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## High-sensitivity C-reactive protein in heart failure with preserved ejection fraction: findings from TOPCAT

### Short communication

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## **Abstract**

*Background:* Inflammation plays a central role in the genesis and progression of heart failure with preserved ejection fraction (HFpEF). C-reactive protein (CRP) is widely used as means to assess systemic inflammation, and elevated levels of CRP have been associated with poor HF prognosis. Identification of chronic low-grade inflammation in outpatients can be performed measuring high-sensitivity CRP (hsCRP). The clinical characteristics and outcome associations of a pro-inflammatory state among outpatients with HFpEF requires further study.

*Aims:* Using a biomarker subset of TOPCAT-Americas (NCT00094302), we aim to characterize HFpEF patients according to hsCRP levels and study the prognostic associations of hsCRP.

*Methods:* hsCRP was available in a subset of 232 participants. Comparisons were performed between patients with hsCRP <2 mg/L and  $\geq$ 2 mg/L. Cox regression models were used to study the association between hsCRP and the study outcomes.

*Results:* Compared to patients with hsCRP <2 mg/L (n =89, 38%), those with hsCRP  $\geq$ 2 mg/L (n =143, 62%) had more frequent HF hospitalizations prior to randomization, chronic obstructive pulmonary disease, orthopnea, higher body mass index, and worse health-related quality-of-life. A hsCRP level  $\geq$ 2 mg/L was associated with an increased risk of cardiovascular death and HF hospitalizations: hsCRP  $\geq$ 2 mg/L vs <2 mg/L adjusted HR 2.36, 95%CI 1.27-4.38, P=0.006. Spironolactone did not influence hsCRP levels from baseline to month 12: gMean ratio =1.11, 95%CI 0.87-1.42, P=0.39.

*Conclusions:* A hsCRP  $\geq$ 2 mg/L identified HFpEF patients with a high risk of HF events and cardiovascular mortality. Spironolactone did not influence hsCRP levels at 12 months.

*Key-words:* Heart failure with preserved ejection fraction; High-sensitivity C-reactive protein; Inflammation; Prognosis.

## **Background**

Heart failure with preserved ejection fraction (HFpEF) affects nearly half of the patients suffering from heart failure (HF) and its prevalence is increasing globally due to the ageing of the population along with the accumulation of comorbidities.<sup>1,2</sup> Inflammation plays a central role in the genesis and progression of HFpEF which is characterized by a pro-inflammatory state.<sup>3,4</sup> Systemic inflammation may contribute to endothelial dysfunction and oxidative stress, which are important features of HF progression.<sup>5</sup>

C-reactive protein (CRP) is widely used as means to assess systemic inflammation, and elevated levels of CRP have been associated with poor HF prognosis.<sup>6</sup> Identification of chronic low-grade inflammation in outpatients can be performed using a high-sensitivity CRP (hsCRP) assay, and a cutoff of 2 mg/L has been used for the identification of patients with a pro-inflammatory state.<sup>7,8</sup>

The clinical characteristics and outcome associations of a pro-inflammatory state among outpatients with HFpEF requires further study.

## **Aims**

Using a biomarker subset of the TOPCAT (Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function; NCT00094302) trial with patients randomized in “the Americas”,<sup>9,10</sup> we aim to characterize HFpEF patients according to hsCRP levels and study the prognostic associations of hsCRP.

## **Methods**

### **Patient population**

TOPCAT was a multinational, double-blind, randomized, placebo-controlled trial that investigated the effects of spironolactone vs placebo on clinical outcomes in patients with HFpEF. The rationale and design of the study have been previously published.<sup>11</sup> Due to important regional variations observed in TOPCAT (as previously reported), we included only patients randomized within “the Americas”: TOPCAT-Americas.<sup>9,12</sup>

All patients provided informed consent. The protocol was approved by the Institutional Review Board at each of the participating centres prior to enrolment of the first patient. The study was overseen by the Institutional Review Board.

The median follow-up time was 3.3 years.

### **Biomarker subpopulation**

hsCRP (Critical Diagnostics®) measurements were available in a subset of 232 participants from TOPCAT-Americas who provided separate, written informed consent to participate in the TOPCAT biorepository. These participants contributed with additional samples of blood and urine at the baseline and month 12 study visits for immediate local storage at -20°C and subsequent transfer to the central repository of the National Heart, Lung and Blood Institute for long-term storage at -70°C. The characteristics of the patients included and not included in the biorepository substudy have been previously published.<sup>13</sup>

### **Statistical analysis**

TOPCAT-Americas patients with available hsCRP at baseline (N =232) were compared between those with a hsCRP level <2 mg/L and ≥2 mg/L. Patients' characteristics are presented in Table 1. Variables with a P-value <0.05 from Table 1 were inserted in a stepwise forward logistic regression model to assess the top predictors of having a hsCRP level ≥2 mg/L. Cox regression models were used to study the association between hsCRP (categorical and continuous Log transformed) and the study outcomes, adjusting for the independent predictors of elevated hsCRP plus NTproBNP. Additional confirmatory analyses were performed with models adjusted on age, sex, race, and independent predictors of primary outcome occurrence. Landmark analyses were conducted to study the association between persistently elevated hsCRP levels at 12 months and the study outcomes. The primary outcome was a composite of cardiovascular death, resuscitated cardiac arrest or HF hospitalization. Two-tailed p values <0.05 were considered statistically significant. No correction for test multiplicity was performed given the exploratory nature of this work. Statistical analyses were performed using STATA® Statistical Software version 17.0 (STATA Corp, College Station, Texas).

Analysis across hsCRP quintiles also suggested the 2 mg/L value as the optimal cutoff associated with an increased risk of the primary outcome (non-linearity P-value =0.002).  
*Supplementary Table 1 & Supplementary Figure 1.*

## **Results**

### **Patient's characteristics**

A total of 232 patients had hsCRP levels available. The median (percentile<sub>25-75</sub>) hsCRP value was 2.8 (1.3-6.1) mg/L. Comparison of the patient's characteristics by hsCRP levels (<2 vs ≥2 mg/L) is shown in *Table 1*. Compared to patients with hsCRP <2 mg/L (n =89, 38%), those with hsCRP ≥2 mg/L (n =143, 62%) had more frequent HF hospitalizations prior to randomization (64 vs 44%), chronic obstructive pulmonary disease (COPD) (15 vs 5%), and orthopnea (29 vs 14%), had higher heart rate (70 vs 65 bpm), higher body mass index (BMI)

(36 vs 32 Kg/m<sup>2</sup>), and worse Kansas City Cardiomyopathy Questionnaire-Overall Symptom Score (KCCQ-OSS) (58 vs 70 points). No significant differences were observed regarding NTproBNP levels. Patient's characteristics by hsCRP levels and spironolactone or placebo assignment are presented in the *Supplementary Table 2*.

The independent predictors of having a hsCRP level  $\geq 2$  mg/L were BMI, orthopnea, prior HFH, heart rate, and COPD. *Supplementary Table 3*.

### **Outcome and associations with hsCRP levels**

A hsCRP level  $\geq 2$  mg/L was associated with an increased risk of cardiovascular death and HF hospitalizations after adjustment for variables independently associated with a hsCRP  $\geq 2$  mg/L: hsCRP  $\geq 2$  mg/L vs  $< 2$  mg/L primary outcome adjusted HR 2.36, 95%CI 1.27-4.38, P =0.006. *Table 2 & Figure 1*. Similar results were found when adjusting for age, sex, and race: hsCRP  $\geq 2$  mg/L vs  $< 2$  mg/L primary outcome adjusted HR 3.02, 95%CI 1.67-5.47, P  $< 0.001$ , and with additional adjustment on primary outcome predictors (age, sex, race, ejection fraction, prior HF hospitalization, heart rate, and NTproBNP) HR 2.20, 95%CI 1.17-4.12, P =0.014, and with the addition of obesity (BMI  $\geq 30$  Kg/m<sup>2</sup>) HR 2.31, 95%CI 1.26-4.26, P =0.007.

Adding hsCRP to the primary outcome predictors did not improve the discriminative capacity of the model: Model 1 (age, sex, race, ejection fraction, prior HF hospitalization, heart rate, and NTproBNP) C-statistics 0.714, 95%CI 0.646-0.781 vs Model 2 (age, sex, race, ejection fraction, prior HF hospitalization, heart rate, NTproBNP plus hsCRP) C-statistics 0.719, 95%CI 0.654-0.784,  $\Delta$ C-statistics 0.005.

Similar associations were found for patients with persistent hsCRP levels  $\geq 2$  mg/L (23 events in 88 patients [26.1%]) vs  $< 2$  mg/L (11 events in 95 patients [11.6%]) at 12 months: primary outcome adjusted HR 3.44, 95%CI 1.67-7.09, P =0.001.

hsCRP was positively correlated with BMI (Rho =0.32) and waist circumference (Rho =0.26), P  $< 0.001$  for both.

### **Effect of spironolactone on hsCRP levels**

Spironolactone did not influence hsCRP levels from baseline to month 12: gMean ratio =1.11, 95%CI 0.87-1.42, P =0.39. Spironolactone also did not influence the odds of having hsCRP  $\geq 2$  mg/L (or hsCRP  $< 2$  mg/L) at month 12 in a statistically significant manner: hsCRP  $\geq 2$  mg/L placebo n =47/88 (52.8%) and spironolactone n =41/88 (43.6%), odds ratio 0.69, 95%CI 0.39-1.24, P =0.21.

### **Conclusions**

The present study shows that elevated hsCRP ( $\geq 2$  mg/L) was present in more than 60% of TOPCAT-Americas biomarker sub-study participants and identified patients with chronic HFpEF at higher risk of HF events and cardiovascular mortality, despite having a higher BMI (which has been associated with better HF outcomes).<sup>6,14</sup> In this population, elevated hsCRP was not associated with mortality from non-cardiovascular causes, suggesting that hsCRP may be used to identify HFpEF patients at high-risk of HF events and cardiovascular death.

Other studies in HFpEF also showed an association of elevated hsCRP and obesity,<sup>15</sup> and in the recently published STEP-HFpEF trial (Research Study to Investigate How Well Semaglutide Works in People Living With Heart Failure and Obesity), semaglutide (a GLP1 receptor agonist) reduced body weight by 10%, improved health related quality of life, and reduced CRP by 39% compared to placebo;<sup>16</sup> supporting the close link between obesity and inflammation.<sup>17</sup>

In the present study, spironolactone did not influence hsCRP levels over a period of 12 months, as previously reported.<sup>13</sup> However, spironolactone may influence other inflammatory pathways, not directly related to hsCRP which is a non-specific inflammatory marker.<sup>18</sup> Trials are ongoing testing anti-inflammatory drugs (targeting the interleukin-6 pathway) for the treatment of HFpEF with systemic inflammation determined by a hsCRP level  $\geq 2$  mg/L (NCT05636176).

Some limitations should be acknowledged in this study. We report associations and no causal role for hsCRP can be inferred from this study. Other inflammatory markers (e.g., interleukin-6 or interleukin-1 $\beta$ ) were not available in the dataset; therefore, we cannot determine whether spironolactone would affect these inflammatory markers. However, spironolactone was shown to impact several important pathophysiologic pathways in incident and prevalent HFpEF, namely the pro-fibrotic pathways.<sup>18,19</sup>

In conclusion, a hsCRP  $\geq 2$  mg/L identified HFpEF patients with a high risk of HF events and cardiovascular mortality. Spironolactone did not influence hsCRP levels over 12 months.

## **Disclosures**

The authors have nothing to disclose regarding the content of this work.

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Table 1. Patient's characteristics by hsCRP levels

Characteristics	hsCRP <2 mg/L	hsCRP ≥2 mg/L	P-value
N. total =232	n =89	n =143	-
Age, years	73 ± 9	71 ± 10	0.15
Men	35 (39.3%)	71 (49.7%)	0.12
White race	79 (88.8%)	122 (85.3%)	0.45
LVEF, %	58.5 ± 7.3	58.0 ± 7.8	0.63
Prior HFH	39 (43.8%)	91 (63.6%)	0.003
AFib	40 (44.9%)	74 (51.7%)	0.31
Prior MI	20 (22.5%)	31 (21.7%)	0.89
Hypertension	84 (94.4%)	135 (94.4%)	0.99
Diabetes	35 (39.3%)	72 (50.3%)	0.10
COPD	4 (4.5%)	21 (14.7%)	0.015
PAD	6 (6.7%)	22 (15.4%)	0.049
NYHA III/IV	35 (41.7%)	57 (41.3%)	0.96
Heart rate, bpm	65 ± 10	70 ± 11	<0.001
SBP, mmHg	126 ± 14	124 ± 14	0.25
BMI, Kg/m <sup>2</sup>	31.6 ± 6.6	35.8 ± 7.7	<0.001
BMI ≥30 Kg/m <sup>2</sup>	49 (55.1%)	111 (77.6%)	<0.001
Waist circ., cm	106 ± 15	115 ± 18	<0.001
ACEi/ARB	70 (78.7%)	106 (74.1%)	0.43
Beta-blocker	73 (82.0%)	120 (83.9%)	0.71
Diuretics	79 (88.8%)	130 (90.9%)	0.59
Potassium, mmol/L	4.2 ± 0.4	4.1 ± 0.5	0.20
eGFR, ml/min	65 ± 19	64 ± 20	0.50
Sodium, mmol/L	139 ± 3	139 ± 3	0.50
Hemoglobin, g/dL	13.2 ± 1.5	12.8 ± 1.6	0.06
Orthopnea	12 (13.5%)	42 (29.4%)	0.005
Rales	11 (12.3%)	16 (11.2%)	0.93
Edema	60 (67.4%)	111 (77.6%)	0.09
KCCQ-OSS	70 ± 20	58 ± 22	<0.001
NTproBNP, pg/mL	894 ± 988	1173 ± 1397	0.53

Legend: hsCRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fraction; HFH, heart failure hospitalization; AFib, atrial fibrillation; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; PAD, peripheral artery disease; SBP, systolic blood pressure; BMI, body mass index; ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; KCCQ-OSS, Kansas City Cardiomyopathy Questionnaire-Overall Symptom Score; NTproBNP, N-terminal pro-brain natriuretic peptide.

Table 2. Outcome associations of hsCRP

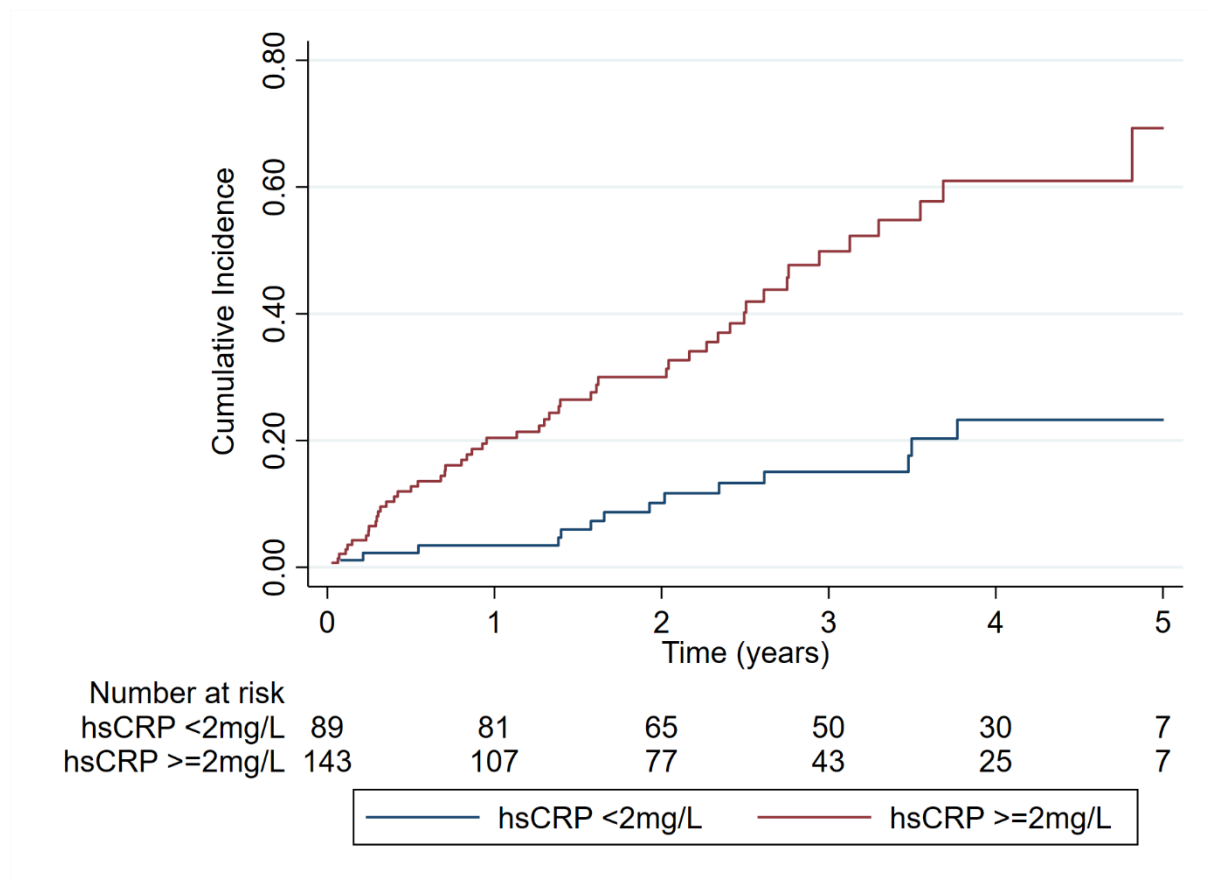
<b>Outcome</b> N =232	<b>hsCRP &lt;2 mg/L</b> n =89	<b>hsCRP ≥2 mg/L</b> n =143	<b>HR (95%CI)* ≥2 vs &lt;2 mg/L</b>	<b>P- value</b>	<b>HR (95%CI)* per Log</b>	<b>P- value</b>
Primary	14 (15.7%) IR =5.1	53 (37.1%) IR =16.0	2.36 (1.27-4.38)	0.006	1.22 (0.99-1.51)	0.061
HFH	9 (10.1%) IR =3.3	36 (25.2%) IR =10.9	2.49 (1.16-5.33)	0.019	1.30 (1.01-1.67)	0.044
CV death	7 (7.9%) IR =2.4	27 (18.9%) IR =6.9	2.32 (0.97-5.56)	0.059	1.18 (0.88-1.59)	0.26
ACM	15 (16.9%) IR =4.9	36 (25.2%) IR =9.0	1.40 (0.74-2.66)	0.30	1.03 (0.82-1.31)	0.78
ACH	55 (61.8%) IR =32.0	91 (63.6%) IR =41.0	1.07 (0.74-1.53)	0.73	1.04 (0.89-1.22)	0.59
WRF	10 (11.2%) IR =3.7	29 (20.3%) IR =8.2	1.59 (0.74-3.41)	0.23	1.18 (0.90-1.54)	0.22
RF	4 (4.5%) IR =1.1	19 (13.3%) IR =5.2	3.30 (0.93-11.7)	0.065	1.29 (0.90-1.95)	0.16

Legend: hsCRP, high-sensitivity C-reactive protein; Primary, primary composite outcome of cardiovascular death, resuscitated cardiac arrest or heart failure hospitalization; HFH, heart failure hospitalization; CV, cardiovascular; ACM, all-cause mortality; ACH, all-cause hospitalization; WRF, worsening renal function (doubling in serum creatinine); RF, renal failure defined by a serum creatinine ≥3 mg/dL.

IR, incidence rate per 100 person-years.

\*Model adjusted for the independent predictors of elevated hsCRP: body mass index, heart rate, othopnea, prior HF hospitalization, and presence of chronic obstructive pulmonary disease (also shown in the Supplementary Table 3).

Figure 1. Primary outcome incidence according to hsCRP levels at baseline



Legend: hsCRP, high-sensitivity C-reactive protein; Primary outcome, composite outcome of cardiovascular death, resuscitated cardiac arrest or heart failure hospitalization.