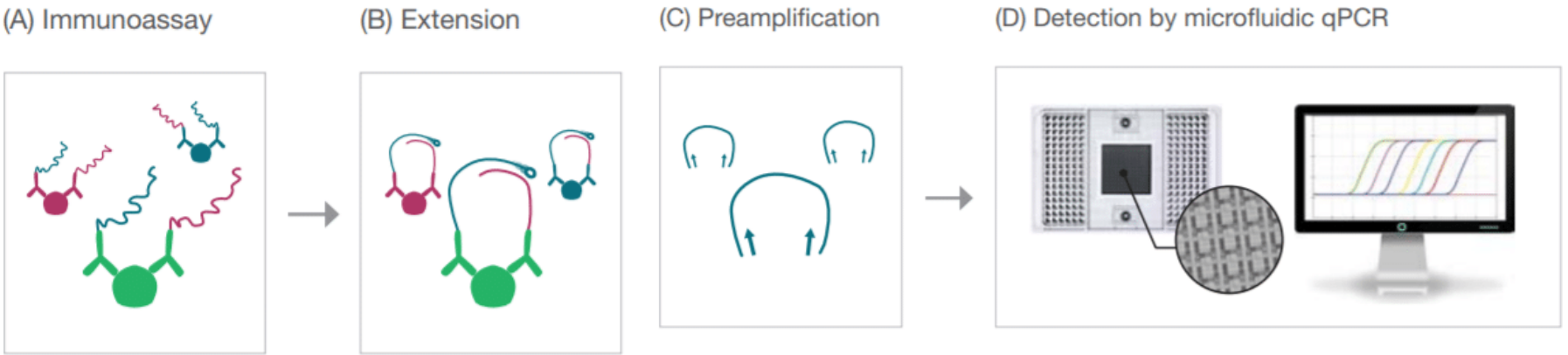
Methods

- Study Population
  - DECLARE-TIMI 58 was a multinational, randomized, placebo-controlled trial evaluating dapagliflozin in patients with T2DM and ASCVD or multiple CV risk factors (median f/u = 4.2 years)
- Biomarkers
  - Blood samples prospectively collected at randomization
  - 184 candidate biomarkers tested using Olink proteomic panels (CVD II & CVD III)
- Clinical Outcome
  - Hospitalization for heart failure (HHF) → centrally adjudicated by TIMI CEC using standard definitions

Methods

Olink Proteomic Panels (Proximity Extension Assay)

- Multiplex arrays that allow simultaneous testing of 92 biomarkers focused on a specific disease area ("targeted" proteomics)
- Pairs of oligonucleotide-labeled Ab allowed to pair-wise bind to target protein present in sample → new PCR target sequence formed by proximity-dependent DNA polymerization



Methods

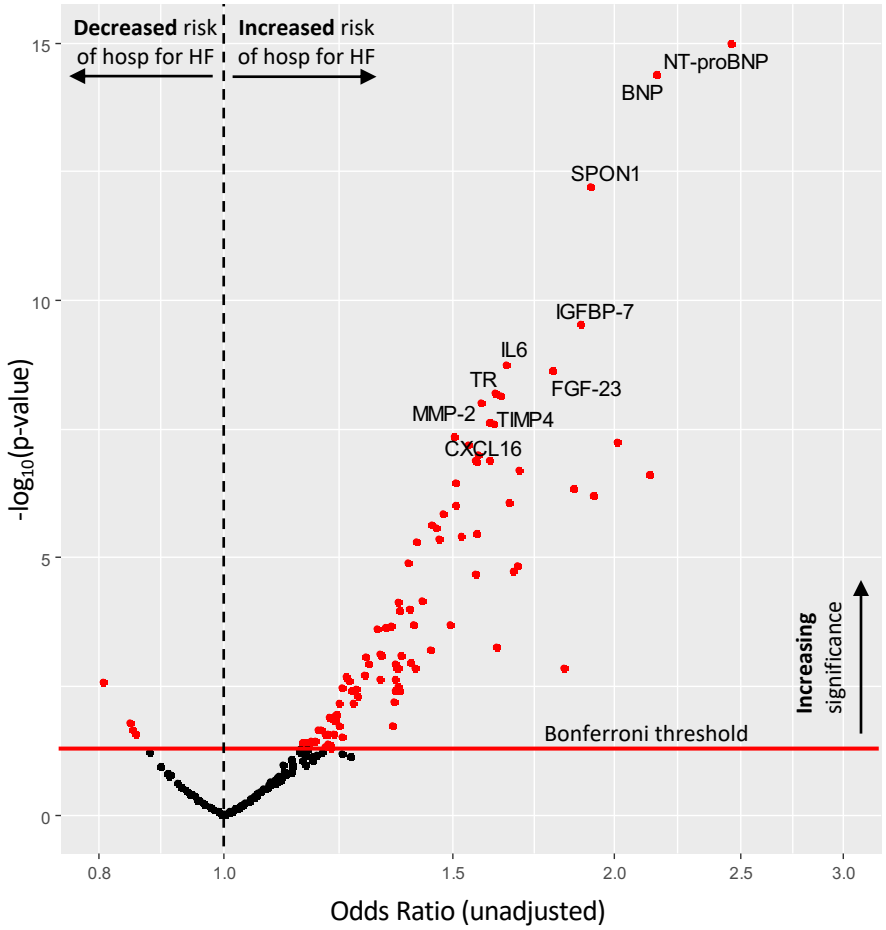
Study Design

- Nested case-control study of 184 candidate biomarkers
  - Cases → patients hospitalized for HF during follow-up (n=432)
  - Controls matched on age, sex, hx HF, hx ASCVD, and f/u time (n=432)
- We evaluated associations between baseline biomarkers and HHF using logistic regression with Bonferroni threshold for statistical significance
- We present odds ratios for top 10 strongest biomarkers (based on Wald χ^2 values), which are further adjusted for components of the TIMI Risk Score for HF in Diabetes (AF, UACR, eGFR, CAD)[1]

[1]Berg DD et al. Circulation. 2019;140(19):1569-1577

Results

Baseline Biomarker Concentrations and Risk of Hospitalization for Heart Failure



- 45 of 184 biomarkers significantly associated with HHF at Bonferroni threshold
- Top 10 strongest associations:

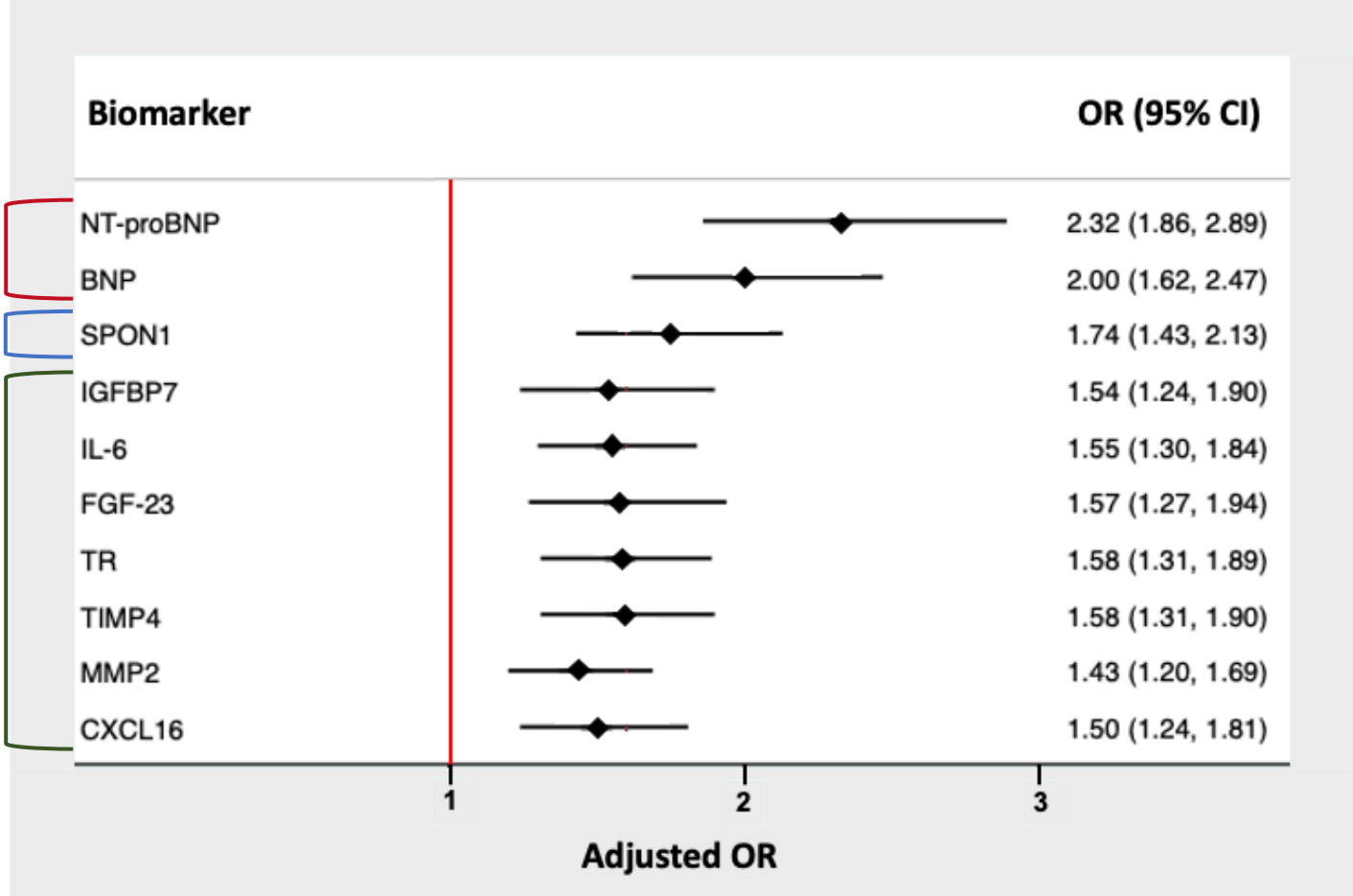
"Established"
- **NT-proBNP** = N-terminal B-type natriuretic peptide
- **BNP** = B-type natriuretic peptide

"Novel"
- **SPON1** = Spondin-1

"Investigational"
- **IGFBP7** = Insulin-like growth factor-binding protein 7
- **IL-6** = Interleukin-6
- **FGF-23** = fibroblast growth factor-23
- **TR** = transferrin receptor protein-1
- **TIMP4** = metalloproteinase inhibitor 4
- **MMP-2** = matrix metalloproteinase-2
- **CXCL16** = C-X-C motif chemokine 16

Results

Adjusted Associations with Risk of Hospitalization for Heart Failure



(Adjusted for components of TRS-HF_{DM})

Conclusions

- A targeted proteomic approach identified established, investigational, and novel biomarkers of risk for HF hospitalization in patients with T2DM
- Further investigation of these candidates may elucidate novel pathways of HF risk and potential therapeutic targets in patients with T2DM