

The New England Journal of Medicine

© Copyright, 2000, by the Massachusetts Medical Society

VOLUME 342

JANUARY 6, 2000

NUMBER 1



THE RELATION BETWEEN BLOOD PRESSURE AND MORTALITY DUE TO CORONARY HEART DISEASE AMONG MEN IN DIFFERENT PARTS OF THE WORLD

PEGGY C.W. VAN DEN HOOGEN, M.Sc., EDITH J.M. FESKENS, Ph.D., NICO J.D. NAGELKERKE, Ph.D.,
ALESSANDRO MENOTTI, Ph.D., M.D., AULIKKI NISSINEN, Ph.D., M.D., AND DAAN KROMHOUT, Ph.D., M.P.H.,
FOR THE SEVEN COUNTRIES STUDY RESEARCH GROUP

ABSTRACT

Background Elevated blood pressure is known to be a risk factor for death from coronary heart disease (CHD). However, it is unclear whether the risk of death from CHD in relation to blood pressure varies among populations.

Methods In six populations in different parts of the world, we examined systolic and diastolic blood pressures and hypertension in relation to long-term mortality from CHD, both with and without adjustment for variability in blood pressure within individual subjects. Blood pressure was measured at base line in 12,031 men (age range, 40 to 59 years) who were free of CHD. During 25 years of follow-up, 1291 men died from CHD.

Results At systolic and diastolic blood pressures of about 140 and 85 mm Hg, respectively, 25-year rates of mortality from CHD (standardized for age) varied by a factor of more than three among the populations. Rates in the United States and northern Europe were high (approximately 70 deaths per 10,000 person-years), but rates in Japan and Mediterranean southern Europe were low (approximately 20 deaths per 10,000 person-years). However, the relative increase in 25-year mortality from CHD for a given increase in blood pressure was similar among the populations. The overall unadjusted relative risk of death due to CHD was 1.17 (95 percent confidence interval, 1.14 to 1.20) per 10 mm Hg increase in systolic pressure and 1.13 (95 percent confidence interval, 1.10 to 1.15) per 5 mm Hg increase in diastolic pressure, and it was 1.28 for each of these increments after adjustment for within-subject variability in blood pressure.

Conclusions Among the six populations we studied, the relative increase in long-term mortality due to CHD for a given increase in blood pressure is similar, whereas the absolute risk at the same level of blood pressure varies substantially. These findings may have implications for antihypertensive therapy in different parts of the world. (N Engl J Med 2000;342:1-8.)

©2000, Massachusetts Medical Society.

BLOOD pressure is directly related to mortality from coronary heart disease (CHD),¹⁻⁴ and previous results from the Seven Countries Study have suggested that the relative increase in mortality from CHD for a given increase in blood pressure is similar among different populations.⁵ In the current investigation, we further explored this relation by investigating whether the relative risk of death due to CHD in relation to systolic and diastolic blood pressures and hypertension is similar among different populations. Because absolute risks are more important than relative risks from the perspective of public health and treatment, we also compared the absolute risk of death due to CHD at a given level of blood pressure among different populations.

Since an individual person's blood pressure can vary substantially, a single measurement will not accurately represent a person's average, or usual, blood-pressure level. When single measurements of blood pressure are used at base line, results with respect to the effect of blood pressure on the risk of death will be biased.^{1,6} In our investigation, data from repeated measurements of blood pressure were available for use in examining the effects of within-subject variability.

METHODS

Study Populations

Between 1958 and 1964, 12,761 men 40 to 59 years old who resided in seven countries were enrolled in the study.⁷ A total of 16 cohorts were included in the United States, Finland (eastern and western), the Netherlands (Zutphen), Italy (Rome, Crevalcore, and

From the Department of Chronic Diseases Epidemiology, National Institute of Public Health and the Environment, Bilthoven, the Netherlands (P.C.W.H., E.J.M.F., N.J.D.N., D.K.); the Netherlands Institute for Health Sciences, Rotterdam (P.C.W.H.); the Division of Epidemiology, School of Public Health, University of Minnesota, Minneapolis (A.M.); and the Department of Public Health and General Practice, University of Kuopio, Kuopio, Finland (A.N.). Address reprint requests to Dr. Kromhout at the National Institute of Public Health and the Environment, P.O. Box 1, 3720 BA Bilthoven, the Netherlands, or to Dr. van den Hoogen at peggy.van.den.hoogen@rivm.nl.

Montegiorgio), Greece (Crete and Corfu), the former Yugoslavia (Dalmatia, Slavonia, Zrenjanin, Velika Krsna, and Belgrade), and Japan (Tanushimaru and Ushibuka). In the United States and Rome, railroad workers were recruited. In the former Yugoslavia, workers from a large cooperative in Zrenjanin and professors from the University of Belgrade were invited. In the town of Zutphen, the Netherlands, for every nine men, four were invited to participate. In the remaining 11 cohorts (all rural), all men 40 to 59 years old who were listed in official registries were invited. Overall, the participation rate was greater than 90 percent, with several cohorts reaching participation rates of almost 100 percent.

To increase the power of the statistical analyses, the cohorts were pooled into six populations: the United States, northern Europe (eastern and western Finland and Zutphen), Mediterranean southern Europe (Montegiorgio, Crete, Corfu, and Dalmatia), inland southern Europe (Rome, Crevalcore, Slavonia, and Belgrade), rural Serbia (Zrenjanin and Velika Krsna), and Japan (Tanushimaru and Ushibuka).⁸ The criteria for pooling were similarities among cohorts in rates of mortality from CHD and similarities among cohorts in culture (such as dietary patterns) and geographic features.

Measurement of Blood Pressure and Clinical Assessment

In all 16 cohorts, major cardiovascular risk factors were measured according to standardized methods at enrollment, after 5 years (except in Japan), and after 10 years (except in the United States). Details of the methods used have been described previously.^{7,9} Blood pressure was measured by a trained physician using a calibrated mercury sphygmomanometer on the right arm, with the subject in the supine position, at the end of the physical examination, according to the method later described in the World Health Organization (WHO) manual *Cardiovascular Survey Methods*.¹⁰ Readings were taken to the nearest 2 mm Hg. The mean of two measurements, taken one minute apart, was computed for both the systolic and the diastolic blood pressure; for the diastolic pressure, the fifth-phase Korotkoff sound was assessed. Hypertension was defined as a systolic blood pressure of 160 mm Hg or higher, a diastolic blood pressure of 95 mm Hg or higher, or both. During the base-line period (1958 to 1964), medications designed to lower blood pressure were rarely prescribed in any of the seven countries, and therefore use of medication was not included in the definition of hypertension.

Nonfasting blood samples were drawn and serum total cholesterol levels were measured in standardized fashion at all laboratories according to the Abell-Kendall method, as modified by Keys et al.⁷ Current cigarette smoking was identified by a positive response on a standardized questionnaire. CHD at enrollment was defined as the presence of definite or possible myocardial infarction, according to predefined clinical and electrocardiographic criteria; definite angina pectoris, according to responses on the WHO questionnaire¹⁰; or chronic CHD manifested as heart failure or chronic arrhythmia, according to predefined clinical criteria.^{9,11} When the Seven Countries Study began, it was not standard practice in clinical research to ask participants for written informed consent or to ask for approval from medical ethics committees.

Assessment of Mortality during Follow-up

To assess mortality in the study populations, all 12,761 subjects were followed for 25 years; 56 men (0.4 percent) were lost to follow-up. The underlying cause of death was coded by a single reviewer according to the criteria of the WHO *International Classification of Diseases, 8th Revision* (ICD-8).¹² The reviewer who coded the cause of death was blinded with respect to the subjects' cardiovascular risk factors. The final cause of death was established on the basis of information from the official death certificate (without other information in not more than 15 percent of all cases), from medical and hospital records, and from relatives of the person deceased or other witnesses and with use of a list of predefined criteria prepared by the primary investigators. In cases in which multiple causes of death were possible, priority was given to violent death, followed by cancer in an advanced stage, CHD, and stroke. The end point of the study was death during the 25 years of follow-up, with the

primary cause established as CHD (ICD-8 codes 410 to 414), or sudden death from cardiac causes (ICD-8 code 795) when a coronary origin was mentioned.

Statistical Analysis

Among the 12,705 subjects with complete follow-up data, 246 (1.9 percent) had CHD at enrollment and for 16 (0.1 percent) data on CHD at enrollment were missing; these subjects were excluded from the analyses. We also excluded 412 subjects (3.2 percent) for whom data on covariates were missing, leaving 12,031 subjects in the analysis. For each population, the age-standardized 25-year rate of death due to CHD was computed by the direct standardization method, with use of the total study population as the reference population. In addition, for each population, the 25-year mortality from CHD, adjusted for age (in years), total cholesterol level (in millimoles per liter), and current cigarette-smoking status (no or yes), was computed per quartile of usual systolic blood pressure and usual diastolic blood pressure (with usual pressures calculated as described below). To do so, we first performed regression analyses for mortality due to CHD to obtain population-specific and quartile-specific regression coefficients for the three covariates (age, total cholesterol, and current smoking status). With these regression coefficients, we estimated multivariate-adjusted, population-specific mortality from CHD for each blood-pressure quartile, given the assumption that the mean level of the covariates for each population-specific quartile was equal to the mean level of the covariates for the total study population.

Cox proportional-hazards analysis, with the cohort as a stratification variable, was performed to estimate relative risks (SAS statistical software, version 6.12, PHREG procedure; SAS, Cary, N.C.). Relative risks of death from CHD were estimated by including either systolic blood pressure (in increments of 10 mm Hg) or diastolic blood pressure (in increments of 5 mm Hg) as a continuous variable in the model. Relative risks of death from CHD were also estimated with respect to the presence or absence of hypertension. In the multivariate analyses, adjustment was made for age and cohort as well as for age, cohort, total cholesterol concentration, and current cigarette-smoking status. To examine whether the relative risks differed among populations with different absolute risks of death due to CHD, we first created an ordinal population variable scored from 1 to 6, where 1 represented the population with the lowest age-standardized 25-year mortality due to CHD and 6 the population with the highest mortality. We subsequently tested for a significant interaction between this ordinal population variable and the blood-pressure variables (where P values of <0.1 by the likelihood-ratio test indicated significance, with one degree of freedom).

Short-term variations in blood-pressure values in individual subjects, resulting from imperfections in measurement or true biologic variability, bias the relation between usual blood pressure and mortality from CHD.^{1,6,13} We corrected for this bias in two steps. First, for each subject, the usual, or average, blood pressures during the first five years of follow-up were estimated from a linear regression model, given the values obtained at enrollment and at the five-year follow-up for systolic and diastolic blood pressures, body-mass index, and cholesterol level.¹⁴ For each subject, the presence or absence of hypertension was then reassessed according to these estimates of usual blood pressures over the first five years. Second, the estimates of usual blood pressures and the new hypertension variable were analyzed in a Cox survival model to estimate regression coefficients for systolic and diastolic blood pressures and hypertension, with adjustment for within-subject variability. To examine the effect of within-person variability in blood pressure on estimated regression coefficients for systolic and diastolic blood pressures, we divided the adjusted regression coefficients by the unadjusted regression coefficients from the survival analysis to obtain population-specific adjustment factors.

RESULTS

The base-line characteristics of each of the six study populations are shown in Table 1. The average sys-

RELATION BETWEEN BLOOD PRESSURE AND DEATH FROM CORONARY HEART DISEASE IN VARIOUS POPULATIONS

TABLE 1. BASE-LINE CHARACTERISTICS OF MEN IN THE SEVEN COUNTRIES STUDY AND AGE-STANDARDIZED 25-YEAR MORTALITY FROM CORONARY HEART DISEASE.*

POPULATION	No. OF SUBJECTS	AGE	SYSTOLIC BLOOD PRESSURE	DIASTOLIC BLOOD PRESSURE	TOTAL CHOLESTEROL LEVEL	HYPERTENSION	CIGARETTE SMOKING	No. OF DEATHS DUE TO CHD	AGE-STANDARDIZED 25-YR MORTALITY FROM CHD
		yr	mm Hg	mm Hg	mmol/liter	% of men			no./10,000 person-yr
United States	2416	49.2±5.7	139.0±20.6	86.0±11.6	6.19±1.16	25.5	59.4	354	73
Northern Europe	2377	49.3±5.5	143.7±20.0	86.6±11.9	6.51±1.32	29.8	66.6	461	100
Mediterranean southern Europe	2516	49.3±5.3	136.9±19.3	82.1±11.0	5.17±1.08	17.3	59.2	116	22
Inland southern Europe	2870	48.7±5.4	141.2±20.6	86.6±12.0	5.28±1.08	27.5	59.3	253	46
Serbia	981	49.3±5.8	132.5±18.8	83.3±10.4	4.24±0.83	15.7	56.1	77	41
Japan	871	49.7±5.6	134.7±24.5	75.7±13.7	4.25±0.91	16.2	74.5	30	17

*Plus-minus values are means ±SD. CHD denotes coronary heart disease.

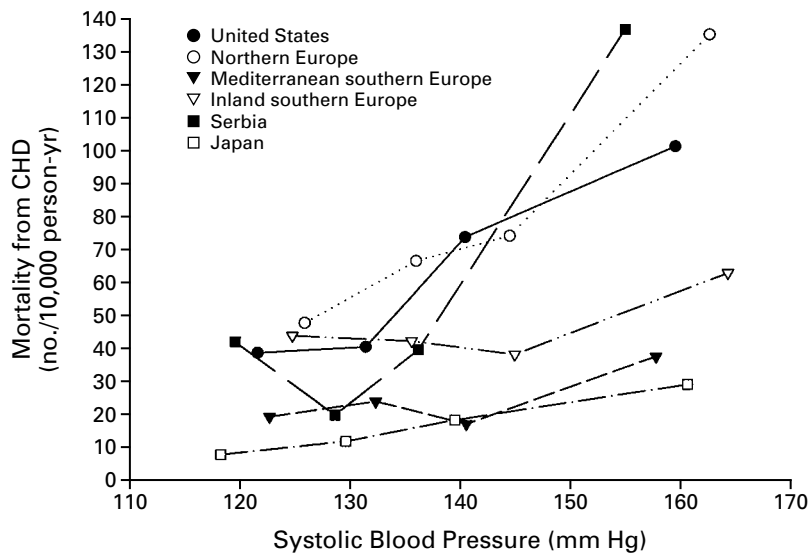


Figure 1. Mortality Due to Coronary Heart Disease per Quartile of Usual Systolic Blood Pressure. Values shown are 25-year rates of death due to coronary heart disease (CHD), adjusted for age, serum total cholesterol level, and cigarette-smoking status. The absolute risk of death at a given level of usual systolic blood pressure varied greatly among the populations.

tolic blood pressure at base line ranged from 132.5 mm Hg in Serbia to 143.7 mm Hg in northern Europe. The average diastolic blood pressure at base line ranged from 75.7 mm Hg in Japan to 86.6 mm Hg in both northern Europe and inland southern Europe. The proportion of men with hypertension was lowest in Serbia and Japan (15.7 percent and 16.2 percent, respectively) and highest in northern Europe (29.8 percent). The age-standardized 25-year rate of death due to CHD was low in Japan and Mediterranean southern Europe, intermediate in inland southern Europe and Serbia, and high in the United States and northern Europe.

In Figure 1, 25-year rates of death from CHD, adjusted for age, serum total cholesterol, and current smoking status, are plotted against the mean level of usual systolic blood pressure within the quartile. This plot shows that the absolute risk of death at a given value for usual systolic blood pressure varied strongly among the populations. For a usual systolic blood pressure of about 140 mm Hg, mortality varied by a factor of more than three, from approximately 20 per 10,000 person-years in Japan and Mediterranean southern Europe, to approximately 70 per 10,000 person-years in northern Europe and the United States. A similar pattern of variation in the absolute

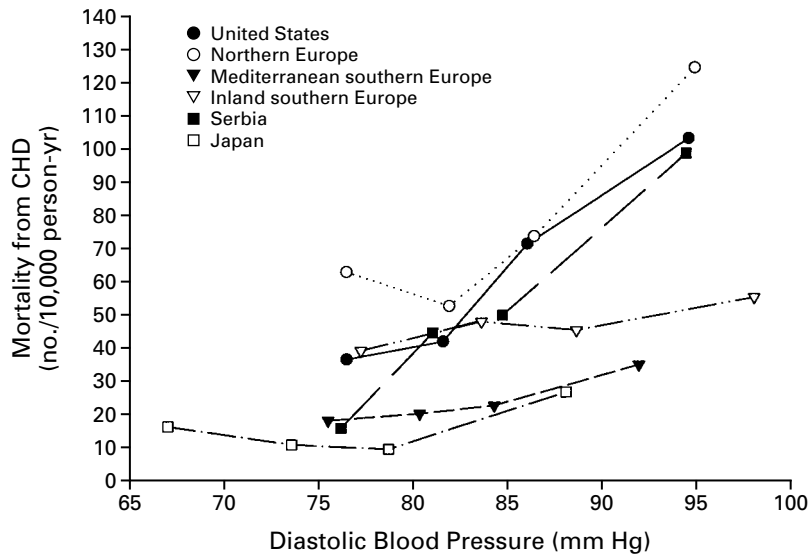


Figure 2. Mortality Due to Coronary Heart Disease per Quartile of Usual Diastolic Blood Pressure.

Values shown are 25-year rates of death due to coronary heart disease (CHD), adjusted for age, serum total cholesterol level, and cigarette-smoking status. The absolute risk of death at a given level of usual diastolic blood pressure varied greatly among the populations.

risk was observed for a usual diastolic blood pressure of about 85 mm Hg (Fig. 2).

For an increase of 10 mm Hg in systolic blood pressure, the multivariate-adjusted relative risk of death from CHD ranged from 1.09 in inland southern Europe to 1.25 in Serbia and Japan (Table 2). The multivariate-adjusted relative risk for all the populations combined was 1.17 before adjustment for within-subject variability in blood pressure and 1.28 after adjustment. For an increase of 5 mm Hg in diastolic blood pressure, the relative risk of death ranged from 1.06 in inland southern Europe to 1.19 in Mediterranean southern Europe, with a relative risk for the total population of 1.13 before adjustment for within-subject variation in blood pressure and 1.28 after adjustment. No significant differences were observed among the populations with respect to the relative risk of death from CHD over the 25-year period for these increments in blood pressure ($P > 0.1$ by the likelihood-ratio test for the interaction between the blood-pressure variables and the ordinal population variable).

The absolute risk of death from CHD that was associated with hypertension was clearly different among the six populations (Table 3). Among subjects with hypertension, the age-standardized 25-year mortality varied by a factor of nearly four, from 44 per 10,000 person-years in Japan and Mediterranean southern Europe to 153 per 10,000 person-years in northern Europe. Hypertension was a significant risk factor for death from CHD in all the populations: the relative risk before adjustment for within-subject variation

ranged from 1.33 in inland southern Europe to 2.80 in Japan, and the overall unadjusted relative risk for hypertension was 1.77. When adjustment for within-subject variation was made by using usual values for systolic and diastolic blood pressure over the first five-year period, instead of single base-line values, to classify subjects as having or not having hypertension, the overall relative risk associated with hypertension became 2.13. No significant differences were observed among the populations with respect to the relative risk of death from CHD that was associated with hypertension ($P > 0.1$ by the likelihood-ratio test for the interaction between the hypertension variable and the ordinal population variable).

DISCUSSION

We observed that the relative risk of death due to CHD in association with given increments in systolic and diastolic blood pressure and the presence of hypertension over 25 years did not differ significantly among the six populations, but that the absolute risk of death at the same level of blood pressure varied substantially. This indicates that the relation between blood pressure and the relative risk of death from CHD over the long term did not differ among populations in which the absolute risk of mortality from CHD varied considerably. This finding is consistent with our a priori hypothesis and agrees with results of large observational studies that have been confined to subjects from single populations.^{2-4,15,16} The narrow confidence limits around the estimated relative risks of death for given increments in blood pressure

TABLE 2. AGE- AND COHORT-ADJUSTED AND MULTIVARIATE-ADJUSTED RELATIVE RISKS OF DEATH FROM CORONARY HEART DISEASE FOR GIVEN INCREMENTS IN BLOOD PRESSURE, BEFORE AND AFTER ADJUSTMENT FOR WITHIN-SUBJECT BLOOD-PRESSURE VARIABILITY.*

POPULATION AND ADJUSTMENTS	INCREMENT OF 10 mm Hg IN SYSTOLIC BLOOD PRESSURE		INCREMENT OF 5 mm Hg IN DIASTOLIC BLOOD PRESSURE	
	UNADJUSTED FOR WITHIN-SUBJECT VARIABILITY	ADJUSTED FOR WITHIN-SUBJECT VARIABILITY	UNADJUSTED FOR WITHIN-SUBJECT VARIABILITY	ADJUSTED FOR WITHIN-SUBJECT VARIABILITY
	relative risk (95% confidence interval)			
United States				
Age and cohort	1.17 (1.12–1.22)		1.15 (1.11–1.20)	
Multivariate	1.18 (1.12–1.23)	1.29 (1.21–1.38)	1.16 (1.11–1.21)	1.32 (1.23–1.41)
Northern Europe				
Age and cohort	1.18 (1.13–1.23)		1.11 (1.07–1.16)	
Multivariate	1.18 (1.13–1.23)	1.30 (1.23–1.38)	1.12 (1.07–1.16)	1.25 (1.18–1.34)
Mediterranean southern Europe				
Age and cohort	1.26 (1.16–1.37)		1.22 (1.13–1.31)	
Multivariate	1.23 (1.13–1.35)	1.35 (1.19–1.52)	1.19 (1.10–1.29)	1.38 (1.22–1.57)
Inland southern Europe				
Age and cohort	1.10 (1.04–1.17)		1.07 (1.02–1.13)	
Multivariate	1.09 (1.03–1.16)	1.17 (1.08–1.27)	1.06 (1.01–1.12)	1.14 (1.06–1.24)
Serbia				
Age and cohort	1.23 (1.10–1.38)		1.15 (1.02–1.28)	
Multivariate	1.25 (1.11–1.40)	1.39 (1.20–1.61)	1.16 (1.04–1.30)	1.34 (1.15–1.56)
Japan				
Age and cohort	1.24 (1.09–1.41)		1.17 (1.02–1.34)	
Multivariate	1.25 (1.10–1.42)	1.36 (1.11–1.65)	1.18 (1.03–1.35)	1.32 (1.07–1.63)
Total				
Age and cohort	1.17 (1.14–1.20)		1.13 (1.10–1.15)	
Multivariate	1.17 (1.14–1.20)	1.28 (1.24–1.33)	1.13 (1.10–1.15)	1.28 (1.23–1.33)

*Multivariate-adjusted relative risks were adjusted for age, cohort, total cholesterol level, and cigarette smoking. Relative risks were adjusted for within-subject variability with use of repeated blood-pressure measurements at enrollment and at the five-year follow-up. The adjustment factors for systolic blood pressure were 1.6, 1.5, 1.4, 1.8, and 1.5 for the United States, northern Europe, Mediterranean southern Europe, inland southern Europe, and Serbia, respectively. The adjustment factors for diastolic blood pressure were 1.9, 2.1, 1.9, 2.2, and 1.9 for the United States, northern Europe, Mediterranean southern Europe, inland southern Europe, and Serbia, respectively. For Japan, relative risks were adjusted for within-subject variability with use of repeated blood-pressure measurements at enrollment and at the 10-year follow-up. The adjustment factors were 1.4 for systolic and 1.7 for diastolic blood pressure. For the total population, average adjustment factors were used (1.6 for systolic and 2.1 for diastolic blood pressure). The adjustment factors for within-subject variability in blood pressure were calculated as explained in the Methods section.

indicate that our study had sufficient power to detect important differences in relative risks.

In all 16 cohorts of the Seven Countries Study, standardized methods were used to measure blood pressure, other cardiovascular risk factors, and causes of death.⁷ This consistency allowed valid comparisons to be made among populations. At the time of the base-line assessments (1958 to 1964), information on the use of antihypertensive drugs was not collected. However, during this period, such drugs were rarely prescribed in any of the seven countries. Furthermore, the estimated relative risks of death due to CHD over the first 10-year period of the study were similar to those for the 25-year period (data not shown). This similarity suggests that the initiation of antihypertensive therapy during the later years of follow-up did not influence the observed relations.

In survival studies of the relation between blood pressure and mortality, the estimated relative risks of death due to CHD associated with an increase of

10 mm Hg in systolic blood pressure varied from 1.2 in a study in Bergen, Norway, to 1.4 in the Western Collaborative Group study.^{1,3,4,17,18} For a single measurement of diastolic blood pressure, the estimated relative risk for an increment of 5 mm Hg varied from about 1.1 in the study in Bergen to 1.3 in a cohort from three European cities (Edinburgh, Budapest, and Prague).^{2,4,19} Estimated relative risks adjusted for within-subject variability in blood pressure have also been published.^{1,6,20} In most of these reports, blood pressure was studied only in relation to total mortality from cardiovascular causes and to mortality from all causes.^{6,20} The combined results of nine prospective, observational studies demonstrated that an increase of 5 mm Hg in diastolic blood pressure was associated with a 20 to 25 percent higher rate of death from CHD over a 10-year period, after adjustment for within-subject variability.¹ The estimated relative risks in the present study are similar.

Previous studies did not evaluate the effect of vari-

TABLE 3. MULTIVARIATE-ADJUSTED RELATIVE RISKS OF DEATH FROM CORONARY HEART DISEASE ASSOCIATED WITH THE PRESENCE OF HYPERTENSION.*

POPULATION AND BLOOD-PRESSURE STATUS	SYSTOLIC BLOOD PRESSURE	DIASTOLIC BLOOD PRESSURE	NO. OF DEATHS DUE TO CHD	AGE-STANDARDIZED 25-YR MORTALITY FROM CHD	MULTIVARIATE-ADJUSTED RELATIVE RISK (95% CI)	
					UNADJUSTED FOR WITHIN-SUBJECT VARIABILITY	ADJUSTED FOR WITHIN-SUBJECT VARIABILITY
	mm Hg			no./10,000 person-yr		
United States						
Normal blood pressure	130.1±12.1	81.1±7.2	223	60	1.00	1.00
Hypertension	164.8±18.5	100.4±9.6	131	116	1.84 (1.48–2.29)	2.06 (1.57–2.70)
Northern Europe						
Normal blood pressure	134.6±11.8	81.2±7.6	276	81	1.00	1.00
Hypertension	165.2±19.0	99.3±10.4	185	153	1.78 (1.46–2.16)	2.14 (1.69–2.71)
Mediterranean southern Europe						
Normal blood pressure	130.6±12.6	78.9±7.8	79	18	1.00	1.00
Hypertension	166.8±17.6	97.8±10.0	37	44	2.13 (1.42–3.19)	2.68 (1.69–4.26)
Inland southern Europe						
Normal blood pressure	132.4±12.4	81.3±7.5	171	41	1.00	1.00
Hypertension	164.5±19.7	100.4±10.5	82	59	1.33 (1.01–1.74)	1.61 (1.20–2.16)
Serbia						
Normal blood pressure	126.9±12.3	80.1±7.2	57	35	1.00	1.00
Hypertension	162.6±19.3	100.3±8.6	20	76	2.73 (1.61–4.63)	3.08 (1.73–5.48)
Japan						
Normal blood pressure	126.7±15.2	72.1±10.2	20	13	1.00	1.00
Hypertension	176.1±21.8	94.9±13.2	10	44	2.80 (1.28–6.11)	2.85 (1.18–6.88)
Total						
Normal blood pressure	131.0±12.7	79.8±8.2	826	46	1.00	1.00
Hypertension	165.5±19.2	99.5±10.4	465	97	1.77 (1.58–2.00)	2.13 (1.85–2.45)

*Plus-minus values are means ±SD. Multivariate-adjusted relative risks were adjusted for age, cohort, total cholesterol level, and cigarette smoking. Relative risks were adjusted for within-subject variability with use of repeated blood-pressure measurements at enrollment and at the five-year follow-up. For Japan, relative risks were adjusted for within-subject variability with use of repeated blood-pressure measurements at enrollment and at the 10-year follow-up. The adjustment factors for within-subject variability in blood pressure were calculated as explained in the Methods section. Hypertension was defined as a systolic blood pressure of 160 mm Hg or greater, a diastolic blood pressure of 95 mm Hg or greater, or both. For each comparison, subjects with normal blood pressure served as the reference group. CHD denotes coronary heart disease.

ability in blood pressure within individual subjects on the strength of the relation between systolic and diastolic blood pressures and mortality due to CHD. We observed that the effect was larger for diastolic pressure than for systolic pressure: the relation became 110 percent stronger for diastolic pressure and 60 percent stronger for systolic pressure after adjustment for within-subject variability. This difference occurs because the ratio of within-subject variability to variability between subjects is greater for diastolic than for systolic blood pressure.^{21,22} Consistent with this finding is the fact that diastolic blood pressure, assessed as the fifth-phase Korotkoff sound by the auscultatory method, is more difficult to measure than systolic blood pressure.²³

Hypertension was a significant risk factor for death from CHD over the 25-year period of our study. The pooled relative risk associated with hypertension, defined as a systolic blood pressure of 160 mm Hg or greater, a diastolic blood pressure of 95 mm Hg or greater, or both, was 1.77 before adjustment for individual variability in blood pressure and 2.13 after

adjustment. When hypertension was defined as a systolic blood pressure of 140 mm Hg or greater, a diastolic blood pressure of 90 mm Hg or greater, or both, the result was an estimated relative risk of 1.5. In the Framingham Study, hypertension was defined according to the latter criteria and was associated with a relative risk of 2.0 for death from CHD.¹⁵ The lower relative risk associated with hypertension in our present study may be due to our longer follow-up period of 25 years.

Because of random within-subject variability in blood pressure, analysis of single measurements of blood pressure may lead to substantial overestimation of the prevalence of hypertension, resulting in underestimation of the associated risk of death.²⁴ In the present study, the overall prevalence of hypertension decreased from 24 percent to 13 percent after adjustment for within-subject variability in blood pressure, yielding a 30 percent stronger relation with mortality due to CHD.

We observed substantial heterogeneity among the populations in rates of death due to CHD at similar

levels of blood pressure. In the Seven Countries Study, similar heterogeneity has been observed for serum cholesterol levels.⁸ These differences in the absolute risk of death from CHD at similar blood pressures and serum cholesterol levels cannot be explained by differences in age or smoking status, because the analysis of mortality included adjustments for these factors. Although genetic differences among populations in susceptibility to CHD may partially explain the observed differences in CHD-associated mortality, other factors should also be considered. Differences in nutritional factors may play an important part, because dietary patterns vary greatly among countries.⁸ As compared with the diets in northern Europe and the United States, the Mediterranean diet at base line contained less meat and fewer dairy products but more olive oil, fish, fruits, vegetables, and alcohol.²⁵ In addition to interventions targeted to classic risk factors for CHD, changes in diet may therefore be important for reducing mortality from CHD in northern Europe and the United States to near the rates in the Mediterranean region and Japan. This process can be illustrated by the decrease in mortality from CHD that occurred at the same time as decreases in major risk factors in Finland during the period from 1972 to 1992.²⁶ A substantial increase in the consumption of vegetables and fruit in Finland starting in the early 1970s also contributed to the decline in mortality from CHD.²⁷

The large difference between the risks of CHD in the United States and northern Europe and those in Japan and Mediterranean southern Europe at the same blood-pressure level may have important implications for the treatment of hypertension. Recently, a task force of European and other societies on the prevention of CHD in clinical practice recommended the use of the absolute risk of CHD, based on all the major CHD risk factors, as a criterion for starting drug treatment.²⁸ According to this criterion, healthy persons whose absolute multifactorial risk of CHD will exceed 20 percent over the next 10-year period, or whose risk will exceed 20 percent if projected to age 60, have a sufficiently high risk to justify the selective use of proven drug therapies. The results of the Seven Countries Study imply that at the same blood-pressure level this criterion will be met at lower blood pressures in the United States and northern Europe than in Japan and Mediterranean southern Europe. Of course, the decision to start drug treatment is not based solely on absolute risk. Other factors, such as the clinical history, age, and sex of the patient and the cost effectiveness of therapy, are also important.

In conclusion, the present study showed that among populations, the increase in the relative risk of death from CHD for a given increase in blood pressure is similar but that the absolute risk at a given blood-pressure value varies substantially. If the absolute risk of coronary heart disease is taken as a criterion for

the use of antihypertensive therapy, this finding will have major implications for clinical practice in different parts of the world.

We are indebted to the principal investigators in the seven countries for carrying out the study for more than 25 years.

REFERENCES

1. MacMahon S, Peto R, Cutler J, et al. Blood pressure, stroke, and coronary heart disease. 1. Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990;335:765-74.
2. Stamler J, Stamler R, Neaton JD. Blood pressure, systolic and diastolic, and cardiovascular risks: US population data. *Arch Intern Med* 1993;153:598-615.
3. Stamler J, Dyer AR, Shekelle RB, Neaton JD, Stamler R. Relationship of baseline major risk factors to coronary and all-cause mortality, and to longevity: findings from long-term follow-up of Chicago cohorts. *Cardiology* 1993;82:191-222.
4. Selmer R. Blood pressure and twenty-year mortality in the city of Bergen, Norway. *Am J Epidemiol* 1992;136:428-40.
5. Menotti A, Keys A, Blackburn H, et al. Comparison of multivariate predictive power of major risk factors for coronary heart diseases in different countries: results from eight nations of the Seven Countries Study, 25-year follow-up. *J Cardiovasc Risk* 1996;3:69-75.
6. Knuiman MW, Divitini ML, Buzas JS, Fitzgerald PEB. Adjustment for regression dilution in epidemiological regression analyses. *Ann Epidemiol* 1998;8:56-63.
7. Keys A, Aravanis C, Blackburn HW, et al. Epidemiological studies related to coronary heart disease: characteristics of men aged 40-59 in seven countries. *Acta Med Scand Suppl* 1966;460:1-392.
8. Verschuren WMM, Jacobs DR, Bloemberg BPM, et al. Serum total cholesterol and long-term coronary heart disease mortality in different cultures: twenty-five-year follow-up of the Seven Countries Study. *JAMA* 1995;274:131-6.
9. Keys A, ed. *Coronary heart disease in seven countries*. American Heart Association monograph number 29. New York: American Heart Association, 1970.
10. Rose GA, Blackburn H. *Cardiovascular survey methods*. World Health Organization monograph series no. 56. Geneva: World Health Organization, 1968.
11. Keys A. *Seven countries: a multivariate analysis of death and coronary heart disease*. Cambridge, Mass.: Harvard University Press, 1980.
12. Manual of the international statistical classification of diseases, injuries, and causes of death: based on the recommendations of the Eighth Revision Conference, 1965, and adopted by the Nineteenth World Health Assembly. Vol. 1. *International classification of diseases*. Geneva: World Health Organization, 1967.
13. Rosner B, Spiegelman D, Willett WC. Correction of logistic regression relative risk estimates and confidence intervals for random within-person measurement error. *Am J Epidemiol* 1992;136:1400-13.
14. Whittemore AS. Errors-in-variables regression using Stein estimates. *Am Stat* 1989;43:226-8.
15. Kannel WB. Blood pressure as a cardiovascular risk factor: prevention and treatment. *JAMA* 1996;275:1571-6.
16. Whelton PK. Epidemiology of hypertension. *Lancet* 1994;344:101-6.
17. Ragland DR, Brand RJ. Coronary heart disease mortality in the Western Collaborative Group Study: follow-up experience of 22 years. *Am J Epidemiol* 1988;127:462-75.
18. Cupples LA, Gagnon DR, Kannel WB. Long- and short-term risk of sudden coronary death. *Circulation* 1992;85:Suppl I:I-11-I-18.
19. Hughes MD, Pocock SJ. Within-subject diastolic blood pressure variability: implications for risk assessment and screening. *J Clin Epidemiol* 1992;45:985-98.
20. Glynn RJ, Field TS, Rosner B, Hebert PR, Taylor JO, Hennekens CH. Evidence of a positive linear relation between blood pressure and mortality in elderly people. *Lancet* 1995;345:825-9.
21. Gordon T, Sorlie P, Kannel WB. Problems in the assessment of blood pressure: the Framingham Study. *Int J Epidemiol* 1976;5:327-34.
22. Gravlee GP, Brockschmidt JK. Accuracy of four indirect methods of blood pressure measurement, with hemodynamic correlations. *J Clin Monit* 1990;6:284-98.
23. Swales JD. *Textbook of hypertension*. Oxford, England: Blackwell Scientific, 1994.
24. Klungel OH, de Boer A, Paes AHP, Seidell JC, Nagelkerke NJD,

Bakker A. Undertreatment of hypertension in a population-based study in the Netherlands. *J Hypertens* 1998;16:1371-8.

25. Kromhout D, Keys A, Aravanis C, et al. Food consumption patterns in the 1960s in seven countries. *Am J Clin Nutr* 1989;49:889-94.

26. Vartiainen E, Puska P, Pekkanen J, Tuomilehto J, Jousilahti P. Changes in risk factors explain changes in mortality from ischaemic heart disease in Finland. *BMJ* 1994;309:23-7.

27. Pietinen P, Vartiainen E, Seppänen R, Aro A, Puska P. Changes in diet in Finland from 1972 to 1992: impact on coronary heart disease risk. *Prev Med* 1996;25:243-50.

28. Wood D, De Backer G, Faergeman O, Graham I, Mancia G, Pyörälä K. Prevention of coronary heart disease in clinical practice: recommendations of the Second Joint Task Force of European and other Societies on Coronary Prevention. *Eur Heart J* 1998;19:1434-503.