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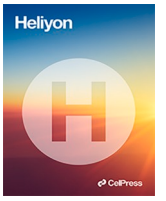

Research article

Association of hypertension burden with stroke risk in patients with heart failure with preserved ejection fraction

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ABSTRACT

Introduction: Whether the hypertension burden is associated with stroke incidence is inconclusive. In this study, we aimed to investigate the relationship between hypertension burden and stroke risk in patients with heart failure with preserved ejection fraction (HFpEF).
Methods: HFpEF patients from the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial were divided into three groups (low, medium, and high risk) according to their hypertension burden values. Higher hypertension burden risk represented the longer duration of hypertension. We evaluated the association of hypertension burden with stroke risk using Fine and Gray's competing risk models.
Results: A total of 3431 HFpEF patients (mean age: 68.5 ± 9.58 years, 51.6% females) were enrolled. During a median follow-up of 3.3 years, per 10-point increase in hypertension burden was associated with any stroke (hazard ratio [HR] 1.15, 95% confidence interval [CI] 1.08–1.21), new-onset stroke (HR 1.14, 95% CI 1.07–1.21), and ischemic stroke (HR 1.10, 95% CI 1.02–1.17). When hypertension burden was analyzed as a categorical variable, any stroke risk was increased in the medium- (HR 1.59, 95% CI 1.01–2.40) and high-risk (HR 3.19, 95% CI 2.05–4.97) groups when compared with the low-risk group. For the outcomes of new-onset (HR 2.92, 95% CI 1.80–4.74) and ischemic stroke (HR 2.46, 95% CI 1.41–4.29), similar results were observed in patients with high-versus low-risk hypertension burden.
Conclusions: Increasing hypertension burden was associated with an increased risk of stroke, suggesting that shortening hypertension duration might appropriately minimize the stroke incidence in HFpEF patients.

1Introduction

Heart failure with preserved ejection fraction (HFpEF), a completely heterogeneous disease, has become the dominant heart failure (HF) subtype, and its prevalence increases with age [1–3]. Patients with HFpEF are at similar or moderately higher stroke risk than those with other HF subtypes, unveiling HFpEF as the significant contributor to stroke [4–6]. Moreover, extensive studies have shown that HFpEF is an independent risk factor for stroke incidence regardless of atrial fibrillation (AF) [7–9]. Although stroke survivors with

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Abbreviations

HFpEF	heart failure with preserved ejection fraction
HF	heart failure
AF	atrial fibrillation
OACs	oral anticoagulants
BP	blood pressure
TOPCAT	Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist
SBP	systolic blood pressure
DBP	diastolic blood pressure
eGFR	estimated glomerular filtration rate
SDs	standard deviations
RCSs	restricted cubic splines
HRs	hazard ratios
CIs	confidence intervals
ACEI/ARB	angiotensin-converting enzyme inhibitors/angiotensin II receptor blocker
CCB	calcium channel blocker
HFrEF	heart failure with reduced ejection fraction

HF have a poor prognosis, oral anticoagulants (OACs) are not included in routine treatment for HFpEF patients with sinus rhythm because they have no net clinical benefits in preventing stroke [10]. Given that stroke risk stratification may be needed to guide the prevention and management, exploring the contributing factors for stroke risk assessment remains an urgent clinical issue in HFpEF patients.

Accumulating evidence has demonstrated that hypertension is a modifiable risk factor for stroke, and thus early and effective blood pressure (BP) management is critical for reducing stroke-related morbidity and mortality [11,12]. Although BP measurement at baseline or single time point offers a strong association with stroke incidence, it does not reflect the dynamic BP fluctuations [13]. In contrast, visit-to-visit BP variability has additional advantages in predicting stroke by incorporating the magnitude of BP changes [14,15]. However, the calculation of this BP index is complex, limiting its clinical application. Hypertension burden, an easily calculated index based on baseline and follow-up BP measurement, is defined as the proportion of hypertension ($\geq$140/90 mmHg) days to the observational period. A prior study has found that a higher hypertension burden is associated with increased dementia risk in general and midlife AF populations, suggesting the potential association of hypertension burden with cerebrovascular events [16]. Nonetheless, whether the hypertension burden is associated with the development of stroke remains unclear. Therefore, we performed a post hoc analysis of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial, aiming to investigate the relationship between hypertension burden and the risk of stroke in patients with HFpEF.

2Methods

2.1Study design and patients

The TOPCAT trial was conducted with the approval of local institutional review boards. The design and the primary findings of this trial have been previously described in detail [17]. Between August 2006 and January 2012, a total of 3445 patients who suffered symptomatic HF with a left ventricular ejection fraction of at least 45% were enrolled at 270 sites in the Americas, Russia, and Georgia. The institutional review board approved the protocol at each participating center, and each patient gave written informed consent. The access to the data set was applied by the Biologic Specimen and Data Repository Information Coordinating Center (BIOLINCC, , " title = "https://biolincc.nhlbi.nih.gov/) , ">https://biolincc.nhlbi.nih.gov/), and obtained from the National Heart, Lung, and Blood Institute (NHLBI). However, the TOPCAT investigators were not included in our current study. Patients aged $\geq$50 years were included according to the following criteria: (1) history of HF hospitalization within the preceding year or an elevated natriuretic peptide level (BNP $\geq$100 pg/mL or N-terminal pro-BNP $\geq$360 pg/mL) within the 60 screening days; (2) controlled BP (defined as a target systolic BP [SBP] of $<$140 mmHg or $\leq$160 mmHg if the patient was taking more than three medications to control hypertension). If patients had the following characteristics: (1) a life expectancy of fewer than three years; (2) history of severe hyperkalemia; (3) estimated glomerular filtration rate (eGFR) $\leq$30 mL/min per 1.73 m^2; (4) known infiltrative or hypertrophic cardiomyopathy, they would be excluded in our study.

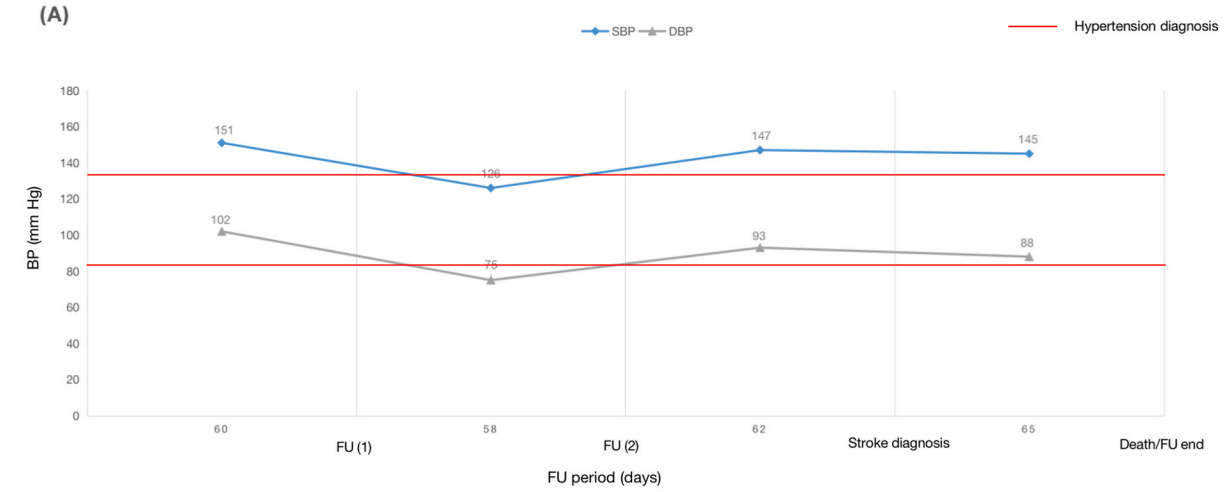
2.2Definition of hypertension burden

75.6% of patients underwent manual BP measurement and 24.4% of patients underwent BP measurement using automated techniques. During the first year of the TOPCAT trial, BP recordings were obtained during six visits (baseline and months 1, 2, 4, 8, and 12). In subsequent follow-ups, BP was determined every six months. In each particular visit, a trained staff measured participants' BP in a setting position at least 3 times after a 5-min rest and calculated the average of 3 BP measurements. Hypertension burden (%) =

(days with BP ≥ 140/90 mmHg/total follow-up days) × 100% [15,16].

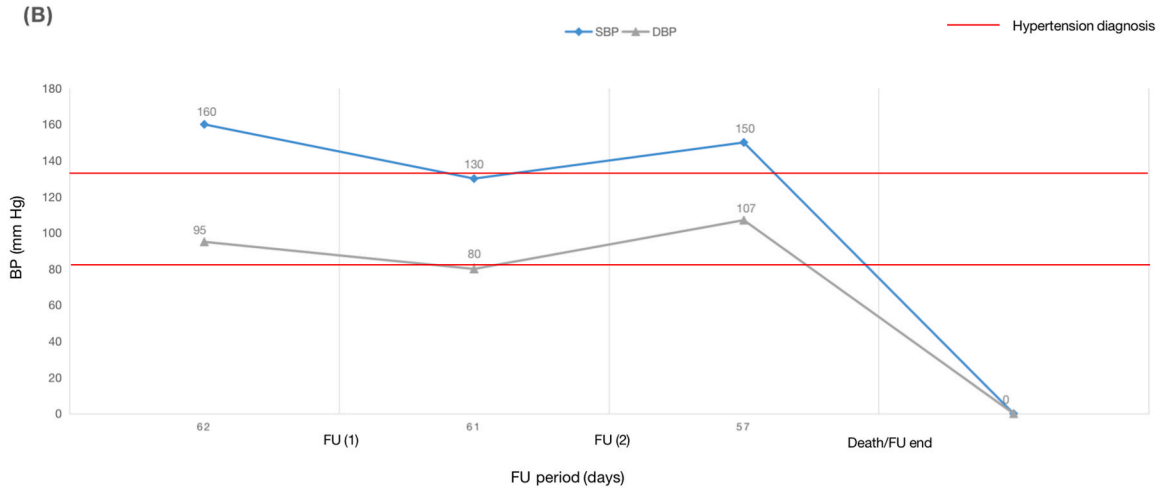
2.3Clinical outcomes

The TOPCAT trial involved hemorrhagic, non-hemorrhagic, and other unknown stroke types as outcomes [18]. Patients were defined as having a hemorrhagic stroke if they were documented or examined to have hemorrhagic events; otherwise, they would be defined as non-hemorrhagic stroke (i.e., ischemic stroke). Unknown stroke type was defined if a hemorrhage was inconclusive in imaging tools. The outcomes of interest in the present study included any stroke, new-onset stroke, and ischemic stroke. At the clinical site, outcomes were determined by subjects' contacts and medical record reviews during the follow-up. The validity and accuracy of each outcome were ascertained by the Clinical Endpoints Center.



FU=follow-up

Pt's hypertension burden = (60+62)/(60+58+62) × 100 = 67.7%



FU=follow-up

Pt's hypertension burden = (62+57)/(62+61+57) × 100 = 66.1%

Fig. 1. **(A)** Estimation of hypertension burden when the stroke occurs before death; **(B)** Estimation of hypertension burden when death occurs early. SBP = systolic blood pressure, DBP = diastolic blood pressure, FU = follow-up.

Table 1
Baseline characteristics of study patients stratified by hypertension burden.

Variable	Total (n = 3431)	Low risk (hypertension burden≤23.9%) (n = 2078)	Medium risk (hypertension burden: 23.9%–62.3%) (n = 857)	High risk (hypertension burden≥62.3%) (n = 496)	p-value
Demographics					
Age, years	68.5 ± 9.58	68.9 ± 9.64	68.6 ± 9.49	67.1 ± 9.40	0.001
Female, n (%)	1769 (51.6%)	1026 (49.4%)	448 (52.3%)	295 (59.5%)	<0.001
White race, n (%)	3049 (88.9%)	1905 (91.7%)	733 (85.5%)	411 (82.9%)	<0.001
Current smoker, n (%)	360 (10.5%)	219 (10.5%)	91 (10.6%)	50 (10.1%)	0.947
Physical and laboratory examination					
SBP, mmHg	130 (120, 140)	127 (119, 134)	132 (128, 140)	140 (130, 149)	<0.001
DBP, mmHg	80.0 (70.0, 80.0)	78.0 (68.0, 80.0)	80.0 (70.0, 84.0)	80.0 (71.0, 90.0)	<0.001
Hypertension burden, %	13.3 (0.00, 43.0)	0.00 (0.00, 10.1)	40.2 (31.4, 49.8)	81.5 (69.7, 96.1)	0
HR, bpm	68.0 (62.0, 76.0)	68.0 (62.0, 75.0)	68.0 (61.0, 76.0)	69.0 (61.0, 78.0)	0.159
BMI, kg/m2	32.1 ± 7.10	31.3 ± 6.74	32.9 ± 7.37	33.8 ± 7.60	<0.001
NYHA class, n (%)					0.001
I-II	2296 (66.9%)	1439 (69.2%)	553 (64.5%)	304 (61.3%)	
III-IV	1135 (33.1%)	639 (30.8%)	304 (35.5%)	192 (38.7%)	
EF (%)	56.0 (51.0, 61.0)	56.0 (50.0, 61.0)	56.0 (51.0, 61.0)	58.0 (52.0, 64.2)	<0.001
eGFR, mL/min*1.73m2	65.4 (53.7, 79.2)	66.0 (54.8, 79.2)	64.4 (52.4, 78.3)	65.8 (52.7, 79.7)	0.048
Comorbidities					
Previous HF Hospitalization, n (%)	2480 (72.3%)	1443 (69.4%)	645 (75.3%)	392 (79.0%)	<0.001
Previous MI, n (%)	891 (26.0%)	557 (26.8%)	221 (25.8%)	113 (22.8%)	0.184
Previous stroke, n (%)	264 (7.69%)	142 (6.83%)	64 (7.47%)	58 (11.7%)	0.001
CABG, n (%)	442 (12.9%)	282 (13.6%)	109 (12.7%)	51 (10.3%)	0.143
PCI, n (%)	497 (14.5%)	314 (15.1%)	120 (14.0%)	63 (12.7%)	0.351
PAD, n (%)	318 (9.27%)	187 (9.00%)	76 (8.87%)	55 (11.1%)	0.317
DM, n (%)	1114 (32.5%)	607 (29.2%)	301 (35.1%)	206 (41.5%)	<0.001
HTN, n (%)	3136 (91.4%)	1851 (89.1%)	811 (94.6%)	474 (95.6%)	<0.001
Dyslipidemia, n (%)	2066 (60.2%)	1184 (57.0%)	558 (65.1%)	324 (65.3%)	<0.001
COPD, n (%)	401 (11.7%)	238 (11.5%)	102 (11.9%)	61 (12.3%)	0.849
Atrial fibrillation, n (%)	1236 (36.0%)	761 (36.6%)	302 (35.2%)	173 (34.9%)	0.659
Thyroid disease, n (%)	537 (15.7%)	306 (14.7%)	145 (16.9%)	86 (17.3%)	0.177
Treatments					
Spironolactone, n (%)	1717 (50.0%)	1090 (52.5%)	418 (48.8%)	209 (42.1%)	<0.001
Diuretics, n (%)	2806 (81.8%)	1640 (78.9%)	741 (86.5%)	425 (85.7%)	<0.001
Beta blocker, n (%)	2670 (77.8%)	1620 (78.0%)	668 (77.9%)	382 (77.0%)	0.897
ACEI/ARB, n (%)	2891 (84.3%)	1727 (83.1%)	731 (85.3%)	433 (87.3%)	0.044
CCB, n (%)	1290 (37.6%)	701 (33.7%)	360 (42.0%)	229 (46.2%)	<0.001
Antihypertensive medicine, n (%)	3405 (99.2%)	2061 (99.2%)	851 (99.3%)	493 (99.4%)	0.922
Anticoagulant, n (%)	826 (24.1%)	516 (24.8%)	199 (23.2%)	111 (22.4%)	0.412
Warfarin, n (%)	785 (22.9%)	485 (23.3%)	194 (22.6%)	106 (21.4%)	0.628
Aspirin, n (%)	2246 (65.5%)	1341 (64.5%)	572 (66.7%)	333 (67.1%)	0.362
Lipid-lowering drug, n (%)	242 (7.05%)	151 (7.27%)	67 (7.82%)	24 (4.84%)	0.099

EF, ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; BMI, body mass index; HF, heart failure; MI, myocardial infarction; PAD, peripheral artery disease; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; DM, diabetes mellitus; HTN, hypertension; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration

rate; BNP, type B natriuretic peptide; ACEI/ARB, angiotensin converting enzyme inhibitors/angiotensin II receptor blocker; CCB, calcium channel blocker.

2.4Statistical analysis

The demographic and clinical characteristics were presented as the means with standard deviations (SDs) (normal distribution) or medians with interquartile ranges (abnormal distribution) for continuous variables. The categorical variables were expressed as counts and percentages. The intergroup differences were assessed using unpaired Student t-tests/one-way analysis of variance for normally distributed variables, the Wilcoxon rank-sum test for non-normally distributed variables, and the Person chi-square test for categorical variables. The x-tile program was used to generate the optimal hypertension burden cutoff points with minimum P value from chi-square tests. Kaplan-Meier methods and log-rank tests were used to analyze the cumulative incidence of stroke. Fine and Gray's competing risk models were applied with all-cause death as a competing event. The adjustment of variables was from a backward stepwise method and included additional clinically relevant factors. We used multivariable Cox regression models with restricted cubic splines (RCSs) to evaluate the hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) of stroke incidence.

The prognostic significance of hypertension burden was further evaluated in the subgroups stratified by gender, age (<65 versus ≥65 years old), region (Americas versus Russia/Georgia), baseline AF status, baseline hypertensive status, baseline SBP (<130 versus ≥130 mmHg), baseline diastolic BP (DBP) (<80 versus ≥80 mmHg), treatment arm (spironolactone versus placebo), baseline treatment with aspirin and anticoagulant. Cox proportional hazard models and likelihood ratio tests were used in these subgroup analyses. In sensitivity analyses, we repeated the analyses mentioned above in HFpEF patients from America and patients without previous strokes.

Statistical analyses were performed with R version 4.1.1 (with Packages Of Compare Groups, Survival, Hmisc, Cmprsk, Survminer, Ggprism, Ggplot2, RiskRegression) with a graphical user interface of GraphPad Prism 6.0. A 2-sided P value of <0.05 was considered statistically significant.

3Results

3.1Baseline characteristics

We excluded participants with missing baseline BP measurements or abnormal follow-up intervals, yielding a final sample of 3431 patients (mean age: 68.5 ± 9.58 years, 51.6% females). Fig. 1A and **B** summarize the calculation of hypertension burden. As shown in Supplementary Fig. 1, the X-tile program was applied to stratify participants into three different risk strata: low risk (hypertension burden ≤23.9%), medium risk (23.9%–62.3%) and high risk (≥62.3%). Table 1 shows the demographic and clinical characteristics of the studied population. 72.3% (n = 2480) and 7.69% (n = 264) of participants had a history of HF hospitalization and stroke, respectively. Patients with higher hypertension burden had higher SBP, DBP, body mass index, elevated levels of left ventricular ejection fraction, and a higher proportion of peripheral artery disease, diabetes, hypertension and dyslipidemia. In the aspect of treatments, higher hypertension burden patients were prone to receive angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACEI/ARB), calcium channel blockers (CCB), and antihypertension medicine.

The echocardiographic indexes for the studied population are presented in Supplementary Table 2. Among patients with different hypertension burden risks, there was a significant difference in interventricular septum thickness (P = 0.004) and mean left ventricular wall thickness (P = 0.015), suggesting that patients had the characteristics of hypertensive heart disease.

3.2Association between hypertension burden and stroke risk

During a mean follow-up of 3.3 years, 117 (3.53%) subjects experienced a stroke. When patients were categorized into three risk strata, the Kaplan-Meier analyses showed a graded increased risk for any stroke (p < 0.001), new-onset stroke (p < 0.001), and ischemic stroke (p = 0.0018) (Fig. 2 a-c).

As shown in Table 2, the average incidence rates of any stroke, new-onset stroke, and ischemic stroke were 1.029, 0.889 and 0.739

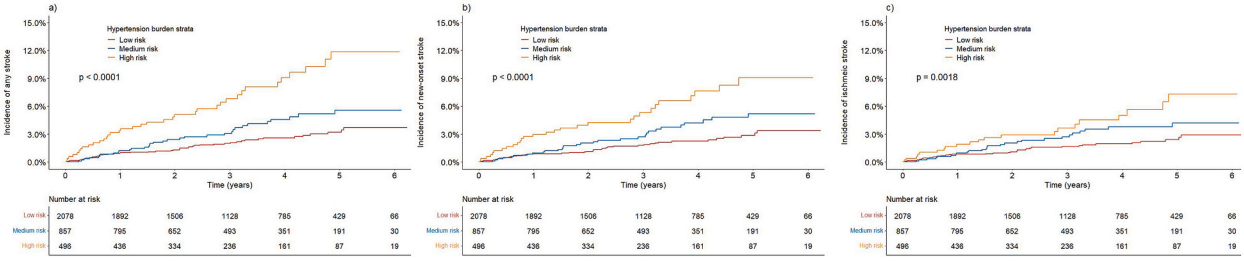


Fig. 2. Cumulative incidence of a) any stroke, b) new-onset stroke, c) ischemic stroke in HFpEF patients according to the hypertension burden strata.

per 100 person-years, respectively. Compared with those within the low-risk group, any stroke risk was significantly increased in medium (unadjusted HR 1.65, 95% CI 1.06–2.57) and high (unadjusted HR 3.45, 95% CI 2.24–5.31) risk groups. After adjusting potential covariates, hypertension burden remained associated with any stroke (medium: HR 1.59, 95% CI 1.01–2.40; high: HR 3.19, 95% CI 2.05–4.97). The multivariable-adjusted HR for the high-risk vs. low-risk was 2.92 (1.80–4.74) and 2.46 (1.41–4.29) for new-onset and ischemic stroke, respectively.

In multivariable analyses with RCSs, per 10-point increase in hypertension burden was associated with any stroke (HR 1.15, 95% CI 1.08–1.21), new-onset stroke (HR 1.14, 95% CI 1.07–1.21), and ischemic stroke (HR 1.10, 95% CI 1.02–1.17) (Table 2). When the hypertension burden elevated above 13.57%, an increase in hypertension burden continuously increased the adjusted risk of any, new-onset and ischemic stroke (Fig. 3a, **3b** and **3c**).

3.3Subgroup analysis and sensitivity analysis

No statistical difference in gender, region, AF, hypertension, baseline BP, randomization or aspirin treatment subgroup analyses were presented in Fig. 4 (p for interaction > 0.05). In the anticoagulant treatment subgroup analysis, increased any stroke risk was presented in participants without anticoagulant (HR 1.21 95% CI 1.13–1.30), but not in those with anticoagulant (HR 1.05, 95% CI 0.95–1.16). Additionally, any stroke risk was higher in patients with ages below 65 years (HR 1.26 95% CI 1.15–1.39) than those ≥65 years (HR 1.08 95% CI 1.00–1.16) (p for interaction < 0.05).

In the sensitivity analysis, we repeated the analyses mentioned above in the America patients and those without previous strokes. Supplementary Figure 2 and Table 3 show that a higher risk of hypertension burden was significantly associated with increased any stroke and ischemic stroke, even when censoring for patients with a previous stroke. In Supplementary Figure 3 and Table 4, the association between hypertension burden and stroke risk in American HFpEF patients remained consistent with the primary analysis.

4Discussion

In this population-based post hoc analysis of HFpEF patients, we investigated the association between hypertension burden and risks of any, new-onset and ischemic stroke. We confirmed that stroke performed as a significant outcome of HFpEF patients, with an incidence rate of 1.029 per 100 person-years. After adjusting for multiple contributing factors, a higher hypertension burden was associated with increased risks of any stroke, new-onset stroke, or ischemic stroke in HFpEF patients. If the hypertension burden

Table 2
The risk of stroke according to hypertension burden in HFpEF patients.

	Events/ N	Person-years	Incidence rates, per 100 person-years	Unadjusted		Model 1		Model 2	
				HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Any stroke[b]									
Overall[a]	117/ 3431	11366	1.029 (0.860, 1.232)	1.16 (1.09–1.22)	< 0.001	1.16 (1.10–1.23)	< 0.001	1.15 (1.08–1.21)	< 0.001
Low risk	47/2078	6868	0.684 (0.515, 0.909)	Reference		Reference		Reference	
Medium risk	33/857	2967	1.112 (0.793, 1.558)	1.65 (1.06–2.57)	0.028	1.62 (1.04–2.54)	0.034	1.59 (1.01–2.40)	0.044
High risk	37/496	1531	2.416 (1.758, 3.313)	3.45 (2.24–5.31)	< 0.001	3.52 (2.29–5.42)	< 0.001	3.19 (2.05–4.97)	< 0.001
New-onset stroke[c]									
Overall[a]	101/ 3431	11366	0.889 (0.732, 1.079)	1.14 (1.07–1.21)	< 0.001	1.14 (1.08–1.21)	< 0.001	1.14 (1.07–1.21)	< 0.001
Low risk	42/2078	6868	0.612 (0.453, 0.825)	Reference		Reference		Reference	
Medium risk	30/857	2967	1.011 (0.709, 1.440)	1.68 (1.05–2.67)	0.03	1.64 (1.02–2.64)	0.040	1.60 (0.99–2.56)	0.054
High risk	29/496	1531	1.894 (1.322, 2.707)	3.01 (1.88–4.84)	< 0.001	3.08 (1.92–4.94)	< 0.001	2.92 (1.80–4.74)	0.001
Ischemic stroke[b]									
Overall[a]	84// 3431	11366	0.739 (0.597, 0.914)	1.10 (1.03–1.17)	0.005	1.10 (1.03–1.18)	0.005	1.10 (1.02–1.17)	0.008
Low risk	37/2078	6868	0.539 (0.391, 0.742)	Reference		Reference		Reference	
Medium risk	26/857	2967	0.876 (0.599, 1.281)	1.65 (0.99–2.72)	0.051	1.58 (0.95–2.63)	0.076	1.57 (0.94–2.61)	0.085
High risk	21/496	1531	1.371 (0.899, 2.087)	2.46 (1.44–4.21)	0.001	2.55 (1.49–4.38)	0.001	2.46 (1.41–4.29)	0.016

HFpEF, heart failure with preserved ejection fraction; Events/100 pt-yrs, events per 100 patient-years.

[a] per 10 points.

[b] Model 1 adjusted by age, gender, white race, and current smoker; Model 2 adjusted by variables in model 1 and previous stroke, previous MI, previous PAD, HTN, diabetes, dyslipidemia, atrial fibrillation, aspirin, anticoagulant, lipid-lowering drugs, and antihypertensive drugs.

[c] adjusted by above-mentioned variables except for previous stroke.

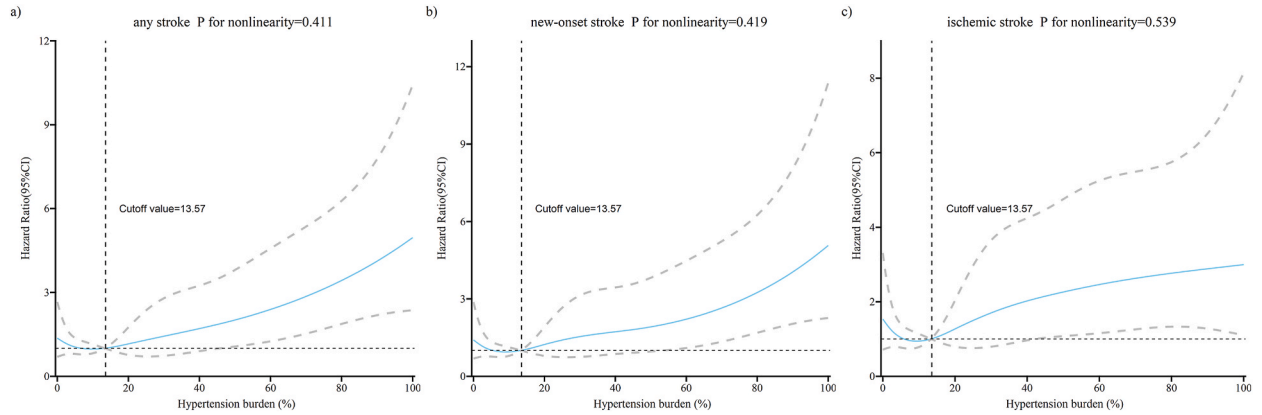


Fig. 3. Association of hypertension burden and a) any stroke, b) new-onset stroke, c) ischemic stroke in an adjusted cubic spline model in HFpEF patients (variables adjusted as Table 2).

Variable	Subgroup	N/event	HR (95%CI)	P value	P for interaction
Total		3431/117	1.15 (1.09, 1.22)	<0.001	
Gender					0.446
	male	1662/55	1.12 (1.03, 1.22)	0.010	
	female	1769/62	1.17 (1.09, 1.26)	<0.001	
Age					0.012
	<65 years old	1260/39	1.26 (1.15, 1.39)	<0.001	
	≥65 years old	2171/78	1.08 (1.00, 1.16)	0.037	
Region					0.201
	Americas	1758/77	1.13 (1.05, 1.22)	0.001	
	Russic/Georgia	1673/40	1.20 (1.09, 1.33)	<0.001	
Atrial fibrillation					0.915
	no	2195/52	1.16 (1.06, 1.26)	0.001	
	yes	1236/65	1.16 (1.07, 1.25)	<0.001	
Hypertension					0.522
	no	295/5	1.24 (0.89, 1.71)	0.198	
	yes	3136/112	1.15 (1.08, 1.21)	<0.001	
SBP					0.537
	<130mmHg	1414/43	1.12 (1.01, 1.25)	0.034	
	≥130mmHg	2017/74	1.16 (1.08, 1.24)	<0.001	
DBP					0.281
	<80mmHg	1633/58	1.11 (1.02, 1.21)	0.017	
	≥80mmHg	1798/59	1.18 (1.09, 1.28)	<0.001	
Randomization					0.761
	Spironolactone	1717/57	1.16 (1.07, 1.26)	0.001	
	Placebo	1714/60	1.14 (1.06, 1.24)	0.001	
Aspirin					0.196
	no	1185/44	1.09 (0.99, 1.19)	0.085	
	yes	2246/73	1.19 (1.11, 1.28)	<0.001	
Anticoagulant					0.015
	no	2605/75	1.21 (1.13, 1.30)	<0.001	
	yes	826/42	1.05 (0.95, 1.16)	0.364	

Fig. 4. Hazard of any stroke by subgroups stratified by gender, age, region, atrial fibrillation, hypertension, baseline SBP, baseline DBP, spironolactone/placebo treatment, treatment with aspirin, and treatment with the anticoagulants.

exceeded 13.57%, an increase in hypertension burden continuously increased the adjusted risks of any, new-onset and ischemic stroke. Furthermore, sensitivity analyses were performed by censoring HFpEF patients with previous strokes and repeating the analyses in the Americas, generating confirmatory results. Considering other confounders of HFpEF patients, our findings provided significant information regarding the effect of hypertension burden on stroke risk, which can be helpful in stroke prevention.

HFpEF is an independent risk factor for stroke regardless of AF. Although featuring the highest CHA2DS2-Vasc score, HFpEF had the lowest thromboembolic risk among all HF subtypes [5]. In contrast, accumulating evidence suggested a similar [19,20] or relatively higher [4,6] thromboembolic risk was found in HFpEF than heart failure with reduced ejection fraction (HFrEF), after censoring for AF. Meanwhile, hypertension plays a predominantly causative role in cerebrovascular events, and several BP-associated indexes have been applied in stroke assessment [21–23]. Current research demonstrated the duration of hypertension was associated with cerebrovascular diseases, evaluated by hypertension burden [24]. However, no clinical study has discussed the relationship between hypertension burden and stroke risk in the HFpEF population.

Higher hypertension burden risk was associated with an increased cumulative incidence of any new-onset and ischemic stroke during the follow-up period, even after censoring for the HFpEF patients with the previous stroke. This suggested intracranial atherosclerosis, vascular rarefaction, abnormal cerebral blood flow and white matter hyperintensity, were the important mechanisms underlying the relationship between hypertension burden and cumulative stroke incidence [25]. A meta-analysis performed by Lee et al. demonstrated baseline prehypertension (SBP 120–139 mm Hg or DBP 80–89 mm Hg) offered a significantly increased stroke risk, driven by higher SBP or DBP values within the prehypertension range [21]. In a population-based cohort study, an increased risk of unspecific and hemorrhagic stroke was presented among stroke-free participants with higher visit-to-visit BP variability in the Netherlands [22]. Similarly, a post hoc analysis revealed greater visit-to-visit SBP or DBP variability was associated with adverse health outcomes, such as stroke, in HFpEF patients [23]. Compared with baseline BP and visit-to-visit BP variability, hypertension burden has the advantage of incorporating a follow-up period into stroke risk assessment, considering the magnitude and duration of BP change, and facilitating a comprehensive assessment of BP effect on stroke incidence.

When the hypertension burden exceeded 13.57%, a continuous increase in hypertension burden was significantly associated with increased stroke risk. Previous population-based cohort studies showed increased vascular and Alzheimer's dementia risks among the general [22] and AF populations [16] with a hypertension burden above 40%. Our result suggested that if the duration of hypertension was controlled within a specific range, we might reach the goal of optimal stroke prevention. This could be an important guideline for BP control in HFpEF patients.

Our sub-group analysis suggested no significant effect of AF history on any stroke risk, and it provided further evidence regarding HFpEF as an independent risk factor regardless of AF. Additionally, OAC offered a lower risk of any stroke than no OAC, while it seemed to contrast with previous studies. In the review performed by Shantsila et al., OAC was a non-superior lowering-stroke option for HFpEF patients with sinus rhythm, with no information regarding the antithrombotic effects of OAC versus antiplatelets [10]. Non-vitamin K oral anticoagulant (NOAC) was a novel marketed anticoagulant for better safety outcomes but had no significant difference in systemic embolism risk among HFpEF patients with AF [26]. Due to the HFpEF heterogeneity and AF history, the efficacy of OAC for stroke reduction in HFpEF patients was still controversial, and hence more data regarding OAC therapy would be provided in future studies.

Early and effective BP control alleviated hypertension duration to reduce stroke incidence, while the establishment of the optimal BP reduction time was uncertain in HFpEF patients [27]. In several randomized clinical trials, a BP of 130/80 mmHg was considered an optimal value for stroke-preventing goals [28,29]. Nevertheless, it remains unclear what specific value of BP control could be beneficial to stroke prevention in HFpEF patients. With the collected data on BP, we might evaluate a BP value corresponding to the lowest stroke incidence. Further studies could confirm the appropriate BP in the early stage of stroke prevention, by providing effective BP control in HFpEF patients. Moreover, the antithrombotic effects of OAC should be further identified in future studies.

5Limitation

Several limitations were acknowledged in our study. First, we performed a post-hoc analysis of the TOPCAT trial, the remaining confounders might affect the reliability of our results. Second, transient ischemic attack and other thromboembolic events of the TOPCAT trial were not included, although the stroke risk was comprehensively assessed. Third, there was a lack of information regarding anticoagulant therapy, such as dosage, initiation, duration and compliance with OAC. Fourth, we should validate our results by performing a population-based cohort study with a large sample size, since the stroke events were relatively low to increase the risks of overfitting of multivariable regression analyses.

6Conclusions

Increasing hypertension burden was associated with an increased risk of stroke, suggesting that shortening hypertension duration might appropriately minimize the stroke incidence in HFpEF patients. Significantly, OACs might offer an anti-thrombolic effect on HFpEF patients, but more evidence regarding OACs therapy should be provided in future studies.

Ethics statement

All participating institutions approved the study in institutional review board, and all participants provided written informed consent at enrollment. Our study is a secondary analysis of TOPCAT trial, and all information were included in the Supplementary Appendix of Spironolactone for Heart Failure with Preserved Ejection Fraction published in The New England Journal of Medicine (PMID: 24716680).

Consent for publication

Not applicable.

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Availability of data and materials

The data underlying this article will be shared upon reasonable request to the corresponding author. The publicly available data of TOPCAT trial can be accessed through the National Institutes of Health database of genotypes and phenotypes (https://www.ncbi.nlm.nih.gov/gap/).

CRediT authorship contribution statement

Siyu Guo: Writing – original draft, Data curation. **Xiao Liu:** Writing – original draft, Data curation. **Zhenbang Gu:** Writing – review & editing, Data curation. **Junyi Sun:** Writing – review & editing, Software, Formal analysis. **Yalin Cao:** Writing – review & editing. **Wengen Zhu:** Writing – review & editing, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e27551.

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