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

David D. Berg, 1 Stephen D. Wiviott, 1 Itamar Raz, 2 Frederick Kamanu, 1 KyungAh Im, 1 Avivit Cahn, 2 Ofri Mosenzon, 2 Deepak L. Bhatt, 3 Petr Jarolim, 4 Lawrence A. Leiter, 5 Darren K. McGuire, 6 John P.H. Wilding, 7 Yong Huo, 8 Jose L. Lopez-Sendon, 9 Diego Ardissino, 10 Ingrid Gause-Nilsson, 11 Marc S. Sabatine, 1 David A. Morrow 1

1 TIMI Study Group, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA; 2 Hadassah Hebrew University Hospital, Harvard Medical School, Jerusalem, Israel; 3 TIMI Study Group, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA; 4 Department of Pathology, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA; 5 Li Ka Shing Knowledge Institute, St. Michael’s Hospital, University of Toronto, Toronto, Canada; 6 University of Texas Southwestern Medical Center and Parkland Health and Hospital System, Dallas, TX; 7 University of Liverpool, Liverpool, United Kingdom; 8 Peking University Frist Hospital, Beijing, China; 9 Hospital Universitario La Paz, Madrid, Spain; 10 Ospedale Maggiore Di Parma, Parma, Italy; 11 AstraZeneca, Goteborg, Sweden
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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 $\rightarrow$ 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 $\chi^2$ values), which are further adjusted for components of the TIMI Risk Score for HF in Diabetes (AF, UACR, eGFR, CAD)\(^1\)

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
    - **IGFBP7** = Insulin-like growth factor-binding protein 7
    - **IL-6** = Interleukin-6
    - **FGF-23** = fibroblast growth factor-23
  - **“Investigational”**
    - **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