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ORIGINAL ARTICLE

Targeting efficacy of spironolactone in patients with heart failure with preserved ejection fraction: the TOPCAT study

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Abstract

Aims We aimed to explore the heterogeneous treatment effects (HTEs) for spironolactone treatment in patients with Heart failure with preserved ejection fraction (HFpEF) and examine the efficacy and safety of spironolactone medication, ensuring a better individualized therapy.

Methods and results We used the causal forest algorithm to discover the heterogeneous treatment effects (HTEs) from patients in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial. Cox regressions were performed to assess the hazard ratios (HRs) of spironolactone medication for cardiovascular death and drug discontinuation in each group. The causal forest model revealed three representative covariates and participants were partitioned into four subgroups which were Group 1 (baseline BMI $\leq$ 31.71 kg/m^2 and baseline ALP $\leq$ 80 U/L, n = 759); Group 2 (BMI $\leq$ 31.71 kg/m^2 and ALP $>$ 80 U/L, n = 1088); Group 3 (BMI $>$ 31.71 kg/m^2, and WBC $\leq$ 6.6 cells/μL, n = 633); Group 4 (BMI $>$ 31.71 kg/m^2 and WBC $>$ 6.6 cells/μL, n = 832), respectively. In the four subgroups, spironolactone therapy reduced the risk of cardiovascular death in high-risk group (Group 4) with both high BMI and WBC count (HR: 0.76; 95% CI 0.58 to 0.99; P = 0.045) but increased the risk in low-risk group (Group 1) with both low BMI and ALP (HR: 1.45; 95% CI 1.02 to 2.07; P = 0.041; P for interaction = 0.020) but showed similar risk of drug discontinuation (P for interaction = 0.498).

Conclusion Our study manifested the HTEs of spironolactone in patients with HFpEF. Spironolactone treatment in HFpEF patients is feasible and effective in patients with high BMI and WBC while harmful in patients with low BMI and ALP. Machine learning model could be meaningful for improved categorization of patients with HFpEF, ensuring a better individualized therapy in the clinical setting.

Keywords Heart failure with preserved ejection fraction; Spironolactone; Machine learning; Efficacy

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Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF), a nonnegligible leading cause of morbidity, mortality, and impaired quality of life worldwide, is a complex clinical syndrome accounting for nearly half of all HF cases. However, to date, medication trials have been generally neutral on the primary outcomes. Very few convincing and effective pharmacological treatments have been identified for patients with HFpEF.[1–3]

Although several traditional therapies can improve clinical outcomes for patients with heart failure with reduced ejection fraction (HFrEF), few of them have been demonstrated to reduce cardiovascular death in HFpEF except empagliflozin.[1,4,5] The Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT)

trial showed a minor reduction for the adverse clinical outcome (HR = 0.89) in spironolactone therapy without achieving the statistical significance.[6] Remarkably, studies have indicated that the neutral or negative average treatment effects might obscure crucial heterogeneous treatment effects (HTEs).[7] Existing evidence has suggested significant heterogeneity in patients with HFpEF.[8] And some studies also tried to discover the hidden HTEs for spironolactone treatment from participants enrolled in TOPCAT. Based on the clinical phenotypes, a *post hoc* analysis of the TOPCAT trial found that patients with HFpEF responded differently to spironolactone administration.[9] Based on the distinct baseline risks, patients at very high risk benefit substantially from spironolactone medication.[10] So it is critical and urgent to identify those patients with HFpEF who might be beneficial or harmful from spironolactone medication.

To overcome the presented limitations of typical subgroup analyses, the causal forest algorithm can be used to estimate subgroups with significant HTEs in the TOPCAT trial. The casual forest model is a predictive model for revealing new insights without a pre-specified hypothesis. It varies subgroups through constructing multiple decision trees from pre-specified covariates in random subsamples of the data and applies the honest estimation approach to avoid additional hypothesis testing, minimize the risk of overfitting and reduce the bias caused by standard subgroup analyses.[11–13] Therefore, we applied the causal forest method to fit Cox proportional hazards models to the TOPCAT data, aiming to detect those patients with HFpEF who would benefit or suffer from spironolactone therapy, enabling physicians to better individualize patient care.

Methods

Study design and participants

The study was performed according to the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) guideline, which is a set of standardized, evidenced-based guidelines for reporting prediction modelling studies.[14]

The study used for model development consists of all participants in the TOPCAT trial, which is a multinational, multicentre, double-blind, randomized, and placebo-controlled trial to assess the efficacy of the mineralocorticoid receptor antagonist (MRA) spironolactone in patients with HFpEF. The important research findings and the details of the study design have been previously published.[6,15] Briefly, patients eligible for inclusion in the trial were aged 50 years and older with existing characteristics of heart failure including left ventricular ejection fraction (LVEF) $\geq$ 45%, controlled systolic blood pressure (SBP) and serum potassium $\leq$5.0 mmol/L. Each patient had to have either a prior HF hospitalization within 12 months as a major component of care or an elevated natriuretic peptide level within 60 days before randomization (a brain natriuretic peptide [BNP] level $\geq$100 pg/mL or an N-terminal pro-BNP [NTproBNP] level $\geq$360 pg/mL). Exclusion criteria included uncontrolled hypertension, severe renal dysfunction, severe systemic illness with a life expectancy of $<$3 years, and specific coexisting conditions, or other acute events defined previously.[6,16]

Eligible participants were randomly assigned to the placebo group and spironolactone group. In addition, all patients provided written informed consent and the institutional review board at each participating centre approved the study protocol.

Study outcomes

The primary outcome was the primary TOPCAT composite outcome of cardiovascular death, aborted cardiac arrest, or HF hospitalization. The safety outcome was drug discontinuation due to adverse effects, including persistent hyperkalaemia (defined as persistent potassium measurements $\geq$5.5 mmol/L with down-titration and serum potassium $\geq$6.0 mmol/L), renal dysfunction (defined as serum creatinine $>$3.0 mg/dL), intolerance, gynaecomastia, and anaphylaxis. All the study outcomes in the analysis were centrally adjudicated by the TOPCAT endpoints adjudication committee.[15]

Statistical analysis

We conduct causal forest[11] which is a nonparametric supervised statistical learning algorithm, designed for identifying subgroups with HTEs for different interventions to subgroup the population in the study. To begin with, we randomly selected the half of the 3445 observations without replacement. Then, those selected patients were divided into two groups. One group was employed to construct a tree, and the other group was to estimate treatment effects. We repeated this procedure 500 times. Consequently, there are 500 causal trees as a causal forest, and each tree has a quarter of observations.

After 500 causal trees were obtained, we need to explore the most representative tree for an explicit and unique subgroup structure/partition. The tree distance metric[17] that measures the similarity of both the covariates used to split the trees and the clustering of patients in the terminal nodes of the trees is employed as a practice. Thus, the most representative tree in the ensemble is chosen to minimize the average distance between a tree and all other trees in the ensemble. We studied 37 baseline predictors to estimate HTEs. All 37 predictors were provided in *Table 1*. The flow chart

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shows the process of the selected most representative tree. Based on the most representative tree, we have divided the patients into four groups (*Figure 1*).

In the next exploration, we excluded the missing data (n = 133) due to missing variables including body mass index (BMI), alkaline phosphatase (ALP), and white blood cell (WBC). Finally, 3312 individuals were included, 1663 in the spironolactone arm and 1649 in the placebo arm. After that, univariable COX proportional hazard regression was performed to report hazard ratios (HRs) and 95% CIs to explore HTEs among four groups. Besides, following the standardized protocol for testing HTE, the Cox model was composed of a subgroup dummy variable, study group assignment, and their interactions.[18] To further explore HTEs among groups, the interaction tests between groups and treatment were conducted through a likelihood ratio test.

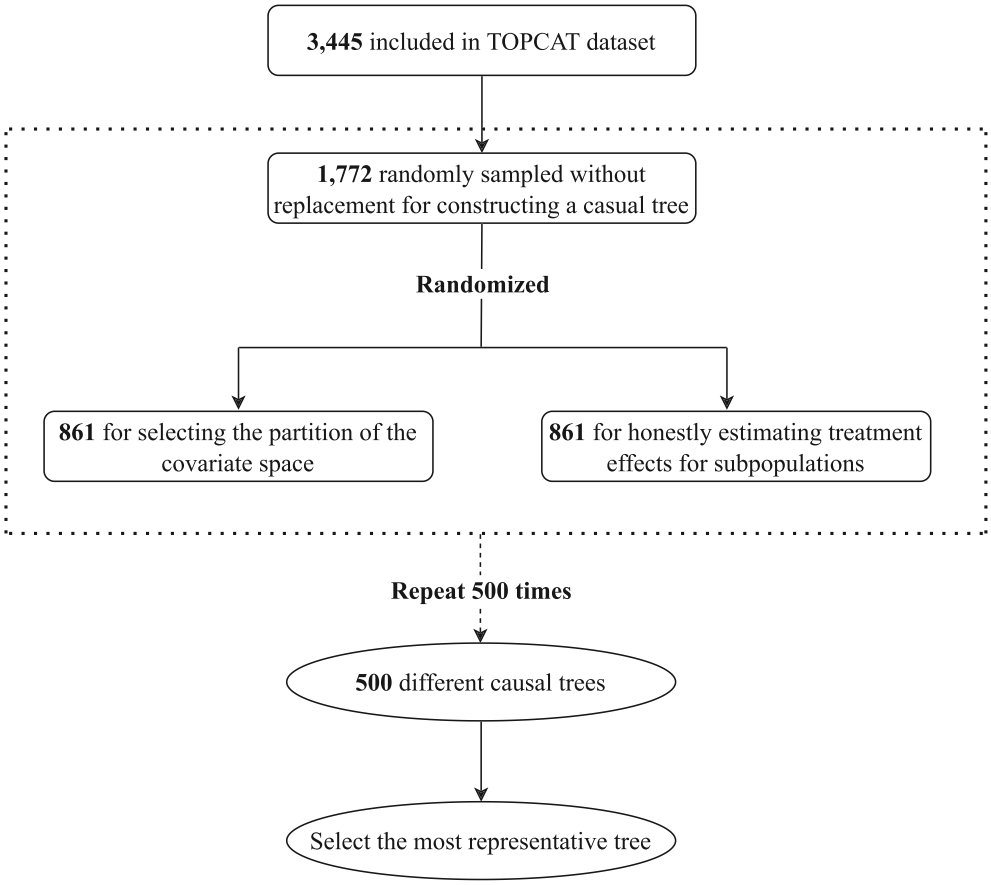
Based on the outcome from the casual forest analysis, we divided the raw data into four subgroups. Baseline characteristics for groups by spironolactone vs. placebo were compared by one-way ANOVA test, χ^2 test, and Kruskal–Wallis

Table 1 Baseline Characteristics of Patients from the study population (n = 3312) at baseline

Characteristic	Overall (n = 3312)	Group 1 (n = 759)	Group 2 (n = 1088)	Group 3 (n = 633)	Group 4 (n = 832)	P-value
Age, years	68.6 ± 9.6	70.1 ± 10.3	69.7 ± 9.6	67.3 ± 8.8	66.8 ± 9.2	<0.001
Male	1599 (48.3)	376 (49.5)	561 (51.6)	250 (39.5)	412 (49.5)	<0.001
Race						<0.001
White	2948 (89.0)	687 (91.8)	1022 (93.9)	535 (84.5)	694 (83.4)	
Black and others	364 (11.0)	62 (8.2)	66 (6.1)	98 (15.5)	138 (16.6)	
BMI, kg/m^2	32.0 ± 7.1	27.2 ± 2.96	27.2 ± 3.06	37.2 ± 5.0	38.9 ± 6.3	<0.001
Waistline, cm	105.0 ± 16.9	95.8 ± 11.6	95.5 ± 11.4	114.7 ± 14.5	118.7 ± 15.2	<0.001
Smoking						<0.001
Never smoker	1748 (52.8)	411 (54.2)	585 (53.8)	363 (57.3)	389 (46.8)	
Former smoker	1218 (36.8)	259 (34.2)	356 (32.7)	235 (37.1)	368 (44.3)	
Current smoker	344 (10.4)	88 (11.6)	147 (13.5)	35 (5.5)	74 (8.9)	
Drinking, per week						0.007
0	2580 (78.0)	569 (75.1)	837 (76.9)	498 (78.8)	676 (81.4)	
1–4	554 (16.7)	129 (17.0)	203 (18.7)	105 (16.6)	117 (14.1)	
5–10	122 (3.7)	42 (5.5)	34 (3.1)	18 (2.8)	28 (3.4)	
11–20	52 (1.6)	18 (2.4)	14 (1.3)	11 (1.7)	9 (1.1)	
Heart rate, b.p.m.	69.1 ± 10.4	68.5 ± 9.8	68.3 ± 9.8	69.4 ± 10.6	70.3 ± 11.4	<0.001
Systolic BP, mmHg	129.3 ± 14.0	129.1 ± 14.4	128.5 ± 12.7	130.2 ± 14.0	130.0 ± 15.2	0.072
Diastolic BP, mmHg	75.8 ± 10.7	76.0 ± 10.7	76.5 ± 10.1	76.6 ± 10.7	74.2 ± 11.2	<0.001
NYHA						<0.001
I and II	2227 (67.3)	571 (75.3)	791 (72.7)	388 (61.4)	477 (57.3)	
III and IV	1083 (32.7)	187 (24.7)	297 (27.3)	244 (38.6)	355 (42.7)	
Ejection fraction, %	57.1 ± 7.4	56.2 ± 7.1	56.9 ± 7.6	58.0 ± 7.7	57.4 ± 7.4	0.050
Creatinine, mg/dL	1.09 ± 0.30	1.05 ± 0.27	1.08 ± 0.29	1.08 ± 0.29	1.15 ± 0.34	<0.001
GFR, mL/min/1.73 m^2	67.8 ± 20.2	69.4 ± 19.5	68.4 ± 21.1	67.6 ± 19.8	65.5 ± 19.9	0.293
Sodium, mmol	141.2 ± 4.2	141.2 ± 4.3	141.5 ± 4.5	141.6 ± 3.7	140.5 ± 4.0	<0.001
Kalium, mmol	4.2 ± 0.4	4.3 ± 0.4	4.3 ± 0.4	4.2 ± 0.5	4.2 ± 0.4	0.029
Chloride, mmol	102.5 ± 5.2	102.8 ± 5.7	102.3 ± 5.2	103.2 ± 5.0	102.1 ± 4.8	0.043
Glucose, mg/dL	115.7 ± 47.8	107.1 ± 34.6	108.2 ± 38.8	115.3 ± 39.6	133.7 ± 66.3	<0.001
WBC, 1000 cells/μL	7.1 ± 3.8	6.7 ± 1.9	7.1 ± 6.0	5.5 ± 0.8	8.6 ± 1.9	<0.001
Haematocrit, vol%	40.1 ± 5.0	40.1 ± 5.4	40.4 ± 4.8	39.5 ± 5.1	40.1 ± 5.0	0.043
Haemoglobin, g/dL	13.3 ± 1.7	13.3 ± 1.7	13.4 ± 1.7	13.1 ± 1.7	13.3 ± 1.7	0.526
Platelets, 1000 cells/μL	231.4 ± 66.6	225.5 ± 57.3	233.5 ± 68.6	216.8 ± 60.2	245.3 ± 73.3	<0.001
ALT, U/L	25.2 ± 14.4	23.3 ± 12.1	25.4 ± 14.6	25.3 ± 13.5	26.5 ± 16.4	0.001
ALP, U/L	105.7 ± 59.2	60.6 ± 14.3	139.0 ± 59.7	109.8 ± 62.4	100.4 ± 53.1	<0.001
AST, U/L	25.4 ± 12.7	25.0 ± 12.3	25.8 ± 11.8	25.8 ± 12.4	25.0 ± 14.5	0.360
ALB, U/L	4.2 ± 2.1	4.2 ± 0.5	4.3 ± 2.5	4.2 ± 2.3	4.1 ± 2.1	0.278
Coronary artery disease	1941 (58.6)	442 (58.2)	681 (62.6)	354 (55.9)	464 (55.8)	0.008
Stroke	252 (7.6)	53 (7.0)	72 (6.6)	43 (6.8)	84 (10.1)	0.020
COPD	386 (11.7)	74 (9.8)	101 (9.3)	71 (11.2)	140 (16.8)	<0.001
Asthma	213 (6.4)	38 (5.0)	36 (3.3)	55 (8.7)	84 (10.1)	<0.001
Hypertension	3029 (91.5)	672 (88.7)	976 (89.7)	592 (93.5)	789 (94.8)	<0.001
PAD	304 (9.2)	60 (7.9)	96 (8.8)	46 (7.3)	102 (12.3)	0.003
Dyslipidaemia	1994 (60.2)	433 (57.1)	567 (52.1)	395 (62.4)	599 (72.0)	<0.001
Atrial fibrillation, %	1165 (35.2)	267 (35.2)	363 (33.4)	231 (36.5)	304 (36.5)	0.436
Thyroid disease, %	524 (15.8)	110 (14.5)	142 (13.1)	107 (16.9)	165 (19.8)	<0.001
Diabetes mellitus	307 (9.3)	50 (6.6)	50 (4.6)	70 (11.1)	137 (16.5)	<0.001
DM complication	855 (25.8)	130 (17.1)	159 (14.6)	201 (31.8)	365 (43.9)	<0.001

Data are mean ± SD, or number (%), unless otherwise indicated.
ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; GFR, glomerular filtrations rate; HF, heart failure; NYHA, New York Heart Association; PAD, peripheral arterial disease; WBC, white blood cell.

Figure 1 An illustrative schematic for the causal tree model. We randomly selected half of the 3445 observations without replacement. Then, those selected patients were divided into two groups. One group was employed to construct a tree, and the other group was used to estimate treatment effects. Repeated this procedure 500 times and acquire 500 causal trees as a causal forest. Then, select the most representative tree from them.



test as appropriate. Kaplan–Meier curves were drawn to estimate the time-to-event outcome. Differences between cumulative incidence curves were assessed by the log-rank test. Absolute risk reduction (ARR) was calculated by subtracting the placebo event rate from the spironolactone event rate.

Statistical analyses were performed by Stata Statistical Software version 15.0 and R version 3.6.0.

Results

The causal forest model revealed three covariates, baseline BMI, ALP, and WBC count, were of primary efficacy in distinguishing individuals with high versus low benefits from the spironolactone intervention. Participants were partitioned into four subgroups which were Group 1 (baseline BMI $\leq$ 31.71 kg/m^2 and baseline ALP $\leq$ 80 U/L, n = 759); Group 2 (BMI $\leq$ 31.71 kg/m^2 and ALP $>$ 80 U/L, n = 1088); Group 3 (BMI $>$ 31.71 kg/m^2, and WBC $\leq$ 6.6 cells/μL, n = 633); Group 4 (BMI $>$ 31.71 kg/m^2 and WBC $>$ 6.6 cells/μL, n = 832), respectively (*Figure 2*).

Baseline characteristics of the included TOPCAT sample are described in *Table 1*. A total of 3312 participants were included (133 participants were excluded due to missing data of BMI, ALP or WBC) (*Figure 3*). At baseline, the mean age was 68.6 ± 9.6 years, 1599 (48.3%) were male and 2948 (89.0%) were white. During the average follow-up period of 3.1 years, 642 (19.4%) of 3312 included participants experienced primary outcome events and 281 (8.5%) of 3312 participants experienced safety outcome events (Supporting Information, *Tables* S1–S2).

Figure 4 and *Table* S1 present subgroup analyses of the primary outcome. Of the four groups, the HRs of spironolactone treatment for Group 1 (P = 0.041) and Group 4 (P = 0.045) were found to be statistically significant (*Table 2* and *Table* S1). So we focused our analysis on these two groups, which accounted for 23% and 25% of the study sample respectively. In Group 1, patients in spironolactone treated arm had an absolute risk increase of the primary outcome of 5.93% (95% CI 0.65 to 11.21; P = 0.029), comparing with the placebo-treated

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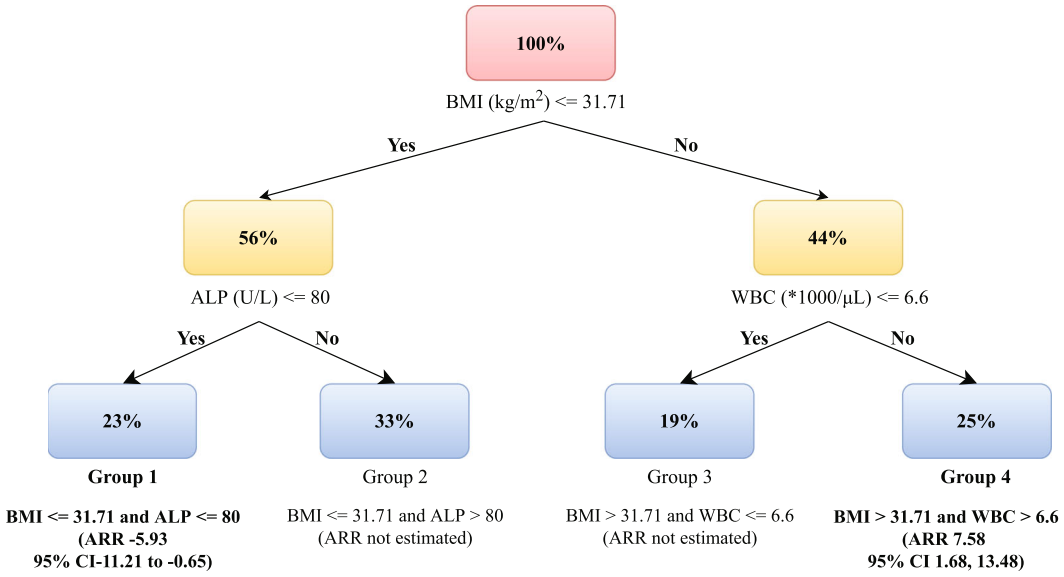
Figure 2 Subgroups identified by the representative causal tree. Nodes indicate the percent of the sample in each subdivision of the data, with the covariate and split point identified underneath. For instance, Group 1 contains 23% of the data and includes participants with baseline BMI ≤ 31.71 and baseline ALP ≤ 80. Absolute risk reduction (ARR) refers to the primary outcome of the TOPCAT trial. BMI = body mass index. ALP, alkaline phosphatase; WBC, white blood cell; ARR, absolute risk reduction; TOPCAT, Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial.



patients. However, in Group 4, patients treated with spironolactone had an absolute risk reduction [ARR] of 7.58% (95% CI 1.68 to 13.48; *P* = 0.012) (*Table 2*). Interestingly, spironolactone therapy significantly reduced the risk of primary outcome in Group 4 (HR: 0.76; 95% CI 0.58 to 0.99; *P* = 0.045) and showed no benefit in Group 2 (HR: 0.75; 95% CI 0.55 to 1.01; *P* = 0.055) and Group 3 (HR: 0.91; 95% CI 0.64 to 1.29; *P* = 0.598) but increased the risk in Group 1 (HR: 1.45; 95% CI 1.02 to 2.07; *P* = 0.041), which indicates the heterogeneity of treatment effects (*P* for interaction = 0.020; *Table 2* and *Table* S1). Besides, Kaplan–Meier's curves across treated and control groups were performed to further demonstrate the HTEs among groups (*Figure 5*).

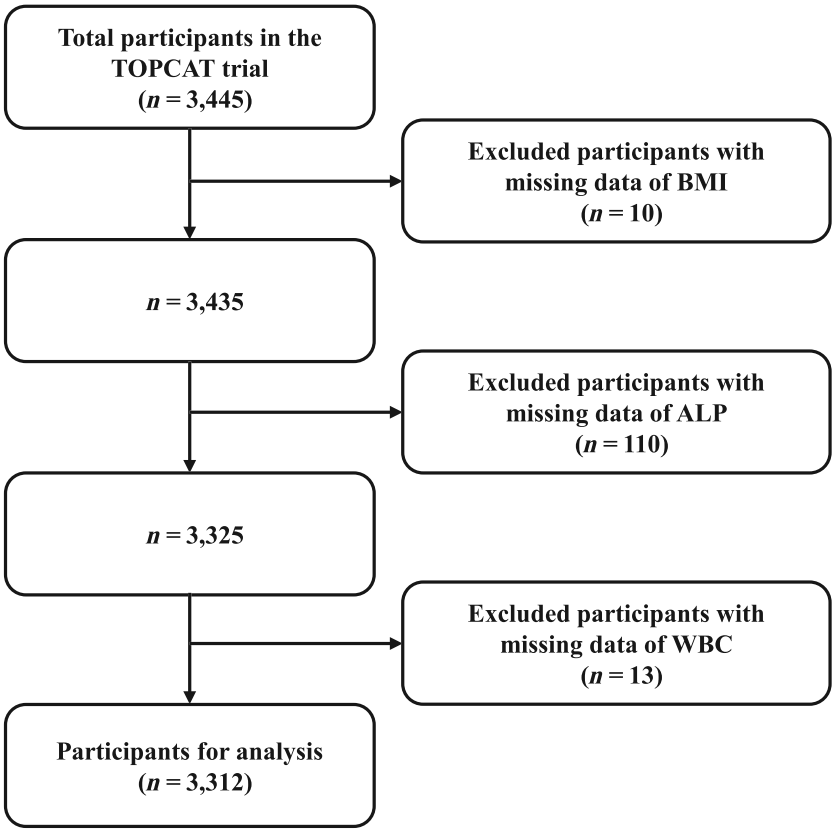
The HRs and event rates of the safety outcome among groups are summarized in *Figure 4* and *Table* S2. In all groups, the HRs for the safety outcome were significantly >1, confirming spironolactone's detrimental ramifications. Of note, in the analysis, side effects are relatively attenuate in the Group 2 (HR: 1.99; 95% CI 1.20 to 3.29; *P* = 0.008) and Group 4 (HR: 2.55; 95% CI 1.64 to 3.96; *P* < 0.001) but increase in Group 1 (HR: 3.28; 95% CI 1.90 to 5.65; *P* < 0.001). Furthermore, no obvious significant difference was detected in the incidence of drug cessation (*P* for interaction = 0.498; *Figure 4*, *Table* S2).

For further research, we also conducted an explorative analysis on some meaningful sub-endpoints. Spironolactone treatment increased the risk of CV death in Group 1 (HR: 1.63; 95% CI 1.00 to 2.65) and decreased the risk in Group 4 (HR: 0.66; 95% CI 0.43 to 1.01) both with borderline *P* values. However, most of the other endpoints shown negative results. Of note, we did not analyse the event of aborted cardiac arrest as an endpoint event because it had only eight cases (*Table* S3).

Discussion

In this analysis of the TOPCAT trial, with the integration of causal forest algorithm and Cox proportional hazards models, we demonstrated significant differences among groups in terms of both primary outcome and safety outcome about spironolactone treatment. The causal forest algorithm revealed three important risk indicators in routine clinical use, BMI, ALP, WBC count, respectively. Spironolactone treatment in HFpEF patients is feasible and effective in Group 2 (BMI ≤ 31.71 kg/m^2 and ALP > 80 U/L; HR, 0.75; 95% CI, 0.55, 1.10) and Group 4 (BMI > 31.71 kg/m^2 and WBC > 6.6 cells/μL; HR, 0.76; 95% CI, 0.58, 0.99) but harmful in Group 1 (BMI ≤ 31.71 kg/m^{2}and baseline ALP ≤ 80 U/L; HR, 1.45; 95% CI, 1.02, 2.07). The results manifested the HTEs of spironolactone in patients with HFpEF. To our knowledge, few studies have identified a group that was treated with spironolactone but increased safety risk. Our findings could improve the classification of heterogeneous clinical syndromes (*Figure 4*), with the ultimate goal of identifying

Figure 3 Flow diagram for subject selection in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial. BMI, body mass index; ALP, alkaline phosphatase; WBC, white blood cell.

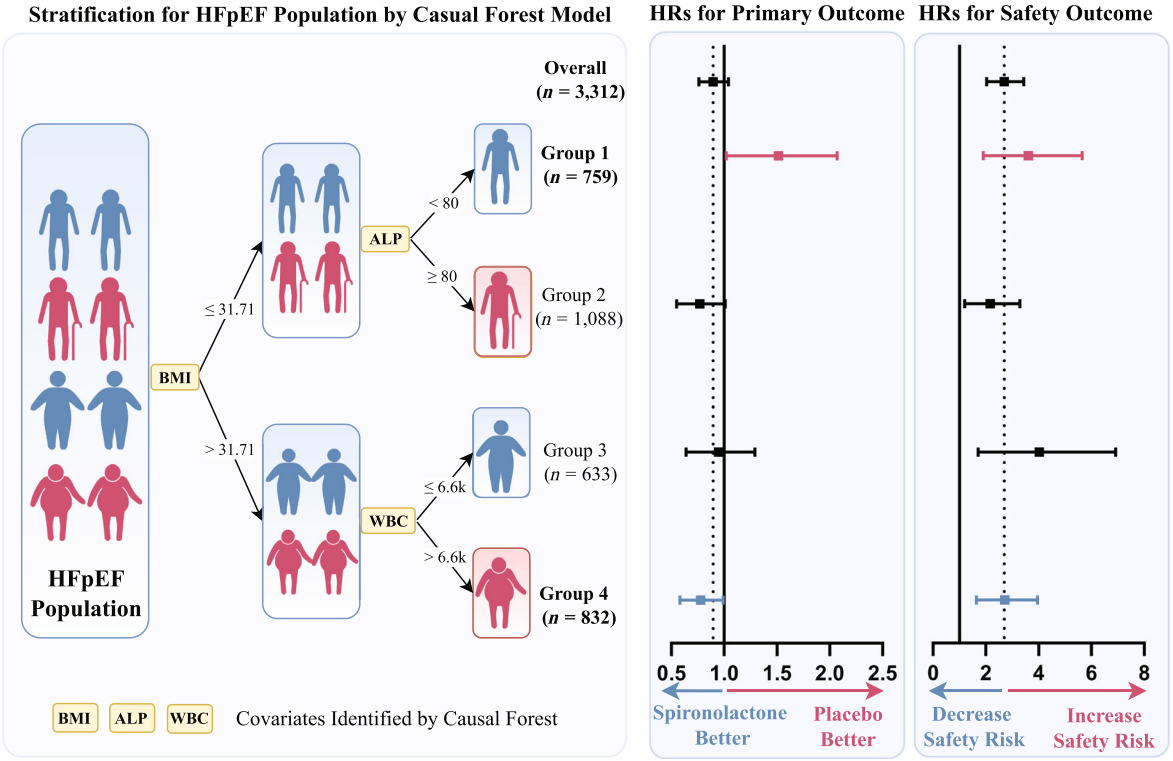


therapeutically effective and harmful subclasses of patients, ensuring a precise personalized therapy.

To date, most large-scale clinical trials to evaluate the efficacy of medical treatments for HFpEF rendered a neutral result, leading to the lack of a convincing and practical tool to provide treatment and predict mortality in patients with HFpEF.[6,19–22] However, the high mortality rate of patients with HFpEF emphasizes the crucial necessity of early identification of patients who benefit most from the therapy like spironolactone use for timely intervention. There have been many studies using multiple approaches to address the diversity of HFpEF. For instance, Cohen *et al*. stratified the patients in TOPCAT based on clinical presentation and identified that the group of obese, diabetic patients with renal impairment and higher inflammation, who were with a high risk of adverse outcome, responded better to spironolactone.[9] However, such a cluster analysis had to limit aspects of the study to subgroups with available data, which is hard to be validated by subsequent Randomized Clinical Trial. There are also many studies related to risk prediction models. The Modified EFFECT score and the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) created the risk prediction models but with 12 risk predictors to ensure outcome accuracy,[23–25] limiting their popularization and application. Besides, although the 3A3B score contains only six common clinical predictors, it showed modest performance (c-index = 0.652) in external validation of TOPCAT, probably due to racial or regional reasons.[26] Recently, Lin *et al*. developed a risk score scheme with five risk predictors for the prediction of cardiovascular death and found that only the patients at very high risk of CV death benefited a lot from spironolactone treatment.[10] Nevertheless, few studies have used the machine learning algorithm to evaluate subgroup treatment effects for spironolactone therapy in patients with HFpEF. Furthermore, few studies have found HFpEF populations in which treatment with spironolactone was instead detrimental.

For these three indicators (BMI, ALP, and WBC count), which were selected from 37 predictors by the causal forest algorithm, there have been numerous studies demonstrating their association with cardiovascular disease including HFpEF. First of all, obesity is a common co-morbidity in patients with HFpEF worldwide and has numerous deleterious effects upon cardiovascular disease, with mediators including altered volume status, metabolism, and inflammation, which are known to promote disease progression.[27–29] High BMI has been known to be the strongest predictor of HFpEF

Figure 4 Central illustration. Clinical subgroups in HFpEF categorized by causal forest model and efficacy and safety of spironolactone versus placebo among subgroups. Four subgroups were categorized according to the three representative covariates (BMI, ALP, and WBC count) screened out by the causal forest model. Four subgroups exhibited differential response to spironolactone medication. In the four subgroups, spironolactone therapy showed a great benefit in reducing the risk of cardiovascular death in the relatively high-risk group (Group 4, HR for primary outcome: 0.76; 95% CI 0.58 to 0.99; P = 0.045) but increased the risk in the low-risk group (Group 1, HR for primary outcome: 1.45; 95% CI 1.02 to 2.07; P = 0.041). The medication showed a similar risk of drug discontinuation compared with other groups. HR, hazard ratio.



development.[30] Second, ALP has been shown to be a novel treatment target for cardiovascular disease and a high level of ALP is associated with vascular calcification, inflammation, atherosclerotic changes, pyrophosphate inhibition and endothelial dysfunction, which might lead to increased mortality.[31] Besides, ALP is a potential serum marker for patients with HFpEF.[32] The apabetalone, a novel bromo-domain and extra motif inhibitor RVX-208, can lower the level of ALP and increase the level of HDL, thus reducing Major Adverse Cardiovascular Events (MACE).[33] All these further indicate the association between ALP and cardiovascular disease. Additionally, WBC count had been found to be independently associated with poor clinical outcomes in HFpEF patients.[32,34] Of note, these three indicators are also commonly used and easily available in clinical practice, ensuring their application and popularization. We can observe that although many studies have suggested that natriuretic peptide is an important biomarker in HF patients,[6,35] the causal forest algorithm did not screen it out, but instead screened out these three important factors, which indicated that they play a greater role in evaluating subgroup treatment effects for spironolactone therapy in patients with HFpEF.

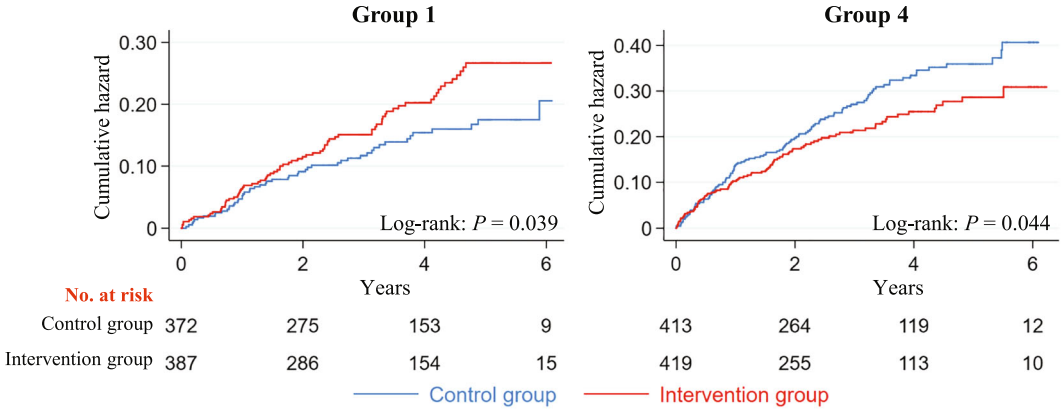
In the four subgroups we separated, we detected not only a therapeutically harmful group (Group 1) but also a therapeutically beneficial subgroup (Group 4), which is seldom seen in other studies. Furthermore, according to the drug discontinuation analyses, adverse effects of spironolactone therapy were relatively attenuated in the therapeutically beneficial groups but increased in the therapeutically harmful group, indicating the hidden subgroup HTEs that deserve further investigation. As mentioned previously, ALP is associated with pathophysiological processes in several organs such as the liver, kidney, skeletal muscle, and peritoneum,[31] which may cause ALP elevation if lesions occur in these areas. Therefore, to some extent, ALP can serve as a great collection health indicator. For instance, Group 1, of which the mean BMI and ALP values were 27.2 and 60.6 U/L, respectively (*Table. 1*), was relatively at low risk and the spironolactone medication in Group 1 showed detrimental effects (*Table* S1), probably owing to the exacerbation of renal impairment by spironolactone[31] and other adverse effects described before. On the contrary, Group 4, with a mean BMI and WBC count of 38.9 and 8600 cells/μL, respectively, were typically in a relatively hyperinflammatory and high-risk state and

Table 2 Observed primary outcome by subgroups identified by causal forest model

	Number of patients treated with the intervention (number of events)	Number of control patients (number of events)	Absolute risk reduction, % (95% CI)	*P-value*	Hazard ratio (95% CI)	*P-value*
Primary outcome: primary TOPCAT composite endpoints of cardiovascular death, aborted cardiac arrest, or HF hospitalization						
Overall	1663 (306)	1649 (336)	1.98 (−0.72, 4.67)	0.150	0.89 (0.76, 1.04)	0.130
Subgroup 1						0.003 (interaction)
Baseline BMI ≤31.71 and ALP ≤80	387 (76)	372 (51)	−5.93 (−11.21, −0.65)	0.029	1.45 (1.02, 2.07)	0.041
Remainder of trial population	1276 (230)	1277 (285)	4.29 (1.18, 7.40)	0.007	0.79 (0.66, 0.94)	0.007
Subgroup 4						0.150 (interaction)
Baseline BMI higher than 31.71 and WBC higher than 6.6	419 (91)	413 (121)	7.58 (1.68, 13.48)	0.012	0.76 (0.58, 0.99)	0.045
Remainder of trial population	1244 (215)	1236 (215)	0.11 (−2.87, 3.09)	0.941	0.97 (0.80, 1.17)	0.708

An absolute risk reduction (ARR) >1 indicates the risk of an outcome was lower for the intervention group than the control group. A hazard ratio (HR) <1 indicates the risk of an outcome was lower for the intervention group than the control group.

Figure 5 Cumulative hazard curves for the primary composite endpoint. Cumulative hazard curves across treated and control groups are shown for participants.



could benefit from spironolactone therapy. Notably, the results of Group 2 should not be overlooked though with a borderline significant *P*-value of 0.055. Nearly half of the people in Group 2 with high ALP levels >120 U/L, indicating high mortality.[31] Similarly, Group 2, with a high inflammatory, high-risk state, also benefited from spironolactone therapy, deserving further study.

Existing studies have demonstrated the role of spironolactone in patients with HF, with spironolactone having anti-inflammatory and anti-fibrotic effects,[2,36] as well as spironolactone antagonizing the calcification of blood vessels and soft tissues caused by aldosterone,[37] thereby reducing cardiovascular morbidity and mortality in patients with HF, which are consistent with our findings, accountable for the beneficial effects on Groups 2 and 4.

Moreover, explorative analyses on some meaningful sub-endpoints were also conducted to further detect the possible association with spironolactone therapy. Spironolactone treatment increased the risk of CV death in Group 1 and decreased the risk in Group 4, which was inconsistent with the main results for primary outcomes and could be explained by the HTEs of spironolactone in these groups. However, most of the results for other sub-endpoints were negative, which should be further explored in further study considering the small sample size.

Strengths and limitations

Several studies have shown that HFpEF is heterogeneous in terms of both aetiology and pathophysiology.[8,38] Traditional subgroup analyses usually fail to identify such HTEs, because they are easily underpowered and susceptible to estimation bias and multiple testing errors. Furthermore, traditional subgroup analyses seldom consider combinations of factors but usually one factor at a time.[39,40] However, the causal forest model is particularly adept at identifying significant HTEs hidden in large subgroups among existing trials, even though trials present average negative effects. Therefore, we deployed a novel analytic technique utilizing robust machine learning algorithms with regularization, to detect therapeutically effective and therapeutically harmful patients from the HFpEF population, which could assist clinicians in making the optimal treatment decisions and lead to a better prognosis. Additionally, the three indicators, which are identified by the causal forest algorithm, are common and easily accessible in the clinical setting and almost every inpatient will be tested for these three indicators, ensuring their applications and popularization. Moreover, we also highlighted a collection health indicator (ALP) that was easily overlooked when treating HF patients in the clinical setting.

Besides, several limitations in our study should not be ignored. First, the analysis is a secondary, *post hoc* subgroup analysis. Therefore, the results should be considered hypothesis-generating and exploratory. So multicentre, randomized control trials are required to validate our results in special HFpEF patients with similar baseline like Group 2 (BMI $\leq$ 31.71 kg/m^2 and ALP $>$ 80 U/L) or Group 4 (BMI $>$ 31.71 kg/m^2 and WBC $>$ 6.6 cells/μL). Second, by splitting the data into separate subsets, we sacrificed some statistical power but reserve the validity of the inference. Third, the cutoff value of three continuous variables can be further reassessed based on the clinical setting. Finally, enhancing the machine learning algorithm to compare HTEs on a relative scale and further conducting prospective random trials to validate the findings before clinical application is necessary.

Conclusion

In conclusion, our study manifested the HTEs of spironolactone in patients with HFpEF. Spironolactone treat-

ment in HFpEF patients is feasible and effective in patients with high BMI (>31.71 kg/m^2) and WBC (>6.6 cells/μL) while harmful in patients with low BMI (≤31.71 kg/m^2) and ALP (≤80 U/L). Machine learning model could be meaningful for improved categorization of patients with HFpEF, ensuring a better individualized therapy in the clinical setting.

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Conflict of interest

The authors declare that they have no competing interests.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Primary Outcome across Subgroups Identified by Causal Forest Model.
Table S2. Safety Outcome across Subgroups Identified by Causal Forest Model.
Table S3. Exploratory analysis of sub-endpoints in TOPCAT trial.
*only 7 events, lacking the power to analyse
CV death, cardiovascular death; HF, heart failure.

References

1. Gladden JD, Chaanine AH, Redfield MM. Heart failure with preserved ejection fraction. *Annu Rev Med*. 2018; **69**: 65–79.
2. Shah SJ, Borlaug BA, Kitzman DW, McCulloch AD, Blaxall BC, Agarwal R, Chirinos JA, Collins S, Deo RC, Gladwin MT, Granzier H, Hummel SL, Kass DA, Redfield MM, Sam F, Wang TJ, Desvigne-Nickens P, Adhikari BB. Research priorities for heart failure with preserved ejection fraction: National Heart, Lung, and Blood Institute working group summary. *Circulation*. 2020; **141**: 1001–1026.
3. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibelund A, ESC Scientific Document Group, de Boer RA, Christian Schulze P, Abdelhamid M, Aboyans V, Adamopoulos S, Anker SD, Arbelo E, Asteggiano R, Bauersachs J, Bayes-Genis A, Borger MA, Budts W, Cikes M, Damman K, Delgado V, Dendale P, Dilaveris P, Drexel H, Ezekowitz J, Falk V, Fauchier L, Filippatos G, Fraser A, Frey N, Gale CP, Gustafsson F, Harris J, Iung B, Janssens S, Jessup M, Konradi A, Kotecha D, Lambrinou E, Lancellotti P, Landmesser U, Leclercq C, Lewis BS, Leyva F, Linhart A, Løchen ML, Lund LH, Mancini D, Masip J, Milicic D, Mueller C, Nef H, Nielsen JC, Neubeck L, Noutsias M, Petersen SE, Sonia Petronio A, Ponikowski P, Prescott E, Rakisheva A, Richter DJ, Schlyakhto E, Seferovic P, Senni M, Sitges M, Sousa-Uva M, Tocchetti CG, Touyz RM, Tschoepe C, Waltenberger J, Adamo M, Baumbach A, Böhm M, Burri H, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gardner RS, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Piepoli MF, Price S, Rosano GMC, Ruschitzka F, Skibelund AK. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021; **42**: 3599–3726.
4. Yancy CW, Jessup M, Bozkurt B, Butler J, de Jr C, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride P, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the Management of Heart Failure: A report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the Heart Failure Society of America. *J Am Coll Cardiol*. 2017; **70**: 776–803.
5. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, Brunner–la Rocca HP, Choi DJ, Chopra V, Chuquiure-Valenzuela E, Giannetti N, Gomez-Mesa JE, Janssens S, Januzzi JL, Gonzalez-Juanatey JR, Merkely B, Nicholls SJ, Perrone SV, Piña IL, Ponikowski P, Senni M, Sim D, Spinar J, Squire I, Taddei S, Tsutsui H, Verma S, Vinereanu D, Zhang J, Carson P, Lam CSP, Marx N, Zeller C, Sattar N, Jamal W, Schnaidt S, Schnee JM, Brueckmann M, Pocock SJ, Zannad F, Packer M. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. 2021; **385**: 1451–1461.

6. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O'Meara E, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, Yang S, McKinlay SM. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. 2014; **370**: 1383–1392 Epub 2014/04/11.
7. Basu S, Sussman JB, Hayward RA. Detecting heterogeneous treatment effects to guide personalized blood pressure treatment: A modeling study of randomized clinical trials. *Ann Intern Med*. 2017; **166**: 354–360.
8. Shah SJ, Kitzman DW, Borlaug BA, van Heerebeek L, Zile MR, Kass DA, Paulus WJ. Phenotype-specific treatment of heart failure with preserved ejection fraction: A multiorgan roadmap. *Circulation*. 2016; **134**: 73–90.
9. Cohen JB, Schrauben SJ, Zhao L, Basso MD, Cvijic ME, Li Z, Yarde M, Wang Z, Bhattacharya PT, Chirinos DA, Prenner S, Zamani P, Seiffert DA, Car BD, Gordon DA, Margulies K, Cappola T, Chirinos JA. Clinical Phenogroups in heart failure with preserved ejection fraction: Detailed phenotypes, prognosis, and response to spironolactone. *JACC Heart Fail*. 2020; **8**: 172–184.
10. Lin Y, Zhong X, Liu M, Zhang S, Xiong Z, Huang Y, Fan Y, Xu X, Guo Y, Li Y, Sun X, Zhou H, Yang D, Ye X, Liao X, Zhuang X. Risk stratification and efficacy of spironolactone in patients with heart failure with preserved ejection fraction: Secondary analysis of the TOPCAT randomized clinical trial. *Cardiovasc Drugs Ther*. 2021; **36**: 323–331.
11. Athey S, Imbens G. Recursive partitioning for heterogeneous causal effects. *Proc Natl Acad Sci U S A*. 2016; **113**: 7353–7360.
12. Wong TY, Bressler NM. Artificial intelligence with deep learning technology looks into diabetic retinopathy screening. *JAMA*. 2016; **316**: 2366–2367.
13. Kavakiotis I, Tsave O, Salifoglou A, Maglaveras N, Vlahavas I, Chouvarda I. Machine learning and data mining methods in diabetes research. *Comput Struct Biotechnol J*. 2017; **15**: 104–116.
14. Moons KG, Altman DG, Reitsma JB, Ioannidis JP, Macaskill P, Steyerberg EW, Vickers AJ, Ransohoff DF, Collins GS. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): Explanation and elaboration. *Ann Intern Med*. 2015; **162**: W1–W73.
15. Desai AS, Lewis EF, Li R, Solomon SD, Assmann SF, Boineau R, Clausell N, Diaz R, Fleg JL, Gordeev I, McKinlay S, O'Meara E, Shaburishvili T, Pitt B, Pfeffer MA. Rationale and design of the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial: A randomized, controlled study of spironolactone in patients with symptomatic heart failure and preserved ejection fraction. *Am Heart J*. 2011; **162**: 966–72.e10.
16. Shah SJ, Heitner JF, Sweitzer NK, Anand IS, Kim HY, Harty B, Boineau R, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Lewis EF, Markov V, O'Meara E, Kobulia B, Shaburishvili T, Solomon SD, Pitt B, Pfeffer MA, Li R. Baseline characteristics of patients in the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial. *Circ Heart Fail*. 2013; **6**: 184–192.
17. Banerjee M, Ding Y, Noone AM. Identifying representative trees from ensembles. *Stat Med*. 2012; **31**: 1601–1616.
18. Kent DM, Rothwell PM, Ioannidis JP, Altman DG, Hayward RA. Assessing and reporting heterogeneity in treatment effects in clinical trials: A proposal. *Trials*. 2010; **11**: 85.
19. Shah SJ, Voors AA, McMurray JJV, Kitzman DW, Viethen T, Bomfim Wirtz A, Huang E, Pap AF, Solomon SD. Effect of Neladenoson Bialanate on exercise capacity among patients with heart failure with preserved ejection fraction: A randomized clinical trial. *JAMA*. 2019; **321**: 2101–2112.
20. Ahmed A, Rich MW, Fleg JL, Zile MR, Young JB, Kitzman DW, Love TE, Aronow WS, Adams KF Jr, Gheorghiade M. Effects of digoxin on morbidity and mortality in diastolic heart failure: The ancillary digitalis investigation group trial. *Circulation*. 2006; **114**: 397–403.
21. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, van Veldhuisen D, Zannad F, Zile MR, Desai AS, Claggett B, Jhund PS, Boytsov SA, Comin-Colet J, Cleland J, Düngen HD, Goncalvesova E, Katova T, Kerr Saraiva JF, Lelonek M, Merkely B, Senni M, Shah SJ, Zhou J, Rizkala AR, Gong J, Shi VC, Lefkowitz MP, PARAGON-HF Investigators and Committees. Angiotensin-Neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med*. 2019; **381**: 1609–1620.
22. Pfeffer MA, Shah AM, Borlaug BA. Heart failure with preserved ejection fraction in perspective. *Circ Res*. 2019; **124**: 1598–1617.
23. Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV. Predicting mortality among patients hospitalized for heart failure: Derivation and validation of a clinical model. *JAMA*. 2003; **290**: 2581–2587.
24. Thorvaldsen T, Claggett BL, Shah A, Cheng S, Agarwal SK, Wruck LM, Chang PP, Rosamond WD, Lewis EF, Desai AS, Lund LH, Solomon SD. Predicting risk in patients hospitalized for acute decompensated heart failure and preserved ejection fraction: The atherosclerosis risk in communities study heart failure community surveillance. *Circ Heart Fail*. 2017; **10**.
25. Pocock SJ, Ariti CA, McMurray JJ, Maggioni A, Køber L, Squire IB, Swedberg K, Dobson J, Poppe KK, Whalley GA, Doughty RN, Meta-Analysis Global Group in Chronic Heart Failure. Predicting survival in heart failure: A risk score based on 39 372 patients from 30 studies. *Eur Heart J*. 2013; **34**: 1404–1413.
26. Kasahara S, Sakata Y, Nochioka K, Tay WT, Claggett BL, Abe R, Oikawa T, Sato M, Aoyanagi H, Miura M, Shiroto T, Takahashi J, Sugimura K, Teng THK, Miyata S, Shimokawa H. The 3A3B score: The simple risk score for heart failure with preserved ejection fraction - a report from the CHART-2 study. *Int J Cardiol*. 2019; **284**: 42–49.
27. Lavie CJ, Alpert MA, Arena R, Mehra MR, Milani RV, Ventura HO. Impact of obesity and the obesity paradox on prevalence and prognosis in heart failure. *JACC Heart Fail*. 2013; **1**: 93–102.
28. Reddy YN, Borlaug BA. Heart failure with preserved ejection fraction. *Curr Probl Cardiol*. 2016; **41**: 145–188.
29. Lauer MS, Anderson KM, Kannel WB, Levy D. The impact of obesity on left ventricular mass and geometry. The Framingham heart study. *JAMA (Russkoe izd)*. 1991; **266**: 231–236.
30. Davis BR, Kostis JB, Simpson LM, Black HR, Cushman WC, Einhorn PT, Farber MA, Ford CE, Levy D, Massie BM, Nawaz S, ALLHAT Collaborative Research Group. Heart failure with preserved and reduced left ventricular ejection fraction in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. *Circulation*. 2008; **118**: 2259–2267.
31. Haarhaus M, Brandenburg V, Kalantar-Zadeh K, Stenvinkel P, Magnusson P. Alkaline phosphatase: A novel treatment target for cardiovascular disease in CKD. *Nat Rev Nephrol*. 2017; **13**: 429–442.
32. Liang W, He X, Wu D, Xue R, Dong B, Owusu-Agyeman M, Zhao J, Cai L, You Z, Dong Y, Liu C. Prognostic implication of liver function tests in heart failure with preserved ejection fraction without chronic hepatic diseases: Insight from TOPCAT trial. *Front Cardiovasc Med*. 2021; **8**: 618816.
33. Wong NCW, Kalantar-Zadeh K, Kulikowski E, Wasiak S, Gilham D, Halliday C, Sweeney M, Johansson J. Apabetalone (RVX-208), a selective bromodomain and extra-terminal (BET) protein inhibitor, decreases abundance and activity of complement proteins in vitro, in mice and in clinical studies. *Nephrol Dial Transplant*. 2016; **31**: i109.
34. Bajaj NS, Kalra R, Gupta K, Aryal S, Rajapreyar I, Lloyd SG, McConathy J, Shah SJ, Prabhu SD. Leucocyte count predicts cardiovascular risk in heart failure with preserved ejection

fraction: Insights from TOPCAT Americas. *ESC Heart Fail*. 2020; **7**: 1676–1687.
35. Borlaug BA. Evaluation and management of heart failure with preserved ejection fraction. *Nat Rev Cardiol*. 2020; **17**: 559–573.
36. Guo C, Ricchiuti V, Lian BQ, Yao TM, Coutinho P, Romero JR, Li J, Williams GH, Adler GK. Mineralocorticoid receptor blockade reverses obesity-related changes in expression of adiponectin, peroxisome proliferator-activated receptor-gamma, and proinflammatory adipokines. *Circulation*. 2008; **117**: 2253–2261.
37. Voelkl J, Alesutan I, Leibrock CB, Quintanilla-Martinez L, Kuhn V, Feger M, Mia S, Ahmed MSE, Rosenblatt KP, Kuro-o M, Lang F. Spironolactone ameliorates PIT1-dependent vascular osteoinduction in klotho-hypomorphic mice. *J Clin Invest*. 2013; **123**: 812–822.
38. Shah AM, Solomon SD. Phenotypic and pathophysiological heterogeneity in heart failure with preserved ejection fraction. *Eur Heart J*. 2012; **33**: 1716–1717.
39. VanderWeele TJ, Knol MJ. Interpretation of subgroup analyses in randomized trials: Heterogeneity versus secondary interventions. *Ann Intern Med*. 2011; **154**: 680–683.
40. Baum A, Scarpa J, Bruzelius E, Tamler R, Basu S, Faghmous J. Targeting weight loss interventions to reduce cardiovascular complications of type 2 diabetes: A machine learning-based post-hoc analysis of heterogeneous treatment effects in the look AHEAD trial. *Lancet Diabetes Endocrinol*. 2017; **5**: 808–815.