Articles

Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies

*Prospective Studies Collaboration**

Summary

Background The age-specific relevance of blood pressure to cause-specific mortality is best assessed by collaborative meta-analysis of individual participant data from the separate prospective studies.

Methods Information was obtained on each of one million adults with no previous vascular disease recorded at baseline in 61 prospective observational studies of blood pressure and mortality. During 12·7 million person-years at risk, there were about 56 000 vascular deaths (12 000 stroke, 34 000 ischaemic heart disease [IHD], 10 000 other vascular) and 66 000 other deaths at ages 40–89 years. Meta-analyses, involving "time-dependent" correction for regression dilution, related mortality during each decade of age at death to the estimated usual blood pressure at the start of that decade.

Findings Within each decade of age at death, the proportional difference in the risk of vascular death associated with a given absolute difference in usual blood pressure is about the same down to at least 115 mm Hg usual systolic blood pressure (SBP) and 75 mm Hg usual diastolic blood pressure (DBP), below which there is little evidence. At ages 40–69 years, each difference of 20 mm Hg usual SBP (or, approximately equivalently, 10 mm Hg usual DBP) is associated with more than a twofold difference in the stroke death rate, and with twofold differences in the death rates from IHD and from other vascular causes. All of these proportional differences in vascular mortality are about half as extreme at ages 80–89 years as at ages 40–49 years, but the annual absolute differences in risk are greater in old age. The age-specific associations are similar for men and women, and for cerebral haemorrhage and cerebral ischaemia. For predicting vascular mortality from a single blood pressure measurement, the average of SBP and DBP is slightly more informative than either alone, and pulse pressure is much less informative.

Interpretation Throughout middle and old age, usual blood pressure is strongly and directly related to vascular (and overall) mortality, without any evidence of a threshold down to at least 115/75 mm Hg.

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Introduction

Meta-analysis of individual participant data

The observed relationships between blood pressure and vascular disease mortality in particular epidemiological studies are subject to appreciable random error, especially at lower blood pressure levels, for which the mortality rates are relatively low. As a consequence, different studies may produce apparently very different results, and unduly selective emphasis on some and not on others could introduce substantial biases. Hence, both to limit purely random errors and to minimise selective biases, meta-analyses of the observational studies of these relations are needed. By combining data from many studies, such meta-analyses can assess reliably the relevance of blood pressure to disease risk in a wide range of circumstances (including the extremes of the usual blood pressure distribution, and different ages). The present collaborative meta-analysis[1] differs from previous meta-analyses[2–4] in several ways that increase its reliability and informativeness: (i) it is large, involving 120 000 deaths among one million participants in 61 cohorts (with parallel analyses of the Multiple Risk Factor Intervention Trial [MRFIT] observational study[5] that involve a further 17 000 vascular deaths); (ii) individual records are available for each of the participants in each study, allowing detailed analyses; (iii) individuals with pre-existing vascular disease recorded were excluded, limiting any effects of disease on blood pressure (ie, avoiding "reverse causality"); (iv) cause-specific mortality data, together with age at death, are generally available; and (v) information on 286 000 repeat measurements made during prolonged follow-up allows appropriate time-dependent correction for "regression dilution".[2,6]

Time-dependent correction for regression dilution

Typically in prospective studies of the relevance to disease of risk factors such as blood pressure, various characteristics of a cohort are recorded at an initial baseline survey and these baseline characteristics of individuals who subsequently develop a particular disease are then compared with those of individuals who do not. But, because of fluctuations in the measured values of a risk factor at baseline, such comparisons often substantially underestimate the strength of the real association between the "usual" (ie, long-term average) level of that risk factor during a particular exposure period and the disease rate during that same, or a later, period.[2] This regression dilution effect may be caused by measurement error, by short-term biological variability (including both transient fluctuations and any diurnal or seasonal variation), or by longer-term within-person fluctuations or trends in risk factor values (which may occur for several reasons, including physical activity, diet, treatment, disease, or age). Information from repeat measurements of the risk factor after just a year or two in a reasonably representative sample of individuals can be used to correct for the effects not only of random measurement error but also of short-

term variability in risk factor levels.[2] If, however, the aim is to estimate the usual risk factor levels 5, 10, or 15 years later then corrections based on remeasurements made relatively soon after baseline may not allow properly for the effects of longer-term within-person variability or trends. Moreover, since the interval between the baseline survey and the occurrence of an event in prospective studies is typically longer among those who suffer events at older ages, such underestimation may well be greater in the elderly. In order to make appropriate time-dependent corrections for these effects of regression dilution, remeasurements during prolonged follow-up can be used to estimate the usual risk factor levels at some particular fixed interval prior to death in each decade of age.[6]

Hence, by combination of individual participant data from many prospective observational studies in a systematic meta-analysis that is appropriately corrected for time-dependent regression dilution, the present report characterises, with greater precision and less bias than has previously been possible, the age-specific and sex-specific relevance of the usual blood pressure to the subsequent rates of death from stroke, ischaemic heart disease (IHD), other vascular causes, and the aggregate of all non-vascular causes.

Methods

Study selection criteria and data collection

As described previously,[1] collaboration was sought from the investigators of all prospective observational studies in which data on blood pressure, blood cholesterol, date of birth (or age), and sex had been recorded at a baseline screening visit, and in which cause and date of death (or age at death) had been routinely sought for all screenees during more than 5000 person-years of follow-up (see appendix A; http://image.thelancet.com/extras/01art8300webappendixA.pdf). Relevant studies were identified through computer searches of Medline and Embase, by hand-searches of meeting abstracts, and by extensive discussions with investigators. To minimise the effects of reverse causality (whereby established disease could change the usual blood pressure), studies were excluded if they had selected participants on the basis of a positive history of stroke or heart disease, and individuals from contributing studies were excluded from the present analyses if they had such a history recorded at baseline.

The primary risk factors for the present meta-analysis are age, and the systolic and diastolic blood pressures (SBP and DBP). Blood pressure was variously measured in different studies using standard or random-zero sphygmomanometers (but, similar results were found with these different methods: data not shown), typically with participants seated and DBP recorded at the disappearance of arterial flow sounds (phase V). Three US studies among doctors, nurses, or other health professionals involved self-reported blood pressure (see footnote to table A1 in appendix A); in aggregate, however, these three studies and the other 58 studies yielded similar results (data not shown). In some studies there was a strong preference for recording blood pressures that ended in zero (eg, 120 mm Hg); hence, the present analyses mostly use categories of baseline blood pressure that are centred on such values (eg, 115–124). Total blood cholesterol and, where available, lipid fractions (HDL and non-HDL cholesterol), diabetes, weight, alcohol consumption, and smoking at baseline were also assessed (but, controlling for these factors did not materially alter the estimated hazard ratios for the effects of blood pressure: data not shown). Information was sought not only from the baseline examination but also from any subsequent examinations during follow-up in order to devise appropriate general formulae for time-dependent correction of regression dilution (see below).[6]

SBP (mm Hg): baseline categories and values			Estimated "usual" SBP (mm Hg) at average of 5 years before death for deaths at ages				
Group	Range	Mean	40–49	50–59	60–69	70–79	80–89
i	<115	107·7	113·4	115·0	116·6	118·3	119·9
ii	115–124	120·0	123·4	124·7	126·0	127·3	128·7
iii	125–134	129·7	130·9	132·0	133·1	134·1	135·2
iv	135–144	139·4	138·1	138·9	139·7	140·5	141·3
v	145–154	149·4	145·2	145·6	146·0	146·4	146·9
vi	155–164	159·4	152·0	152·0	152·1	152·1	152·2
vii	165–174	169·4	158·6	158·1	157·7	157·3	157·0
viii	175–184	179·5	164·8	163·9	163·0	162·1	161·2
ix	185–194	189·6	170·7	169·2	167·8	166·4	165·0
x	⩾195	210·0	181·8	179·6	177·6	174·6	171·7
Difference (x–i)		102·3	68·4	64·6	60·5	56·3	51·8
Regression dilution ratio*		..	0·67	0·62	0·58	0·54	0·49
Years from baseline†		..	2	4	6	8	10

*Ratio of the cited difference (x–i) in usual SBP at the start of each decade to that in baseline SBP.[6] †Mean years from baseline to start of age range, for those who died in it (estimated as 5 years less than mean years from baseline to death). Hence, regression dilution ratios for usual blood pressure at an average of about 1 year before death in each decade are equivalent to those for years from baseline to start of age range plus 4 years (eg, 0·58, rather than 0·67, for usual SBP at age 40–49 years).

Table 1: **Mean baseline values and estimated usual values of systolic blood pressure (SBP)**

Cause-specific mortality was sought in the greatest detail available, down to three-digit International Classification of Diseases (ICD) coding. In most studies the cause of death was initially taken from the death certificate, but in many cases confirmation was then sought from medical records, autopsy findings, or other sources. Information was provided on stroke deaths (with, for about half, attribution of probable stroke type: cerebral ischaemia, cerebral haemorrhage, or subarachnoid haemorrhage) and on IHD deaths in all but one study (ie, for 99·8% of the 12·7 million person-years at risk). Vascular causes of death other than stroke and IHD could be further subdivided, according to a predefined list,[1] in all but seven studies (ie, for 76% of the person-years at risk: see footnote to table A1 in appendix A).

Statistical methods

The main analyses are age-specific, and are of cause-specific death rates during five decades of age at risk (40–49, 50–59, . . . , 80–89 years), ignoring the few deaths outside the age range 40–89 years.

Age at risk (years)	Person-years at risk ($\times 10^3$)	Number of deaths by attributed cause					
		Stroke	IHD	Other vascular	Non-vascular	Unknown cause	All causes
<40	2020	74	98	57	1302	91	1622
40–49	3269	414	1322	386	4386	265	6773
50–59	3843	1372	5594	1377	12 228	847	21 418
60–69	2482	2939	10 450	2549	18 771	1686	36 395
70–79	913	4327	10 852	3227	16 112	1716	36 234
80–89	177	2636	5649	2251	7436	895	18 867
⩾90	7	198	318	245	562	84	1407
Total*	12 711	11 960	34 283	10 092	60 797	5584	122 716

*For parallel analyses of the MRFIT study, which involved men dying only at ages 40–49, 50–59, and 60–69 years, respectively, there were 107, 461, and 717 stroke deaths; 1084, 4597, and 5679 IHD deaths; and 296, 1484, and 2359 other vascular deaths.

Table 2: **Numbers of deaths attributed to stroke, ischaemic heart disease (IHD), other vascular causes, and non-vascular causes, by age at risk**

Correction for time-dependent regression dilution—For SBP, the baseline measurement was used to divide people into ten categories (<115, 115–124, . . . , ≥195 mm Hg at baseline: table 1). The analyses relate the risk of death during each particular decade of age to the estimated "usual" blood pressure at the start of that decade (eg, age 40 years for death at ages 40–49 years).[6] The mean intervals from the baseline survey until death (from any cause) varied with age at death, being 7, 9, 11, 13, and 15 years for those dying at ages 40–49, 50–59, 60–69, 70–79, and 80–89 years, respectively, in these studies. For those who die in a particular decade of age, the mean age at death is about the middle of that decade (ie, an average of about 5 years after the start of the decade). Hence, the mean intervals from the time of the baseline survey to the start of the decade of age in which death occurred were 2, 4, 6, 8, and 10 years, respectively (table 1). Information on a total of 286 000 blood pressure remeasurements in the different studies (see footnote to table A1 in appendix A) was used to provide estimates of age-specific usual SBP after these particular intervals for each category of baseline SBP (details in appendix B; http://image.thelancet.com/extras/01art8300webappendixB.pdf).

Estimation of hazard ratios for given differences in usual blood pressure—The five age ranges and ten SBP categories yielded a total of 50 different groups, one of which was taken as the reference group with a hazard ratio of 1·0. Relative to this, the other 49 hazard ratios for SBP were estimated simultaneously by Cox's method,[7] stratified for sex and study (with an additional term that allowed the hazard ratio in each decade of age to be estimated as the geometric mean of the hazard ratios in the first and second half of that decade). Fitting each of these 50 separate values avoids any assumptions as to whether the proportional relationships of risk to usual SBP are similar in different decades of age. Collectively, the 50 hazard ratios are "floating" (ie, all are related to the absolute death rates in a particular population by some common constant of proportionality), and so they are presented as "floating absolute risks".[8] This does not change their estimated values, but it does mean that an "effective variance" can be assigned to each log risk (including that for the reference group), which reflects the

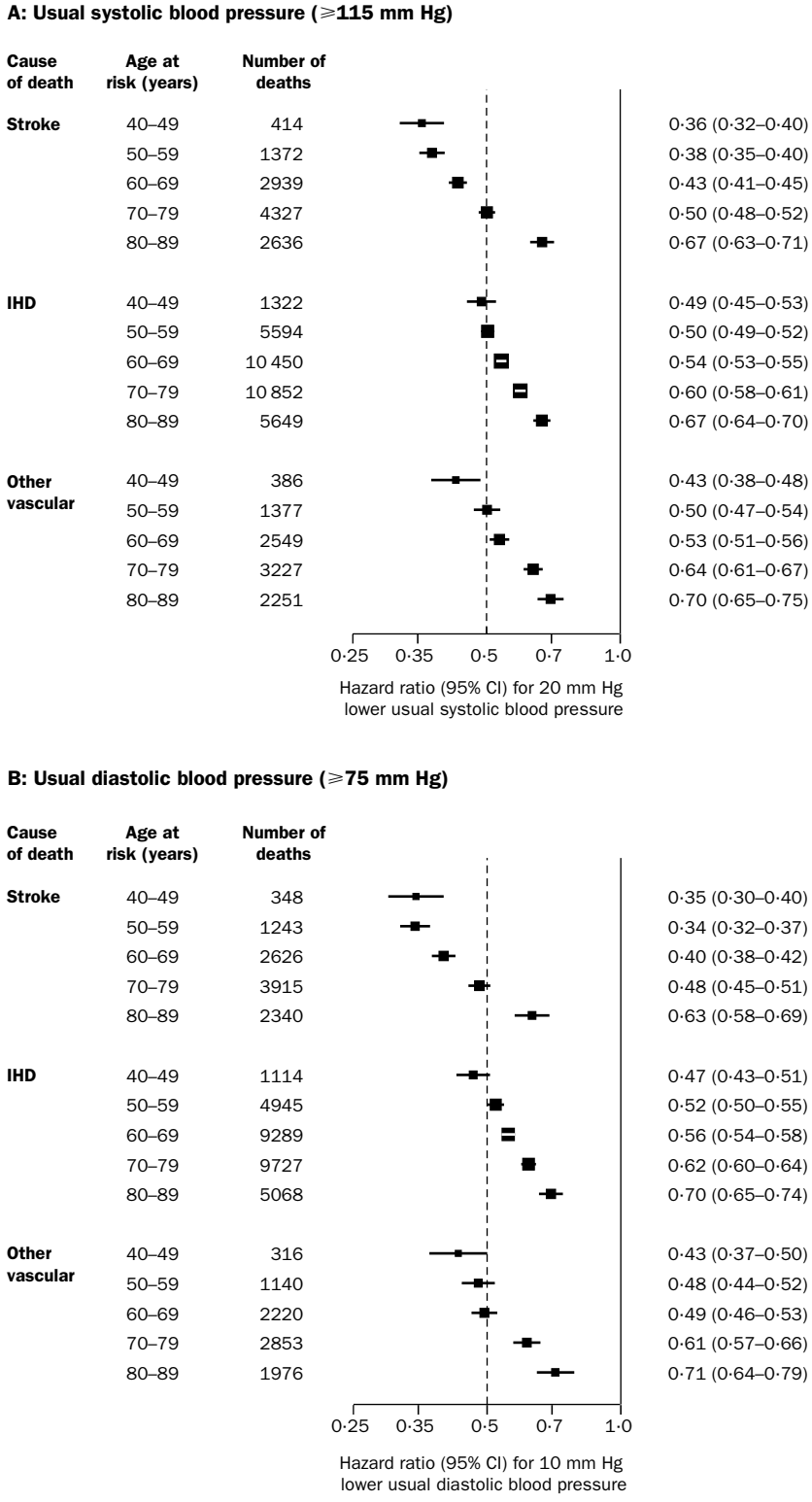

Figure 1: **Stroke, ischaemic heart disease (IHD), and other vascular mortality: age-specific hazard ratios for given differences in usual blood pressure**
The values plotted are the hazard ratios in each decade of age associated with (A) 20 mm Hg lower usual systolic blood pressure (SBP); and (B) 10 mm Hg lower usual diastolic blood pressure (DBP) at the start of that decade. Each square has area inversely proportional to the effective variance of the log hazard ratio, with the vertical broken line indicating a hazard ratio of 0·5. In parallel analyses of the large MRFIT study, a 20 mm Hg lower usual SBP at the start of the decade for deaths at ages 40–49, 50–59, and 60–69 years, respectively, was associated with hazard ratios of (i) stroke: 0·30 (95% CI 0·23–0·40), 0·33 (0·29–0·38), and 0·35 (0·31–0·40); (ii) IHD: 0·42 (0·38–0·47), 0·44 (0·42–0·46), and 0·46 (0·44–0·48); and (iii) other vascular: 0·35 (0·30–0·42), 0·42 (0·39–0·46), and 0·44 (0·41–0·48).

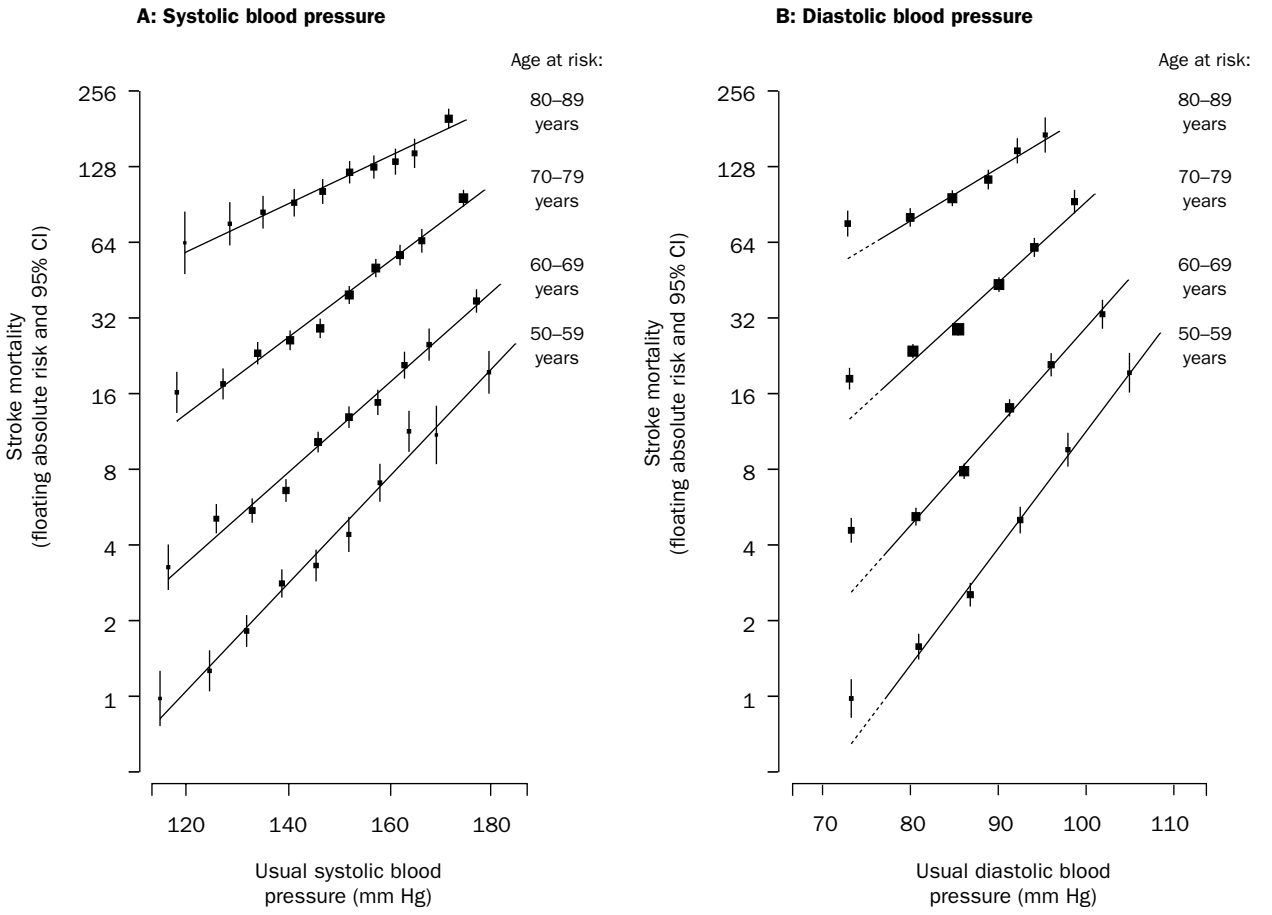

Figure 2: **Stroke mortality rate in each decade of age versus usual blood pressure at the start of that decade**
Rates are plotted on a floating absolute scale, and each square has area inversely proportional to the effective variance of the log mortality rate. For diastolic blood pressure, each age-specific regression line ignores the left-hand point (ie, at slightly less than 75 mm Hg), for which the risk lies significantly above the fitted regression line (as indicated by the broken line below 75 mm Hg).

amount of information underlying that particular group (details in appendix C; http://image.thelancet.com/extras/01art8300webappendixC.pdf). The statistical comparisons between groups then take the 50 log risks for SBP to be mutually independent with these 50 variances. The analyses for DBP were similar to those for SBP, except that the baseline DBP measurement was used to divide people into only six categories, reflecting the narrower range of values (see table B2 in appendix B).

The present report describes the hazard ratios (and 95% CIs) that are associated with 20 mm Hg lower usual SBP, and with 10 mm Hg lower usual DBP. If the slope of log risk against usual SBP (calculated as in appendix C) is x, then the hazard ratio for a 20 mm Hg lower usual SBP is exp(–20x). Hence, for example, to obtain the hazard ratio for a 10 mm Hg lower usual SBP, one would raise the hazard ratio for a 20 mm Hg lower usual SBP to the power 10/20 (ie, take its square root).

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Study populations

Individual records for each of 958 074 participants in 61 studies were included in this meta-analysis, with 70% of the participants from Europe, 20% from North America or Australia, and the remainder from Japan or China (table A1 in appendix A). During 12·7 million person-years at risk (mean of 12 years to death), there were 11 960 deaths attributed to stroke, 34 283 attributed to IHD, 10 092 attributed to other vascular causes, and 60 797 attributed to non-vascular causes (while a further 5584 deaths were of unknown cause: table 2 and table A1 in appendix A). Of the deaths from a specified type of stroke, one-sixth of those at ages 40–59 years, one-third of those at 60–69 years, and half those at 70–89 years were attributed to cerebral ischaemia. Individual records were not available for inclusion in the meta-analysis from participants in the MRFIT study, which involved 16 784 vascular deaths at ages 40–69 years among 353 168 men (see footnote to table 2). But parallel analyses using the same methods of that one large study yielded similar findings, and these are given separately.

Age-specific hazard ratios

Figure 1 summarises the age-specific hazard ratios for death from stroke (top), from IHD (middle), and from other vascular causes (bottom) that are associated with a 20 mm Hg lower usual SBP throughout the range down to 115 mm Hg (figure 1A); or, approximately equivalently, with a 10 mm Hg lower usual DBP throughout the range down to 75 mm Hg (figure 1B). At ages 60–69 years, such differences in usual blood pressure are associated with slightly more than a twofold difference in the risk of stroke death and with almost a

twofold difference in death from IHD and from other vascular causes. (In figure 1, this twofold difference in risk is represented by the vertical broken line through a hazard ratio of 0·5.) The hazard ratios are about twice as extreme for vascular deaths at ages 40–49 years as at ages 80–89 years, but the associations with each of these three categories of vascular mortality remain strong even in old age. Thus, although a 20 mm Hg lower usual SBP is associated with more than a twofold difference in vascular mortality at ages 40–49 years (hazard ratios of 0·36 for stroke, 0·49 for IHD, and 0·43 for other vascular mortality), it is still associated with about one-third less vascular mortality at ages 80–89 years (hazard ratios of 0·67, 0·67, and 0·70, respectively). Parallel analyses of the MRFIT study yield similar age-specific results for the relevance of usual SBP to vascular mortality (see legend to figure 1).

Stroke mortality and usual blood pressure

Figure 2 shows that the relationship of stroke mortality to usual blood pressure is strong and direct at all ages, with no good evidence of a threshold at any age in the range of usual SBP above 115 mm Hg or of usual DBP above 75 mm Hg. A "doubling" (ie, proportional, or log) scale has been used for mortality rates, with a 95% CI for each point that reflects the amount of information underlying each risk estimate (see Methods). Because these mortality rates are collectively "floating", multiplication of all of them by some constant appropriate for a particular population would allow prediction of the absolute rates in that population. For usual SBP, all ten points within each age-group are well fitted by the age-specific regression lines plotted (figure 2A). These approximately "log-linear" relationships imply that the proportional difference in the age-specific risk of stroke death associated with a given absolute difference in usual blood pressure is about the same at all levels of usual SBP down to at least 115 mm Hg. For usual DBP, the age-specific regression lines were fitted to five points only, ignoring the left-hand point (corresponding to slightly less than 75 mm Hg) for which the risk lies significantly above the fitted regression line but still below that of the adjacent point (figure 2B). The slopes of these regression lines were used to calculate the age-specific hazard ratios for stroke death associated with a 20 mm Hg lower usual SBP, or 10 mm Hg lower usual DBP, that were given in figure 1. Throughout middle age, such differences in usual blood pressure are associated with more than a twofold difference in the risk of stroke death. Although the strength of the association between the proportional risk of stroke death and usual blood pressure declines to some extent with increasing age at death, stroke is so much more common in old age than in middle age that the absolute annual difference in stroke death associated with a given difference in blood pressure increases with increasing age. For example, the

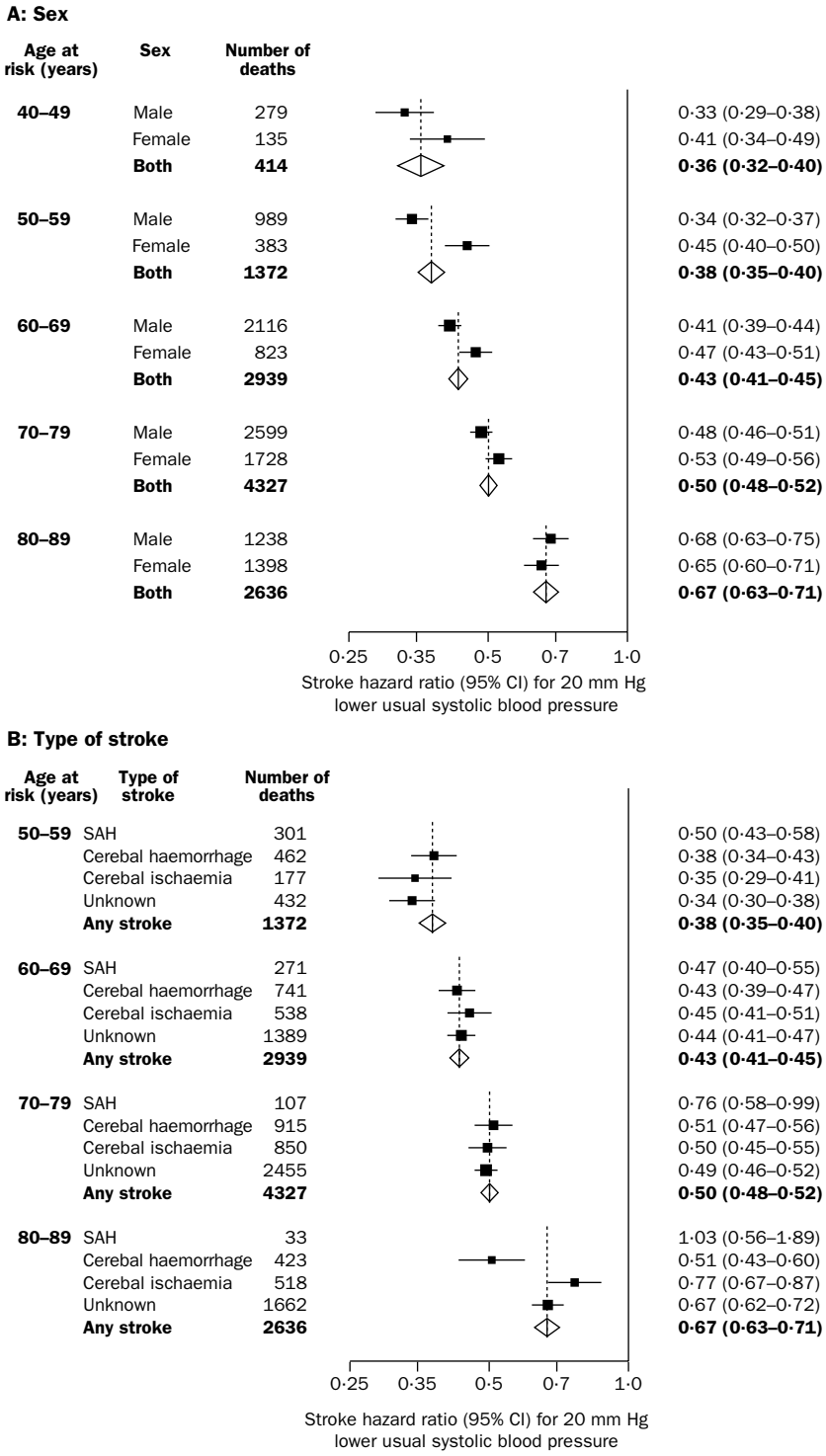

Figure 3: **Stroke mortality: sex-specific and type-specific hazard ratios for 20 mm Hg lower usual systolic blood pressure**

Conventions as in figure 1. Hazard ratios (95% CIs) for subarachnoid haemorrhage (SAH) are given numerically but are not plotted.

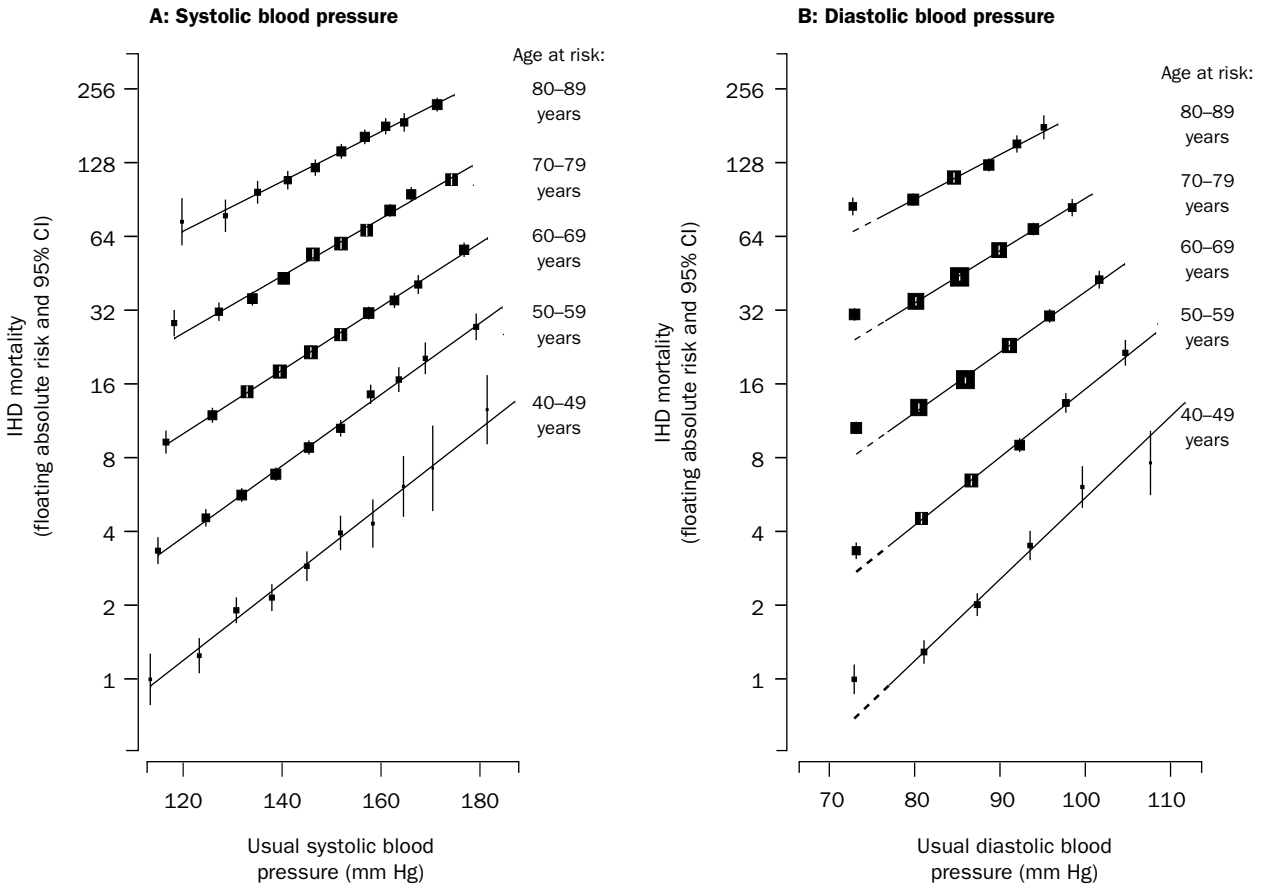

Figure 4: **Ischaemic heart disease (IHD) mortality rate in each decade of age versus usual blood pressure at the start of that decade**
Conventions as in figure 2.

20 mm Hg difference in usual SBP between 120 and 140 mm Hg (or between 140 and 160 mm Hg) is associated with an annual difference in absolute risk that is nearly ten times larger at ages 80–89 years than that at ages 50–59 years (figure 2A).

Reverting to proportional risks, the age-specific associations of stroke mortality with blood pressure appear to be slightly less extreme for women than for men (figure 3A). Comparing different regions of the world, a 20 mm Hg difference in usual SBP is associated with age-standardised hazard ratios for stroke mortality at ages 40–89 years of 0·49 (95% CI 0·48–0·51) in the studies conducted in Europe, 0·50 (0·47–0·53) in the USA or Australia, and 0·42 (0·39–0·46) in Asia. Overall, the probable nature of about half of these fatal strokes was reported, with the remainder being of unknown type. Among people of the same age (at least up to age 80 years), the hazard ratios for death attributed to cerebral haemorrhage and to cerebral ischaemia appear similar (figure 3B). The proportion of stroke deaths considered to be due to cerebral haemorrhage was greater at younger ages, when the strength of the

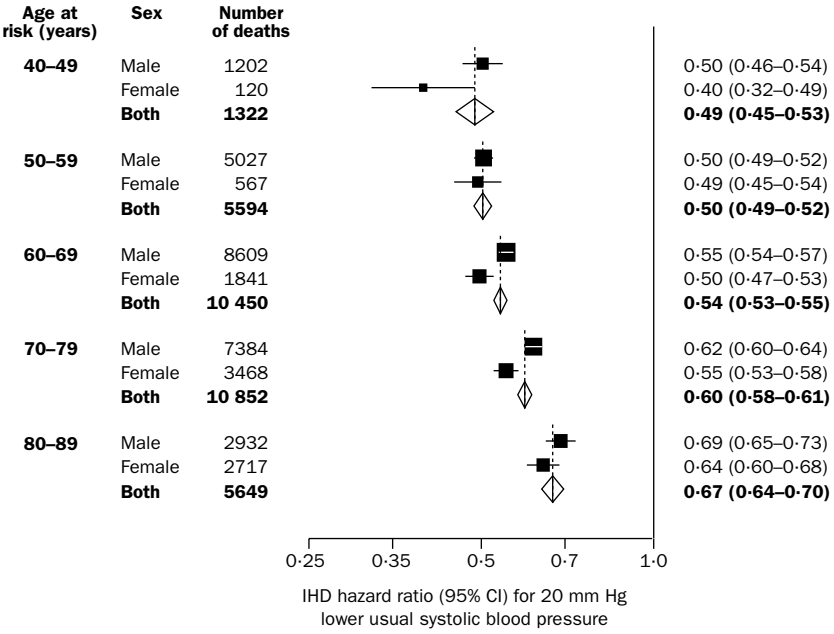

Figure 5: **Ischaemic heart disease (IHD) mortality: sex-specific hazard ratios for 20 mm Hg lower usual systolic blood pressure**
Conventions as in figure 1.

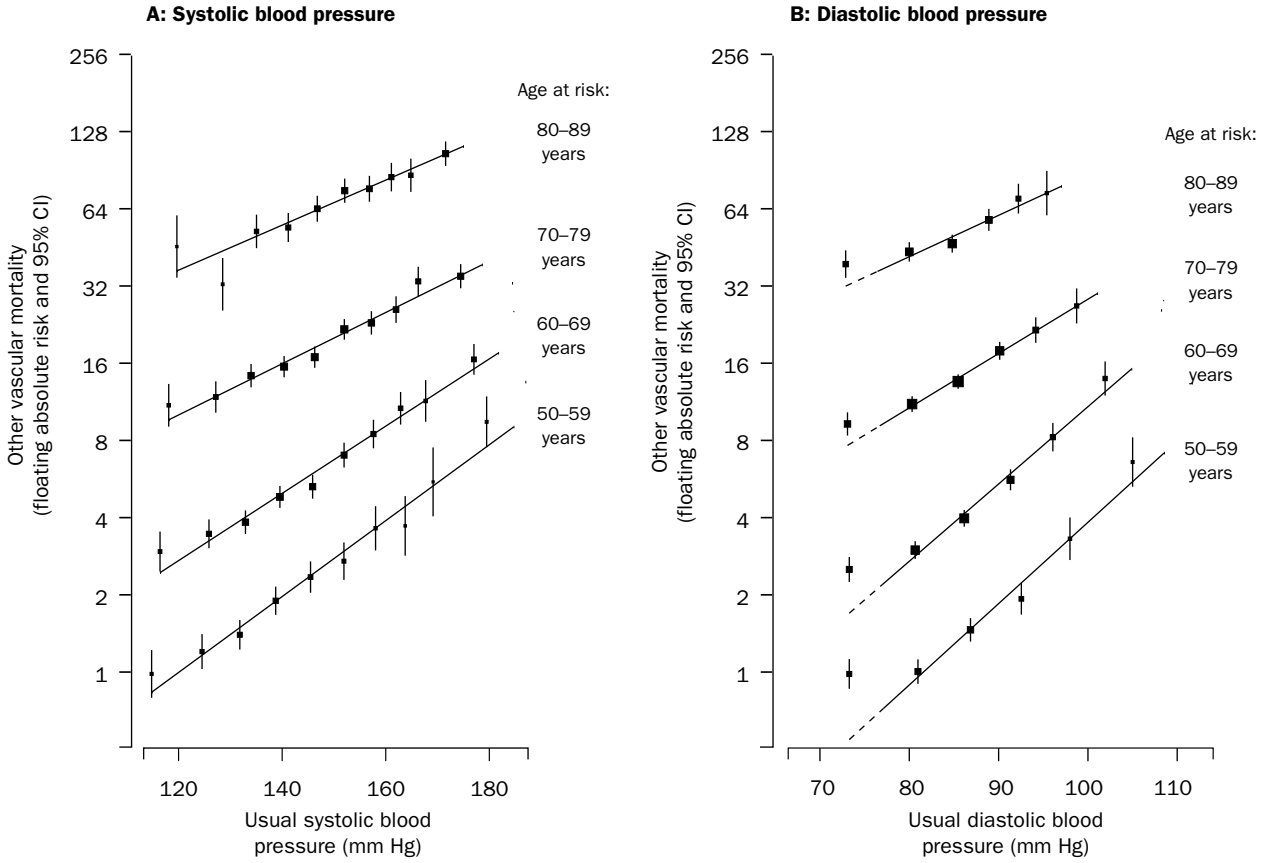

Figure 6: **Other vascular (not stroke or ischaemic heart disease) mortality rate in each decade of age versus usual blood pressure at the start of that decade**
Conventions as in figure 2.

association with stroke is stronger (and misclassification of the type of fatal stroke is less likely). Hence, analyses that are not stratified appropriately by age might suggest that the associations with blood pressure are stronger for deaths due to cerebral haemorrhage than for those due to cerebral ischaemia,[4] even though the age-specific associations are actually about the same for strokes attributed to each cause.

Relatively few deaths were attributed to subarachnoid haemorrhage and, at all ages, the associations of mortality with blood pressure appear to be weaker for this outcome than for other types of stroke (figure 3B). Even so, throughout middle age (ie, at ages 40–69 years), a difference of 20 mm Hg in usual SBP is associated with about a twofold difference in the mortality rate from subarachnoid haemorrhage. (Note that the hazard ratios for subarachnoid haemorrhage are given in figure 3B, but they are not plotted in order that their wide CIs do not dominate the figure.)

IHD mortality and usual blood pressure

Usual blood pressure levels are also strongly and directly associated with IHD mortality at all ages (figure 4), although the relative strength of the association in middle age is somewhat weaker for IHD than for stroke mortality (figure 1). Throughout the range of usual SBP that was studied (ie, down to at least 115 mm Hg), the slope of the association between IHD mortality, plotted on a doubling scale, and the usual level of SBP is approximately constant within each age range (figure 4A). The same also appears to be true for the relationship between IHD mortality and usual DBP down to at least 75 mm Hg (figure 4B), and within this range the age-specific hazard ratios associated with 10 mm Hg differences in usual DBP are similar to those associated with 20 mm Hg differences in usual SBP (figure 1). Throughout middle age, such differences in usual blood pressure are associated with about a twofold difference in IHD mortality. Although the strength of the association between the proportional risk of IHD death and usual blood pressure declines to some extent with increasing age at death (but not as markedly as for stroke: figure 1), the absolute annual difference in IHD death associated with a given difference in blood pressure increases with increasing age.

Reverting to proportional risks, the age-specific associations of IHD mortality with blood pressure appear to be slightly more extreme for women than for men (figure 5). This is the opposite of the slight trend seen for stroke (figure 3A), but in neither case are the effects of sex substantial. Hence, for vascular mortality as a whole (data not shown), sex is of little relevance to the age-specific hazard ratios associated with a given difference in usual blood pressure. Comparing different regions, a 20 mm Hg difference in usual SBP is associated with age-standardised hazard ratios for IHD mortality at ages 40–89 years of 0·57 (95% CI 0·56–0·58) in the studies conducted in Europe, 0·54 (0·51–0·56) in the USA or Australia, and 0·55 (0·48–0·63) in Asia.

Other vascular mortality and usual blood pressure

Likewise, for the aggregate of all vascular causes of death other than stroke or IHD, both SBP and DBP are strongly and directly associated with mortality in each age range. As is the case for stroke and IHD, there appears to

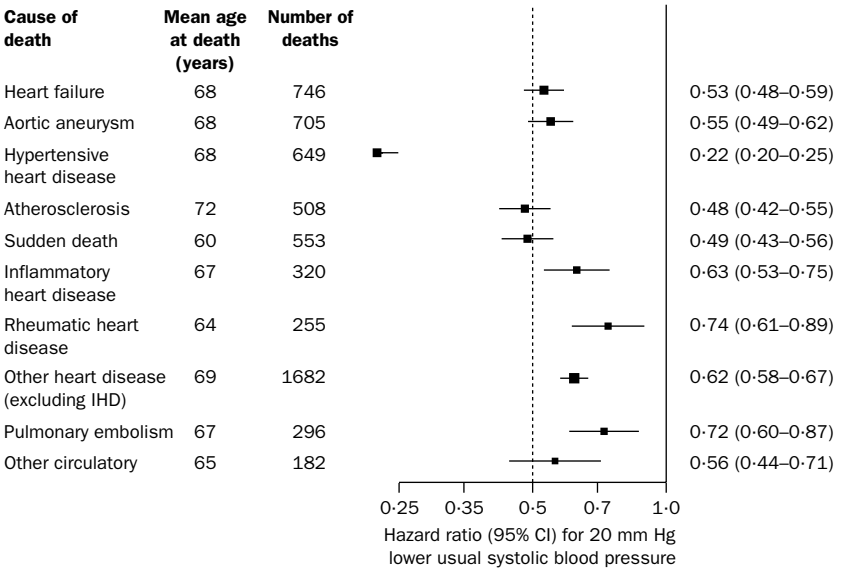

Figure 7: **Mortality from other vascular causes (not stroke or ischaemic heart disease): hazard ratios for 20 mm Hg lower usual systolic blood pressure**
Conventions as in figure 1. Only 54 of the studies subdivided these other vascular causes (see table A1 in appendix A).

be an approximately log-linear relationship between usual blood pressure and mortality from these other vascular causes (and, indeed, with mortality from the aggregate of all vascular causes; data not shown), with no evidence of a threshold down to at least 115/75 mm Hg (figure 6). Again, the strength of the association between the proportional risk of such deaths and the usual blood pressure declines to some extent with increasing age at death (figure 1). Three large, and four small, studies did not provide any subdivision of these other vascular causes of death (table A1 in appendix A), but the 5896 such deaths at ages 40–89 years in the remaining studies can be further subdivided by cause (figure 7). In these age-standardised analyses, a 20 mm Hg difference in usual SBP is associated with about a fourfold difference in mortality from hypertensive heart disease, with about a twofold difference in mortality from each of heart failure, aortic aneurysm, atherosclerosis, and sudden death, and with differences that were less extreme, although still significant (each $p<0·01$), in mortality from inflammatory heart disease, rheumatic heart disease, and pulmonary embolism.

Non-vascular mortality and usual blood pressure

Of the 120 000 deaths at ages 40–89 years, about 60 000 were attributed to non-vascular causes (table 2) and 5000 to an unknown cause (presumably about half vascular and half not). Throughout the range of usual blood pressures down to 115/75 mm Hg, mortality from the aggregate of all non-vascular causes is also positively related to blood pressure, although the relationship is much shallower than that for vascular mortality, with each 20 mm Hg lower usual SBP corresponding to an age-standardised hazard ratio for non-vascular mortality of 0·88 (95% CI 0·87–0·89). If the deaths from an unknown cause are included then this relationship becomes slightly steeper (data not shown). A separate report will describe the associations of blood pressure with deaths attributed to specific non-vascular causes (some of which, such as renal and hepatic diseases, may be partially related to vascular disease). But, at least down to about 115/75 mm Hg, there is no good evidence of any net hazard attributable to lower blood pressure.

Blood pressure index	Informativeness* for prediction of	
	Stroke	IHD
Systolic blood pressure (SBP)	89%	93%
Diastolic blood pressure (DBP)	83%	73%
Pulse pressure (SBP–DBP)	37%	43%
Mean arterial pressure (2/3DBP+1/3SBP)	100%	97%
Mid blood pressure (1/2SBP+1/2DBP)	100%	100%

*Informativeness of the given index (as indicated by the age-stratified χ^2 statistic relating it to cause-specific mortality), as a percentage of the informativeness of the mid blood pressure. Age-specific values are provided in appendix D (http://image.thelancet.com/extras/01art8300webappendixD.pdf).

Table 3: **Relative ability of different blood pressure indices (measured once only) to predict stroke and ischaemic heart disease (IHD) mortality rates**

Predictive power of different blood pressure indices

Using just the blood pressure measurements recorded in these studies at baseline (ie, without any allowance for regression dilution), the relative abilities of a single SBP measurement, of a single DBP measurement, or of some combination of them to predict subsequent mortality from stroke or IHD at different ages were assessed (table 3). This relative "informativeness" of a given blood pressure index was estimated from the age-stratified χ^2 statistic relating it to cause-specific mortality. For, within each particular age range, the more informative a particular blood pressure index is about a particular risk the larger the corresponding χ^2 statistic will tend to be.

Of the indices considered, the most informative about stroke mortality is "mid blood pressure" (defined as 1/2SBP+1/2DBP), partly because any random measurement errors that just affect SBP or that just affect DBP are halved in calculating the average. By comparison, measurements of SBP and of DBP are, respectively, only 89% and 83% as informative about stroke mortality as is mid blood pressure, and pulse pressure is only 37% as informative. Mean arterial pressure (2/3DBP+1/3SBP) is highly correlated with mid blood pressure, and is about as informative. For IHD mortality, a similar pattern is seen, although the superiority of a single measurement of SBP over a single measurement of DBP is more definite. Again, mid blood pressure is the most informative of these measurements, with SBP 93% as informative, DBP 73% as informative, and pulse pressure only 43% as informative. If each decade of age at death is considered separately, then SBP is still a much more informative index of stroke or IHD risk than is pulse pressure, and again mid blood pressure is slightly better than SBP (details in appendix D; http://image.thelancet.com/extras/01art8300webappendixD.pdf). For, at a given measured value of SBP, the measured value of DBP is still very significantly positively related (as in mid blood pressure), rather than negatively related (as in pulse pressure), to stroke and to IHD mortality.

Discussion

Continuous positive associations between blood pressure and disease risk

In the present meta-analysis of data from 61 prospective observational studies on deaths from vascular disease among individuals without known vascular disease at baseline (and in parallel analyses of the large MRFIT study), blood pressure is associated strongly with the age-specific mortality rates from stroke, almost as strongly with the mortality rates from IHD and with those from other vascular causes, and much less strongly (although still positively) with the age-specific mortality rates from the aggregate of all non-vascular causes. In general, a 20 mm Hg difference in usual SBP is approximately equivalent in its hazards to a 10 mm Hg difference in usual DBP. These relationships with vascular mortality continue steeply down at least as far as a usual SBP of 115 mm Hg and a usual DBP of 75 mm Hg, below which there is little evidence. (Note that a single measurement of 110/70 mm Hg would, in these populations, indicate a usual blood pressure of just over 115/75 mm Hg [table 1 and appendix B], which lies within the range of the steep dose-response relationship.) Throughout this blood pressure range, the proportional difference in risk associated with a given absolute difference in usual blood pressure is similar at all blood pressure levels (ie, the relationship is approximately log-linear). This refutes the recent suggestion that there might be a threshold level of SBP at about 140–160 mm Hg (depending on age),[9] below which lower blood pressure levels are not associated with lower disease risks. Indeed, the vascular mortality rates are only about half as great at 120 as at 140 mm Hg usual SBP, with no apparent net adverse effect on non-vascular mortality.

The present analyses of the relevance of usual blood pressure to cause-specific mortality show that the strengths of these age-specific associations with particular causes of death differ. By contrast, analyses of the association of usual blood pressure with the aggregate of all causes of death[9] would tend to obscure both the continuous log-linear associations with particular vascular causes of death and the much weaker associations with non-vascular mortality. Consequently, although misclassification of causes of death may have some impact on the observed associations, such cause-specific analyses are more informative than analyses of all-cause mortality. Moreover, these analyses of cause-specific mortality can be generalised more reliably to different circumstances in which the proportions of deaths due to particular causes differ from those in the studies contributing to the present analyses.

Strength of associations after time-dependent correction for regression dilution

After making time-dependent corrections for regression dilution in these prospective studies, usual blood pressure has been found to be more strongly related to vascular disease risk than previously estimated,[2–4] particularly for deaths at older ages. The proportional differences in vascular mortality associated with a given difference in blood pressure remain greater in middle than in old age, but the absolute annual differences in vascular mortality are greater at older ages than in middle age because the underlying rates of vascular disease are higher. The age-specific proportional differences in vascular mortality are also about the same for men and for women, and (in contrast with analyses that combine information from widely different ages[4]) are similar for haemorrhagic stroke and for ischaemic stroke. Moreover, other risk factors (such as blood cholesterol, diabetes, smoking, and weight) were not found to have any material influence on the proportional differences in vascular mortality associated with a given absolute difference in usual blood pressure.

These analyses related the risks of death during a particular decade of age to the estimated usual systolic and diastolic blood pressure levels at the start of that decade. The choice of which exposure period is most appropriate depends on the rapidity with which a change in the usual blood pressure would change the mortality rates. If blood pressure levels over the previous decade or so are all of comparable relevance then it might be appropriate (as in the present analyses) to relate risk to the usual blood pressure about 5 years before death. At least for stroke, however, the main changes in risk may well occur quite rapidly after a change in the usual blood pressure (to judge from the substantial reductions in risk observed within just a few years in randomised trials of blood pressure lowering[10–13]). If so, then the present analyses should perhaps have related stroke mortality to estimates of what the usual blood pressure levels would have been (in the absence of any effects of disease) shortly before death. In that case, the associations of blood pressure with risk would be about one-sixth stronger for usual SBP and one-third stronger for usual DBP than in the present report (as indicated by comparison of the regression dilution ratios at the start of each age range with those at the middle of each age range; see footnotes to table 1 and to table B2 in appendix B).

If just one single measurement of blood pressure is to be used to predict risk then, irrespective of age, the measured SBP is slightly more informative than the measured DBP, their average (ie, the mid blood pressure) is slightly more informative than either alone, and their difference (ie, the pulse pressure) is much less informative, contrary to the findings of some much smaller studies.[14,15] Indeed, among people of a given age whose measured SBP is the same, the pulse pressure is actually inversely correlated with risk (because the measured DBP is positively correlated with risk).

Implications for disease prevention

Among people with no previous vascular disease recorded, the usual blood pressure is positively related to the risks of death from vascular disease not only among individuals who might be considered hypertensive, but also among those who would usually be considered normotensive (at least down to usual blood pressure levels of 115/75 mm Hg). Moreover, throughout this range, lower blood pressure is also associated with a slightly lower overall risk of death from non-vascular causes, although some of this may represent reverse causality (eg, renal disease exacerbating hypertension) or misclassification of deaths caused (at least in part) by vascular disease. Given the continuous relationship observed between blood pressure and risk of death from vascular disease, the absolute benefits of a lower blood pressure level are likely to be greatest for those at greatest absolute risk of vascular disease, largely irrespective of their blood pressure level (except insofar as it is one of the factors that influences this risk). So, even though the present meta-analysis did not include people who already had some history of vascular disease recorded at baseline (in order to avoid reverse causality, whereby established disease reduces or increases the blood pressure), it may

well be that those who are at high risk because of pre-existing disease (or age, or other factors) would gain particular benefit from lowering blood pressure, even if they would currently be classified as normotensive. This is supported by the limited evidence available from subgroups within meta-analyses of randomised trials of blood-pressure-lowering treatment[10,16,17] and by the large-scale randomised evidence that is now emerging in higher-risk settings.[18,19] Hence, blood-pressure-lowering treatment should be considered for a wide range of patients with evidence of occlusive vascular disease, largely irrespective of their current blood pressure or the use of other medication.

Not only do the present analyses confirm that there is a continuous relationship with risk throughout the normal range of usual blood pressure (down at least as far as 115/75 mm Hg), but they also demonstrate that within this range the usual blood pressure is even more strongly related to vascular mortality than had previously been supposed.[2–4] Randomised trials (which typically last only a few years) have shown that blood-pressure lowering can produce rapid reductions in vascular disease risk,[10–13] and this meta-analysis of observational studies provides complementary evidence of the even greater differences in risk that are likely to be produced by really prolonged differences in blood pressure. For example, a 10 mm Hg lower usual SBP or 5 mm Hg lower usual DBP (as have typically been assessed in previous randomised trials of just a few years of blood pressure lowering[10–13]) would, in the long term, be associated with about 40% lower risk of stroke death and about 30% lower risk of death from IHD or other vascular causes throughout middle age (and with only slightly smaller proportional differences at older ages). Indeed, even a 2 mm Hg lower usual SBP would involve about 10% lower stroke mortality and about 7% lower mortality from IHD or other vascular causes in middle age. So, for the general normotensive population, producing persistent reductions in average blood pressure of just a few mm Hg by some widely practicable methods (such as, perhaps, reducing sodium intake in manufactured foods[20–22]) should avoid large absolute numbers of premature deaths and disabling strokes,[23] especially in places that, perhaps for other reasons, have relatively high stroke rates (such as Northern China[24,25]) or high IHD rates (such as Eastern Europe[26]).

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Conflict of interest statement
None declared.

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Uses of error

Brugada syndrome

S R Vavricka, A Himmelmann, A Schaffner

A 50-year-old white man in previously good health was found unresponsive on the street by a bystander. Lay cardiopulmonary resuscitation was started and paramedics were called. The squad found the patient in ventricullar fibrillation.

Defibrillation was successful without neurological sequelae. In hospital serum electrolytes were normal. At cardiac catheterisation a normal ventriculography and normal coronary arteries were found. The ECG demonstrated normal sinus rhythm with normal PR, QT, and QTc intervals. However, we suspected Brugada syndrome because of ST-segment elevation in V1 and V2 and an incomplete right bundle-branch block. Furthermore left-axis deviation was present. Therefore, we implanted a cardioverter defibrillator (ICD) on the sixth day of hospitalisation. Because of oxygenation problems computed tomography was done on the fourth day of hospitalisation which showed a paracentral embolism in the right pulmonary artery originating from a deep venous thrombosis. We started treatment with low molecular weight heparin. ECG on day five showed disappearance of the ST-segment elevation and the incomplete right bundle-branch block. 20 months after implantation of the ICD the patient feels fine and there has been no discharge of the ICD to the present day. A thrombophilia screen including APC-resistance, protein C and S deficiency, and fibrinogen mutation were negative.

Brugada syndrome is a recognised cause of ventricular fibrillation in the absence of structural heart disease, for which there are no stringent diagnostic criteria. Typical ECG findings are ST-segment elevation in the right precordial leads and a right bundle branch block. Other causes must be ruled out before implanting an ICD. As with the long QT syndrome, prevalence is estimated to be 1 per 5000. Currently, an ICD is the only effective therapy to prevent sudden death. Therefore, not least because of cost-effectiveness, an unequivocal diagnostic definition of this life-threatening syndrome is needed. Nevertheless, Brugada syndrome is currently a diagnosis of exclusion and the possibility of structural or coronary heart disease, or pulmonary embolism should first be pursued. Pulmonary embolism can lead to ECG-changes such as ST-segment elevation and right bundle branch block and thus mimic Brugada syndrome.

Our case also demonstrates that the focus of over-specialisation sometimes results in dramatic increases in health-care costs.

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