Association of CA-125 with markers of congestion, and effect of empagliflozin on CA-125 in patients with type 2 diabetes, or prediabetes, and heart failure with reduced ejection fraction (SUGAR-DM-HF)

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On behalf of SUGAR-DM-HF Trial Investigators

Background: Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of heart failure hospitalisation and cardiovascular death in patients with heart failure and reduced ejection fraction (HFrEF). However, their effects on carbohydrate antigen 125 (CA-125) are uncertain. CA-125 has a potential role in HFrEF in the assessment of congestion, guiding decongestive therapies, and predicting outcome.

Purpose: This exploratory biomarker substudy of the SUGAR-DM-HF trial investigated the relationship of CA-125 levels with markers of congestion, and the effect of the SGLT2 inhibitor empagliflozin on serum CA-125 levels.

Methods: We conducted a multicentre, randomised, double-blind, placebo-controlled trial investigating the effects of empagliflozin in patients with New York Heart Association functional class II-IV, left ventricular ejection fraction (LVEF) ≤40%, and type 2 diabetes or prediabetes.[1] Patients were randomly assigned 1:1 to empagliflozin 10mg daily or placebo. Blood biomarker samples were collected at baseline, weeks 12 and 36. Other measures of congestion assessed included cardiovascular magnetic resonance (CMR), kidney magnetic resonance imaging (MRI), transthoracic echocardiography (TTE), lung ultrasound (LUS), and bioelectrical impedance analysis (BIA).

Results: Among 105 patients [mean age 68.7 (SD, 11.1) years, 77 (73.3%) male, 82 (78.1%) diabetes and 23 (21.9%) prediabetes, mean LVEF 32.5% (9.8%)], median [IQR] CA-125 was 11.2 [8.9-17.6] U/mL. At baseline, those with higher CA-125 had a longer duration of diabetes, higher heart rate, lower LVEF, higher N-terminal pro-B-type natriuretic peptide (NT-proBNP), were more likely to have a pleural effusion and be on a loop diuretic, but serum creatinine was similar. At baseline, CA-125 levels weakly correlated with NT-proBNP, the presence of a pleural effusion, number of B-lines, inferior vena cava (IVC) diameter, tricuspid regurgitation velocity, E/e' average, apparent extracellular volume (aECV) of the right whole kidney,[2] and total body water (FIGURE 1). CA-125 levels were not significantly different between groups at week 12 or 36 (FIGURE 2). The beneficial effect of empagliflozin on reducing left ventricular end-systolic volume index (LVESVi) was not modified by baseline CA-125 (p interaction = 0.93). Change in CA-125 was not associated with change in the co-primary outcomes (LVESVi and left ventricular global longitudinal strain) at week 36, nor with change in NT-proBNP or change in body weight at week 12 or 36.

Conclusion: Among patients with HFrEF, CA-125 levels were not strongly associated with markers of congestion assessed with CMR, kidney MRI, TTE, LUS and BIA. CA-125 levels were not different between groups at week 12 or 36, although this trial was not powered for this outcome.
Correlation heatmap (Spearman’s rho).

### Baseline

- **Empagliflozin**
  - (n=52)
- **Placebo**
  - (n=53)

### 12 weeks

- **Empagliflozin**
  - (n=47)
- **Placebo**
  - (n=45)

### 36 weeks

- **Empagliflozin**
  - (n=53)
- **Placebo**
  - (n=52)

#### Between-group difference from baseline to:
- **12 weeks**: 8% (95% CI -4% to 21%), p=0.18
- **36 weeks**: 5% (95% CI -11% to 23%), p=0.57

Data presented as geometric mean (95% confidence intervals). Treatment effect calculated using linear regression model adjusted for treatment group, age at baseline, diabetes status, and baseline value of outcome. Follow-up and baseline values of outcome used in analysis model have been log-transformed and treatment effect estimate is reported as % change (95% CI) with p value.

Change in CA-125 levels.