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

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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).

Table 1: Baseline characteristics

sST2 quartiles	Q1 (N=3,643)	Q2 (N=3,643)	Q3 (N=3,643)	Q4 (N=3,643)
Age, median	64	64	63	64
Male Sex (%)	45	58	69	79
White (%)	73	81	84	86
BMI, median	31	32	32	32
syst. BP, median	134	135	135	136
ASCVD (%)	37	40	42	45
History of CAD (%)	29	32	35	38
History of HF (%)	9	10	11	10
HbA1c, Median	7.9	8.0	8.0	8.1
eGFR, Median	89	89	88	88
Insulin use (%)	36	40	43	46

FIGURE 1: adj. HR per quartile of sST2 in the Placebo group

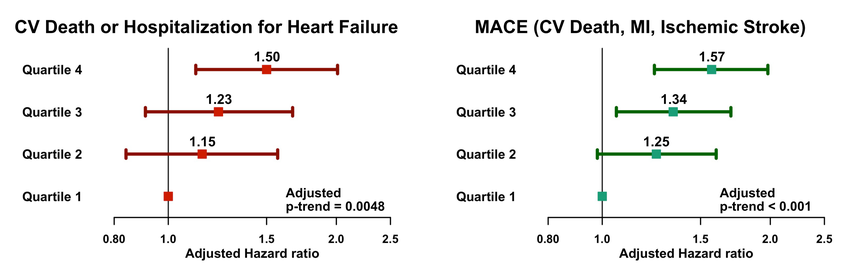


Fig 1: Adjusted hazard ratios by quartiles of sST2 in the placebo group.

FIGURE 2: adj. HR per 1-SD of sST2 in the Placebo group

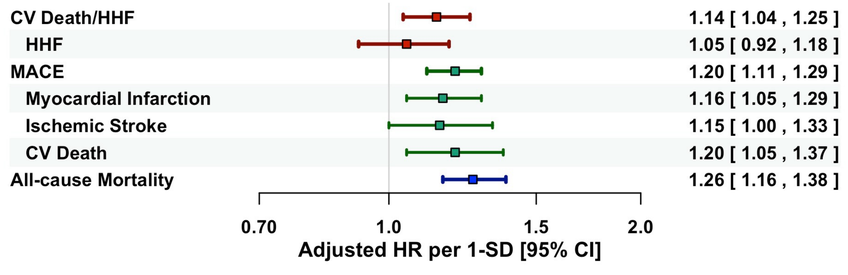


Fig 2+3: Adjusted hazard ratios per 1-SD of sST2 for (**Fig. 2**) different components of the primary endpoints and all-cause death, and (**Fig. 3**) for both primary endpoints by sub-groups of prevalent HF, or established atherosclerotic cardiovascular disease (ASCVD) in the placebo group.

FIGURE 3: adj. HR per 1-SD in sub-groups in the Placebo group

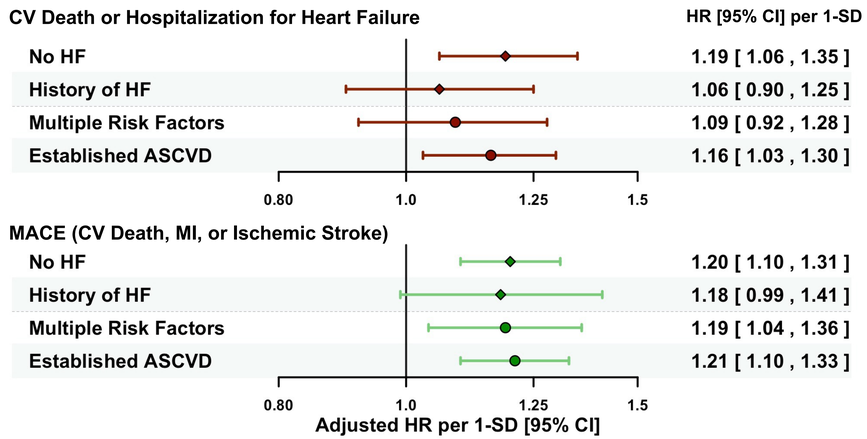
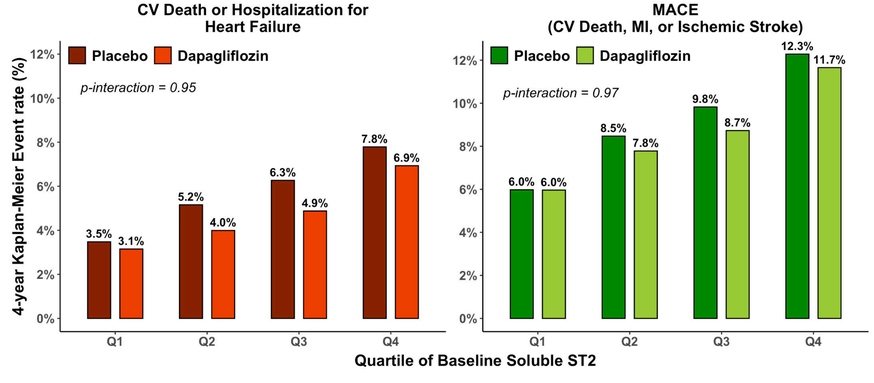


FIGURE 4: KM-incidence per quartiles of sST2 and by group allocation



CONCLUSION

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

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