Public health aspects of blood pressure

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CHAPTER 1

Introduction

Although the age-specific mortality rates from cardiovascular diseases (CVD) are decreasing, CVD are still the number one cause of death in the Netherlands, with yearly over 50,000 deaths from these diseases.[1] The most important CVD are coronary heart disease (CHD) and cerebrovascular accidents (CVA). In 1999, CHD constituted 36% (n=18,304), and CVA 25% (n=12,501) of total CVD deaths in the Netherlands.[1]

One of the major risk factors for CVD in general and for CVA in particular is elevated blood pressure.[2] Until recently, elevated blood pressure or hypertension was defined as a systolic blood presssure (SBP) of 160 mmHg or greater and/or a diastolic blood pressure (DBP) of 95 mmHg or greater.[3] In the Netherlands, the prevalence of hypertension according to this definition was 9.2% in men and 7.1% in women aged 20-59 years from 1993 to 1995.[4] The prevalence of hypertension increases with age. Among Dutch men and women aged 55 years and over living in Rotterdam, 22.6% respectively 27.1% had systolic or diastolic blood pressure levels of ≥160/95 mmHg from 1990 to 1993.[4] Recently the WHO classification was revised and the threshold for hypertension was lowered to 140/90 mmHg.[5] However every threshold is arbitrary, as results from most large observational studies have demonstrated that there is no clear threshold below which a lower level of blood pressure is not associated with a lower risk of CHD or CVA.[2,6-8]

A recent reanalysis of Framingham data contests this viewpoint and suggests that systolic blood pressure is not related to mortality from CVD and all-causes for all pressures below an age- and sex-dependent threshold.[9] As this finding could have implications for targeting risk groups for blood-pressure-lowering intervention, examining the threshold hypothesis in other populations than in Framingham is required.

For public health purposes, it is important to quantify blood pressure related risk in terms of excess numbers of CVD events in the population due to elevated blood pressure. This requires accurate estimation of the strength of the relationship between blood pressure and CVD, expressed by the relative risk. This is the risk to

develop CVD for an individual with a defined or high level of blood pressure divided by that for an individual with a reference or low level of blood pressure.[10]

An individual's blood pressure varies substantially over time, due to imperfections in measurement and biological variability.[11] A single measurement will therefore not accurately represent a person's average, or usual blood pressure level. When single measurements of blood pressure are used to estimate the relative increase in risk of CVD for a given increase in blood pressure, results will be biased. [6,11,12] Relative risk estimates adjusted for within-person variability in blood pressure are thus needed, but are scarce.

It is not clear whether the strength of the relation between blood pressure and CVD differs among subjects from different cultures, and what the impact of adjustment for within-person variability on this relation will be. In addition, studies on blood pressure and CVD incidence in different populations will give more insight into the impact of blood pressure, relative to that of other risk factors, on CVD incidence in different cultures.

There is strong evidence both from observational studies and clinical trials that elevated systolic blood pressure remains an important risk factor for CVD up to at least 75 years of age.[13-14] Whether diastolic blood pressure is positively related to CVD in the elderly is less well established. Positive relations have been observed in most[15-18], but not all[13] longitudinal studies. In some studies among elderly populations, J- or U-shaped relations have been found showing an increased risk at low diastolic blood pressure levels compared to higher levels.[14,19-20] This paradoxal finding may be explained by low diastolic blood pressure due to a poor general health status prior to disease.[21] However, J- or U-shaped relations have also been found in some observational studies that adjusted for poor health status.[14,20] It has been suggested that due to increased large-artery stiffness with aging, systolic blood pressure continues to rise while diastolic blood pressure falls, making low diastolic blood pressure and pulse pressure (=SBP minus DBP) indicators of elevated cardiovascular risk.[14,22]

The beneficial effect of pharmacological treatment of hypertension on the incidence of CVA and CHD has been demonstrated in several randomized clinical trials.[23-25] In spite of the potential reduction of CVD by pharmacological treatment, from 1987 to 1995 47% of Dutch hypertensive men and 30% of Dutch hypertensive women still had elevated blood pressure levels despite pharmacological treatment,

or were not treated while they should have been treated according to the guideline of the Dutch society of general practitioners (1997).[26] In 2000, the Dutch consensus guideline for blood pressure lowering therapy has been revised.[27] The new guideline prescribes drug therapy to hypertensive individuals with a high short-term absolute risk of CVD.[27] The absolute risk of CVD defines the probability of an individual to develop CVD over a finite period of time.[10] Besides blood pressure, the absolute risk of CVD is determined by the presence of other risk factors such as sex, age, total/HDL cholesterol ratio, smoking and diabetes mellitus. In the guideline, a blood pressure above 140/90 mmHg till age 60, and above 160/90 mmHg after age 60, in combination with a 10-year multifactorial absolute risk of CVD of 20% or greater is defined as a risk sufficiently high to justify the use of antihypertensive drug therapy.[27] Because of the high prevalence of undertreatment of hypertension in the Dutch population, the potential reduction in number of CVD events by adequate pharmacological treatment according to the revised guideline is expected to be high, but unknown. Quantification of this number clarifies the extent of elevated blood pressure as a public health problem.

Current guidelines focus on treatment of individuals with severe hypertension and treatment of individuals with mild or moderate hypertension (140-179 systolic or 90-109 diastolic or both) in combination with a high short-term (≥20% within 10 years) absolute risk of CVD.[27,28] These guidelines reflect the general belief that the absolute level of risk can be reversed by modifying risk factors later in life.[29]

Insight in long-term persistence of the effects of blood pressure on CVD, i.e. whether elevated blood pressure levels at younger age lead to increased risk of cardiovascular events at old age, could support a policy aimed at population-wide reductions in blood pressure. Such a policy has two advantages. First, it will lead to prevention, not merely treatment of elevated blood pressure, and to subsequent prevention or postponement of CVD on the long-term.[29,30] Second, it has a greater potential for reducing the burden of CVD in the total population than a policy that is mainly focused on treatment of the relatively small proportion of patients at high short-term risk.[31] This can be illustrated by the population attributable risk (PAR). In case of blood pressure, the PAR is the proportion of CVD events in the population attributable to (suboptimal) blood pressure levels.[10] The PAR depends both on the relative risk and on the proportion of individuals with blood pressure levels above

optimal (SBP ≥ 120 mmHg or DBP ≥ 80 mmHg or both). As this proportion is high in the Netherlands, and because of the continuous relation of blood pressure with CVD, the total burden of CVD among this group is considerable. A population strategy, aimed at blood pressure reductions in the population as a whole, will therefore theoretically result in a much larger absolute decline in number of CVD cases than a high risk strategy, even at moderate blood pressure reductions.[31] Small population-wide reductions of blood pressure may be reached by stimulating lifestyle changes, such as changes in diet and increased physical activity, in the total population.[32-36] The number of CVD events that could be prevented in this way in the Netherlands is unknown. Quantification of this number could enlarge commitment of physicians, policy makers and scientists in the field of public health to population-wide strategies of intervention.

Aim and outline of the thesis

The aim of the observational studies described in this thesis was to study the (strength and nature of) the relation between blood pressure and CVD, and to quantify the achievable health benefit in the population by different blood pressure lowering strategies. In chapter 2 the relations between blood pressure and CVD mortality with an emphasis on coronary death among middle-aged men from the Seven Countries Study (SCS) are quantified. In chapter 2.1 persistence of the relation between blood pressure and mortality from CHD with time is studied, using repeated measurements from the SCS. In chapter 2.2 we used the SCS data to examine whether there is a threshold in the relation between blood pressure and mortality from CVD and all-causes. In chapter 2.3 the relative and absolute impact of blood pressure on long-term mortality from CHD was compared between men from the different populations of the SCS. In chapter 2.4 the implications of the findings from the SCS for treatment and prevention of hypertension in relation to CHD are discussed.

In chapter 3 the relations between blood pressure and CVD in the elderly are described. In chapter 3.1, the relation between blood pressure and risk of myocardial infarction among men and women aged 55 years and over from the Rotterdam Study is described. The relation between blood pressure and mortality from CVD among men aged 65-84 years from different European countries is described in chapter 3.2.

In chapter 4, the impact of different blood pressure lowering interventions on the primary prevention of CVD and on healthy life expectancy in the Netherlands is quantified. A general discussion of the different topics presented in this thesis is given in chapter 5.

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CHAPTER 2.1

The persistence of the effect of blood pressure on coronary heart disease mortality risk

Abstract

The authors tried to separate an independent effect of past systolic blood pressure (SBP) on coronary heart disease (CHD) mortality from a proxy effect through "current" SBP, i.e. SBP close to time of death, taking into account both within-person variation and the correlation structure of blood pressure. SBP was measured at enrolment and at 5-year follow-up in 9,444 middle-aged men from the Seven Countries Study. During 20 years of follow-up, 1,000 men died from CHD. An independent effect of past SBP was estimated using a survival model including both past SBP and the best predictor of "current" SBP, given the correlation between repeated SBP measurements. Including "current" SBP into the model, the relative risk of death from CHD per 10 mmHg increase in past SBP was 1.03 (95% CI 0.89 - 1.19). This cohort study suggests that past SBP does not predict long-term risk of CHD mortality, after adjustment for a proxy effect of 'current' SBP.

Introduction

Results from epidemiological studies have established clear associations between single or casual blood pressure measurements and subsequent risk of death from coronary heart disease (CHD).[1,2] However, the interpretation of such associations in terms of etiological mechanisms is not unequivocal. One can distinguish two competing hypotheses:

- hypothesis 1 stating that elevated past blood pressure levels (i.e. near the time of enrolment) cause accumulated damage to the circulatory system which leads to increased risk of coronary events in subsequent years. Effects of blood pressure on the risk of CHD mortality persist for many years or decades.
- hypothesis 2 stating that risk of mortality from CHD is largely determined by "current" blood pressure levels (i.e. in the years before death), that is the effects of blood pressure on mortality risk are transient and reversible. The apparent effect of past blood pressure on future risk is caused by the fact that blood pressure is correlated over time, and past blood pressures therefore act as proxy variables for "current" pressures. Elevated blood pressure levels mainly act as triggers for the occurrence of acute complications of already existing atherosclerotic disease, such as coronary trombosis and arrhythmias.

These two hypotheses have analogues in the relationship between smoking and CHD and lung cancer respectively. While the effects of smoking on lung cancer persist long after cessation of smoking, the effects of smoking on CHD appear to be short lived and reversible.[3,4] Thus, *current* smoking is the major determinant of CHD death, while a history of smoking is not.

Continuous blood pressure levels over prolonged periods of time (decades), up to the time of death, of a large cohort, are needed to distinguish between the two hypotheses directly. While smoking behaviour is relatively easy to monitor continuously, and can even be ascertained retrospectively, this is not feasible for blood pressures. In most cohort studies, at most several blood pressure measurements, usually long before death, are available. This makes "current" blood pressure levels in the years before death unavailable for most participants. This would appear to make the problem of which of the two competing hypotheses is valid undecidable.

As the different hypotheses may have important implications for blood pressure intervention strategies this is hard to accept. In order to circumvent this problem, we used a statistical model of the development of blood pressure over time. Using this model, we estimated (predicted) "current" blood pressure levels, i.e. beyond the latest of two repeated blood pressure measurements taken at fixed points in time. These estimated levels were used in lieu of actual measurements in standard survival analysis of CHD mortality. This approach allowed us to separate an independent effect of past systolic blood pressure (SBP) on CHD mortality from a proxy effect through "current" SBP. We tried to distinguish the two competing hypotheses as follows. If the best predictor of "current" levels summarizes all information contained in the blood pressure measurement about future risk of death, then the data support hypothesis 2. If, by contrast, the earlier of the two measurements has an independent additional (i.e. in addition to its effect through the best linear predictor of "current" levels) effect on the risk of death, then this should be considered as evidence supporting hypothesis 1. In summary, if estimated "current" blood pressure would appear to be the only determinant of CHD death then this should be construed as supporting hypothesis 2. However, if a history of high blood pressure would also be a determinant of CHD death then this would lend weight to hypothesis 1. Data from the Seven Countries Study were used for this purpose.

Two features of blood pressure are essential for a correct analysis of repeated blood pressure measurements. First, blood pressure has substantial within-person variation.[5] Second, blood pressure levels in individuals over time are correlated.[5] These two features formed the basis of our statistical model of the development of blood pressure over time.

Materials and methods

Study population

Between 1958 and 1964, 12,761 men aged 40 through 59 years from seven countries were enrolled in the study.[6] A total of 16 cohorts were examined in the following countries: the United States, Finland (eastern and western), the Netherlands (Zutphen), Italy (Rome Railroad, Crevalcore and Montegiorgio), Greece (Crete and Corfu), former Yugoslavia (Dalmatia, Slavonia, Zrenjanin, Velika Krsna

and Belgrade), and Japan (Tanushimaru and Ushibuka). Overall, the participation rate was over 90 percent, with several cohorts reaching almost 100 percent. In the present paper, only the pooled cohorts of the United States and Europe were used. The Japanese cohorts were excluded (n = 1,010) because blood pressure was not remeasured after five years in Japan.

Measurements

In all cohorts the major cardiovascular risk factors were measured in a standardized way at enrolment and at five years. Details of the methods used have been reported elsewhere.[6,7] Blood pressure was measured on the right arm, in supine position, with a calibrated mercury sphygmomanometer at the end of the physical examination by trained physicians, following the methods described in the World Health Organization (WHO) manual *Cardiovascular Survey Methods.*[8] Readings were taken to the nearest two mmHg. At each point in time, the average of two measurements taken one minute apart was computed for systolic and diastolic (fifth Korotkoff phase) blood pressure, and these average values were used in the analyses. In this paper, the analysis is confined to systolic blood pressure (SBP) because SBP is measured with less intra-individual variation (relative to total population variation) than diastolic blood pressure.[5] At the enrolment survey, information on the use of antihypertensive drugs was not collected. However, during the period 1958 to 1964 these drugs were rarely prescribed in the participating countries.

Total cholesterol was measured in a nonfasting blood sample according to the Abell-Kendall method, modified by Anderson and Keys, in standardized laboratories.[6] Current cigarette smoking (no/yes) was established by means of a standardized questionnaire. Presence of CHD at enrolment was defined by definite and possible myocardial infarction based on pre-defined clinical and ECG criteria, definite angina pectoris based on the Rose questionnaire and chronic CHD manifested as heart failure or chronic arrhythmia based on pre-defined clinical criteria.[7,9]

Mortality follow-up

All men were followed for mortality during 25 years but 56 (0.4 percent) were lost to follow-up. The underlying cause of death was coded in a standardized way by

a single reviewer, using the eighth revision of the WHO *International Classification of Diseases.*[10] The final cause of death was adjudicated on the basis of information from the official death certificate, in combination with information from medical and hospital records and from relatives or any other witnesses of the dead person. The coder of the causes of death was blinded to the risk factor status of the subject. In the case of multiple causes of death, priority was given to violent death, followed by cancer in advanced stages, CHD, and stroke. In this study, the endpoint was a fatal CHD occuring during 20 years of follow-up (from year 5 to 25), defined as primary cause of death with ICD-8 codes 410-414 or primary cause of sudden cardiac death with ICD-8 code 795 when a coronary origin was mentioned.

Statistical methods

In order to predict "current" SBP we used both the measurement of SBP at enrolment [m(0)] and at five year follow-up [m(5)]. Our statistical model used to predict blood pressure levels had two components, one relating true SBP to its measurements, and one describing the development of true blood pressure over time. The following simple model was used to relate measurements to true levels:

$m(t) = \mu(t) + \varepsilon$,

where m(t) is the measured value at time t, $\mu(t)$ denotes the "true" blood pressure level at time t, and ε is short-term within-person variation in blood pressure (including measurement error due to imperfect instruments or observers). We assume that successive values of ε are uncorrelated (note, that this is probably only true for measurements taken a reasonable period, e.g. days, apart). Thus the correlation between successive values of m(t) is induced by the correlation between corresponding values of $\mu(t)$. To model this correlation (the second component of our model) we assumed that $\mu(t)$ behaves like a Gauss-Markov (G-M) model, implying that the correlation of $\mu(t)$ declines exponentially,

i.e. $r(\mu(t_1),\mu(t_2)) = \exp(-a(t_2-t_1))$.[11] Under this model, the variance in blood pressure measurements $\sigma_m^2(t) = \sigma_\mu^2(t) + \sigma_\varepsilon^2(t)$, and the correlation between measurements $m(t_1)$ and $m(t_2)$ $(t_1 < t_2)$ is given by $r.\exp(-a(t_2-t_1))$,

with $r = \sigma_\mu^2(t) / \{\sigma_\mu^2(t) + \sigma_\varepsilon^2(t)\}$.

Under the G-M model, using standard multivariate theory[12], one can show that the best predictor of SBP at time t ($t \geq 5$; given m(0) and m(5)) is:

$E(\mu(t)|m(0),m(5)) = (\gamma_0 m(0) + \gamma_5 m(5))e(t) + \pi(t)(1-e(t))$

Where:

$\pi(t)$ denotes the population average SBP in year t; $e(t) = \exp(-at)$; and

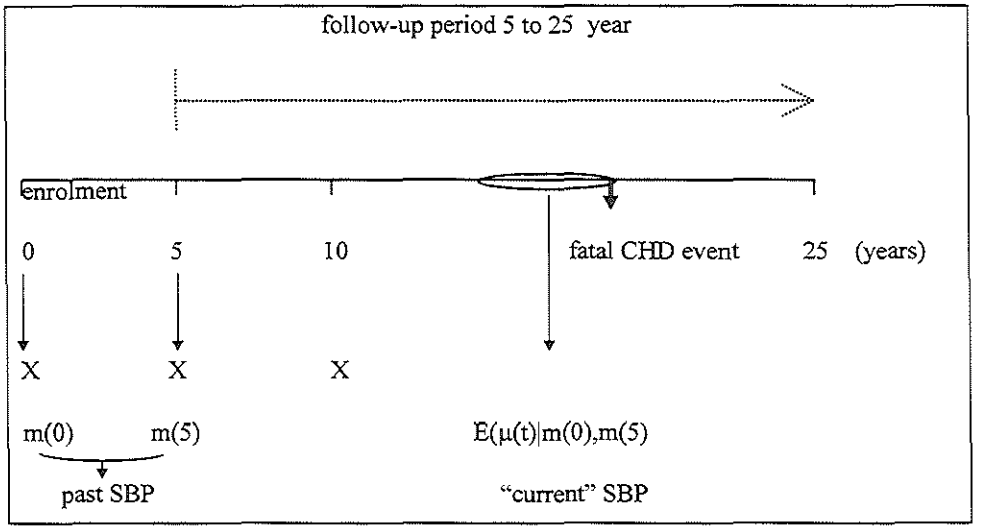
$\gamma_0 = r(1-r)/(1-r^2(e(5))^2)$; $\gamma_5 = r(e(-5)-re(5))/(1-r^2(e(5))^2)$.

In a subgroup of men, SBP was also remeasured at ten years of follow-up (n = 7,031; 60.1 percent). To obtain estimates for r and a, the G-M model was fitted to the observed five and ten year interval correlations in this group of men with three blood pressure measurements (i.e. at enrolment, at five, and ten year follow-up). In estimating r and a we ignored the problem of intervening, possibly selective, mortality. As this mortality was low, we did not expect this to seriously bias our estimates.

To distinguish the two competing hypotheses for the effect of SBP on CHD mortality we used a Cox model with time dependent SBP covariables. The predictor $E(\mu(t)|m(0),m(5))$ was used as a time dependent covariable representing 'current' SBP levels. As indicator of past SBP we used the average M(0,5) of m(0) and m(5). A fatal CHD event occurring between five and 25 years of follow-up was used as endpoint. "Current" SBP values were obtained by taking t = time of such event, in the above expressions. Our method is illustrated in figure 1.

We excluded men with prevalent CHD at year 5 (n=353;3 percent) and men with missing data on SBP at enrolment (n = 12) or five year follow-up (n = 1,232;10.5 percent) or on one of the covariates (n = 1,971;16.9 percent). In total 2,251 men were excluded (19.2 percent), leaving 9,444 for analysis. Of these 1,000 (8.6 percent) died from CHD. In addition, the possible confounders cohort, age (years), total cholesterol (mmol/L) at 5 year follow-up, and current cigarette smoking (no/yes) at 5 year follow-up, were included. Relative risks were calculated per 10 mmHg increase in M(0,5) and $E(\mu(t)|m(0),m(5))$. A positive effect of M(0,5) on survival would be consistent with hypothesis 1, whereas no effect of M(0,5) on survival would suggest that only hypothesis 2 is true.

Figure 1. Used method for separating an independent effect of past SBP on long term mortality from CHD, from a proxy effect through "current" SBP: the pooled American and European cohorts of the Seven Countries Study, 1960 and 1965.



CHD, coronary heart disease; SBP, systolic blood pressure; X, blood pressure measurement; m(0), measured SBP at enrolment; m(5), measured SBP at 5-year follow-up; $E(\mu(t)|m(0),m(5)$, the best predictor of "current" SBP, i.e. the expected SBP at t = time of a fatal CHD event ($t \geq 5$ years of follow-up), given measured SBP at enrolment and at 5-year follow-up.

Results

Average SBP measured at enrolment and at five year follow-up was 139.0 (19.6) mmHg and 140.0 (21.4) mmHg respectively (table 1). The correlation between SBP measured at enrolment and at five and ten year follow-up is shown in table 2.

Table 1. Characteristics of men aged 40 to 59 years: the pooled American and European cohorts of the Seven Countries Study, 1960 and 1965.

Characteristic	Mean±SD
Systolic blood pressure (mmHg)	
Enrolment	139.0±19.6
5-year follow-up	140.0±21.4
Age (years)†	53.9±5.5
Total cholesterol (mmol/L)†	5.8±1.3
Current smoking† (%)	56.0

SD, Standard deviation; † Measured at 5-year follow-up

This table demonstrates that the correlation decreases with time. Fitting the Gauss-Markov model to the correlations as observed in table 2 yielded an estimate of 0.76 for r and of 0.028 for a. As among the survivors of the Finnish, Dutch and Italian cohorts, SBP was also remeasured at 25 (n = 1,659) and 30 (n = 988) years of follow-up, we could validate the Gauss-Markov model. The predicted correlation between SBP measured at enrolment and at 25 and 30 years of follow-up was 0.38 and 0.33 respectively, whereas values of 0.22 and 0.19 were observed. This suggests that the Gauss-Markov model for SBP performs reasonably well over a period of several decades. The somewhat lower observed than predicted correlation may be due to the increasing use of antihypertensive drugs after 1980 and to selective mortality.

Table 2. Correlation between repeated measurements of systolic blood pressure among the subgroup of men with three measurements (n = 7,031).

Measurement period	Correlation
Enrolment and 5-year follow-up	0.65
5- and 10-year follow-up	0.67
Enrolment and 10-year follow-up	0.58

Knowing the model parameters r and a, and given measured SBP at enrolment [m(0)] and at five year follow-up [m(5)], the obtained best predictor of "true" SBP at t year follow-up was $\exp(-0.028(t))(0.67m(5) + 0.33m(0)) + \pi(t)(1-\exp(-0.028(t))$ (where $\pi(t)$ denotes the population average SBP in year t).

Cox proportional hazard's analysis with M(0,5) and $E(\mu(t)|m(0),m(5))$ as covariates and a fatal CHD event occurring in 20 years of follow-up yielded a relative risk estimate [RR] of 1.03 (95 percent confidence interval [CI] 0.89 - 1.19) per 10 mmHg increase in past SBP and of 1.24 (95 percent CI 1.03 - 1.51) per 10 mmHg increase in "current" SBP (table 3).

Table 3. Results from a multivariate Cox model including past SBP and the best predictor of current SBP: the pooled American and European cohorts of the Seven Countries Study.

Model †	Regression coefficient ‡ (SE)	Rate ratio ‡ (95% CI)
M(0,5) §	0.03 (0.08)	1.03 (0.89 - 1.19)
E(μ(t)|m(0),m(5)) ||	0.22 (0.10)	1.24 (1.03 - 1.51)

SBP, systolic blood pressure; SE, standard error; CI, confindence interval; † Besides the blood pressure variables also age, total cholesterol at 5-year follow-up and smoking at 5-year follow-up were included in the Cox model; ‡ Per 10 mmHg increase in systolic blood pressure; § Indicator of past SBP, i.e. (measured SBP at enrolment + measured SBP at 5-year follow-up)/2; || Best predictor of "current" SBP, i.e. the expected SBP at t = time of a fatal CHD event ($t \geq 5$ years of follow-up), given measured SBP at enrolment and at 5-year follow-up.

Discussion

Continuous monitoring of blood pressure is not feasible in large observational studies. Therefore, understanding the effect of this variable on subsequent mortality from CHD will be based on - at best - several measurements, often taken a substantial time before the endpoint occurs. In this study, we used repeated measurements from the Seven Countries Study to explore a novel approach to study the effect of blood pressure on the development of fatal CHD during follow-up. In this approach we tried to separate an independent effect of past SBP on subsequent fatal CHD from a proxy effect through its correlation with "current" SBP. Taking into account both within-person variation and the correlation structure of blood pressure over time, our data suggest that the effects of past blood pressure on later risk of CHD mortality are transient. However, confidence limits around the relative risk estimate of past blood pressure in the present study do not completely exclude possible presence of some long-term effect of past blood pressure.

Previous analyses on the effect of repeated measurements of blood pressure have mainly focused on the effect of *changes* in blood pressure over time on disease risks.[13-17] Many of these analyses have fit some type of regression model that included both the observed change in blood pressure and the measured value at enrolment as covariate.[15-17] Their results have suggested that blood pressure changes are independent predictors of cardiovascular diseases. However, this method of adjustment for the baseline level can produce misleading results when the measured values differ from the 'true' values due to substantial within-person

variation, as is always the case for blood pressure.[18] What may appear as a statistically significant relationship between change in risk factor and outcome may in fact be merely a statistically artefact of within-person variation.[18] In the Framingham Heart Study, repeated measurements of blood pressure over time were used to estimate the effect of past blood pressure experience on future development of cardiovascular diseases.[19] It was suggested from that study that past SBP history, especially if it averages 160 mmHg or more, is a weak but significant estimator of future cardiovascular diseases, in addition to current measured SBP level.[19]

However, even if within-person variation had been completely adjusted for in the Framingham Study, it is not clear whether the observed relation between past SBP and future cardiovascular risk was causal. In fact, past SBP may only appear to be a risk factor for subsequent disease because it is correlated with attained blood pressure levels later in life, which are the "true" risk factors.

Although the difference in used methodology may fully explain the discrepancy between results from the present study and those from the Framingham Study, other explanations are possible. In the Framingham Study past blood pressure levels were calculated as the average of two to 11 measurements, each taken 2 years apart.[19] Therefore, in the Framingham Study past levels may better reflect someone's true lifetime exposure, whereas in the present study past levels may present an individual's blood pressure status during too short a period for deleterious effects to become apparent (measurable). It is thus possible that elevated blood pressure levels mainly exert their deleterious effects when they persist for a prolonged period of time. Nevertheless, our failure to detect a long-term detrimental effect caused by past elevated blood pressure levels is surprising, as there is a strong biological rationale for this hypothesis. Hypertension has been clearly established as a major promoting factor for the development of coronary atherosclerosis and its complications.[20,21] As the development of atherosclerosis takes some decades,[20] the duration of hypertension is expected to be directly related to the amount of atherosclerosis and thereby to the risk of CHD in current life.

Nevertheless, the results from the present cohort study suggest that past SBP does not strongly predict long-term risk of CHD mortality, after adjustment for a proxy effect of "current" SBP. Application of the methodology developed in this paper to other cohort studies is required to decide whether this is a consistent finding.

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CHAPTER 2.2

Relation between blood pressure and mortality: is there a threshold?

Research letter

Data from observational studies and clinical trials have consistently shown that higher blood pressure implies higher (cardiovascular and all-cause) mortality risk.[1,2] However, recent reanalysis of the 18-year Framingham data demonstrated a threshold in the relation, with risk being unrelated to systolic blood pressure below (at least) the 70th percentile, corresponding to 150 mmHg for 60-year old men.[3,4] This implies that with the currently used cut-off value for hypertension of 140 mmHg, many people are incorrectly considered to be at increased risk. We used the Seven Countries Study to examine whether the threshold hypothesis also applies to other populations than Framingham's. We studied both systolic and diastolic blood pressure in relation to 25-year cardiovascular and all-cause mortality. Repeated measurements of blood pressure at baseline and at five year follow-up were available to obtain better estimates of usual blood pressure.

Of the 12,250 men without a history of cardiovascular disease who were included in the analyses, 5722 died during follow-up, 2783 (48.6%) from cardiovascular causes. Details of the study have been described previously.[5] Per age group (40 to 49 years and 50 to 59 years old), mortality risk was determined for each of the 10 decile classes and then these age group-specific risks were pooled by decile class to plot the relation of risk of death as a function of blood pressure. Both the logistic- and the Cox proportional hazard-spline model, with cohort and age as stratification variables, were used to analyze whether there is a threshold in the relation between blood pressure and mortality risk.[3] Since results were similar, reported results are based on the Cox proportional hazard-spline model.[3] To demonstrate existence of a threshold, thereby invalidating the conventional linear model, it suffices to show that for some choice of the knot in the spline model the left and right slopes differ significantly. For this knot we chose the 70th percentile of either blood pressure, i.e. 141 mmHg systolic and 86 mmHg diastolic blood pressure

for 40-49 years and 150 mmHg systolic and 88 mmHg diastolic blood pressure for 50-59 years. Additionally, we fitted the model with the knot at the 50th, 60th, 80th and 90th percentile for each age group, and at pressure levels between the 70th and 80th percentile.

The relation between blood pressure and all-cause mortality was stronger at the higher end of the blood pressure distribution (figure 1). The right slopes were 1.85 (systolic) and 2.27 (diastolic) times larger than the left slopes ($p<0.0005$) (table 1). The relation between blood pressure and all-cause mortality was weaker for pressures below the 70th percentile, but still significant ($p<0.0005$ for both systolic and diastolic blood pressure). With other choices of the knot, the slope of the relation below the threshold remained highly significant (all $p<0.0005$). The Cox proportional hazard-spline model fitted the data better than the conventional linear Cox proportional hazard -model ($p<0.0005$ for both systolic and diastolic blood pressure, maximum likelihood ratio (MLR) test).

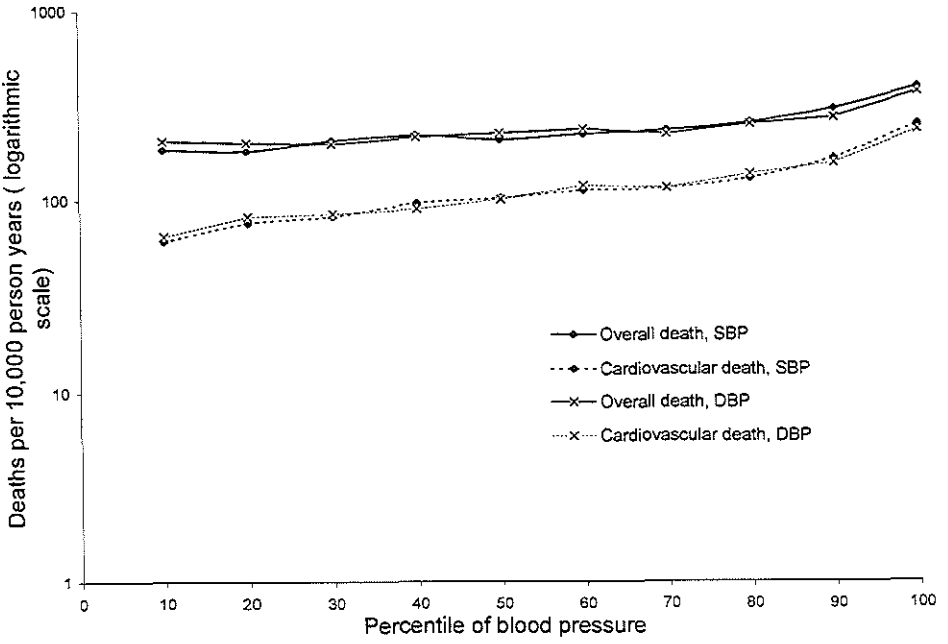

Figure 1. Age-adjusted death rates related to percentiles of blood pressure among men aged 40-59 years from the Seven Countries Study.

Table 1. Estimates of left and right slopes† (SE) for the relation between blood pressure and mortality from cardiovascular and all causes; Seven Countries Study, 25 years of follow-up.

N=12,250	Systolic blood pressure			Diastolic blood pressure		
25-year Mortality	Left ‡ Slope (SE)	Right § Slope (SE)	Difference Between Slopes	Left ‡ Slope (SE)	Right § Slope (SE)	Difference Between Slopes
All causes	0.0117* (0.0017)	0.0216* (0.0045)	*	0.0201* (0.0037)	0.0456* (0.0095)	*
Cardiovascular	0.0247* (0.0026)	0.0294* (0.0065)	ns	0.0526* (0.0057)	0.0607* (0.0140)	ns

SE, standard error; ns, non-significant; * $p < 0.0005$; † Estimates are adjusted for total cholesterol and smoking status and pooled after stratification by age group and cohort; ‡ Below 70th percentile, i.e. 141 mmHg systolic and 86 mmHg diastolic blood pressure for 40-49 years and 150 mmHg systolic and 88 mmHg diastolic blood pressure for 50-59 years; § Above 70th percentile

By contrast, the relative increase in risk of cardiovascular death for a specified increase in blood pressure was similar below and above the 70th percentile of blood pressure (table 1). Absence of a threshold is also suggested by visual inspection (figure 1). There was no choice of the knot for which the left and right slopes differed significantly. In addition, the Cox proportional hazard -spline model did not improve the fit of the linear Cox proportional hazard -model ($p>0.2$ for both systolic and diastolic blood pressure; MLR test).

In conclusion, the Seven Countries Study corroborates the conventional "linear" model for the relation of cardiovascular mortality with systolic and diastolic blood pressure, but not for the relation of these pressures with all-cause mortality. Higher blood pressure is related to higher risk of all-cause mortality over the whole range of blood pressure, but this association is weaker for moderately elevated pressures. The difference with Framingham may be due to the greater power of the present study and to differences in study populations. Considering that antihypertensive treatment is currently prescribed on the basis of multiple risk factors, our results do not suggest a direct need to reassess current hypertension guidelines.

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CHAPTER 2.3

The relation between blood pressure and mortality due to coronary heart disease among men in different parts of the world

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 1,291 men died from CHD.

Results. At systolic and diastolic blood pressures of about 140 and 85 mmHg, 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. 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 mmHg increase in systolic pressure, and 1.13 (95 percent confidence interval, 1.10 to 1.15) per 5 mmHg 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.

Introduction

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 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 pressuse 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 mmHg. 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 mmHg or higher, a diastolic blood pressure of 95 mmHg or higher, or both. During the base-line period (1958 to 1964), medications designed to lower the blood pressure were rarely prescribed in any of the seven countries, and therefore use of medicarition was not included in the definition of hypertension.

Nonfasting blood sample 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 questionnaire; 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 and 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.*[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. The coder of the causes of death was blinded to the risk factor status of the subject. In cases in which multiple causes of death were possible, priority was given to violent death, followed by cancer in advanced stage, CHD, and stroke. The endpoint of the study was death during 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 methods

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 package, release 6.12, procedure PHREG). Relative risks of death from CHD were estimated by including either systolic blood pressure (in increments of 10 mmHg) or diastolic blood pressure (in increments of 5 mmHg) 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 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 systolic blood pressure at base line ranged from 132.5 mmHg in Serbia to 143.7 mmHg in northern Europe. The average diastolic blood pressure at base line ranged from 75.7 mmHg in Japan to 86.6 mmHg 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 populations. For a usual systolic blood pressure of about 140 mmHg, 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 risk was observed for a usual diastolic blood pressure of about 85 mmHg (Fig. 2).

For an increase of 10 mmHg 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 mmHg 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

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-y mortality from CHD
		years	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

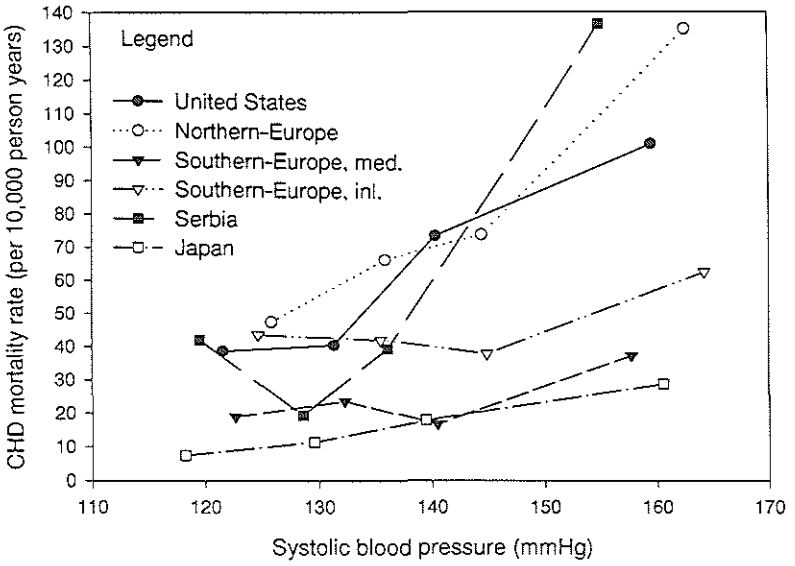

Figure 1. Mortality due to coronary heart disease per quartile of usual systolic blood pressure. Values shown are 25-year rates of death due to coronary heart disease (CHD), adjusted for age, serum total cholesterol level, and cigarette smoking status. The absolute risk of death at a given level of usual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

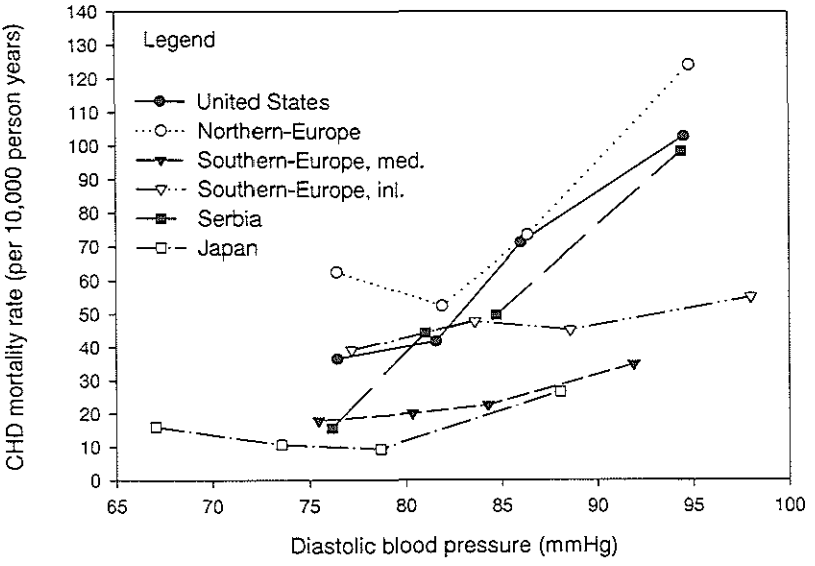

Figure 2. Mortality due to coronary heart disease per quartile of usual diastolic blood pressure. Values shown are 25-year rates of death due to coronary heart disease (CHD), adjusted for age, serum total cholesterol level, and cigarette smoking status. The absolute risk of death at a given level of usual diastolic blood pressure varied greatly among the populations.

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 5 mmHg in systolic blood pressure		Increment of 5 mmHg in diastolic blood pressure	
	Unadjusted for within-sunject variability	Adjusted for within-subject variabilty	Unadjusted for within-sunject variability	Adjusted for within-subject variabilty
	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. Fot 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.

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).

Table 3. Multivariate-adjusted relative risks (95 percent confidence intervals) 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-standard. 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.

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 interaction between the hypertension variable and the ordinal population variable).

Discussion

We observed that the relative risks 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 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 initiaiton of antihypertensive therapy during the later years of follow-up did not influence the observed relations.

In survival studies on the relation between blood pressure and mortality, the estimated relative risks of death due to CHD associated with an increase of 10 mmHg 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 mmHg 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 mmHg 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 reports did not evaluate the effect of variability in blood pressure in 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 mmHg or greater, a diastolic blood pressure of 95 mmHg 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 mmHg or greater, a diastolic blood pressure of 90 mmHg or greater, or both, the result was an estimated relative risk of 1.5. In the Framingham Study, hypertension was defined 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 classical 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 occured 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 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.

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CHAPTER 2.4

Blood pressure and long-term coronary heart disease mortality in the Seven Countries Study: implications for clinical practice and public health

Introduction

High blood pressure is a well-established risk factor for coronary heart disease (CHD). Therefore, management of high blood pressure is needed to reduce the burden of CHD and consequently to increase healthy life-expectancy. Gain in healthy years of life is of importance for both individuals and populations. In clinical practice, treatment of high blood pressure is focused on achieving health benefit for individuals, whereas public health is focused on prevention of high blood pressure in populations.

In *clinical medicine*, a high-risk strategy is used for CHD prevention, i.e. detection and treatment of high blood pressure in patients who are most likely to benefit from it. Two components of risk are important for treatment strategies. The *absolute risk* or absolute rate defines the probability of an individual to develop a disease over a finite period of time.[1] Recent guidelines on the management of hypertension have recommended the multifactorial absolute risk as the basis of clinical desicion-making, in terms of antihypertensive drug therapy.[2-6] This multifactorial or overall level of risk will often be determined to a greater extent by the presence of other risk factors, such as age, gender, smoking status, total and HDL cholesterol level and family history of premature cardiovascular disease, than by blood pressure level.[2] Consideration of absolute level of risk, in addition to blood pressure level, is mainly aimed at healthy individuals with mild and moderate hypertension, ie systolic blood pressures of 140-179 mmHg and/or diastolic blood pressures of 90-109 mmHg. Individuals with severe hypertension and patients with a history of CHD in combination with mild or moderate hypertension are already at high risk and are qualified for drug treatment anyway. The *relative risk* is the ratio of absolute risk for an individual with a defined level of risk (based on one or more risk factors) to that for an individual at a reference level of risk, i.e. either a low or an

average level (based on one or more risk factors).[7] The relative risk provides information about the aetiological significance of a risk factor.[1] A high relative risk implies a strong association between a risk factor and the occurrence of a disease.

To prevent high blood pressure in a *public health* context, blood pressure-reducing interventions should be selected based on their potential to reduce the incidence of CHD in the population as a whole.[8] In public health, the *population attributable risk (PAR)* is a widely used measure of risk. In cases of hypertension, the PAR is the proportion of all diseased individuals in the population at large, in both normotensive and hypertensive individuals, to whom hypertension is attributable.[1] PAR not only depends on the relative risk, but also on the proportion of the total population that is exposed, i.e. on the prevalence of hypertension.

Epidemiologic measures of risk can thus be used as a basis for developing effective strategies for prevention of blood-pressure-related diseases, both in clinical medicine and public health. This hotline editorial deals with such an application of these risk measures, in view of the results of a recently published study on blood pressure and mortality from CHD in the Seven Countries Study.[9] The study and its main findings are described and the implications for treatment and prevention of hypertension in relation to CHD are discussed.

The study and its findings

The aim of the study was to compare the mortality rates from CHD at a given level of blood pressure among different populations. The study also investigated whether the relative risk for death due to CHD in relation to systolic and diastolic blood pressure was similar in different populations.

The study included 12,031 men aged 40-59 years who were enrolled in the Seven Countries Study between 1958 and 1964 and who were free of CHD at enrolment. A total of 16 cohorts were examined in the following countries: the United States, Finland (eastern and western), the Netherlands (Zutphen), Italy (Rome Railroad, Crevalcore and Montegiorgio), Greece (Crete and Corfu), former Yugoslavia (Dalmatia, Slavonia, Zrenjanin, Velika Krsna and Belgrade), and Japan (Tanushimaru and Ushibuka). To increase the power of the statistical analyses the 16 cohorts were pooled into six populations e.g. the United States, northern Europe (East and West Finland and Zutphen), Mediterranean southern Europe (Crete,

Corfu, Montegiorgio, and Dalmatia), Inland southern Europe (Rome, Crevalcore, Slavonia, and Belgrade), Serbia (Velika Krsna and Zrenjanin) and Japan (Ushibuka and Tanushimaru). The criteria for grouping cohorts into one population were similarities among cohorts in CHD mortality rates and similarities among cohorts in cultural (e.g. dietary patterns) and geographic features.[9] In all cohorts the major cardiovascular risk factors were measured in a standardized way at enrolment and after 5 (except Japan) and 10 years (except USA).[10,11] During 25 years of follow-up, 1291 (10.7%) men died from CHD.

The main study finding is that, at the same blood pressure level, the mortality rates from CHD varied substantially among populations. In all populations, however, men whose blood pressure increased a given amount experienced a similar relative increase in risk of dying from CHD. At systolic and diastolic blood pressures of 140 and 85 mmHg, respectively, 25-year mortality rates from CHD 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 low in Japan and Mediterranean southern Europe (approximately 20 deaths per 10,000 person-years).

Differences of 10 mmHg in casual systolic blood pressure and of 5 mmHg in casual diastolic blood pressure were associated with, respectively, a 17% and 13% difference in the risk of death from CHD. After adjustment for within-subject variability in blood pressure, the relative risk was 1.28 for each of these differences, making the relation 60% stronger for systolic blood pressure and twice as strong for diastolic blood pressure. A continuous, graded relation between blood pressure and risk of CHD mortality, ie the lower the blood pressure the lower the risk and vice versa, has also been demonstrated in other large observational studies.[12-15]

Other investigators contest this viewpoint and suggest that systolic blood pressure is not related to risk of all-cause and cardiovacular disease death for all pressures lower than an age- and sex-dependent threshold.[16] For a 40-year old man, they suggest that the threshold for systolic blood pressure should be about 140 mmHg, and for a 60-year old man about 150 mmHg. However, their end-points were different and their numbers were smaller. More studies are needed to draw definite conclusions about this issue.

Clinical implications

The large differences between the CHD death rates in the USA and northern Europe and those in Japan and Mediterranean southern Europe among men with similar blood pressure levels have implications for the treatment of hypertension in different parts of the world. It emphasizes the limited usefulness of hypertension as a diagnostic category in clinical decision making, and the importance of an individual's total risk of developing CHD. In the 1998 recommendations of the Joint Task Force of European Societies on prevention of CHD in clinical practice, a 10-year multifactorial CHD risk greater than 20%, or in young persons a risk exceeding 20% if projected to age 60, is arbitrarily defined as a risk sufficiently high to justify the selective use of antihypertensive drug therapy in healthy individuals.[6]

In populations with high CHD mortality rates, a large proportion of individuals has a high absolute level of risk. Our results show that at each level of blood pressure, this 'absolute risk' criterion is passed more often in the USA and northern Europe than in Japan and Mediterranean southern Europe. Thus, according to the 'absolute risk' criterion, a higher percentage of men in the USA and northern Europe with mild and moderate hypertension would be treated for this condition than in Japan and the Mediterranean.

In the recommendations of the Joint European Task Force, risk stratification charts derived from Framingham risk functions are used to estimate an individual's multifactorial absolute risk.[6] Although these risk charts predict absolute risk reasonably well in high-risk populations, e.g. the USA and northern Europe, they overestimate the risk in low-risk populations, e.g. Japan and the Mediterranean.[17,18] This means that, in the latter, an excess of people would be treated by drugs using the Framingham risk function based charts. These findings indicate the importance of developing and comparing risk functions derived from prospective population-based studies carried out in different parts of Europe, with different CHD mortality rates. For that purpose, the SCORE project was started in 1997.[17]

Of course, the definition of 'high risk' status, with regard to need for antihypertensive therapy is not solely based on considerations from observational epidemiology and clinical trials. Cost-effectiveness issues play also a role.[19] In addition, due to limitations in professional and financial resources, the need to establish priorities in health care may play a role in targeting risk groups for drug

treatment. Because these aspects may vary in different countries, the definition of 'high risk' status may vary from country to country.

Public health implications

In clinical medicine, a high risk approach to CHD prevention is used. Mainly patients with severe hypertension and patients with mild or moderate hypertension who have a high short-term absolute risk of developing CHD, e.g. within 10 years are treated. Most individuals have, however, average, mildly or moderately elevated blood pressure levels and a low short-term absolute CHD risk. Most of these individuals will not be included in the high risk strategy.

In a public health context, the aim of CHD prevention is to reduce the incidence of CHD in the population as a whole. Viewed from a population perspective, the potential benefit of blood–pressure reducing interventions is determined by the population attributable risk (PAR). The PAR depends both on the relative risk and on the proportion of individuals with blood pressure levels above optimal, e.g. a systolic blood pressure above 120 mmHg and/or a diastolic blood pressure above 80 mmHg. In the present study, we found that any increase in blood pressure was associated with an increase in the relative risk for CHD mortality, irrespective of an individual's blood pressure level. These positive associations and the large number of individuals with blood pressure levels above optimal (who will not be targeted by clinicians) indicate that the total burden of CHD among this group is considerable.[13,15] A population strategy, aimed at blood pressure reductions in the population as a whole, will therefore theoretically result in a much larger absolute decline in the number of CHD cases than a high risk strategy, even at moderate blood pressure reductions.[8] Small population-wide reductions of blood pressure may be achieved by stimulating lifestyle changes, such as increased physical activity and changes in diet, in the total population.[20-24] An advantage of such lifestyle interventions is that they also have a beneficial effect on other CHD risk factors such as total cholesterol.[8,20,23] Furthermore, they may prevent 'medicalization' of the population by avoiding the need for, or reducing the intensity of, antihypertensive drug therapy.[25,26]

An important role of lifestyle factors in reducing the burden of CHD is suggested by the results of the present study. The observed differences in CHD

mortality rates between populations at similar levels of blood pressure could not be explained by the major causal CHD risk factors: prevalence of diabetes was very low in all cohorts and CHD death rates were adjusted for age, smoking status and total cholesterol level. Although there may be some residual confounding, other factors such as genetic susceptibility for CHD, biological factors such as low HDL-cholesterol and coagulation factors, and life style factors, should thus be considered. Dietary patterns differed greatly between the populations. Compared with the northern European and U.S. diets, the Mediterranean diet at baseline contained less meat and dairy products but more olive oil, fish, fruits, vegetables, and wine.[27] Lifestyle factors, such as diet, are therefore suggested to be major determinants of differences in CHD death rates.

Conclusion

From a public health perspective, the high risk and the population strategy with respect to prevention of CHD are complementary. Adequate treatment of patients at high risk is needed because they will benefit most. This is, however, not enough to reduce the population burden of CHD and should be complemented by a population approach in order to obtain a maximal benefit of CHD prevention.

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CHAPTER 3.1

Systolic, diastolic and pulse pressure and 10-year cardiovascular mortality among elderly men in Finland, Italy, and the Netherlands

Abstract

Objective. To determine whether systolic, diastolic and pulse pressure are related to cardiovascular mortality in elderly men.

Design. Prospective cohort study.

Setting. The Finland, Italy and the Netherlands Elderly (FINE) Study, a population-based study.

Participants. 1152 men aged 65-84 years with no history of cardiovascular diseases (CVD) and not taking antihypertensive drugs.

Main outcome measures. Fatal CVD (n=201) during 10 years of follow-up.

Results. Neither systolic nor diastolic blood pressure were individually related to cardiovascular mortality. In the combined population of the FINE Study, men in the highest tertile of pulse pressure (≥73 mmHg) had a significantly increased risk of cardiovascular mortality compared with men in the lowest tertile (RR=1.54, 95% confidence interval [CI] 1.06-2.24).

Conclusion. The FINE Study indicates that elevated pulse pressure is related to an increased risk of cardiovascular mortality in elderly men. Neither systolic nor diastolic blood pressure were individually related to risk of cardiovascular mortality among elderly men without CVD from Finland, the Netherlands and Italy.

Introduction

In middle-aged men, systolic and diastolic blood pressure are individually important predictors of cardiovascular and all-cause mortality.[1] In elderly men there is evidence that elevated systolic blood pressure remains associated with increased cardiovascular and total mortality at least up to 80 years of age.[2,4] The association of diastolic blood pressure with both endpoints is less clear in the elderly. Besides curvilinear associations, some investigators have found weaker or no associations, and some observed excess mortality in elderly subjects with low diastolic blood pressure.[2,4-6] There is mounting evidence that low diastolic blood pressure is not causally related to increased cardiovascular risk.[4,7] Increased arterial stiffness with aging, indicated by a higher pulse pressure, and pre-existing diseases may be the primary factors causing increased risk, with low diastolic blood pressure being mostly a secondary phenomenon.[4] Concordantly, positive relations of pulse pressure with CVD mortality have been reported.[4] Current literature is however not conclusive on the role of elevated DBP in the etiology of CVD in the elderly. Results from some studies suggest that elevated DBP remains a risk factor for CVD mortality.[5,6] In two recent observational studies among large elderly cohorts, however, elevated DBP was not related to CVD mortality, also when potential confounding effects of pre-existing diseases were taken into account.[2,4]

The aim of the present study is to further establish the associations of systolic, diastolic and pulse pressure with mortality from cardiovascular diseases in elderly men in the Finland, Italy and the Netherlands Elderly (FINE) Study. Previous reports on the FINE Study are based on a follow-up period of five years. In this investigation, using 10-year follow-up and a sufficient number of events, we restricted the analysis to elderly men without a history of cardiovascular diseases who did not use anti-hypertensive drugs. This made it possible to study the etiologic association between various blood pressure components and cardiovascular mortality in elderly men.

Subjects and Methods

Study population

For this study, data of the survivors of the Finnish, Italian and Dutch cohorts of the Seven Countries Study were used.[8] They were re-examined after 25 years of follow-up and this re-examination was the baseline of the FINE Study, a prospective study on risk factors and health in elderly men aged 65 to 84 years.

In Finland, 716 men from two rural cohorts known as eastern and western Finland were re-examined in 1984. In Italy, 682 men from two rural cohorts, Crevalcore and Montegiorgio, were re-examined in 1985. In the Netherlands, 380 survivors of the Dutch cohort from the small town of Zutphen were re-examined in 1985, together with a new random sample consisting of 507 men aged 65 to 84 years from Zutphen who did not participate earlier in the Zutphen Study. The response rates were 94% in Finland, 76% in Italy, and 70% in The Netherlands.

Measurements

In all cohorts major cardiovascular risk factors were measured according to standardized methods at enrollment and after five years of follow-up. Details of the methods used have been described previously.[8,9]

In all three countries, blood pressure was measured on the right arm in supine position after five minutes rest with a sphygmomanometer (random zero in the Netherlands), according to a standardized protocol.[8,10] Blood pressure was measured by a specially trained nurse (Finland), or by trained physicians (Italy and the Netherlands). Readings were taken to the nearest two mmHg. The mean of two consecutive measurements was computed for systolic (1st Korotkoff phase) and diastolic (5th Korotkoff phase) blood pressure. For both systolic and diastolic blood pressure we distinguished between three fixed categories ('<140, 140-159, ≥160 mmHg' systolic and '<85, 85-94, ≥95 mmHg' diastolic). For pulse pressure (=systolic minus diastolic blood pressure) we presented tertiles. The lowest category was always used as reference.

Information on use of anti-hypertensive drugs was obtained from a questionnaire. In Finland and the Netherlands information was available about anti-hypertensive drugs used for different indications. In Italy this information was

restricted to anti-hypertensive drug use for the indication hypertension. Total and HDL cholesterol were determined enzymatically according to the criteria of the WHO Lipid Reference Laboratories in Prague or Atlanta, Georgia.[11] Height and weight were measured in light clothing without shoes and body mass index was calculated (kg/m^2). Known clinical history of diabetes mellitus and cancer, cigarette smoking, alcohol drinking and living independently were established by means of a standardized questionnaire. The presence of cardiovascular diseases at the baseline survey was defined by clinical criteria, obtained from questionnaires occasionally combined with information from reported clinical records and additional questions from the examining physician.[12] Cardiovascular diseases were considered to be present when either definite myocardial infarction, angina pectoris, heart failure (only present in case of both a clinical diagnosis and medication for heart failure), intermittent claudication, stroke or TIA had been diagnosed by a clinician.

Follow-up

Complete information on the vital status of the participants, obtained through official death certificates until 14 October 1994 in Finland, 1 May 1995 in Italy and 31 December 1994 in the Netherlands (10 year follow-up), was available for 99.7% of the FINE population. In Finland, only information on causes of death obtained through official death certificates was available. However, validity of the routine mortality statistics in Finland is high.[13] In The Netherlands and Italy, causes of death were occasionally validated through review of clinical records from the general practitioner or hospital. Final causes of death were adjudicated by a single reviewer using the 9th revision of the WHO-ICD[14] adopting a hierarchical order when multiple causes were given, as follows: violent causes, cancer, coronary heart disease, stroke and other causes. The endpoint considered in this study is mortality from cardiovascular diseases during 10 years of follow-up, with cardiovascular mortality defined as primary cause of death with ICD-9 codes 401 through 458.

Statistical analyses

Persons with missing data on blood pressure (n=6;0.3%) or other covariates (n=149;6.5 %) at baseline, in total 155 (6.8%), were excluded from the analyses. We also excluded men with a history of cardiovascular diseases at baseline (n=628; 29.5%) and men using anti-hypertensive medication regardless of an indication for

hypertension (n=636; 29.9%), leaving 1,152 (50.4%) men in the present analyses. Medication users were excluded because antihypertensive therapy may have influenced baseline blood pressure readings and thus their relation to cardiovascular risk.

Age-standardized 10-year mortality rates from cardiovascular diseases were computed for each blood pressure category by weighing the mortality rates for five-year age categories to the age distribution of the total study population.

Relative risks for the relation between both the categorical and the continuous (per 10 mmHg increase in systolic and pulse pressure and 5 mmHg increase in diastolic pressure) blood pressure variables and cardiovascular mortality were estimated using Cox's proportional-hazard analysis, pooled after stratification by cohort, with adjustment for age (years), total and HDL cholesterol (mmol/L), body mass index (kg/m^2), known history of diabetes mellitus (yes/no), smoking (never/ex/current), cancer (yes/no), living independently (yes/no) and current alcohol drinking (yes/no). Tests for quadratic trends were carried out with systolic and diastolic blood pressure put into the model as continuous variables. No significant quadratic trends were observed (all p-values > 0.05).

For the total population of the FINE Study (three countries pooled) we repeated the Cox analysis using estimated usual, or average, blood pressures for each individual instead of the casual baseline blood pressures. Usual blood pressures were estimated from a linear regression model, given the values obtained at enrollment and at five-year follow-up for systolic and diastolic blood pressure, body-mass index and cholesterol level. This yielded relative risk estimates adjusted for within-subject variability in blood pressure.[15]

We repeated the analyses after excluding deaths occuring in the first two years of follow-up, and separately for predefined subgroups of men aged 65-74 years and 75-84 years. Because these results were essentially the same, the results in this article are only reported for all deaths included and for both age-groups combined. The SAS computer package (version 6.12) was used for all statistical analyses (SAS Institute Inc., Cary, North Carolina, USA, 1989).

Results

At baseline, 47.4% of the Finnish, 61.6% of the Dutch, and 50.2% of the Italian men were free from cardiovascular diseases and did not use anti-hypertensive drugs. These apparently healthy men were included in the analysis. The included group had a significantly lower age-standardized 10-year cardiovascular mortality rate than the excluded group (239 per 10,000 person years versus 525 per 10,000 person years; $p<0.05$). At baseline (Table 1), average systolic and diastolic blood pressure varied from 148.6 (19.6) and 84.7 (10.9) in the Netherlands to 162.8 (21.0) and 90.4 (10.5) in Italy. The proportion of men classified as hypertensive (≥140/90 mmHg) ranged from 35% in the Netherlands to 61% in Italy.

Table 1. Baseline characteristics for elderly men without a history of cardiovascular diseases and not using antihypertensive drugs in Finland, the Netherlands and Italy.

Baseline characteristic	Finland	the Netherlands	Italy
N (%)	315 (47.4%)	545 (61.6%)	292 (50.2%)
		Mean (SD)	
Age (years)	71.5 (5.3)	71.1 (5.3)	71.6 (4.5)
Systolic blood pressure (mmHg)	152.3 (20.9)	148.6 (19.6)	162.8 (21.0)
Diastolic blood pressure (mmHg)	86.7 (10.2)	84.7 (10.9)	90.4 (10.5)
Body mass index (kg/m^2)	25.3 (3.9)	25.3 (3.0)	25.5 (3.8)
Total cholesterol (mmol/L)	6.15 (1.15)	6.08 (1.09)	5.86 (1.12)
HDL cholesterol (mmol/L)	1.29 (0.32)	1.14 (0.28)	1.33 (0.33)
		%	
Hypertension †	40.0	35.0	61.0
Anti-hypertensive use	-	-	-
Current smoking	18.1	32.3	29.8
Ex-smoking	52.7	49.4	39.7
History of diabetes	5.7	4.6	7.2
History of CVD	-	-	-
10-year cardiovascular mortality ‡	293	218	222

SD standard deviation; † systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg; ‡ age-standardized and per 10,000 person years.

The relation between the three blood pressure components and subsequent cardiovascular mortality was studied in men free from cardiovascular diseases and not using anti-hypertensive medication. During 10 years of follow-up, the number of elderly men among this group that died from cardiovascular causes was 66 (21.0%) in Finland, 88 (16.1%) in the Netherlands, and 47 (16.1%) in Italy. Correlations

Table 2. Age-adjusted mortality rates from CVD and multiple adjusted † relative risks and 95% confidence limits of mortality from CVD associated with systolic blood pressure in elderly men without a history of CVD and not using anti-hypertensive drugs in Finland, the Netherlands and Italy.

	Systolic blood pressure (mmHg)			
	<140	140-159	≥160	10 mmHg increase
		Finland (n=315)		
Total number	100	108	107	
N of CVD deaths	18	21	27	
Rate	346	234	291	
RR (95% CI)	1.00	0.78 (0.41-1.48)	0.94 (0.48-1.82)	1.05 (0.93-1.20)
		the Netherlands (n=545)		
Total number	190	195	160	
N of CVD deaths	25	35	28	
Rate	176	236	239	
RR (95% CI)	1.00	1.30 (0.78-2.18)	1.28 (0.75-2.21)	1.03 (0.93-1.15)
		Italy (n=292)		
Total number	34	101	157	
N of CVD deaths	3	17	27	
Rate	158	267	202	
RR (95% CI)	1.00	1.84 (0.52-6.52)	1.90 (0.55-6.54)	0.99 (0.87-1.12)
		FINE Study (n=1152)		
Total number	324	404	424	
N of CVD deaths	46	73	82	
Rate	215	243	241	
RR (95% CI)	1.00	1.15 (0.79-1.67)	1.22 (0.83-1.78)	1.03 (0.97-1.11)
RR ‡ (95% CI)				1.00 (0.89-1.12)

CVD cardiovascular disease; RR relative risk; CI confidence interval. † adjusted for age, total and HDL cholesterol, body mass index, known history of clinical diabetes and cancer, cigarette smoking, living independently and current alcohol drinking. ‡ adjusted for within-subject variability in blood pressure.

among blood pressure components were r=0.62 for systolic – diastolic pressure, r=0.86 for systolic – pulse pressure, and 0.13 for diastolic – pulse pressure.

Using the categorical as well as continuous blood pressure variables, neither systolic nor diastolic blood pressure were individually associated with cardiovascular mortality in elderly men in Finland, the Netherlands and Italy and in the total population of the FINE Study (Table 2 and 3).

In each separate country, pulse pressure was positively but not significantly related to cardiovascular mortality (Table 4). In the pooled country-group, however, men in the highest tertile of pulse pressure (≥73 mmHg) had a significantly increased risk of cardiovascular mortality compared with men in the lowest tertile (RR=1.54,

Table 3. Age-adjusted mortality rates from CVD and multiple adjusted † relative risks and 95% confidence limits of mortality from CVD associated with diastolic blood pressure in elderly men without a history of CVD and not using anti-hypertensive drugs in Finland, the Netherlands and Italy.

	Diastolic blood pressure (mmHg)			
	<85	85-95	≥95	5 mmHg increase
		Finland (n=315)		
Total number	139	105	71	
N of CVD deaths	26	22	18	
Rate	261	262	362	
RR (95% CI)	1.00	0.98 (0.54-1.79)	1.39 (0.73-2.64)	1.02 (0.91-1.15)
		the Netherlands (n=545)		
Total number	280	158	107	
N of CVD deaths	50	20	18	
Rate	236	186	232	
RR (95% CI)	1.00	0.75 (0.44-1.27)	1.09 (0.63-1.90)	0.96 (0.87-1.06)
		Italy (n=292)		
Total number	80	118	94	
N of CVD deaths	15	19	13	
Rate	303	198	159	
RR (95% CI)	1.00	0.85 (0.42-1.71)	0.70 (0.32-1.53)	0.88 (0.75-1.02)
		FINE Study (n=1152)		
Total number	499	381	272	
N of CVD deaths	91	61	49	
Rate	247	218	236	
RR (95% CI)	1.00	0.88 (0.63-1.23)	1.08 (0.75-1.55)	0.97 (0.90-1.03)
RR ‡ (95% CI)				0.95 (0.84-1.07)

CVD cardiovascular disease; RR relative risk; CI confidence interval. † adjusted for age, total and HDL cholesterol, body mass index, known history of clinical diabetes and cancer, cigarette smoking, living independently and current alcohol drinking. ‡ adjusted for within-subject variability in blood pressure.

95% confidence interval [CI] 1.06-2.24), and the increase in risk per 10 mmHg increase in pulse pressure was borderline significant (1.08, 95% CI 1.00-1.18). Adjustment for within-subject variability in blood pressure hardly changed the observed associations in the pooled population (Table 2, 3 and 4). None of the three blood pressures components were related to all-cause mortality (data not shown). In the total FINE Study population, including men with a history of cardiovascular disease and men using antihypertensive medications (n=2130), a significant U-shaped association between diastolic blood pressure and all-cause mortality (p-value quadratic trend <0.005), and a significant positive association between pulse

Table 4. Age-adjusted mortality rates from CVD and multiple adjusted † relative risks and 95% confidence limits of mortality from CVD associated with pulse pressure in elderly men without a history of CVD and not using anti-hypertensive drugs in Finland, the Netherlands and Italy.

	Tertiles of Pulse pressure (mmHg)			10 mmHg increase in pulse pressure
		Finland (n=315)		
Pulse pressure	<58	58-72	≥73	
N of CVD deaths	18	20	28	
Rate	315	227	328	
RR (95% CI)	1.00	0.75 (0.39-1.45)	1.09 (0.57-2.09)	1.07 (0.91-1.26)
		the Netherlands (n=545)		
Pulse pressure	<57	57-70	≥71	
N of CVD deaths	19	32	37	
Rate	164	216	264	
RR (95% CI)	1.00	1.27 (0.71-2.27)	1.44 (0.81-2.55)	1.09 (0.95-1.25)
		Italy (n=292)		
Pulse pressure	<64	64-79	≥80	
N of CVD deaths	12	16	19	
Rate	212	234	229	
RR (95% CI)	1.00	1.59 (0.73-3.44)	1.61 (0.76-3.42)	1.07 (0.93-1.24)
		FINE Study (n=1152)		
Pulse pressure	<59	59-72	≥73	
N of CVD deaths	45	70	86	
Rate	187	230	274	
RR (95% CI)	1.00	1.27 (0.87-1.86)	1.54 (1.06-2.24)	1.08 (1.00-1.18)
RR ‡ (95% CI)				1.04 (0.90-1.20)

CVD cardiovascular disease; RR relative risk; CI confidence interval. † adjusted for age, total and HDL cholesterol, body mass index, known history of clinical diabetes and cancer, cigarette smoking, living independently and current alcohol drinking. ‡ adjusted for within-subject variability in blood pressure

pressure and cardiovascular mortality (RR per 10 mmHg increase in pulse pressure=1.08, 95% CI 1.03-1.13) was observed (data not shown). We found no other significant associations between the blood pressure variables and cardiovascular and all-cause mortality in the total FINE Study population.

Discussion

This study indicates that elevated pulse pressure is related to increased cardiovascular mortality in elderly men from Finland, the Netherlands and Italy. The FINE Study does not provide evidence for an increased risk of cardiovascular

mortality at high or low levels of systolic and diastolic blood pressure in apparently healthy elderly men.

Pulse pressure was not studied before in the FINE Study but the positive association with cardiovascular mortality in the present study is in line with the literature.[4,6,16] Several mechanisms may explain the association between pulse pressure and cardiovascular disease. Elevated pulse pressure is an indicator of increased large-artery stiffness.[17] Arterial stiffness may promote the development of atheroma.[18] It causes ischemia[19] and is correlated with the presence of atherosclerosis.[20] Arterial stiffness is also strongly correlated with left ventricular hypertrophy,[21] a known risk indicator for cardiovascular events.[22]

Pulse pressure was not related to all-cause mortality in the present study, in contrast to the results of other studies.[4,16] This may be due to a dilution effect of the positive association with cardiovascular diseases by other causes of death. Indeed 49% of the men who died, died of causes other than cardiovascular diseases.

At middle-age, both systolic and diastolic blood pressure have strong linear relationships with cardiovascular and total mortality among the different populations of the Seven Countries Study[15,23] and among other middle-aged populations.[1] In the present study, the positive relationship of systolic blood pressure with cardiovascular and total mortality was strongly reduced and no longer significant, and that of diastolic blood pressure had disappeared among the elderly Finnish, Italian and Dutch survivors of the Seven Countries Study. Contrary to our findings, most researchers found persisting positive relations of systolic blood pressure with cardiovascular and all-cause mortality among elderly populations.[2,4] The literature on the relation of diastolic blood pressure with both end-points in the elderly is less consistent, also when restricting to studies that adjusted for confounding by comorbidity and poor health. Some authors observed positive associations,[5,6] while others observed no or U-shaped associations.[2,4]

Lack of associations of systolic and diastolic blood pressure with cardiovascular and total mortality in the present study may be due to increased comorbidity and underlying poor health. Preexisting cardiovascular diseases, cancer, diabetes, and deteriorating health indicated by cognitive impairment, low body mass index and limitations in activities of daily living may obscure the relation of blood pressure with (CVD) mortality. They are related to both reductions in blood pressure and excess deaths.[4,24,25] The present study was confined to a relatively healthy

elderly cohort and we adjusted the analysis for various health-related factors. However, there may be residual confounding by incomplete adjustment for all aspects of poor health. Incomplete adjustment for poor health may also explain the U-shaped associations between blood pressure and five-year all-cause mortality found in earlier reports on the FINE Study.[26,27]

It is unlikely that our findings regarding systolic and diastolic blood pressure are due to the dilution effect of regression towards the mean caused by use of inaccurate blood pressure measurements made on a single occasion.[28] Using average blood pressures based on repeated measurements during the first five years of follow-up, we found similar relative risk estimates.

Our male study population was relatively healthy compared with the general elderly population aged 65 to 84 years for several reasons. In spite of a high response rate, older persons and especially those with health problems are less likely to participate.[29] In addition, we excluded men who used antihypertensive medication and men with a history of cardiovascular diseases. The first were excluded because we were interested in the relation between untreated blood pressures and mortality risk in the elderly. Nevertheless we found no significant interaction between the blood pressure variables and antihypertensive treatment and the reported associations were the same for non-users and users of antihypertensive drugs (results not shown). This is in line with results from other observational studies.[2,4]

In conclusion, the FINE Study indicates that elevated pulse pressure is related to an increased risk of cardiovascular mortality in elderly men. Neither systolic nor diastolic blood pressure were individually related to cardiovascular mortality among relatively healthy elderly men from Finland, the Netherlands and Italy. This is in accord with the results of other studies concerning pulse and diastolic pressure. However, evidence from other population-based observational studies and from randomized trials[30] suggest that high systolic blood is an important risk factor also in the elderly.

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CHAPTER 3.2

Blood pressure and risk of myocardial infarction in elderly men and women: The Rotterdam Study

Abstract

Objective. To study the association between blood pressure and risk of myocardial infarction in elderly subjects.

Design. Prospective cohort study.

Setting. The Rotterdam Study, a Dutch population-based study.

Participants. 6004 men and women aged ≥ 55 years.

Main outcome measures. Fatal or non-fatal myocardial infarction (n = 190) during a 4-year follow-up.

Results. After excluding participants using blood pressure lowering medication and participants with a history of myocardial infarction, increasing levels of systolic blood pressure (SBP) were associated with increasing risk of first myocardial infarction (P for trend < 0.0001). The relative risk (RR) for an SBP of 160 mmHg or higher was 5.7 (95% confidence interval (CI), 1.9-17.1) compared with an SBP below 120 mmHg. Increasing diastolic blood pressure (DBP) was also associated with increasing risk of first myocardial infarction, with the RR reaching 2.5 (95% CI, 1.4-4.5) in subjects with values of 80-90 mmHg compared with values below 70 mmHg (P for trend < 0.05). Analyses in subjects aged 70 years and over showed that the positive associations between SBP and DBP and risk of first myocardial infarction remained at older age.

Conclusion. These findings in a relatively healthy cohort of elderly subjects do not provide evidence for a J- or U-shaped relation between SBP and DBP and risk of first myocardial infarction. They suggest that the risk of first myocardial infarction increases with increasing level of systolic and diastolic blood pressure and that this relationship persists into older age.

Introduction

In middle-aged populations, curvilinear associations between levels of systolic and diastolic blood pressure and risk of coronary heart disease have consistently been found.[1,2] In elderly people, the nature and strength of the association is still unclear. Results from several studies have suggested that elevated systolic and diastolic blood pressure remain associated with increased coronary heart disease in the elderly.[3-6] In contrast, other investigators have found weaker or no associations,[7,8] and some observed an increased mortality from coronary heart disease in elderly subjects with low systolic or diastolic blood pressure.[8-10] A possible explanation for an increased mortality at the lower end of the blood pressure distribution is the presence of other morbidity in the elderly, resulting in both blood pressure reduction and excess mortality.[11-16] A low diastolic blood pressure, in the presence of severe narrowing of the coronary arteries, may also increase the risk of death by compromising coronary blood flow.[17-20] Finally, it has been proposed that a decline in diastolic blood pressure with advancing age reflects vessel wall stiffening associated with atherosclerosis and consequently with excess mortality.[21-22]

In the present study, we examined the associations of systolic and diastolic blood pressure with risk of myocardial infarction in subjects aged 55 years and over. We also examined whether the associations persisted after age 70.

Subjects and Methods

The Rotterdam Study

The Rotterdam Study is a population-based prospective cohort study on the occurrence and determinants of chronic disabling diseases at older age. All residents of a suburb of Rotterdam, aged 55 years or over, were invited to take part in the study. The design of the study has been described in detail elsewhere.[23] Of the 10,275 men and women approached, a total of 7,983 (78%) agreed to participate. During a home interview, information was obtained on current health status, medical history and family history of diseases by means of a computerized questionnaire. The participants subsequently visited the study centre twice for physical examinations. All baseline measurements took place from March 1990 to July 1993.

Examinations

The physical examinations were carried out by research assistants according to a standardized protocol. Systolic (first Korotkoff phase) and diastolic (fifth Korotkoff phase) blood pressure were measured in duplicate on the right arm using a random-zero sphygmomanometer with a 14 x 38 cuff, after the participant had been seated for at least five minutes. The mean of the two blood pressure values was used in the analyses. For both diastolic and systolic blood pressure, we distinguished four fixed categories with the lowest as reference. Height was measured to the nearest 0.1 cm and body weight was measured to the nearest 0.5 kg. Body mass index (weight (kg)/height^2 (m)) was calculated. Serum total cholesterol was determined by an automated enzymatic procedure in a non-fasting blood sample. High-density lipoprotein (HDL) was measured after precipitation of the non-HDL fraction with phosphotungstate-magnesium. A history of diabetes mellitus was defined as a non-fasting blood glucose before or after a glucose tolerance test >11.1 mmol/l and/or use of anti-diabetic medication.[24] Data on indication for use of blood pressure lowering medication are based on information collected by a physician at the research centre. In case of missing information, data from the home interview was taken. In addition, information was collected on the type of medication used, which the participants had been asked to bring with them to the study centre. Data on smoking habits were obtained during the home interview. Smoking was classified as never, former or current smoking. History of myocardial infarction was defined as a self-reported myocardial infarction verified by hospital discharge data, written information from the subject's general practitioner or electrocardiographic measurements. Subjects with pathological Q-waves measured on the electrocardiogram during the physical examination, in the absence of symptoms, were also classified as having a history of myocardial infarction.[25]

Follow-up

The follow-up period, starting at the baseline examination and lasting until April 1996, was 3-6.5 years (mean 4.2). With respect to the vital status of the participants, information was obtained at regular intervals from the municipal register in Rotterdam. Information on fatal and non-fatal endpoints was obtained on a weekly basis from the general practitioners working in the study district of Ommoord and yearly from general practitioners outside Ommoord. Complete follow-up information

was available for 7054 subjects (88.4%) in the present analysis. Participants for whom no follow-up information was available were on average 3 years older, had a 6 mmHg lower systolic blood pressure and a 2 mmHg lower diastolic blood pressure. All information obtained from the general practitioners on possible events was coded independently by two research physicians from the Rotterdam Study. If there was disagreement, consensus was reached in a plenary session. Finally, all these events were verified by a medical expert in the field of cardiovascular disease. In case of discrepancies, the judgment by this expert was considered definite. Classification of myocardial infarction was based on the International Classification of Diseases, 10th version, codes I21-24.[26] In this analysis, the endpoint was a first or recurrent myocardial infarction during follow-up; fatal and non-fatal myocardial infarction were combined in the analyses.

Data analyses

We excluded persons who lived in a nursing home, in which blood pressure measurement was not part of the protocol (n=629; 8.9%), and persons with missing data on blood pressure (n=83;1.2%) or other covariates (n=338; 4.8%). The total number of persons excluded for one or more reasons was 1,050 (14.9%), so 6004 persons were available for the present analyses. A two-sided P-value <0.05 was considered statistically significant. Crude incidence rates (per 10,000 person years) of myocardial infarction were computed per blood pressure category. Cox's proportional-hazard analysis was carried out to estimate relative risks (RR) with corresponding 95% confidence intervals. Both univariate and multivariate adjusted RRs were computed. Because the univariate results did not differ from the multivariate adjusted results, only the latter are described in the results section. Adjustments were made for age, sex, body mass index, total and HDL cholesterol, cigarette smoking, use of blood pressure lowering drugs, history of myocardial infaction and history of diabetes mellitus. Dummy variables for the categories of blood pressure and cigarette smoking were used in the analyses.

The analyses were repeated after excluding participants using blood pressure-lowering medication regardless of an indication for hypertension (n=1936; 32.2%) and those with a history of myocardial infarction (n=758; 12.6%), leaving 3732 subjects in the analyses. To study whether the effects of blood pressure varied

by sex or age, we repeated these latter analyses separately for men and women and for predefined subgroups of subjects aged 55-69 years and ≥ 70 years. Additionally, a possible interaction of systolic and diastolic blood pressure with sex or age was tested by including a product term of the blood pressure variables with sex or age in the model, and by testing the statistical significance of its regression coefficient at a P-value<0.10. The number of events in those with a history of myocardial infarction was too small to study the effect of blood pressure within this group separately. All statistical analyses were carried out using the BMDP statistical package.

Results

At baseline (Table 1), the mean age±standard deviation was 69.1±8.7 years. Average systolic blood pressure was 139.9±22.4 mmHg and average diastolic blood pressure was 73.8±11.6 mmHg. The percentage of subjects with a systolic blood pressure of ≥160 mmHg was 19%, and 18% had systolic pressure levels below 120 mmHg. The proportion of subjects with a diastolic blood pressure ≥ 90 mmHg was 9%, and 36% had diastolic pressure levels below 70 mmHg.

Table 1. Baseline characteristics of men and women in the Rotterdam Study (n=6004).

Characteristic	Mean±SD or %
Age (years)	69.1±8.7
Systolic blood pressure (mm Hg)	139.9±22.4
Diastolic blood pressure (mm Hg)	73.8±11.6
Body mass index (kg/m^2)	26.3±3.7
Total cholesterol (mmol/l)	6.6±1.2
HDL cholesterol (mmol/l)	1.3±0.4
Current smokers	21.1
Former smokers	40.6
History of diabetes mellitus	10.4
History of myocardial infarction	12.6
Use of blood presssure-lowering medication [a]	32.2
Hypertension [b]	35.9

SD standard deviation a Regardless of an indication for hypertension. b Systolic blood pressure ≥ 160 mmHg and/or diastolic blood presure ≥ 95 mmHg and/or use of blood presssure lowering medication with an indication for hypertension. HDL, high-density lipoprotein.

The percentage of subjects classified as hypertensive was 35.9% and the percentage of subjects using blood pressure-lowering drugs, regardless of an indication for hypertension, was 32.2%. The most commonly used blood pressure-lowering drugs were β-blocking agents (11.0%) and diuretics (10.7%), and 4.1% was using both. The proportion of subjects with a history of myocardial infarction was 12.6%.

During the 4-year follow-up period, 190 subjects (3.2%) suffered a first or recurrent myocardial infarction, of which 40 were fatal (21%). The overall incidence rate for myocardial infarction was 80 per 10,000 person-years. In the whole group analyses, including subjects using blood pressure lowering medication and subjects with a history of myocardial infarction, a direct association between systolic blood pressure and risk of myocardial infarction was found (P for trend < 0.05). For diastolic blood pressure, the observed association was less clear (P for trend = 1.0) (data not shown). After excluding subjects using blood pressure lowering medication, regardless of an indication for hypertension, and subjects with a history of myocardial infarction, increasing levels of systolic and diastolic blood pressure were associated with increasing risk of first myocardial infarction (Table 2).

Table 2. Rates [per 10,000 person-years (py)] and adjusted relative risks (RR) of myocardial infarction (MI) by systolic and diastolic blood pressure category in elderly men and women without a history of myocardial infarction and not using blood pressure-lowering medication.

Blood pressure (mmHg)	Number of subjects	Number of events	Rate	RR [a]	95% CI
Systolic					
<120	794	4	12	1.0	
120-139	1315	24	45	3.2	1.1 - 9.3
140-159	1056	34	82	5.4	1.9 - 15.4
≥160	567	19	88	5.7	1.9 - 17.1
P linear trend				*P<0.0001*	
Diastolic					
<70	1428	20	34	1.0	
70-79	1266	28	55	1.6	0.9 - 2.9
80-89	733	26	91	2.5	1.4 - 4.5
≥90	305	7	63	1.9	0.8 - 4.5
P linear trend				*P<0.05*	

CI, confidence interval. a Adjusted for age, sex, body mass index, serum total and HDL cholesterol, cigarette smoking and diabetes mellitus. Rate cat_1 (per 10,000 py) = [(number of MI events in cat_1) x 10.000]/[(total n of subjects in cat_1) x (mean survival time, cat_1)].

The RR of first myocardial infarction was 5.7 (95% CI, 1.9-17.1) for a systolic blood pressure of 160 mmHg or higher compared with a pressure below 120 mmHg (P for trend < 0.0001). For diastolic blood pressure, the RR reached 2.5 (1.4-4.5) in subjects with values between 80 and 90 mmHg compared with subjects with a diastolic blood pressure below 70 mmHg (P for trend < 0.05).

Subgroup analyses were carried out for subjects aged 55-69 years (mean 62.4) and ≥ 70 years (maximum 99; mean 77.0) (Table 3). In both age groups, systolic and diastolic blood pressure were positively associated with risk of first myocardial infarction, but in the age group of 70 years and over, the associations were weaker than in the younger age group. Compared to the reference category (systolic blood pressure < 140 mmHg), the RR for subjects with a systolic blood pressure ≥ 160 mmHg was 3.1 (1.3-7.4) in the 55 to 69 age group versus 1.8 (0.8-4.0) in the 70^{+} group. The RR for a diastolic blood pressure ≥ 80 mmHg compared to < 70 mmHg was 3.0 (1.27-6.97) in the younger group versus 2.3 (1.1-4.8) in the older age group. The differences in strength of the associations of systolic and diastolic blood pressure with first myocardial infarction between the two age groups were not statistically significant (P for interaction term=0.16 and 0.70, respectively). Separate analyses for men and women revealed a similar trend as observed in the combined group (data not shown). There was no evidence for a sex difference in the association of systolic and diastolic blood pressure with risk of first myocardial infarction (P for interaction term=0.61 and 0.44 respectively). Both in men and women, those with the lowest systolic and diastolic pressure levels had the lowest risk.

Table 3. Rates [per 10,000 person-years (py)] and adjusted relative risks (RR) of myocardial infarction (MI) by blood pressure category and age in subjects without a history of myocardial infarction and not using blood pressure lowering medication.

	55 - 69 years (n=2385)					≥70 years (n=1346)				
	Number of Sunjects	Number of Events	Rate	RR [a]	95% CI	Number of Sunjects	Number of events	Rate	RR [a]	95% CI
Systolic										
<140	1528	15	25	1.0		581	13	54	1.0	
140-159	580	16	71	2.7	1.3 - 5.6	476	18	95	1.7	0.8 - 3.6
≥160	278	8	77	3.1	1.3 - 7.4	289	11	98	1.8	0.8 - 4.0
P linear trend				*P <0.005*					P = 0.14	
Diastolic										
<70	865	8	23	1.0		563	12	52	1.0	
70-79	828	14	43	1.9	0.8 - 4.5	438	14	79	1.4	0.6 - 3.1
≥80	693	17	64	3.0	1.3 - 7.0	345	16	122	2.3	1.1 - 4.8
P linear trend				P < 0.05					P < 0.05	

CI, confidence interval. a Adjusted for age, sex, body mass index, serum total and HDL cholesterol,cigarette smoking and diabetes mellitus. Rate cat_i (per 10,000 py) = [(number of MI events in cat_1) x 10.000]/[(total n of subjects in cat_1) x (mean survival time, cat_i)].

Discussion

Our data from a large cohort of older men and women showed that the risk of first myocardial infarction increased with increasing levels of systolic and diastolic blood pressure. This relationship persisted into older age.

Results from previous studies of blood pressure and coronary heart disease in the elderly are inconsistent. In several studies among elderly subjects, no clear associations of systolic and diastolic blood pressure with coronary heart disease morbidity or mortality were found.[7,8] In other studies, an increased mortality from coronary heart disease in elderly people with low systolic [9,10] or diastolic [8-10] blood pressure was observed. Only a limited number of studies reported linear associations in elderly subjects. A report from the Framingham Study describing men and women aged 65-94 years and a report from the Chicago Heart Association Study describing 2733 men and women aged 60-74 years documented significantly positive associations of systolic [3,6] and diastolic [3] blood pressure with coronary heart disease risk in both sexes. In addition, results from a large Norwegian study among 52064 men and women aged 30-89 years also showed significant positive associations between systolic and diastolic blood pressure and coronary heart disease mortality, unadjusted for confounding variables.[4] However, relative risks in the latter study decreased with increasing decades of age. In the 70-79 years age group (n = 5665), an increased risk was still present, but in the oldest age group (≥ 80 years; n = 1302), the association disappeared.[4]

Several explanations for the unclear or absent associations between blood pressure and risk of coronary heart disease found in former studies among elderly cohorts have been suggested. High baseline rates of coronary heart disease [27] and selective survival of elderly persons with high blood pressure values who are relatively insensitive for the effects of blood pressure elevation [20] may have weakened the association. The U- or J-shaped association found in earlier studies [7-10] may be partially explained by increased morbidity with advancing age.[15,27] Deteriorating health may lower the blood pressure and increase the risk of death at the same time.[12] A possible confounding effect of poor health is supported by the results from some recent cohort studies among subjects aged 65 years and over.[8,13-15] In these studies, U- or J-shaped associations between blood pressure and

mortality from cardiovascular or all causes largely disappeared or changed into positive ones after excluding subjects with known prevalent diseases and/or users of blood pressure-lowering medication, or by excluding events occuring during the first years of follow-up.[8,13-15]

Only a limited number of studies examined the association between blood pressure and mortality from cardiovascular or all causes in the very old (over age 75 years), while adjusting for confounding by poor health.[11,16,28] Two recent community-based studies reported similar findings to those observed in populations of younger elderly, e.g. an increased all cause mortality with low systolic and diastolic blood pressure, which was no longer significant after adjustment for poor health indicators (including pre-existing cardiovascular disease, limitation in activities of daily living and cognitive impairment).[11,16] In one of these studies, with a mean population age of 90 years, diastolic blood pressure was positively related to mortality from cardiovascular causes after adjustment for health status.[11] In contrast to these two studies, another recent population-based study in the very old reported an inverse relation between blood pressure and all-cause mortality that persisted after adjustment for clinically significant diseases at baseline and exclusion of early deaths.[28] An explanation for their different result might be that the variables measured in their study do not completely account for all age-related aspects of poor health.

A low diastolic blood pressure, in the presence of severe narrowing of the coronary arteries, may also increase the risk of death by compromising coronary blood flow [19,20]. Consistent with this hypothesis, Lindblad et al [18] and D'Agostino et al [17] found that negative or U-and J-shaped associations between diastolic blood pressure and coronary heart disease only existed in subjects with severe ischaemic heart disease and not in healthy people without these diseases. However, studies are not consistent on this issue since J-shaped relations have also been found in subjects without ischaemic heart disease.[19,29-31]

In our study of older men and women, we confirm the absence of a J- or U-shaped relation in elderly subjects without a history of coronary heart disease. Instead, we observed a continuous increase in risk of first myocardial infarction with increasing blood pressure level. This relationship persisted into older age, although the relative risks were somewhat lower in the oldest group and lost significance for systolic blood pressure.

In studies among middle-aged persons, the shape and strength of the association between systolic and diastolic blood pressure and coronary heart disease has been found to be the same in both men and women.[1,4] Also in studies among elderly subjects, no differences in the adjusted association between men and women have been observed.[4,17] The results from the present study are consistent with those findings.

To appreciate the findings of this study, certain methodological aspects should be considered. First, our study population is relatively healthy compared to the total elderly population for several reasons. In spite of a high response rate, older persons and those with health problems are less likely to participate.[32] Furthermore, subjects living in nursing homes, in which blood pressure measurement was not part of the protocol, were excluded from the analyses, as well as users of blood pressure lowering drugs. Our findings thus apply to apparently healthy subjects from the general population. The relation between blood pressure and myocardial infarction may be different in a population including a higher proportion of elderly with poor health. Twelve percent of the participants were excluded from the analyses because of incomplete follow-up information at the time of the analyses. This group mainly consisted of subjects who had a general practitioner without an automated patient registry, changed their general practitioner during the follow-up period or moved outside the study district. Based on these main reasons for incomplete follow-up information, we expect that the loss of follow-up has not influenced the observed relationships, although some selection towards a more healthy population may have taken place. In addition, 4.8% of the participants was excluded because of missing data on covariates other than blood pressure. Replacement of missings by sex- and age-specific mean levels of co-variates showed that possible bias caused by missing measurements of covariates in this study was negligible.

The number of subjects with a diastolic blood pressure above 90 mmHg is small in our study. This may reflect the effects of decreasing diastolic blood pressure with age and selective mortality of elderly subjects with high blood pressure. Thus the cohort barely reaches the hypertensive range for diastolic blood pressure and this may explain why we could not accurately assess elevated risk of myocardial infarction in the upper category of diastolic blood pressure in our study.

In this study, we used information on blood pressure levels obtained on a single occasion, and did not adjust estimated effects for regression dilution bias. This may have underestimated the true risks associated with high blood pressure because of large intra-individual variation in blood pressure in the elderly.[2,15,33] Another aspect that must be considered when interpreting the results is the relatively short follow-up period of four years. Because of this short follow-up period, we could not exclude events occuring during the first years of follow-up. This may have reduced the real effect of blood pressure if the early events were associated with an underlying poor health causing low blood pressure.[14,15] However, we observed a positive relation between blood pressure and myocardial infarction that might have been stronger if a potential confounding effect of poor health at baseline could have been adjusted for by excluding early events.

In conclusion, the results from this prospective study of relatively healthy older men and women do not provide evidence for a J- or U-shaped relation between SBP and DBP and risk of first myocardial infarction. They suggest that the risk of first myocardial infarction increases with increasing level of systolic and diastolic blood pressure and that this relationship persists into older age.

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CHAPTER 4

Primary prevention of cardiovascular diseases through blood pressure lowering: quantifying the impact of different intervention strategies

Abstract

Objective.To quantify the potential impact of different blood pressure lowering interventions on the primary prevention of cardiovascular diseases (CVD).

Methods. Recent data on distribution of risk factors from two Dutch population-based studies, in total 13,309 men and women 40 to 74 years old and free from CVD, were used. We used the Framingham risk function to estimate the individual 10-year absolute risk of CVD. We simulated the effects of a high-risk pharmacological intervention, a population-wide dietary intervention and a combination of both. In the pharmacological intervention, hypertensive individuals were considered to be treated according to current guidelines. In the dietary intervention, we hypothesized that all individuals complied with a healthy diet similar to the one used in the Dietary Approaches to Stop Hypertension (DASH) trial.

Results. Within 10 years, 1.8% (n=6,682) of CVD events among subjects aged 40-59 years, and 1.5% (n=7,799) of CVD events among subjects aged 60-74 years could theoretically have been prevented by pharmacological treatment of high-risk individuals. The fraction of CVD events that could theoretically have been prevented in the population-wide dietary intervention was 8.6% (n=32,382) and 6.5% (n=32,536) respectively. This yielded a total potential benefit of 10.4% (n=39,064) and 8.0% (n=40,335) within 10 years in the combined intervention.

Conclusion. A high risk approach complemented by a population approach is needed to achieve maximal health benefit. Blood pressure lowering in the whole population through dietary changes is potentially an effective tool for population-wide prevention of CVD.

Introduction

Although the age-specific mortality rates from cardiovascular diseases (CVD) are decreasing, CVD are still the number one cause of death in the Netherlands.[1] Every year, over 50,000 men and women die from these diseases, which is more than one third of all deaths in the Netherlands.[1] Blood pressure is an important risk factor, showing a continuous, linear relationship with CVD.[2] This, in combination with the high prevalence of elevated blood pressure in the Dutch population (i.e. 10% of adult men and 13% of adult women had blood pressure levels ≥160/95 mmHg in 1994),[3] makes control of raised blood pressure an important strategy in the primary prevention of CVD.

Blood pressure levels can be lowered through different strategies aimed at high risk groups only or at the total population. In a high-risk strategy focused on hypertensive individuals with a high absolute risk of CVD, blood pressure is mainly lowered by antihypertensive medication. In 2000, a revised version of the Dutch consensus guideline for blood pressure lowering therapy was published.[4] This guideline prescribes drug therapy to hypertensive individuals with a 20% risk of CVD in 10 years, taking the effects of concommitant risk factors into account.[4] In a population strategy, focused on lowering blood pressure levels in the general population, changes in lifestyle such as weight reduction, increase in physical activity and healthy dietary patterns could be induced.[5]

The aim of the present study is to quantify the potential impact of three blood pressure lowering interventions, a high-risk pharmacological intervention, a population-wide dietary intervention and a combination of both, on several health outcomes. Health outcomes included the number of people needing blood pressure lowering medication, the number of prevented CVD events, and the average gain in healthy life expectancy in the general Dutch population free from CVD. We focused on a healthy diet rich in fruits, vegetables and low-fat dairy products and low in salt, as population-wide lifestyle intervention because the effects of this intervention on blood pressure have been studied both in normo- and hypertensives.[6,7] Furthermore, such a diet fits into to the general Dutch recommendations for a healthy dietary pattern[8] and may have an additional beneficial effect on associated cardiovascular risk factors[9-11] and on diseases other than CVD such as cancer and chronic obstructive lung disease.[12,13]

Methods

Simulation model

We used a simulation model to quantify the impact of different blood pressure lowering interventions on various outcome parameters. The model consists of four steps: (1) a baseline dataset with individual data on cardiovascular risk factors; (2) a procedure to estimate the effects of different interventions on blood pressure; (3) a risk function (Framingham) to estimate the risk to develop a cardiovascular event in the next 10 years for each individual in the dataset, based on a combination of risk factors;[14,15] (4) and a method to calculate the occurrence of CVD in the general Dutch population.

Study population and measurements

We restricted our study population to Dutch men and women 40 to 74 years old, because the prevalence of high blood pressure is very low below age 40 years (<3%)[16] and because the applied risk function is restricted to subjects below age 75 years.[15] For subjects 40 to 59 years we used data from the Monitoring Project on Risk Factors for Chronic Diseases (MORGEN-project), a population-based cross-sectional study conducted from 1993 to 1997 in the Netherlands. Yearly, a new random sample of men and women aged 20 to 59 years in three towns was invited.[17] In total, 22,769 subjects were examined with response rates varying between 40 and 48 percent for the different years. For subjects aged 60 to 74 years we used data from the Rotterdam Study, a population-based longitudinal study with baseline measurements from 1990 to 1993. All 10,275 residents of a suburb of Rotterdam, aged 55 years and over, were invited to participate and 7,983 (78%) subjects agreed to participate.[18]

In both studies, we excluded subjects with cardiovascular diseases (CVD) at baseline (n=474 (3.9%) in the MORGEN-population aged 40 to 59 years and n=828 (19.7%) in the Rotterdam population aged 60 to 74 years) and subjects with missing values for the risk factors used (n=2,220 (16.9%) in the MORGEN-project and n=521 (12.4%) in the Rotterdam Study). Subjects free of CVD were selected because we aimed to study different primary prevention strategies. The final datasets consisted

of 4,895 men and 5,603 women aged 40 to 59 years from the MORGEN-project and 1,121 men and 1,690 women aged 60 to 74 years from the Rotterdam Study.

In both the MORGEN-project and the Rotterdam Study, blood pressure was measured twice on a single occasion on the upper arm with the participant in sitting position using a random-zero sphygmomanometer. Systolic (SBP) en diastolic (DBP) blood pressure were recorded at the appearance (first Korotkoff phase) and disappearance (fifth Korotkoff phase) of sounds, respectively. In the present study we adjusted blood pressures levels for within-person variability. Corrected blood pressures were used to increase comparability with Dutch general practice, where elevated blood pressure is diagnosed as the average after several measurements during several weeks.[4] Corrected blood pressures were estimated according to equation 1 and 2

$$S^2_{obs} = S^2_b + S^2_{wb} + S^2_{ww}/2 \qquad (1)$$

$$BP^c_i = BP_p + (BP_i - BP_p) * F \qquad (2)$$

where S^2_{obs}, S^2_b, S^2_{wb}, and S^2_{ww} denote the observed variance in the population, between-person, within-person – between-visit, and within-person – within-visit variances, respectively, and BP^c_i, BP_i, BP_p and F denote the corrected blood pressure for individual *i*, the average of the two measurements for individual *i*, the average blood pressure of the population, and the shrinkage factor (S^2_b / S^2_{obs}), respectively.[19] BP_p was estimated using a linear mixed effect model with blood pressure as dependent, and smoking, total/HDL cholesterol ratio and body mass index as independent variables, stratified by sex and 10-year age group . We used a value of 40 for S^2_{wb} based on an external reproducibility study.[19] Hypertension was subsequently defined as corrected SBP ≥ 140 mmHg or corrected DBP ≥90 mmHg, or both.[5]

Non-fasting serum total and HDL cholesterol were determined in two laboratories that are permanent members of the international Cholesterol Reference Network. In both studies, total cholesterol was determined enzymatically, using a Boehringer test-kit.[20] HDL cholesterol was determined after precipitation of apo-B-containing lipoproteins with magnesium phosphotungstate.[21] The prevalence of

diabetes mellitus was self-reported or was based on a random non-fasting serum glucose level of ≥ 11.1 mmol/L in the MORGEN-project. In the Rotterdam Study, prevalence of diabetes mellitus was based on the use of antidiabetic medication or a random or post-load serum glucose level ≥ 11.1 mmol/L. In both studies, information on current smoking behaviour was obtained with a standardised questionnaire. Current smokers included subjects who currently smoked one cigarette or more per day and ex-smokers included subjects who had quit smoking within the past year. Information on left ventricular hypertrophy (LVH) was not available in both studies. We assigned presence of LVH randomly, using the age-specific LVH prevalence of the Framingham Study.[15] To exclude subjects with manifest CVD at baseline, information on history of myocardial infarction, stroke, heart operations and claudicatio intermittens was obtained in both studies with a questionnaire. In the Rotterdam Study, subjects with a history of angina pectoris were additionally excluded. Subjects who said that they used drugs with the purpose to lower the blood pressure were considered pharmacologically treated for hypertension. In the Rotterdam Study, this information was validated with information on the type of medication used.

Interventions

We simulated a pharmacological intervention solely focused on hypertensive individuals, a dietary intervention focused on the total population, and a combination of the pharmacological and dietary intervention. We compared these interventions with a reference strategy of no intervention. In the reference strategy, we used the individual data on risk factors from the MORGEN-project and the Rotterdam Study.

The pharmacological intervention implies that all currently untreated hypertensive subjects who need blood pressure lowering medication according to the recent Dutch consensus guideline, are detected and receive medication.[4] Consistent with other recent guidelines,[5,22-25] this guideline prescribes drug therapy to individuals with a high absolute risk for CVD.

The dietary intervention is aimed at lowering blood pressure in the whole population, including both untreated and treated, and normo- and hypertensive subjects, by strict compliance with a healthy diet, in conjunction with a reduction of the sodium intake with 0.9 g/day, according to the Dietary Approaches to Stop

Hypertension (DASH) and the DASH Sodium trial.[6,7] The healthy diet is defined as a diet low in salt and rich in fruits, vegetables and low-fat dairy products and with low intake of saturated fat and cholesterol.[6,7] The nutrient compositions of the average Dutch diet and of the control diet and healthy diet from the DASH (Sodium) trial are described in Table 1. In general, the average diet of the Dutch population was comparable to that of the DASH control diet. The intake of (low-fat) dairy products and of potassium, calcium and magnesium was however higher among the Dutch population.

Table 1. Comparison of average daily intake of macro- and micronutrients, and of different food groups between the Dutch population and the control and intervention groups of the DASH trial.

Average daily intake †	Dutch population ‡	DASH trial §	
		Control diet group	Healthy diet group
Macronutrients (en%)			
Total fat	36.8	35.7	25.6
Saturated fat	14.7	14.1	7.0
Monounsaturated fat	12.8	12.1	9.9
Polyunsaturated fat	6.9	6.2	6.8
Carbohydrates	42.6	50.5	56.5
Protein	16.3	13.8	17.9
Micronutrients (mg/d)			
Potassium	3793	1752	4415
Sodium	3700	3500 ‖	2600 ‖
Calcium	1050	443	1265
Magnesium	340	176	480
Cholesterol	230	233	151
Food groups (g/d)			
Fruits, juices and vegetables	361	385	992
Fruits	139	82	281
Juices	56	166	411
Vegetables	166	137	300
Total dairy	391	89	485
Low-fat dairy	289	3	458
Fiber	23	9	31

DASH, Dietary Approaches to Stop Hypertension; † Values are for diets designed to provide a daily energy level of 2190 kcal (Dutch population) and 2100 kcal (DASH trial); ‡ Dutch population aged 50 to 64 years[26]; § subjects aged 22 years or older (mean age 44 years)[6]; ‖ average sodium intake in the DASH Sodium trial[7].

In the combined pharmacological/dietary intervention, all currently untreated hypertensive subjects who need blood pressure lowering medication according to

the Dutch consensus guideline[4] receive medication, and all individuals from the total population strictly comply with the DASH diet and reduce their sodium intake with 0.9 g/day. We simulated that the three interventions lowered SBP because the Dutch consensus guideline uses SBP to estimate 10-year absolute risk of CVD.[4] The applied SBP reductions per intervention are described in Table 2. It should be noted that these reductions reflect those obtained in randomized controlled trials.

Table 2. Simulated effects of the pharmacological, dietary and combination intervention on systolic blood pressure in normotensive and hypertensive individuals.

Intervention	Simulated reduction in SBP per individual (mmHg) †
Pharmacological ‡	10.5
Dietary §	
Normotensives	2.7
Hypertensives	7.5
Combination ||	
Normotensives	2.7
Hypertensives, not eligible for drug therapy ¶	7.5
Hypertensives, eligible for drug therapy ¶	18.0

SBP systolic blood pressure; † compared to the reference strategy; ‡ SBP reduction based on a meta-analysis of clinical trials[27] and independent of baseline SBP. The SBP reduction of 10.5 mmHg reflects a true difference in SBP level between control and intervention group. Because the Framingham risk is defined for empirical or casual blood pressure levels, we transformed the true difference to the difference in terms of empirical blood pressure levels. We did this by multiplying the true difference with the inverse of the shrinkage factors as estimated earlier in the methods section; § SBP reduction based on the DASH trial, e.g. 2.0 mmHg for normotensive and 6.3 mmHg for hypertensive whites.[28] The extra reduction induced by lowering sodium intake from 3.5 g/day to 2.6 g/day, above that of the DASH diet, is based on the DASH Sodium trial, e.g. 0.7 mmHg for normotensive, and 1.2 mmHg for hypertensive whites;[7] || based on the assumption that the effects of the pharmacologocal and dietary interventions on SBP are completely additive; ¶ according to the Dutch consensus guideline on high blood pressure;[4] eligibility for drug therapy estimated before applying the SBP reductions.

Calculation method of outcome variables

The outcome variables in our study are the number of subjects treated with blood pressure lowering medication, the number of CVD events, and the (healthy) life expectancy in the general Dutch population, by gender and age group (40 to 59 and 60 to 74 years old). We estimated the number of subjects currently treated with blood pressure lowering medication by using the current prevalence data on pharmacological treatment in the MORGEN and Rotterdam dataset. To calculate the number of untreated subjects that should be treated according to the Dutch

consensus guideline, we estimated the proportion of currently untreated individuals in the two datasets that met the criteria for treatment based on their current levels of risk factors.

To estimate the number of CVD events for each strategy of intervention, we first estimated the risk to develop a fatal or nonfatal CVD event within 10 years for each individual in the dataset based on the Framingham risk function.[15] The risk function included age, SBP (i.e. the reduced SBP levels in the blood pressure lowering interventions), cigarette smoking, total/HDL cholesterol ratio, diabetes and ECG left ventricular hypertrophy.[14] All individual risks were then summed, which results in the expected 10-year incidence rate for CVD. We subsequently extrapolated these data to the general Dutch population using demographic data from Statistics Netherlands.[29] Comparison of CVD incidence rates estimated using the Framingham risk function with those based on Dutch incidence data showed some differences. We adjusted for these differences by applying correction factors on the Framingham-based incidence rates.[30]

To estimate life expectancy (LE) for each strategy of intervention, we first estimated the number of years lived for individuals that did not develop a CVD event within 10 years using the life table method. Sex and age specific total mortality rates were derived from Statistics Netherlands for 1994.[31] Secondly, for individuals that did develop a CVD event within 10 years, we estimated the average number of years lived until the event, specified to type of CVD event. To estimate healthy life expectancy (HLE), for each individual, we multiplied average number of years lived after a nonfatal CVD event by disease-specific disability weights from the Global Burden of Disease Study.[32] Average (age-specific) number of years lived until, or after, a CVD event were derived from incidence data based on registries of Dutch general practitioners.[33] To finally estimate (H)LE we summed all individual number of (healthy) years lived.

To estimate the effect of blood presssure lowering on number of CVD events and (H)LE, the outcomes calculated in the blood pressure lowering interventions were subtracted from the outcomes in the reference strategy of intervention.

To examine sensitivity of our main outcome measure to variability in the size of the intervention effect on SBP, we increased the applied SBP reduction by one mmHg and evaluated how results changed. To examine sensitivity of our main outcome measure to variability in the size of the strength of the SBP – CVD

relationship, we multiplied the regression coefficient (Framingham risk function) by 1.10 (i.e. a 10% stronger relationship) and evaluated how results changed.

Results

Baseline characteristics of the populations from the MORGEN-project and the Rotterdam Study are shown in table 3. In men aged 40 to 59 years average SBP and DBP were higher than in women of that age. The difference in average SBP and DBP between men and women aged 60 to 74 years was much smaller. According to the WHO classification of blood pressure, 72.7% respectively 52.0% of the younger men and women, and 86.0% respectively 82.4% of the older men and women had suboptimal systolic or diastolic blood pressure levels.[5] The prevalence of hypertension according to the WHO definition was 20.2% respectively 12.5% among the younger, and 41.4% respectively 41.6% among the older men and women. In total, 22.8% respectively 16.8% of the younger men and women, and 46.1% respectively 48.8% of the older men and women had hypertensive blood pressure levels or used anti-hypertensive medication.

Table 4 gives the number of Dutch subjects currently treated with blood pressure lowering medication (reference scenario), and the number of Dutch subjects currently untreated but needing treatment according to the Dutch consensus guideline for high blood pressure. More women than men are currently treated. In the younger age group, more men than women need treatment according to the consensus guideline (n=140,283 [7.5%] versus n=43,715 [2.3%]). In contrast, in the older age group more women than men need treatment (n=109,817 [10.6%] versus n=81,605 [11.5%]). Most untreated men and women needing treatment do so because of a mildly to moderately elevated SBP combined with other risk factors (such as smoking), leading to a 10-year risk of CVD exceeding 20% (Table 4).

The estimated number of cardiovascular events in the next 10 years in Dutch men aged 40 to 59 years is nearly twice the number in Dutch women of the same age group (247,569 versus 126,897) (Table 5). In men and women aged 60 to 74 years, the estimated number of future cardiovascular events is comparable (250,799 versus 252,510). In the pharmacological intervention, 5,337 (2.2%) events in men and 1,345 (1.1%) events in women aged 40 to 59 years, and 3,382 (1.3%) events in men and 4,417 (1.7%) events in women aged 60 to 74 years would be prevented

Table 3. Mean, standard deviation and prevalence of risk factors in men and women aged 40 to 59 years from the MORGEN-project† and in men and women aged 60 to 74 years from the Rotterdam Study†.

Risk factor	MORGEN-project, population aged 40-59		Rotterdam Study, population aged 60-74	
	Men (n=4895)	Women (n=5603)	Men (n=1121)	Women (n=1690)
			Mean	
Age (years)	49.3 (5.6)	49.1 (5.6)	66.6 (4.1)	67.0 (4.3)
Systolic blood pressure* (mmHg)	127.4 (13.4)	121.7 (14.5)	137.9 (17.6)	137.1 (18.2)
Diastolic blood pressure* (mmHg)	81.0 (8.1)	77.3 (8.3)	77.1 (8.9)	75.1 (8.4)
Total/HDL cholesterol	4.98 (1.70)	3.86 (1.25)	5.41 (1.53)	4.06 (1.52)
Body mass index (kg/m^2)	26.1 (3.5)	25.4 (4.2)	25.7 (2.8)	26.7 (4.0)
			%	
Diabetes mellitus	2.7	1.6	8.6	8.3
Smoking	33.9	34.8	33.4	22.3
Blood pressure lowering medication	5.4	6.6	11.2	17.0
Blood pressure status*				
Normal (<130/<85)	57.3	72.0	35.2	35.7
Optimal (<120/<80)	*27.3*	*48.0*	*14.0*	*17.6*
High-normal (130-139/85-89)	22.5	15.5	23.3	22.7
Mild hypertension (140-159/90-99)	17.1	10.4	30.6	30.7
Moderate hypertension (160-179/100-109)	2.6	1.9	8.7	9.8
Severe hypertension (≥180/(≥110)	0.5	0.2	2.1	1.1

† free from cardiovascular diseases; * on basis of blood pressure values corrected for within-subject variability in blood pressure

Table 4. Subjects (n [%]) currently treated with blood pressure lowering medication, and subjects untreated but needing treatment according to the Dutch consensus guideline in the general Dutch population free of CVD, by age and sex.

	Number of treated subjects							
	Dutch population 40 to 59 years (N=3,737,244)				Dutch population 60 to 74 years (N=1,750,262)			
Treatment status	Men N	%	Women N	%	Men N	%	Women N	%
Currently treated	93,998	5.0	117,197	6.3	80,669	11.4	179,851	17.3
Untreated, should be treated †*								
Criteria for treatment:								
SBP ≥180 mmHg or DBP ≥100 mmHg or both	28,421	1.5	15,882	0.9	15,139	2.1	11,082	1.1
(SBP 140-179 mmHg or DBP 90-99 mHg or both) and diabetic	12,553	0.7	4,326	0.2	22,241	3.1	37,528	3.6
SBP 140-179 mmHg and 10-year risk of CVD ≥20%	99,309	5.3	23,507	1.3	44,225	6.2	61,206	5.9
Total untreated, should be treated	140,283	7.5	43,715	2.3	81,605	11.5	109,817	10.6

† needing treatment according to the Dutch consensus guideline on high blood pressure[4]; * on basis of blood pressure values corrected for within-subject variability in blood pressure.

Table 5. Number (%) of fatal and non-fatal cardiovascular events (prevented) in the next 10 years for the reference scenario and for the different blood pressure lowering interventions in the general Dutch population free of CVD, by age and sex.

	Number (%) of cardiovascular events							
	Dutch population 40 to 59 years				Dutch population 60 to 74 years			
Strategy of intervention	Men		Women		Men		Women	
	N	%	N	%	N	%	N	%
Reference scenario								
Number (%) of cardiovascular events	247,569		126,897		250,799		252,510	
Number (%) of cardiovascular events **prevented** *:								
Pharmacological intervention	5,337	2.2	1,345	1.1	3,382	1.3	4,417	1.7
Dietary intervention	20,637	8.3	11,745	9.3	14,528	5.8	18,008	7.1
Combination of pharmacological and dietary intervention	25,974	10.5	13,090	10.3	17,910	7.1	22,425	8.9

* number of cardiovascular events in reference scenario minus number of events in blood pressure lowering intervention

Table 6. (Gain in) mean healthy life expectancy for the reference scenario and for the different blood pressure lowering interventions in the general Dutch population free of CVD, by age and sex.

	Mean healthy life expectancy (months)			
	Dutch population 40 to 59 years		Dutch population 60 to 74 years	
Strategy of intervention	Men	Women	Men	Women
Reference scenario				
Mean healthy life expectancy	339	410	163	207
Gain in mean healthy life expectancy*:				
Pharmacological intervention	0.7	0.2	0.8	0.8
Dietary intervention	2.7	1.7	3.3	3.0
Combination of pharmacological and dietary intervention	3.4	1.9	4.1	3.8

*compared to the reference scenario

within 10 years (Table 5). In the dietary intervention, more CVD events would be prevented than in the pharmacological intervention, both in men and women and in both age groups. Compared to the pharmacological intervention, the prevented number of cardiovascular events in the next 10 years in the combined pharmacological/dietary intervention would be more than four times larger (in total 39,064 in the general Dutch population aged 40 to 59, and 40,335 in those aged 60 to 74).

We evaluated sensitivity of our main outcome measure to variability in two parameters. Increasing the blood pressure lowering effect of the different interventions by one mmHg resulted in an increase in number of prevented CVD events of 3000 to 5000 in the different age and gender groups. Simulation of a 10% stronger effect of SBP on CVD risk, by multiplying the regression coefficient for SBP in the Framingham risk function by 1.10, yielded an increase in number of prevented CVD events of 1000 to 4000 in the different age and gender groups.

The gain in mean healthy life expectancy was modest for all three interventions and varied from almost zero for the pharmacological intervention in women aged 40 to 59 years (because of the low prevalence of hypertension and the low incidence of CVD), to four months for the combined pharmacological/dietary intervention in men and women aged 60 to 74 years (Table 6). Similar results were obtained with respect to the gain in mean total life expectancy (data not shown).

Discussion

Pharmacological treatment focused on blood pressure lowering in hypertensive individuals with a high absolute risk of CVD, would prevent only a small fraction of the population burden of CVD. In this simulation study, the decline in number of CVD events could theoretically be at least four times larger if blood pressure lowering by pharmacological treatment of high-risk individuals is combined with a healthy dietary pattern in the Dutch population as a whole. The average gain in total and healthy life expectancy in the whole population due to the different interventions was small and ranged from zero to four months, depending on the age and sex of the population.

It is important to emphasize that the present study, as any theoretical modelling exercise, has several limitations. First, our results are subject to variation.

Using sensitivity analysis, we showed that the estimated number of prevented CVD events was sensitive to variation in the size of the intervention effect on SBP, and to variation in the strength of the relation between SBP and risk of CVD. Second, two different datasets were used in this study, data from the MORGEN-project for the population aged 40 to 59 years and data from the Rotterdam Study for the population aged 60 to 74 years. The measurement protocols of most variables were comparable, but there were some differences. Because of these differences we should be careful in making direct comparisons between the younger and the older age group. Third, the results from this study relate to a Dutch population aged 40 to 74 years and free from CVD. The generalizability of these results to those of other populations depends on the specific distribution of risk factors, on the CVD incidence rate, and on the ratio of coronary heart disease (CHD) to stroke events in those populations.[34] Furthermore, the proportion of a population eligible for pharmacological treatment, and thereby the potential decline in number of CVD events achievable by drug therapy, depends on the proportion of currently untreated hypertensive individuals in that population. As the prevalence of untreated hypertension is high in the Netherlands compared to other countries such as the United States, the potential health benefit of drug therapy is expected to be large in the Netherlands.[16,35]

We found that on the population level, a dietary intervention aimed at moderate population-wide reductions in SBP would prevent more CVD events than pharmacological treatment of hypertensive individuals with a high absolute risk of CVD. This result is consistent with our expectations based on the philosophy of Rose.[36] He argued that a population-wide strategy aimed at shifting the entire blood pressure distribution in the population toward lower values will theoretically result in a larger decline in number of CVD events than a blood pressure lowering strategy restricted to hypertensive individuals.[36] The substantial proportion of the Dutch population aged 40 to 74 years having suboptimal blood pressure levels, compared to the relatively small proportion having hypertensive levels in combination with a high absolute risk (63% versus 8%), and the continuous dose-response relationship between blood pressure and CVD risk[2] explains this.

In the present study, the average gain in healthy life expectancy (HLE) in the whole population was small. This may be partly explained by the fact that HLE of most individuals is not changed by the interventions as they remain free of

hypertension and CVD during their lives. However, the increase in HLE for high-risk individuals in which a cardiovascular event is prevented or postponed due to blood pressure lowering intervention may be as large as several years. A relatively small gain in HLE on the population level is thus compatible with a large one for high risk individuals. The gain in HLE may be underestimated because we only simulated the number of extra years lived (in health) due to prevention of CVD. However, blood pressure lowering may also decrease the occurrence and consequences of other diseases, such as dementia, [37] which was not taken into account in the calculation of (healthy) life expectancy.

Several points should be noted in view of our findings. Beneficial effects of pharmacological treatment, both on long-term (two to six years) blood pressure levels and on cardiovascular endpoints, have been well established in clinical trials[38-40] and in the population.[41] The potential blood pressure lowering effects of a healthy dietary pattern have only been established in a limited number of trials.[6,7,42,43] Their results are in line with those from observational studies that showed inverse associations of blood pressure with intake of magnesium, potassium, calcium, fiber, and protein.[44-49] In subjects with hypertension, the blood pressure lowering effect of a healthy diet like the DASH/reduced sodium diet is smaller in magnitude than that observed in trials of drug therapy (about 75% of the drug effect), but still substantial. [40]

The beneficial effects of the healthy DASH diet are suggested to be partly due to the high intake of potassium, calcium and magnesium (two to three times higher compared to the control diet).[6] The average intake of these micronutrients in the Dutch population is already high compared to the intake in the control group from the DASH trial.[26] Therefore, the effect of the healthy DASH diet on blood pressure levels and on outcome variables is expected to be lower in the Dutch population.

Trials on diet and blood pressure studied short-term effects on blood pressure (e.g. one to six months), and did not study effects on health outcomes.[6,7] In the present study we assumed that a dietary intervention lowers long-term blood pressure levels and subsequently reduces risk of CVD, based on the results of trials in which blood pressure was lowered by drug therapy. Possible effects of a dietary intervention via changes in other cardiovascular risk factors were not taken into account. A diet rich in fruits, vegetables and low-fat dairy products, and low in cholesterol and saturated fat, however, also has a beneficial impact on other

cardiovascular risk factors such as total cholesterol, insulin resistance, obesity and atherothrombotic factors like LDL-oxidation and coagulation factors.[9-11] In addition, it may have a beneficial impact on noncardiovascular diseases such as chronic obstructive pulmonary diseases and cancer,[12,13] and it may restore biological normality.[36] Furthermore, it is suggested that a reduction in dietary salt intake may have cardiovascular benefits by mechanisms independent from blood pressure.[50,51] There is also mounting evidence from trials that antihypertensive drugs have direct effects on the cardiovascular system, aside from their blood pressure lowering effects. For example, drugs that lower blood pressure by about the same amount have very different effects on outcomes.[52] Furthermore, the HOPE trial demonstrated that ACE inhibitors provided profound cardiovascular benefits, with only trivial differences in blood pressure between the treatment and control groups.[53,54] This means that the overall health impact of the pharmacological and dietary intervention is potentially larger than expected on the basis of blood pressure levels only.

The aim of the present simulation study was to estimate numbers of cardiovascular events in the general population that could be theoretically prevented by different blood pressure lowering interventions. The practical achievable health benefit will largely depend on the feasibility of the different interventions in a free-living population. Data on feasibility of blood pressure lowering interventions are limited however. Efficacy of drug therapy is determined by compliance of physicians with guidelines for detection and treatment of hypertension, and by compliance of patients with respect to medication use and readiness to control. Compliance of a whole population with the healthy diet from the DASH trial, a controlled feeding study, is even more difficult to achieve than compliance with drug therapy. It requires substantial changes in dietary habits of the public. Therefore, in every day practice the effects of the different intervention strategies described in this paper will be smaller.

We concluded that a large proportion of the Dutch population has elevated blood pressure levels. Adequate detection and treatment of hypertensive patients at high risk is needed because they benefit most of it. Population-wide reductions in blood pressure by changes in diet could however potentially prevent more CVD events than drug treatment. The high risk approach should therefore be complemented by a population approach to effectively control elevated blood pressure in the community and to obtain maximal health benefit.

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CHAPTER 5

General discussion

The aim of this thesis is to provide information from observational studies as a basis for developing effective strategies for management of elevated blood pressure, and to quantify the achievable health benefit in the population by different blood pressure lowering interventions. In this chapter, first the main findings are summarised. Subsequently, the internal and external validity of the results described in this thesis are discussed. Thereafter the strength and shape of the relation between blood pressure and cardiovascular diseases (CVD) in the elderly is discussed. Finally, the implications of our results for public health are delineated.

Main findings

To study long-term persistence (≥ 20 years) of the effects of blood pressure on mortality from coronary heart disease (CHD), i.e. whether elevated blood pressure levels at middle-age lead to increased risk of CHD mortality at older age, we used novel methodology. This methodology was based on repeated measurements of blood pressure over time from the Seven Countries Study (chapter 2.1). It allowed us to separate an independent effect of past systolic blood pressure (i.e. near the time of two repeated measurements taken 5 years apart) on CHD mortality from a proxy effect through 'current' systolic blood pressure (i.e. beyond the latest of the two repeated blood pressure measurements). Our results suggested that past systolic blood pressure does not predict long-term risk of CHD mortality, after adjustment for a proxy effect of current systolic blood pressure, and that the effects of blood pressure on risk of CHD mortality are transient and reversible.

Recently it has been questioned whether the relationship between blood pressure and risk of mortality from coronary, cardiovascular and all causes is strictly increasing.[1] The concept that lower blood pressure implies lower risk is derived mainly from the use of linear models. Using the Seven Countries Study data, we showed that the "linear" model was valid for the relation of systolic and diastolic

blood pressure with mortality from cardiovascular diseases (CVD), but not for all-cause mortality (chapter 2.2). Higher blood pressure was related to higher risk of all-cause mortality over the whole range of blood pressure, but this relation was not strictly linear, i.e. less steap at the lower end of the blood pressure distribution.

Using data from the Seven Countries Study we showed that at identical levels of blood pressure, 25-year rates of mortality from CHD greatly varied among men (age 40-59 years) from different populations (chapter 2.3). Rates were high in the United States and northern Europe and low in Japan and Mediterranean southern Europe. However, the relative increase in long-term mortality from CHD for a given increase in blood pressure was similar among the populations. The overall relative risk of death due to CHD, adjusted for within-subject variability in blood pressure, was 1.28 per 10 mmHg increase in systolic and per 5 mmHg increase in diastolic blood pressure.

To study the relation between blood pressure and cardiovascular endpoints in the elderly, we used data from two prospective studies, one carried out among men aged 65-84 years from Finland, Italy and the Netherlands (the Finland, Italy and the Netherlands Elderly [FINE] Study), and one carried out among men and women aged 55 years and over from the Netherlands (the Rotterdam Study). Results of the FINE Study indicated that elevated pulse pressure was related to an increased risk of CVD mortality. Considering each pressure individually, neither systolic nor diastolic blood pressure were significantly related to mortality from CVD in elderly men from the FINE Study (chapter 3.1). Results from the Rotterdam Study suggested that increasing levels of systolic and diastolic blood pressure were associated with increasing risk of first myocardial infarction and that this relationship, though weaker, persists into older age (chapter 3.2). In both studies among relatively healthy elderly populations we found no evidence for an increased CVD risk at low levels of systolic and diastolic blood pressure.

We quantified the potential impact of different blood pressure lowering interventions on the primary prevention of CVD and on healthy life expectancy in the Netherlands with a simulation model (chapter 4). Within 10 years, 1.8% (n=6,682) of CVD events among subjects aged 40-59 years, and 1.5% (n=7,799) of CVD events among subjects aged 60-74 years could be theoretically prevented if all high-risk individuals were adequately treated pharmacologically according to the revised Dutch consensus guideline.[2] The fraction of CVD events that could be theoretically

prevented with a dietary intervention, aimed at population-wide compliance with a healthy diet, would be 8.6% (n=32,382) and 6.5% (n=32,536) respectively. If the high risk approach would be complemented by the population approach, this could yield a total prevented fraction of CVD events of 10.4% (n=39,064) and 8.0% (n=40,335) within 10 years. The average gain in total and healthy life expectancy in the whole population due to the different interventions was small and ranged from zero to four months, depending on the age and sex of the population.

Methodological considerations

Several methodological issues deserve attention. First, we discuss the internal validity of the results presented in this thesis. Internal validity is the extent to which the results are valid for the target population. It may be influenced by selection bias, within-person variability in blood pressure, measurement method of endpoints, and confounding. Second, the external validity or generalizability of our results is discussed.

Internal validity of results

Selection bias

Selection bias results from procedures used to recruit subjects for a study, that lead to an effect estimate among subjects included in the study which differs from the true estimate in the entire target population.[3] In the Seven Countries Study among middle-aged men (chapter 2), the average response rate was very high (>90%), with several cohorts reaching participation rates of almost 100%. Furthermore, the fraction of subjects excluded from the analyses because of CHD at enrollment (1.9%) or missing data (3.4%) was small (5.3%). Therefore, it is not likely that selection bias has influenced relative risk estimates in the studied middle-aged cohorts.

In the studies among elderly cohorts described in this thesis, the Rotterdam Study and the FINE Study, the target population was the general elderly population (chapter 3). The final study populations were, however, confined to apparently healthy subjects from the general elderly population, due to self-selection of subjects

and post-hoc exclusion criteria. First, in spite of relatively high response rates (70% – 94%), older persons and those with health problems were less likely to participate in both studies.[4,5] Secondly, in both studies we excluded subjects with diagnosed clinical manifestation of the endpoints of interest at the baseline examination and users of antihypertensive drugs (reasons for exclusion: see 'confounding' on page 110 and 111) . Thirdly, in the Rotterdam Study subjects living in nursing homes and subjects with incomplete follow-up at the time of the analysis were excluded. The latter participants were on average older and had lower blood pressure levels. Due to these selections, exclusion from the two study populations was related to health status. It is likely that excluded subjects had more progressive states of atherosclerosis. As this 'health-related' exclusion from the final study population in both studies may be related to blood pressure status independent of its relation to the outcome, relative risk estimates may not be valid for the general elderly population. However, results are judged to be valid with respect to the role of blood presure in the etiology of CVD in apparently healthy subjects from the general elderly population, without manifest CHD and extensive atherosclerosis.

Selective survival may partly explain the observed lower relative risks at older age compared to younger age in both the Rotterdam Study and the FINE Study.[6,7] In the FINE Study, only 43% of the men who already had elevated blood pressure or cholesterol levels at middle-age survived until the baseline examination of the present study. These men who were still alive at old age, were possibly less susceptible to CVD and may have a similar risk for CVD as those with normal levels. Whereas those with high levels of risk factors who are susceptible for CVD, are more likely to have died before reaching old age.

Within-person variability in blood pressure

Successive measurements of blood pressure of individual subjects vary substantially over time, as a result of both random variation and systematic effects.[8,9] Random within-person variability includes classical measurement error from imperfect instruments or observers and biological variation over time due to recent diet, ambient temperature, and so on.[10] An example of a systematic effect is white coat hypertension, i.e. an individual's blood pressure level is elevated when measured in the medical environment (due to anxiousness) but not when measured ambulatory.[11]

For random within-person variability, the average value of many repeated measurements will approach an individual's true exposure level, which is frequently considered as that person's long-term average or usual level.[9] For systematic within-person effects, the average value of many repeated measurements will not approach an individual's true level. To reduce within-person variability in casual blood pressure measurements, standardized methods were used to measure the blood pressure in all studies in this thesis. In these studies systolic and diastolic blood pressure were measured twice at the baseline examination with a sphygmomanometer, on a single occasion. In addition, in the Seven Countries Study and in the FINE Study standardized measurements were repeated after several years. Despite use of standardized measurements, much of the within-person variability in repeated blood pressure measurements persists under usual conditions of observation.[12]

The effect of random within-person variability is generally to bias relative risks estimates toward the null values.[10,13-15] This effect is described by the term 'regression dilution', i.e. the attenuation in a regression coefficient that occurs when a single measurement of blood pressure is used instead of the usual or average value over a period of time.[15] In this thesis, we corrected relative risks for the effect of random within-person variability in blood pressure by relating baseline measurements of blood pressure to replicate measurements at five year (chapter 4: one year) follow-up. For statistical correction there is no need to distinguish between the various sources of random variation, since the effects on associations are the same if the long-term average exposure over several years is of interest.[9] This was the case in the studies described in this thesis. In the Rotterdam Study (chapter 3.2), relative risks estimates were not corrected for the effect of random within-person variability in blood pressure. The magnitude of the dilution in regression coefficients that has occurred due to use of single blood pressure measurements in the Rotterdam Study depends on the ratio of within-person variability to variability between subjects. This ratio is suggested to be larger at old compared to middle-age.[8]

Random within-person variability leads to overestimation of the prevalence of hypertension.[16] We corrected the prevalence of hypertension for the effect of random within-person variability in blood pressure by using correction factors based on repeated blood pressure measurements (chapter 4). These factors were partly derived from an external reproducibility study. Klungel et al showed that the

(remaining) overestimation of hypertension that occurs after this type of correction is only in the order of 4-12%.[17] Therefore, we do not expect to have seriously overestimated the number of untreated hypertensives in the Netherlands needing pharmacological treatment according to the revised guideline,[2] and consequently, the number of CVD events that can be theoretically prevented by treatment of this high-risk group.

Systematic within-person effects may bias relative risk estimates in any direction, depending on the nature of the systematic error and on whether the direction and magnitude of the systematic error affects subjects non-randomly.[9] In case of blood pressure measurement, some elements of systematic within-person effects are likely to exist and can seldom be corrected for. Especially in the elderly cohorts studied in this thesis (chapter 3), increased arterial stiffness and diminished reactivity of the baroreceptor reflex are factors accounting for systematic within-person effects in blood pressure. They may lead to pseudohypertension (falsely increased SBP as determined by the sphygmomanometer) respectively white coat hypertension,[18-20] and are likely to have underestimated relative risk estimates in the elderly cohorts. Furthermore, in the Rotterdam Study, diastolic blood pressure may have been systematically underestimated in elderly subjects with thin arms (arm circumference < 24 cm), due to use of too large a cuff size in these subjects (only one standard cuff size of 14 cm x 38 cm was used in this study).[2] Especially in elderly cohorts it is likely that underweight is related to health status.[21] If DBP was mainly underestimated in a subgroup of elderly subjects with thin arms due to underlying illness, this may have reduced the real effect of DBP in the Rotterdam Study (chapter 3.1). However, we observed a positive relation between DBP and myocardial infarction that might have been even stronger if a potential confounding effect of systematic measurement error had been avoided.

In chapter 4, the prevalence of hypertension in Dutch subjects aged 60-74 years may have been underestimated as it was also based on DBP levels from the Rotterdam Study. Consequently, the number of untreated hypertensives in the Netherlands needing pharmacological treatment according to the revised guideline,[2] and the number of CVD events that can be theoretically prevented by treatment of this high-risk group may have been underestimated.

Measurement of endpoints

In all studies described in this thesis, standardized methods were used to measure fatal and nonfatal endpoints. Because the prevalence of comorbidity is high in the elderly, proper diagnosis of (nonfatal) CVD is difficult in this age group.[7,19] In the Rotterdam Study, the endpoint was a fatal or nonfatal myocardial infarction (MI), including silent MI defined by ECG measurements in the absence of symptoms. Therefore, the prevalence of unrecognized MI is expected to be low in the Rotterdam Study and was probably not a major concern.

In the Seven Countries Study and the FINE Study, the enpoint was only mortality (from CVD and all causes). Also in case of these 'hard' endpoints, however, fatal CVD cases may have been misdiagnosed, especially in the elderly due to the high prevalence of comorbidity. We used only CVD as primary cause of death. In case of multiple causes, we used a hierarchical method to code final causes of death in the following order: violent causes, cancer CHD stroke and other causes. This may have lead to underestimation of the true number of CVD deaths in the Seven Countries Study and the FINE Study.

Confounding

In the etiologic relation between blood pressure and endpoints, a confounder is a factor that is related to both blood pressure and the outcome and is not an intermediate in the causal pathway between both.[3] A confounder is, at least in part, responsible for the apparent association between blood pressure and endpoints.[3] As confounding leads to biased estimates,[3] we adjusted in the statistical analyses for known confounders. It was not always possible to control for all known confounders. For the male population of the Seven Countries Study for instance (chapter 2), no information on the prevalence of diabetes was collected at the enrollment period of the Seven Countries Study in the 1960's. Information on the medical history of diabetes was however collected at 10-year follow-up in all countries except the United States. The prevalence of a medical history of diabetes was low after 10 years in the Seven Countries Study and varied from 1.9% to 5.2% among the different populations. Furthermore, the estimated relative risks of death due to CHD for the 10 to 25-year follow-up period, taking 10-year data as the baseline, did not differ before and after adjustment for diabetes. Both the low prevalence of diabetes

and this similarity in relative risk estimates suggest that diabetes did not influence the observed relations.

Use of antihypertensive medication acts as a confounder of the relation between blood pressure and CVD, as it is related to blood pressure level and may be associated with CVD independently of blood pressure.[22-24] This may lead to the – mistaken – belief that adjustment for antihypertensive therapy (e.g. by means of multivariate regression methods, or by stratification) will lead to a correct estimate of the effect of blood pressure on CVD. In observational studies, allocation to (type and intensity of) drug therapy is not random and depends, besides current blood pressure level, on other factors "X" that may be independent predictors for CVD.[25] These, at least partly, unmeasured factors include past (pretreatment) blood pressure and (family) history of CVD.[2] Treatment is thus affected by both current blood pressure and factors "X". Adjusting for such "collision nodes" (here: treatment) induces (rather than removes!) an association between "X" and blood pressure. The association between blood pressure and CVD is therefore affected by confounding by indication.[26] In this case, statistical methods used to control for confounding by adjusting for medication use (yes/no) do not adequately deal with the bias introduced to the effect estimate.[27] In the Seven Countries Study, information on the use of antihypertensive drugs was not collected at the baseline survey. However, during the period 1958 to 1964 these drugs were rarely prescribed in the seven countries. We could not adjust for initiation of antihypertensive therapy during later years of follow-up in the Seven Countries study. Similarity of relative risk estimates for 10-year CHD mortality to those for 25-year mortality, however, suggests that this has not influenced the observed relationships (see discussion chapter 2.3).

In the elderly cohorts from the Rotterdam Study and the FINE Study (chapter 3), we chose to exclude users of antihypertensive medication at the baseline survey. Reason for this was the high prevalence of antihypertensive drug use among this age group, and the consequently large potential bias that could not be adequately adjusted for. In the Italian cohorts of the FINE Study, only information was available on the use of blood pressure lowering drugs used for treatment of hypertension. These drugs can also be used for other indications but this information was not available. This may have biased estimates of relative risk in the Italian cohorts. In the FINE Study, we could adjust for initiation of antihypertensive therapy during later years of follow-up by including a time-dependent medication variable in the analysis.

Results remained similar after this adjustment. In the Rotterdam Study, we did not adjust for initiation of drug therapy during follow-up. This may have lead to underestimation of the relative risk estimates from this study.

In the elderly, underlying poor health and comorbidity may also lead to a bias in the relation between blood pressure and outcome as they may be related to both reductions or increases (e.g. diabetes) in blood pressure as well as an increased risk of cardiovascular deaths.[28-32] Comorbidity is defined as the co-existence of diagnosed or undiagnosed diseases other than CVD such as cancer and diabetes.[7] Comorbidity is very common in elderly people. In the FINE Study, we adjusted for confounding by comorbidity and underlying poor health in two ways. We included several measured indicators of ill health as additional covariates in the statistical analysis, and we excluded deaths occurring during the first two years of follow-up. In the Rotterdam Study, we could not exclude early events because of the short follow-up period of four years.

The presence of CVD at the baseline survey may act as a confounder, effect modifier or intermediate variable in the relation between blood pressure and CVD. In the first case, it is suggested that pre-existing CVD cause both reductions in blood pressure (through weight loss or some other metabolic disturbance caused by the disease) and excess (recurrent) cardiovascular events.[33] This may effect the strength and nature of the relationship. In case of an effect modifier, the effect of blood pressure on cardiovascular endpoints varies among individuals with and without pre-existing CVD.[3] Though this may be a plausible hypothesis (see page 113 first paragraph), the numbers of events in the groups with prevalent CVD were too small in the studies described in this thesis to study the effects of blood pressure within these groups. In case of an intermediate variable, presence of CVD is an intermediate step in the causal path between blood pressure and risk of (recurrent or fatal) CVD.[3] For instance, an individual's current blood pressure level has lead to presence of myocardial infarction (at the baseline survey), and this subsequently increases risk of a future recurrent (fatal) myocardial infarction. Adjustment for presence of myocardial infarction in this situation will attenuate the observed associations. As blood pressure largely influences endpoints via cardiovascular mechanisms, we chose to exclude subjects with CVD in all studies described in this thesis.

Proper diagnosis of both cardiovascular and non-cardiovascular diseases in the elderly is difficult for several reasons.[7,19] Due to lower pain perception related to autonomic dysfunction, the prevalence of unrecognized clinical diseases is high in the elderly.[19] As an example, the high prevalence of silent myocardial infarction in the elderly may be the result of an increased pain threshold for angina.[19] Confusion and dementia, and the belief of some elderly people as well as clinicians that a certain degeneration in their health is a normal concomitant of aging, may also contribute to a high prevalence of undiagnosed disease.[19] With respect to diagnosis of CVD, frequent concomitant diseases (pulmonary, gastrointestinal, or musculoskeletal disorders) may mask CVD-related symptoms. Due to this high prevalence of undiagnosed and thus unmeasured disease, resulting in residual confounding, relative risk estimates for the elderly cohorts described in this thesis are likely to have been underestimated.

External validity of results

External validity refers to the generalizability of the results. The Seven Countries Study (SCS) and the FINE Study were confined to men. Women were not included in these studies because at the initiation of the SCS around 1960, CHD was viewed as a major health problem of men but not of women. Other large observational studies among middle-aged and elderly populations, in which both men and women are included, indicate that the shape and strength of the relation between SBP and DBP and cardiovascular endpoints is similar in men and women.[34,35] We therefore do not expect that the observed relative effects are different in women. Consistent with this expectation, we found similar relative risk estimates among the older men and women in the Rotterdam Study.

The absolute effect of blood pressure on CHD, i.e. the rate difference or absolute number of excess CHD events due to elevated blood pressure, is generally higher in men than in women.[36,37] This can be explained by higher CHD incidence rates in men compared to women in most westernized countries.[38] In the Rotterdam Study, the observed difference in incidence rate of myocardial infarction (per 10,000 person years) between the highest and lowest blood pressure categories was however similar in men and women. This was possibly due to the small number of events per blood pressure category, resulting in imprecise rate estimates.

We confined all our studies to subjects without manifest CVD at baseline. Moreover, our studies among elderly subjects were carried out in apparently healthy subjects from the general elderly population due to several selections (selections: see page 105, section 'selection bias', second paragraph). Whether our results are generalizable to less healthy subjects with severe atherosclerosis and overt CVD remains to be established. Results from most large observational studies among middle-aged and elderly populations suggest that the relation between blood pressure and cardiovascular endpoints is similar in subjects with and without ischaemic heart disease.[13,32,35,39] In several studies among middle-aged and elderly populations, however, negative or U-shaped relations between DBP and CHD were found in subjects with severe ischaemic heart disease, but not in healthy people without these diseases.[40,41] It is suggested that this is not a treatment-induced causal relation as it was observed both in treated and untreated subjects.[40-43] An explanation could be that in subjects with ischaemic heart disease, a low DBP can add to increased cardiovascular risk by decreasing coronary perfusion pressure and thereby decreasing cardiac oxygen supply.[44] In healthy subjects without atherosclerosis, a decreased coronary perfusion pressure can be compensated by coronary vasodilatation. In subjects with coronary atherosclerosis, however, the vasodilatory reserve is limited and a decreased perfusion pressure, in these circumstances, can lead to decreased oxygen supply.[45]

Results in this thesis concerning elderly populations mainly apply to subjects younger than 80 years of age. The observed relationships of blood pressure with cardiovascular endpoints may be different in subjects older than 80 years of age. In two observational studies, however, similar results were found among elderly subjects below and above the age of 75.[28,35] Data confined to very old cohorts, that adjusted for confounding effects of poor health, are scarce and conflicting.[29,31,46] Two recent community-based studies reported similar findings as observed in populations of younger elderly, i.e. an increased all cause mortality with low systolic and diastolic blood pressure, that was no longer significant after adjustment for poor health indicators (including preexisting cardiovascular diseases, limitation in activities of daily living and cognitive impairment).[29,31] In one of these studies, in elderly with a mean age of 90 years, diastolic blood pressure was positively related to mortality from CVD after adjustment for health status.[29] In contrast to these two studies,

another population-based study in very old subjects reported an inverse relation between blood pressure and all-cause mortality that persisted after adjustment for clinically significant diseases at baseline and exclusion of early deaths.[46] An explanation for these different results could be that the variables measured in the latter study did not completely account for all age-related aspects of poor health. To date, the role of potential confounding factors that might explain this paradoxical relationship in the very old is however not fully established.[47] A possible true modification of age on the impact of blood pressure on health outcomes can not be excluded.[30] It must be emphasized that the endpoint in the 'very elderly' studies was (cardiovascular and all cause) mortality, and not nonfatal cardiovascular morbidity.

In chapter 4 we estimated that more than 79,000 first CVD events could be theoretically prevented within 10 years in the CVD-free Dutch population (age 40-74), if all individuals in that population complied with a healthy diet, and if all high-risk individuals were adequately treated pharmacologically according to the revised Dutch consensus guideline.[2] The number of (recurrent) non-fatal and fatal CVD events that could be theoretically prevented by effective lifestyle intervention and drug therapy in the whole population, including those with established CVD, is expected to be much higher. This can be explained by the enlarging pool of patients with CVD (20% of the 60-74 year aged Dutch population), including coronary patients, due to ageing populations, and the improving prognosis of coronary patients due to more effective treatments for acute coronary heart disease, revascularization and use of prophylactic drug therapies.[48] Results of the second EUROpean Action on Secondary Prevention through Intervention to Reduce Events (EUROASPIRE II) survey, undertaken in 15 countries including the Netherlands, showed a high prevalence of unhealthy lifestyles, modifiable risk factors and inadequate use of drug therapies among coronary patients.[49] Among the Dutch population of coronary patients for instance, 52% had hypertension (≥140/90 mmHg), and less than half of those pharmacologically treated for this condition had their blood pressure levels controlled (<140/90 mmHg).[49] There is thus considerable potential to further reduce CHD morbidity and mortality in the general population through more effective interventions in patients with established CVD, who are at increased risk of CHD and will benefit most of prevention.

Relation between blood pressure and CVD in the elderly

In middle-aged adults, the relationship between SBP and DBP and risk of CVD has been characterized as 'continuous, graded, strong, independent and etiologically significant'.[13,50] Several studies in older subjects (≥65 years) have raised questions about the strength and shape of the association in this age group. Results from several observational studies have suggested that the relation of SBP and DBP with cardiovascular endpoints and with all-cause mortality is attenuated or even absent in the elderly.[35,37,51,52] Moreover, in several studies among elderly cohorts it was concluded that risk of mortality from cardiovascular and all causes was increased at low levels of blood pressure compared to intermediate levels, showing J- or U-shaped relations.[53-55] Furthermore, several other studies in older subjects emphasized the importance of pulse pressure, which combines the effects of both high SBP and low DBP, as a predictor of CVD.[32,34,56,57] Age-related changes in blood pressure may play a role in changing relationships between blood pressure and CVD with age. In this paragraph, we will first describe these age-related changes in blood pressure. Thereafter, we will discuss the observed relations between blood pressure and cardiovascular outcomes among the elderly cohorts in this thesis (chapter 3) in light of the literature.

Age-related changes in blood pressure

Average SBP in most Western populations rises linearly with age until the eigth or ninth decade in both men and women.[58] Average DBP also shows a gradual but less steep rise with age until the age of approximately 55 years in both men and women and subsequently declines.[58] As a consequence, average pulse pressure (= SBP minus DBP) increases progressively with age and the rate of rise accelerates after age 50 years.[58] The rise in SBP and DBP with age up to age 55 years is due mainly to increasing peripheral vascular resistance. The continuous rise in SBP after age 55 is due primarily to increased stiffness of the large arteries, though increased peripheral vascular resistance still contributes. The decrease in DBP after age 55, and the associated steep rise in pulse pressure, are also primarily due to an increase in large artery stiffness.[58] This makes increased pulse pressure and decreasing DBP indicators for large artery stiffness after age 55.[58] Factors that contribute to the increase in peripheral vascular resistance with aging are increased thickness of the

arterial intima and media and decreased elasticity of the connective tissue.[59] It is suggested that large artery stiffness is caused by increased collagen and calcium deposition in the large arteries in combination with a decreased elasticity of the connective tissue.[58] Hypertrophy of the smooth muscle cells in the medial layers of the arteries also contributes to the increase in large artery stiffness with aging.[60]

Blood pressure – CVD relation in the elderly

In this thesis, using data from two population-based studies among elderly subjects, we found no evidence for J- or U-shaped relations of SBP and DBP with endpoints. In contrast, results from the Rotterdam Study suggested that increasing levels of SBP and DBP were associated with increasing risk of first myocardial infarction and that this relationship, though weaker, persists into older age. Results of the FINE Study indicated that neither systolic nor diastolic blood pressure were significantly related to mortality from CVD in elderly men, when viewing each pressure individually. However, elevated pulse pressure was related to increased CVD mortality in the FINE Study. This is in line with the literature.[32,34,56,57,61] Several mechanisms may explain the relation between pulse pressure, as an indicator of large artery stiffness, and CVD. Several cross-sectional studies uniformly showed increased large artery stiffness in subjects with previous CVD.[62-65] Large artery stiffness increases afterload leading to an increase in cardiac oxygen demand.[62-66] Furthermore, it is associated with atherosclerosis [66-69] and with decreased cardiac oxygen supply.[62] This may increase risk of ischaemia in subjects with increased large artery stiffness as their coronary arteries can not compensate for the decreased cardiac oxygen supply.[70] Large artery stiffness is also strongly correlated with left ventricular hypertrophy, a known risk factor for cardiovascular events.[71]

Several factors may explain reduced or J- and U-shaped relations of SBP and DBP with cardiovascular outcomes found in previous studies, and lack of a significant relation observed in the FINE Study. Selective survival (see last paragraph section 'selection bias', page 106) and high baseline rates of cardiovascular events may have weakened the associations in the elderly.[7] In addition, a high prevalence of comorbidity and incomplete adjustment for the confounding effects of co-morbidity may partially explain unclear or J/U-shaped associations. Comorbidity and underlying deteriorating health may cause both reductions in blood pressure and excess events.[28-32] In a large number of studies,

J/U-shaped relations disappeared or changed into positive ones by excluding subjects with known prevalent CVD or subjects who used blood pressure lowering medication, excluding events occuring during the first years of follow-up, or by including several health-related factors as covariates into the statistical model.[28-30,51,54,55] A summary of large observational studies (n>1000) that adjusted for comorbidity and health status is given in table 1.

Based on the consistent results of the studies from table 1, it is concluded that SBP remains an important risk factor for CHD and for CVD and all-cause mortality in the elderly, showing higher risk at higher levels of SBP. Results from observational studies are confirmed by a meta-analysis of clinical trials.[72] This meta-analysis showed significant reductions in stroke, coronary events, and in CVD and all-cause mortality by antihypertensive drug treatment in elderly patients with isolated systolic hypertension. Our finding from the Rotterdam Study concerning SBP and risk of myocardial infarction in the elderly is in line with the evidence from observational studies and trials.

The literature is not conclusive on the relation of DBP with cardiovascular endpoints and with all-cause mortality, also when the studies were restricted to those that adjusted for poor health (table 1). Some studies reported positive relations,[28,34,37,57] but others found no or J/U-shaped relations.[32,35,55] Currently it is strongly suggested that, at least in elderly subjects without severe atherosclerosis and ischaemic heart disease, a *low* DBP is not causally related with an increased risk of CVD. There is mounting evidence that underlying large artery stiffness and increased comorbidity lead to a decline in DBP and are the primary factors causing increased cardiovascular risk, with low DBP being mostly a secondary phenomenon.[32,56] This may also partly explain the discrepant results with respect to the effect of *elevated* DBP. That is, studies that found increasing risk at increasing levels of DBP may have been less confounded by low DBP due to large artery stiffness. Whereas in studies that found no positive relation between DBP and CVD, relations may have been masked by a considerable number of subjects with an increased cardiovascular risk in combination with a low DBP due to large artery stiffness. Results from two large observational studies support this hypothesis. Researchers from the Framingham Study reported a positive relation between DBP and risk of CHD.[34] The number of subjects with a low DBP together with a high SBP, i.e. with an elevated pulse pressure indicating large artery stiffness, was however

Table 1. Summary of observational studies (n>1000) on the relation between blood pressure and mortality from cardiovascular and all causes in elderly subjects that adjusted for comorbidity and health status.

Study	Reference	No.	Age	Follow-up	Fatal Endpoint(s)	No. of Events	Relation Blood pressure - endpoint			Analysis Adjusted for	Excluded from the analysis
							SBP	DBP	PP		
			years					mm Hg			
East Boston Senior Health Project	Glynn ea 1995[28]	3657	≥65	10.5	CVD	567	+	+	n.a.	a,b,c,d,e,f,g,h.i .j.k	1
					All causes	1223	+	+ (n.s.)	n.a.	a,b,c,d,e,f,g,h.i .j.k	1
Norway	Vatten ea 1995[55]	18022	≥65	6	All causes	4700	men: 0	U	n.a.	a,c,e,l,m	1, 2
							women: 0	0	n.a.	a,c,e,l,m	1, 2
SPAA	Alli ea 1999[35]	3858	≥65	10	CVD	709	+	0	n.a.	a,b,c,d,e,g,j,k, l,n,o,p	no exclusions
					All causes	1561	+	0	n.a.	a,b,c,d,e,g,j,k, l,n,o,p	no exclusions
Framingham Heart Study	Franklin ea 1999[34]	1924	50 - 79	14.3	CHD *	433	+	+	+	a,b,c,d,l,q	2,3
EPESE	Glynn ea 2000[32]	9413	≥65	10.6	CVD	2304	+	0	+	a,b,c,d,e,f,g,h, i,j,k, †	no exclusions
					All causes	4528	+	0	+	a,b,c,d,e,f,g,h, i,j,k, †	no exclusions
The Cardiovascular Health Study	Psaty ea 2001[57]	5888	≥65	6.7	MI *	572	+	+	+	a,b,d,e,l	no exclusions
					Stroke *	385	+	+	+	a,b,d,e,l	no exclusions
					All causes	896	+	0	0	a,b,d,e,l	no exclusions

CVD cardiovascular diseases, MI myocardial infacrtion, SPAA Studio sulla Pressione Arteriosa nell'Anziano, EPESE Established Populations for Epidemiologic Studies of the Elderly; + positive relation, *0* no relation, *U* U-shaped relation; n.a. not applicable; *a* age, *b* sex, *c* body mass index, *d* smoking, *e* history of CVD, *f* history of cancer, *g* use of antihypertensives, *h* activities of daily living, *i* physical function, *j* activity level, *k* use of alcohol, *l* diabetes, *m* self-assessed health, *n* cognitive impairment, *o* history of hypertension, *p* frailty, *q* total cholesterol/HDL ratio; *1* events occuring during first years of follow-up, *2* use of antihypertensives *3* CVD history; * fatal and non-fatal;† relation between diastolic blood pressure and endpoint additionally adjusted for pulse pressure

very low (n=39) in that study. In contrast, researchers from the EPESE Study found a U-shaped relation between DBP and mortality from CVD and all causes.[32] The number of subjects with an elevated pulse pressure, and thus the number of subjects with a low DBP probably due to large artery stiffness, was much larger in this study (n=571). Moreover, in the latter study the U-shaped relation disappeared after including pulse pressure as a suggorate measurement for large artery stiffness into the statistical model. This finding suggests that underlying large artery stiffness at least partly explains the unclear relation of DBP with endpoints in elderly populations.

In conclusion, it is suggested that, at least in elderly subjects without severe atherosclerosis and ischaemic heart disease, increasing DBP is related to increased cardiovascular risk. The positive relation of DBP with risk of myocardioal infarction in the Rotterdam Study described in this thesis is in line with the evidence from literature. Further support that elevated DBP remains a cardiovascular risk factor in the elderly comes from the Hypertension Optimal Treatment (HOT)-trial.[73] Results from this trial showed that a gradual reduction in risk of stroke and cardiovascular events occurs when lowering DBP from 105 mmHg to at least 80-85 mmHg.[73]

Public health implications

In clinical medicine a high risk approach to CVD prevention is generally favored. Mainly patients with severe hypertension and patients with mild or moderate hypertension who have a high short-term absolute risk to develop CVD, i.e. 20% or more within 10 years, are treated. Most individuals have however average, mildly or moderately elevated blood pressure levels and a short-term absolute CVD risk less than 20% within 10 years. The greater part of these individuals with suboptimal blood pressure levels will not be eligible for treatment in a high risk strategy. As any increase in blood pressure is associated with an increase in the relative risk for CVD, however, these individuals do have an increased CVD risk. These associations and the large number of individuals with blood pressure levels above optimal (who will not be targeted by clinicians) indicate that the avoidable burden of CVD among this group is considerable.[36,74] A population strategy, aimed at moderate blood pressure reductions in the population as a whole, will therefore have a much larger potential

for reducing the burden of CVD in our population than a high risk strategy.[75] Small population-wide reductions of blood pressure and subsequent reduction in CVD mortality may be achieved by stimulating lifestyle changes, such as changes in diet and increased physical activity, in the total population. This can be illustrated by the remarkable decrease in CHD mortality in Finland during the period 1972 to 1992, that occurred at the same time as reductions in major risk factors such as blood pressure, cholesterol and smoking. A reduction in the consumption of salt and saturated fat and a substantial increase in the consumption of vegetables and fruit in Finland starting in the early 1970s have been important determinants.[76,77]

Using statistical modeling we showed that within 10 years, at least four times as much (i.e. 64,918 versus 14,481) CVD events could *theoretically* be prevented in the Netherlands by a population-wide dietary intervention, compared with drug therapy confined to high-risk individuals (chapter 4). A high risk approach should therefore be complemented by a population approach to achieve maximal health benefit for the total population.

The health benefit that can be achieved in *practice* will largely depend on the feasibility of the interventions in a free-living population. Adequate management of hypertensive individuals with a high absolute risk depends on several factors. First, it depends on the sensitivity and specificity of detection of hypertension by physicians. According to the revised Dutch hypertension guideline, physicians are recommended to measure blood pressure only in patiens with an increased risk of CVD due to presence of other risk factors (such as diabetes and elevated cholesterol level).[2] Patients with severe hypertension without a known history of high blood pressure and without unfavorable levels of other risk factors are thus not likely to be detected by these guidelines.[2] Using statistical modeling (chapter 4), we estimated that 69% of patients who are potentially eligible for antihypertensive drug therapy are detected if physicians follow detection guidelines (69% sensitivity).

After having detected and diagnosed a patient as hypertensive, the effect of treatment on blood pressure depends on subsequent management strategies of physicians. Many physicians find it difficult to accurately assess cardiovascular risk and are not agressive enough in their approach to hypertension.[78,79] Compliance of patients with respect to intake of medication and readiness to let their blood pressure levels regularly be controlled by their physician, also determine the success of treatment.[2] It is suggested that, due to inadequate management of hypertension, this

condition is currently uncontrolled (≥140/90 mmHg) in about 50% of treated patients.[2] In line with this, Klungel et al estimated that 33% of drug treated hypertensives in the Netherlands still have blood pressure levels above 160/90 mmHg.[16]

However, management of hypertension in high-risk individuals can possibly be much improved.[2] In a pilot screeningsproject among Dutch general practitioners, the feasibility of systematic detection and (eventually) treatment of patients with an increased cardiovascular risk, including those with hypertension, has recently been studied. Results from this project suggest that systematic management is feasible in clinical practice.[80] Use of a simple computer program to estimate a patient's cardiovascular risk profile can further facilitate hypertension management.[2] Feasibility of blood pressure management in clinical practice can also be improved by additional support of ancillary personnel (physician assistants, practice nurses, dieticians) and by use of electronic patient registers.[80,81] In addition, clinicians can improve the effects of treatment by improving the information and assistance to their patients, and by improved anticipation of failure of therapy by adapting the dose or the type of medication.[2,80] An improved understanding of patients beliefs and behaviors about pharmacological and behavorial treatment options may assist clinicians in developing more effective treatment strategies.

To model the health benefit that can be potentially achieved by blood pressure lowering through adherence of a 'healthy diet' in the general population, we used results from the Dietary Approaches to Stop Hypertension (DASH) and the DASH-Sodium trial.[82,83] These trials are controlled dietary interventions, in which people were supplied with diets and in which adherence to the study diets was very high (>90%). In a free-living population, achieving blood pressure lowering by adherence to the DASH diet requires large changes in dietary habits from the whole population.

No community-based interventions have currently been performed that specifically studied the effect of diet on blood pressure levels in a free-living population. Several community intervention programs aimed at improving healthy life-style, including nutrition, have been conducted however.[84-88] Some of these programmes were directed at the community as a whole,[84,86,87] while others were

directed at specific populations (elderly) or sites (work).[88] All programmes focused on simultaneously lowering levels of multiple determinants (such as smoking, cholesterol and blood pressure). In most programmes, blood pressure levels were lowered by 1-4% due to intervention.[89] These reductions are lower than those observed in small scale controlled intervention studies as the DASH trial. As expected, interventions among high-risk groups were more effective than those focused on the general population.[89] Since these studies had a multifactorial approach, it is not possible to distinguish the contribution of dietary change from effects of changes in smoking behavior and pharmacological treatment of blood pressure. However, as mentioned earlier, blood pressure levels were markedly reduced in Finland in the period 1972 – 1992 and general dietary changes seem to have been an important determinant.[76]

An alternative to community-wide changes in dietary behavior are changes in the nutrient composition of foods. This type of modifications do not require active participation of individuals but can be provided to the entire population, and may be an attractive and effective alternative. As an illustration, we calculated that at least 70% of the decline in CVD incidence rate achieved by the DASH/reduced sodium diet could also be achieved by blood pressure lowering through replacement of one third of daily salt consumption by a low sodium, high potassium mineral salt, largely by consumption of industrial foods containing mineral salt.[90] An intervention study has shown that use of 2g/day of this salt lowers SBP by 8 mmHg.[90]

To be most effective, a community dietary intervention should not focus solely on educating the public about the effects of (un)healthy dietary patterns, and about the skills for changing them. It should also incorporate understanding of the barriers preventing dietary change.[89] Furthermore, population-wide educational interventions should be complemented with structural measures that facilitate and reinforce sustainable changes in dietary behaviour of individuals throughout life.[89] These measures include improved accessibility to healthy foods, price policies, development of sound nutrition policies by the government, and involvement of the food industry, food distributors, retailers (e.g. supermarkets, restaurants) and consumers.

Involvement of physicians may link the population dietary and lifestyle strategy to the high-risk strategy. Physicians and other health care practitioners (practice nurses, dietitians) can facilitate and support hypertensive patients in their

efforts to favorably modify life habits.[91,92] Involvement of physicians in the application of non pharmacological therapy such as changes in dietary behavior offers the greatest assurance that a combination of pharmacological and non-pharmacological therapy will be used appropriately.[91]

In conclusion, community control of blood pressure both by pharmacological therapy of high-risk individuals and by population-wide changes in diet and lifestyle is difficult to achieve and requires commitment from individuals, community resources and health care professionals. This two-pronged approach however has several advantages. First, it will prevent hypertension in those with high-normal levels and thereby reduce the prevalence of hypertension in adulthood and at older ages.[11] Secondly, in subjects with hypertension, the substantial reduction in blood pressure that can be achieved by dietary changes might be an effective alternative to drug therapy in people with stage I hypertension (SBP 140-159 and/or DBP 90-99) and might prevent or delay the initiation of drug therapy in people with blood pressure levels near the thresholds for drug treatment.[82] Thirdly, a strategy aimed at population-wide lifetime prevention of CVD is likely to be more cost-effective in the long-term than one that is mainly focused on treatment of high-risk hypertensive individuals.[91] Fourthly, if populations are willing and able to make the necessary dietary changes, a high risk approach complemented by a population approach could *theoretically* reduce the occurrence of blood-pressure-related CVD by 9% within 10 years (this thesis). The overall potential health benefit of the combined pharmacological and dietary intervention is expected to be larger than that expected on the basis of blood pressure levels alone. The DASH diet also has a beneficial impact on other cardiovascular risk factors than blood pressure such as cholesterol,[93] and on noncardiovascular diseases (chronic obstructive pulmonary disease, cancer).[94,95] Furthermore, there is mounting evidence from trials that antihypertensive drugs have direct beneficial effects on the cardiovascular system, aside from their blood pressure lowering effects.[22-24]

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Summary

Although the age-specific mortality rates from cardiovascular diseases (CVD) are decreasing, CVD are still the number one cause of death in the Netherlands, with yearly over 50,000 men and women dying from these diseases. As elevated blood pressure is an important risk factor for CVD, and because it has a high prevalence, the health benefit that can be achieved by blood pressure lowering is potentially large.

The main aim of this thesis was to quantify the impact of different blood pressure lowering interventions on different health outcomes in the Netherlands. This requires knowledge of the relation between blood pressure and CVD. Data from several population-based observational studies were used to study the (strength and nature of) the relation between blood pressure and CVD. Specific attention was paid to the effect of within-subject variability in blood pressure on the strength of the relation, the shape and duration of the relation, and the relation among elderly subjects.

It is known that lower blood pressure is related to lower risk of CVD. Accurate data on the strength of this relationship, corrected for within-subject variability in blood pressure, are however lacking. The exact nature of the relation, e.g. continuous or non-continuous, temporal or persistent, is also unclear. In most large observational studies, it has been demonstrated that blood pressure continuously lowers risk, without a threshold were below blood pressure is no longer related to CVD. However, a recent reanalysis of Framingham data contests this viewpoint and suggested the existence of such a threshold. In addition, more insight into the duration of the harmful effects of blood pressure on CVD may support an intervention strategy aimed at achieving blood pressure lowering in the total population. Finally, the relation between blood pressure and CVD in the elderly is still controversial and needs more evidence.

To gain more insight into the strength and nature of the relationship between blood pressure and CVD, and on the absolute impact of blood pressure on CVD in the middle-aged, we used data from the Seven Countries Study (**chapter 2**). In this study, more than 12,000 men aged 40 to 59 years who resided in seven countries were enrolled between 1958 and 1964.

In **chapter 2.1** long-term persistence (≥ 20 years) of the effects of blood pressure on mortality from coronary heart disease (CHD), i.e. whether elevated blood pressure levels at middle-age lead to increased risk of CHD mortality at older age, was studied using a novel methodology. This methodology was based on repeated measurements of blood pressure over time from the Seven Countries Study. It allowed us to separate an independent effect of past systolic blood pressure (i.e. near the time of two repeated measurements taken five years apart) on CHD mortality from a proxy effect through "current" systolic blood pressure (i.e. beyond the latest of the two repeated blood pressure measurements). Our results suggested that past systolic blood pressure does not predict long-term risk of CHD mortality, after adjustment for a proxy effect of "current" systolic blood pressure, and that the effects of blood pressure on risk of CHD mortality are transient and reversible. Application of this novel methodology in other observational studies is however required to decide on the consistency of this finding.

In **chapter 2.2** the Seven Countries Study data were used to examine whether lower blood pressure continuously lowers risk of CVD and all-cause mortality, and whether this relation is strictly linear. The Seven Countries Study corroborated the conventional "linear" model for the relation of CVD mortality with systolic and diastolic blood pressure, but not for the relation of these pressures with all-cause mortality. Lower blood pressure was related to lower risk of all-cause mortality over the whole range of blood pressure, but this relation was weaker at the lower end of the blood pressure distribution. In contrast, results from the Framingham Study suggested that systolic blood pressure was not related to mortality from CVD and all-causes for all pressures below an age- and sex-dependent threshold. The difference between both studies may be due to the greater power of the Seven Countries Study and to differences in study populations.

In **chapter 2.3**, the relative and absolute risk of blood pressure on mortality from CHD were compared between the different populations of the Seven Countries Study. At systolic and diastolic blood pressures of about 140 and 85 mmHg respectively, 25-year rates of mortality from CHD 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 relative risk (RR) of death due to CHD was 1.17 (95% confidence interval [CI] 1.14 to 1.20) per 10 mmHg increase in systolic pressure and 1.13 (95% CI 1.10 to 1.15) per 5 mmHg increase in diastolic blood pressure, and increased to 1.28 for each of these increments after adjustment for within-subject variability in blood pressure. In conclusion, the increase in the relative risk of death from CHD for a given increase in blood pressure was similar among populations but the absolute risk at a given blood-pressure value varied substantially.

The implications of the results from chapter 2.3 for treatment and prevention of elevated blood pressure were described in **chapter 2.4**. The results emphasized the limited usefulness of hypertension as a diagnostic category in clinical decision making, and the importance of an individual's total risk of developing CHD, based on a combination of risk factors. In recent guidelines, a 10-year absolute CHD risk greater than 20% is arbitrarily defined as a risk sufficiently high to justify the selective use of antihypertensive drug therapy in healthy individuals. Our results showed that according to this 'absolute risk' criterion, a higher percentage of men in the USA and northern Europe with mild and moderate hypertension would be treated for this condition than in Japan and the Mediterranean. Finally, it was concluded from our results that a population strategy, aimed at moderate blood pressure reductions in the population as a whole by stimulating lifestyle changes, such as changes in diet, would theoretically result in a much larger absolute decline in the number of CHD cases than a high risk strategy.

In **chapter 3** the relation between blood pressure and CVD in the elderly was studied. For this, we used data from two population-based prospective studies; one carried out in Finland, Italy and the Netherlands (the FINE Study), and one in the Netherlands (the Rotterdam Study). The relation of systolic, diastolic and pulse pressure with mortality from CVD was studied in the FINE Study among 1152 men aged 65 to 84 years without a history of CVD and not taking antihypertensive medication (**chapter 3.1**). During 10 years of follow-up, 201 men died from CVD. Neither systolic nor diastolic blood pressure were individually associated with mortality from CVD in elderly men in each separate country, and in the total population of the FINE Study. In each separate country, pulse pressure was positively but not significantly related to cardiovascular mortality. In the pooled

analysis, however, men in the highest tertile of pulse pressure (≥73 mmHg) had a significantly increased risk of cardiovascular mortality (RR=1.54, 95% CI 1.06-2.24) compared to men in the lowest tertile (<59 mmHg), and the increase in risk per 10 mmHg increase in pulse pressure was borderline significant (RR=1.08, 95% CI 1.00-1.18).

In **chapter 3.2** the relations of systolic and diastolic blood pressure with risk of fatal or nonfatal myocardial infarction were studied in the Rotterdam Study among 3731 men and women aged 55 years and over without a history of myocardial infarction and not taking antihypertensive medication. During 4 years of follow-up, 81 subjects had a first myocardial infarction. Increasing levels of systolic and diastolic blood pressure were associated with increasing risk of first myocardial infarction. The RR of first myocardial infarction was 5.7 (95% CI 1.9-17.1) for a systolic blood pressure of 160 mmHg or higher compared with a pressure below 120 mmHg (p for trend < 0.0001). For diastolic blood pressure, the RR reached 2.5 (95% CI 1.4-4.5) in subjects with values between 80 and 90 mmHg compared with subjects with a diastolic blood pressure below 70 mmHg (p for trend < 0.05). Subgroup analyses in subjects aged 70 years and over showed that the positive associations between SBP and DBP and risk of first myocardial infarction remained at older age, though weaker. In addition, there was no evidence for a gender difference in the association of systolic and diastolic blood pressure with risk of first myocardial infarction in the elderly.

In conclusion, in both studies among relatively healthy elderly populations we found no evidence for a J- or U-shaped relation between systolic and diastolic blood pressure and CVD. Persistence of a positive relation between systolic blood pressure and risk of myocardial infarction among elderly in the Rotterdam Study is consistent with evidence from other observational studies and randomised trials on systolic blood pressure and CHD in the elderly. Literature on the relation of diastolic blood pressure with both end-points is less consistent. Lack of associations of systolic and diastolic blood pressure with CVD mortality in the FINE Study may be due to residual confounding by incomplete adjustment for all aspects of poor health. The positive association between pulse pressure and CVD mortality among elderly in the FINE Study is in line with the results from other recent studies. It is suggested that pulse pressure, which is an indicator of large-artery stiffness and incorporates

the combined effects of both high systolic blood pressure and low diastolic blood pressure, is at least as important in predicting cardiovascular risk in the elderly as both pressures individually.

We quantified the potential impact of different blood pressure lowering interventions on the primary prevention of CVD and on healthy life expectancy in the Netherlands with a simulation model that used several sources of information (**chapter 4**). Recent individual data from two large Dutch population-based studies, including in total 13,309 men and women aged 40 to 74 years, were used to estimate the distribution of risk factors in the Netherlands. The Framingham equation was used to estimate the individual risk to develop a cardiovascular event in the next 10 years, based on a combination of risk factors. To estimate the effects of different interventions on blood pressure levels, data from clinical trials were used. We simulated a high-risk pharmacological intervention and a population-wide dietary intervention. In the pharmacological intervention, all hypertensive individuals with a high absolute risk of CVD were treated with blood pressure lowering medication, according to the revised Dutch consensus guideline for high blood pressure (CBO 2000). In the dietary intervention, all individuals complied with a healthy diet rich in fruits, vegetables and low-fat dairy products and with low intake of salt. In total, 1.8% (n=6,682) of CVD events among subjects aged 40 to 59 years, and 1.5% (n=7,799) of CVD events among subjects aged 60 to 74 years could be prevented within the next 10 years by pharmacological treatment of high-risk individuals according to the Dutch consensus guideline. The prevented number of CVD events within the next 10 years in the population-wide dietary intervention would be 8.6% (n=32,382) and 6.5% (n=32,536), respectively. These results show that a high risk approach complemented by a population approach is needed to effectively control elevated blood pressure in the community and to obtain maximal health benefit. Furthermore, blood pressure lowering in the whole population via changes in diet may be an effective tool for population-wide prevention of CVD.

In **chapter 5** we first discussed the main findings of the studies described in this thesis with respect to methodological aspects of epidemiological research on the relation between blood pressure and CVD. Important methodological issues were the effects of within-person variability in blood pressure on the strength of the relation, how to deal with users of blood pressure lowering medication and persons with a history of CVD in the analyses, and residual confounding by comorbidity and poor

health. The latter is an important issue in epidemiological research in elderly populations because of the high prevalence of comorbidity, and the difficulty of proper diagnosis of diseases in this age group.

Finally, the implications of the findings for public health were discussed. It was concluded that community control of blood pressure both by effective pharmacological therapy of high-risk individuals and by population-wide measures could *theoretically* reduce the occurrence of CVD by at least 10% within 10 years in the Dutch population. To reach this considerable health benefit, commitment from individuals, community resources and health care professionals is required.

Samenvatting

Hart- en vaatziekten vormen nog steeds de belangrijkste doodsoorzaak in Nederland, ondanks een daling in de leeftijd-specifieke sterfte sinds 1972. Jaarlijks overlijden meer dan 50.000 mensen hieraan. Een verhoogde bloeddruk, gedefinieerd als een bovendruk (systolische bloeddruk) van 140 mmHg of hoger, een onderdruk (diastolische bloeddruk) van 90 mmHg of hoger, of beide, is een belangrijke risicofactor is voor hart- en vaatziekten. Omdat een verhoogde bloeddruk oftewel hypertensie veel voorkomt, kunnen maatregelen die gericht zijn op verlaging van de bloeddruk tot uitstel of preventie van hart- en vaatziekten leiden.

Het voornaamste doel van dit proefschrift was het kwantificeren van het potentiële effect van verschillende bloeddrukverlagende interventies op het aantal gevallen van hart- en vaatziekten, en op de gezonde levensverwachting, in Nederland. Hiervoor is kennis nodig over de relatie tussen bloeddruk en hart- en vaatziekten. Gegevens uit verschillende observationele onderzoeken zijn gebruikt om de (sterkte en aard van de) relatie tussen bloeddruk en hart- en vaatziekten te bestuderen. Specifieke aandacht is hierbij besteed aan het effect van binnen-persoonsvariatie in bloeddruk op de sterkte van de relatie, de continuïteit en duur van de relatie, en de relatie bij ouderen.

Het is bekend dat lagere bloeddrukwaardes de kans op het krijgen van een hart- en vaatziekte verkleinen. Nauwkeurige gegevens over de sterkte van dit verband, waarbij rekening is gehouden met variatie in de bloeddruk binnen personen, ontbreken echter. Ook is de precieze aard van de relatie, dit wil zeggen continu of niet-continu, tijdelijk of langdurig, onduidelijk. In de meeste observationele studies is aangetoond dat een lagere bloeddruk continu tot een lager risico leidt, en er geen (drempel)waarde van de bloeddruk bestaat, waar beneden deze niet gerelateerd is aan hart- en vaatziekten. De resultaten van een recente analyse van gegevens uit de Framingham Studie suggereren echter het bestaan van een dergelijke drempelwaarde. Verder kan beter inzicht in de duur van het schadelijk effect van bloeddruk op hart- en vaatziekten een interventiebeleid ondersteunen dat gericht is op het bereiken van bloeddrukverlaging in de gehele bevolking. Tot slot is de relatie tussen bloeddruk en hart- en vaatziekten bij ouderen nog controversieel en dient verder onderzocht te worden.

Om kennis te vergroten over de sterkte en aard van de relatie tussen bloeddruk en hart- en vaatziekten, en het absoluut risico op hart- en vaatziekten bij een bepaalde hoogte van de bloeddruk, hebben we gegevens van de Zeven Landen Studie geanalyseerd (**hoofdstuk 2**). Aan het basisonderzoek, in de periode 1958-1964, namen meer dan 12.000 mannen van middelbare leeftijd deel. In **hoofdstuk 2.1** is onderzocht of het schadelijk effect van verhoogde bloeddruk langdurig is, en een verhoogde bloeddruk op middelbare leeftijd (40-59 jaar) tot een verhoogd risico op sterfte aan coronaire hartziekten op oudere leeftijd leidt (≥ 65 jaar). Hiervoor hebben we een nieuwe methode toegepast. De methode is gebaseerd op het gebruik van herhaalde metingen van de bloeddruk over een periode van meerdere jaren, afkomstig uit de Zeven Landen Studie. Het is op deze wijze mogelijk het onafhankelijk effect van eerder gemeten bloeddruk (gedefinieerd op grond van twee bloeddrukmetingen met een tussenliggende periode van vijf jaar) op sterfte aan coronaire hartziekten te scheiden van een proxy-effect van de 'huidige' bloeddruk (gedefinieerd als de bloeddruk in de tijdsperiode ná de tweede herhaalde bloeddrukmeting). Onze resultaten suggereren dat 'eerdere' bloeddruk geen voorspeller is voor lange-termijn sterfte (≥ 20 jaar) aan coronaire hartziekten ná correctie voor een proxy-effect van de 'huidige' bloeddruk. Ze duiden erop dat het risicoverhogend effect van bloeddruk op sterfte aan coronaire hartziekten slechts tijdelijk en reversibel is. Toepassing van deze methode in andere observationele studies is echter nodig om vast te stellen of dit resultaat reproduceerbaar is.

In **hoofdstuk 2.2** zijn gegevens van de Zeven Landen Studie gebruikt om te onderzoeken of een lagere bloeddruk continu tot een lager risico op cardiovasculaire en totale sterfte leidt, en of dit verband lineair is. Onze resultaten laten zien dat gebruik van het lineair statistisch model valide is voor de relatie van systolische en diastolische bloeddruk met sterfte aan hart- en vaatziekten, maar niet voor de relatie van beide bloeddrukken afzonderlijk met totale sterfte. Het risico op totale sterfte neemt weliswaar af met afnemende bloeddruk, maar deze relatie is zwakker voor lagere bloeddrukniveaus. In de Framingham Studie werd daarentegen gevonden dat systolische bloeddruk niet gerelateerd is aan cardiovasculaire en totale sterfte bij personen met een bloeddrukniveau beneden een gegeven drempelwaarde. De inconsistentie tussen beide studies kan het gevolg zijn van onvoldoende power in de Framingham Studie en van verschillen in onderzoekspopulaties.

In **hoofdstuk 2.3** hebben we het absolute en relatieve risico van bloeddruk op sterfte aan coronaire hartziekten vergeleken tussen de verschillende populaties van de Zeven Landen Studie. Bij een systolische en diastolische bloeddruk van circa 140 en 85 mmHg, respectievelijk, varieerde de 25-jaars sterfte aan coronaire hartziekten met een factor van meer dan drie tussen de populaties. In de Verenigde Staten en Noord-Europa was de sterfte aan coronaire hartziekten hoog (circa 70 sterfgevallen per 10.000 persoonsjaren [pj]), terwijl deze in Japan en Mediterraan Zuid-Europa laag was (circa 20 sterfgevalen per 10.000 pj). De toename in het 25-jaars risico op sterfte aan coronaire hartziekten voor een gegeven toename in de bloeddruk, het zogenaamde relatieve risico (RR), verschilde niet tussen de populaties. In de totale populatie van de Zeven Landen Studie bedroeg het relatieve risico 1,17 (95% betrouwbaarheidsinterval [BI] 1,14–1,20) per 10 mmHg toename in de systolische bloeddruk en 1,13 (95% BI 1,10–1,15) per 5 mmHg toename in de diastolische bloeddruk. Na correctie voor binnen-persoonsvariatie in bloeddruk nam het relatieve risico voor beide bloeddrukken toe tot 1,28. Concluderend kan gesteld worden dat het relatieve risico op sterfte aan coronaire hartziekten, geassocieerd met een gegeven toename in de bloeddruk, vergelijkbaar was tussen de verschillende populaties van de Zeven Landen Studie, terwijl het absolute risico bij een zelfde bloeddrukniveau sterk verschilde.

De gevolgen van de resultaten uit hoofdstuk 2.3 voor de behandeling en preventie van verhoogde bloeddruk werden beschreven in **hoofdstuk 2.4**. De resultaten benadrukken de beperkte bruikbaarheid van hypertensie alléén als diagnostisch criterium voor behandeling en ze geven het belang aan van individuele risicoschatting op basis van het absolute risico voor coronaire hartziekten. In recente richtlijnen voor de klinische praktijk wordt een multifactorieel absoluut 10-jaarsrisico op coronaire hartziekten groter dan 20% gedefinieerd als een voldoende hoog risico om het voorschrijven van antihypertensiva bij gezonde personen te rechtvaardigen. Onze resultaten laten zien dat bij elke bloeddrukwaarde dit 'absolute-risico'-criterium vaker wordt overschreden in de Verenigde Staten en Noord-Europa dan in Japan en de mediterrane landen. Tot slot kunnen we op basis van de resultaten concluderen dat een strategie gericht op het bereiken van een matige bloeddrukverlaging in de gehele bevolking, middels veranderingen in leefstijlfactoren zoals voeding, in theorie tot een veel grotere absolute vermindering in het aantal gevallen van coronaire hartziekten zal leiden dan een hoogrisicostrategie.

In **hoofdstuk 3** werd de relatie tussen bloeddruk en hart- en vaatziekten bij ouderen onderzocht. Hierbij maakten we gebruik van gegevens van twee prospectieve studies: één onderzoek uitgevoerd in Finland, Italië en Nederland (de Finland, Italy and the Netherlands Elderly [FINE] studie), en één uitgevoerd in Nederland (de Erasmus Rotterdam Gezondheid en Ouderen [ERGO] studie). De relatie tussen systolische, diastolische bloeddruk en polsdruk en sterfte aan hart- en vaatziekten werd bestudeerd in de FINE studie bij 1152 mannen van 65-84 jaar (**hoofdstuk 3.1**). Alle mannen hadden geen (geschiedenis van) hart- en vaatziekten tijdens het basisonderzoek en gebruikten geen bloeddrukverlagende medicatie. Gedurende een follow-up periode van 10 jaar stierven 201 mannen aan hart- en vaatziekten. Systolische en diastolische bloeddruk waren individueel niet gerelateerd aan sterfte aan hart- en vaatziekten in elk van de drie landen, en in de totale populatie van de FINE studie. In elk land afzonderlijk was polsdruk niet-significant positief geassocieerd met sterfte aan hart- en vaatziekten. Echter, wanneer de drie landen werden samengenomen, hadden mannen in het hoogste tertiel van de polsdruk (≥ 73 mmHg) een significant verhoogd risico op sterfte aan hart- en vaatziekten in vergelijking met mannen in het laagste tertiel (<59 mmHg). De relatieve toename in het risico op sterfte aan hart- en vaatziekten per 10 mmHg toename in polsdruk was op de grens van statistische significantie (RR 1,08, 95% BI 1,00-1,18).

In **hoofdstuk 3.2** is de relatie tussen systolische en diastolische bloeddruk en het risico op een myocard infarct onderzocht in de ERGO studie bij 3731 mannen en vrouwen van 55 jaar en ouder. De onderzochte personen hadden geen (geschiedenis van) myocard infarct tijdens het basisonderzoek en gebruikten geen bloeddrukverlagende medicatie. Tijdens een follow-up periode van gemiddeld vier jaar ontwikkelden 81 personen een eerste myocard infarct. Toenemende niveaus van systolische en diastolische bloeddruk waren gerelateerd aan een toenemend risico op een eerste infarct. Het relatieve risico op een eerste infarct was 5,7 (95% BI 1,9-17,1) voor personen met een systolische bloeddruk van 160 mmHg of hoger ten opzichte van personen met een systolische bloeddruk lager dan 120 mmHg (p-waarde voor trend < 0.0001). Voor de diastolische bloeddruk bereikte het relatieve risico een waarde van 2.5 (95% BI 1,4-4,5) voor personen met een diastolische bloeddruk van 80-90 mmHg vergeleken met personen met een waarde beneden de

70 mmHg (p-waarde voor trend < 0.05). Subgroepanalyses bij personen van 70 jaar en ouder toonden aan dat de positieve relaties tussen systolische en diastolische bloeddruk en het risico op een eerste myocard infarct op oudere leeftijd nog aanwezig waren, hoewel het verband zwakker was in deze leeftijdsgroep. Er was geen verschil tussen mannen en vrouwen.

Concluderend kan gesteld worden dat de resultaten van beide studies in hoofdstuk 3 niet duiden op een J- of U-vormig verband tussen systolische en diastolische bloeddruk en het risico op hart- en vaatziekten bij relatief gezonde ouderen. Een blijvend positief verband tussen systolische bloeddruk en het risico op een eerste infarct bij ouderen in de ERGO studie werd ook gevonden in andere studies bij ouderen. De literatuur is minder consistent wat betreft de relatie tussen diastolische bloeddruk en eindpunten. Het niet kunnen aantonen van een relatie tussen systolische en diastolische bloeddruk en sterfte aan hart- en vaatziekten in de FINE studie kan een gevolg zijn van residuele confounding door comorbiditeit en een verminderde gezondheid. Een positieve relatie tussen polsdruk en sterfte aan hart- en vaatziekten zoals gevonden bij ouderen in de FINE studie, komt overeen met de literatuur. De polsdruk geeft een afspiegeling van het schadelijk effect van zowel een hoge systolische als een lage diastolische bloeddruk, en is een indicator van vaatwandstijfheid, een belangrijke voorspeller voor hart- en vaatziekten. Gesuggereerd wordt dat polsdruk bij ouderen een minstens zo belangrijke voorspeller is voor hart- en vaatziekten als beide bloeddrukken afzonderlijk.

Het potentiële effect van verschillende bloeddrukverlagende interventies op de primaire preventie van hart- en vaatziekten en op de gezonde levensverwachting in Nederland werden gekwantificeerd met behulp van een simulatiemodel (**hoofdstuk 4**). Recente individuele gegevens uit twee grote Nederlandse observationele studies, die samen in totaal 13.309 mannen en vrouwen van 40-74 jaar omvatten, werden gebruikt om de verdeling van risicofactoren in Nederland te schatten. De Framingham risicofunctie werd gebruikt om het individuele risico te schatten op een cardiovasculaire gebeurtenis in de komende 10 jaar, op basis van een combinatie van risicofactoren. Om het effect van verschillende interventies op bloeddrukniveaus te schatten, werd gebruik gemaakt van gegevens uit experimenteel onderzoek. We simuleerden een farmacologische interventie gericht op hoog-risico individuen en een populatie-brede voedingsinterventie. In de farmacologische interventie werd verondersteld dat alle personen met hypertensie

en een hoog absoluut risico op hart- en vaatziekten behandeld werden met bloeddrukverlagende medicatie. De omvang van de groep die voor behandeling in aanmerking kwam, werd bepaald op grond van de herziene Richtlijn Hoge Bloeddruk (CBO 2000). In de voedingsinterventie werd verondersteld dat de gehele bevolking gezond at, en een voeding gebruikte die veel fruit, groenten en vetarme zuivelproducten bevatte, en weinig zout. In totaal zouden 6682 (1.8%) van de nieuwe gevallen van hart- en vaatziekten bij personen van 40-59 jaar, en 7799 (1.5%) van de nieuwe gevallen bij personen van 60-74 jaar, in de komende 10 jaar in Nederland voorkómen kunnen worden, indien personen met een hoog risico volgens de herziene Richtlijn Hoge Bloeddruk farmacologisch behandeld zouden worden. Het aantal nieuwe gevallen van hart- en vaatziekten dat in de komende 10 jaar voorkómen zou kunnen worden door een populatie-brede voedingsinterventie zou 32.382 (8.6%) en 32.536 (6.5%) bedragen, respectievelijk. Op grond van deze resultaten kan geconcludeerd worden dat een hoog-risico benadering in samenhang met een populatie-brede benadering nodig is om verhoogde bloeddruk in de bevolking effectief te behandelen, en om maximale gezondheidswinst te behalen. Tevens maken onze resultaten aannemelijk dat bloeddrukverlaging in de gehele bevolking via veranderingen in de voeding een effectief middel kan zijn ter preventie van hart- en vaatziekten in de gehele Nederlandse bevolking.

Tenslotte zijn in **hoofdstuk 5** de belangrijkste bevindingen bediscussieerd. Hierbij werden eerst methodologische aspecten van epidemiologisch onderzoek naar de relatie tussen bloeddruk en hart- en vaatziekten onder de loep genomen. Belangrijke methodologische aandachtspunten waren de invloed van binnen-persoonsvariatie in bloeddruk op de sterkte van de relatie, hoe om te gaan met gebruikers van bloeddrukverlagende medicijnen en personen met een voorgeschiedenis van hart- en vaatziekten in de analyse, en residuele confounding door comorbiditeit en verslechterde gezondheid. Dit laatste punt speelt vooral bij ouderen een rol omdat comorbiditeit bij deze groep veel voorkomt en dikwijls moeilijk is te diagnostizeren.

Daarnaast werd aandacht besteed aan de implicaties van onze resultaten voor de volksgezondheid. Op basis hiervan werd geconcludeerd dat verlaging van de bloeddruk in de bevolking middels effectieve farmacologische behandeling van hoog-risico individuen, én middels maatregelen gericht op de totale populatie, in theorie de incidentie van hart- en vaatziekten in Nederland in de komende 10 jaar

met tenminste 10% kan verlagen. Om deze aanzienlijke gezondheidswinst te bereiken is echter betrokkenheid van de gehele bevolking, professionals in de gezondheidszorg en de voedingsmiddelenindustrie vereist.

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Het boekje is af! Al voelt het nog niet zo, en verzekert iedereen die mij voorging dat het pas helemaal af is na de grote dag, het echte werk zit erop. Heerlijk. Tijd voor een nieuwe fase. Maar niet zonder iedereen te bedanken die op een of andere wijze heeft bijgedragen er iets moois van te maken.

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About the author

Peggy van den Hoogen was born on January 20th, 1971 in Heerlen. In 1989 she completed secondary school (VWO) at the 'St. Janscollege' in Hoensbroek. From 1989 to 1995 she studied Biological Health Sciences with majors in nutrition and epidemiology at the Maastricht University. From the end of 1994 until November 1996 she worked as an epidemiologist at the general health service in Breda. In November 1996 she started the work described in this thesis at the Department of Chronic Diseases Epidemiology of the National Institute of Public Health and the Environment in Bilthoven and at the Department of Epidemiology & Biostatistics of the Erasmus University School in Rotterdam. In 1999 she obtained a Master of Science in Epidemiology at the Netherlands Institute for Health Sciences in Rotterdam. In October 2001 she started to work as an epidemiologist at the general health service in s' Hertogenbosch.