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Application of the H_2FPEF score to a global clinical trial of patients with heart failure with preserved ejection fraction: the TOPCAT trial

Diagnostic uncertainties and lack of standardized strategies to enrich baseline risk have posed significant challenges to the effective conduct of global trials of heart failure with preserved ejection fraction (HFpEF). Differences in event rates across regions in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial (TOPCAT, NCT00094302) underscore the importance of consistent standards for HFpEF diagnosis.[1] The recent H_2FPEF-score, which uses six routinely available clinical and echocardiographic variables, is the first validated diagnostic algorithm for identification of HFpEF in patients with unexplained dyspnoea[2] and offers promise as a screening measure in clinical trials. The TOPCAT trial presents a unique opportunity to evaluate the application of this score in a trial population with known background heterogeneity, and to understand its relationship with risk of clinical events.

TOPCAT was a global, phase 3, double-blind, placebo-controlled randomized clinical trial of spironolactone in HFpEF enrolling patients from the Americas (United States, Canada, Brazil, Argentina), Russia, and the Republic of Georgia.[3] Eligible patients were those $\geq$ 50 years with symptomatic HF and left ventricular ejection fraction (EF) $\geq$ 45%, well-controlled blood pressure, and a serum potassium $<$ 5.0 mmol/L as well as a recent heart failure (HF) hospitalization within 12 months or elevated natriuretic peptide (NP) concentrations within 60 days. In a subset, pre-randomization echocardiograms were submitted to a central core laboratory.[4] The primary outcome was time to composite hospitalization for HF, cardiovascular death, or aborted cardiac arrest.

The H_2FPEF score was developed from a retrospective analysis of patients referred for invasive haemodynamic exercise testing for the evaluation of unexplained dyspnoea at a tertiary care centre.[2] Analyses in this TOPCAT substudy were performed in 362 patients with available data necessary to calculate the H_2FPEF score: age, body mass index, hypertension medication use, history of atrial fibrillation, pulmonary artery systolic pressure (PASP, estimated from the modified Bernoulli equation of the peak tricuspid valve regurgitation velocity + 5 mmHg as a surrogate of right atrial pressure) and E/e'.

We estimated diagnostic probabilities of HFpEF reported in the original derivation report of the H_2FPEF score.[2] We assessed the association between H_2FPEF score and baseline NP levels (either B-type NP or N-terminal pro-B-type NP), which were log-transformed and standardized (expressed per 1 standard deviation; Z-score). Multivariable Cox proportional hazards models were used to assess the association between H_2FPEF score and the primary composite outcome. Restricted cubic splines models with the number of knots selected based on the lowest Akaike Information Criterion were used to flexibly model the relationship between H_2FPEF score and standardized NPs and the incidence of the primary endpoint. All patients provided written informed consent, and the study was approved by institutional review board or ethics committees at each participating institution. All statistical analyses were performed using STATA 14.1 (StataCorp., College Station, TX, USA).

Of the 313 (18%) patients from the Americas and 49 (3%) from Russia/Georgia with available data, the median H_2FPEF score was 6 (interquartile range 4–7) and 5 (interquartile range 3–6), respectively ($P = 0.01$ for difference between regions) (*Figure 1A*), and there were no differences between patients enrolled by HF hospitalization or NP strata ($P = 0.83$). Of the total 362 patients, 216 (60%) had body mass index $>$ 30 kg/m^2 (2 points), 344 (95%) used $\geq$ 2 antihypertensive drugs (1 point), 177 (49%) had a history of atrial fibrillation (paroxysmal or persistent, 3 points), 171 (47%) had PASP $>$ 35 mmHg (1 point), 315 (87%) were older than 60 years (1 point), and 307 (85%) had E/e' $>$ 9 (1 point). Overall, 74% and 59% of patients had H_2FPEF scores $\geq$ 5 (corresponding to HFpEF diagnostic probabilities of $>$ 80%) in the Americas and Russia/Georgia, respectively ($P = 0.026$). Patients with higher scores were more likely to be men, enrolled in the Americas region, carry a history of diabetes mellitus, have lower estimated glomerular filtration rate and greater left atrial and left ventricular volumes, in addition to parameters included in the H_2FPEF score (all $P < 0.01$) (*Table 1*). There was a trend for greater concentrations of NPs with higher H_2FPEF score, although this did not reach statistical significance ($P = 0.07$) (*Figure 1B*).

Over a 2.7-year mean follow-up, 112 primary outcome events occurred. Higher H_2FPEF scores (per point) were associated with increased risk of the primary outcome [hazard ratio (HR) 1.12, 95% confidence interval (CI) 1.02–1.23; $P = 0.02$] (*Figure 1C*). Similar, yet not statistically significant, associations between the H_2FPEF score and the primary endpoint were found in analysis restricted to patients with left ventricular EF $\geq$ 50% ($n = 319$) (HR 1.09, 95% CI 0.98–1.21; $P = 0.12$). The incidence rate of the primary outcome in patients with H_2FPEF score $\leq$ 4, 5–6, and $\geq$ 7 was 8.3 (95% CI 5.6–12.4), 11.8 (95% CI 8.7–16.0), and 13.7 (95% CI 10.2–18.3), respectively. The association between the H_2FPEF score and the primary endpoint did not differ by enrolment strata (recent HF hospitalization or elevated NP) ($P_{interaction} = 0.57$). Higher H_2FPEF scores (per point) were also associated with increased risk of HF hospitalization (HR 1.14, 95% CI 1.01–1.27; $P = 0.03$) and cardiovascular death (HR 1.15, 95% CI 0.98–1.34; $P = 0.10$) separately, although the latter association did not reach statistical significance.

HFpEF is a syndrome that is challenging to differentiate from non-cardiac sources of dyspnoea based on clinical examination alone. Although invasive and/or exercise haemodynamic assessments are available to affirm the HFpEF diagnosis, cost, complexity, procedural risk, and limited availability preclude their use in large clinical trials. In addition, risk enrichment strategies applied in HFpEF trials are subject to important limitations. Thresholds for hospitalization for HF may vary globally and across health systems.[5] NP concentrations have traditionally been used to identify HFpEF patients with greater certainty and to enrich risk, however these vary substantially and may be systematically

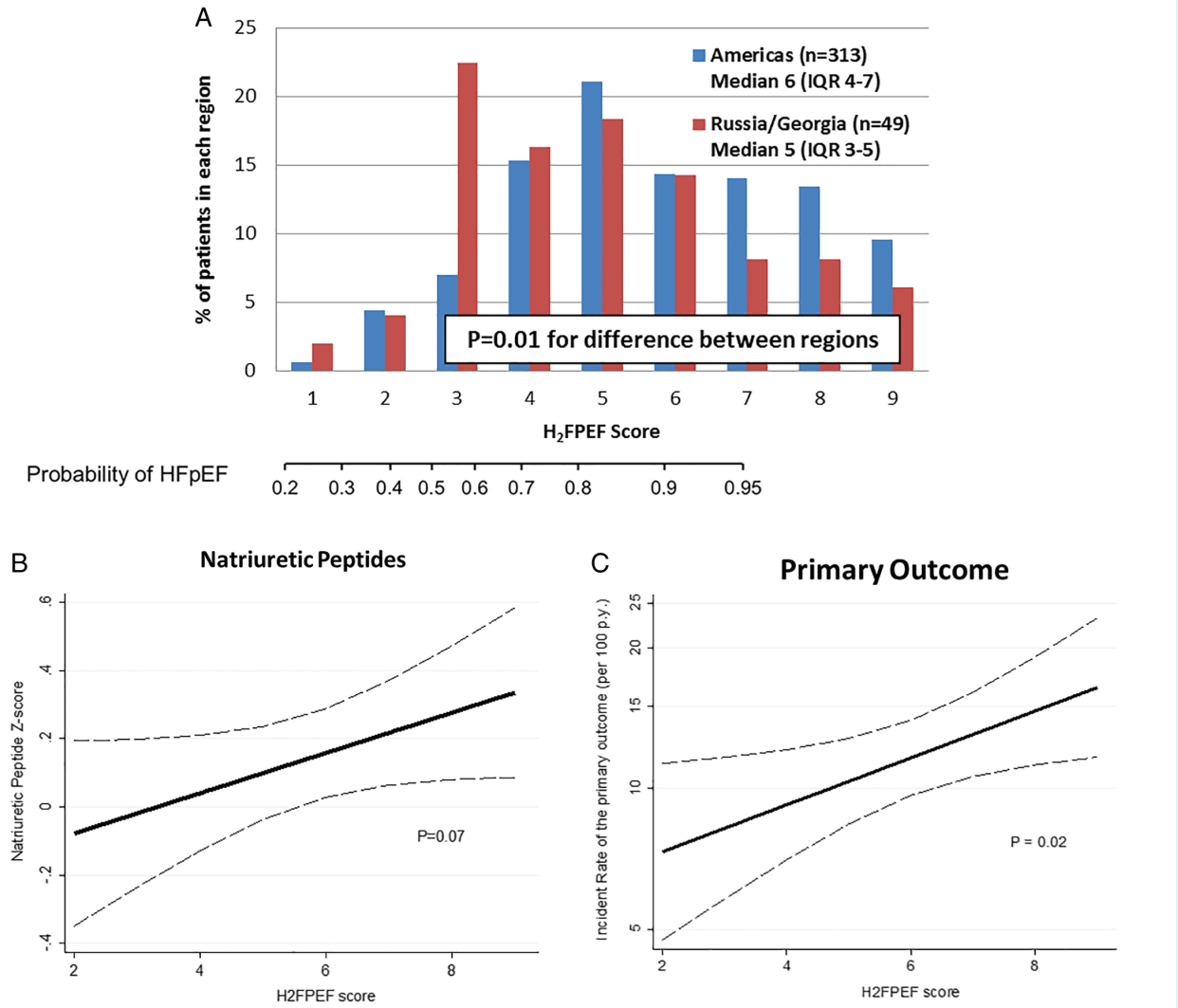

Figure 1 Distribution of the H_2FPEF score in the global TOPCAT trial, and its association with concentrations of natriuretic peptides and the primary composite outcome. Overall, 362 patients had available data to calculate the H_2FPEF score. (*A*) Distribution of scores in patients enrolled in the Americas and Russia/Georgia. (*B*) Association between the H_2FPEF score and log-transformed, standardized natriuretic peptide concentrations as a continuous variable. (*C*) Association between the H_2FPEF score and incidence of the primary composite endpoint. Natriuretic peptide levels (either B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide) were log-transformed and standardized (expressed per 1 standard deviation; Z-score). The primary outcome for the TOPCAT trial and for this analysis was time to composite hospitalization for heart failure, cardiovascular death, or aborted cardiac arrest. The dotted lines reflect the 95% confidence interval.

lower in select populations (including black and obese patients).[6]

In this study, we demonstrate that the H_2FPEF score correlates with increased risk of adverse cardiovascular events in the TOPCAT trial. Despite variation in analytic approaches, another group recently independently supported the prognostic value of the H_2FPEF score in TOPCAT.[7] We further demonstrate that the H_2FPEF score was only partially and non-significantly associated with NPs, suggesting that these two parameters may provide orthogonal and incremental information.

Among patients determined eligible for enrolment in a large HFpEF trial, we observed that 25% of patients in TOPCAT Americas had diagnostic probabilities of HFpEF < 55% as estimated by the H_2FPEF score, while 41% of patients enrolled in TOPCAT Russia/Georgia fell into this lower diagnostic probability. These findings are in keeping with regional differences in event rates suggesting a four-fold lower risk of the primary outcome in Russia/Georgia as compared with the Americas.[1] When applied to a referral cohort from Alberta, Canada, the discriminatory value of the H_2FPEF score was lower than that observed in the original derivation and internal validation cohorts.[8] Taken together, these data emphasize the ongoing need to understand the variability in distribution and performance of the H_2FPEF score across global, heterogeneous populations.

The study is subject to certain limitations, including the restricted number of patients with available data for H_2FPEF score calculation, which may introduce selection bias. The H_2FPEF score was derived from a population of patients with unexplained dyspnoea, while we applied it retrospectively to patients deemed to have symptomatic

Table 1 Baseline characteristics of patients in TOPCAT by categories of H_2FPEF score ($n = 362$)

	H_2FPEF score			
	≤4 ($n = 100$, 28%)	5 and 6 ($n = 130$, 36%)	≥7 ($n = 132$, 36%)	*P*-value
Age (years)	69.9 ± 11.2	70.7 ± 9.4	74.7 ± 8.7	<0.001
Male sex	34 (34.0%)	61 (46.9%)	68 (51.5%)	0.009
Black race	19 (19.0%)	33 (25.4%)	15 (11.4%)	0.09
Region				0.017
Russia and Georgia	20 (20.0%)	17 (13.1%)	12 (9.1%)	
The Americas	80 (80.0%)	113 (86.9%)	120 (90.9%)	
Eligibility criteria				0.64
Prior HF hospitalization in 12 months	61 (61.0%)	82 (63.1%)	77 (58.3%)	
Elevated NP in 60 days	39 (39.0%)	48 (36.9%)	65 (41.7%)	
NYHA class III or IV	41 (41.4%)	56 (43.4%)	63 (47.7%)	0.33
Hypertension	94 (94.0%)	118 (90.8%)	122 (92.4%)	0.71
Diabetes mellitus	35 (35.0%)	59 (45.4%)	59 (44.7%)	0.16
Previous myocardial infarction	22 (22.0%)	29 (22.3%)	31 (23.5%)	0.78
Previous cerebrovascular accident	12 (12.0%)	9 (6.9%)	17 (12.9%)	0.72
Peripheral artery disease	10 (10.0%)	19 (14.6%)	9 (6.8%)	0.35
History of atrial fibrillation	1 (1.0%)	44 (33.8%)	132 (100.0%)	<0.001
Body mass index (kg/m^2)	29.5 ± 8.2	34.0 ± 8.2	34.4 ± 7.4	<0.001
Waist circumference (cm)	98.7 ± 16.1	107.0 ± 16.0	110.9 ± 16.1	<0.001
Systolic blood pressure (mmHg)	128.5 ± 16.6	125.4 ± 16.3	123.7 ± 15.0	0.025
eGFR (mL/min/1.73 m^2)	65.8 ± 21.3	64.4 ± 20.9	59.7 ± 18.1	0.018
N-terminal proBNP (ng/L)	791 [437–2054]	1068 [475–1615]	1354 [751–2023]	0.32
BNP (ng/L)	234 [155–698]	208 [130–375]	329 [165–568]	0.21
Baseline medication use				
β-blocker	76 (76.0%)	106 (81.5%)	102 (77.3%)	0.89
Calcium channel blocker	38 (38.0%)	63 (48.5%)	55 (41.7%)	0.67
Diuretic	81 (81.0%)	113 (86.9%)	123 (93.2%)	0.005
ACEi/ARB	72 (72.0%)	107 (82.3%)	109 (82.6%)	0.06
Aspirin	72 (72.0%)	82 (63.1%)	70 (53.0%)	0.003
Statin	66 (66.0%)	86 (66.2%)	89 (67.4%)	0.81
Baseline echocardiography				
LV ejection fraction (%)	60.6 ± 8.1	60.1 ± 7.4	58.8 ± 7.9	0.07
LV mass index (g/m^2)	104.8 ± 32.1	109.4 ± 26.7	109.5 ± 33.2	0.28
LV end diastolic volume index (mL/m^2)	49.8 ± 15.9	49.3 ± 15.1	43.8 ± 12.9	0.002
LA volume index (mL/m^2)	29.1 ± 10.9	31.4 ± 9.6	36.5 ± 18.7	<0.001
E/e' lateral ratio	12.4 ± 5.4	12.4 ± 6.6	13.1 ± 7.0	0.41
Pulmonary artery systolic pressure (mmHg)	35.7 ± 10.8	35.0 ± 11.0	40.1 ± 11.4	0.002

Data are reported as *n* (%), mean ± standard deviation, or median [quartile 1 to quartile 3].
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; HF, heart failure; LA, left atrial; LV, left ventricular; NYHA, New York Heart Association; NP, natriuretic peptide.

HFpEF by a site investigator in a randomized clinical trial. TOPCAT enrolled patients with left ventricular EF ≥45%, which is below accepted diagnostic cut-offs for HFpEF; sensitivity analysis restricted to patients with left ventricular EF ≥50% yields directionally consistent, but non-significant findings. Finally, it is uncertain whether its prognostic value can be attributed to the composite score or to individual component elements.

Disease heterogeneity and diagnostic uncertainty have long been concerns in explaining the failures of previous HFpEF trials. This simple score based on six routinely collected clinical and echocardiographic variables represents an attractive option as a risk enrichment strategy in enrolment for future global clinical trials of HFpEF. However, future prospective studies are needed to externally validate this diagnostic algorithm in larger samples, determine the scope of its applicability in a broad range of patients with dyspnoea syndromes, and test its utility as a metric of clinical trial eligibility and risk enrichment in HFpEF against current strategies (prior hospitalization for HF and NPs).

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