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2017 AHA/ACC blood pressure classification and incident peripheral artery disease: the Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Aims: To evaluate the associations of blood pressure (BP) categorization based on the 2017 American Heart Association and the American College of Cardiology guideline with the risk of peripheral artery disease (PAD).

Methods: Among 13,113 middle-aged participants, we investigated the associations of 2017 BP categories (systolic <120 and diastolic <80 mmHg [normal if no anti-hypertensive medications; reference], 120–129 and <80 [elevated], 130–139 and/or 80–89 [stage 1 hypertension], and 140 and/or 90 [stage 2 hypertension]) with incident PAD (hospitalizations with a diagnosis or leg revascularization) using Cox regression models. Analyses were separately conducted in individuals with and without anti-hypertensive medications.

Results: During a median follow-up of 25.4 years, 466 incident PAD occurred (271 cases in 9,858 participants without anti-hypertensive medications). In participants without anti-hypertensive medications, we observed significant hazard ratios of PAD in elevated BP (1.80 [1.28–2.51]) and stage 2 hypertension (2.40 [1.72–3.34]), but not in stage 1 hypertension. Analyzing systolic and diastolic BP separately, higher systolic BP categories showed significant associations with incident PAD in a graded fashion whereas, for diastolic BP, only 90 mmHg did.

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Authors' Contributions

YL, and KM conceived, designed the research, and wrote the manuscript. YL conducted the statistical analyses. SB, HT, MS, GH, and JC participated in the critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

Declaration of conflicting interests:

The Author(s) declare(s) that there is no conflict of interest

Generally similar patterns were seen among participants on anti-hypertensive medication, while they had higher risk of PAD than those without at each BP category.

Conclusions: Systolic BP, including the category of 130–139 mmHg, showed stronger associations with incident PAD than diastolic BP. Consequently, elevated BP conferred similar or even greater risk of PAD than stage 1 hypertension, with implications on how to interpret new BP categories in terms of leg vascular health.

Keywords

Blood pressure; peripheral artery disease; critical limb ischemia

Introduction:

Lower-extremity peripheral artery disease (PAD) affects more than 200 million individuals around the world.¹ Among traditional atherosclerotic risk factors (e.g., smoking, diabetes, and hypertension), elevated blood pressure (BP) is an important contributor to the total burden of PAD.² For example, a US study reported the population attributable fraction of hypertension for PAD to be 41%.³

Despite the well-acknowledged contribution of BP to the development of PAD, some prior studies were cross-sectional and could not infer temporality between BP and PAD.^{4–6} This design is particularly suboptimal for assessing the BP-PAD relationship, since brachial BP is used to determine ankle-brachial index (the ratio of ankle systolic BP [SBP] to brachial SBP), which is both the exposure and the outcome to define PAD. Although there were several prospective studies,^{3, 7–11} many have investigated selected populations (e.g., diabetic patients,⁷ white race,^{3, 7–11} older adults,⁹ only women¹¹ or men,^{3, 10} and those with multiple cardiovascular risk factors¹⁰). In addition, most previous prospective studies had a relatively short follow up of <10 years.^{7–9}

More importantly, the 2017 American Heart Association (AHA) and the American College of Cardiology (ACC) Hypertension Guideline redefined hypertension as SBP ≥130 or diastolic BP (DBP) ≥80 mmHg, classifying 103.3 million US adults as having hypertension.¹² None of the aforementioned previous prospective studies evaluated the association with PAD using this new classification. Although a few previous studies explored this study question for other cardiovascular outcomes like coronary heart disease and stroke,^{13, 14} specific investigation for PAD is necessary since risk factor profile differs across vascular beds.¹⁵

Therefore, using data from a community-based middle-aged cohort at baseline, the Atherosclerosis Risk in Communities (ARIC) Study, we primarily aimed to assess the association of BP, in the context of the 2017 AHA/ACC BP classification, with incident PAD over a 25-year follow-up. A large sample size with long follow-up allowed us to uniquely evaluate critical limb ischemia (CLI), the severe form of PAD with tissue loss, as an outcome. Since a few recent studies have shown that BP components other than SBP and DBP, e.g., pulse pressure (PP) and mean arterial pressure (MAP),¹⁶ may provide additional

information on some subtypes of cardiovascular disease, we also secondarily explored those BP components for PAD risk.

Methods:

Study population

The ARIC study enrolled 15,792 middle-aged adults from four US communities (Forsyth County, North Carolina; Jackson, Mississippi; suburban Minneapolis, Minnesota; and Washington County, Maryland) during the period of 1987–1989.¹⁷ Subsequent follow-up visits were performed in 1990–1992, 1993–1995, 1996–1998, and 2011–2013, respectively. For the current analysis, we included 13,113 participants with complete BP assessment, PAD follow-up, and information on covariates of interests. Excluded participants were summarized in Supplementary Material. The study protocol was approved by the Institutional Review Boards of all ARIC study sites, and all participants provided a written informed consent.

Blood pressure components

The sitting arm BP was measured three times, after 5 minutes of quiet rest, with a standardized Hawksley random-zero sphygmomanometer at each visit.¹⁸ Due to the well-known BP variability notwithstanding the fact that its measurement was standardized (Supplementary material Figure 1), we averaged second and third readings for the analysis. Primary BP components of interest were SBP and DBP. As secondary BP components, MAP was calculated as $(\text{SBP} + 2 \times \text{DBP})/3$ and rounded to the nearest integer, and PP was defined as SBP minus DBP.¹⁶

Outcomes

First hospitalization with PAD diagnosis or leg revascularization was identified using International Classification of Disease (ICD)-9 codes.¹⁹ Details are provided in the Supplementary Material.

Covariates

A detailed description of covariates is provided in the Supplementary Material.

Statistical analysis

All analyses were conducted separately for those with and without anti-hypertensive medications. Baseline characteristics were summarized across 2017 BP categories:²⁰ 1) SBP <120 and DBP <80 (normal BP if no anti-hypertensive medications); 2) SBP 120–129 and DBP <80 (elevated BP); 3) SBP 130–139 and/or DBP 80–89 (stage 1 hypertension); and 4) SBP ≥140 and/or DBP ≥90 (stage 2 hypertension).

Kaplan-Meier estimates were used for PAD- and CLI-free survival across BP categories. Cox proportional hazards models were used to quantify the prospective associations of BP categories with PAD and CLI. We adjusted for the following potential confounders: age, gender, race, education, smoking and drinking status, body mass index (BMI), total and

high-density lipoprotein (HDL) cholesterol, cholesterol-lowering medication, estimated glomerular filtration rate (eGFR), and prevalent diabetes.

We also explored SBP and DBP categories separately according to 2017 ACC/AHA Hypertension Guideline:²⁰ <120, 120–129, 130–139, and ≥140 and <70, 70–79, 80–89, ≥90, respectively. We split DBP <80 into <70 and 70–79 to have four categories as SBP. We evaluated whether the associations of BP categories differed for incident CLI vs. PAD without CLI, using seemingly unrelated estimation.²¹

We secondarily repeated analyses for MAP and PP. MAP and PP were categorized in 10 mmHg increments from the first quartile cutoff point rounding to the nearest tens: <80, 80–89, 90–99, ≥100 and <40, 40–49, 50–59, ≥60, respectively. Pearson correlation coefficients were calculated among four BP components of SBP, DBP, MAP, and PP. To allow direct comparison among BP components, each single BP component was scaled by 1 standard deviation (SD) and modeled continuously. Then we combined DBP, MAP, and PP, in turn, together with SBP since previous studies have shown SBP as the strongest BP-related predictor of cardiovascular events.¹⁶

Finally, to confirm the robustness of our results, we performed a few sensitivity analyses. First, we conducted subgroup analyses stratified by age, gender, race, smoking, and diabetes status. Potential multiplicative interactions with BP components were evaluated using the likelihood ratio test. Second, we censored PAD hospitalizations that occurred in the first 1–5 years of follow up, thus, likely preserving the temporal relationship of BP with PAD. Finally, we applied time-varying analysis using BP values and covariates collected at up to five follow-up visits, with the last available data carried forward in case of missing values.

All analyses were performed with Stata version 14.0, and a p-value <0.05 was considered statistically significant.

Results:

Of 13,113 ARIC participants, 9,858 individuals (75.2%) were not taking anti-hypertensive medications at baseline. For participants without anti-hypertensive medications, the mean age was 53.5 (SD, 5.7) years, with 53.2% female and 21.0% black. Compared to participants with normal BP, those with higher BP categories were more likely to be older and black but less likely to be well educated, and current drinkers. They also had higher BMI, total cholesterol, and prevalence of diabetes. There was a J-shaped or inverse J-shaped association with proportion of female, current smokers, and cholesterol-lowering medication (Table 1). Largely consistent patterns were also observed for participants with anti-hypertensive medications (Supplementary material Table 1).

We observed largely similar distributions of participant characteristics across levels of SBP, DBP, MAP, and PP, although there was an inverse association between age and DBP categories, and between female proportion and DBP as well as MAP (Supplementary material Tables 2–5). These four BP components were weakly to highly correlated with each other for participants without anti-hypertensive medications (Supplementary material Table 6). Similar pattern was seen for participants with anti-hypertensive medications.

During a median follow-up of 25.4 years (maximum of 28.1 years), 466 incident PAD and 178 CLI cases were identified (271 and 89 cases respectively in those without anti-hypertensive medications). Among those without anti-hypertensive medications, the lowest PAD-free survival was seen for stage 2 hypertension and the highest survival for normal BP (Figure 1A; log-rank $P < 0.001$). Stage 1 hypertension and elevated BP showed similar PAD-free survival up to ~18 years but then elevated BP had a lower PAD-free survival than stage 1 hypertension. Generally similar patterns were observed for corresponding BP categories among participants on anti-hypertensive medications but with lower PAD-free survival (Figure 1B; $P < 0.001$). CLI-free survival showed similar patterns although the SBP 120–129 and DBP < 80 and SBP 130–139 or DBP 80–89 showed almost identical survival estimates (Supplementary material Figure 2; $P < 0.001$ for panels A and B).

These patterns were consistent after accounting for potential confounders (Figure 2). Specifically, in participants without anti-hypertensive medications, hazard ratios of PAD were 1.80 (95% CI 1.28–2.51) in elevated BP and 2.40 (1.72–3.34) in stage 2 hypertension. In contrast, stage 1 hypertension did not demonstrate a significant hazard ratio (1.37 [0.98–1.91]). Generally similar results were observed for CLI in this population, although elevated BP did not reach statistical significance (hazard ratio 1.82 [0.95–3.49]). Stage 2 hypertension showed a hazard ratio of 3.19 (1.83–5.58) for CLI which was significantly greater than that for PAD without CLI (Supplementary material Table 7). We generally observed similar patterns among participants with anti-hypertensive medications, but the hazards of PAD and CLI at a given BP category were consistently higher for those with anti-hypertensive medications than those without (Figure 2).

Analyzing SBP and DBP separately among participants without antihypertensive medications, for PAD, with SBP < 120 mmHg as a reference, the hazard ratio was 2.63 (1.88–3.67) for SBP 140, 1.57 (1.08–2.30) for 130–139, and 1.63 (1.20–2.21) for SBP 120–129 mmHg. The corresponding estimates for CLI were 3.31 (1.89–5.80), 2.33 (1.27–4.30), and 1.63 (0.91–2.93), with SBP 130–139 showing a significantly higher hazard ratio for CLI than PAD without CLI (Supplementary material Table 7). By contrast, the graded pattern was not evident for DBP, with significant associations with PAD and CLI only in the DBP category ≥ 90 mmHg (hazard ratios, 2.15 [1.37–3.37] for PAD and 2.70 [1.38–5.27] for CLI). Participants on anti-hypertensive medications generally demonstrated similar patterns but again, at a given BP category, those with anti-hypertensive medications had greater risk of PAD and CLI than those without (Figure 3).

We also explored MAP or PP categories (Supplementary material Figure 3). Like DBP, the significant associations with PAD and CLI were seen only in the highest MAP category ≥ 100 mmHg (hazard ratios, 1.94 [1.32–2.87] for PAD and 3.03 [1.47–6.25] for CLI). We observed a similar graded pattern for PP as what we saw in SBP. Subsequently, we compared the four BP components, by modeling as their 1 SD increment (Table 2). For those without anti-hypertensive medications, each BP component demonstrated a significant association with increased PAD and CLI risks when modeled separately, with the highest adjusted hazard ratio for SBP followed by PP, MAP, and DBP. However, none of DBP, MAP, and PP remained significant for both PAD and CLI when modeled together with SBP. Generally similar patterns were seen among participants on anti-hypertensive medications.

One exception was that PP showed a stronger association than SBP with both PAD and CLI when they were modeled simultaneously (e.g., hazard ratio of PAD 1.30 [1.06–1.59] for PP vs. 1.14 [0.91–1.44] for SBP).

Sensitivity analysis

In demographic and clinical subgroups explored, we only observed a significant multiplicative interaction for diabetes with SBP (P for interaction 0.036 for PAD, Supplementary material Figure 4) among no hypertensive treatment group, and for gender with BP (P = 0.041 for PAD), age with SBP (P = 0.014 for PAD) among hypertensive treatment group. Although the patterns were somewhat heterogeneous, in general SBP 140 mmHg and stage 2 hypertension demonstrated highest hazard ratios for PAD. In other sensitivity analyses, after censoring PAD and CLI cases occurring in the first 1–5 years of follow-up, our results remained virtually the same (Supplementary material Figure 5–9). Similarly, results were consistent when we performed time-varying analysis of SBP and DBP (Supplementary material Figure 10).

Discussion:

In this large-scale prospective cohort study of middle-aged men and women with more than 25 years of follow-up, among those without anti-hypertensive medications, the 2017 AHA/ACC categories of elevated BP and stage 2 hypertension, but not stage 1 hypertension, were significantly associated with incident PAD. When SBP and DBP were analyzed separately, we saw an overall gradient of PAD- and CLI-risk associated with increasing SBP but, for DBP, only the 90 mmHg conferred significant risk. Importantly, SBP 130–139 mmHg, newly considered as a part of stage 1 hypertension, showed significant associations with both incident PAD and CLI, with more evident results for the latter. Generally similar patterns were observed in participants on anti-hypertensive medications, but they had higher PAD- and CLI-risk compared to those without anti-hypertensive medications at a given BP category. In participants without anti-hypertensive medications, SBP was more strongly and robustly associated with PAD than DBP, MAP or PP. In contrast, among those with anti-hypertensive medications, PP showed a more robust association with PAD than SBP.

A growing body of evidence showing poor prognosis of PAD patients indicates the importance of preventing PAD.^{22–24} In this context, hypertension is an established risk factor of PAD,^{3, 7–11} but our study extended previous literature in a few aspects. First, to our knowledge, this is the first study quantifying the association of 2017 AHA/ACC BP categories for PAD risk. Our results highlight some caveats (e.g., elevated BP actually conferring higher risk of PAD than stage 1 hypertension), which is discussed subsequently. Second, our study uniquely assessed CLI, the most severe form of PAD, in a community-based cohort, and the association was significantly stronger for CLI than for PAD without CLI in several BP categories. Third, we explored a comprehensive contribution of BP in developing PAD beyond SBP and DBP, and contrasted the magnitude of hazard ratios of PAD across four BP components including MAP and PP.

The fact that newly defined stage 1 hypertension did not necessarily relate to a higher risk of PAD and CLI deserves some discussion. Consistent with previous observations for other

cardiovascular diseases,²⁵ we observed that SBP was more consistently and strongly associated with PAD and CLI than DBP. For DBP, only its category ≥ 90 mmHg was related to an increased PAD risk. Thus, isolated high DBP (particularly between 80–90 mmHg), accounting for 47.2% stage 1 hypertension in our study (Supplementary material Figure 11), did not contribute to an increased PAD risk, which can explain less evident results for stage 1 hypertension compared with elevated BP defined by elevated SBP.

In our study, several high BP categories demonstrated a stronger association with CLI than PAD without CLI, particularly among participants without anti-hypertensive medications. Although exact mechanisms are not clear, this may be explained by the fact that the development of CLI is not a simple progression of PAD but involve other pathophysiologic changes such as microcirculation abnormality impairing collateral formation and wound healing.²⁶ Indeed, high BP is postulated to cause microvascular rarefaction and inadequate perfusion of surrounding tissues, which contribute to tissue injury and end-organ damages.²⁷

At the same BP level, participants with anti-hypertensive medications had a greater risk of incident PAD and CLI than those without. It is likely that this was due to “confounding by indication” whereby participants on anti-hypertensive medications had higher risk conditions than those not on anti-hypertensive medications (e.g., due to higher BP, longer duration of hypertension, and other comorbidities such as diabetes). Thus, this observation should not be interpreted as meaning that anti-hypertensive medications increase PAD risk.

In contrast to SBP as the most potent predictor of PAD in individuals without anti-hypertensive medications, PP was more strongly related to PAD than SBP among those with anti-hypertensive medications. Wide PP reflects arterial stiffness and the declined vascular function to constantly perfuse blood to peripheral tissues through Windkessel effect.²⁸ Under anti-hypertensive treatment, wide PP may additionally reflect inadequate SBP reduction²⁹ and/or an excess reduction in DBP.³⁰ 2017 ACC/AHA Hypertension Guideline on the management of hypertension did not specifically mention PP;¹² in contrast, the 2018 European Society of Cardiology/European Society of Hypertension Guideline acknowledged PP as an important cardiovascular predictor in hypertensive patients.³¹ Our results thus support the importance of PP in hypertension management from the perspective of leg vascular health. Nonetheless, more studies and trials would be needed to explore values of PP for hypertension management.

This study has some limitations. First, the identification of PAD and CLI relied on discharge ICD-9 codes. This approach has been often used¹⁹ but is likely to miss mild PAD cases. Nonetheless, it is important to quantify the association of 2017 BP categories with severe PAD cases, since severe PAD cases are main drivers for medical expenditure related to PAD and substantially impaired quality of life.³² Secondly, ARIC included individuals who, at baseline, were aged 45–64 years and both whites and blacks and, thus, caution is needed to generalize the results outside this age range and to other racial/ethnic groups. Finally, as for any observational study, we cannot exclude the possibility of residual confounding.

In conclusion, SBP showed stronger associations with incident PAD and CLI than DBP. Consequently, elevated BP defined by elevated SBP, conferred similar, or even greater risk

of PAD than stage 1 hypertension including elevated SBP or DBP, with implications on how to interpret 2017 AHA/ACC BP categories in terms of leg vascular health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Reference:

1. Hirsch AT and Duval S. The global pandemic of peripheral artery disease. *Lancet* (London, England) 2013; 382: 1312–1314. 2013/08/07. DOI: 10.1016/s0140-6736(13)61576-7.
2. Criqui MH and Aboyans V. Epidemiology of peripheral artery disease. *Circulation research* 2015; 116: 1509–1526. 2015/04/25. DOI: 10.1161/circresaha.116.303849. [PubMed: 25908725]
3. Joosten MM, Pai JK, Bertola ML, et al. Associations between Conventional Cardiovascular Risk Factors and Risk of Peripheral Artery Disease in Men. *JAMA: the journal of the American Medical Association* 2012; 308: 1660–1667. DOI: 10.1001/jama.2012.13415. [PubMed: 23093164]
4. Selvin E and Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999–2000. *Circulation* 2004; 110: 738–743. 2004/07/21. DOI: 10.1161/01.cir.0000137913.26087.f0. [PubMed: 15262830]
5. Criqui MH, Vargas V, Denenberg JO, et al. Ethnicity and peripheral arterial disease: the San Diego Population Study. *Circulation* 2005; 112: 2703–2707. 2005/10/26. DOI: 10.1161/circulationaha.105.546507. [PubMed: 16246968]
6. Subramaniam T, Nang EE, Lim SC, et al. Distribution of ankle-brachial index and the risk factors of peripheral artery disease in a multi-ethnic Asian population. *Vascular medicine* (London, England) 2011; 16: 87–95. 2011/03/31. DOI: 10.1177/1358863x11400781.
7. Adler AI, Stevens RJ, Neil A, et al. UKPDS 59: hyperglycemia and other potentially modifiable risk factors for peripheral vascular disease in type 2 diabetes. *Diabetes care* 2002; 25: 894–899. 2002/04/30. [PubMed: 11978687]
8. Emdin CA, Anderson SG, Callender T, et al. Usual blood pressure, peripheral arterial disease, and vascular risk: cohort study of 4.2 million adults. *BMJ (Clinical research ed)* 2015; 351: h4865. 2015/10/01. DOI: 10.1136/bmj.h4865.
9. Kennedy M, Solomon C, Manolio TA, et al. Risk factors for declining ankle-brachial index in men and women 65 years or older: the Cardiovascular Health Study. *Archives of internal medicine* 2005; 165: 1896–1902. 2005/09/15. DOI: 10.1001/archinte.165.16.1896. [PubMed: 16157835]
10. Baker JF, Schumacher HR and Krishnan E. Serum uric acid level and risk for peripheral arterial disease: analysis of data from the multiple risk factor intervention trial. *Angiology* 2007; 58: 450–457. 2007/09/19. DOI: 10.1177/0003319707303444. [PubMed: 17875958]
11. Powell TM, Glynn RJ, Buring JE, et al. The relative importance of systolic versus diastolic blood pressure control and incident symptomatic peripheral artery disease in women. *Vascular medicine* (London, England) 2011; 16: 239–246. 2011/07/07. DOI: 10.1177/1358863x11413166.

12. Muntner P, Carey RM, Gidding S, et al. Potential U.S. Population Impact of the 2017 ACC/AHA High Blood Pressure Guideline. *Journal of the American College of Cardiology* 2018; 71: 109–118. 2017/11/18. DOI: 10.1016/j.jacc.2017.10.073. [PubMed: 29146532]
13. Colantonio LD, Booth JN 3rd, Bress AP, et al. 2017 ACC/AHA Blood Pressure Treatment Guideline Recommendations and Cardiovascular Risk. *Journal of the American College of Cardiology* 2018; 72: 1187–1197. 2018/09/08. DOI: 10.1016/j.jacc.2018.05.074. [PubMed: 30189994]
14. Yano Y, Reis JP, Colangelo LA, et al. Association of Blood Pressure Classification in Young Adults Using the 2017 American College of Cardiology/American Heart Association Blood Pressure Guideline With Cardiovascular Events Later in Life. *Jama* 2018; 320: 1774–1782. 2018/11/07. DOI: 10.1001/jama.2018.13551. [PubMed: 30398601]
15. O'Rourke MF. Pressure and flow waves in systemic arteries and the anatomical design of the arterial system. *Journal of applied physiology* 1967; 23: 139–149. 1967/08/01. DOI: 10.1152/jappl.1967.23.2.139. [PubMed: 5340142]
16. Mosley WJ 2nd, Greenland P, Garside DB, et al. Predictive utility of pulse pressure and other blood pressure measures for cardiovascular outcomes. *Hypertension (Dallas, Tex: 1979)* 2007; 49: 1256–1264. 2007/04/11. DOI: 10.1161/hypertensionaha.106.083592.
17. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. *American journal of epidemiology* 1989; 129: 687–702. 1989/04/01. [PubMed: 2646917]
18. Atherosclerosis Risk in Communities study Protocol Manual 11: Sitting Blood Pressure. https://www2.csc.unc.edu/aric/sites/default/files/public/manuals/Sitting_Blood_Pressure_and_Postural_Changes_in_Blood_Pressure_and_Heart_Rate.1_11.pdf.
19. Vart P, Coresh J, Kwak L, et al. Socioeconomic Status and Incidence of Hospitalization With Lower-Extremity Peripheral Artery Disease: Atherosclerosis Risk in Communities Study. *Journal of the American Heart Association* 2017; 6 2017/09/02. DOI: 10.1161/jaha.116.004995.
20. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension (Dallas, Tex: 1979)* 2017 2017/11/15. DOI: 10.1161/hyp.0000000000000065.
21. White H Estimation Inference and Specification Analysis. Cambridge: Cambridge University Press, 1994.
22. Bonaca MP, Nault P, Giugliano RP, et al. Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With Peripheral Artery Disease: Insights From the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk). *Circulation* 2018; 137: 338–350. 2017/11/15. DOI: 10.1161/circulationaha.117.032235. [PubMed: 29133605]
23. Cea Soriano L, Fowkes FGR, Johansson S, et al. Cardiovascular outcomes for patients with symptomatic peripheral artery disease: A cohort study in The Health Improvement Network (THIN) in the UK. *European journal of preventive cardiology* 2017; 24: 1927–1937. 2017/10/21. DOI: 10.1177/2047487317736824. [PubMed: 29053020]
24. De Buyzere ML. Do not hesitate: Peripheral artery disease is a fatal condition! *European journal of preventive cardiology* 2018; 25: 260–262. 2017/12/16. DOI: 10.1177/2047487317748218. [PubMed: 29243499]
25. Rapsomaniki E, Timmis A, George J, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. *Lancet (London, England)* 2014; 383: 1899–1911. 2014/06/03. DOI: 10.1016/s0140-6736(14)60685-1.
26. Varu VN, Hogg ME and Kibbe MR. Critical limb ischemia. *Journal of vascular surgery* 2010; 51: 230–241. 2010/02/02. DOI: 10.1016/j.jvs.2009.08.073. [PubMed: 20117502]
27. Schmieder RE. End organ damage in hypertension. *Deutsches Arzteblatt international* 2010; 107: 866–873. 12/10. DOI: 10.3238/arztebl.2010.0866. [PubMed: 21191547]

28. Van Bortel LM, Struijker-Boudier HA and Safar ME. Pulse pressure, arterial stiffness, and drug treatment of hypertension. *Hypertension (Dallas, Tex: 1979)* 2001; 38: 914–921. 2001/10/20.
29. Williams B, Lindholm LH and Sever P. Systolic pressure is all that matters. *The Lancet* 2008; 371: 2219–2221. DOI: 10.1016/S0140-6736(08)60804-1.
30. Vaccarino V, Berger AK, Abramson J, et al. Pulse pressure and risk of cardiovascular events in the systolic hypertension in the elderly program. *The American journal of cardiology* 2001; 88: 980–986. 2001/11/13. [PubMed: 11703993]
31. Zanchetti A, Dominiczak A, Coca A, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *European Heart Journal* 2018; 39: 3021–3104. DOI: 10.1093/eurheartj/ehy339. [PubMed: 30165516]
32. Chase MR, Friedman HS, Navaratnam P, et al. Comparative Assessment of Medical Resource Use and Costs Associated with Patients with Symptomatic Peripheral Artery Disease in the United States. *Journal of managed care & specialty pharmacy* 2016; 22: 667–675. 2016/05/28. DOI: 10.18553/jmcp.2016.15010. [PubMed: 27231794]

Figure 1. Kaplan-Meier curves showing cumulative probability of survival free from incident peripheral artery disease by BP category for individuals without (A) and with (B) anti-hypertensive medication.

Figure 2.

Association of BP-medication category with peripheral artery disease (A) and critical limb ischemia (B). Model was adjusted for age, gender, race, education, smoking status, drinking status, body mass index, total and HDL cholesterol, cholesterol-lowering medication, diabetes, and eGFR.

Figure 3.

Association of SBP- (A and B) and DBP-medication (C and D) category with peripheral artery disease (A and C) and critical limb ischemia (B and D). Model was adjusted for age, gender, race, education, smoking status, drinking status, body mass index, total and HDL cholesterol, cholesterol-lowering medication, diabetes, and eGFR.

Table 1.

Baseline characteristics of participants without anti-hypertensive medication according to BP categories.

Characteristic	BP Category			
	Normal	Elevated	Stage 1 hypertension	Stage 2 hypertension
N	5436	1368	1839	1215
Age (years)	52.6 (5.5)	55.0 (5.7)	53.7 (5.7)	55.1 (5.8)
Female (%)	3111 (57.2)	721 (52.7)	844 (45.9)	570 (46.9)
Black (%)	755 (13.9)	247 (18.1)	553 (30.1)	512 (42.1)
Education				
<High school (%)	838 (15.4)	295 (21.6)	392 (21.3)	355 (29.2)
High school or vocational school (%)	2317 (42.6)	599 (43.8)	763 (41.5)	472 (38.8)
College, graduate, or professional school (%)	2281 (42.0)	474 (34.6)	684 (37.2)	388 (31.9)
Smoking status				
Current (%)	1512 (27.8)	341 (24.9)	422 (22.9)	298 (24.5)
Former (%)	1688 (31.1)	458 (33.5)	638 (34.7)	379 (31.2)
Never (%)	2236 (41.1)	569 (41.6)	779 (42.4)	538 (44.3)
Drinking status				
Current (%)	3424 (63.0)	812 (59.4)	1058 (57.5)	679 (55.9)
Former (%)	919 (16.9)	223 (16.3)	333 (18.1)	206 (17.0)
Never (%)	1093 (20.1)	333 (24.3)	448 (24.4)	330 (27.2)
Body mass index (kg/m ²)	26.0 (4.2)	27.5 (4.9)	27.9 (5.2)	28.5 (5.7)
Total cholesterol (mg/dL)	210.0 (39.4)	213.8 (39.0)	215.1 (41.0)	218.2 (42.9)
HDL (mg/dL)	53.1 (17.1)	52.4 (17.1)	52.5 (17.9)	52.7 (18.0)
Cholesterol-lowering medication (%)	94 (1.7)	31 (2.3)	38 (2.1)	11 (0.9)
eGFR (mL/min/1.73 m ²)				
<60 (%)	19 (0.3)	8 (0.6)	8 (0.4)	13 (1.1)
60–89 (%)	642 (11.8)	187 (13.7)	240 (13.1)	171 (14.1)
90 (%)	4775 (87.8)	1173 (85.7)	1591 (86.5)	1031 (84.9)
Diabetes (%)	293 (5.4)	109 (8.0)	160 (8.7)	149 (12.3)

Values are mean (SD), or n (%).

BP, blood pressure; SD, standard deviation; HDL, high-density lipoprotein, eGFR, estimated glomerular filtration rate

Table 2.

Hazard Ratios (95% Confidence Intervals) for associations between BP components and incident peripheral artery disease and critical limb ischemia

		PAD		CLI	
		HR (95%CI) - per 1 SD ^a of BP components		HR (95%CI) - per 1 SD ^a of BP components	
		No medication	Medication	No Medication	Medication
Single BP component					
SBP	1.44 (1.29–1.62)	1.46 (1.29–1.65)	1.63 (1.37–1.94)	1.42 (1.18–1.69)	
DBP	1.25 (1.10–1.42)	1.12 (0.97–1.30)	1.32 (1.07–1.63)	1.06 (0.85–1.33)	
MAP	1.37 (1.21–1.55)	1.33 (1.16–1.52)	1.51 (1.25–1.83)	1.27 (1.04–1.56)	
PP	1.41 (1.25–1.58)	1.44 (1.29–1.60)	1.62 (1.36–1.92)	1.41 (1.21–1.64)	
Dual BP components					
SBP+DBP					
SBP	1.54 (1.31–1.82)	1.65 (1.42–1.91)	1.87 (1.46–2.39)	1.61 (1.31–1.99)	
DBP	0.91 (0.76–1.08)	0.80 (0.68–0.95)	0.81 (0.61–1.07)	0.77 (0.61–0.99)	
SBP+MAP					
SBP	1.68 (1.26–2.23)	1.98 (1.53–2.55)	2.23 (1.44–3.45)	2.00 (1.39–2.87)	
MAP	0.85 (0.63–1.14)	0.69 (0.52–0.92)	0.70 (0.44–1.11)	0.65 (0.43–0.98)	
SBP+PP					
SBP	1.31 (1.07–1.61)	1.14 (0.91–1.44)	1.32 (0.95–1.84)	1.05 (0.75–1.48)	
PP	1.13 (0.91–1.39)	1.30 (1.06–1.59)	1.29 (0.93–1.79)	1.36 (1.02–1.82)	

BP, blood pressure; PAD, peripheral artery disease; CLI, critical limb ischemia; HR, hazard ratio; CI, confidence interval; SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure.

Model adjusted for: age, gender, race, education, smoking status, drinking status, body mass index, total and HDL cholesterol, cholesterol-lowering medication, diabetes, and eGFR;

^a1 SD increment: SBP, 18.3 mmHg; DBP, 11.1 mmHg; MAP, 12.4 mmHg; PP, 13.2 mmHg;