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Myocardial reperfusion reverses the J-curve association of cardiovascular risk and diastolic blood pressure in patients with left ventricular dysfunction and heart failure after myocardial infarction
Insights from the EPHESUS trial

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AIMS: The described association of low diastolic blood pressure (DBP) with increased cardiovascular outcomes could be due to reduced coronary perfusion or is simply due to reverse causation. If DBP is physiologically relevant, coronary re-perfusion after myocardial infarction might influence DBP-risk association.

Methods and Results: The relation of achieved DBP with cardiovascular death or cardiovascular hospitalization, cardiovascular death and all-cause death was explored in 5929 patients after acute myocardial infarction with impaired left ventricular function, signs and symptoms of heart failure or diabetes in the EPHESUS trial according to their reperfusion status. Cox regression models were used to assess the impact of reperfusion status on the association of DBP and systolic BP (SBP) with outcomes in an adjusted fashion. In patients without reperfusion, lower DBP <70 mmHg was associated with increased risk for all-cause death (adjusted hazard ratios (HR) 1.80; 95% confidence interval (CI) 1.41-2.30, p<0.001), cardiovascular death (HR 1.70 95%-CI 1.3-3.22, p<0.001), cardiovascular death or cardiovascular hospitalization (HR 1.54 95%-CI 1.26-1.87, p<0.001). In patients with reperfusion, the risk increase at low DBP was not observed. At low SBP, risk increased independently of reperfusion. A sensitivity analysis in the subgroup of patients with optimal SBP of 120-130 mmHg showed again risk reduction of reperfusion at low DBP. Adding the treatment allocation to eplerenone or placebo into the models had no effects on the results.

Conclusion: Patients after acute myocardial infarctions with a low DBP had an increased risk, which was sensitive to reperfusion therapy. Low BP after MI identifies in patients with particular higher risk. These data support the hypothesis that low DBP in patients with stenotic coronary lesions is associated with risk, potentially involving coronary perfusion pressure and the recommendations provided by guidelines suggesting lower DBP boundaries for these high-risk patients.

Key words: Acute myocardial infarction – heart failure – systolic blood pressure - diastolic blood pressure – J-curve – blood pressure risk association – coronary perfusion

Clinical trial registration: not applicable

Introduction

Guidelines recommend a strict blood pressure (BP) control in patients with hypertension to reduce cardiovascular outcomes (1, 2). However, a J-shaped relationship between cardiovascular outcomes, in particular with low diastolic blood pressure (DBP), has been described in the Framingham population (3), in hypertension (4), coronary artery disease (5) and in patients with high cardiovascular risk after cardiovascular events or with peripheral arterial disease (6). The recent European guidelines have therefore introduced lower BP boundaries for systolic (SBP) and DBP target values of >120 mmHg and >70 mmHg, respectively (2). In heart failure, the J-shape curve converts into a U-shape curve with a particular high risk at lower SBP and DBP (7, 8), specifically when low BP accompanies high resting heart rates (9). While the increase of risk at low SBP or DBP has been often referred to an effect called “reverse causation”, which might associate with the progression of heart failure after myocardial infarction, increasing comorbidities and frailty (10), a low DBP could cause impaired myocardial perfusion (11) resulting in an enhanced risk associated with intensive DBP lowering (12). The presence of reverse causation is difficult to prove, as is the evidence that low DBP has an impact on cardiovascular outcomes, in particular in patients with stenotic coronary arteries, which are not re-vascularized, thereby, compromising myocardial perfusion. EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study, 13) randomized patients to eplerenone (25 mg od) or matching placebo after an acute myocardial infarction with impaired left ventricular ejection fraction of 40% or lower, diabetes, clinical heart failure (pulmonary rales, congestion on chest radiography) or the presence of a third heart sound. In EPHESUS, 45% of patients received re-perfusion, the remaining 55% of 6642 patients were not re-perfused. Herein, we report the association of mean achieved in-trial DBP with the key outcomes cardiovascular death or cardiovascular hospitalization, cardiovascular death and all-cause death in patients with or without reperfusion. The objective was to explore the hypothesis that reperfusion changes the risk-outcome association according to DBP.

Methods

Study Design and population

We report the outcome data of patients after AMI with clinical signs or symptoms of heart failure, impaired left ventricular ejection fraction or diabetes after acute myocardial infarction. Primary results of EPHESUS were published previously (13). Between December 27, 1999 and December 31, 2001, 6642 patients were either assigned to placebo (n=3313) or to eplerenone (n=3319). Patients were randomized 3-14 days after AMI documented by standard criteria, reduced left ventricular ejection fraction of 40% or lower, clinical signs of heart failure (pulmonary rales, signs of congestion or chest radiography, presence of a third heart sound) or diabetes. Patients received optimal medical therapy including ACE inhibition, angiotensin-receptor blockers, diuretics, beta-blockers, as well as coronary reperfusion, which was at the discretion of the treating physician. The two primary endpoints were time to death from any cause and time to death from cardiovascular causes or first hospitalization for a cardiovascular event**.** All patients gave written informed consent. The ethics committees at each individual site approved the protocol of the trial.

Procedures

Baseline procedures and screening were done during the hospitalization for the index AMI. Follow-up visits occurred at one and four weeks, three month and every three months thereafter until study termination. At each visit brachial SBP and DBP was measured in a sitting position after resting time of three minutes using an automated validated device (Omron model HEM-757, Omron, Kyoto, Japan) and the measurements were attended by the nurses or investigators. Patients had at least three SBP-BP measurements. BP was recorded at every visit using a standard sphygmomanometer with an appropriately sized cuff at the non-dominant arm in a sitting position after 5 minutes of rest. The mean number of BP measurements was 6.3 ± 1.8 and the median follow-up time

was 21 months. Patients were divided into subgroups on the basis of mean achieved in-trial seated clinic BP according to the following cut-offs: DBP ≤70 mmHg, 71-≤75 mmHg, 76-≤80 mmHg, >80 mmHg and SBP ≤110 mmHg, 111-≤120 mmHg, 121-≤140 mmHg and >140 mmHg.

Statistical analysis

Groups were tested for differences using ANOVA for continuous data and the Chi-square test for categorical data. Event rates per 100 patient/years and Kaplan Meier curves for all outcomes were analyzed by DBP categories. Cox regression models were performed to assess the associations between BP (both continuous and categorical) and the study outcomes. The BP-outcome associations were tested both in unadjusted/crude and adjusted fashion. Covariates for adjustment were: age, sex, body mass index, heart rate, left ventricular ejection fraction, estimated glomerular filtration rate, sodium, potassium, previous MI, peripheral vascular disease, previous heart failure, atrial fibrillation, diabetes, hypertension history, previous stroke, COPD, ACEi/ARB, beta-blocker, and loop diuretic use, Q-wave index MI, Killip class, reperfusion of index MI, and study drug (eplerenone or placebo). These covariates were selected based on their clinical relevance, prognostic association, and as used in previous reports. Prespecified interactions (based on the clinical hypothesis) between DBP and revascularization status plus the study drug were performed. Analyses of subgroups were conducted whenever a significant interaction was found. Cox proportional hazards assumptions were tested by plotting the Schoenfeld residuals vs. time without proportional hazards violation found. The associations between the various DBP and SBP measures and their changes expressed as continuous variables were also analyzed non-parametrically with restricted cubic splines that allowed exploration of non-linear relationships, using a piecewise model with 5 knots. All analyses were performed using STATA version 15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

Results

A population of 5929 patients was separated according to the mean achieved in-trial DBP groups. The clinical and demographic characteristics of the EPHESUS patients are shown in **Table 1** according to DBP and SBP. Patients with a lower DBP were older, more likely to be male, had a lower BMI and lower SBP values. Patients with lower BP had not less, but more revascularization procedures. Heart rates were not different between the groups. Furthermore, ejection fraction was slightly lower at low DBP.

Figure 1 shows the Kaplan Meier curves for cardiovascular death or cardiovascular hospitalization in patients with no reperfusion (**A**) and reperfusion (**B**). At DBP ≤70 mmHg, cardiovascular death and cardiovascular hospitalization was more incident in patients with no reperfusion than in patients with reperfusion. At higher DBP the curves were super-imposable for DBP ≥71 mmHg. **Figure 2** summarizes the adjusted Hazard ratios (HRs) of achieved DBP with no reperfusion (left) and reperfusion (right) for cardiovascular death or cardiovascular hospitalization (**Figure 2A**), cardiovascular death (**Figure 2B**) and all cause death (**Figure 2C**). Cardiovascular death or cardiovascular hospitalization and all cause death and in trend cardiovascular death risk occurred more frequently at lower DBP. In general, the event rates per 100 patient-years tended to be higher in patients with no reperfusion compared to patients after reperfusion. Eplerenone slightly reduced DBP by 0.8 mmHg (-1.2 - -0.3 mmHg ($p<0.001$) and SBP by 2.1 mmHg (-2.85 – -1.35 mmHg ($p<0.001$). **Table 2** summarizes the effects depicted in Figure 2 with the corresponding p-values. These data were adjusted for potential confounders. However, adding the BP effects of eplerenone to the model had no effect on the association of risk for SBP or DBP for all outcomes. Adding revascularization though had an impact on DBP association to the outcomes of cardiovascular death, cardiovascular hospitalization or all cause death, while, there was no effect of revascularization on the association of risk to SBP (Table 2). Cubic splines analyses for non-linear relationships or for mean DBP as continuous variable was done and related to the primary composite of cardiovascular death and

cardiovascular hospitalization (**Figure 3A**), cardiovascular death (**Figure 3B**), and all cause death (**Figure 3C**) in patients with no reperfusion (left) and reperfusion (right). In patients with no reperfusion, there was an increase of all outcomes at lower DBP approximately <70 mmHg. However, this increase was not observed in patients after reperfusion. In contrast, a J- or U-shaped curve was observed for achieved SBP in patients with no reperfusion and with reperfusion. As a sensitivity analysis, we evaluated the association of risk to DBP in patients with guideline-recommended SBP of 120-130 mmHg to prevent interference of SBP and low DBP on coronary blood flow. The results were similar to those in the total population with higher risk at low DBP in patients without compared with patients with reperfusion (Supplement Figure 2).

Discussion

Our study shows that patients after AMI with signs and symptoms of heart failure or with low ejection fraction (<40%) exhibited a particular higher risk at low DBP, when they were not re-perfused. In contrast, in patients with reperfusion compared to those without, elevated risk at low DBP was abolished. At low SBP, reperfusion status had no impact on outcomes. These findings extend previous observations that low DBP associates with increased risk (3-8) and is sensitive to reperfusion therapy after AMI.

Myocardial perfusion is critically dependent on DBP, as 85% of left ventricular perfusion occurs during diastole (14). Metabolic microvascular vasodilatation, referred to as coronary autoregulation, adjusts perfusion pressure in ischemia or increased workload conditions (15). However, it is unknown, whether outcomes are increased when DBP is low and filling pressures raise with a subsequent drop in effective myocardial perfusion pressure. Potentially due to ischemia or impaired left ventricular function, effective coronary perfusion pressure, which is the difference of DBP and left ventricular filling pressures, could impact outcomes (15). In healthy dogs, a perfusion pressure as low as 35 mmHg was observed to be sufficient to maintain perfusion of the heart, however, this

situation might change when coronary artery stenoses or microvascular diseases are present. These data from EPHESUS clearly show that myocardial reperfusion in patients after AMI with signs and symptoms of heart failure abolish the J-shape association. This indicates that indeed a low DBP of ≤70 mmHg might be deleterious in these patients. A cross sectional area reduction by 85-90% is associated with impaired resting blood flow (17). However, low DBP in these patients without coronary reperfusion and significant coronary stenoses might render the myocardium more sensitive to ischemia and adverse outcomes. Mechanistically, stiff vessels may reduce DBP by impairing the reservoir function (Windkessel) of the aorta. Therefore, a low DBP can be regarded as marker of aortic stiffness and pre-existing in vascular disease. This is supported by findings showing that patients with stiff arteries and presumably low DBP have a lower ischemic threshold than control individuals (18). In the PROVE-IT TIMI 22 trial (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction), the J-curve was particular pronounced in patients with coronary artery disease (19). Studies in hypertension are pointing to a similar direction. In the INVEST study (International Verapamil SR-Trandolapril Study) in patients with hypertension and coronary artery disease, the J-curve was prominent in patients without coronary artery revascularization compared to those with revascularization (11). While in INVEST patients with hypertension and with and without revascularization (mostly coronary bypass grafting) were investigated, we herein extended those findings to patients with acute coronary syndroms with heart failure. As in these patients filling pressures might have been high, the effect of revascularization might be of particular importance to maintain coronary perfusion pressure. In concert, low DBP in a population with excluded obstructive coronary artery disease showed no evidence for a J-curve of DBP-risk association (20). One might suggest that sicker patients with lower BP might have fewer revascularization procedures, because they are sicker. However, herein, revascularization was performed even more frequently at low than at higher BP. There was also no influence of no-diabetes

versus diabetes with potentially more diffuse vascular or microvascular disease here in EPHESUS.

However, the association of low SBP to increased outcomes was unaffected by reperfusion status in the present study. Reverse causation is always a potential explanation, which might be due to increased comorbidities and frailty in these patients. In EPHESUS (13), all patients had signs or symptoms of heart failure, a condition, in which the association of risk to low SBP is particularly expressed (7,8). In patients at low SBP, physicians are often reluctant to apply guideline-directed therapies, which improve outcomes, because treatments might further reduce BP. The magnitude of changes induced by eplerenone was actually modest and adding the treatment allocation to eplerenone or placebo into the models neither had effects on the results nor did it alter the beneficial effects of eplerenone on cardiovascular outcomes in patients revascularized and in those who were not (p value for interaction 0.62) as previously reported (13). An under-treatment in particular in patients at low SBP on follow-up could have contributed to the increased risk at low SBP (8). The treatment intensity for heart failure during follow-up could not be evaluated in this dataset. Therefore, an effect of reverse causation cannot be excluded completely and is likely involved in the low SBP-risk association. However, in patients at high cardiovascular risk, the increased risk at low SBP and DBP was not influenced by adjusting the risk to develop cardiovascular and non-cardiovascular morbidity (6). Thus, the role for potential confounders leading to reverse causation could not be proven (6). However, the data herein clearly show that low DBP associated with increased risk, which is affected by reperfusion in patients with AMI with signs or symptoms of heart failure.

Limitations

This study has some limitations and strengths. This analysis shows a reversal of increased risk at low DBP, which is sensitive to reperfusion therapies. This association is

often referred uncritically to as reverse causation without direct proofs. In contrast, reverse causation could be present and cannot be ruled out in the J- or U-shape association of risk to SBP. Since this is a retrospective observational analysis of a controlled randomized trial dataset, patients' allocations to DBP or SBP groups are not subject to randomization. As this can create a source of confounding and bias, this analysis is hypothesis-generating by nature. Nevertheless, the large number of patients and the rigorous follow-up suggest that these data are highly solid and clinically relevant. Reperfusion strategies were left at physicians' discretions and were not further specified. It is therefore impossible to investigate outcomes according to choice of reperfusion or success of the selected approaches.

Conclusions

In conclusion, patients with a low DBP had an increased risk at DBP <70 mmHg, which was sensitive to reperfusion therapy after AMI with signs and symptoms of heart failure. The results of this analysis identifies patients at high risk, which need to be managed with special attention when DBP is low and when the presence of remaining coronary artery stenoses after an acute coronary syndrome is high, potentially accounting for inappropriate myocardial perfusion pressure (see Take Home Figure). These data support current guidelines suggesting lower DBP boundaries for high-risk patients as well as guideline-directed revascularization (21).

Supplementary material is available at European Heart Journal online.

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Legends to Figures

Figure 1

Kaplan-Meier estimates for cardiovascular death or cardiovascular hospitalization in patients with (left) or with no reperfusion (right) after myocardial infarction with signs or symptoms of heart failure separated by achieved diastolic blood pressure (DBP). Patients were divided into subgroups on the basis of mean achieved.

Figure 2

Hazard ratios (HR) and event rates per 100 patient years (PY) for cardiovascular death or cardiovascular hospitalization (A), cardiovascular death (B) and all cause death (C) according to achieved diastolic blood pressure (DBP). HR (Cox regression) were adjusted for

age, sex, body mass index, heart rate, left ventricular ejection fraction, estimated glomerular filtration rate, sodium, potassium previous myocardial infarction, peripheral artery disease, previous heart failure, atrial fibrillation, diabetes, hypertension history, previous stroke, chronic obstructive pulmonary disease, treatment with beta blockers, ACE-inhibitors or angiotensin-receptor blockers, loop-diuretics, Q-wave index myocardial infarction, Killip class, reperfusion of index MI and study drug (eplerenone or placebo).

Figure 3

Hazard ratios (HR) according to mean achieved diastolic blood pressure (DBP) for cardiovascular death or cardiovascular hospitalization (A), cardiovascular death (B) and all cause death (C). HR were adjusted for the same variables as described in Figure 2.

Figure 4

Hazard ratios (HR) according to mean achieved systolic blood pressure (SBP) for cardiovascular death or cardiovascular hospitalization (A), cardiovascular death (B) and all cause death (C). HR were adjusted for the same variables as described in Figure 2.

Supplement Figure 1

Hazard ratios (HR) according to mean achieved systolic blood pressure (SBP) for cardiovascular death or cardiovascular hospitalization (A), cardiovascular death (B) and all cause death (C). HR were adjusted for the same variables as described in Figure 2.

Supplement Figure 2

Hazard ratios (HR) according to mean achieved diastolic blood pressure (DBP) for cardiovascular death or cardiovascular hospitalization (A), cardiovascular death (B) and all cause death (C) in a subgroup of patients with recommended SBP of 120-130 mmHg. HR were adjusted for the same variables as described in Figure 2.

Table 1

	Diastolic blood pressure (DBP) groups				
	≤ 70	71 – ≤ 75	76 – ≤ 80	> 80	p-value
N. (Total =5929)	1464	1291	1557	1617	-
Age (years)	65.3 ± 12.2	63.1 ± 11.8	63.0 ± 11.2	62.8 ± 10.6	<0.001
Male sex	1053 (71.9%)	963 (74.6%)	1118 (71.8%)	1100 (68.0%)	0.001
BMI (Kg/m2)	26.7 ± 4.5	26.9 ± 4.3	27.6 ± 4.4	28.5 ± 4.7	<0.001
Baseline SBP (mmHg)	111.8 ± 14.9	115.4 ± 14.4	120.6 ± 15.2	127.6 ± 16.4	<0.001
Baseline DBP (mmHg)	65.6 ± 9.4	70.2 ± 9.4	73.9 ± 9.3	78.1 ± 9.9	<0.001
Heart rate (bpm)	74.6 ± 12.4	74.3 ± 11.3	74.2 ± 11.4	74.2 ± 11.1	0.80
LVEF (%)	31.5 ± 6.7	33.1 ± 5.9	34.0 ± 5.7	34.4 ± 5.1	<0.001
Killip III/IV	313 (21.7%)	214 (16.7%)	291 (18.7%)	284 (17.6%)	0.005
eGFR (ml/min/1.73m2)	68.3 ± 24.5	70.9 ± 22.2	69.2 ± 21.5	69.0 ± 21.4	0.028
Sodium (mmol/L)	138.3 ± 3.9	139.3 ± 4.8	139.9 ± 4.2	140.5 ± 4.2	<0.001
Potassium (mmol/L)	4.2 ± 0.5	4.3 ± 0.4	4.3 ± 0.4	4.3 ± 0.4	0.015
Previous MI	469 (32.0%)	339 (26.3%)	372 (23.9%)	390 (24.1%)	<0.001
History of heart failure	269 (18.4%)	145 (11.2%)	174 (11.2%)	255 (15.8%)	<0.001
Atrial fibrillation	211 (14.4%)	138 (10.7%)	179 (11.5%)	209 (12.9%)	0.015
Peripheral vascular disease	203 (13.9%)	134 (10.4%)	182 (11.7%)	188 (11.6%)	0.038
History of hypertension	663 (45.3%)	663 (51.4%)	1002 (64.4%)	1258 (77.8%)	<0.001
Diabetes	504 (34.4%)	402 (31.1%)	478 (30.7%)	501 (31.0%)	0.099
Prior stroke	130 (8.9%)	100 (7.7%)	120 (7.7%)	156 (9.6%)	0.16
COPD	176 (12.4%)	105 (8.3%)	125 (8.1%)	122 (7.6%)	<0.001
Hemoglobin (g/dL)	13.0 ± 1.8	13.3 ± 1.7	13.5 ± 1.7	13.5 ± 1.6	<0.001
ACEi/ARB	1257 (85.9%)	1018 (78.9%)	1232 (79.1%)	1328 (82.1%)	<0.001
Beta-blocker	1029 (70.3%)	919 (71.2%)	1110 (71.3%)	1135 (70.2%)	0.86
Loop diuretic	871 (61.6%)	673 (53.3%)	748 (48.6%)	825 (51.7%)	<0.001
Anti-platelet	545 (38.5%)	407 (32.2%)	400 (26.0%)	357 (22.4%)	<0.001
Index Q-wave acute MI	953 (67.4%)	952 (74.9%)	1161 (75.2%)	1168 (73.1%)	<0.001
Reperfusion therapy/revascularization	755 (51.6%)	665 (51.5%)	694 (44.6%)	649 (40.1%)	<0.001
N. DBP measurements to death or censoring	6.9±2.2	7.4±2.1	7.4±2.0	7.6±2.1	<0.001
N. DBP measurements to CV hosp. or death or censoring	5.9±2.8	6.8±2.5	6.9±2.5	6.8±2.8	<0.001

Table 1 (continued)

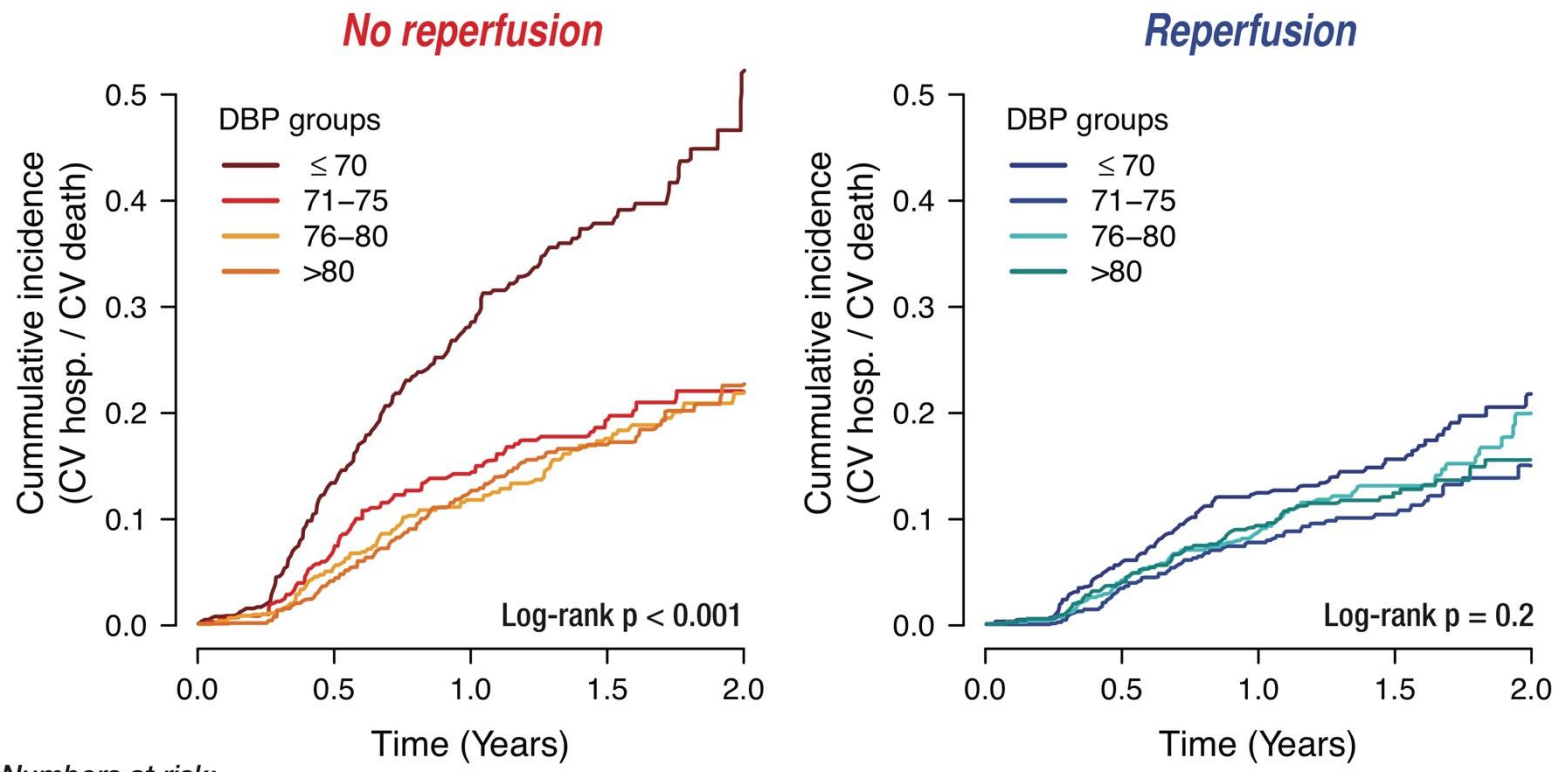
	Systolic blood pressure (SBP) groups				
	≤ 110	111 – ≤ 120	121 – ≤ 140	> 140	p-value
N. (Total =5929)	909	1399	2768	853	-
Age (years)	59.8 ± 12.3	61.3 ± 12.0	64.5 ± 10.8	67.9 ± 9.5	<0.001
Male sex	704 (77.4%)	1108 (79.2%)	1968 (71.1%)	454 (53.2%)	<0.001
BMI (Kg/m2)	26.6 ± 4.2	27.0 ± 4.5	27.7 ± 4.5	28.2 ± 5.0	<0.001
Baseline SBP (mmHg)	106.6 ± 11.9	113.0 ± 12.7	121.9 ± 14.6	134.0 ± 17.2	<0.001
Baseline DBP (mmHg)	66.1 ± 9.3	69.7 ± 9.6	73.8 ± 10.1	77.6 ± 10.9	<0.001
Heart rate (bpm)	76.6 ± 12.7	74.7 ± 11.7	73.8 ± 11.1	73.1 ± 11.2	<0.001
LVEF (%)	30.9 ± 6.8	33.0 ± 6.2	34.0 ± 5.5	34.0 ± 5.4	<0.001
Killip III/IV	192 (21.4%)	237 (17.0%)	498 (18.1%)	175 (20.6%)	0.023
eGFR (ml/min/1.73m2)	73.7 ± 25.8	72.7 ± 21.1	68.2 ± 21.5	62.6 ± 21.4	<0.001
Sodium (mmol/L)	138.5 ± 3.9	139.1 ± 4.0	139.9 ± 4.6	140.2 ± 4.2	<0.001
Potassium (mmol/L)	4.2 ± 0.5	4.2 ± 0.4	4.3 ± 0.4	4.3 ± 0.5	<0.001
Previous MI	259 (28.5%)	388 (27.7%)	711 (25.7%)	212 (24.9%)	0.17
History of heart failure	119 (13.1%)	187 (13.4%)	381 (13.8%)	156 (18.3%)	0.003
Atrial fibrillation	98 (10.8%)	174 (12.4%)	347 (12.5%)	118 (13.8%)	0.28
Peripheral vascular disease	75 (8.3%)	136 (9.7%)	353 (12.8%)	143 (16.8%)	<0.001
History of hypertension	327 (36.0%)	650 (46.5%)	1879 (67.9%)	730 (85.6%)	<0.001
Diabetes	226 (24.9%)	381 (27.2%)	933 (33.7%)	345 (40.4%)	<0.001
Prior stroke	52 (5.7%)	114 (8.1%)	229 (8.3%)	111 (13.0%)	<0.001
COPD	90 (10.2%)	121 (8.9%)	247 (9.1%)	70 (8.4%)	0.59
Hemoglobin (g/dL)	13.2 ± 1.9	13.4 ± 1.7	13.4 ± 1.7	13.2 ± 1.7	0.001
ACEi/ARB	760 (83.6%)	1115 (79.7%)	2233 (80.7%)	727 (85.2%)	0.002
Beta-blocker	644 (70.8%)	1011 (72.3%)	1971 (71.2%)	567 (66.5%)	0.024
Loop diuretic	518 (58.6%)	722 (52.9%)	1388 (50.9%)	489 (58.4%)	<0.001
Anti-platelet	385 (43.6%)	471 (34.5%)	684 (25.1%)	169 (20.2%)	<0.001
Index Q-wave acute MI	696 (78.5%)	1037 (75.5%)	1955 (71.7%)	546 (65.3%)	<0.001
Reperfusion therapy/revascularization	537 (59.1%)	741 (53.0%)	1197 (43.2%)	288 (33.8%)	<0.001
N. DBP measurements to death or censoring	6.8±2.1	7.2±2.1	7.5±2.1	7.6±2.1	<0.001
N. DBP measurements to CV hosp. or death or censoring	5.6±2.8	6.6±2.5	7.0±2.5	6.4±2.1	<0.001

Table 2

Outcome/BP cat.	HR (95%CI)	p-value	Epl*BP	Revasc.*BP
All-cause death				
SBP (mmHg)				
≤ 110	2.51 (1.98-3.17)	<0.001	0.22	0.77
111 - ≤ 120	1.32 (1.05-1.66)	0.017		
121 - ≤ 140	Ref.	-		
> 140	0.64 (0.48-0.86)	0.003		
DBP (mmHg)				
≤ 70	1.80 (1.41-2.30)	<0.001	0.10	0.009*
71 - ≤ 75	1.11 (0.85-1.45)	0.45		
76 - ≤ 80	Ref.	-		
> 80	0.84 (0.65-1.10)	0.21		
CV death				
SBP (mmHg)				
≤ 110	2.44 (1.88-3.16)	<0.001	0.57	0.30
111 - ≤ 120	1.36 (1.05-1.74)	0.018		
121 - ≤ 140	Ref.	-		
> 140	0.70 (0.51-0.95)	0.023		
DBP (mmHg)				
≤ 70	1.70 (1.30-2.22)	<0.001	0.23	0.015*
71 - ≤ 75	1.10 (0.82-1.48)	0.54		
76 - ≤ 80	Ref.	-		
> 80	0.91 (0.68-1.21)	0.51		
CV death / CV hosp.				
SBP (mmHg)				
≤ 110	2.05 (1.66-2.53)	<0.001	0.18	0.20
111 - ≤ 120	1.41 (1.17-1.69)	<0.001		
121 - ≤ 140	Ref.	-		
> 140	0.99 (0.80-1.20)	0.86		
DBP (mmHg)				
≤ 70	1.54 (1.26-1.87)	<0.001	0.20	0.002*
71 - ≤ 75	0.99 (0.79-1.23)	0.91		
76 - ≤ 80	Ref.	-		
> 80	0.93 (0.77-1.14)	0.51		

Legend: SBP, systolic blood pressure; DBP, diastolic blood pressure; Epl, eplerenone (or placebo); Revasc., index event revascularization (yes or no).
Models adjusted on: age, sex, BMI, heart rate, LVEF, eGFR, sodium, potassium, previous MI, peripheral vascular disease, previous heart failure, AF, diabetes, hypertension history, previous stroke, COPD, ACEi/ARB, beta-blocker, loop diuretic, Q-wave index MI, Killip class, Reperfusion of index MI, and study drug (eplerenone or placebo).
*See Table 4 and Figure 1 for subgroup analyses.
Note: Only patients with 3 or more BP measurements during the follow-up were considered.

Figure 1



Numbers at risk:

≤ 70	594	511	374	177	–	671	629	509	253	–
71-75	551	509	375	183	–	605	582	494	267	–
76-80	795	750	586	284	–	640	613	505	255	–
>80	913	872	684	354	–	597	572	473	282	–

Figure 2

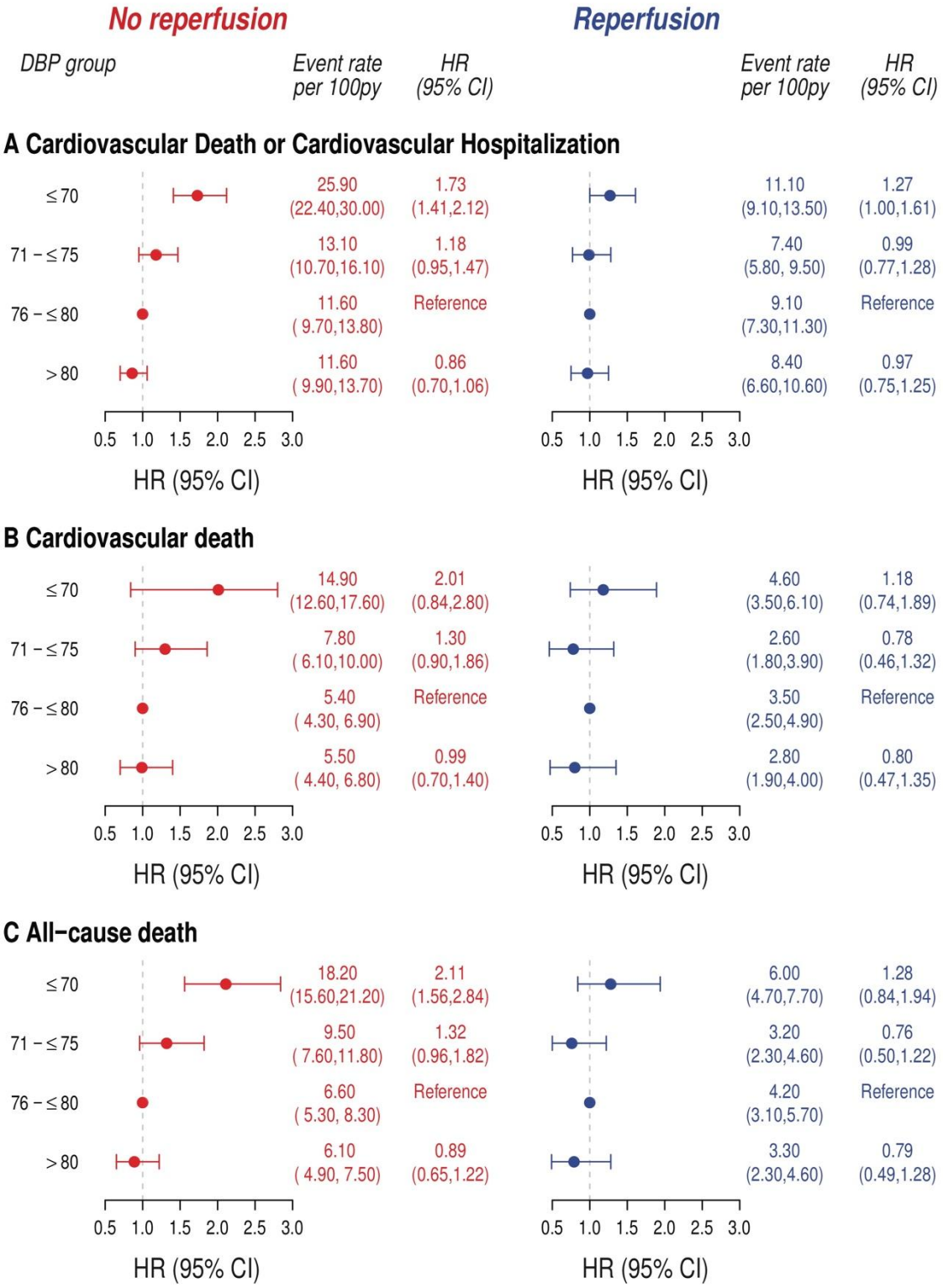

No reperfusion
Reperfusion
DBP group
Event rate per 100py
HR (95% CI)
Event rate per 100py
HR (95% CI)
A Cardiovascular Death or Cardiovascular Hospitalization
≤70
25.90 (22.40,30.00)
1.73 (1.41,2.12)
11.10 (9.10,13.50)
1.27 (1.00,1.61)
71 – ≤75
13.10 (10.70,16.10)
1.18 (0.95,1.47)
7.40 (5.80, 9.50)
0.99 (0.77,1.28)
76 – ≤80
11.60 (9.70,13.80)
Reference
9.10 (7.30,11.30)
Reference
>80
11.60 (9.90,13.70)
0.86 (0.70,1.06)
8.40 (6.60,10.60)
0.97 (0.75,1.25)
0.5 1.0 1.5 2.0 2.5 3.0
HR (95% CI)
B Cardiovascular death
≤70
14.90 (12.60,17.60)
2.01 (0.84,2.80)
4.60 (3.50,6.10)
1.18 (0.74,1.89)
71 – ≤75
7.80 (6.10,10.00)
1.30 (0.90,1.86)
2.60 (1.80,3.90)
0.78 (0.46,1.32)
76 – ≤80
5.40 (4.30, 6.90)
Reference
3.50 (2.50,4.90)
Reference
>80
5.50 (4.40, 6.80)
0.99 (0.70,1.40)
2.80 (1.90,4.00)
0.80 (0.47,1.35)
0.5 1.0 1.5 2.0 2.5 3.0
HR (95% CI)
C All-cause death
≤70
18.20 (15.60,21.20)
2.11 (1.56,2.84)
6.00 (4.70,7.70)
1.28 (0.84,1.94)
71 – ≤75
9.50 (7.60,11.80)
1.32 (0.96,1.82)
3.20 (2.30,4.60)
0.76 (0.50,1.22)
76 – ≤80
6.60 (5.30, 8.30)
Reference
4.20 (3.10,5.70)
Reference
>80
6.10 (4.90, 7.50)
0.89 (0.65,1.22)
3.30 (2.30,4.60)
0.79 (0.49,1.28)
0.5 1.0 1.5 2.0 2.5 3.0
HR (95% CI)

Figure 3

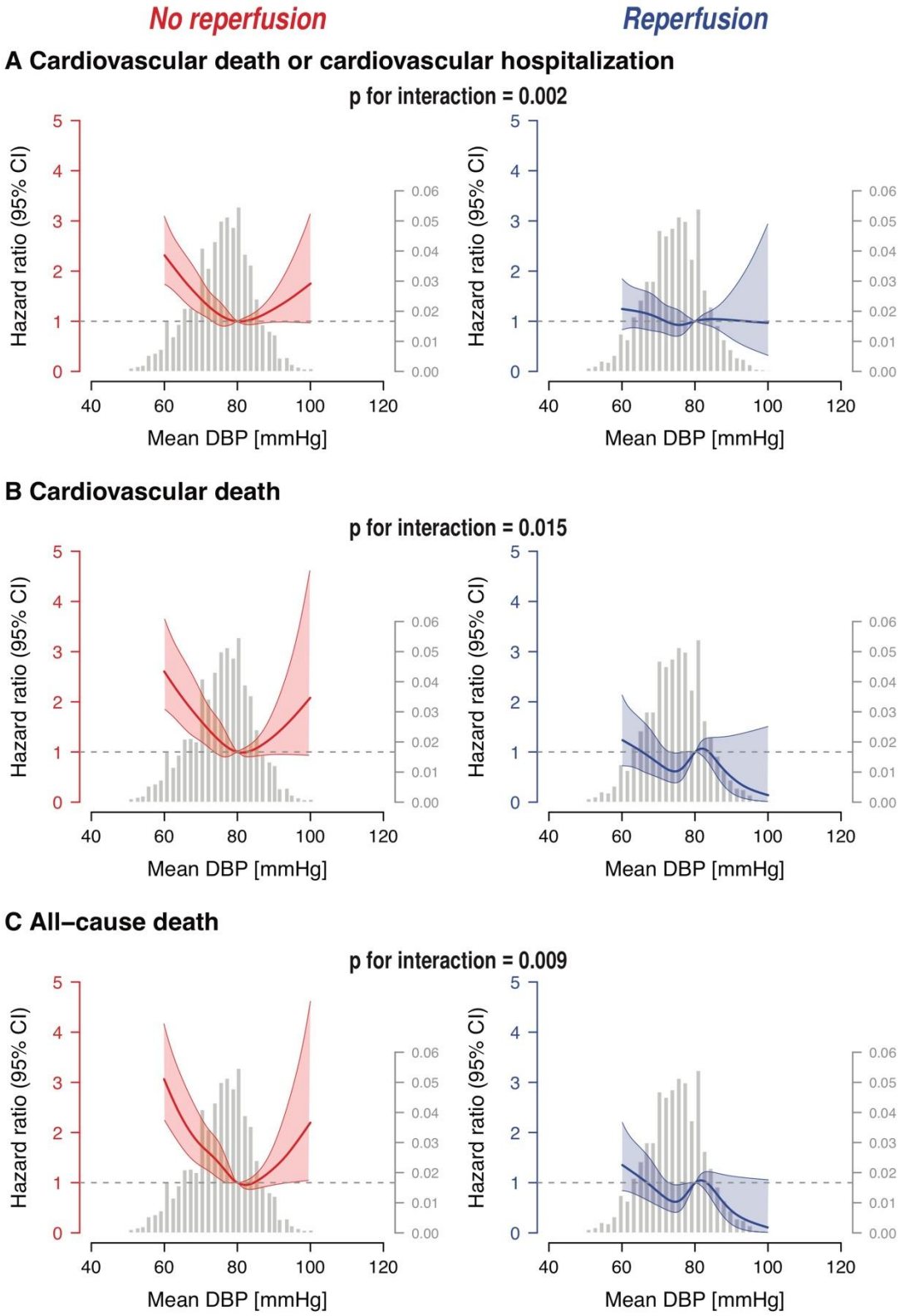
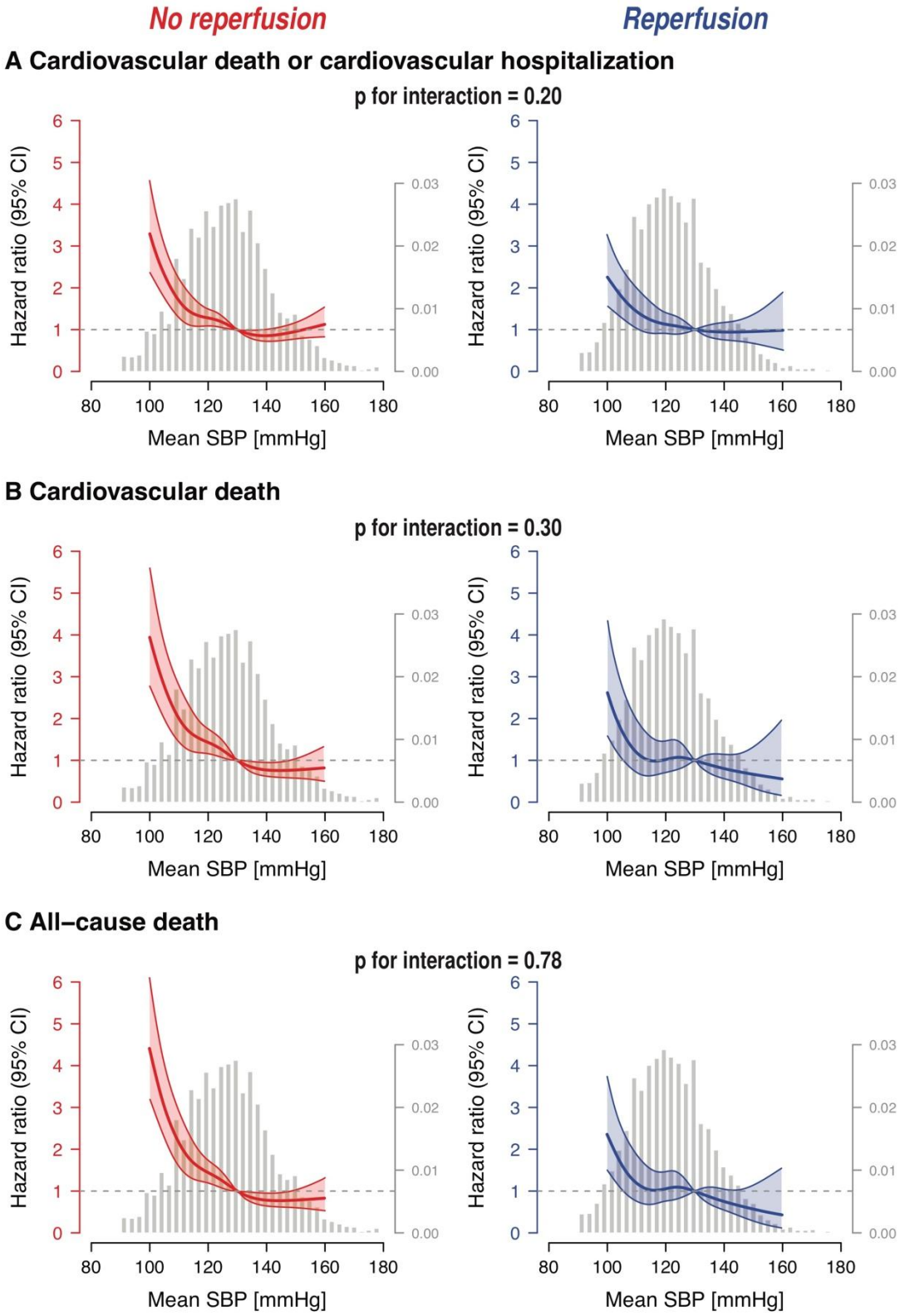
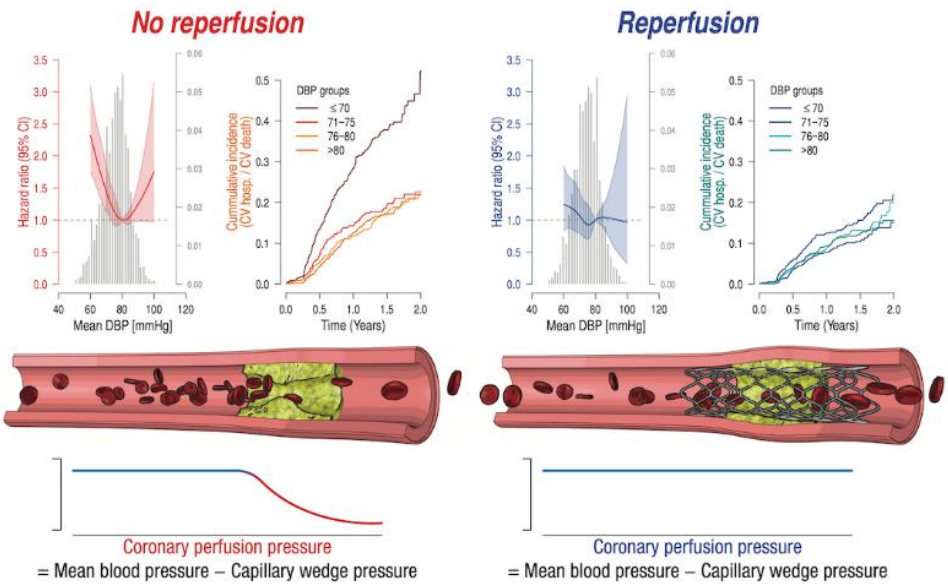

No reperfusion
Reperfusion
A Cardiovascular death or cardiovascular hospitalization
p for interaction = 0.002
Hazard ratio (95% CI)
Mean DBP [mmHg]
B Cardiovascular death
p for interaction = 0.015
Hazard ratio (95% CI)
Mean DBP [mmHg]
C All–cause death
p for interaction = 0.009
Hazard ratio (95% CI)
Mean DBP [mmHg]

Figure 4


No reperfusion
Reperfusion
A Cardiovascular death or cardiovascular hospitalization
p for interaction = 0.20
Hazard ratio (95% CI)
Mean SBP [mmHg]
B Cardiovascular death
p for interaction = 0.30
Hazard ratio (95% CI)
Mean SBP [mmHg]
C All–cause death
p for interaction = 0.78
Hazard ratio (95% CI)
Mean SBP [mmHg]

Take Home Figure



Legend: Reperfusion eliminates risk at low diastolic blood pressure (DBP) by maintaining perfusion pressure