ORIGINAL RESEARCH

Cohort Study Examining the Association Between Blood Pressure and Cardiovascular Events in Patients With Peripheral Artery Disease

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***Background*—**Hypertension is an important risk factor for cardiovascular events in patients with peripheral artery disease; however, optimal blood pressure targets for these patients are poorly defined. This study investigated the association between systolic blood pressure (SBP) and cardiovascular events in a prospectively recruited patient cohort with peripheral artery disease.

***Methods and Results*—**A total of 2773 patients were included and were grouped according to SBP at recruitment (≤120 mm Hg, n=604; 121–140 mm Hg, n=1065; and >140 mm Hg, n=1104). Adjusted Cox proportional hazards analyses suggested that patients with SBP ≤120 mm Hg were at greater risk of having a major cardiovascular event (myocardial infarction, stroke, or cardiovascular death) than patients with SBP of 121–140 mm Hg (adjusted hazard ratio, 1.36; 95% CI, 1.08–1.72; *P*=0.009). Patients with SBP >140 mm Hg had an adjusted hazard ratio of 1.23 (95% CI, 1.00–1.51; *P*=0.051) of major cardiovascular events compared with patients with SBP of 121–140 mm Hg. These findings were similar in sensitivity analyses only including patients receiving antihypertensive medications or focused on patients with a minimum of 3 months of follow-up.

***Conclusions*—**This cohort study suggests that patients with peripheral artery disease and SBP ≤120 mm Hg are at increased risk of major cardiovascular events. The findings suggest caution in intensive SBP lowering in this patient group. **(*J Am Heart Assoc*. 2019;8:e010748. DOI: 10.1161/JAHA.118.010748.)**

Key Words: blood pressure • major adverse cardiac event • myocardial infarction • peripheral artery disease • stroke

Peripheral artery disease (PAD) comprises a group of occlusive and aneurysmal diseases resulting from narrowing and occlusion of the peripheral arteries, which are estimated to affect 10% of adults worldwide.[1–4] Approximately 20% of patients with PAD die from a cardiovascular event within 5 years of diagnosis; therefore, medical management of cardiovascular risk factors is the primary focus of treatment.[5,6] Hypertension is an important risk factor for complications in patients with PAD. Prior studies suggest the prevalence of hypertension in patients with PAD to be between 35% and 55%.[7] There is evidence from randomized clinical trials suggesting that administering antihypertensive medications in patients with PAD and hypertension reduces the incidence of cardiovascular events by 20% to 30%.[8,9] Therefore, current clinical guidelines recommend that patients with PAD should receive antihypertensive medications if their blood pressure (BP) is >140/90 mm Hg.[10] The current definition of what constitutes clinically important hypertension warranting medical treatment is controversial.[11,12] Recent American College of Cardiology/American Heart Association guidelines recommend commencing antihypertensive treatment when systolic BP (SBP) is ≥130 mm Hg, whereas other guidelines recommend antihypertensive treatment if BP is >140/90 mm Hg.[11–13]

A recent study in patients with PAD has suggested poor control of BP in this population.[14] One possible reason for this could be the limited data on the value of BP control specifically in discrete populations of patients with PAD. A recent Cochrane review concluded that there was no overwhelming evidence available on the benefit of treating hypertension in patients with PAD.[15] The level to which the BP

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Accompanying Tables S1 through S3 and Figures S1 through S3 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.010748

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Clinical Perspective

What Is New?

- The optimal blood pressure (BP) targets in patients with peripheral artery disease are controversial.
- This large observational study found that patients with peripheral artery disease who had systolic BP ≤120 mm Hg at recruitment were at increased risk of subsequent major cardiovascular events than those with systolic BP of 121 to 140 mm Hg at recruitment.

What Are the Clinical Implications?

- This study identifies patients with peripheral artery disease and systolic BP ≤120 mm Hg as at high risk of major cardiovascular events.
- The findings also raise some concern over aggressive BP lowering in patients with peripheral artery disease.

should be lowered in these patients is also controversial. Recently, 2 large trials that included patients with PAD, performed by the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial and SPRINT (SBP Intervention Trial) research groups, assessed the efficacy of intensive SBP lowering to <120 mm Hg, as opposed to more conventional SBP targets (<140 mm Hg), to reduce major cardiovascular events.[16,17] The trials had contradictory results. Findings from SPRINT suggested that intensive SBP lowering reduced the incidence of cardiovascular events substantially, whereas the ACCORD trial results indicated that intense SBP lowering did not reduce cardiovascular events.[16,17] Another trial that also included patients with PAD reported that the incidence of cardiovascular events was lowest among patients with an average SBP between 135 and 145 mm Hg.[18] The relationship between SBP and cardiovascular events was best represented by a J-shaped curve. Several studies have demonstrated this relationship in a variety of different populations.[19–22]

These data emphasize that the optimal SBP target for patients with PAD remains controversial. Randomized trials frequently include only selected patients with PAD and, therefore, data for heterogeneous cohorts of real-world patients are important to qualify findings from such trials. In this current study, the relationship between SBP and cardiovascular events was examined in a large heterogeneous group of patients with PAD. The aims of this study were to examine the following:

1. The prevalence of hypertension using different definitions based on SBP targets in previous trials, including >120 and >140 mm Hg.[12,13,16]
2. The association of SBP categories (≤120, 121–140, and >140 mm Hg) with cardiovascular events.

Methods

Requests for access to data, analytic methods, and study materials should be made to the corresponding author.

Study Design and Participants

This investigation was designed as part of an ongoing prospective cohort study that aims to identify risk factors associated with PAD diagnosis and outcome. The study commenced in 2002 and remains ongoing. Patients were recruited from inpatient and outpatient vascular services in Australia, including The Townsville Hospital, the Mater Hospital Townsville, Gosford Vascular Services, and The Royal Brisbane and Women's Hospital.

For inclusion in the current study, patients had to have PAD, including lower/upper limb atherothrombosis; carotid stenosis or aneurysm of the aorta or peripheral arteries, diagnosed by a vascular specialist; and the assessment of BP at recruitment. BP, risk factors, and medications of the patients were only recorded at study entry. The study was performed in accordance with the Declaration of Helsinki, and ethical approval was granted from the respective institutional ethics committees. Written informed consent was also obtained from all participants.

Definition and Measurements of Risk Factors

Smoking status was classified as ever (including current and former smoker) or never smoker.[23–25] Hypertension and diabetes mellitus were defined by a history of diagnosis or treatment for these conditions.[23–25] Coronary heart disease (CHD) was defined by a history of myocardial infarction (MI), angina, or treatment for CHD.[23–25] Body mass index was measured as previously described.[26] Estimated glomerular filtration rate was calculated, as previously described, using the Chronic Kidney Disease Epidemiology collaboration group formula because we have previously reported this to most accurately predict complications in patients with PAD.[27]

Definition of Presenting Problem

Patients presenting with one of the following PAD problems were included in this study: (1) Asymptomatic carotid artery stenosis: Diagnosed when at least one carotid artery has ≥50% stenosis or occlusion, identified by carotid duplex, but the absence of physician-confirmed symptoms of focal transient ischemic attack, amaurosis fugax, or stroke, as previously described.[28] (2) Nonthreatening limb ischemia: This included patients with symptoms related to obstruction of limb arteries, as confirmed by a vascular specialist by identification of absence of limb pulses, ankle-brachial

pressure index <0.9, and/or significant stenosis (>50%) or occlusion of limb arteries on computed tomographic angiography or duplex imaging that did not meet criteria for critical limb ischemia.[24,26] (3) Aneurysm of the aorta or peripheral arteries: Aortic aneurysm was defined as maximum aortic diameter ≥30 mm.[24–26] Iliac artery aneurysm was defined by common or internal iliac artery diameters ≥15 and ≥8 mm, respectively. Femoral artery aneurysm was defined by common femoral or superficial femoral artery diameter of ≥15 mm. Popliteal artery aneurysm was defined as popliteal artery diameter ≥9 mm, as previously described.[29] (4) Symptomatic carotid artery stenosis: Defined as the presence of ≥50% stenosis or occlusion of at least one carotid artery identified with carotid duplex with the presence of physician-confirmed symptoms of focal transient ischemic attack, amaurosis fugax, or stroke, as previously described.[28] (5) Critical limb ischemia: Rest pain, arterial ulcer, or gangrene of the limb attributable to atherothrombosis of the limb arteries. Peripheral atherothrombosis was confirmed, as detailed above.[24,26]

Blood Pressure

This was measured at recruitment using a digital BP monitor, Omron Intellisense (HEM–907), according to current clinical guidelines.[13] Resting BP was measured at the patient's first visit.

Medications

The patient's medications were recorded at recruitment, including antiplatelets, diuretics (frusemide, thiazides, potassium sparing, and indapamide), α blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β blockers, calcium channel blockers, statins, fibrates, metformin, and insulin.

Outcomes

Participants were followed up as outpatient or inpatient as part of their normal care. Outcome data were recorded during clinical reviews on prospectively defined case report forms. A vascular specialist also reviewed charts and hospital electronic records of patients. Data were linked with hospital admission records, as previously described.[30,31] Linked data were obtained from the Queensland Hospital Admitted Data Collection, which is regularly audited to minimize data inaccuracies.[32] The primary outcome was the first occurrence of a major cardiovascular event, including MI, stroke, or cardiovascular death. The secondary outcomes included the components of the primary outcome considered individually and all-cause mortality. Patients were censored at the outcome event date or at the date of the last follow-up for those who had not experienced the outcome.

Statistical Analysis

Patients were categorized into 3 groups, according to their SBP: (1) SBP ≤120 mm Hg (representing patients who had SBP controlled according to SPRINT),[16] (2) SBP 121 to 140 mm Hg (represents those who had BP controlled as recommended within some PAD treatment guidelines [European Society of Cardiology/Gabb et al][10,13] [reference group]), and (3) SBP >140 mm Hg (patients who did not meet European Society of Cardiology/Gabb et al guideline-defined control of SBP).[10,13]

Data were analyzed using the SPSS v 23 and R statistical software packages. The quantitative data were not normally distributed, which was confirmed using the Shapiro-Wilk test. Hence, continuous data are presented as median and interquartile range and were compared between groups using Kruskal-Wallis tests. Nominal data are reported as count and percentages and were compared using χ^2 tests. Monte-Carlo simulations suggest that a multivariate regression model is powered sufficiently when 10 outcome events per *df* of the predictor variable were observed.[33–35] A recent study conducted by our vascular research group recorded 505 outcome events, including MI, stroke, and death, in 2137 patients during a median follow-up of 1.3 years. The event rate during this follow-up was 23.6%.[27] Hence, the incidence of primary outcome for this study was estimated to be ≈20%. We planned to adjust our analysis for a maximum of 9 independent traditional cardiovascular risk factors and potential confounders, of which 2 had multiple categories. On the basis of these estimates, a sample size of >2000 patients was planned because this would be well powered to determine the association of different SBP categories with cardiovascular outcomes. Cox proportional hazard analyses were used to assess the association between SBP and the primary and secondary outcomes using multivariable models adjusted for age (categorized into 3 groups based on tertiles), sex, PAD presenting problem (categorized into 5 groups, as discussed above), smoking, diabetes mellitus, CHD, body mass index, and statin and frusemide prescription. These covariates were chosen for inclusion in the Cox models because they are established predictors of cardiovascular events or because they were significantly unequally distributed among the SBP groups. These analyses were conducted in 2574 patients with complete data for all of these covariates. Additional analyses were performed to analyze the association between diastolic BP (DBP; n=2496) or pulse pressure (PP; n=2496), with the outcomes of interest including the covariates listed above, except SBP, in the models. For these analyses, patients were categorized into 3 groups according to their DBP ([1] <80 mm Hg, [2] 80 to 89 mm Hg, and [3] ≥90 mm Hg) or

PP tertiles ([1] ≤53 mm Hg, [2] 54–68 mm Hg, and [3] >68 mm Hg). Sensitivity analyses were performed, including estimated glomerular filtration rate, SBP, and DBP (not PP) as well as all the other risk factors and medications listed above into the models in 2358 patients. Further sensitivity analyses were also performed by excluding patients with follow-up <3 months (1835 patients included) and excluding patients who were not taking any antihypertensive medications (2030 patients included). None of the adjusted models presented violated the assumptions for Cox proportional hazards analyses. $P<0.05$ was considered significant for all the analyses.

Results

Study Population

A total of 2773 patients diagnosed with PAD were included in the first aim of this study. The main presenting problems of the patients were asymptomatic carotid disease (236 [8.5%]), nonthreatening limb ischemia (614 [22.1%]), aortic or peripheral aneurysm (1288 [46.5%]), symptomatic carotid disease (358 [12.9%]), and critical limb ischemia (277 [10.0%]).

At recruitment, 604 patients (21.8%) had an SBP ≤120 mm Hg, 1065 (38.4%) had an SBP between 121 and 140 mm Hg, and the remaining 1104 (39.8%) had an SBP >140 mm Hg. Hence, according to different definitions, the prevalence of hypertension in this cohort was 78.2% (SBP >120 mm Hg) or 39.8% (SBP >140 mm Hg).

The patients from the 3 different SBP groups significantly differed in the prevalence of the following risk factors and medications: age, sex, history of an aneurysm, CHD, and prescription of diuretics (frusemide and potassium-sparing diuretics) and antihypertensive medications, such as angiotensin receptor blockers and calcium channel blockers (Table 1). All other risk factors and medications were distributed similarly between the 3 SBP groups.

Primary Outcome

The association of BP with the primary composite outcome of MI, stroke, or cardiovascular death was assessed in a subpopulation of 2574 patients with complete clinical data. During a median follow-up of 1.7 years (interquartile range, 0.1–4.9 years), 563 patients (21.9%) had an MI, stroke, or cardiovascular death. Adjusted Cox proportional hazards analyses suggested that patients with SBP ≤120 mm Hg (hazard ratio, 1.36; 95% CI, 1.08–1.72; $P=0.009$) were at greater risk of having a major cardiovascular event compared with patients with SBP between 121 and 140 mm Hg (Table 2, Figure 1). Patients with SBP >140 mm Hg had an adjusted hazard ratio of 1.23 (95% CI, 1.00–1.51; $P=0.051$; Table 2) of major cardiovascular events.

Secondary Outcomes

MI, stroke, cardiovascular death, and all-cause mortality occurred in 279 (10.8%), 183 (7.1%), 283 (11.0%), and 534 (20.7%) of patients, respectively. As for the primary outcome, the adjusted Cox proportional hazards analyses suggested an increased risk of MI alone in patients with SBP >140 or ≤120 mm Hg compared with patients in the reference SBP group (Table 2, Figure 2). No increased risk of stroke alone was observed in patients with SBP ≤120 or >140 mm Hg by comparison to those with SBP 121 to 140 mm Hg (Table 2, Figure S1). An increased risk of cardiovascular and all-cause mortality was also detected in patients with SBP ≤120, but not >140, mm Hg in comparison to those with SBP 121 to 140 mm Hg (Table 2, Figures S2 and S3).

Sensitivity Analyses

Sensitivity analysis, including the additional covariates of DBP and estimated glomerular filtration rate, showed similar findings (n=2358) (Table S1). A sensitivity analysis including only patients who were taking ≥1 antihypertensive medication (n=2030) demonstrated similar findings to the main analysis (Table 2). Patients with SBP ≤120 or >140 mm Hg were at increased risk of major cardiovascular events and MI alone (Table 2). An increased risk of stroke alone, cardiovascular death, and all-cause mortality was also observed in patients with SBP ≤120 mm Hg compared with those with SBP 121 to 140 mm Hg in this sensitivity analysis (Table 2). A second sensitivity analysis was performed, only including patients who had at least 3 months of follow-up (n=1835). After adjusting for other risk factors, patients with SBP ≤120 and >140 mm Hg had an increased risk of major cardiovascular events (Table 2). In this sensitivity analysis, only patients with SBP >140 mm Hg had an increased risk of MI alone. Patients with SBP ≤120 mm Hg had an increased risk of all-cause mortality (Table 2).

Association of DBP and PP With Events

There was no association observed between DBP, PP, and outcomes of interest (Tables S2 and S3).

Discussion

The current study suggests that poorly controlled SBP remains prevalent in patients with PAD. Depending on the definition, the prevalence of poorly controlled SBP in this study was ≈40% (SBP >140 mm Hg) or ≈80% (SBP >120 mm Hg) at recruitment. Patients with PAD and SBP >140 mm Hg were at increased risk of MI, emphasising the importance of SBP control. In contrast, patients with PAD and

Table 1. Demographic and Baseline Characteristics of the Patients According to SBP

	Demographic and Clinical Characteristics	SBP, mm Hg (n=2773)			*P* Value
		≤120	121–140	>140	
1	N	604	1065	1104	
2	Age, y	69.2 (62.5 – 75.7)	70.8 (64.1 – 76.2)	71.7 (65.7 – 77.8)	<0.001
3	Sex				0.016
	Male	445 (73.7)	848 (79.6)	842 (76.3)	
	Female	159 (26.3)	217 (20.4)	262 (23.7)	
4	BMI, kg/m^2	27.4 (23.7 – 30.8)	27.8 (24.9 – 31.0)	27.6 (24.5 – 31.0)	0.085
5	PAD problem				0.079
	Asymptomatic carotid stenosis	43 (7.1)	84 (7.9)	109 (9.9)	0.097
	Nonthreatening limb ischemia	129 (21.4)	220 (20.6)	265 (24.0)	0.150
	All aneurysms	281 (46.5)	530 (49.8)	477 (43.2)	0.009
	Symptomatic carotid stenosis	85 (14.1)	131 (12.3)	142 (12.9)	0.583
	Critical limb ischemia	66 (10.9)	100 (9.4)	111 (10.0)	0.600
6	Smoking				
	Never	95 (15.8)	150 (14.1)	178 (16.1)	0.401
	Ever	508 (84.2)	912 (85.9)	925 (83.9)	
7	DM	167 (27.6)	296 (27.9)	306 (27.7)	0.992
8	Hypertension	457 (75.7)	818 (76.8)	896 (81.2)	<0.001
9	CHD	309 (51.2)	520 (49.0)	499 (45.2)	0.042
10	Stroke	71 (11.8)	141 (13.4)	142 (12.9)	0.656
11	eGFR (ml/min/1.73 m(2))	77 (60 – 90)	76 (59 – 89)	74 (57 – 88)	0.073
12	No. of antihypertensive agents				
	0	146 (24.2)	244 (22.9)	214 (19.4)	0.038
	1	158 (26.2)	258 (24.2)	330 (29.9)	0.011
	2	164 (27.2)	308 (28.9)	348 (31.5)	0.140
	3	102 (16.9)	197 (18.5)	152 (13.8)	0.010
	4	26 (4.3)	45 (4.2)	47 (4.3)	0.997
	5	7 (1.2)	10 (0.9)	13 (1.2)	0.847
13	Medications				
	Aspirin	389 (64.5)	718 (67.6)	740 (67.0)	0.417
	Other antiplatelets	133 (22.1)	220 (20.7)	235 (21.3)	0.812
	CCB	154 (25.5)	323 (30.4)	355 (32.2)	0.016
	Frusemide	78 (12.9)	120 (11.3)	79 (7.2)	<0.001
	Thiazides	48 (7.9)	96 (9.0)	107 (9.7)	0.485
	Potassium-sparing diuretic	19 (3.1)	16 (1.5)	8 (0.7)	0.001
	Indapamide	14 (2.3)	50 (4.7)	47 (4.3)	0.050
	α Blocker	13 (2.2)	22 (2.1)	30 (2.7)	0.568
	β Blocker	232 (38.5)	372 (35.0)	360 (32.6)	0.051
	ACEI	251 (41.6)	427 (40.2)	426 (38.6)	0.453
	ARB	122 (20.2)	268 (25.2)	326 (29.5)	<0.001
	Statins	415 (68.8)	768 (72.3)	779 (70.6)	0.309

Continued

Table 1. Continued

	Demographic and Clinical Characteristics	SBP, mm Hg (n=2773) ≤120	121–140	>140	*P* Value
	Fibrates	15 (2.5)	47 (4.4)	43 (3.9)	0.134
	Metformin	89 (14.8)	172 (16.2)	186 (16.8)	0.533
	Insulin	26 (4.3)	63 (5.9)	64 (5.8)	0.331
14	Follow-up, y	2.0 (0.1 – 5.3)	2.0 (0.2 – 5.1)	1.5 (0.1 – 4.4)	0.085

The data are expressed as median (interquartile range) for continuous data and number (percentage) for categorical data. Some of the data were missing, as follows: BMI, n=192; smoking, n=5; DM, n=6; hypertension, n=5; ischemic heart disease, n=6; stroke, n=16; eGFR, n=151; and medications, n=9. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CCB, calcium channel blocker; CHD, coronary heart disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; PAD, peripheral artery disease; SBP, systolic blood pressure.

SBP ≤120 mm Hg had an increased incidence of major cardiovascular events, MI alone, cardiovascular death alone, and all-cause mortality. These findings were similar in sensitivity analyses.

There are several possible explanations for the excess of events in patients with low SBP. First, it could be attributable to an excess of cardiovascular morbidity, such as heart failure, in patients with SBP ≤120 mm Hg. The prescription of frusemide (a medication commonly used to treat heart failure) was more common in patients with SBP ≤120 mm Hg than in patients in the other SBP groups. However, SBP ≤120 mm Hg was still associated with a higher incidence of cardiovascular events in analyses adjusted for other cardiovascular risk factors (including frusemide), suggesting the high incidence of cardiovascular events in patients with SBP ≤120 mm Hg was not explained by an excess of cardiovascular risk factors.

Another possible explanation could be that some patients had an adverse response to SBP lowering. In a sensitivity

Table 2. Association of Different SBP Categories With Outcome Events in the Whole Cohort, Only Patients Taking Antihypertensive Medications, and Patients With >3 Months of Follow-Up

Outcome	SBP, mm Hg	Whole Cohort (n=2574) HR (95% CI)	*P* Value	Patients Treated With Antihypertensive Medications (n=2030) HR (95% CI)	*P* Value	Excluding Patients With <3 mo of Follow-Up (n=1835) HR (95% CI)	*P* Value
Major CVE*	121–140	1.00 (Reference)	N/A	1.00 (Reference)	N/A	1.00 (Reference)	N/A
	≤120	1.36 (1.08–1.72)†	0.009	1.55 (1.21–1.99)†	<0.001	1.34 (1.05–1.70)†	0.017
	>140	1.23 (1.00–1.51)†‡	0.051	1.25 (1.00–1.57)†	0.049	1.27 (1.03–1.56)†	0.027
MI	121–140	1.00 (Reference)	N/A	1.00 (Reference)	N/A	1.00 (Reference)	N/A
	≤120	1.38 (1.00–1.91)§	0.053	1.51 (1.06–2.13)§	0.021	1.32 (0.95–1.84)§	0.103
	>140	1.44 (1.08–1.91)§	0.013	1.44 (1.06–1.96)§	0.019	1.44 (1.08–1.92)§	0.012
Stroke	121–140	1.00 (Reference)	N/A	1.00 (Reference)	N/A	1.00 (Reference)	N/A
	≤120	1.24 (0.83–1.84)‖	0.290	1.59 (1.05–2.41)‖	0.029	1.23 (0.82–1.83)	0.312
	>140	1.09 (0.77–1.54)‖	0.637	1.05 (0.71–1.55)‖	0.812	1.08 (0.76–1.54)	0.653
Cardiovascular death	121–140	1.00 (Reference)	N/A	1.00 (Reference)	N/A	1.00 (Reference)	N/A
	≤120	1.39 (1.01–1.91)	0.044	1.47 (1.04–2.07)	0.029	1.33 (0.95–1.86)	0.097
	>140	1.13 (0.84–1.53)	0.404	1.23 (0.89–1.68)	0.210	1.19 (0.88–1.61)	0.263
All-cause mortality	121–140	1.00 (Reference)	N/A	1.00 (Reference)	N/A	1.00 (Reference)	N/A
	≤120	1.34 (1.07–1.69)	0.013	1.34 (1.04–1.73)	0.024	1.31 (1.03–1.66)	0.025
	>140	1.03 (0.83–1.28)	0.779	1.04 (0.83–1.32)	0.717	1.03 (0.82–1.28)	0.810

Regression models were adjusted for age categories, sex, peripheral artery disease presenting problem, smoking, diabetes mellitus, coronary heart disease, body mass index, and statin and frusemide prescription. CVE indicates cardiovascular event; HR, hazard ratio; MI, myocardial infarction; N/A, not applicable; SBP, systolic blood pressure.

*Defined as MI, stroke, or cardiovascular death.

†Patient presenting problem and age at recruitment were stratified in this model to conform to the proportional hazards assumption.

‡The lower limit of the CI was 0.993, which was rounded off to the second decimal place.

§Coronary heart disease was stratified in this model to conform to the proportional hazards assumption.

‖Diabetes mellitus was stratified in this model to conform to the proportional hazards assumption.

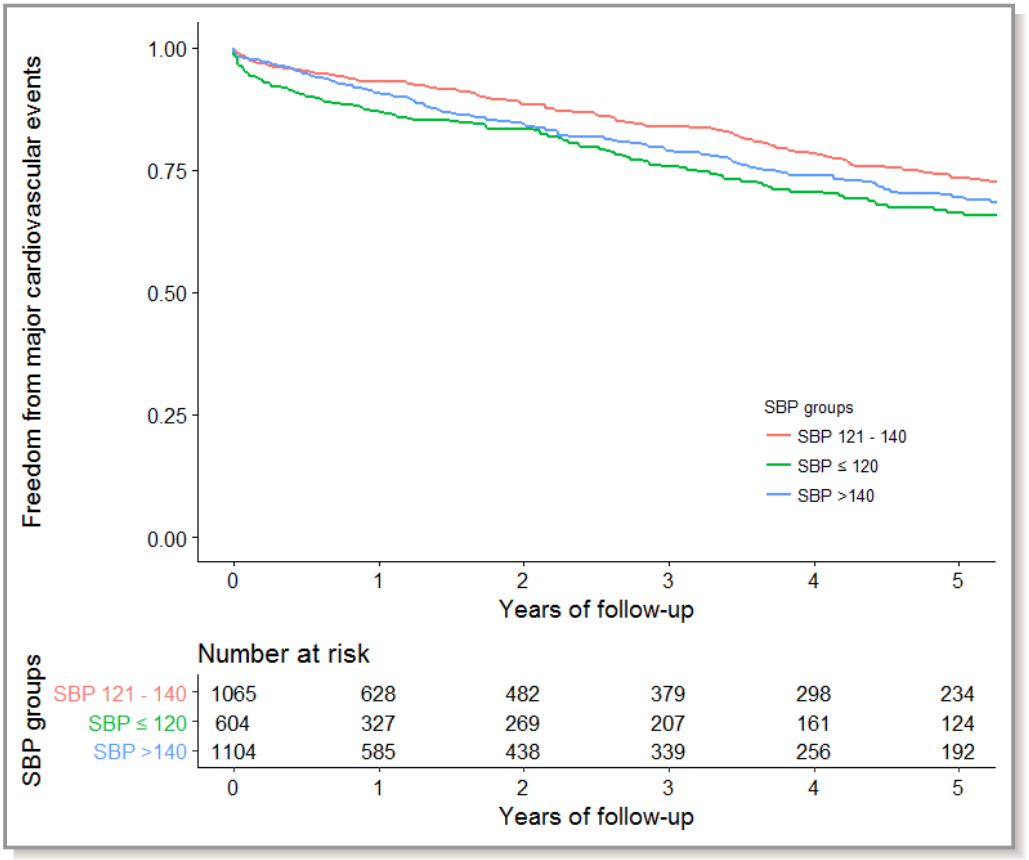

Figure 1. Kaplan-Meier survival curves illustrating freedom from major cardiovascular events (composite of myocardial infarction, stroke, or cardiovascular death), according to systolic blood pressure (SBP) in patients with peripheral artery disease. The red line represents patients with SBP between 121 and 140 mm Hg. The blue line represents patients with SBP >140 mm Hg, and the green line represents patients with SBP ≤120 mm Hg. Numbers below the table indicate the number of patients at risk at each time point. Differences were compared using the log-rank test (*P*=0.029).

analysis, the association between SBP ≤120 mm Hg and events remained in patients receiving antihypertension medications, supporting the possibility that intense lowering of SBP could have harmful effects in some patients with PAD. It is possible, although unproven, that not all patients with cardiovascular diseases should be treated so aggressively for hypertension, which may, in part, explain the disparate findings of the SPRINT and ACCORD trials.

Most current guidelines suggest that the SBP level of patients should be maintained at ≤140 mm Hg.[8,11–13] SPRINT demonstrated a 43% decrease in the relative risk of death from cardiovascular causes in patients randomized to intensive SBP lowering targeted at <120 mm Hg compared with patients allocated to less intensive SBP lowering targeted at <140 mm Hg.[16] On the contrary, the ACCORD trial did not establish any significant reduction in cardiovascular events, with intensive antihypertensive treatment aimed at lowering SBP to <120 mm Hg.[17] The prevalence of cardiovascular risk factors among patients in SPRINT was less when compared with the cohort of patients in this study. The proportion of patients who had ever smoked in the current cohort was significantly higher than in SPRINT (84.6% versus 55.5%). SPRINT also excluded patients with a history of stroke and diabetes mellitus, whereas these patients were included in both the ACCORD trial and the current study. The higher cardiovascular risk of the patients in this current study was apparent by higher event rates in the current study compared with SPRINT.

The optimal target BP in patients with PAD has not been specifically investigated. Although SPRINT included a subset of patients with PAD, the researchers recommendations cannot be generalized in a clinical setting because SPRINT excluded patients with diabetes mellitus and previous studies have suggested a strong association between diabetes mellitus and PAD.[36–39] Patients with PAD often present with concomitant diseases, and more than a quarter of the patients in this cohort had diabetes mellitus at recruitment. The INVEST (INternational VErapamil SR-Trandolapril) trial, which included patients with concomitant CHD and PAD, demonstrated a J-shaped relationship between SBP and the

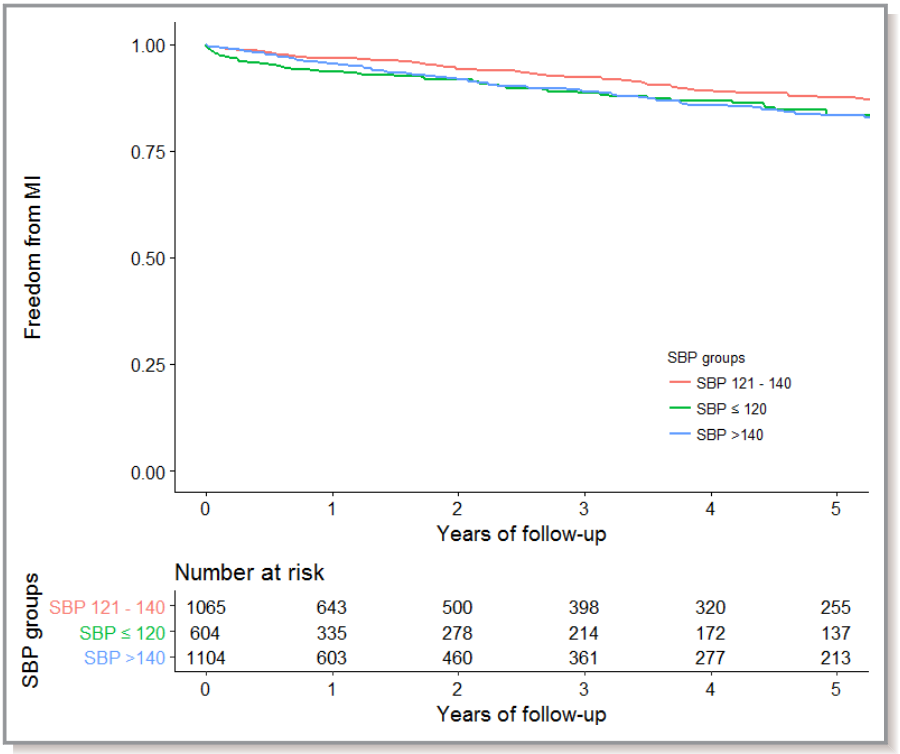

Figure 2. Kaplan-Meier survival curves illustrating freedom from myocardial infarction (MI) according to systolic blood pressure (SBP) in patients with peripheral artery disease. The red line represents patients with SBP between 121 and 140 mm Hg. The blue line represents patients with SBP >140 mm Hg, and the green line represents patients with SBP ≤120 mm Hg. Numbers below the table indicate the number of patients at risk at each time point. Differences were compared using the log-rank test (*P*=0.073).

composite of all-cause mortality, nonfatal MI, or stroke.[18] Patients without PAD did not demonstrate this relationship, suggesting that patients with PAD may require a different BP target. The lowest rate of cardiovascular events in the INVEST trial was observed in patients with SBP 135 to 145 mm Hg. The results of this study are consistent with the prospective observational study by the CLARIFY (ProspeCtive observational LongitudinAl RegIstry oF patients with stable coronary arterY disease) group, which included patients with stable CHD, and also with previous post hoc analyses from trials in patients with CHD and hypertension.[19,21,40] Previous studies have also demonstrated the J-shaped relationship between SBP and cardiovascular events in high-risk patients with cardiovascular diseases, diabetes mellitus, or target organ damage.[41,42]

This study has several strengths and limitations. The strength of the study included the recruitment of a large cohort of patients presenting to vascular clinics on a routine basis and treated in real-life practice. There was a difference in sample sizes of the 3 SBP groups, which may have influenced the findings. Overall, the study was well powered, however, because the smallest SBP group (≤120 mm Hg) still included >600 patients. The study was part of a prospective cohort study and not a randomized trial. Thus, the associations demonstrated are subject to the possibility of residual confounding, which we attempted to minimize by adjusting for recognised cardiovascular risk factors. It remains possible that factors we did not measure and, therefore, could not adjust for led to residual confounding. Also, SBP was routinely recorded only at recruitment and, thus, we could not assess the association of SBP recorded over time with cardiovascular events. Furthermore, because this is an observational study, not an interventional trial targeting a specific SBP, there is potential for reverse causality. Because data on heart failure were not collected during recruitment, frusemide prescription was selected to reflect this. This may have caused additional confounding.

Additional analyses were performed to analyze the association between DBP or PP and cardiovascular events. The findings support past research, suggesting that SBP has a stronger association with clinical events than other markers of high BP.[43,44]

In conclusion, the findings of the current observational study identify patients with PAD and SBP ≤120 and >140 mm Hg as at high risk of cardiovascular events and death. The findings of this study do not contradict those of

well-designed clinical trials targeting BP reduction given the different design of those studies, which address different questions.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Association of different systolic blood pressure categories with outcome events in the subgroup including additional covariates DBP and eGFR.

Outcome	SBP (mmHg)	Subgroup (n = 2358)	
		HR (95%CI)	P value
Major CVE*	121 - 140	1.00 (ref)	N/A
	≤ 120	1.30 (1.02 – 1.65)†	0.036
	>140	1.24 (1.00 – 1.54)†	0.049
MI	121 - 140	1.00 (ref)	N/A
	≤ 120	1.30 (0.93 – 1.82)ǂ	0.131
	>140	1.44 (1.07 – 1.94)ǂ	0.016
Stroke	121 - 140	1.00 (ref)	N/A
	≤ 120	1.07 (0.70 – 1.62)§	0.767
	>140	1.20 (0.83 – 1.72)§	0.334
Cardio-vascular death	121 - 140	1.00 (ref)	N/A
	≤ 120	1.32 (0.95 – 1.85)	0.102
	>140	1.12 (0.82 – 1.52)	0.483
All- cause mortality	121 - 140	1.00 (ref)	N/A
	≤ 120	1.31 (1.03 – 1.67)	0.029
	>140	1.01 (0.81 – 1.26)	0.933

The results are expressed in Hazards ratio (HR) and 95% confidence interval (CI). Regression models were adjusted for age categories, sex, PAD presenting problem, smoking, diabetes, CHD, DBP, BMI, eGFR, prescriptions for statin and frusemide.

*Defined as MI, stroke or cardiovascular death.

† Patient presenting problem and age at recruitment were stratified in this model to conform to the proportional hazards assumption.

ǂ CHD was stratified in this model in order to conform to the proportional hazards assumption.

§ Diabetes was stratified in this model in order to conform to the proportional hazards assumption.

BMI – Body mass index, CHD – coronary heart disease, CVE – cardiovascular event, DBP – Diastolic blood pressure, eGFR – estimated glomerular filtration rate, MI – myocardial infarction, SBP – systolic blood pressure.

Table S2. Association of different diastolic blood pressure categories with outcome events in the whole cohort.

Outcome	DBP (mmHg)	Whole cohort (n = 2496)	
		HR (95%CI)	P value
Major CVE*	80 - 89	1.00 (ref)	N/A
	< 80	1.00 (0.81 – 1.23)†	0.991
	≥ 90	0.91 (0.65 – 1.27)†	0.567
MI	80 - 89	1.00 (ref)	N/A
	< 80	1.13 (0.83–1.53)ǂ	0.431
	≥ 90	1.08 (0.68–1.73)ǂ	0.743
Stroke	80 - 89	1.00 (ref)	N/A
	< 80	1.06 (0.75–1.51)§	0.742
	≥ 90	0.58 (0.30–1.13)§	0.109
Cardio- vascular death	80 - 89	1.00 (ref)	N/A
	< 80	0.82 (0.61–1.10)	0.193
	≥ 90	0.77	0.299

		(0.47–1.26)	
All-cause mortality	80 - 89	1.00 (ref)	N/A
	< 80	0.92 (0.74–1.14)	0.444
	≥ 90	0.86 (0.61–1.23)	0.413

The results are expressed in Hazards ratio (HR) and 95% confidence interval (CI). Regression models were adjusted for age categories, sex, PAD presenting problem, smoking, diabetes, CHD, BMI, statin and frusemide prescription.

*Defined as MI, stroke or cardiovascular death.

† Patient presenting problem and age category were stratified in this model to conform to the proportional hazards assumption.

ǂ CHD was stratified in this model in order to conform to the proportional hazards assumption.

§ Diabetes was stratified in this model in order to conform to the proportional hazards assumption.

BMI – Body mass index, CHD – coronary heart disease, CVE – cardiovascular event, DBP – diastolic blood pressure, MI – myocardial infarction.

Table S3. Association of different pulse pressure categories with outcome events in the whole cohort.

Outcome	PP (mmHg)	Whole cohort (n = 2496)	
		HR (95%CI)	P value
Major CVE*	54 - 68	1.00 (ref)	N/A
	≤ 53	0.97 (0.78 – 1.21)†	0.784
	> 68	1.07 (0.86 – 1.33)†	0.548
MI	54 - 68	1.00 (ref)	N/A
	≤ 53	0.90 (0.65–1.24)ǂ	0.517
	> 68	1.13 (0.84 –1.52)ǂ	0.406
Stroke	54 - 68	1.00 (ref)	N/A
	≤ 53	0.93 (0.63–1.37)§	0.705
	> 68	1.14 (0.79–1.65)§	0.470
Cardio-vascular death	54 - 68	1.00 (ref)	N/A
	≤ 53	1.06 (0.77–1.46)	0.734
	> 68	1.05	0.778

		(0.77–1.42)	
All-cause mortality	54 - 68	1.00 (ref)	N/A
	≤ 53	1.05 (0.84–1.32)	0.662
	> 68	0.97 (0.78–1.22)	0.823

The results are expressed in Hazards ratio (HR) and 95% confidence interval (CI). Regression models were adjusted for age categories, sex, PAD presenting problem, smoking, diabetes, CHD, BMI, statin and frusemide prescription.

*Defined as MI, stroke or cardiovascular death.

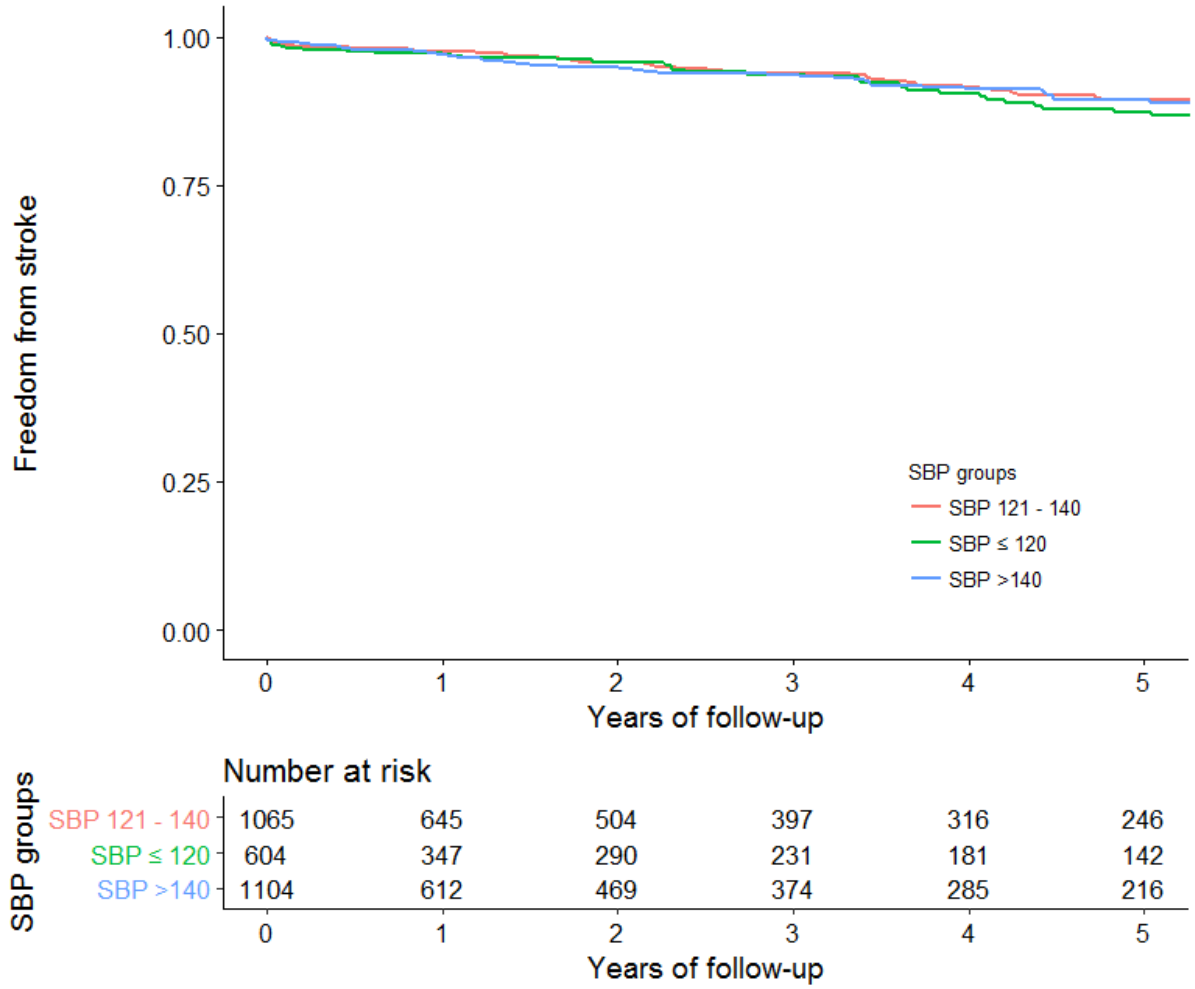
† Patient presenting problem and age category were stratified in this model to conform to the proportional hazards assumption.

ǂ CHD and statin were stratified in this model in order to conform to the proportional hazards assumption.

§ Diabetes was stratified in this model in order to conform to the proportional hazards assumption.

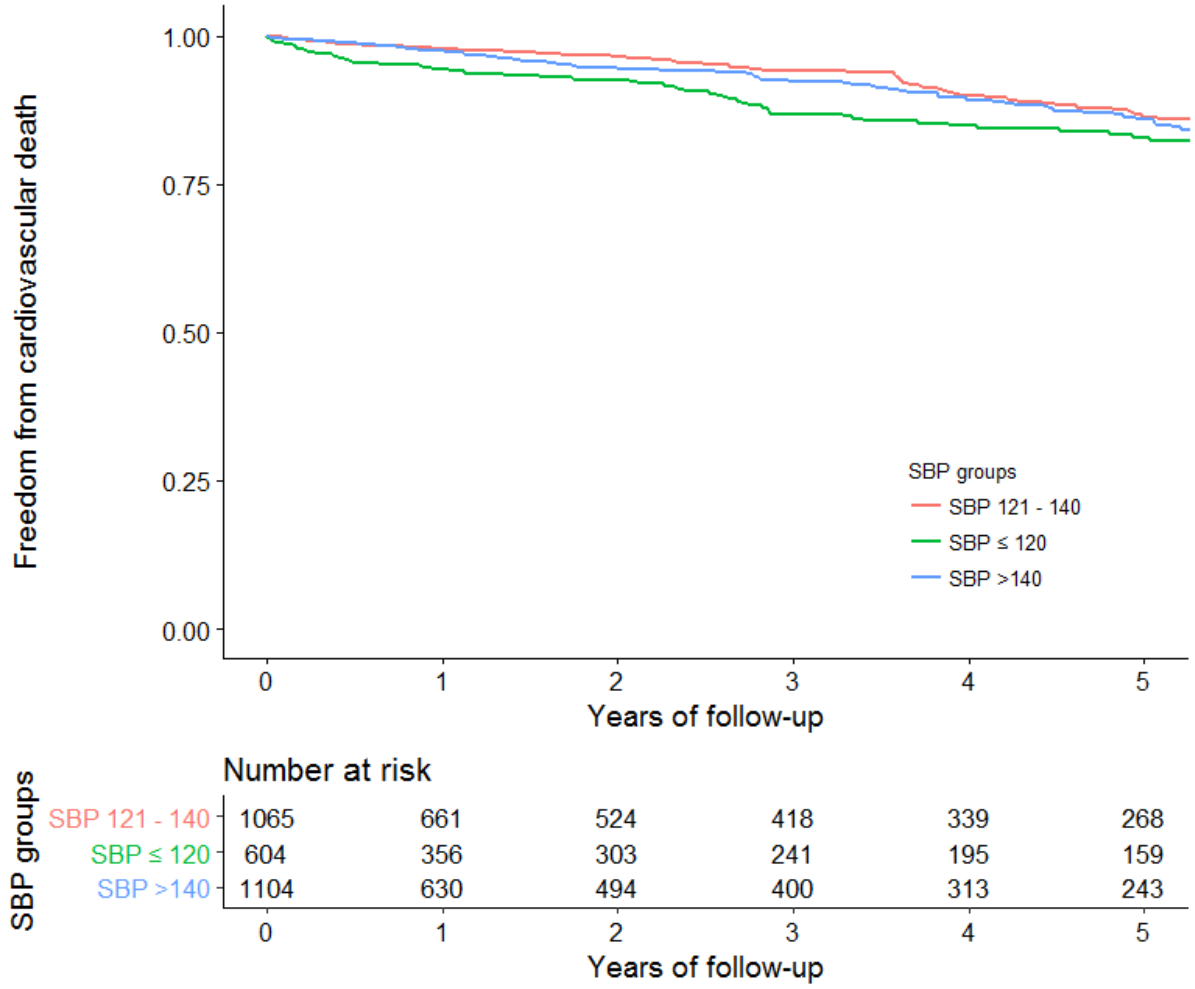
BMI – Body mass index, CHD – coronary heart disease, CVE – cardiovascular event, MI – myocardial infarction, PP - pulse pressure.

Figure S1. Kaplan- Meier survival curves illustrating freedom from stroke according to SBP in patients with PAD.



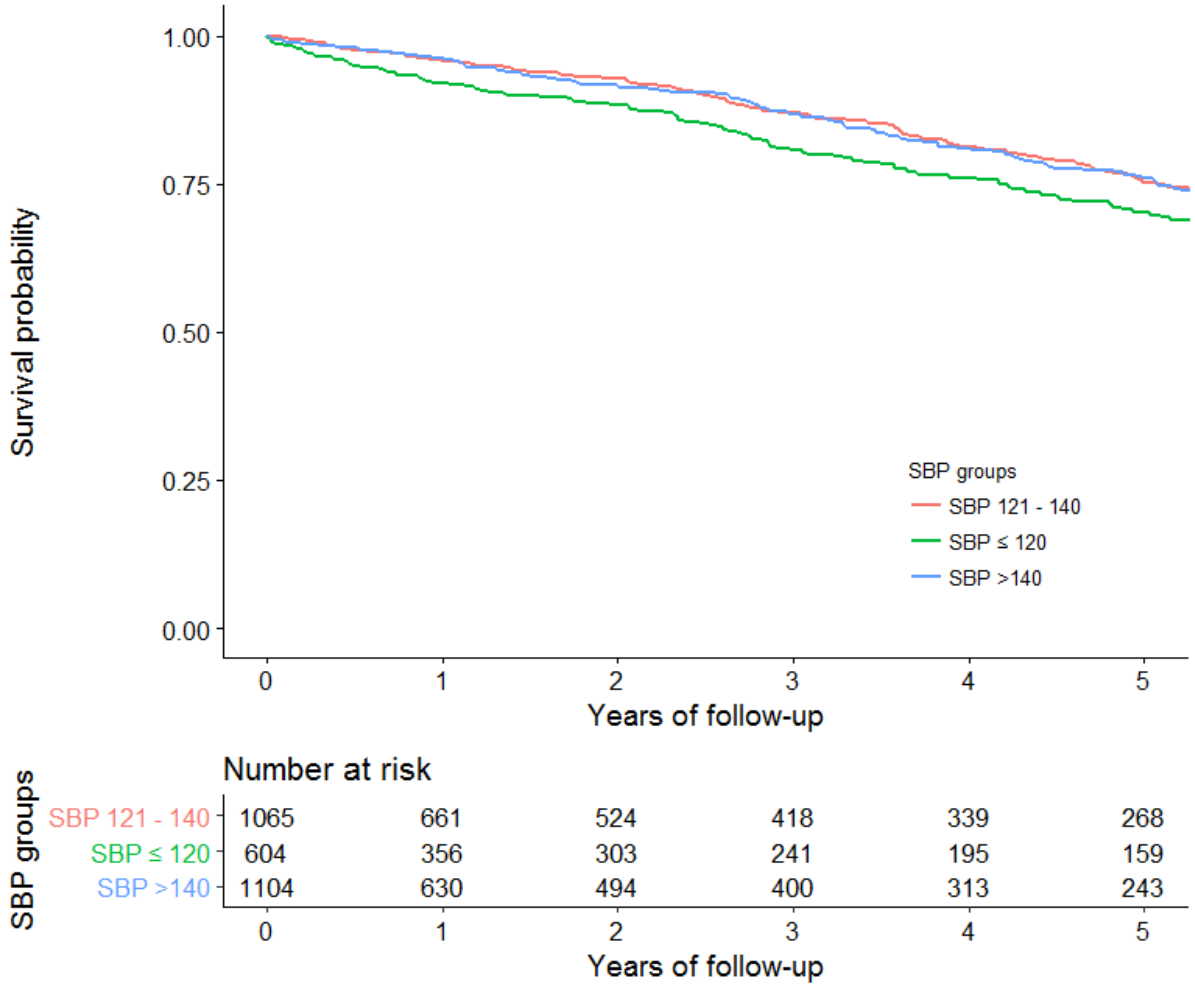
The red line represents patients with SBP between 121 to 140 mmHg. The blue line represents patients with SBP >140 mmHg and green line represents patients with SBP ≤ 120 mmHg. Numbers below the table indicate the number of patients at risk at each time point. Differences were compared using log-rank test (p=0.52). Abbreviations: PAD – peripheral artery disease and SBP – systolic blood pressure.

Figure S2. Kaplan- Meier survival curves illustrating freedom from cardiovascular death according to SBP in patients with PAD.



The red line represents patients with SBP between 121 to 140 mmHg. The blue line represents patients with SBP >140 mmHg and green line represents patients with SBP ≤ 120 mmHg. Numbers below the table indicate the number of patients at risk at each time point. Differences were compared using log-rank test (p=0.15). Abbreviations: PAD – peripheral artery disease and SBP – systolic blood pressure.

Figure S3. Kaplan- Meier survival curves illustrating freedom from all-cause mortality according to SBP in patients with PAD.



The red line represents patients with SBP between 121 to 140 mmHg. The blue line represents patients with SBP >140 mmHg and green line represents patients with SBP ≤ 120 mmHg. Numbers below the table indicate the number of patients at risk at each time point. Differences were compared using log-rank test (p=0.082). Abbreviations: PAD – peripheral artery disease and SBP – systolic blood pressure.