European Journal of Heart Failure (2018) **20**, 323–331
doi:10.1002/ejhf.1131

RESEARCH ARTICLE

Association between mean systolic and diastolic blood pressure throughout the follow-up and cardiovascular events in acute myocardial infarction patients with systolic dysfunction and/or heart failure: an analysis from the High-Risk Myocardial Infarction Database Initiative

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Received 2 October 2017; revised 28 November 2017; accepted 30 November 2017; online publish-ahead-of-print 4 January 2018

Background Observational data have described the association of blood pressure (BP) with mortality as 'J-shaped', meaning that mortality rates increase below a certain BP threshold. We aimed to analyse the associations between BP and prognosis in a population of acute myocardial infarction (MI) patients with heart failure (HF) and/or systolic dysfunction.

Methods and results The datasets included in this pooling initiative are derived from four trials: CAPRICORN, EPHESUS, OPTIMAAL, and VALIANT. A total of 28 771 patients were included in this analysis. Arithmetic means of all office BP values measured throughout follow-up were used. The primary outcome was cardiovascular death. The mean age was 65 ± 11.5 years and 30% were female. Patients in the lower systolic BP (SBP) quintiles had higher rates of cardiovascular death (reference: SBP 121–128 mmHg) [adjusted hazard ratio (HR) 2.49, 95% confidence interval (CI) 2.26–2.74 for SBP ≤112 mmHg, and HR 1.29, 95% CI 1.16–1.43 for SBP 113–120 mmHg]. The findings for HF hospitalization and MI were similar. However, stroke rates were higher in patients within the highest SBP quintile (reference: SBP 121–128 mmHg) (HR 1.38, 95% CI 1.11–1.72). Patients who died had a much shorter follow-up (0.7 vs. 2.1 years), less BP measurements (4.6 vs. 9.8) and lower mean BP (−8 mmHg in the last SBP measurement compared with patients who remained alive during the follow-up), suggesting that the associations of low BP and increased cardiovascular death represent a reverse causality phenomenon.

Conclusion Systolic BP values <125 mmHg were associated with increased cardiovascular death, but these findings likely represent a reverse causality phenomenon.

Keywords Blood pressure • Myocardial infarction • Heart failure • Cardiovascular outcomes

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Introduction

Although it is indisputable that lowering blood pressure (BP) improves outcome of hypertensive patients,[1] the threshold to which BP should be lowered is a matter of debate and likely to be population-specific.[2–4] In addition, several observational studies and post-hoc analyses have suggested that lowering BP below a certain threshold may be deleterious, as reflected by the so-called 'J-curve phenomenon'.[5–7] An observational study in 22 672 'real-life' patients with stable coronary artery disease treated for hypertension, low systolic BP (SBP <120 mmHg) and diastolic BP (DBP <70 mmHg) were associated with an increased risk of cardiovascular events, supporting the J-curve phenomenon, and suggesting that in patients with coronary artery disease a low BP may be deleterious.[8]

Recently, the Systolic Blood Pressure Intervention Trial (SPRINT) showed that assigning high cardiovascular risk patients (but without diabetes or prior stroke) to an intensive BP treatment arm with the goal of lowering SBP below 120 mmHg vs. a standard treatment arm with the goal of lowering SBP below 140 mmHg, improved outcomes in this population, notably by reducing the rates of heart failure (HF) hospitalizations and death (both cardiovascular and all-cause).[9] The SPRINT trial results were also reinforced by a recent meta-analysis of trials allocating patients in intensive vs. standard treatment arms,[10] although in this meta-analysis the mean BP in the intensive therapy group was 133/76 mmHg, compared to 140/81 mmHg in the standard therapy group. Therefore, a discrepancy exists between data derived from randomized trials and data derived from observational studies. One potential explanation is that observational data are prone to bias, notably residual confounding and reverse causality. The latter is particularly relevant, i.e. it is not lower BP that causes the adverse outcomes, but rather the 'sicker' patients have lower BP near their life-end.[11]

The aim of the present study is to evaluate the association between BP levels and cardiovascular outcomes in a large cohort of acute myocardial infarction (MI) patients with systolic dysfunction and/or HF.

Methods

Study population

The High-Risk MI Initiative consists of a previously published cohort of pooled patient data derived from four clinical trials.[12] Briefly, the main objectives of the project are to provide a comprehensive and statistically robust analysis of long-term clinical outcomes in high-risk survivors of MI. The datasets included in this pooling initiative were: the effect of Carvedilol on Outcome after Myocardial Infarction in Patients with Left Ventricular Dysfunction trial (CAPRICORN),[13,14] the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS),[15,16] the Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL),[17,18] and the Valsartan in Acute Myocardial Infarction trial (VALIANT).[19,20] Full details of total enrolled patients, the inclusion and exclusion criteria for each trial, the endpoints as well as the results have previously been published.[12] Each trial enrolled patients with left ventricular systolic dysfunction, HF or both between 12 h and 21 days after acute MI.

The respective chairpersons of the Steering Committees of the four trials initiated the pooling project.

The studies were all conducted in accordance with the Declaration of Helsinki and approved by site ethics committees. All participants gave written informed consent to participate in the studies.

Blood pressure measurements

In each trial, the investigators measured patients' office BP after a rest of 5 min in the sitting position at each ~4-month interval using an automated electronic sphygmomanometer. Three BP measurements were performed at each visit and the mean BP at each visit was used in the present study. The main analysis was done with the arithmetic means of all BP values measured throughout the follow-up, from the baseline visit to the visit before an event or (in patients without an event) up to the last visit. All analyses were done for SBP and DBP, separately (Pearson correlation SBP/DBP =0.67). Patients were categorized into five groups (i.e. balanced quintiles) for both SBP and DBP.

Outcomes

The primary outcome was cardiovascular death. Secondary outcomes were hospitalization for HF, MI, stroke, and all-cause death. We only analysed patients with at least one BP measurement before the outcome. Endpoints were independently adjudicated in the respective trials.

Statistical analysis

In descriptive analyses, continuous variables are expressed as mean ± standard deviation as they were normally distributed. Categorical variables are expressed as frequencies and proportions (%).

One-way analysis of variance (ANOVA) was used to compare BP across quintiles. Baseline laboratory measurements were obtained at the time of inclusion. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[21]

Cox proportional hazard regression models were used to model the associations between BP and long-term events both in univariable and multivariable analysis. Cox model assumptions were verified and BP measurements were analysed as quintiles and also converted to restricted cubic splines as association with outcomes was non-linear. In the multivariable models, the covariates were chosen from demographic (age and gender), clinical (body mass index, smoking, hypertension, diabetes, HF history, previous stroke, previous MI, peripheral artery disease, atrial fibrillation, and heart rate), laboratory (eGFR), and concomitant treatments (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, beta-blockers, and diuretics). All variables were previously found to be clinically relevant and associated with outcomes.[22] An interaction term between BP measures and age was pre-specified in the statistical analysis plan and was non-significant for all outcomes ($P > 0.1$). No multiple imputation was performed and only variables with <10% of missing values were used for adjustment. Left ventricular ejection fraction, glucose, electrolytes and haemoglobin were not included for adjustment in the models due to a high percentage (>75%) of missing values.

Model calibration was assessed visually by plotting the mean of model-predicted survival at 2 years in each decile of predicted survival against the observed survival estimated by the Kaplan–Meier method as previously described.[23]

Statistical analyses were performed using the R software (The R Foundation for Statistical Computing, Vienna, Austria). A *P*-value of <0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 28 771 patients were included in the present analysis (no patients were excluded). The mean age was 65 ± 11.5 years and 30% were female. The overall mean follow-up was 2.0 ± 1.0 years (2.1 ± 0.8 years in the group of patients who remained alive during follow-up vs. 0.7 ± 0.6 years in those who died from cardiovascular causes).

By quintiles of SBP, patients in the lower quintiles were younger, more often male, active smokers, with history of previous MI, and had lower body mass index, lower left ventricular ejection fraction, lower serum sodium levels, higher heart rate, and better eGFR (all $P < 0.0001$) (*Table 1*). Patients in the lower quintiles of DBP were older, more often diabetic, and with worse renal function, but they also had lower ejection fraction, body mass index, and serum sodium, were more often smokers, and had previous MI more often reported, as described for SBP (supplementary material online, *Table S1*).

Mean blood pressure outcome associations

Patients in the lower quintiles of SBP had higher rates of cardiovascular death compared to patients with SBP 121–128 mmHg (reference category) [adjusted hazard ratio (HR) 2.49, 95% confidence interval (CI) 2.26–2.74 for SBP ≤112 mmHg and HR 1.29, 95% CI 1.16–1.43 for SBP 113–120 mmHg] (*Table 2*). Patients in the higher SBP quintile had the lower rate of cardiovascular death (adjusted HR 0.76, 95% CI 0.68–0.85 for SBP >137 mmHg) compared with the same reference group. Consistent findings were also observed for HF hospitalization and MI (*Table 2*). Regarding stroke, patients in the higher and lower mean SBP quintile had a higher stroke risk (HR 1.38, 95% CI 1.11–1.72 and HR 1.66, 95% CI 1.32–2.10, respectively, compared with the reference group of SBP 121–128 mmHg) (*Table 2*). Patients in the lowest quintiles of DBP also presented an increased risk of cardiovascular death (adjusted HR 1.88, 95% CI 1.70–2.07 for DBP ≤68 mmHg and HR 1.23, 95% CI 1.10–1.36 for DBP 69–72 mmHg). High DBP was also independently associated with an increased stroke rate (HR 1.41, 95% CI 1.13–1.75) (supplementary material online, *Table S2*). Sensitivity analysis excluding patients with diabetes, stroke history and eGFR <45 mL/min/1.73 m^2 and additional adjustment for each trial and oral anticoagulant use, provided similar results to those observed in the whole population (supplementary material online, *Tables S3* and *S4*). Restricted cubic spline graphical representations of the relationship between BP and the outcomes of interest are depicted in *Figure 1*.

Blood pressure analysis and comparison of patients with and without events

Compared to those who were alive, patients who died from cardiovascular causes during the follow-up had similar absolute BP values at baseline (i.e. at randomization) [121/72 mmHg (alive) vs. 122/72 mmHg (dead)], but lower BP before the fatal event [129/76 mmHg (alive) vs. 121/72 (dead); absolute difference in SBP +1 mmHg in those who died at baseline vs. −8 mmHg in those who died in the last available recording]. Patients who died from cardiovascular causes also had fewer BP measurements during the follow-up (5 vs. 10 measures) and a much shorter mean follow-up (0.7 vs. 2.1 years). Consistently, in the patients who died during follow-up, the mean BP was lower than in patients who remained alive (*Table 3*). Patients with non-fatal events (HF hospitalization, MI, stroke) also had fewer BP measurements (~4 vs. 9) and a much shorter follow-up (0.7 vs. 1.9 years) compared to patients with fatal events. Patients with HF hospitalization and MI also presented lower last BP values compared to patients who did not have these events (128/76 vs. 123/73 for HF hospitalization and 128/76 vs. 125/73 for MI). On the other hand, patients who had a stroke had higher last BP values compared to patients without stroke events (127/75 vs. 129/76) (supplementary material online, *Table S5*). The associations between baseline BP values (i.e. at randomization) and last BP values (i.e. before cardiovascular death or last available if alive) are represented graphically in the supplementary material online, *Figures S1–S5*.

Discussion

The results of the present study in a specific population of patients with systolic dysfunction or overt HF after MI, show that BP levels <125/75 mmHg are associated with worse outcomes. The so-called 'J-shaped phenomenon' (i.e. higher cardiovascular risk below a certain BP threshold) was also observed in this large dataset. However, we found that patients with a fatal event had fewer BP measurements and lower last BP values compared to patients who remained alive during follow-up. Therefore, their mean BP approached the end-life values, suggesting a reverse causation as explanation for these findings.

In our study, patients with lower mean BP were also those with higher heart rate, lower body mass index, with higher proportion of previous MI, and current smoking. All these variables have been associated with worse outcomes in patients with HF and/or MI[24–27] and are likely to carry residual confounding, accounting, in part, for the reported associations. In the present study, after adjusting for potential confounders, having a low SBP (<125 mmHg) and DBP (<75 mmHg) was associated with non-fatal cardiovascular events (MI, stroke, HF hospitalization) and also death (both cardiovascular and all-cause). Overlapping results were observed in a subpopulation with less co-morbidities (i.e. no diabetes, no previous history of stroke and with eGFR >45 mL/min/1.73 m^2). Interestingly, in this population having high SBP (>140 mmHg) was only independently associated with a higher risk of stroke (but not cardiovascular death, MI or HF hospitalization). Patients who had a stroke were the only

Table 1 Demographic and baseline characteristics of the patients, for the total population and for systolic blood pressure quintiles

Population characteristics	n	Total	SBP Q1 ≤112 mmHg	SBP Q2 113–120 mmHg	SBP Q3 121–128 mmHg	SBP Q4 129–137 mmHg	SBP Q5 >137 mmHg	P-value
Age (years)	28 771	65.0 ± 11.5	61.2 ± 12.3	63.0 ± 11.9	64.7 ± 11.2	66.6 ± 10.4	68.6 ± 9.7	<0.0001
Female gender	28 771	8582 (29.8%)	1249 (22.6%)	1315 (23.1%)	1451 (27.0%)	1775 (32.0%)	2388 (43.3%)	<0.0001
Heart rate (b.p.m.)	28 691	75.7 ± 12.8	77.3 ± 13.2	75.9 ± 12.7	75.3 ± 12.5	74.9 ± 12.2	74.3 ± 12.5	<0.0001
Mean SBP (mmHg)	27 644	124.9 ± 14.9	105.4 ± 5.3	116.4 ± 2.3	123.9 ± 2.2	132.1 ± 2.7	146.9 ± 8.6	<0.0001
Mean DBP (mmHg)	27 644	74.3 ± 8.0	66.5 ± 5.7	71.6 ± 5.5	74.5 ± 5.7	77.3 ± 6.2	81.7 ± 7.4	<0.0001
Number of BP measures	28 771	8.4 ± 3.7	7.8 ± 3.7	8.7 ± 3.4	9.1 ± 3.2	9.1 ± 3.1	9.2 ± 3.2	<0.0001
BMI (kg/m^2)	28 098	27.5 ± 4.8	26.8 ± 5.1	27.2 ± 4.6	27.6 ± 4.7	27.8 ± 4.7	28.1 ± 4.9	<0.0001
LVEF (%)	19 903	34.3 ± 8.9	32.3 ± 8.8	34.0 ± 8.6	34.8 ± 8.6	35.2 ± 8.3	36.1 ± 9.3	<0.0001
eGFR (mL/min/1.73 m^2)	27 703	70.2 ± 36.8	74.6 ± 51.9	72.6 ± 29.9	71.3 ± 29.4	68.5 ± 32.3	65.6 ± 37.2	<0.0001
Haemoglobin (g/L)	12 862	133.5 ± 16.0	132.0 ± 16.5	134.3 ± 16.0	134.2 ± 15.8	134.1 ± 15.9	133.0 ± 15.7	<0.0001
Sodium (mmol/L)	13 177	139.4 ± 3.8	138.5 ± 3.8	139.1 ± 3.6	139.4 ± 3.6	139.7 ± 4.2	140.0 ± 3.5	<0.0001
Potassium (mmol/L)	13 115	4.2 ± 0.5	4.2 ± 0.5	4.3 ± 0.5	4.3 ± 0.5	4.3 ± 0.4	4.2 ± 0.5	0.001
Glucose (mmol/L)	13 088	7.4 ± 3.4	7.4 ± 3.7	7.3 ± 3.3	7.4 ± 3.6	7.4 ± 3.2	7.6 ± 3.3	0.015
Current smoker	28 735	9051 (31.5%)	1768 (32.0%)	1817 (32.0%)	1686 (31.4%)	1730 (31.3%)	1654 (30.1%)	<0.0001
Previous MI	28 769	7490 (26.0%)	1481 (26.8%)	1492 (26.2%)	1324 (24.6%)	1406 (25.4%)	1372 (24.9%)	0.049
Atrial fibrillation	28 771	3754 (13.0%)	672 (12.1%)	683 (12.0%)	620 (11.5%)	742 (13.4%)	784 (14.2%)	<0.0001
HF history	28 771	11 181 (38.9%)	2138 (38.7%)	2089 (36.7%)	1893 (35.2%)	2014 (36.4%)	2233 (40.5%)	<0.0001
Peripheral artery disease	28 769	2357 (8.2%)	363 (6.6%)	428 (7.5%)	407 (7.6%)	506 (9.1%)	526 (9.5%)	<0.0001
Hypertension history	28 771	15 570 (54.1%)	1813 (32.8%)	2369 (41.7%)	2859 (53.2%)	3583 (64.7%)	4225 (76.7%)	<0.0001
Diabetes history	28 771	7386 (25.7%)	1131 (20.4%)	1225 (21.5%)	1381 (25.7%)	1561 (28.2%)	1726 (31.3%)	<0.0001
Previous stroke	28 771	2264 (7.9%)	353 (6.4%)	389 (6.8%)	373 (6.9%)	470 (8.5%)	542 (9.8%)	<0.0001
ACEIs	23 287	12935 (55.5%)	2698 (56.4%)	2598 (55.8%)	2382 (55.7%)	2461 (57.0%)	2366 (57.2%)	0.54
ARBs	23 287	346 (1.5%)	62 (1.3%)	55 (1.2%)	72 (1.7%)	62 (1.4%)	77 (1.9%)	0.053
Beta-blockers	26 802	17 824 (66.5%)	3497 (68.9%)	3560 (67.5%)	3392 (67.7%)	3392 (65.9%)	3330 (64.4%)	<0.0001
Diuretics	28 761	13 013 (45.2%)	2515 (45.5%)	2422 (42.6%)	2251 (41.9%)	2473 (44.7%)	2587 (47.0%)	<0.0001
CVM	28 742	4380 (15.2%)	1328 (23.1%)	927 (15.2%)	675 (12.4%)	717 (12.6%)	733 (12.8%)	<0.0001
HF hospitalization	28 742	3385 (11.8%)	845 (15.3%)	666 (11.7%)	544 (10.1%)	589 (10.6%)	630 (11.4%)	<0.0001
MI	28 742	3112 (10.8%)	781 (13.6%)	657 (10.8%)	491 (9.0%)	542 (9.5%)	641 (11.2%)	<0.0001
Stroke	28 742	931 (3.2%)	181 (3.1%)	172 (2.8%)	142 (2.6%)	182 (3.2%)	254 (4.4%)	<0.0001
All-cause death	28 742	5103 (17.8%)	1500 (26.1%)	1095 (17.9%)	789 (14.5%)	836 (14.7%)	883 (15.4%)	<0.0001

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CVM, cardiovascular mortality; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate by the Chronic Kidney Disease Epidemiology Collaboration formula; HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; SBP, systolic blood pressure.

population with a non-fatal event that had higher BP values before the event. These findings (positive association of low BP with all cardiovascular events and high BP only with stroke) may support the theoretical notion that patients with coronary artery disease may require higher BP levels to maintain coronary perfusion.[8] However, in SPRINT,[9] the intensive treatment benefit was observed regardless of the presence of previous cardiovascular disease (*P* for interaction =0.39) and the attained mean BP levels in the intensive treatment group were 121.4/68.7 mmHg vs. 136.2/76.3 mmHg in the standard treatment group. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial enrolled diabetic patients at high cardiovascular risk and also targeted SBP of <120 mmHg.[2] However, in the ACCORD trial intensive treatment did not reduce the primary composite outcome of nonfatal MI, nonfatal stroke, or death from cardiovascular causes, but it reduced the pre-specified secondary outcome of annual rates of stroke (although the ACCORD trial might have been underpowered to detect between-group differences for the primary outcome as it had half of the sample size of SPRINT and did not incorporate HF hospitalizations in the primary outcome). In the Heart Outcomes Prevention Evaluation (HOPE)-3 trial, BP lowering in intermediate risk persons without cardiovascular disease also did not reduce the co-primary composite outcome of cardiovascular death, MI or stroke, but the pre-specified subgroup of patients with baseline SBP >143.5 mmHg seemed to benefit from anti-hypertensive therapy.[28] Although patients included in the HOPE-3 trial represent a completely different setting from those studied herein, no event rate increase was observed in patients with lower baseline BP. On the other hand, in observational studies the association with adverse prognosis steeply increases with BP levels <125/75 mmHg (like in the present study),[4,5,8,29] however (in addition to potential residual confounding bias, as above referred)

Table 2 Crude and adjusted hazard ratios for quintiles of systolic blood pressure

SBP quintiles	Crude HR (95% CI)	*P*-value	Adjusted HR[a] (95% CI)	*P*-value
Cardiovascular death				
≤112 mmHg	2.128 (1.942–2.332)	<0.0001	2.486 (2.257–2.739)	<0.0001
113–120 mmHg	1.203 (1.089–1.329)	<0.0001	1.291 (1.164–1.432)	<0.0001
121–128 mmHg	1	–	1	–
129–137 mmHg	0.998 (0.899–1.107)	0.96	0.893 (0.801–0.996)	0.041
>137 mmHg	0.958 (0.863–1.064)	0.42	0.760 (0.681–0.847)	<0.0001
Heart failure hospitalization				
≤112 mmHg	2.117 (1.884–2.378)	<0.0001	2.663 (2.355–3.011)	<0.0001
113–120 mmHg	1.321 (1.167–1.495)	<0.0001	1.497 (1.317–1.703)	<0.0001
121–128 mmHg	1	–	1	–
129–137 mmHg	1.037 (0.910–1.181)	0.59	0.935 (0.817–1.070)	0.33
>137 mmHg	1.238 (1.093–1.403)	0.001	0.934 (0.819–1.065)	0.31
Myocardial infarction				
≤112 mmHg	1.706 (1.525–1.91)	<0.0001	1.953 (1.735–2.198)	<0.0001
113–120 mmHg	1.225 (1.09–1.376)	0.001	1.284 (1.137–1.45)	<0.0001
121–128 mmHg	1	–	1	–
129–137 mmHg	1.040 (0.92–1.174)	0.53	0.958 (0.845–1.087)	0.51
>137 mmHg	1.208 (1.075–1.359)	0.002	1.034 (0.915–1.169)	0.59
Stroke				
≤112 mmHg	1.424 (1.142–1.776)	0.002	1.661 (1.317–2.095)	<0.0001
113–120 mmHg	1.135 (0.907–1.419)	0.27	1.234 (0.979–1.556)	0.074
121–128 mmHg	1	–	1	–
129–137 mmHg	1.271 (1.02–1.582)	0.032	1.165 (0.928–1.461)	0.18
>137 mmHg	1.684 (1.371–2.07)	<0.0001	1.381 (1.113–1.715)	0.003
All-cause death				
≤112 mmHg	2.054 (1.887–2.237)	<0.0001	2.410 (2.203–2.637)	<0.0001
113–120 mmHg	1.216 (1.109–1.332)	<0.0001	1.314 (1.195–1.446)	<0.0001
121–128 mmHg	1	–	1	–
129–137 mmHg	0.982 (0.892–1.082)	0.72	0.888 (0.803–0.982)	0.021
>137 mmHg	0.989 (0.899–1.089)	0.83	0.792 (0.717–0.876)	<0.0001

CI, confidence interval; HR, hazard ratio; SBP, systolic blood pressure.
P for interaction with age for SBP =0.53.
[a]Models adjusted for age, gender, body mass index, estimated glomerular filtration rate, smoking status, history of hypertension, diabetes, heart failure history, previous myocardial infarction, previous stroke, peripheral artery disease, atrial fibrillation, heart rate, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, beta-blockers, and diuretics (not adjusted for haemoglobin, glucose, electrolytes, or left ventricular ejection fraction due to high percentage of missing values).

one should account for reverse causation bias. In a post-hoc analysis derived from the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET) and the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND)[29]—that tested the efficacy and safety of angiotensin receptor blockers on high cardiovascular risk populations—the authors found a 'J-shaped association' of SBP and DBP with cardiovascular death, MI, and HF (but not stroke). Nonetheless, the authors also state that they cannot rule out a reverse causality effect on their findings, as multiple co-morbidities may cause BP decrease and are associated with higher morbidity and mortality rates during the trial. The present analysis demonstrates that patients who died had lower BP values compared to those who remained alive during follow-up (despite similar mean BP values at baseline). A recent population-based study also showed lower mean BP values in patients who died, suggesting that non-randomized epidemiological associations of low SBP with higher mortality may be due to reverse causation, because participants with lower BP values are closer, on average, to the end of life.[30] These findings suggest that a reverse causation bias is likely to drive the present associations as patients approaching death have lower BP values, which may be due to poor health conditions (e.g. 'pump' failure, systemic inflammation, renal disease) and deteriorating nutritional status toward the end of life.[31,32] Therefore, one should be very cautious in mixing apples and oranges, as data from randomized controlled trials provide much stronger evidence than observational or retrospective analysis. Hence, the findings reported herein (and in other observational data) may simply represent associations between 'sicker' populations and increased adverse outcomes, and any causality inference should be strongly discouraged.

Previous observational studies have yielded conflicting results for the risk of stroke, in which the J-shaped phenomenon has not been consistently observed.[8,29,33,34] However, stroke was a less frequent outcome in most analyses which, as a result, meant that many lacked statistical power to assess the relationship between BP and

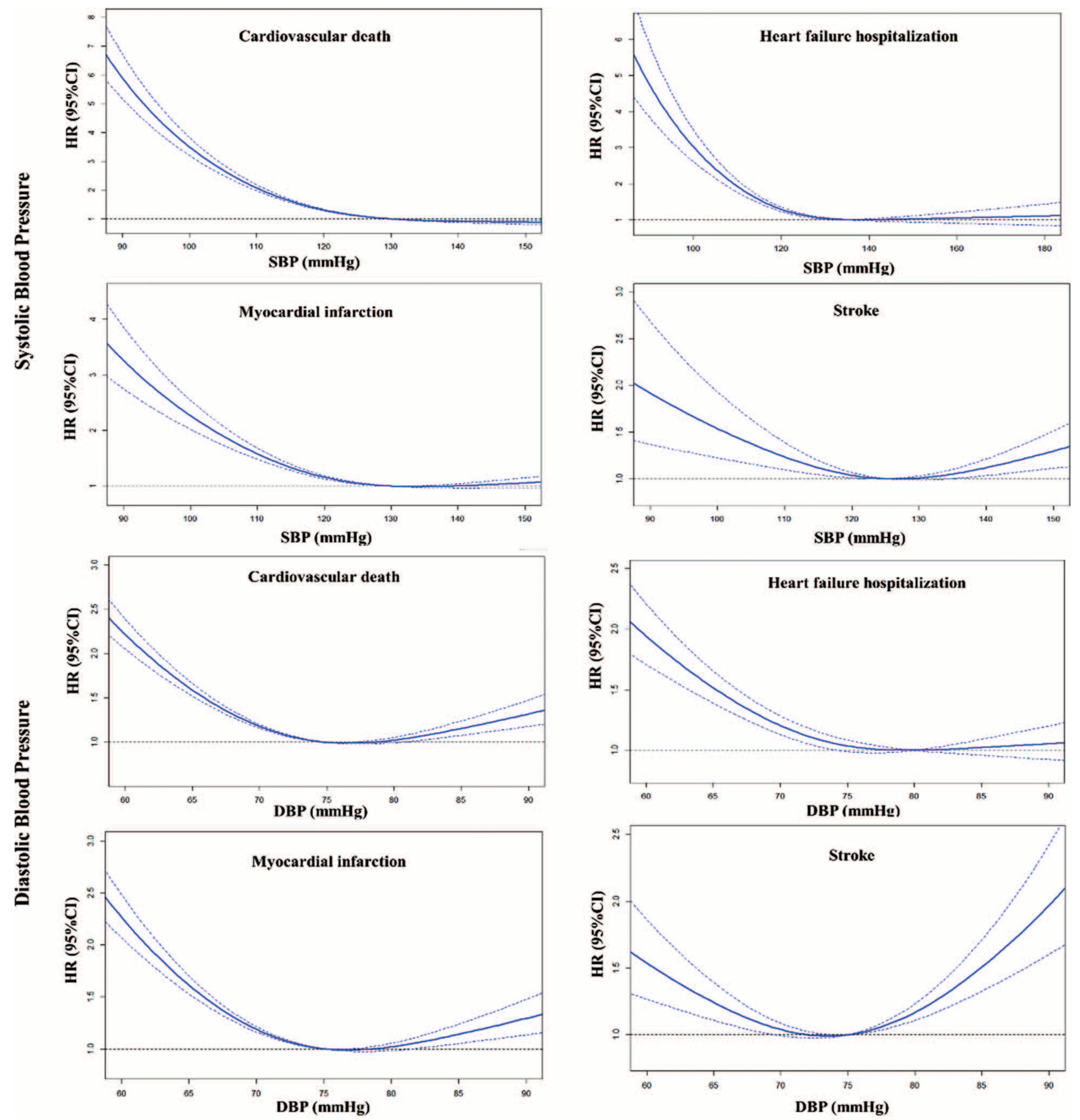

Figure 1 Adjusted associations between mean blood pressure and the studied outcomes. All models are adjusted for age, gender, body mass index, estimated glomerular filtration rate, smoking status, history of hypertension, diabetes, heart failure history, previous myocardial infarction, previous stroke, peripheral artery disease, atrial fibrillation, and heart rate. CI, confidence interval; DBP, diastolic blood pressure; HR, hazard ratio; SBP, systolic blood pressure.

stroke. Moreover, in SPRINT, stroke rates were not reduced by intensive BP lowering,[9] but it should be acknowledged that stroke was a component of the primary outcome (and not the primary outcome on which sample size calculations were based), hence this trial was also underpowered to assess the effect of intensive BP lowering on stroke. Our study population had more than 900 adjudicated stroke events (almost twice the total primary outcome events reported in SPRINT) and allows the study of the association between BP levels and stroke risk in an adequately powered fashion, and show that both higher and lower BP are associated with higher stroke rates, suggesting a J-shaped phenomenon in this population.

Table 3 Patient characteristics and blood pressure analysis according to the primary outcome event

	Alive ($n = 24\,371$)	CV death ($n = 4400$)	*P*-value
Age (years)	64.0 ± 11.3	70.3 ± 10.7	<0.0001
Female	6966 (28.6%)	1616 (36.7%)	<0.0001
Heart rate (b.p.m.)	75.2 ± 12.5	78.9 ± 13.8	<0.0001
Current smoker	8691 (35.7%)	1809 (41.2%)	<0.0001
Body mass index (kg/m^2)	27.6 ± 4.8	27.1 ± 4.9	<0.0001
eGFR (mL/min/1.73 m^2)	71.8 ± 38.0	61.4 ± 27.7	<0.0001
Myocardial infarction	5687 (23.3%)	1803 (41.0%)	<0.0001
Atrial fibrillation	2781 (11.4%)	973 (22.1%)	<0.0001
Heart failure	8809 (36.1%)	2372 (53.9%)	<0.0001
Peripheral artery disease	1790 (7.3%)	567 (12.9%)	<0.0001
Hypertension	12881 (52.9%)	2689 (61.1%)	<0.0001
Diabetes	5861 (24.0%)	1525 (34.7%)	<0.0001
Stroke	1689 (6.9%)	575 (13.1%)	<0.0001
Mean SBP (mmHg)	125.3 ± 14.6	121.4 ± 16.0	<0.0001
Mean DBP (mmHg)	74.6 ± 7.7	71.8 ± 9.4	<0.0001
Baseline SBP (mmHg)	120.8 ± 16.6	121.8 ± 17.6	0.0002
Baseline DBP (mmHg)	71.7 ± 10.7	71.6 ± 11.5	0.45
Last SBP (mmHg)	128.5 ± 19.7	120.5 ± 21.3	<0.0001
Last DBP (mmHg)	76.0 ± 10.9	71.7 ± 12.5	<0.0001
Number of SBP measures	9.8 ± 2.8	4.6 ± 2.7	<0.0001
Number of DBP measures	9.8 ± 2.8	4.6 ± 2.7	<0.0001
Follow-up (years)	2.1 ± 0.8	0.7 ± 0.6	<0.0001

CV, cardiovascular; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

The data presented herein are the first to describe the association of mean BP with several cardiovascular outcomes in a large population of MI patients with systolic dysfunction and/or HF. Importantly, these findings suggest that the association between low BP levels and worse cardiovascular outcomes may be driven by a reverse causation phenomenon (as also suggested from population-based studies[30]), hence caution is warranted when interpreting associations between BP and outcomes in observational data.

Limitations

Several limitations of this study should be acknowledged: (i) this is a post-hoc analysis of 'high-risk' acute MI trial populations in which hypertension history (although more than half of the patients were hypertensive) was not an entry criteria, hence the results presented herein cannot be extrapolated to other populations; (ii) the retrospective nature of these results makes them prone to confounding and causality cannot be presumed nor even suggested; (iii) despite extensive adjustment, many unmeasured variables could account for residual confounding bias; (iv) the lower BP values observed near the end of life, and the lower mean BP described in patients who died from cardiovascular causes suggest a reverse causation phenomenon as responsible for the associations of low BP with cardiovascular death; however, this phenomenon should be highlighted and data from randomized controlled trials should be preferred to observational associations; (v) patients with cardiovascular events also had a shorter follow-up, which may have contributed for reverse causation to have influenced the associations described in the present study; (vi) BP measurements were made at the office in trial visits and did not use standardized techniques across trial and centres; however, given the great number of patients and measures the occurrence of systematic error is unlikely; (vii) clinical variables and outcome events were ascertained in each trial by the study investigators and independent adjudication committees, respectively. Errors in clinical records and event adjudication might have occurred; however, these are also unlikely to be systematic and influence the associations presented herein in a systematic fashion; (viii) medication doses or changes during follow-up are not available in the dataset, therefore we cannot ascertain which patients had treatment intensification during the trial; (ix) biomarkers (e.g. N-terminal pro-B-type natriuretic peptide and troponins) could help in better stratifying patients' risk; however, biomarker data were not available in the dataset; (x) the datasets were transferred by the sponsors with no information on treatment allocation, hence the possible influence of the treatment allocation on BP and outcomes cannot be assessed in the present study.

Conclusions

The results of the present study in a selected population of MI patients with systolic dysfunction or HF, show that BP values <125/75 mmHg were associated with worse cardiovascular outcomes. Patients with a fatal event had fewer BP measurements and lower mean BP near the deadly event. Therefore, their mean BP was lower, suggesting that a reverse causation phenomenon accounts for the association of low BP and cardiovascular death in this setting.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Demographic and baseline characteristics of the patients, for the total population and for diastolic blood pressure quintiles.

Table S2. Crude and adjusted hazard ratios for quintiles of diastolic blood pressure.

Table S3. Adjusted hazard ratios for quintiles of systolic blood pressure in sensitivity analysis excluding patients with diabetes mellitus, history of stroke and estimated glomerular filtration rate < 45 mL/min/1.73 m^2.

Table S4. Adjusted hazard ratios for quintiles of systolic blood pressure with further adjustment on each study and oral anticoagulant use.

Table S5. Patient characteristics and blood pressure analysis according to heart failure hospitalization, myocardial infarction and stroke events.

Figure S1. Adjusted associations between mean blood pressure and all-cause death.

Figure S2. Adjusted associations between baseline blood pressure and the studied outcomes.
Figure S3. Adjusted associations between baseline blood pressure and all-cause death.
Figure S4. Associations between the last blood pressure measurement and the studied outcomes.
Figure S5. Associations between the last blood pressure measurement and all-cause death.

Acknowledgements

The authors acknowledge Pierre Pothier for the editing of the manuscript.

Conflict of interest: J.P.F. have received Board Membership fees from Novartis and speaker fees from Roche. P.R. has received Board Membership fees from CTMA, CVRx, Fesenius Medical Care, Novartis, Relypsa, Vifor Fresenius Medical Renal Pharma and Steathpeptides. F.Z. has received fees for serving on the board of Boston Scientific; consulting fees from Novartis, Takeda, AstraZeneca, Boehringer Ingelheim, GE Healthcare, Relypsa, Servier, Boston Scientific, Bayer, Johnson & Johnson, and Resmed; and speakers' fees from Pfizer and AstraZeneca. F.Z. and P.R. are CardioRenal co-founders. All other authors have no conflicts of interests to disclose.

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