Systolic Blood Pressure and Vascular Disease in Men Aged 65 Years and Over

The HIMS (Health in Men Study)

Ben Lacey, Jonathan Golledge, Bu B. Yeap, Sarah Lewington, Kieran A. McCaul, Paul E. Norman, Leon Flicker, Osvaldo P. Almeida, Graeme J. Hankey

Abstract—There is uncertainty about the relation between blood pressure and vascular disease at older age. We assessed the association of systolic blood pressure (SBP) and major vascular events in a prospective cohort study of 7564 men aged 65 to 94 years, recruited in 1996–1999 from the general population in Perth, Western Australia. SBP was measured at baseline and again at resurvey in 2001–2004. Participants were monitored for fatal and nonfatal vascular events. To limit the effect of reverse causality, analyses were restricted to men without previous vascular disease at baseline. Hazard ratios were estimated by Cox regression, with adjustment for age and education (further adjustment did not materially change the associations). During a mean follow-up of 11 years, there were 1557 major vascular events. Continuous log-linear associations were found between usual SBP and risk of major vascular events throughout the SBP range examined (145–170 mm Hg). Overall, 10 mm Hg higher usual SBP was associated with ≈20% higher risk of major vascular events (hazard ratio, 19%; 95% confidence interval, 13%–26%; mean age at event 80 years). There was evidence of positive associations with both ischemic heart disease and stroke and effect modification by age, with shallower associations at older ages. Even at 85 to 94 years, however, there was evidence of a positive association: 10 mm Hg higher usual SBP was associated with 14% (95% confidence interval, 1%–30%) higher risk of major vascular events. **(*Hypertension*. 2017;69:1053-1059. DOI: 10.1161/HYPERTENSIONAHA.117.09150.)** ● **Online Data Supplement**

Key Words: blood pressure ■ elderly ■ epidemiology ■ hypertension ■ vascular diseases

Vascular disease, including ischemic heart disease and stroke, is a leading cause of death and disability worldwide.[1] Blood pressure is an established risk factor for vascular disease, but few prospective cohort studies have specifically investigated the effects of raised blood pressure at older age and, particularly, in the very elderly (such as those aged ≥85 years).

Meta-analyses of prospective studies have described strong positive associations between blood pressure and vascular disease in middle age, but much shallower associations in later life.[2–4] These meta-analyses have been limited, however, in their ability to assess the effect of raised blood pressure on vascular outcomes in the elderly: they have not been able to conduct the detailed assessment for confounding and reverse causality that a single study allows. Furthermore, clinical trials of blood pressure–lowering medication have tended to have few elderly participants, so there is some uncertainty about the effect of blood pressure–lowering medication on ischemic heart disease and stroke in this patient group.[5–7]

We report the association between systolic blood pressure (SBP) and incidence of major vascular events in an Australian population-based prospective cohort study of men aged ≥65 years. We investigate whether the association varies by age (including findings for those aged 85–94 years) and by type of vascular event and assess which blood pressure index (systolic, diastolic, or some combination of these) is the most predictive of major vascular events in this age group.

Methods

Study Design and Participants

Men recruited into the HIMS (Health in Men Study) were originally part of a population-based randomized trial of screening for abdominal aortic aneurysm conducted in Perth, Western Australia. The trial methods have been described in detail elsewhere.[8] In brief, all men

Received January 26, 2017; first decision February 4, 2017; revision accepted March 23, 2017.

From the Western Australian Centre for Health & Ageing, Centre for Medical Research (B.L., K.A.M., L.F., O.P.A.), School of Medicine and Pharmacology (B.L., B.B.Y., K.A.M., L.F., O.P.A., G.J.H.), School of Surgery (P.E.N.), and School of Psychiatry and Clinical Neurosciences (O.P.A.), University of Western Australia, Crawley; Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), Nuffield Department of Population Health, University of Oxford, United Kingdom (B.L., S.L.); Queensland Research Centre for Peripheral Vascular Disease, College of Medicine and Dentistry, James Cook University, Townsville, Australia (J.G.); The Department of Vascular and Endovascular Surgery, The Townsville Hospital, Australia (J.G.); Department of Endocrinology and Diabetes, Fiona Stanley and Fremantle Hospitals, Perth, Australia (B.B.Y.); Department of Geriatric Medicine, Royal Perth Hospital, Australia (L.F.); and Department of Neurology, Sir Charles Gairdner Hospital, Perth, Australia (G.J.H.).

The online-only Data Supplement is available with this article at http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYPERTENSIONAHA.117.09150/-/DC1.

Correspondence to Ben Lacey, WA Centre for Health & Ageing (M573), University of Western Australia, 35 Stirling Highway, Crawley, WA 6009, Australia. E-mail ben.lacey@ndph.ox.ac.uk

resident in Perth and projected to be aged 65 to 79 years at the midpoint of screening were randomly selected from the electoral roll in 1996–1999 and invited to undergo ultrasound screening of their abdominal aorta. Of 19 352 potentially eligible men, 12 203 attended a screening visit. At this visit, they completed a questionnaire on sociodemographic factors, lifestyle, and medical history. Physical measurements were also made, including blood pressure, height, and weight. Screened men received a letter (together with a copy for their general practitioner) with information on the size of their aorta. The letter did not attempt to influence the clinical management of the general practitioner, and no further intervention was made as part of the trial. All screened men were recruited into the HIMS cohort. Participants were monitored for deaths and hospital admissions using the Western Australian Data Linkage System.[9]

For the present study, we excluded men with missing information on key variables (n=54); those with extreme SBP values (<80 or >250 mm Hg; n=6); those with a history of heart disease (n=3419) or stroke (n=1735) at baseline, to limit the effect of reverse causality; and those with an abdominal aortic aneurysm (≥30 mm in diameter) identified at screening (n=875) because these individuals are likely to have received medical intervention to address their risk of a major vascular event. The remaining 7564 men contributed person-years until the censoring date (December 31, 2010), first major vascular event, or death.

Ethics approval for the study was obtained from the Human Research Ethic Committee of the University of Western Australia, and all men provided written informed consent to participate.

Blood Pressure Measures at Baseline and Resurvey

At baseline, SBP was measured twice on the upper arm of each participant (after they remained seated for at least 5 minutes) using an automated sphygmomanometer and recorded to the nearest 2 mm Hg. The mean of the 2 SBP measurements was used in all analyses. SBP was measured again at resurvey in 2001–2004 (5.8 years, on average, after the baseline survey) using the same procedures. All participants of the baseline survey were invited to the resurvey and 4263 attended. Participants excluded at baseline in the main analyses of the present study (see Statistical Analysis) were also excluded from analyses of resurvey blood pressure, leaving 2862 men. Resurvey blood pressure was used to correct hazard ratios (HRs) for regression dilution bias.[10] Rosner's regression method was used to calculate the regression dilution ratio for SBP, the ratio being equal to the slope of the regression line between baseline and resurvey blood pressures.[11,12]

Outcome Measures

The Western Australian Data Linkage System collects information on deaths and inpatient hospital admissions throughout Western Australia, with records from 1970 onwards. The underlying cause of death and hospital discharge diagnoses were coded to the *International Classification of Diseases* (ICD) 9-10. The primary outcome in this study was first major vascular event. This was defined as first hospitalization or death from ischemic heart disease (nonfatal myocardial infarction [ICD-10: I21-23] or death from ischemic heart disease [ICD-10: I20-25]), stroke (nonfatal stroke or stroke death [ICD-10: I60-61, I63-64, H34.1]), or other vascular death (vascular deaths [ICD-10: I60-99] except from stroke or ischemic heart disease; see Table S1 in the online-only Data Supplement for details).

Statistical Analysis

Cox regression models, with attained age at the underlying time variable, were used to calculate HRs for first major vascular event versus SBP. Analyses were adjusted for age at risk and highest level of education (some primary, some high school, completed high school, and completed university). Assessment was made for further confounding by region of birth (Australia, Europe, Mediterranean, and other), smoking (never smoker, ex-smoker, and current smoker), quantity of weekly alcohol intake (none, 1–7, 8–14, and ≥15 U), weekly vigorous activity (yes and no), body mass index (<22.5, 22.5–24.9, 25.0–27.4, 27.5–29.9, and ≥30.0 kg/m^2), self-reported diabetes mellitus (yes and no), and use of cholesterol medication (yes and no). There were no missing data on age, highest level of education, or blood pressure; missing values of other variables formed a separate category in each variable.

In continuous analyses, log risk was regressed on SBP, and HRs were given per 10 mm Hg higher usual SBP. In categorical analyses, which were used to assess the shape of the association, men were divided into 5 groups according to baseline blood pressure <140, 140 to <150, 150 to <160, 160 to <170, and ≥170 mm Hg SBP. Hazard ratios for major vascular events were calculated relative to the lowest blood pressure group and plotted against usual SBP in these baseline-defined categories. The 95% confidence intervals (CIs) about the HRs in the categorical analyses were calculated using the variance of the log risk.[13] The absolute risk of higher blood pressure was illustrated by multiplying the HRs by a common factor to make the inverse-variance weighted average of the HRs match the annual incidence of major vascular events in this cohort (the annual incidence rates were calculated as the unweighted average of the component 5-year incidence rates; see Table S2).[14]

The association of usual SBP and first major vascular event was reported by age at risk (65–74, 75–84, and 85–94 years) and by type of major vascular event (ischemic heart disease, stroke, and other vascular deaths). Age-specific associations were also reported for ischemic heart disease and stroke, but not for other vascular deaths because there were too few events in this category. Chi-squared tests for heterogeneity and, where appropriate, tests for trend were applied to HRs to assess for effect modification. Tests for trend by age used mean age at event in each age group. Sensitivity analyses, to assess for reverse causality from preclinical vascular disease at baseline, were conducted by excluding the first 2 years of follow-up.

Using measurements of blood pressure recorded at baseline only (ie, not correcting for regression dilution bias), the relative importance of different blood pressure indices was assessed by comparing HRs for a 1-SD difference in each index and by likelihood ratio χ^2 tests. Hazard ratio (adjusted for age at risk and education) was calculated for the association of each blood pressure index to incidence of major vascular events. The likelihood ratio χ^2 statistic of each of these regression models was compared with the χ^2 statistic of the same models excluding the given blood pressure index, the difference indicating the improvement of goodness-of-fit between models (more predictive blood pressure indices would tend to have a greater effect on χ^2 values).[2,15] The χ^2 values were expressed as a proportion of the χ^2 values for SBP. A range of blood pressure indices were compared: SBP, DBP, mid-blood pressure (1/2 SBP+1/2 DBP), mean arterial pressure (1/3 SBP+2/3 DBP), and pulse pressure (SBP−DBP).

Analyses were performed using Stata (v12.0), and figures were plotted using R (v3.0).

Results

After exclusions, there were 7654 men aged 65 to 83 years at baseline without a history of vascular disease. Their mean age at recruitment was 73 (SD 4) years, and they were followed up for 11 (SD 4) years, on average, to December 31, 2010. During that period, 1557 incident major vascular events occurred: 833 ischemic heart disease events, 551 strokes, and 173 other vascular deaths. The mean age at event was 80 (SD 6) years.

Mean SBP at baseline was 158.1 (SD 21) mm Hg and ranged from 156.1 mm Hg at age 65 to 69 years to 161.7 mm Hg at age 80 to 83 years. Table 1 shows the characteristics of participants by tertile of baseline SBP. Both age and body mass index were positively associated with SBP. Those in the lowest SBP tertile also had a lower proportion of self-reported diabetics and weekly drinkers than those in the higher SBP tertiles. There was a slight negative association between baseline SBP and the proportion of men undertaking weekly vigorous exercise, but no evidence of an association with smoking. Overall, 28% of men reported taking blood pressure–lowering

Table 1. Characteristics of the 7564 Participants, by Level of Baseline SBP

Characteristics	Baseline SBP		
	<150 mm Hg	150–169 mm Hg	≥170 mm Hg
Number of participants	2701	2764	2099
Mean (SD) age, y	71.2 (4.2)	71.6 (4.3)	72.2 (4.4)
No education beyond primary school, n (%)	568 (21.0)	593 (21.5)	454 (21.6)
Born in Australia, n (%)	1423 (52.7)	1566 (56.7)	1127 (53.7)
Current smokers, n (%)	305 (11.3)	298 (10.8)	237 (11.3)
Weekly drinkers, n (%)*	1691 (65.2)	1877 (71.0)	1391 (69.7)
Weekly vigorous exercise, n (%)	757 (28.0)	731 (26.4)	529 (25.2)
Mean (SD) BMI, kg/m^2	26.2 (3.6)	27.0 (3.6)	27.2 (3.8)
Self-reported diabetes mellitus, n (%)	232 (8.6)	280 (10.1)	229 (10.9)
Using cholesterol-lowering medication, n (%)*	235 (9.1)	299 (11.3)	206 (10.3)
Using blood pressure–lowering medication, n (%)*	462 (17.8)	761 (28.8)	763 (38.2)

BMI indicates body mass index; and SBP, systolic blood pressure.
*Information on alcohol intake and medication use was not collected in 332 men.

medication, and this proportion increased from 18% in the lowest SBP tertile to 38% in the highest SBP tertile.

The characteristics of resurveyed men differed slightly from the characteristics of the participants surveyed at baseline (Table S3). Those resurveyed tended to be better educated (resurvey 21% versus baseline 14%), were slightly less likely to smoke (11% versus 8%), a higher proportion undertook weekly vigorous exercise (34% versus 27%), and a slightly lower proportion had diabetes mellitus (7% versus 10%). The association between SBP at baseline and resurvey was linear (Figure 1), and the regression dilution ratio was 0.42. There was no evidence of confounding of this relationship by age or education or effect modification by age, neither was it materially affected by excluding participants taking blood pressure–lowering medication at baseline or resurvey (Tables S4 and S5).

At age 65 to 94 years, there was a positive log-linear association between usual SBP and incidence of major vascular events throughout the range of blood pressure measurements examined (145–170 mm Hg usual SBP; Table 2 and Figure 2; Table S6). Adjusting for age and education (and correcting for regression dilution bias), 10 mm Hg higher usual SBP was associated with ≈20% higher risk of major vascular events (HR, 1.19; 95% CI 1.13–1.26]). Progressive adjustment for a set of major potential confounders did not materially affect the strength of the association and neither did the exclusion of events during the first 2 years of follow-up or of those taking blood pressure–lowering medication at baseline (Table S7).

There were strong, positive associations at all ages between usual SBP and incidence of major vascular events (Table 2). The proportional increase in risk was somewhat greater at younger than at older ages, but even at old age, there

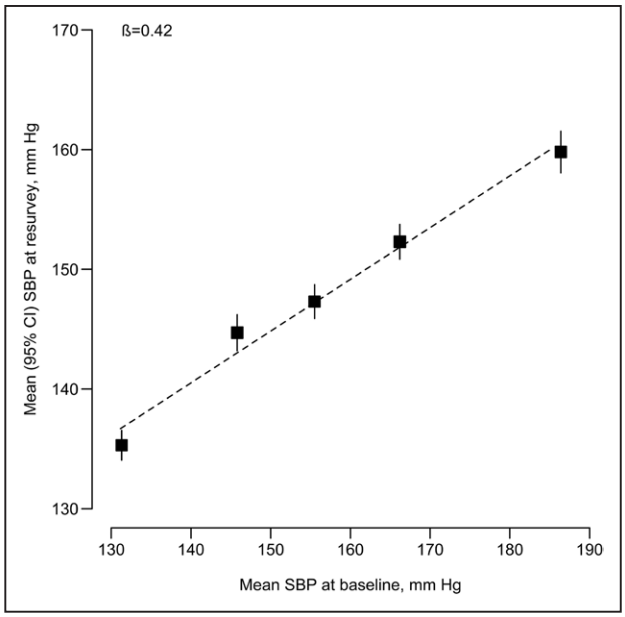

Figure 1. Resurvey blood pressure versus baseline blood pressure (among 2862 resurveyed participants) β=slope of the regression line (equal to the regression dilution ratio). CI indicates confidence interval; and SBP, systolic blood pressure.

was evidence of a positive association (age 85–94 years; HR, 1.14; 95% CI, 1.01–1.30). Because the incidence of major vascular events was so much greater at older age, however, the annual absolute difference in incidence associated with

Table 2. Incidence of Major Vascular Events: Hazard Ratios per 10 mm Hg Higher Usual SBP, by Age at Risk and Type of Vascular Event (Among 7564 Participants)

Overall, and by Age at Risk and Type of Event	Number of Events	Mean Age at Event, y	Hazard Ratio (95% CI)
Overall	1557	79.8	1.19 (1.13–1.26)
Age at risk, y			
65–74	316	71.8	1.31 (1.15–1.48)
75–84	936	79.9	1.17 (1.09–1.26)
85–94	305	88.0	1.14 (1.01–1.30)
			Trend, 3 groups: χ^2_1=2.4 (P=0.12)
Type of event			
Ischemic heart disease	833	79.4	1.19 (1.10–1.28)
Stroke	551	79.5	1.16 (1.05–1.27)
Other vascular	173	82.8	1.35 (1.14–1.59)
			Heterogeneity: χ^2_2=2.5 (P=0.5)

Hazard ratios were adjusted for age at risk and education. CI indicates confidence interval; and SBP, systolic blood pressure.

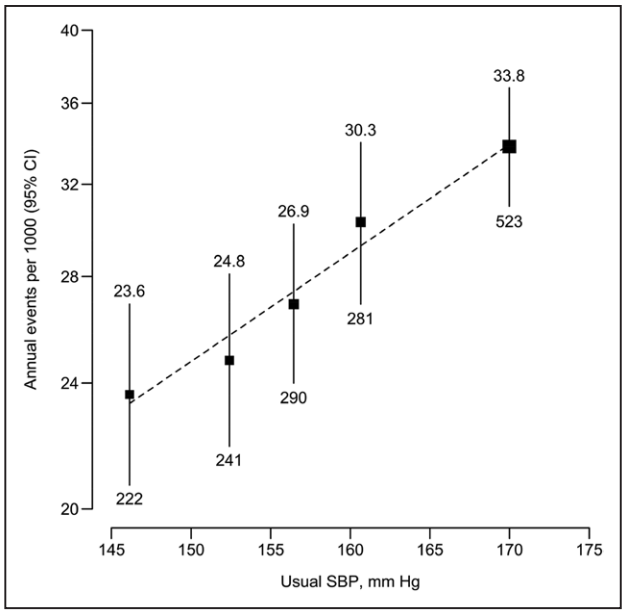

Figure 2. Incidence of major vascular events versus usual systolic blood pressure (SBP; among 7564 participants). Hazard ratios (adjusted for age at risk and education) at ages 65 to 94 years for major vascular events versus usual SBP were multiplied by a common factor (ie, floated) to make the weighted average match the annual incidence of major vascular events in this cohort. Annual incidence was the unweighted average of the component 5-year incidence rates. For each category, area of square is inversely proportional to the variance of the category-specific log risk, which also determines the confidence interval (CI). Incidence shown above each square and numbers of events below. Mean age at event was 80 years.

a given difference in usual SBP was greater at older than younger ages (Figure S1).

Ischemic heart disease accounted for over half (54%) the number of major vascular events and stroke for about a third (35%). Both diseases were positively, and roughly log-linearly, associated with usual SBP throughout the blood pressure range (Figure S1). The strength of the association for ischemic heart disease (HR, 1.19; 95% CI, 1.10–1.28) was much the same as that of stroke (HR, 1.16; 95% CI, 1.05–1.27; Table 2). There was some evidence, however, that the proportional increase in risk was greater at younger than older ages for both ischemic heart disease and stroke, with this effect being more pronounced for stroke than ischemic heart disease (Table 3).

There was no significant heterogeneity (P=0.4) across HRs by subtype of stroke event, although there was limited power to detect any difference: at ages 65 to 94 years, HRs per 10 mm Hg higher SBP were 1.26 (95% CI, 1.11–1.44) for ischemic stroke, 1.08 (0.85–1.36) for intracerebral hemorrhage, and 1.05 (0.88–1.24) for other or unspecified stroke (Table S8). There was a strong association with other vascular deaths combined (HR, 1.35; 95% CI, 1.14–1.59) but too few deaths in this category (n=173) to stratify further this association by disease group (Table S9). Also, there was no evidence that blood pressure had an effect on risk of nonvascular death (Table S10).

There was no strong evidence that the HRs for the associations of major vascular events with blood pressure (using baseline measures of blood pressure only) differed between blood pressure indices (Table 4). However, when comparing χ^2 values for Cox regression models with and without each blood pressure index, SBP was found to improve the goodness-of-fit more than other blood pressure indices: relative to SBP, the χ^2 values were 90% for mid-blood pressure, 79% for mean arterial pressure, 72% for pulse pressure, and 41% for diastolic blood pressure (Table S11). The prospective associations of usual DBP with major vascular events are given in the online-only Data Supplement (Tables S12 and S13).

Discussion

In this cohort of older men, we undertook a detailed assessment of the relation between usual SBP and incidence of major vascular disease. We found that at age 65 to 94 years, the proportional difference in risk of major vascular events associated with a given absolute difference in usual SBP was constant throughout the blood pressure range examined (145–170 mm Hg usual SBP). There was evidence of a positive association with both ischemic heart disease and stroke and effect modification by age, with shallower associations at older ages. However, even at old age (85–94 years), there

Table 3. Incidence of Ischemic Heart Disease and Stroke: Hazard Ratios per 10 mm Hg Higher Usual SBP, by Age at Risk (Among 7564 Participants)

	Ischemic Heart Disease			Stroke		
Age at Risk, y	Number of Events	Mean Age at Event, y	Hazard Ratio (95% CI)	Number of Events	Mean Age at Event, y	Hazard Ratio (95% CI)
65–74	200	71.8	1.28 (1.09–1.50)	103	71.8	1.43 (1.15–1.77)
75–84	472	79.7	1.21 (1.09–1.34)	362	79.8	1.12 (0.99–1.26)
85–94	161	88.0	1.04 (0.87–1.24)	86	87.5	1.02 (0.80–1.30)
			Trend, 3 groups: χ^2_1=2.8 (P=0.09)			Trend, 3 groups: χ^2_1=4.5 (P=0.03)
All	833	79.4	1.19 (1.10–1.28)	551	79.5	1.16 (1.05–1.27)

Hazard ratios are adjusted for age at risk and education. CI indicates confidence interval; and SBP, systolic blood pressure.

Table 4. Comparison of Different Blood Pressure Indices (Measured Once Only at Baseline) as Predictors of Major Vascular Events: Hazard Ratios per 1-SD Higher Baseline Levels of Each Blood Pressure Index (Among 7564 Participants)

Blood Pressure Index	Hazard Ratio (95% CI) per 1-SD*			
	Ischemic Heart Disease (833 Events)	Stroke (551 Events)	Other Vascular (173 Events)	All Major Vascular Events (1557 Events)
SBP	1.16 (1.09–1.24)	1.14 (1.05–1.23)	1.29 (1.12–1.49)	1.17 (1.11–1.23)
DBP	1.09 (1.02–1.17)	1.12 (1.03–1.22)	1.13 (0.97–1.31)	1.10 (1.05–1.16)
Mid blood pressure	1.15 (1.07–1.23)	1.14 (1.05–1.24)	1.26 (1.09–1.45)	1.16 (1.10–1.22)
Mean arterial pressure	1.14 (1.06–1.22)	1.14 (1.05–1.24)	1.23 (1.06–1.42)	1.15 (1.09–1.21)
Pulse pressure	1.14 (1.07–1.22)	1.09 (1.00–1.19)	1.28 (1.11–1.47)	1.14 (1.09–1.20)

Mid blood pressure=1/2 SBP+1/2 DBP; mean arterial pressure=1/3 SBP+2/3 DBP; pulse pressure=SBP−DBP. CI indicates confidence interval; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

*Hazard ratios are adjusted for age at risk and education, and uncorrected for regression dilution bias. SD of each blood pressure index: 20.7 mm Hg for SBP, 11.4 mm Hg for DBP, 14.7 mm Hg for mid blood pressure, 13.2 mm Hg for mean arterial pressure, and 15.8 mm Hg for pulse pressure.

was strong evidence of a positive association. For predicting the incidence of major vascular events from a single blood pressure measurement at baseline, SBP was found to be more predictive than other blood pressure indices.

The overall findings for ischemic heart disease are broadly consistent with those of large meta-analyses of prospective.[2–4] The Prospective Studies Collaboration meta-analysis of 61 prospective cohort studies (conducted mainly in the West) found that at ages 75 to 84 years, 10 mm Hg higher usual SBP was associated with 26% (95% CI, 25%–28%) increased risk of ischemic heart disease.[4] In the Asia Pacific Cohort Studies Collaboration meta-analysis of 37 prospective cohort studies (conducted mainly in East Asia but with about a fifth of participants from Australia and New Zealand), 10 mm Hg higher usual SBP was associated with 21% (12%–31%) higher risk of ischemic heart disease at ages 75 to 84 years.[4] Our findings from the present study indicate that this increased risk for vascular events extends to men aged 85 to 94 years.

For stroke, the Prospective Studies Collaboration found that at ages 75 to 84 years, 10 mm Hg higher usual SBP was associated with 25% (21%–31%) increased risk of ischemic stroke and 31% (24%–39%) increased risk of intracerebral hemorrhage.[2,4] Similar findings were reported by the Asia Pacific Cohort Studies Collaboration for this same age group, with 10 mm Hg higher SBP associated with 33% (24%–42%) increased risk of ischemic stroke and 26% (19%–34%) increased risk of intracerebral hemorrhage.[3,4] Most strokes in the present study were ischemic, and the strength of this association was consistent with the aforementioned studies.

Few meta-analyses of clinical trials have described the effect of blood pressure–lowering medication on cardiovascular events in older adults.[6,7,16] A meta-analysis of 31 clinical trials using individual participant data reported that at ≥65 years of age (mean age at entry was 72 years), each 5 mm Hg reduction in SBP was associated with a 9.1% (95% CI, 3.6%–14.3%) reduction in risk of major cardiovascular events.[6] The strength of this association is equivalent to 21% (95% CI, 8%–36%) higher risk per 10 mm Hg higher SBP, consistent with the overall association in the present study. The association by type of major vascular event or at older ages was not reported. An observational study, assembled using electronic health records of 1.25 million patients registered with primary care practices in the United Kingdom, described shallower age-specific associations than the present study for myocardial infarction and stroke.[17] The reason for this is unclear and may reflect the lack of a formal resurvey of blood pressure in this study.

The HYVET (Hypertension in the Very Elderly Trial), for which the results were published subsequently to the aforementioned meta-analysis, addressed the effect of a blood pressure–lowering medication in those aged ≥80 years (mean age at entry was 84 years).[18] At median follow-up of 2 years, blood pressure had been reduced by 15.0 mm Hg SBP and 6.1 mm Hg DBP, on average, in the active-treatment group relative to the control group (the target blood pressure was 150 mm Hg SBP and 80 mm Hg DBP). The effect on risk of cardiovascular death in this trial was in keeping with the overall finding of the present study for major vascular events: standardized to 10 mm Hg higher SBP, the association was equivalent to 19% (95% CI, −1% to 41%) increased risk of cardiovascular death. There was strong evidence of an adverse effect of higher blood pressure on death from any cause in this trial (there was a 17% [95% CI, 3%–33%] increased risk per 10 mm Hg SBP), but substantial uncertainty about the effect for incident (fatal and nonfatal) myocardial infarction (24% [−30% to 23%]) and incident stroke (27% [−1% to 61%]). Thus, the benefits of blood pressure-lowering therapy on specific cardiovascular diseases is less well established at age ≥80 years than at younger ages.

The present study found that when using a single blood pressure measurement, SBP was statistically more predictive of major vascular events overall than diastolic blood pressure

or other blood pressure indices (as assessed using likelihood ratio χ^2 tests), although the magnitude of this was small. This is in contrast to some studies conducted in younger populations, which find mid-blood pressure or mean arterial pressure to be more predictive than either SBP or DBP alone.[2] This finding might reflect the weaker predictive ability of DBP in this older population.

The present study had several major strengths: blood pressure was measured using standardized procedures; the resurvey of blood pressure meant it was possible to assess for regression to the mean and correct analyses for regression dilution bias; the baseline survey allowed assessment for confounding by a broad range of factors, and the established data linkage system, used to identify causes of death and hospitalizations in study participants, is likely to have high diagnostic accuracy and case ascertainment of major vascular events (although it was not possible to assess formally losses to follow-up).[19,20]

The study would have benefited from a greater number of events because this would have allowed the strength of associations to have been estimated more precisely. Another limitation is that men who attended the baseline survey may have subsequently made efforts to address their risk factors for vascular disease. However, excluding men from the analyses who were identified with abdominal aortic aneurysm at baseline is likely to have limited this effect. There was also some evidence that those resurveyed differed somewhat from those not resurveyed, given they had a lower prevalence of several vascular risk factors than those surveyed at baseline overall. There is, however, no evidence to suggest the regression dilution ratios for SBP would have been affected by these differences. Also, recruiting only men meant that the overall associations were unconfounded by sex, but limited the study because it was not possible to assess whether the associations were different in women. Finally, the study would have benefited from baseline information on blood lipids, although other studies have found lipids not to be an important confounder of the associations described and adjusting for treatment of high cholesterol (statin use) in the present study did not materially change the strength of the main association (Table S7).

Further research is required to investigate whether the strengths of the age-specific associations differ by stroke subtypes; whether there is effect modification of the associations for ischemic heart disease and stroke subtypes by other vascular risk factors, such as smoking or alcohol intake; whether blood pressure is associated with less common vascular outcomes (such as atrial fibrillation, aortic aneurysm, and heart failure); and also whether the findings are similar in women.

This study supports and strengthens the evidence that even at old age, there is a strong positive association between SBP and incidence of major vascular events. The present analyses did not include people with a history of vascular disease, to limit reverse causality, but clinical trials have found no evidence that the strength of association differs in those with and without a history of vascular disease. As those with a history of vascular disease are at high absolute risk of a major vascular events, the absolute effect of lowering blood pressure in this group is likely to be greater, on average, than those without such a history. These findings help to inform the decisions of clinicians and their patients when weighing the potential risks and benefits of hypertensive treatment. They also support public health initiatives, which advocate lifestyle changes to address factors in this patient group known to raise blood pressure, such as, obesity, physical inactivity, high alcohol intake and high dietary salt intake.

Perspectives

In this prospective cohort study of older men, there was a positive association at age 65 to 94 years (mean age at event 80 years) between usual SBP and incidence of major vascular events throughout the blood pressure range examined (145–170 mm Hg SBP). Each 10 mm Hg higher usual SBP was associated with ≈20% higher risk of major vascular events. There was evidence of a positive association with both ischemic heart disease and stroke and effect modification by age with shallower associations at older ages. Even at old age (85–94 years), however, there was strong evidence of a positive association. Additional studies are warranted to determine the optimal timing and intensity for blood pressure–lowering interventions over the lifespan from middle to the oldest ages.

Acknowledgments

B. Lacey and G.J. Hankey conceived the original idea for the article. B. Lacey conducted the data analyses and produced the initial draft of the article. B. Lacey, J. Golledge, B.B. Yeap, S. Lewington, K.A. McCaul, P.E. Norman, L. Flicker, O.P. Almeida, and G.J. Hankey were involved in the interpretation of the analyses and writing of the article. B. Lacey, J. Golledge, B.B. Yeap, S. Lewington, K.A. McCaul, P.E. Norman, L. Flicker, O.P. Almeida, and G.J. Hankey approved the final version of the article and take responsibility for its content. The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. We thank the staff of the Data Linkage Unit, Health Department of Western Australia, Australia, for their excellent technical assistance and the staff and management of Shenton Park Hospital for their support of the study. We especially thank all the men and staff who participated in the Western Australian Abdominal Aortic Aneurysm Program and the Health in Men Study.

Sources of Funding

B.B. Yeap is recipient of a Clinical Investigator Award from the Sylvia and Charles Viertel Charitable Foundation, New South Wales, Australia. J. Golledge is supported by grants from the National Health and Medical Research Council (1079369, 1079193, 1063476, 1022752, 1003707, 1021416, and 1000967), the Queensland Government and the Townsville Hospital Private Practice Trust. J. Golledge holds a Practitioner Fellowship from the National Health and Medical Research Council, Australia (1019921), and a Senior Clinical Research Fellowship from the Queensland Government. S. Lewington is funded by the UK Medical Research Council. The Health In Men Study is supported by grants from the National Health and Medical Research Council of Australia (964145, 139093, 403963, 455811, 1021416, 1000967, 1045710, and 1060557) with additional funding from the National Heart Foundation, the Western Australian Health Promotion Foundation (Healthway), and Fremantle Hospital Medical Research Foundation. The funding bodies played no role in generation of the data presented in this publication.

Disclosures

None.

References

1. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380:2095–2128. doi: 10.1016/S0140-6736(12)61728-0.
2. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360:1903–1913.
3. Lawes CM, Rodgers A, Bennett DA, Parag V, Suh I, Ueshima H, MacMahon S, Asia Pacific Cohort Studies Collaboration. Blood pressure and cardiovascular disease in the Asia Pacific region. *J Hypertens*. 2003;21:707–716. doi: 10.1097/01.hjh.0000052492.18130.07.
4. Singh GM, Danaei G, Farzadfar F, et al; Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group; Asia-Pacific Cohort Studies Collaboration (APCSC); Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe (DECODE); Emerging Risk Factor Collaboration (ERFC); Prospective Studies Collaboration (PSC). The age-specific quantitative effects of metabolic risk factors on cardiovascular diseases and diabetes: a pooled analysis. *PloS One*. 2013;8:e65174. doi: 10.1371/journal.pone.0065174.
5. Bejan-Angoulvant T, Saadatian-Elahi M, Wright JM, Schron EB, Lindholm LH, Fagard R, Staessen JA, Gueyffier F. Treatment of hypertension in patients 80 years and older: the lower the better? A meta-analysis of randomized controlled trials. *J Hypertens*. 2010;28:1366–1372. doi: 10.1097/HJH.0b013e328339f9c5.
6. Blood Pressure Lowering Treatment Trialists Collaboration; Turnbull F, Neal B, Ninomiya T, Algert C, Arima H, Barzi F, Bulpitt C, Chalmers J, Fagard R, Gleason A, Heritier S, Li N, Perkovic V, Woodward M, MacMahon S. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. *BMJ*. 2008;336:1121–1123. doi: 10.1136/bmj.39548.738368.BE.
7. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ*. 2009;338:b1665.
8. Norman PE, Flicker L, Almeida OP, Hankey GJ, Hyde Z, Jamrozik K. Cohort Profile: The Health In Men Study (HIMS). *Int J Epidemiol*. 2009;38:48–52. doi: 10.1093/ije/dyn041.
9. Holman CD, Bass AJ, Rouse IL, Hobbs MS. Population-based linkage of health records in Western Australia: development of a health services research linked database. *Aust N Z J Public Health*. 1999;23:453–459.
10. Clarke R, Shipley M, Lewington S, Youngman L, Collins R, Marmot M, Peto R. Underestimation of risk associations due to regression dilution in long-term follow-up of prospective studies. *Am J Epidemiol*. 1999;150:341–353.
11. Rosner B, Willett WC, Spiegelman D. Correction of logistic regression relative risk estimates and confidence intervals for systematic within-person measurement error. *Stat Med*. 1989;8:1051–1069; discussion 1071.
12. Fibrinogen Studies Collaboration; Wood AM, White I, Thompson SG, Lewington S, Danesh J. Regression dilution methods for meta-analysis: assessing long-term variability in plasma fibrinogen among 27,247 adults in 15 prospective studies. *Int J Epidemiol*. 2006;35:1570–1578.
13. Easton DF, Peto J, Babiker AG. Floating absolute risk: an alternative to relative risk in survival and case-control analysis avoiding an arbitrary reference group. *Stat Med*. 1991;10:1025–1035.
14. Prospective Studies Collaboration; Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, Qizilbash N, Collins R, Peto R. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet*. 2009;373:1083–1096. doi: 10.1016/S0140-6736(09)60318-4.
15. Lawes CM, Bennett DA, Parag V, Woodward M, Whitlock G, Lam TH, Suh I, Rodgers A; Asia Pacific Cohort Studies Collaboration. Blood pressure indices and cardiovascular disease in the Asia Pacific region: a pooled analysis. *Hypertension*. 2003;42:69–75. doi: 10.1161/01.HYP.0000075083.04415.4B.
16. Lawes CM, Bennett DA, Feigin VL, Rodgers A. Blood pressure and stroke: an overview of published reviews. *Stroke*. 2004;35:776–785. doi: 10.1161/01.STR.0000116869.64771.5A.
17. Rapsomaniki E, Timmis A, George J, Pujades-Rodriguez M, Shah AD, Denaxas S, White IR, Caulfield MJ, Deanfield JE, Smeeth L, Williams B, Hingorani A, Hemingway H. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1·25 million people. *Lancet*. 2014;383:1899–1911. doi: 10.1016/S0140-6736(14)60685-1.
18. Beckett NS, Peters R, Fletcher AE, et al; HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med*. 2008;358:1887–1898. doi: 10.1056/NEJMoa0801369.
19. Barr EL, Tonkin AM, Welborn TA, Shaw JE. Validity of self-reported cardiovascular disease events in comparison to medical record adjudication and a statewide hospital morbidity database: the AusDiab study. *Intern Med J*. 2009;39:49–53. doi: 10.1111/j.1445-5994.2008.01864.x.
20. Jamrozik E, Hyde Z, Alfonso H, Flicker L, Almeida O, Yeap B, Norman P, Hankey G, Jamrozik K. Validity of self-reported versus hospital-coded diagnosis of stroke: a cross-sectional and longitudinal study. *Cerebrovasc Dis*. 2014;37:256–262. doi: 10.1159/000358583.

Novelty and Significance

What Is New?

- We conducted analyses that quantified the relation of systolic blood pressure and incidence of major vascular events in older men (≥65 years). This study extends the findings of previous reports to show that even at old age (85–94 years), there was strong evidence of a positive association.

What Is Relevant?

- The findings of this study add to the limited evidence on the relation between blood pressure and vascular disease at old age.

Summary

Overall, 10 mm Hg higher usual systolic blood pressure was associated with ≈20% higher risk of major vascular events (hazard ratio, 19%; 95% confidence interval, 13%–26%; mean age at event, 80 years). There was strong evidence of positive associations with ischemic heart disease, stroke, and other vascular disease. The associations were shallower at older ages, but even at age 85 to 94 years, 10 mm Hg higher usual systolic blood pressure was associated with 14% (1%–30%) higher relative risk of major vascular events.

Hypertension
Journal of the American Heart Association

Systolic Blood Pressure and Vascular Disease in Men Aged 65 Years and Over: The HIMS (Health in Men Study)

Ben Lacey, Jonathan Golledge, Bu B. Yeap, Sarah Lewington, Kieran A. McCaul, Paul E. Norman, Leon Flicker, Osvaldo P. Almeida and Graeme J. Hankey

Hypertension. 2017;69:1053-1059; originally published online April 24, 2017;
doi: 10.1161/HYPERTENSIONAHA.117.09150
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0194-911X. Online ISSN: 1524-4563

Online Supplement

Systolic blood pressure and vascular disease in men aged 65 and over: the Health In Men Study (HIMS)

Ben Lacey, MBChB, DPhil, FFPH, [1,2,3] Jonathan Golledge, MChir, FRACS, [4,5]
Bu B. Yeap, MBBS, FRACP, PhD, [2,6] Sarah Lewington, DPhil, [3]
Kieran A. McCaul, MPH, PhD, [1,2] Paul E. Norman, DS, FRACS,[7]
Leon Flicker, MBBS, PhD, FRACP, [1,2,8] Osvaldo P. Almeida, MD, PhD, [1,2,9]
Graeme J. Hankey, MD, FRACP, FAHA [2,10]

[1]Western Australian Centre for Health & Ageing, Centre for Medical Research, University of Western Australia, Australia; [2]School of Medicine and Pharmacology, University of Western Australia; [3]Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), Nuffield Department of Population Health, University of Oxford, United Kingdom; [4]Queensland Research Centre for Peripheral Vascular Disease, College of Medicine and Dentistry, James Cook University, Australia; [5]The Department of Vascular and Endovascular Surgery, The Townsville Hospital, Townsville, Australia; [6]Department of Endocrinology and Diabetes, Fiona Stanley and Fremantle Hospitals, Perth, Australia; [7]School of Surgery, University of Western Australia, Australia; [8]Department of Geriatric Medicine, Royal Perth Hospital, Perth, Australia; [9]School of Psychiatry and Clinical Neurosciences, University of Western Australia, Australia; [10]Department of Neurology, Sir Charles Gairdner Hospital, Perth, Australia

Supplementary Tables

Supplementary Figure

Table S1: Vascular disease endpoints and their ICD-9 and ICD-10 codes

Vascular disease endpoints	ICD-9	ICD-10	Note
Ischaemic heart disease			
Myocardial infarction	410	I21-I23	
Other ischaemic heart disease*	411-414	I20, I24-I25	
Stroke			
Ischaemic stroke	433-434, 362.3	I63, H34.1	Includes central retinal artery occlusion
Intracerebral haemorrhage	431	I61	
Subarachnoid haemorrhage	430	I60	
Unspecified stroke	436	I64	
Other vascular disease*			
Aortic aneurysm	441	I71	
Pulmonary embolism	415	I26	
Heart failure	428	I50	
Hypertensive disease	401-405	I10-I15	Includes hypertension, hypertensive heart disease and hypertensive renal disease
Atherosclerosis & other arterial disease	440, 442-448	I70, I72-I79	Includes peripheral arterial disease, and diseases of arterioles/capillaries
Inflammatory heart disease	420-424	I30-I41	Includes pericarditis, myocarditis, endocarditis
Rheumatic heart disease	390-398	I00-I09	Includes acute and chronic rheumatic heart disease
Other heart disease (not IHD)	416-417,425-427, 429	I27-I28, I42-I49, I51-I52	Includes pulmonary heart disease, cardiomyopathy, dysrhythmia
Other cerebrovascular disease (not stroke)	435, 437-438	I62, I65-69	Includes remainder of cerebrovascular disease ICD-9/10 subchapters not classified as stroke†
Other circulatory disease	451-459	I80-I99	Includes venous disease (including oesophageal varices) and lymphatic disease
All vascular disease	390-459, 362.3	I00-99, H34.1	

* Deaths only (where disease was considered the underlying cause)
† There were no transient ischaemic attack deaths (435 or G45)
n.b. Baseline exclusions: participants with a baseline history of major heart disease or stroke/TIA with the following ICD-9 codes: chronic rheumatic heart disease (393-398); hypertensive heart disease (402,404); pulmonary heart disease (415-416); heart failure (428); ischaemic heart disease (410-414); and stroke/TIA (362.3,430-431,433-436).

Table S2: Number of major vascular events, by age at risk and type of vascular event (among 7564 participants)

Rates age-standardised by taking the unweighted average of the component five-year incidence rates.

Age at risk, years	Person-years at risk	Number of events (rate per 1000 person-years)			
		Ischaemic heart disease	Stroke	Other vascular	All
65-74	28775	200 (6.7)	103 (3.5)	13 (0.3)	316 (10.6)
75-84	44279	472 (10.9)	362 (8.5)	102 (2.6)	936 (22.0)
85-94	6615	161 (28.0)	86 (14.0)	58 (11.1)	305 (53.1)
All ages	79669	833 (15.2)	551 (8.7)	173 (4.7)	1557 (28.6)

Table S3: Baseline characteristics of the 7564 participants and the 2862 resurveyed participants

Characteristics	All men at baseline	Resurveyed men at baseline
Number of participants	7564	2862
Mean (SD) age, years	71.6 (4.3)	71.0 (4.0)
No education beyond primary school, n (%)	1615 (21.4)	408 (14.3)
Born in Australia, n (%)	4116 (54.4)	1760 (61.5)
Current smokers, n (%)	840 (11.1)	218 (7.6)
Weekly drinkers, n (%)*	4959 (68.6)	1949 (71.9)
Weekly vigorous exercise, n (%)	2017 (26.7)	981 (34.3)
Mean (SD) BMI, kg/m^2	26.7 (3.7)	26.6 (3.3)
Self-reported diabetes, n (%)	741 (9.8)	188 (6.6)
Using cholesterol-lowering medication, n (%)*	740 (10.2)	259 (9.6)
Using blood pressure-lowering medication, n (%)*	1986 (27.5)	681 (25.1)

*Information on alcohol intake and medication use was not collected in 332 men at baseline (of whom 152 were resurveyed)

Table S4: Baseline and resurvey blood pressure, by SBP quintile at baseline (among 2862 resurveyed participants)

SBP, by quintile at baseline	Number of participants	Mean SBP (SD) at baseline	Mean SBP (SD) at resurvey
Quintile 1	628	131.3 (7.2)	135.3 (15.5)
Quintile 2	541	145.8 (2.9)	144.7 (17.9)
Quintile 3	584	155.5 (2.9)	147.3 (16.3)
Quintile 4	548	166.2 (3.4)	152.3 (17.4)
Quintile 5	561	186.4 (11.7)	159.8 (20.1)

Table S5: Excluding participants using blood pressure-lowering medication: baseline and resurvey blood pressure, by SBP quintile at baseline (among 1895 resurveyed participants)

SBP, by quintile at baseline	Number of participants	Mean SBP (SD) at baseline	Mean SBP (SD) at resurvey
Quintile 1	415	128.7 (6.8)	133.2 (14.4)
Quintile 2	409	143.1 (3.1)	141.8 (16.5)
Quintile 3	410	153.4 (2.9)	146.2 (15.2)
Quintile 4	334	163.7 (3.2)	151.7 (17.7)
Quintile 5	327	182.4 (11.4)	159.9 (19.8)

Table S6: Incidence of major vascular events versus usual SBP

Hazard ratios at ages 65-94 years, adjusted for age at risk and education. Mean age at event 80 years.

SBP (mmHg), range of each baseline SBP group	Usual SBP*	Number of events	Hazard ratio (95% CI)
<140	146.3	222	1.00 (0.88-1.14)
140-<150	152.4	241	1.05 (0.93-1.19)
150-<160	156.6	290	1.14 (1.02-1.28)
160-<170	160.7	281	1.28 (1.14-1.44)
≥170	169.0	523	1.44 (1.32-1.57)

*Usual SBP in each baseline SBP group was estimated using a regression dilution ratio of 0.42.

Table S7: Incidence of major vascular disease (1557 events): hazard ratios per 10 mm Hg higher usual SBP, progressively adjusted for major potential confounders (among 7564 participants)

Hazard ratios at ages 65-94 years, corrected for regression dilution bias (regression dilution ratio of 0.42). Mean age at event was 80 years.

Potential confounders	**Hazard ratio (95% CI)**
Age and education	1.19 (1.13-1.26)
Plus place of birth	1.19 (1.13-1.26)
Plus smoking	1.19 (1.13-1.26)
Plus alcohol intake	1.19 (1.13-1.26)
Plus vigorous exercise	1.19 (1.13-1.26)
Plus BMI	1.18 (1.11-1.24)
Plus diabetes	1.17 (1.11-1.24)
Plus cholesterol-lowering medication use	1.17 (1.11-1.24)
Age and education, excluding:	
First 2 years of follow-up	*1.17 (1.10-1.25)*
Participant taking blood pressure-lowering medication	*1.16 (1.08-1.24)*

Table S8: Stroke events: hazard ratios per 10 mm Hg higher usual SBP, by age at risk (among 7564 participants)

Hazard ratios at ages 65-94 years, adjusted for age at risk and education.

Stroke subtype	Number of events	Mean age at event, years	Hazard ratio (95% CI)
Ischaemic stroke	284	78.9	1.26 (1.11-1.44)
Intracerebral haemorrhage	93	79.7	1.08 (0.85-1.36)
Other/Unspecified	174	80.5	1.05 (0.88-1.24)
			Heterogeneity: χ^2_2 =3.2 (p=0.4)
All	551	79.5	1.16 (1.05-1.27)

Table S9: Incidence of vascular deaths (other than ischaemic heart disease or stroke): hazard ratios per 10 mm Hg higher usual SBP, by type of vascular death (among 7564 participants)

Hazard ratios at ages 65-94 years, adjusted for age at risk and education.

Type of vascular death	Number of events	Mean age at event, years	Hazard ratio (95% CI)
Aortic aneurysm	18	81.6	1.36 (0.81-2.27)
Pulmonary embolism	5	80.4	2.64 (1.09-6.41)
Heart failure	17	83.4	1.55 (0.93-2.60)
Hypertensive disease	30	83.2	1.54 (1.04-2.28)
Atherosclerosis & other arterial disease	15	83.7	1.82 (1.06-3.11)
Inflammatory heart disease	20	83.6	1.45 (0.89-2.35)
Rheumatic heart disease	1	80.9	3.19 (0.47-21.57)
Other heart disease (not IHD)	39	82.7	1.04 (0.72-1.49)
Other cerebrovascular disease (not stroke)	21	83.6	1.22 (0.76-1.97)
Other circulatory disease	7	78.4	0.47 (0.18-1.25)

Table S10: Non-vascular death: hazard ratios per 10 mm Hg higher usual SBP, by age at risk (among 7564 participants)

Hazard ratios at ages 65-94 years, adjusted for age at risk and education.

Age at risk, years	Number of events	Mean age at event, years	Hazard ratio (95% CI)
65-74	325	72.2	0.89 (0.78-1.01)
75-84	1495	80.6	1.00 (0.94-1.06)
85-94	735	88.6	0.96 (0.89-1.05)
			Heterogeneity: χ^2_2 =2.7 (p=0.4)
All	2555	81.8	0.95 (0.91-1.00)

Table S11: Comparison of different blood pressure indices (measured once only at baseline) as predictors of major vascular events (among 7564 participants)

Blood pressure index	Likelihood ratio X^2 statistic, % of value for SBP*			
	Ischaemic heart disease (833 events)	Stroke (551 events)	Other vascular (173 events)	All major vascular events (1557 events)
SBP	100	100	100	100
DBP	33	77	21	41
Mid blood pressure	85	108	78	90
Mean arterial pressure	73	105	63	79
Pulse pressure	81	46	94	72

Mid blood pressure = 1/2SBP+1/2DBP, mean arterial pressure = 1/3SBP+2/3DBP, pulse pressure = SBP-DBP.

* The likelihood ratio X^2 statistic of Cox regression models (adjusting for age and education) relating each blood pressure index to incidence of major vascular events were compared to the X^2 statistic of models excluding the given blood pressure index. The difference indicating the improvement of goodness of fit between models (more predictive blood pressure indices would tend to have a greater effect on the X^2 values). The X^2 values are expressed as a proportion of the X^2 values for SBP.

Table S12: Incidence of major vascular events versus usual DBP

Hazard ratios at ages 65-94 years, adjusted for age at risk and education. Mean age at event 80 years.

DBP (mmHg), range of each baseline DBP group	Usual DBP*	Number of events	Hazard ratio (95% CI)
<80	85.3	222	1.00 (0.88-1.14)
80-89	88.8	451	0.97 (0.89-1.07)
90-99	92.1	512	1.07 (0.98-1.17)
100-109	95.3	246	1.17 (1.03-1.32)
≥110	99.2	126	1.48 (1.24-1.76)

*Usual DBP in each baseline DBP group was estimated using a regression dilution ratio of 0.34. Mean DBP at baseline was 91.0 mmHg.

Table S13: Incidence of major vascular events: hazard ratios per 5 mmHg higher usual diastolic blood pressure, by age at risk and type of vascular event (among 7564 participants)

Hazard ratios at ages 65-94 years, adjusted for age at risk and education.

Overall, and by age at risk and type of event	Number of events	Mean age at event, years	Hazard ratio (95% CI)
Overall	1557	79.8	1.14 (1.07-1.21)
Age at risk, years			
65-74	316	71.8	1.22 (1.06-1.40)
75-84	936	79.9	1.16 (1.07-1.26)
85-94	305	88.0	1.01 (0.87-1.16)
			Trend, 3 groups: χ^2_1=3.4 (p=0.07)
Type of event			
Ischaemic heart disease	833	79.4	1.12 (1.02-1.22)
Stroke	551	79.5	1.16 (1.04-1.29)
Other vascular	173	82.8	1.17 (0.97-1.41)
			Heterogeneity: χ^2_2 =0.3 (p=0.9)

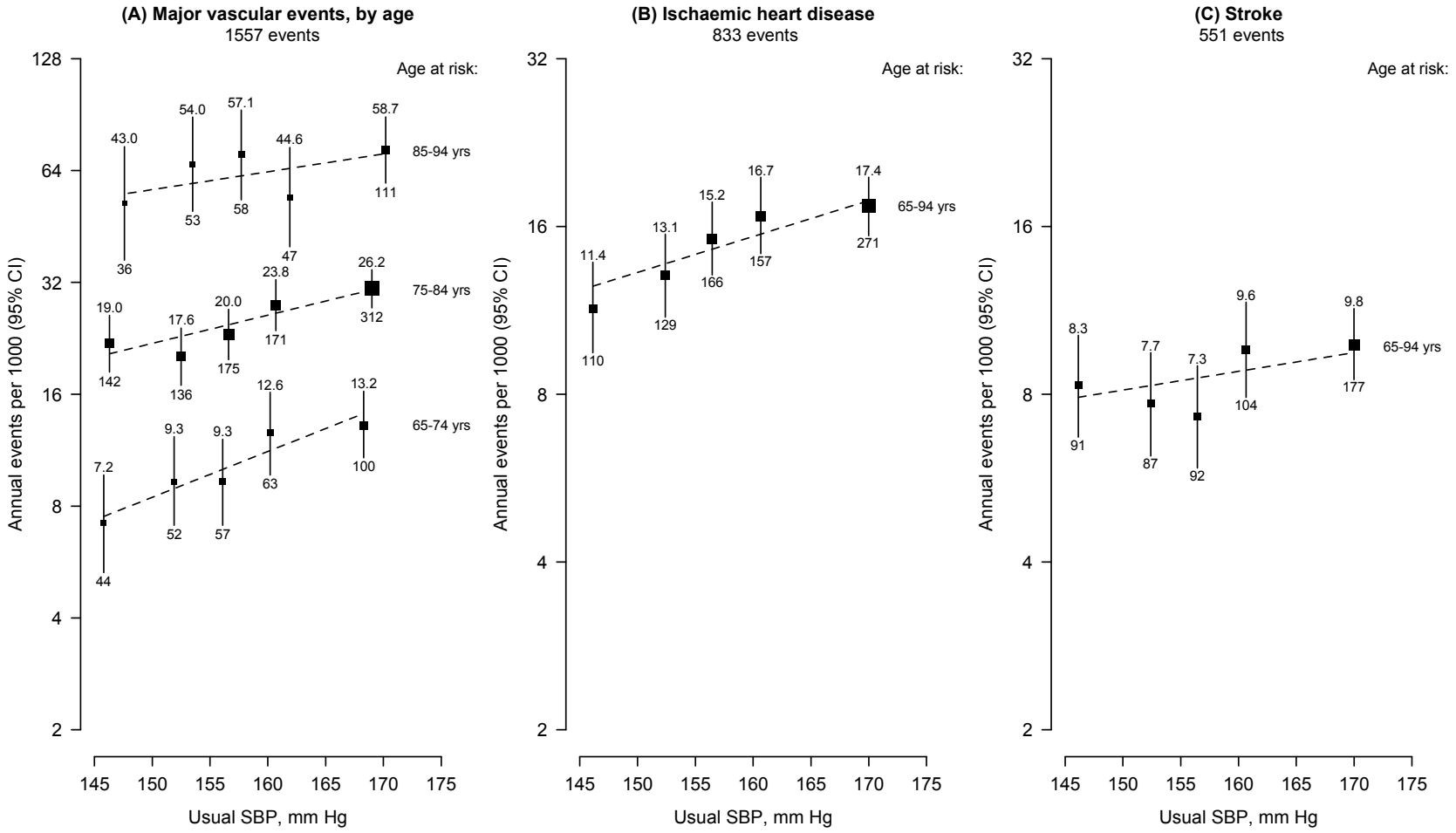

Figure S1: Incidence of major vascular events versus usual SBP by age at risk and type of vascular event (among 7564 participants) (A) Major vascular events, by age at risk. (B) Ischaemic heart disease. (C) Stroke. Hazard ratios at ages 65-94 year (adjusted for age at risk and education) for each type of vascular event versus usual SBP were multiplied by a common factor (ie. floated) to make the weighted average match the age-specific annual incidence for each type of vascular event at in this cohort. Annual incidence was the unweighted average of the component five-year incidence rates in each age at risk group. For each category, area of square is inversely proportional to the variance of the category-specific log risk, which also determines the confidence interval. Incidence shown above each square and numbers of events below.