Discovery and Validation of Plasma Renin and TNF-related apoptosis-inducing ligand (TRAIL) as Circulating Biomarkers of Heart Failure Risk in Patients with Type 2 Diabetes Mellitus

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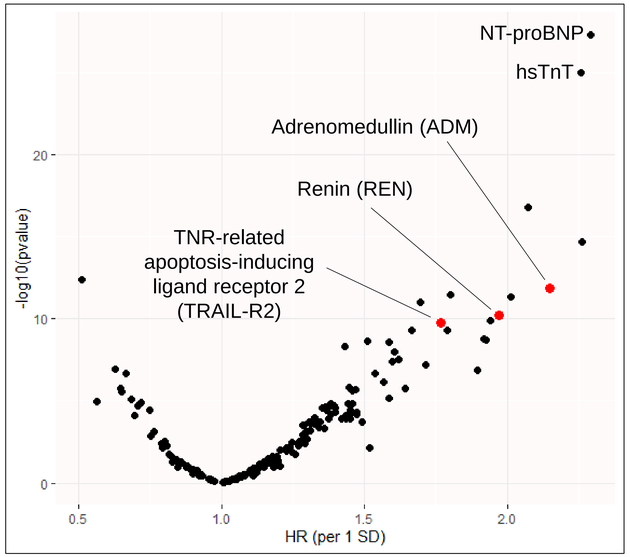
BACKGROUND

- Circulating biomarkers can improve heart failure (HF) risk assessment in patients with type 2 diabetes (T2D)
- We aimed to identify and validate novel biomarkers associated with risk of adverse HF events in patients with T2D using targeted proteomics.

METHODS

- SAVOR-TIMI 53 (median f/u 2.1 yrs) and DECLARE-TIMI 58 (median f/u 4.2 yrs) were clinical trials that enrolled patients with T2D and elevated CV risk.
- **Discovery**: In SAVOR-TIMI 53, we used a case-cohort design to compare baseline (BL) proteomic profiles (Olink CVD II & III) between pts experiencing hosp for HF (HHF) during follow-up (n=71) and a random subcohort (n=74). Associations evaluated using weighted Cox regression (robust SE estimates).
- **Confirmation**: Selected biomarkers underwent confirmation testing with immunoassays in SAVOR-TIMI 53 using a nested case-control design (n=640), with controls matched (1:1) on age, h/o HF, eGFR, UACR, f/u time. Biomarker associations with HHF risk evaluated using conditional logistic regression.
- **Validation**: Two candidates selected for validation in DECLARE-TIMI 58 biomarker cohort (n=14,330).
  - Biomarkers: Plasma renin (R&D Systems) and TRAIL (*Ella*, ProteinSimple) measured at BL.
  - Primary outcome: HHF or CV death (adjudicated)
  - Hazard ratios adjusted for age, sex, BMI, T2D duration, HTN, ASCVD, h/o HF, AF, eGFR, UACR, hsTnT, NT-proBNP, hsCRP (Cox regression)

Figure 1. Volcano plot summarizing associations between circulating cardiovascular biomarkers and risk of hosp for HF.



- Of the top candidate biomarkers identified in our targeted proteomic screen, 3 were selected for confirmation based on prior epidemiologic studies and biological relevance:
  - **Adrenomedullin** (regulator of vasomotor tone)
  - **Renin** (regulator of blood volume & vasomotor tone)
  - **TRAIL** (pro-apoptotic cytokine)*

** Note: Given analytical challenges of measuring TRAIL receptors (eg TRAIL-R2), which are present at very low circulating concentrations, TRAIL (ligand) was selected for assessment as a clinical biomarker*

RESULTS

- The associations of plasma renin and TRAIL, but not of adrenomedullin, with risk of HHF were confirmed with immunoassays in SAVOR-TIMI 53 (**Table 1**).

Table 1. Confirmation of selected candidate biomarkers.

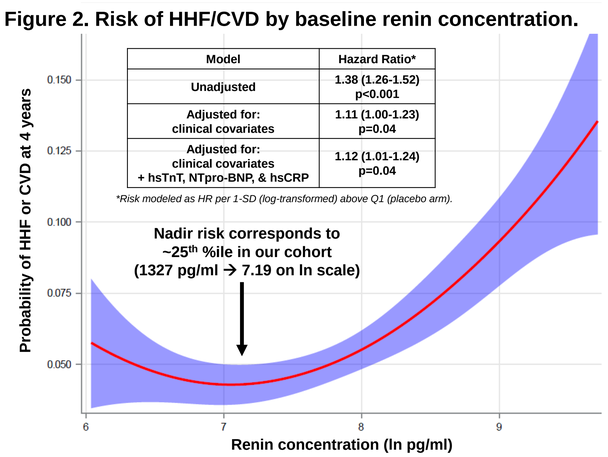
Biomarker	Discovery (SAVOR Olink) Hazard Ratio (per 1-SD)	Confirmation (SAVOR ELISA) Odds Ratio (per 1-SD)
Renin (REN)	HR 1.97 (p=0.004)	OR 1.34 (p=0.001)
TRAIL	--	OR 0.71 (p<0.001)
Adrenomedullin (ADM)	HR 2.15 (p<0.001)	OR 1.09 (p=0.31)

- In DECLARE-TIMI 58, BL renin and TRAIL concentrations were weakly correlated with established cardiovascular biomarkers (**Table 2**).

Table 2. Correlation coefficients with CV biomarkers.

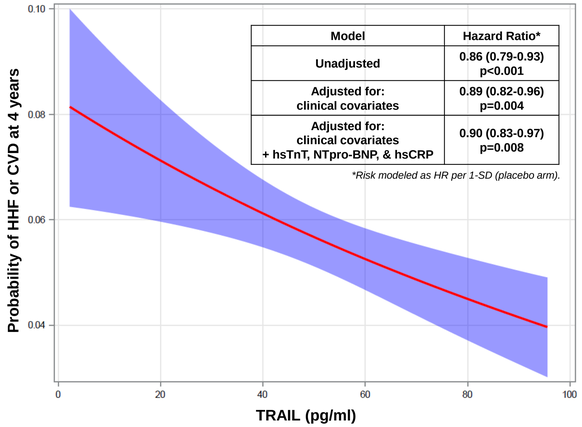
Biomarker	hsTnT	NT-proBNP	hsCRP
Renin (REN)	0.25	-0.04	0.04
TRAIL	<0.001	-0.03	-0.04

Figure 2. Risk of HHF/CVD by baseline renin concentration.



- There was a J-shaped relationship between renin concentration and risk of HHF/CVD. For renin values in Q2-Q4, there was a graded direct association with risk of HHF/CVD (**Figure 2**).
- By contrast, there was an inverse relationship between TRAIL and risk of HHF/CVD (**Figure 3**)

Figure 3. Risk of HHF/CVD by baseline TRAIL concentration.



CONCLUSIONS

- High plasma renin (regulator of blood volume & vasomotor tone) and low plasma TRAIL (pro-apoptotic cytokine) concentrations are independently associated with higher risk of HF events in patients with T2D.

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