Soluble Suppression of Tumorigenicity 2 (sST2) and Cardiovascular Outcomes in Persons With Type 2 Diabetes Randomized to Dapagliflozin vs Placebo - Analysis From the DECLARE-TIMI 58 Trial

Paul M. Haller1,2, Stephen D. Wiviott3, Petr Jarolim3, Erica L. Goodrich1, Deepak L. Bhatt4, Ingrid Gause-Nilsson5, Lawrence A. Leiter4, Darren K. McGuire6, Itamar Raz4, John P.H. Wilding7, Marc S. Sabatine1, David A. Morrow1

1TIMI Study Group, Cardiovascular Division, Brigham & Women’s Hospital, Boston, MA, USA; 2University Heart and Vascular Center Hamburg, Department of Cardiology, Hamburg, Germany; 3Department of Pathology, Brigham & Women’s Hospital, Boston, MA, USA; 4Mount Sinai Fuster Heart Hospital, Icahn School of Medicine at Mount Sinai Health System, New York, NY, USA; 5BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden; 6Li Ka Shing Knowledge Institute, St. Michael’s Hospital, University of Toronto, Toronto, Canada; 7Division of Cardiology, University of Texas Southwestern Medical Center, Dallas, TX, USA; 8Diabetes Unit, Department of Endocrinology and Metabolism, Hadassah Medical Center, Hebrew University of Jerusalem, Faculty of Medicine, Jerusalem, Israel; 9Institute of Ageing and Chronic Disease, University of Liverpool, UK.

BACKGROUND

- ST2 is involved in inflammation and fibrosis, and its soluble form (sST2) is associated with heart failure (HF) and cardiovascular (CV) outcomes.
- Patients (pts) with type 2 diabetes mellitus (T2DM) are at high risk for both.

METHODS

- 14,572 pts in DECLARE-TIMI 58 trial of dapagliflozin vs. placebo in pts w/ T2D with or at high risk for ASCVD with available biomarker (84.9% of parent trial).
- sST2 measured at baseline (Ella, Protein Simple).
- Outcomes: adjudicated MACE (CV death, myocardial infarction, or ischemic stroke), and CV death or hospitalization for HF (HHF), median f/u = 4.2 years.
- Hazard ratios for log-transformed sST2 were adjusted for age, sex, race, BMI, hypertension, prevalent CV disease, prior HF, eGFR, hs-CtNT, and NT-proBNP.
- The effects of dapagliflozin vs. placebo were assessed stratified by baseline sST2 quartiles.

RESULTS

- Median sST2 at BL was 26.8 (IQR 20.7, 35.0) ng/mL.
- Higher sST2 was associated with male sex, white race & established ASCVD, CAD, and insulin use (Table 1).
- There was a stepwise gradient of higher risk for CV Death/HHF and MACE (Fig. 1) with higher sST2 remaining significant in adjusted analyses.
- Results were similar across individual components of both composite endpoints, and all-cause death (Fig. 2).
- There was no heterogeneity across the subgroups of pts with or without HF, or established ASCVD, respectively, for both primary endpoints (Fig. 3).
- The estimated effect of dapagliflozin on outcomes did not statistically differ across sST2 quartiles (Fig. 4).

CONCLUSION

- Baseline sST2 is independently associated with higher risk for multiple adverse CV outcomes in T2DM pts.
- The benefit of dapagliflozin was consistent for CV/HHF, irrespective of baseline sST2.

![Table 1: Baseline characteristics](image)

![Figure 1: adj. HR per quartile of sST2 in the Placebo group](image)

![Figure 2: adj. HR per 1-SD of sST2 in the Placebo group](image)

![Figure 3: KM-incidence per quartiles of sST2 and by group allocation](image)

DISCLOSURES: PMH is funded by Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – grant 100861/1. DAM reports CONSULTANT FEES/HONORARIA from Abbott, ARCA biopharma, Inc, Infinamet, Merck and Company, Novartis, Roche Diagnostics; DATA SAFETY MONITORING BOARD - iPEARL, RESEARCH/RESEARCH GRANTS - Abbott, Amsino, Amgen, Anthras Therapeutics, ARCA biopharma, Inc., AstraZeneca, Bayer, Boehringer Ingelheim, Corrona, Daiichi Sankyo Ltd, Eisai Corporation, Gilead Sciences, Inc, Johnson & Johnson, Merck and Company, Novartis Pharmaceuticals, Pfizer, Regeneron, Roche Diagnostics, Siemens Medical Solutions, SoftCell.

The DECLARE-TIMI 58 was supported and sponsored by AstraZeneca.