International Journal of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Low diastolic blood pressure and adverse outcomes in heart failure with preserved ejection fraction

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ARTICLE INFO

Article history:
Received 14 November 2017
Received in revised form 24 January 2018
Accepted 6 April 2018
Available online xxxx

Keywords:
Heart failure with preserved ejection fraction
Diastolic blood pressure
J-curve relationship
TOPCAT trial
Cardiovascular events
Mortality

ABSTRACT

Background: It remains unknown whether a low diastolic blood pressure (DBP) increases the risks of cardiovascular events and death in patients with heart failure with preserved ejection fraction (HFpEF).
Methods: We used data from the TOPCAT trial. The primary outcome was a composite of all-cause death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure. Hazard ratios (HRs) were analyzed for DBPs of <60, 60–69, 70–79, and ≥90 mm Hg in comparison with a DBP of 80–89 mm Hg using multivariable Cox proportional hazard models.
Results: This study included 3417 patients with HFpEF who had a controlled blood pressure. In the mean follow-up period of 3.0 years, 881 patients experienced at least one confirmed primary outcome event. Compared with patients with a DBP of 80–89 mm Hg, the adjusted HRs for primary outcome events were significantly higher in those with DBPs of <60 mm Hg (HR: 2.19 [95% confidence interval,1.72–2.78]) and 60–69 mm Hg (HR: 1.52 [1.23–1.87]). Similarly, the adjusted HRs for all-cause death, major cardiovascular events, and hospitalization for heart failure, but not stroke, were significantly higher in patients with a DBP of <70 mm Hg. A relationship between a low DBP and adverse outcomes was found in HFpEF patients with a systolic blood pressure of ≥120 mm Hg; however, a low systolic blood pressure with a DBP of ≥70 mm Hg was not associated with these event risks.
Conclusions: A low DBP increased the risks of adverse outcomes in patients with HFpEF.

1. Introduction

Heart failure with preserved ejection fraction (HFpEF) is a clinical syndrome characterized by typical symptoms and signs of heart failure in patients with normal or near normal left ventricular ejection fraction [1]. Hypertension is a common comorbidity in patients with HFpEF [2]. However, no studies have assessed appropriate blood pressure (BP) control in these patients, and the target levels of systolic blood pressure (SBP) and diastolic blood pressure (DBP) remain unknown. Several studies have reported that a low DBP was associated with reduced coronary blood flow, subclinical myocardial damage, and cardiovascular events [3–7]. The aim of this study was to assess whether a low DBP increases the risks of cardiovascular events and death in patients with HFpEF. In addition, we assessed whether a low SBP in patients with preserved DBP is associated with an increased risk of these adverse outcomes.

2. Methods

2.1. Study design and patients

To investigate the association between DBP and cardiovascular events and death, we used data from the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial, in which the patients had a controlled BP [8]. A detailed description of the TOPCAT design and protocol has previously been reported [2,9]. In brief, the TOPCAT study was an international, multicentre, randomized, double-blind, placebo-controlled trial. From August 10, 2006 to January 31, 2012, a total of 3445 patients at 233 sites in six countries were randomly assigned to receive spironolactone or a placebo. Patients aged ≥50 years were included if they had at least one sign and one symptom of heart failure from a prespecified list of clinically defined signs and symptoms, a left ventricular ejection fraction of ≥45% measured at the local site by echocardiography or radionuclide ventriculography, and controlled BP (defined as a target SBP of <140 mm Hg or ≤160 mm Hg if the patient was taking ≥3 medications to control BP). This study was approved by the institutional review board of the National Center for Global Health and Medicine. The National Heart, Lung, and Blood Institute (NHLBI) approved our use of the TOPCAT data.

Abbreviations: HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; TOPCAT, Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist; GFR, glomerular filtration rate; NHLBI, National Heart, Lung, and Blood Institute; NYHA, New York Heart Association; BMI, body mass index; HR, hazard ratio; CI, confidence interval; CAD, coronary artery disease.

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https://doi.org/10.1016/j.ijcard.2018.04.031

Table 1
Baseline characteristics of study patients with HFpEF based on diastolic blood pressure groups[a].

Diastolic blood pressure (mm Hg)	<60	60–69	70–79	80–89	≥90	P for between-group comparison[d]
	n = 227	n = 546	n = 849	n = 1371	n = 424	
Age (years)	74.0 (9.9)	72.8 (8.9)	69.3 (9.6)	66.7 (9.0)	64.7 (8.8)	<0.001
Female sex (%)	45.8	48.3	52.5	51.1	58.5	0.008
Race and ethnicity (%)						
White	81.0	83.9	86.9	92.9	89.6	<0.001
Black	12.8	11.9	10.4	5.7	8.3	<0.001
Others	6.2	4.2	2.7	1.4	2.1	<0.001
Smoking status (%)						
Never	35.2	42.7	53.1	57.0	60.8	<0.001
Former	60.8	51.5	37.2	30.0	26.2	<0.001
Current	4.0	5.9	9.7	13.0	13.0	<0.001
Alcohol drinks/week (%)						
0	75.8	71.6	79.6	79.2	80.0	0.002
1–5	14.1	21.2	15.9	16.2	17.0	0.04
6–10	7.0	5.5	3.0	3.3	2.1	0.002
11–	3.1	1.7	1.5	1.3	0.9	0.26
NYHA functional classification (%)						
I/II	56.4	62.4	68.8	68.0	71.9	<0.001
III/IV	43.6	37.6	31.2	32.0	28.1	
Body mass index (kg/m^2)[b]	32.3 (8.6)	33.4 (8.6)	32.1 (7.3)	31.4 (6.1)	32.3 (6.7)	<0.001
Diabetes (%)	51.5	43.6	35.0	24.4	28.3	<0.001
Hypertension (%)	90.8	86.8	90.3	92.7	96.0	<0.001
Dyslipidemia (%)	78.4	72.7	65.4	55.6	38.9	<0.001
History of cardiovascular events (%)						
Myocardial infarction	31.3	22.3	27.4	28.2	17.7	<0.001
Angina pectoris	33.0	33.9	45.3	53.3	54.5	<0.001
Percutaneous coronary intervention	22.9	21.8	19.0	9.9	7.1	<0.001
CABG surgery	24.7	22.9	13.4	8.9	4.7	<0.001
Implanted cardioverter defibrillator	2.6	3.7	1.1	0.5	0.5	<0.001
Pacemaker	19.8	14.7	7.5	4.2	4.5	<0.001
Hospitalization for heart failure	60.8	58.6	68.6	78.4	84.7	<0.001
Atrial fibrillation	40.1	43.2	39.2	33.0	21.9	<0.001
Stroke	11.9	9.2	7.8	6.4	7.8	0.03
Peripheral arterial disease	13.7	14.1	9.5	7.4	5.7	<0.001
COPD (%)	15.9	18.3	12.6	9.0	7.1	<0.001
Medication (%)						
ACE-I/ARB	78.4	77.1	79.9	87.7	94.1	<0.001
Calcium channel blockers	40.5	37.4	35.0	37.5	42.0	0.14
Diuretics	90.8	89.6	78.3	77.9	86.3	<0.001
Beta-blockers	80.6	81.9	77.5	75.6	78.3	0.03
Aspirin	67.0	61.9	65.1	65.3	70.8	0.07
Statins	76.2	67.6	58.4	44.6	32.3	<0.001
Randomization arm						
Spironolactone (%)	49.3	48.5	51.9	49.8	49.3	0.75
Estimated GFR (mL/min/1.73 m^2)	58.1 (18.4)	62.4 (20.2)	68.1 (21.3)	69.3 (18.7)	72.9 (19.8)	<0.001
Systolic blood pressure (mm Hg)	117.4 (16.9)	121.0 (14.6)	126.6 (12.7)	131.6 (9.8)	143.6 (10.2)	<0.001
Diastolic blood pressure (mm Hg)	53.8 (4.3)	63.4 (3.1)	72.6 (3.0)	81.4 (2.4)	91.9 (3.5)	<0.001
Heart rate (beats per minute)	65.5 (10.3)	67.7 (10.1)	68.5 (10.5)	69.5 (10.0)	72.4 (10.7)	<0.001
Health state[c]	62.7 (19.8)	62.2 (20.4)	60.7 (17.9)	58.8 (16.3)	60.2 (15.1)	<0.001

HFpEF, heart failure with preserved left ventricular ejection fraction; NYHA, New York heart association; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; GFR, glomerular filtration rate.

[a] Data are presented as number of participants, percent, or mean (standard deviation).

[b] Body mass index was calculated as weight in kilograms divided by the square of height in meters.

[c] Health state was assessed using a visual analog scale (0–100: the worst state is marked 0 and the best state is marked 100).

[d] *P* value was calculated based on analysis of variance for continuous variables and χ^2 tests for categorical variables.

2.2. Outcome measurements

The primary outcome was a composite of all-cause death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure. The secondary outcomes included all-cause death, major cardiovascular events, and hospitalization for heart failure. Major cardiovascular events included non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death, including fatal myocardial infarction, heart failure, fatal stroke, or pulmonary embolism, or sudden death. All events were adjudicated by a clinical end-point committee at Brigham and Women's Hospital, Boston, USA, according to prespecified criteria [9]. Study patients were evaluated every 4 months during their first year and every 6 months thereafter. In the present study, patients were followed-up for a maximum of 5 years. More detailed information on the evaluation of outcomes has previously been reported [8].

2.3. Statistical analysis

Patients were divided into five groups according to their baseline DBPs (<60, 60–69, 70–79, 80–89, and ≥90 mm Hg) [4–6]. Demographic data are presented as numbers, proportions (%), or means with standard deviations. Descriptive statistics for patient characteristics were calculated using analysis of variance for continuous variables and chi-squared tests for categorical variables. Event rates for primary and secondary outcomes based on BP categories were calculated. In addition, we calculated the age-standardized event rates in all the study participants according to the DBP levels using the census 2000 US population data as the standard. These analyses were conducted separately for men and women. Kaplan–Meier survival curves were constructed for primary and secondary outcomes for the five DBP groups, and we used multivariate Cox proportional hazard models for the analyses of primary and secondary outcomes. Compared with patients with a DBP of 80–89 mm Hg, we analyzed hazard ratios

Please cite this article as: T. Tsujimoto, H. Kajio, Low diastolic blood pressure and adverse outcomes in heart failure with preserved ejection fraction, Int J Cardiol (2017), https://doi.org/10.1016/j.ijcard.2018.04.031