

J-curve revisited: an analysis of blood pressure and cardiovascular events in the Treating to New Targets (TNT) Trial[†]

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Aim

In patients with coronary artery disease (CAD), a J-curve relationship has been reported between blood pressure (BP) and future cardiovascular events. However, this is controversial. The purpose of the study was to determine the relationship between on-treatment BP and cardiovascular outcomes in patients with CAD.

Methods and results

We evaluated 10 001 patients with CAD and a low-density lipoprotein (LDL) cholesterol level <130 mg/dL, randomized to atorvastatin 80 vs. 10 mg, enrolled in the TNT trial. The post-baseline, time-dependent BPs [systolic blood pressure (SBP) and diastolic blood pressure (DBP)] were categorized into 10 mmHg increments. The primary outcome was a composite of death from coronary disease, non-fatal myocardial infarction (MI), resuscitated cardiac arrest, and fatal or non-fatal stroke. Among the 10 001 patients, 982 (9.82%) experienced a primary outcome at 4.9 years (median) of follow-up. The relationship between SBP or DBP and primary outcome followed a J-curve with increased event rates above and below the reference BP range, both unadjusted and adjusted (for baseline covariates, treatment effect, and LDL levels). A time-dependent, non-linear, multivariate Cox proportional hazard model identified a nadir of 146.3/81.4 mmHg where the event rate was lowest. A similar non-linear relationship with a higher risk of events at lower pressures was found for most of the secondary outcomes of all-cause mortality, cardiovascular mortality, non-fatal MI, or angina. However, for the outcome of stroke, lower was better for SBP.

Conclusion

In patients with CAD, a low BP (<110–120/<60–70 mmHg) portends an increased risk of future cardiovascular events (except stroke).

Keywords

Blood pressure • J-Curve • TNT trial

Introduction

The seventh report of the Joint National Committee (JNC-7) on prevention, detection, evaluation, and treatment of high blood pressure (BP) states that 'The relationship between BP and risk of cardiovascular events is *continuous*, consistent, and independent of other risk factors'.¹ Data from the observational studies in adults with no previous vascular disease have indicated that death from

both ischaemic heart disease and stroke increases progressively and *linearly* with BP.² Such a linear relationship might be true in the general population (although not in the elderly). However, in patients with cardiovascular disease and specifically in those with coronary artery disease (CAD), the relationship between BP and cardiovascular outcomes follows a bimodal distribution resulting in a 'J'- or a 'U'-shaped curve with higher event rates at low and very high BP.^{3–10}

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The observation of a J-curve has led to some hotly debated issues and is controversial. The JNC-7 thus states that 'There is no definitive evidence of an increased risk of aggressive treatment (J-curve) unless the diastolic blood pressure (DBP) is lowered to <55 or 60 mmHg by treatment'.¹

We thus sought to examine the relationship between BP variables and the risk of cardiovascular events in patients enrolled in the Treating to New Targets (TNT) trial.

Methods

Patient population

The design and the main results of the TNT study have been described in detail previously.^{11,12} Briefly, this was a double-blind, parallel group study in patients 35–75 years of age who had clinically evident CAD, defined by one or more of the following: previous myocardial infarction (MI), previous or current angina with objective evidence of atherosclerotic CAD, or a history of coronary revascularization, with a low-density lipoprotein (LDL) <130 mg/dL who were randomized to atorvastatin 80 vs. 10 mg.

Follow-up

Patients were followed up at Week 12 and at Months 6, 9, and 12 during the first year and then every 6 months thereafter. At each visit, vital signs, clinical endpoints, adverse events, and concurrent medication information were collected. In addition, on alternating visits (i.e. annually), physical examinations and electrocardiograms were performed, and laboratory specimens were collected.

Study outcomes

The primary outcome for this analysis was the occurrence of a major cardiovascular event, defined as death from coronary heart disease (CHD), non-fatal, non-procedure-related MI, resuscitation after cardiac arrest, or fatal or non-fatal stroke at the end of follow-up. Secondary outcomes were all-cause mortality, death from CHD, non-fatal MI, stroke, and angina considered individually.

Statistical analyses

Average BP measurements [systolic blood pressure (SBP) or DBP] were plotted against time. Baseline characteristics were compared among the average post-baseline, prior to the occurrence of the primary composite event, BP categories (in 10 mmHg interval, ≤110 to >160 mmHg for SBP, and ≤60 to >100 mmHg for DBP) using one-way analysis of variance model for continuous variables and χ^2 statistics for categorical variables.

The relationship between cardiovascular events and post-baseline BP was assessed by a time-dependent, non-linear, Cox proportional hazard (PH) model¹³ in which linear and quadratic terms of post-baseline BP measurements were included in the model as the major time-dependent predictor variables (i.e. taking account of varying BP between subsequent visits) in univariate analysis, and adjusting for the following variables in the multivariate analysis: age, gender, smoking, baseline body mass index, hypertension, or use of anti-hypertensive medications, diabetes or use of anti-diabetic medications, coronary artery bypass graft surgery, coronary angioplasty, angina pectoris, cerebrovascular disease, peripheral arterial disease, heart failure, arrhythmia, treatment effect, and average post-baseline LDL levels. All of the time-dependent, Cox PH analyses were performed using time intervals at 3 months and at each annual post-baseline visit thereafter (from Years 1 to 5). Based on the unadjusted or adjusted Cox PH model, the nadir BP was

calculated using the delta method, as the coefficient of the linear term divided by $-2 \times$ coefficient of the quadratic term.

In addition, the time-dependent, post-baseline BPs were categorized into 10 mmHg increment from ≤110 to >160 mmHg for SBP and ≤60 to >100 for DBP and analysed accordingly to the Cox PH model. The unadjusted and adjusted hazard ratios for each category of BP were calculated in reference to the SBP group >130 to ≤140 mmHg or DBP group of >70 to ≤80 mmHg (pre-defined cut points) where the hazard ratio was considered as 1.

All of the above analyses were performed for the entire cohort and for the two-treatment groups separately, in accordance with the intention to treat principle.

Interaction analyses were also performed based on the similar model described above for the covariates: age (>65 vs. ≤65 years), gender, diabetes, hypertension, heart failure, prior MI, prior angioplasty, and prior coronary artery bypass graft surgery. The significance of the interactions between the J-shaped curve (linear and quadratic BP measurements) and each of the above covariates were assessed by likelihood ratio test comparing a full, time-dependent, non-linear, Cox PH model (unadjusted or adjusted) including the covariate of interest (as dichotomous dummy variable), time-dependent BP linear and quadratic terms, and the two corresponding interaction terms [i.e. covariate \times (BP linear) and covariate \times (BP squared)] vs. a reduced Cox PH model excluding the two aforementioned interaction terms. The *P*-values were reported accordingly based on the likelihood ratio test. To account for multiple testing, the significant level for the interaction tests was reduced to 0.007 (i.e. 0.05 divided by a total of pre-specified seven subgroup analyses).

For exploratory purposes, the unadjusted and adjusted relationships between BP and studied cardiovascular events were also

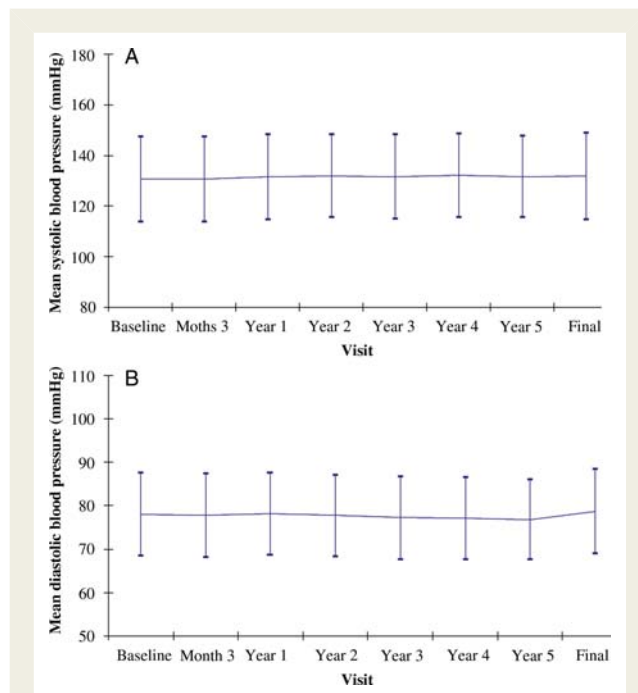


Figure 1 Baseline and post-baseline measurements over time. (A) Mean systolic blood pressure \pm 1 standard deviation at baseline and post-baseline visits at Month 3 and at annual visits thereafter from Years 1 to 5. (B) Mean diastolic blood pressure \pm 1 standard deviation at baseline and post-baseline visits at Month 3 and at annual visits thereafter from Years 1 to 5.

Table 1 Demographic and baseline characteristics of the intention to treat cohort by average on-treatment systolic blood pressure categories

Parameters	Average systolic blood pressure categories							P- value*
	≤110 mmHg (n = 396)	>110 to ≤120 mmHg (n = 1492)	>120 to ≤130 mmHg (n = 2811)	>130 to ≤140 mmHg (n = 2927)	>140 to ≤150 mmHg (n = 1616)	>150 to ≤160 mmHg (n = 551)	>160 mmHg (n = 208)	
Age, years, mean (SD)	57.3 (9.0)	57.8 (9.1)	59.7 (8.9)	61.8 (8.5)	63.7 (7.8)	65.4 (6.9)	65.5 (7.3)	<0.0001
Men, n (%)	346 (87.4)	1257 (84.2)	2365 (84.1)	2326 (79.5)	1268 (78.5)	393 (71.3)	144 (69.2)	<0.0001
White, n (%)	376 (94.9)	1416 (94.9)	2659 (94.6)	2750 (93.9)	1496 (92.6)	519 (94.2)	194 (93.3)	0.1005
Body mass index, kg/m ² , mean (SD)	26.9 (4.0)	27.9 (4.2)	28.4 (4.5)	28.9 (4.7)	28.9 (4.7)	28.8 (4.3)	29.4 (5.4)	<0.0001
Never smoked, n (%)	66 (16.7)	310 (20.8)	644 (22.9)	696 (23.8)	421 (26.1)	145 (26.3)	56 (26.9)	0.0002
Known hypertensives, n (%)	105 (26.5)	509 (34.1)	1257 (44.7)	1766 (60.3)	1175 (72.8)	422 (76.6)	178 (85.6)	<0.0001
Diabetes, n (%)	45 (11.4)	158 (10.6)	337 (12.0)	476 (16.3)	312 (19.3)	113 (20.5)	60 (28.8)	<0.0001
Myocardial infarction, n (%)	291 (73.5)	1022 (68.5)	1676 (59.6)	1622 (55.4)	848 (52.5)	263 (47.7)	111 (53.4)	<0.0001
Coronary artery bypass graft surgery, n (%)	160 (40.4)	628 (42.1)	1260 (44.8)	1369 (46.8)	814 (50.4)	321 (58.3)	102 (49.0)	<0.0001
Angioplasty, n (%)	224 (56.6)	869 (58.2)	1599 (56.9)	1562 (53.4)	812 (50.2)	240 (43.6)	101 (48.6)	<0.0001
Angina pectoris, n (%)	328 (82.8)	1189 (79.7)	2290 (81.5)	2398 (81.9)	1311 (81.1)	462 (83.8)	172 (82.7)	0.3786
Peripheral vascular disease, n (%)	29 (7.3)	127 (8.5)	278 (9.9)	362 (12.4)	232 (14.4)	103 (18.7)	42 (20.2)	<0.0001
Congestive heart failure, n (%)	59 (14.9)	137 (9.2)	205 (7.3)	191 (6.5)	120 (7.4)	46 (8.3)	23 (11.1)	<0.0001
Arrhythmia, n (%)	70 (17.7)	260 (17.4)	511 (18.2)	552 (18.9)	306 (18.9)	106 (19.2)	29 (13.9)	0.5581
LDL-C, mg/dL, Mean (SD)	98.2 (17.8)	96.9 (17.5)	97.5 (17.5)	97.7 (17.4)	96.9 (17.8)	98.5 (17.8)	98.7 (18.4)	0.3045
Use of anti-hypertensive agents								
At baseline	379 (95.7)	1441 (96.6)	2666 (94.8)	2798 (95.6)	1547 (95.7)	520 (94.4)	205 (98.6)	0.0367
At end of follow-up	378 (95.5)	1394 (93.4)	2632 (93.6)	2807 (95.9)	1589 (98.3)	548 (99.5)	208 (100.0)	<0.0001
SBP change from baseline to follow-up	-3.63 ± 11.03	-0.84 ± 11.14	0.11 ± 11.83	1.37 ± 12.56	2.46 ± 13.70	3.47 ± 14.69	8.42 ± 19.48	<0.0001
DBP change from baseline to follow-up	-2.44 ± 8.36	-0.83 ± 7.42	-0.31 ± 7.55	-0.17 ± 7.82	-0.15 ± 7.62	0.17 ± 8.04	1.01 ± 9.04	<0.0001

*P-values are based on one-way analysis of variances for continuous variables and by Pearson's χ^2 test for the remaining categorical variables.

Table 2 Demographic and baseline characteristics of the intention to treat cohort by average on-treatment diastolic blood pressure categories

Parameters	Average diastolic blood pressure categories						P-value*
	≤60 mmHg (n = 85)	>60 to ≤70 mmHg (n = 1399)	>70 to ≤80 mmHg (n = 4979)	>80 to ≤90 mmHg (n = 3185)	>90 to ≤100 mmHg (n = 335)	>100 mmHg (n = 18)	
Age, years, mean (SD)	64.9 (9.3)	63.7 (8.6)	61.5 (8.8)	59.4 (8.7)	57.8 (8.4)	56.7 (7.4)	<0.0001
Body mass index, kg/m ² , mean (SD)	26.9 (5.5)	27.7 (4.7)	28.3(4.5)	29.1 (4.5)	29.4 (4.5)	29.9 (5.5)	<0.0001
Men, n (%)	58 (68.2)	1043 (74.6)	4005 (80.4)	2685 (84.3)	292 (87.2)	16 (88.9)	<0.0001
White, n (%)	80 (94.1)	1323 (94.6)	4719 (94.8)	2975 (93.4)	298 (89.0)	15 (83.3)	<0.0001
Never smoked, n (%)	19 (22.4)	292 (20.9)	1159 (23.3)	793 (24.9)	74 (22.1)	1 (5.6)	0.0275
Known hypertensives, n (%)	41 (48.2)	629 (45.0)	2476 (49.7)	1993 (62.6)	257 (76.7)	16 (88.9)	<0.0001
Diabetes, n (%)	28 (32.9)	282 (20.2)	742 (14.9)	412 (12.9)	36 (10.8)	1 (5.6)	<0.0001
Myocardial infarction, n (%)	52 (61.2)	858 (61.3)	2907 (58.4)	1803 (56.6)	199 (59.6)	14 (77.8)	0.0301
Coronary artery bypass graft surgery, n (%)	53 (62.4)	714 (51.0)	2329 (46.8)	1407 (44.2)	145 (43.3)	6 (33.3)	<0.0001
Angioplasty, n (%)	45 (52.9)	762 (54.5)	2759 (55.4)	1675 (52.6)	155 (46.3)	11 (61.1)	0.0098
Angina pectoris, n (%)	74 (87.1)	1164 (83.2)	4080 (81.9)	2556 (80.3)	263 (78.5)	13 (72.2)	0.0442
Peripheral vascular disease, n (%)	23 (27.1)	248 (17.7)	615 (12.4)	265 (8.3)	20 (6.0)	2 (11.1)	<0.0001
Congestive heart failure, n (%)	25 (29.4)	179 (12.8)	379 (7.6)	172 (5.4)	25 (7.5)	1 (5.6)	<0.0001
Arrhythmia, n (%)	24 (28.2)	323 (23.1)	934 (18.8)	505 (15.9)	47 (14.0)	1 (5.6)	<0.0001
LDL-C: mg/dL, mean (SD)	96.2 (16.2)	95.7 (17.4)	97.4 (17.4)	98.1 (17.9)	100.5 (17.6)	99.1 (15.4)	<0.0001
Use of anti-hypertensive agents							
At baseline	79 (92.9)	1346 (96.2)	4744 (95.3)	3048 (95.7)	322 (96.1)	17 (94.4)	0.5314
At end of follow-up	83 (97.7)	1347 (96.3)	4733 (95.1)	3046 (95.6)	329 (98.2)	18 (100.0)	0.0357
SBP change from baseline to follow-up	-7.75 ± 14.62	-0.41 ± 12.59	0.66 ± 12.42	1.90 ± 12.64	3.06 ± 15.67	9.28 ± 22.69	<0.0001
DBP change from baseline to follow-up	-8.75 ± 9.18	-2.30 ± 7.67	-0.66 ± 7.59	0.89 ± 7.38	2.40 ± 8.81	7.71 ± 12.03	<0.0001

*P-values are based on one-way analysis of variances for continuous variables and by Pearson's χ^2 test for the remaining categorical variables.

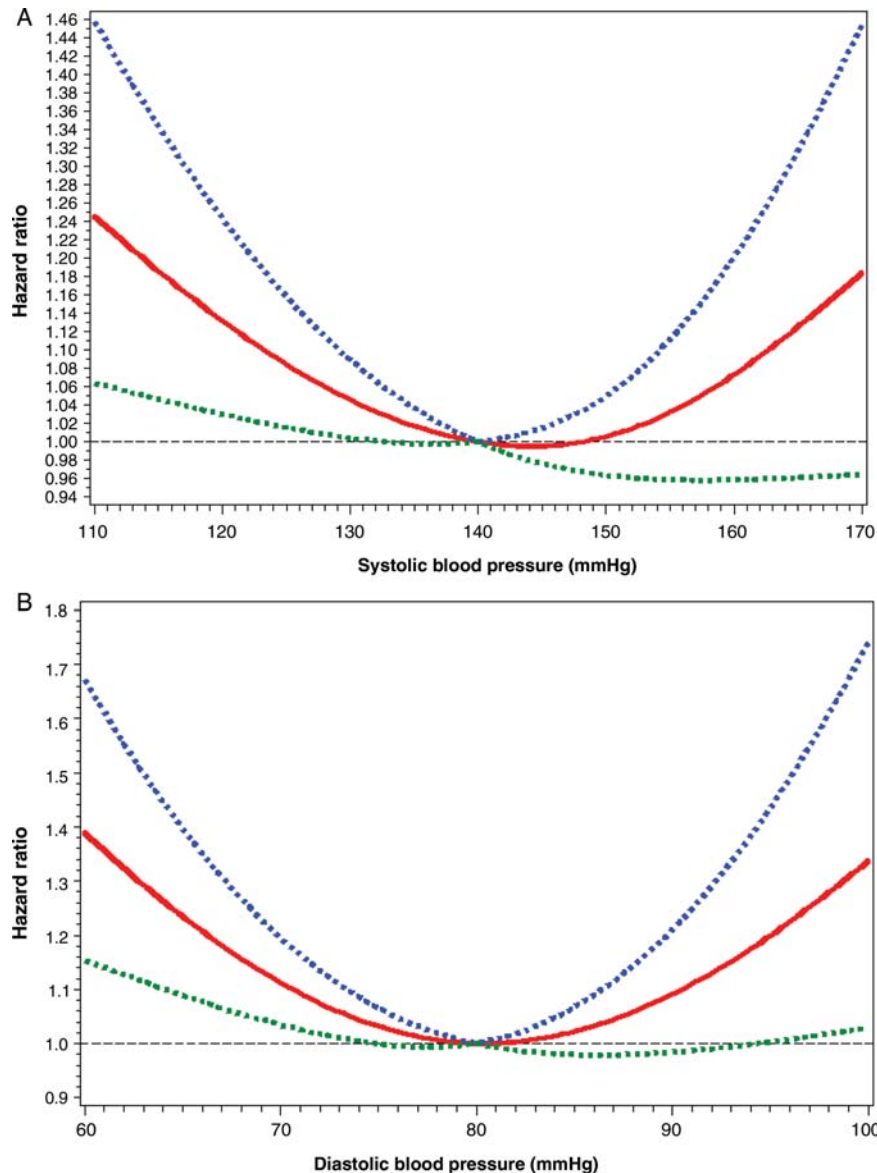


Figure 2 Systolic pressure and primary outcome. (A) Relationship between systolic pressure as a continuous variable and risk of primary outcome. Results were obtained by multivariable Cox regression with restricted splines including systolic pressure as a time-dependent covariate with three knots at 110, 150, and 170 mmHg. The upper and lower 95% confidence intervals are denoted by dotted lines. (B) Relationship between diastolic pressure as a continuous variable and risk of primary outcome. Results were obtained by multivariable Cox regression with restricted splines including diastolic pressure as a time-dependent covariate with three knots at 60, 80, and 100 mmHg. The upper and lower 95% confidence intervals are denoted by dotted lines.

assessed by a time-dependent, Cox PH model with restricted cubic splines¹⁴ using a SAS macro.¹⁵ The non-linear relationships were depicted based on this model with three knots placed at 110, 150, and 170 mmHg for SBP, and with three knots at 60, 80, and 100 mmHg for DBP.

Sensitivity analysis was performed to evaluate if the J-curve was due to increase in non-cardiovascular deaths. Further analysis was performed to evaluate the effect of pulse pressure.

A *P*-value of <0.05 (two-sided) was considered statistically significant for all tests except where mentioned. All analyses were performed using SAS software version 9.0 (SAS Institute, Cary, NC, USA).

Results

Patients

A total of 10 001 patients with clinically evident CHD and LDL cholesterol levels of <130 mg/dL were randomly assigned to receive either atorvastatin 10 vs. 80 mg. The main results of the trial have been discussed elsewhere.¹²

Blood pressure over time

Blood pressure measurements at baseline and post-baseline at Month 3 and at each annual visit thereafter are presented in

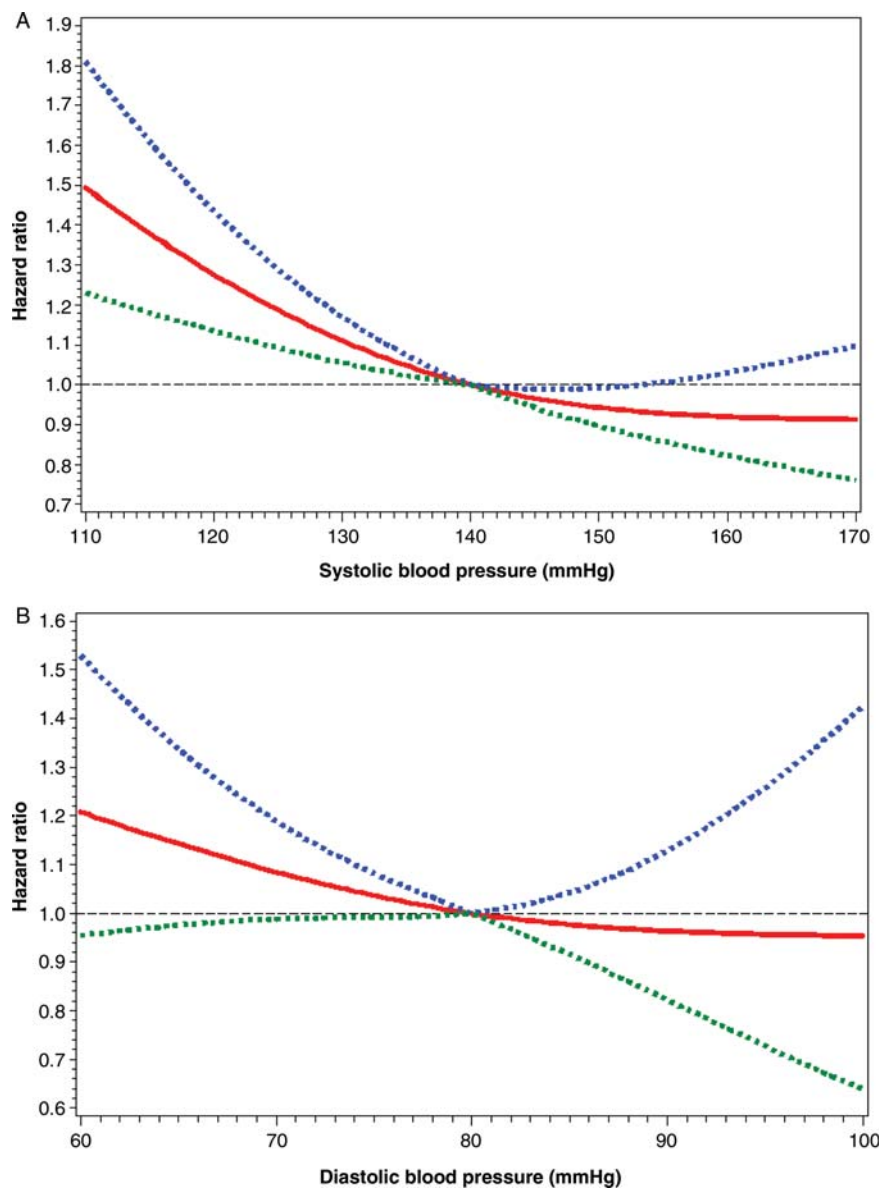


Figure 3 Blood pressure and all-cause mortality. (A) Adjusted hazard ratios for all-cause mortality by time-dependent systolic pressure. Results were obtained by multivariable Cox regression with restricted splines including systolic pressure as a time-dependent covariate with three knots at 110, 150, and 170 mmHg. The upper and lower 95% confidence intervals are denoted by dotted lines. (B) Adjusted hazard ratios for all-cause mortality by time-dependent diastolic pressure. Results were obtained by multivariable Cox regression with restricted splines including diastolic pressure as a time-dependent covariate with three knots at 60, 80, and 100 mmHg. The upper and lower 95% confidence intervals are denoted by dotted lines.

Figure 1A for SBP and Figure 1B for DBP. The variations over time for both SBP and DBP were small. Blood pressure measurements ranged from 130.7 to 132 mmHg for SBP, and 76.5 to 78.7 mmHg for DBP.

Baseline characteristics

Tables 1 and 2 summarize the baseline characteristic by average on-treatment, prior to primary outcome SBP and DBP categories (in 10 mmHg increment), respectively. Patients with low SBP were younger, leaner, less likely to be hypertensive, diabetics, or

have history of coronary bypass graft surgery, or peripheral arterial disease but more likely to be men, those with a prior MI, heart failure, and angioplasty, compared with patients with high SBP (Table 1). Patients with low DBP were older, leaner, less likely to be men, hypertensive, having prior history of MI, or those with angioplasty but more likely to be diabetics, with prior MI, coronary artery bypass graft surgery, heart failure, peripheral arterial disease, and those with angina pectoris, compared with patients with high DBP.

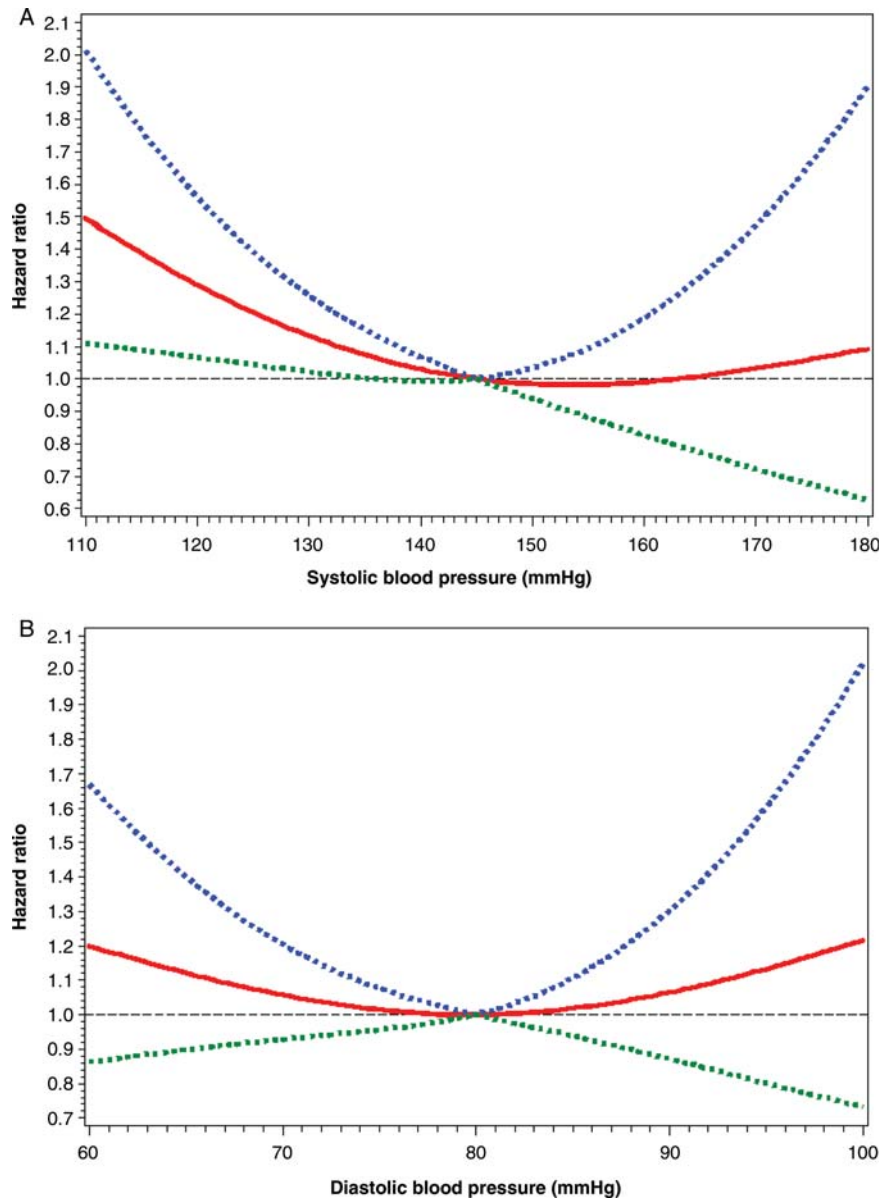


Figure 4 Blood pressure and death from coronary heart disease. (A) Adjusted hazard ratios for death from coronary heart disease by time-dependent systolic pressure. Results were obtained by multivariable Cox regression with restricted splines including systolic pressure as a time-dependent covariate with three knots at 110, 150, and 170 mmHg. The upper and lower 95% confidence intervals are denoted by dotted lines. (B) Adjusted hazard ratios for death from coronary heart disease by time-dependent diastolic pressure. Results were obtained by multivariable Cox regression with restricted splines including diastolic pressure as a time-dependent covariate with three knots at 60, 80, and 100 mmHg. The upper and lower 95% confidence intervals are denoted by dotted lines.

Primary outcome

The relationship between SBP and the incidence of primary outcome followed a J-shaped curve, with increased hazard rates at low and high SBP. In a multivariable model, using time-dependent BP as a covariate, adjusting for baseline covariates, the treatment effect and the average post-baseline LDL levels, the risk of primary outcome with SBP ≤ 110 mmHg was similar to or higher than that risk with the group with SBP > 160 mmHg (Figure 2A). This non-linear relationship was assessed initially by a time-dependent,

Cox PH model with restricted cubic splines (Figure 2A) and confirmed by a non-linear, Cox PH model including linear and quadratic time-dependent, BP terms ($\chi^2 = 7.5, df = 2, P = 0.02$). Furthermore, based on the latter model, a nadir of 146.3 mmHg where the event rate was the lowest was identified.

The relationship between DBP and the incidence of primary outcome also followed a J-shaped curve, with increased hazard rate at low and high DBPs (Figure 2B). This non-linear relationship was assessed by a Cox PH model with restricted cubic splines

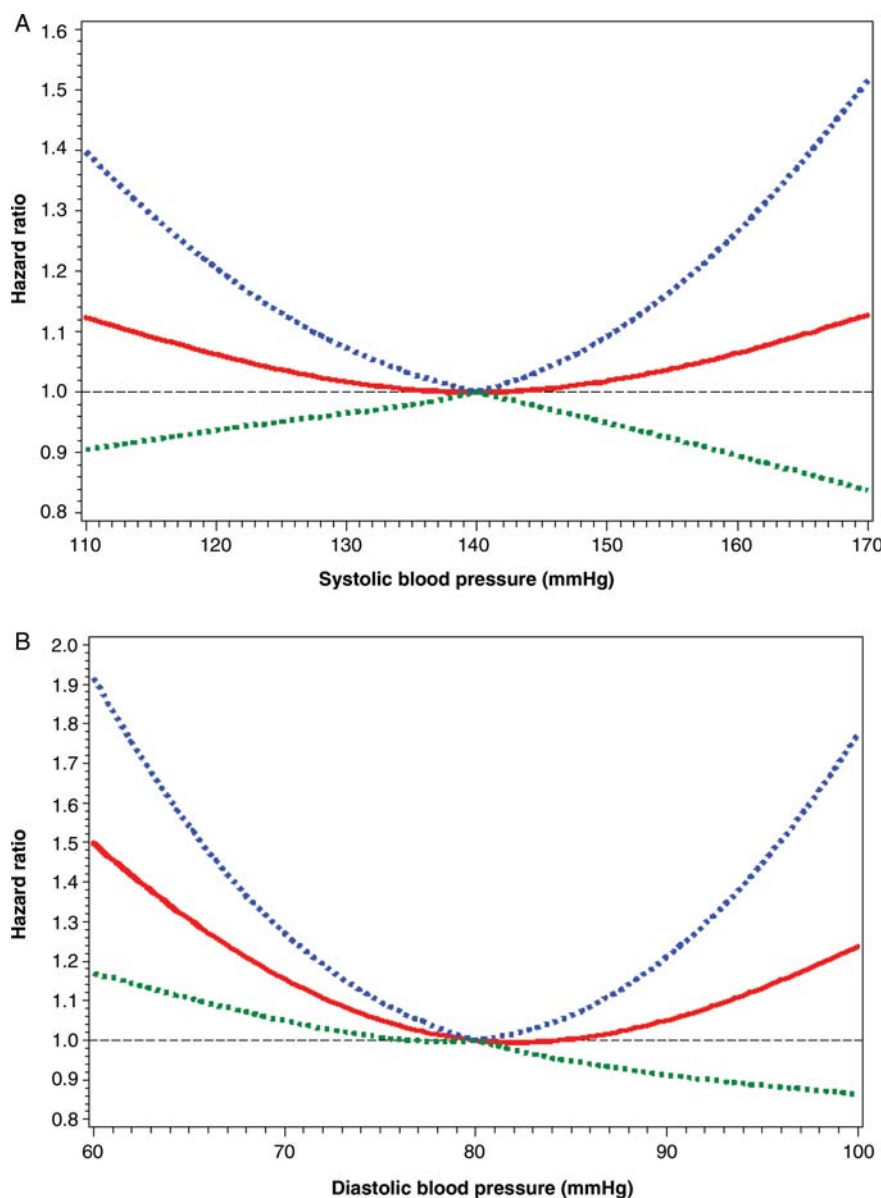


Figure 5 Blood pressure and non-fatal myocardial infarction. (A) Adjusted hazard ratios for non-fatal myocardial infarction by time-dependent systolic pressure. Results were obtained by multivariable Cox regression with restricted splines including systolic pressure as a time-dependent covariate with three knots at 110, 150, and 170 mmHg. The upper and lower 95% confidence intervals are denoted by dotted lines. (B) Adjusted hazard ratios for non-fatal myocardial infarction by time-dependent diastolic pressure. Results were obtained by multivariable Cox regression with restricted splines including diastolic pressure as a time-dependent covariate with three knots at 60, 80, and 100 mmHg. The upper and lower 95% confidence intervals are denoted by dotted lines.

(Figure 2B) and confirmed by a non-linear, Cox PH model including linear and quadratic BP terms ($\chi^2 = 15.0$, $df = 2$, $P = 0.0006$). Based on the latter model, a nadir of 81.4 mmHg was identified.

Secondary outcomes

For the secondary outcomes, a similar non-linear relationship, with increased risk at lower BP categories was found for all-cause mortality (SBP: $\chi^2 = 17.5$, $df = 2$, $P = 0.0002$; DBP: $\chi^2 = 3.3$, $df = 2$, $P = 0.19$; Figure 3A and B), death from CHD (SBP: $\chi^2 = 6.5$, $df = 2$, $P = 0.04$; DBP: $\chi^2 = 2.3$, $df = 2$, $P = 0.32$; Figure 4A and B),

and non-fatal MI (SBP: $\chi^2 = 1.3$, $df = 2$, $P = 0.51$; DBP: $\chi^2 = 10.5$, $df = 2$, $P = 0.005$; Figure 5A and B). For the outcome of stroke, lower SBPs were associated with lower risk of stroke, but a J-shaped relationship was seen with DBP (Figure 6A and B). Similarly, lower BP was associated with a higher risk of angina for both SBP and DBP (Figure 7A and B).

Sensitivity analysis

In a sensitivity analysis, evaluating the risk of non-cardiovascular death, a similar non-linear relationship, with higher risk at lower

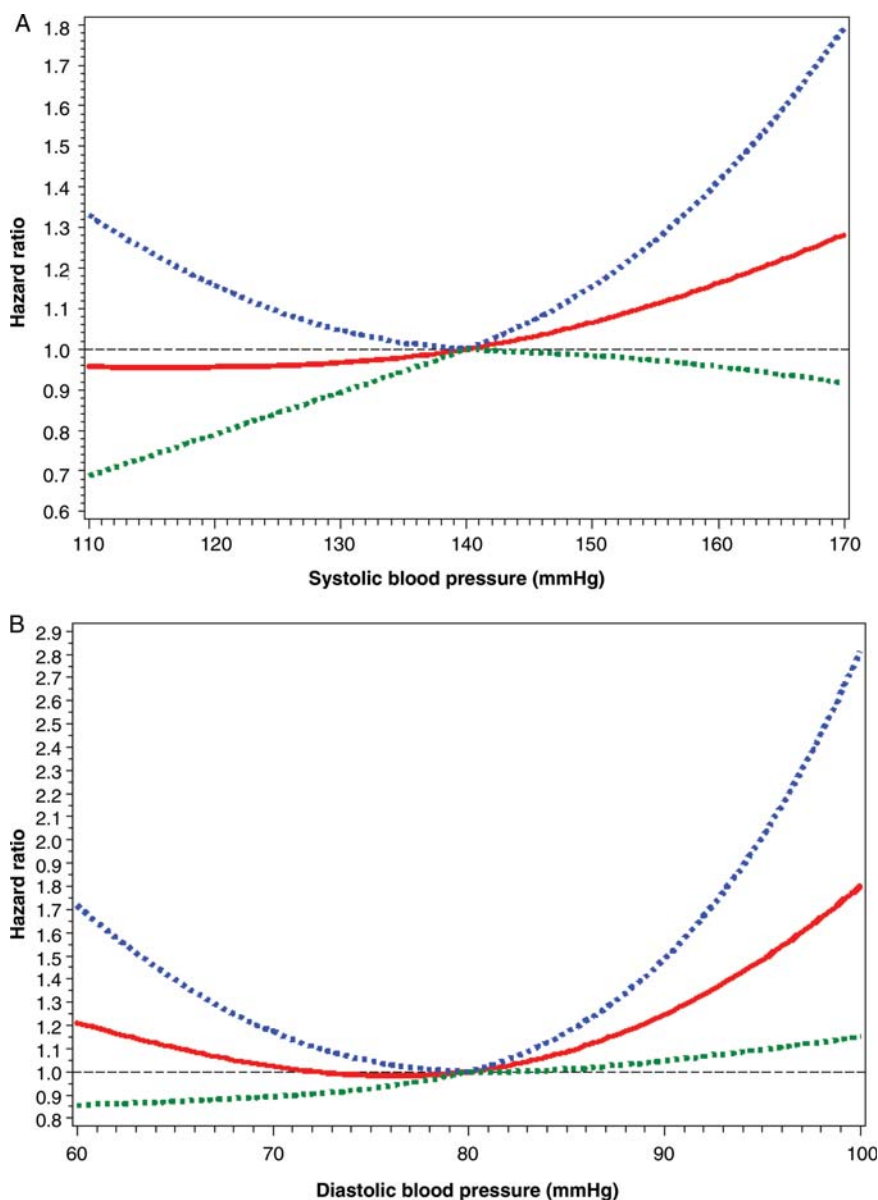


Figure 6 Blood pressure and stroke. (A) Adjusted hazard ratios for stroke by time-dependent systolic pressure. Results were obtained by multivariable Cox regression with restricted splines including systolic pressure as a time-dependent covariate with three knots at 110, 150, and 170 mmHg. The upper and lower 95% confidence intervals are denoted by dotted lines. (B) Adjusted hazard ratios for stroke by time-dependent diastolic pressure. Results were obtained by multivariable Cox regression with restricted splines including diastolic pressure as a time-dependent covariate with three knots at 60, 80, and 100 mmHg. The upper and lower 95% confidence intervals are denoted by dotted lines.

BP was seen for SBP ($\chi^2 = 11.8$, $df = 2$, $P = 0.003$) and inverse relationship for DBP. A similar J-curve relationship between primary outcome and SBP ($\chi^2 = 46.0$, $df = 6$, $P < 0.0001$) or DBP ($\chi^2 = 33.8$, $df = 5$, $P < 0.0001$) was seen after controlling for pulse pressure. Interaction analyses revealed no significant effect modification by age, gender, diabetes, hypertension, heart failure, and prior MI on the relationship between BP and primary outcomes. However, a significant interaction of SBP with prior bypass surgery was detected ($P_{\text{interaction}} = 0.004$). Those with prior bypass surgery had higher event rates at low SBP compared

with those without prior bypass surgery (Figure 8). In addition, patients with prior bypass surgery tolerated higher SBP pressure when compared with those without bypass surgery.

Discussion

Our analysis of a high-risk population with CAD enrolled in the TNT trial showed that a J- or U-shaped curve relationship or a non-linear relationship with increased risk at lower pressures exists between BP and most cardiovascular events with a nadir

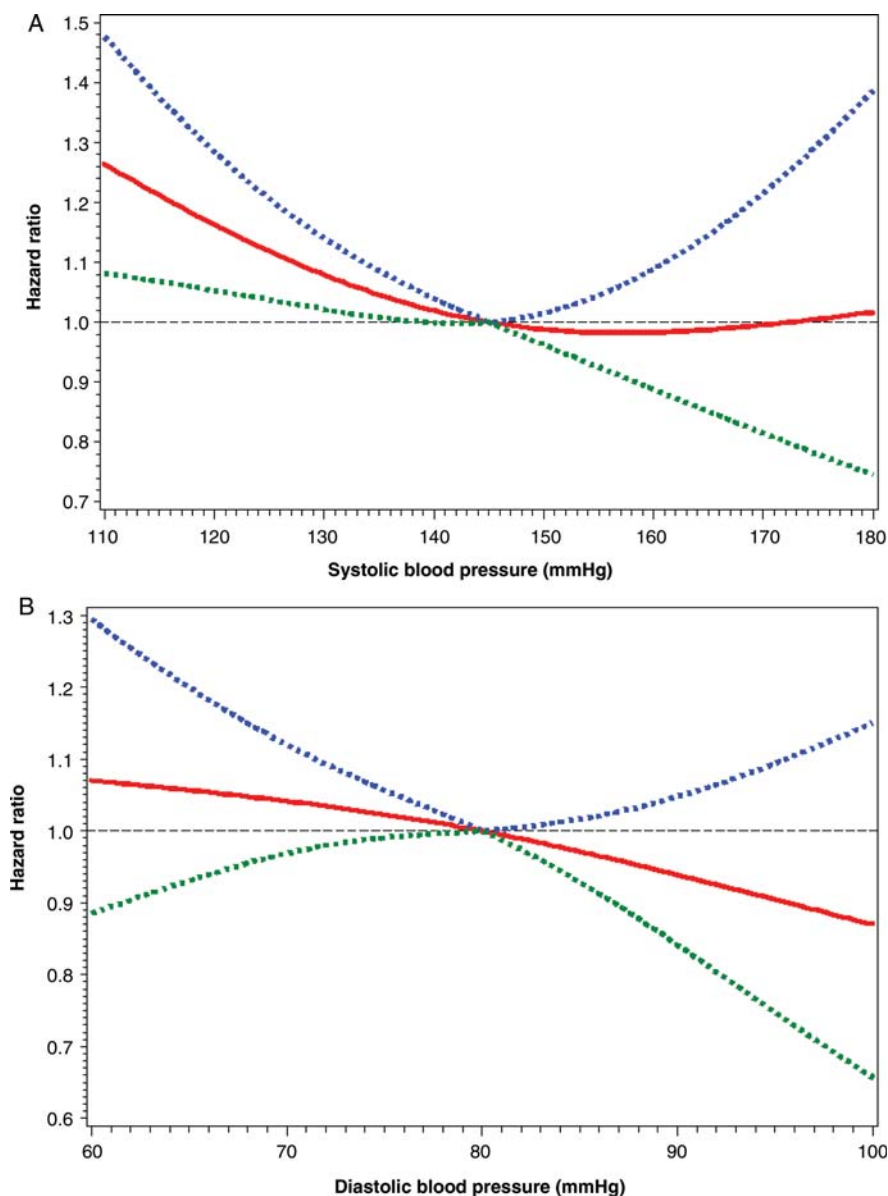


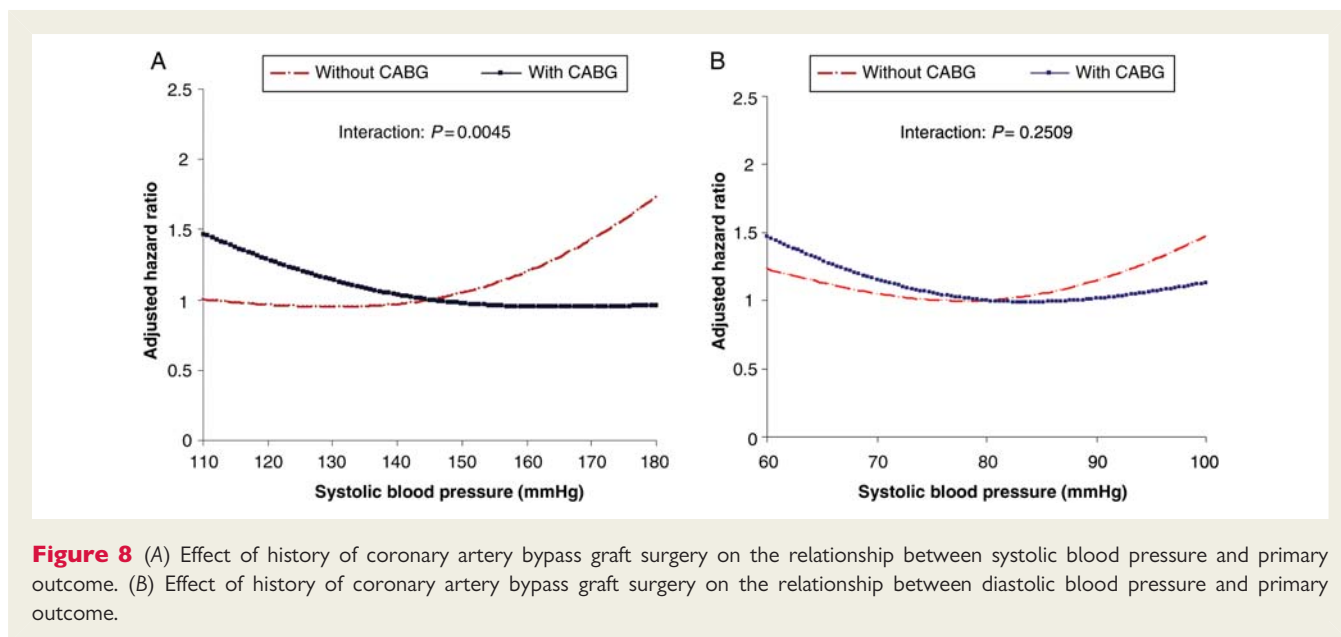
Figure 7 Blood pressure and angina. (A) Adjusted hazard ratios for angina by time-dependent systolic pressure. Results were obtained by multivariable Cox regression with restricted splines including systolic pressure as a time-dependent covariate with three knots at 110, 150, and 170 mmHg. The upper and lower 95% confidence intervals are denoted by dotted lines. (B) Adjusted hazard ratios for angina by time-dependent diastolic pressure. Results were obtained by multivariable Cox regression with restricted splines including diastolic pressure as a time-dependent covariate with three knots at 60, 80, and 100 mmHg. The upper and lower 95% confidence intervals are denoted by dotted lines.

of 146.3/81.4 mmHg where the risk of primary outcome was the lowest. It should be noted that in the present analysis the curve was relatively flat for BPs 140–120/80–70 mmHg, with exponential increase in the risk of primary outcome for BP <110–120/<60–70 mmHg. However, for the outcome of stroke, lower was better with SBP.

J-curve phenomenon and blood pressure

The vast majority of the studies that attempted to evaluate the J-curve phenomenon were in patients with hypertension but

without CAD, where the literature is controversial regarding the existence of a J-curve.^{7,16–22} However, concordant to our study, this J-curve phenomenon has been shown in the limited number of studies, which evaluated this relationship in patients with CAD [International Verapamil SR-Trandolapril Study (INVEST),³ CAD cohorts of Cruickshank et al.,⁷ Framingham Heart Study,²⁰ and Syst-Eur²³]. Our study is unique in several ways: Firstly, the above studies were in hypertension cohort (randomized or observational), where anti-hypertensive therapy could have modulated some of the effects. Our study was from a randomized trial in



patients with CAD, though majority of patients had hypertension and were on anti-hypertensive agents (but not randomized to treatment). However, the management of BP was left to the discretion of the treating physician, creating a real-world treatment effect. Secondly, the J-curve phenomenon was true in this cohort of patients where other cardiovascular risk factors like LDL cholesterol were aggressively managed and was not mitigated by statin treatment (which is known to have various pleiotropic effects).

Pathophysiological mechanisms for J-curve phenomenon

Four potential 'pathophysiological' mechanisms have been proposed to explain the existence of a J-curve.

First, the J-curve may be an epiphenomenon of a more severe and debilitating underlying chronic condition (including cancer) and the low pressure maybe a mere marker of this illness thereby increasing mortality.²⁴ However, this is controversial.⁴ Our analysis is from a randomized controlled trial where the patients with chronic debilitating conditions and poor short-term prognosis (life expectancy of <1 year) are excluded. However, the non-linear relationship was seen even with non-cardiovascular deaths, suggesting that the effect of non-measured indicators of poor health cannot be completely ruled out.

Second, low pressure may be an epiphenomenon of impaired cardiac function.²⁵ However, others have shown that low DBP was a significant predictor of events even after controlling for left ventricular function.⁴ In the present analyses, patients with an ejection fraction <30% were excluded from the trial, making this less likely, though not completely ruling out this possibility.

Third, the J-curve may represent an epiphenomenon of increased arterial stiffness, i.e. a low DBP might be simply a marker for high pulse pressure and hence the increase in mortality.²⁶ In our analyses, we noticed a J-curve phenomenon not just for DBP but also for SBP, where the pulse pressure theory

would not be applicable. Moreover, in our sensitivity analysis, the relationship persisted after controlling for pulse pressure.

Finally, low DBP may compromise coronary perfusion. Since coronary perfusion occurs in diastole, diastolic hypotension could lead to coronary hypoperfusion in patients with compromised coronary flow reserve such as those with CAD. Messerli *et al.*³ had previously shown in an analysis of the INVEST, a similar J-shaped relationship between BP, especially diastolic and the risk of cardiovascular events, where we noted a significant interaction effect of revascularization, suggesting that patients who had revascularization before enrolment tolerated lower DBP relatively better than those who did not have revascularization.³ In the present analysis, lower BPs were associated with increased risk of MI but not stroke (for SBP). In addition, at lower pressure, there was an increase in the risk of angina, providing a pathophysiological rationale of decreased coronary perfusion with lower pressures. Our results could be explained by any of the above four pathophysiological mechanisms, either singly or in combination.

Lower is not always better

Recent trials have questioned the lower the better hypothesis for BP. In the ACCORD trial of patients with diabetes,²⁷ intensive BP lowering (to 120 mmHg SBP) was not associated with a reduction in the risk of cardiovascular outcomes when compared with the standard therapy group (to 140 mmHg SBP). However, in ACCORD, the risk of stroke was reduced with the intensive BP strategy. Our results are concordant with these findings.

Study limitations

This is a post-hoc analysis from a CAD population with tight control of cholesterol levels and was from a cohort not specifically enrolled for the management for BP and hence the results cannot be extrapolated to other population. Our results do not propose a causal relationship between low BP and risk of cardiovascular

events. Though we adjusted our analysis for baseline confounders, any unmeasured confounders could have been missed. We also did not adjust our analyses for dosage of anti-hypertensive agents received or for other confounders (because of lack of data), especially those that are predictors of poor health, socio-economic status, job stress, or mental health.

Conclusions

In patients with CAD, a J-curve relationship or a non-linear relationship persists between BP and cardiovascular events such that a low BP (<110–120/60–70 mmHg) portends an increased risk of future cardiovascular events. Our findings negate the dictum that with BP, lower is always better (except perhaps for SBP and stroke).

Authors' roles

C.C.W. and S.B. had full access to all of the data for this study and take responsibility for the integrity of the data and the accuracy of the data analysis. S.B. and F.H.M. involved in study concept and design. C.C.W., S.B., and F.H.M. involved in the analysis and interpretation of data, S.B. and F.H.M. drafted the manuscript. Critical revision of the manuscript for important intellectual content was done by D.D.M., A.L.Z., J.B.K., and J.L.R. Statistical analysis was performed by C.C.W., and this study was supervised by D.D.M. and S.B., F.H.M., and A.L.Z.

Conflict of interest: F.H.M. was Speakers' Bureau at Abbott, GlaxoSmithKline, Novartis, Pfizer, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Forest, Sankey, Sanofi and received research/grants from GlaxoSmithKline, Pfizer, Novartis, and CardioVascular Therapeutics. C.C.W., A.L.Z., and D.D.M. are Pfizer employees.

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