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ORIGINAL ARTICLE

The effects of control of systolic and diastolic hypertension on cardiovascular and all-cause mortality in a community-based population cohort

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The objective of this study (follow-up of 26 113 people) was to investigate differences in the risk of cardiovascular disease (CVD) and all-cause mortality among hypertensive people according to the control of systolic blood pressure (SBP) and diastolic blood pressure (DBP). People with a history of coronary heart disease, heart failure, cancer or incomplete data at baseline ($n = 1113$) were excluded from the study. The participants were classified into six groups according to their blood pressure status. Treated hypertensive individuals with controlled SBP and DBP did not experience an increase in all-cause mortality compared with normotensive people. The increase in all-cause mortality was 1.48-fold (95% confidence interval (CI) 1.09–2.01) among those who were treated with antihypertensive drugs and had only their DBP controlled and 1.45-fold (95% CI 1.04–2.02) among those who were treated and had only their SBP controlled. Treated patients with both SBP and DBP controlled did not have an increased risk of CVD mortality when compared with normotensive people. The risk of CVD mortality was statistically significantly higher in treated hypertensive people with SBP alone, DBP alone or both SBP and DBP uncontrolled. Our study indicates that uncontrolled SBP alone and DBP alone are risk factors of all-cause and CVD mortality.

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INTRODUCTION

There is convincing evidence from epidemiological studies that elevated blood pressure (BP) is an independent and strong risk factor for cardiovascular diseases (CVD), including coronary heart disease and stroke.[1,2] It has been estimated that worldwide, 7.1 million deaths (12.8% of the global total) and 64.3 million disability-adjusted life years (4.4% of the global total) were due to nonoptimal BP.[3] Both the systolic and diastolic components of BP predict CVD complications in clinical trials[4] and prospective observational studies.[5–8] In addition, the benefit of antihypertensive drug treatment in reducing the risk for CVD events in people with high BP has been well established in a multitude of randomized controlled trials, although by design such trials typically have had a relatively short follow-up time,[9,10] and they have had specified inclusion and exclusion criteria.

Studies comparing CVD and all-cause mortality between treated hypertensive patients and untreated normotensive individuals have shown that treated hypertensive patients with controlled BP are still at higher risk for CVD than normotensive individuals.[11–15] However, these studies used higher cutoff values of systolic blood pressure (SBP) and diastolic blood pressure (DBP) than the currently recommended value of 140/90 mm Hg.[16] Furthermore, controversial results have been published regarding health outcomes prospectively in normotensive people compared with those in treated and previously untreated hypertensive patients.[14,17–20] Some studies did not find any significant difference in CVD mortality between normotensive men and those receiving antihypertensive medication and having SBP adequately controlled.[14,19] Others reported that people with controlled hypertension had higher CVD mortality than normotensive ones.[17,18,20]

In addition, studies including women are rare,[15,20–22] and only one observational study has assessed the impact of control of SBP alone, DBP alone or both SBP and DBP on all-cause and CVD mortality in women.[20]

The aim of this population-based study was to investigate whether differences exist in the risk of CVD and all-cause mortality among hypertensive men and women by the control status of SBP, DBP and both SBP and DBP at baseline.

MATERIALS AND METHODS

Study population

Four independent cross-sectional surveys were carried out at 5-year intervals between 1982 and 1997 within the framework of the FINMONICA among men and women aged 25–64 years.[23] An independent random sample was drawn from the national population register for each survey. The samples were stratified by sex and 10-year age categories according to the World Health Organisation Multinational Monitoring of trends and determinants of CVD (WHO MONICA) protocol.[24] The FINMONICA study

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was the Finnish part of the multinational MONICA project. The surveys were conducted initially in three regions: the provinces of North Karelia, Kuopio and the region of Turku-Loimaa in south-western Finland. The survey expanded to other regions in 1992 (cities of Helsinki and Vantaa) and in 1997 (province of Oulu). Individuals who took part in more than one survey were in these analyses included only in their first survey cohort. The total sample comprised 25 543 people. The participation rates varied in the survey cohorts between 63 and 83% in men and between 72 and 88% in women. Informed written consent was obtained starting from the participants of the 1997 survey. At the time of the earlier surveys, it was not customary or mandated by ethical rules in Finland to ask for a written consent in epidemiological studies, but the participants were informed about the purpose of the study in both writing and orally. These surveys were conducted according to the ethical rules of the National Public Health Institute and the investigations were performed in accordance with the Declaration of Helsinki.

Assessment of risk factors for cardiovascular disease

A self-administered questionnaire was mailed to the participants in advance. The questionnaire included questions on smoking habits, education, physical activity and medical history. Self-reported smoking habits were classified according to three categories: never smokers, ex-smokers (those who had smoked regularly but had stopped smoking at least 6 months before the survey) and current smokers.

Education level, measured as the total number of school years, was divided into birth cohort-specific tertiles.

The participants reported their occupational and leisure time physical activity. These were merged and regrouped into three categories (low, moderate and high) of total physical activity as described in previous publications.[25,26]

At the study site, specially trained nurses measured height, weight and BP using a standardized protocol.[24] Height and weight were measured without shoes and with light clothing. BP was measured twice from the right arm of the participant in sitting position after at least a 5-min rest. A standard mercury sphygmomanometer was used. The fifth phase of the Korotkoff's sounds was recorded as the diastolic BP. In 1982 and 1987, a different cuff bladder (42 cm long and 13 cm wide) was used than in the surveys (40 cm long and 14 cm wide) in 1992 and 1997, respectively). Starting from 1982, BP was measured twice and the mean of these two BP measurements was used in the analyses. An individual was considered to have hypertension when the average of these two BP measurements was at least 140 mm Hg systolic or 90 mm Hg diastolic, or if he or she reported having taken antihypertensive drugs during the preceding 7 days. Information on the use of antihypertensive drugs was obtained with a self-administered questionnaire. People on antihypertensive drug treatment, whose measured BP level was $<140/90$ mm Hg, were considered to be adequately treated (controlled) in this analysis. The study population was classified into six groups according to their BP treatment and control status: (1) normotensive participants (measured BP level $<140/90$ mm Hg and without any hypertensive drug treatment); (2) hypertensive patients treated with antihypertensive drugs and controlled for both SBP (measured SBP <140 mm Hg and DBP (measured DBP <90 mm Hg); (3) hypertensive patients treated with antihypertensive drugs and controlled for only SBP but not DBP; (4) hypertensive patients treated with antihypertensive drugs and controlled for only DBP but not SBP; (5) hypertensive patients with antihypertensive drugs but uncontrolled for both SBP and DBP; and (6) hypertensive people not treated with antihypertensive drugs.

Serum total cholesterol was determined by using an enzymatic method (CHOD-PAP, Boehringer Mannheim, Mannheim, Germany). All samples were analysed in the same central accredited laboratory.

The FINRISK function was calculated using a logistic regression model for the estimated 10-year risk for both a major coronary event (fatal or nonfatal) and stroke event.[27] The overall CVD risk was calculated by adding the coronary risk to the stroke risk.

Participants who reported that they had diabetes on the questionnaire, or who had had a hospital discharge diagnosis of diabetes, or the approval for free-of-charge medication for diabetes before the baseline survey or during the follow-up, were classified as having diabetes. Data on diabetes medication were ascertained from the national Social Insurance Institution's register on special reimbursement for antidiabetic drugs available since 1964. Antidiabetic drugs prescribed by a physician are free of charge in Finland and are subject to approval of a physician of the Institution who reviews each case history. People with self-reported history of coronary heart disease, heart failure or cancer, or who had incomplete data at baseline ($n=1113$), were excluded from the study. The final sample comprised 11 690 men and 13 157 women.

Outcome definition

The original survey data were complemented by record linkage to the nationwide death register of Statistics of Finland according to the unique national personal identification number that every resident in Finland has. These records covered the period from January 1982 to December 2005. The Eighth, Ninth and Tenth Revisions of the International Classification of Diseases were used for coding the causes of death. The codes used for CVD death were 390–459 (I00–I99). The end point of the follow-up was the date of death or the end of December 2005.

Statistical analyses

Statistical analyses were performed with SPSS for Windows 17.0. The Cox proportional hazards model was used to estimate the association between hypertension subgroups and the risk for total and CVD mortality. Analyses were adjusted first for age, sex, study area and study year (model A) and for age, sex, study region, study year, education, history of diabetes, smoking status, cholesterol level, body mass index and total physical activity (model B). The data of all four surveys were pooled together, because no first-level interaction was found between BP treatment and control groups and these variables regarding CVD or total mortality. As there was no statistically significant interaction between sex and hypertension group, a joint analysis of men and women together was performed. BP treatment and control group variables were entered into the model as categorical variables, and the statistical significance of different categories of BP treatment and control groups was tested in the same models, with the normotensive category as reference group. The proportional hazards assumption in the Cox model was assessed with graphical methods. Estimated hazard ratios (HRs) and their 95% confidence intervals (CIs) are presented.

RESULTS

The baseline characteristics of the study population are presented in Table 1. Normotensive people seemed to be younger and had lower initial body mass index and serum cholesterol level and higher level physical activity than people classified to any of the five treatment and control groups.

During a median follow-up of 16 years, 3265 men died, 43% (1403) because of CVD (Tables 2 and 3). All-cause mortality was higher in those hypertensive subgroups where either SBP or DBP were uncontrolled (Table 2). The increase in all-cause mortality was 1.48-fold (95% CI 1.09–2.01) among those who were treated with antihypertensive drugs and had only their DBP controlled and 1.45-fold (95% CI 1.04–2.02) among those who were treated and had only their SBP controlled when adjusted for age, body mass index, smoking, serum cholesterol, education, diabetes and different forms of physical activity. Treated hypertensive people with controlled SBP and DBP did not experience any increase in the risk of all-cause mortality compared with normotensive ones (HR 0.80; 95% CI 0.53–1.19).

Table 3 presents the HRs for CVD mortality for each hypertensive subgroup. No statistically significant increase in the risk of CVD mortality was found in the drug-treated group with both SBP and DBP controlled compared with normotensive individuals (HR 1.18; 95% CI 0.65–2.15). The risk of CVD mortality was statistically significantly higher in treated hypertensive patients with either SBP or DBP uncontrolled or both SBP and DBP uncontrolled compared with the normotensive people. Treated hypertensive people (HR 0.76; 95% CI 0.24–2.41) with SBP controlled but DBP uncontrolled had a 2.32-fold increased risk of CVD mortality when compared with normotensive people (95% CI 1.44–3.74). The respective HR for people with DBP controlled but SBP uncontrolled was 2.87 (95% CI 1.89–4.35).

Table 1. Baseline characteristics of different blood pressure categories according to treatment and control among Finnish men and women

	Normotensive	*Hypertensive, treated, SBP and DBP controlled*	*Hypertensive, treated, SBP controlled, DBP uncontrolled*	*Hypertensive, treated, SBP uncontrolled, DBP controlled*	*Hypertensive, treated, SBP and DBP uncontrolled*	*Hypertensive, not treated*
n	13 257	392	280	515	2148	9541
Age (years)	40.3 (10.3)[a]	51.5 (8.3)[a]	49.8 (7.6)[a]	55.0 (7.5)[a]	52.1 (7.9)[a]	46.8 (10.7)[a]
Body mass index (kg m^{-2})	24.76 (3.66)[a]	28.62 (4.82)[a]	29.08 (5.10)[a]	29.18 (5.05)[a]	29.39 (4.80)[a]	27.10 (4.29)[a]
SBP (mm Hg)	123 (10)[a]	129 (8)[a]	133 (5)[a]	157 (15)[a]	166 (20)[a]	152 (15)[a]
DBP (mm Hg)	76 (8)[a]	82 (6)[a]	95 (4)[a]	84 (5)[a]	102 (9)[a]	90 (10)[a]
Serum total cholesterol (mmol l^{-1})	5.48 (1.10)[a]	6.10 (1.12)[a]	6.37 (1.15)[a]	6.25 (1.31)[a]	6.63 (1.13)[a]	6.10 (1.20)[a]
CVD risk (%)						
0–4.9%	92	65	71	43	39	66
5–9.9%	6	23	18	26	27	18
10–14.9%	1	6	4	13	14	7
⩾15%	1	6	8	18	10	9
Education (%)						
Low	27	29	24	31	28	28
Medium	32	33	36	35	35	33
High	41	38	40	34	37	38
Smoking (%)						
Never	54	59	56	72	64	52
Ever	16	21	23	16	20	18
Current	30	20	21	12	16	30
History of diabetes (%)	1	6	4	8	6	1
Total physical activity (%)						
Low	8	13	13	14	17	10
Moderate	32	38	34	43	35	35
High	60	49	53	43	48	55

Abbreviations: CVD, cardiovascular disease; DBP, diastolic blood pressure; SBP, systolic blood pressure. [a]Mean (s.d.).

Table 2. HRs for total mortality in normotensive[a], participants and in different categories of blood pressure treatment and control with various forms of adjustment[b]

	Number of deaths	*Person-years*	*Adjusted HRs (95% CI)*	
			A	*B*
			All-cause mortality	
Normotensive	768	179 565	1.00	1.00
Hypertensive, treated, SBP and DBP controlled	66	4976	0.86 (0.57–1.28)	0.80 (0.53–1.19)
Hypertensive, treated, SBP controlled, DBP uncontrolled	67	4084	1.48 (1.06–2.05)	1.45 (1.04–2.02)
Hypertensive treated, SBP uncontrolled, DBP controlled	158	6355	1.44 (1.06–1.95)	1.48 (1.09–2.01)
Hypertensive treated, SBP and DBP uncontrolled	861	34 528	1.68 (1.45–1.94)	1.61 (1.39–1.88)
Hypertensive, not treated	1345	135 747	1.32 (1.17–1.48)	1.26 (1.13–1.42)

Abbreviations: 95% CI, 95% confidence interval; DBP, diastolic blood pressure; HR, hazard ratio; SBP, systolic blood pressure. [a]Measured BP level $<$140/90 mm Hg and without any hypertensive drug treatment. [b]A: adjusted for age, sex, study area and study year; B: adjusted for age, sex, study area, study year, body mass index, serum cholesterol level, education, history of diabetes, smoking status and total physical activity.

DISCUSSION

This population-based prospective study showed that in hypertensive people with both SBP and DBP controlled, the risk of all-cause and CVD mortality decreased to the same level as observed in normotensive people. Control of SBP or DBP alone was not sufficient to reduce all-cause or CVD mortality.

Our results are in contrast to the finding of the Primary Preventive Trial in Gothenburg where treated hypertensive middle-aged men had an increased risk of mortality from coronary heart disease compared with normotensive men of similar age despite a reduction of their BP.[11–13] All-cause mortality was increased by approximately one-third in treated hypertensive patients during a follow-up of 25–28 years.[11] However, it is important to notice that their threshold for treatment of hypertension was defined as a sitting casual SBP $>$175 mm Hg and/or DBP $>$115 mm Hg. In treated hypertensive men, although BP decreased by 21/15 mm Hg, their BP levels were still much higher than the currently recommended goal of $<$140/90 mm Hg according to the most recent guidelines.[16] When we used $<$160/95 mm Hg as the optimal treatment goal as recommended in Finland during a large part of the follow-up time of our study, our results tended to be similar than those observed in the Swedish studies.[15] However, after considering the recent criteria for treatment of hypertension, decreasing SBP to $<$140 mm Hg

Table 3. HRs for cardiovascular mortality in normotensive[a], people and in different categories of hypertension treatment and control with various forms of adjustment[b]

	Number of deaths	*Person-years*	*Adjusted HRs (95% CI)*	
			A	*B*
			CVD mortality	
Normotensive	182	179 565	1.00	1.00
Hypertensive, treated, SBP and DBP controlled	29	4976	1.36 (0.75–2.48)	1.18 (0.65–2.15)
Hypertensive, treated, SBP controlled, DBP uncontrolled	36	4084	2.64 (1.64–4.23)	2.32 (1.44–3.74)
Hypertensive treated, SBP uncontrolled, DBP controlled	88	6355	2.82 (1.86–4.27)	2.87 (1.89–4.35)
Hypertensive treated, SBP and DBP uncontrolled	515	34 528	3.10 (2.43–3.96)	2.74 (2.14–3.51)
Hypertensive, not treated	553	135 747	2.12 (1.72–2.63)	1.95 (1.57–2.41)

Abbreviations: 95% CI, 95% confidence interval; CVD, cardiovascular disease; DBP, diastolic blood pressure; HR, hazard ratio; SBP, systolic blood pressure. [a]Measured BP level $<140/90$ mm Hg and without any hypertensive drug treatment. [b]A: adjusted for age, sex, study area and study year; B: adjusted for age, sex, study area, study year, body mass index, serum cholesterol, education, diabetes, smoking status and total physical activity.

and DBP to <90 mm Hg seemed to be beneficial with regard to CVD and all-cause mortality in hypertensive individuals.

In line with our study, the Copenhagen City Heart Study did not find a significant difference in CVD mortality between men who received antihypertensive medication and had their SBP and DBP adequately controlled and normotensive men.[14] In contrast to our study, others reported that men with controlled hypertension had higher CVD mortality than normotensive ones.[17,18,20] However, their follow-up times were shorter than in our study, 7 years[17] and 5 years.[18]

Large, randomized, placebo-controlled trials have well demonstrated the beneficial effect of treating both systolic and diastolic hypertension.[28–30] Data from clinical trials have consistently shown that higher blood pressure implies higher (CVD and all-cause) mortality risk.[1] In our study, hypertensive people with control of SBP alone or DBP alone did reveal a similar magnitude in risk increase with regard to all-cause or CVD mortality compared with normotensive individuals. Some population studies, however, have indicated that SBP is a stronger predictor than DBP in middle-aged people.[19,31] Trials in people with isolated systolic hypertension have unequivocally shown that BP lowering in such individuals will result in significant reductions in CVD mortality and incidence.[28,29]

Observational studies from several countries have revealed that among treated hypertensive patients, the proportion of those who are well controlled is $<30\%$, and that only 6% of hypertensive patients presented BP levels below the goal of 140/90 mm Hg.[32–34] Although treatment of hypertension care has remarkably improved in Finland during 1982–2007, the difference between the actual situations at the population level compared with the treatment goals presented by the hypertension guidelines remains far from optimal.[33] It is important to keep in mind that the prognosis of hypertensive individuals also depends on risk factors other than BP alone, and comorbidity and the target organ damage.[34] Finally, the risk increase of CVD and all-cause mortality in the groups with uncontrolled SBP alone and DBP alone may be because of blood pressure *per se* or because of factors leading to poor response of SBP or DBP treatment.

Our study is population based, comprising a large number of people from a homogeneous population. The median follow-up, 16 years, was long enough to accumulate a large number of outcome events that were ascertained virtually without any loss of follow-up with computer-based record linkage using the national personal identification number. The participation rates in the baseline surveys were high, which makes it possible to apply the results directly to the general population.

Naturally, our study had some limitations. The baseline assessment of our cohort is limited to the examination on a single day when participants entered the study, as typical for large cohort studies. It cannot account for changes in compliance or a shift of participants between categories during the study period. It is however well known from a plethora of long-term controlled trials in hypertension that those patients who in early stages of follow-up show difficulties to reach target BP levels are the same who during subsequent years belong to the same category. We are aware that this may cause misclassification that underestimates the true effect of hypertension control. We cannot completely exclude the effects of confounding because of some unmeasured dietary and other lifestyle factors that may influence BP. Although the results of the analysis were adjusted for the most common CVD risk factors, it would have been useful to control the results for other risk factors such as chronic kidney diseases, microalbuminuria, duration and control of diabetes mellitus, level of compliance to antihypertensive treatment, type and doses of hypertension treatment in the past or during the follow-up as the impact of different therapeutic options on prognosis of cardiovascular and all-cause mortality may vary. Unfortunately, this information was not available from the study population. Furthermore, it has to be kept in mind that the results may be affected by white coat hypertension that has been reported to be more prevalent in women than men, and by masked hypertension that is much more common in men than women.[35]

In conclusion, our results strengthen the evidence that uncontrolled SBP alone and uncontrolled DBP alone are risk factors of all-cause and CVD mortality.

What is known about this topic

- Elevated blood pressure (BP) is an independent and strong predictor for cardiovascular disease including coronary heart disease and stroke.
- Controversial results have been published regarding health outcomes in normotensive people compared with those in treated and previously untreated hypertensive patients.
- Only one observational study has assessed the impact of control of SBP alone, DBP alone or both SBP and DBP on all-cause and CVD mortality in women.

What this study adds

- Treated hypertensive men and women with controlled SBP and DBP did not experience an increase in all-cause or CVD mortality compared with normotensive people.
- Uncontrolled SBP alone and DBP alone are risk factors of all-cause and CVD mortality.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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