High blood pressure at old age : The Leiden 85 plus study

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CHAPTER 2

In a population-based prospective study no association between high blood pressure and mortality after age 85 years.

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Abstract

Objective: To study the impact of a history of hypertension and current blood pressure on mortality in the oldest old.

Design: An observational population-based cohort study.

Setting: Community city of Leiden, the Netherlands.

Participants: Five hundred and ninety-nine inhabitants of the birth-cohort 1912-1914 were enrolled on their 85th birthday. There were no selection criteria related to health or demographic characteristics.

Interventions: The mean follow-up was 4.2 years. The medical histories were obtained from general practitioners. Medication histories were obtained from the participant's pharmacist. Blood pressure was measured twice at baseline.

Main outcome measures: All cause and cardiovascular mortality.

Results: Five hundred and seventy-one participants were included, 39.2% had a history of hypertension. During follow-up 290 participants died, 119 due to cardiovascular causes. Compared to participants without a history of hypertension, those with a history of hypertension had increased mortality from cardiovascular causes [relative risk (RR) 1.60, confidence interval (CI) 1.06-2.40] but equal mortality from all causes (RR 1.19, CI 0.91-1.55). High blood pressure at baseline (age 85) was not a risk factor for mortality. Baseline blood pressure values below 140/70 mmHg (n=48) were associated with excess mortality, predominantly in participants with a history of hypertension.

Conclusion: In the oldest old, high blood pressure is not a risk factor for mortality, irrespective of a history of hypertension. Blood pressure values below 140/70 are associated with excess mortality.

Introduction

The role of high blood pressure as a risk factor for morbidity and mortality in the oldest old is still subject to debate, despite the fact that people aged 85 years and older often have a history of hypertension [1-9]. The relatively scarce observational data in people aged 80 years and over are contradictory, showing either an increased risk or an inverse relationship for high blood pressure with mortality [4-8].

Some of the different results found might be due to the differences between current blood pressure and former blood pressure [5]. Normal blood pressure in the face of a longstanding history of hypertension might have a considerable different impact on prognosis than high blood pressure without a history of hypertension.

Placebo-controlled clinical trials are also inconclusive, because hardly any subjects older than 80 years are included in these studies [2,10-14]. The only study designed for people older than 80 years reported a reduced risk for strokes but an increased total mortality rate in the actively treated group [2]. Those findings could be arguments for clinicians to be reluctant to treat high blood pressure in old age.

The aim of the present study was to disentangle the relationship between a positive history of hypertension and current blood pressure in very old men and women participating in the population-based Leiden 85-plus Study. With this study we elaborate on the previous findings in the former cohort of the Leiden 85-plus Study, showing that elevated blood pressure was associated with better survival in this age group [4].

Methods

Study population

The Leiden 85-plus Study is a prospective population-based study of all 85-year old inhabitants of Leiden, The Netherlands. The study design and characteristics of the cohort have been described in detail previously [15,16]. In short, between September 1997 and September 1999 all 705 members of the 1912 to 1914-birth cohort in the city of Leiden were asked to participate in the month after their 85th birthday. There were no selection criteria related to health or demographic characteristics.

At baseline, 85-year old participants were visited three times at their place of residence to administer extensive data on health, functioning and well-being. In addition, a medical history was obtained from participant's general practitioner or nursing home physician, and information on the use of medication was obtained from participant's pharmacist. Participants gave oral informed consent and for people who were severely cognitively impaired, a guardian gave informed consent. The Medical Ethics Committee of the Leiden University Medical Center approved the study.

History of hypertension and baseline blood pressure

The definition of a positive history of hypertension was fulfilled when at baseline the diagnosis hypertension could be obtained from the medical records. This was assessed independently of the baseline blood pressure (age 85 years).

An experienced research nurse measured blood pressure twice at baseline with a mean interval of 2 weeks. Blood pressure was measured in seated position after at least 5 min of rest and no vigorous exercise during the preceding 30 min. The cuff was inflated to 30 mmHg above the pressure after the disappearance of the radial pulse. The systolic value was measured at the onset of Korotkoff phase 1 and the diastolic value was measured at the onset of Korotkoff phase 5. For the analysis of blood pressure we used the mean of the measured systolic values and the mean of the measured diastolic blood pressures.

Mortality

All participants were followed for mortality up until the censor date (1 April 2004). Shortly after the civil registry reported the death of a participant, the general practitioner or nursing home physician was interviewed to obtain the specific cause of death. Two senior specialists of internal medicine determined the primary causes of death by consensus without knowledge of medical history and the research aims. Primary causes of death were classified according to the tenth version of the International Classification of Diseases (ICD-10) [17] and were divided into two groups: cardiovascular mortality (ICD-codes I00-I99, I20-I25 and I60-I69) and non-cardiovascular mortality (all other ICD-codes).

Demographic and clinical characteristics

At baseline, a research nurse collected information concerning the demographic characteristics. Low education was defined as primary school only. At baseline the Mini-Mental State Examination (MMSE) was administered to screen for cognitive impairment [18]. Disability in basic activities of daily living (ADL) and instrumental activities of daily living (IADL) were assessed with the Groningen Activity Restriction Scale [19]. The presence of cardiovascular disease was defined as a previous history of cerebrovascular accident, angina pectoris, myocardial infarction, peripheral vascular disease or an electrocardiogram revealing myocardial ischaemia or infarction (Minnesota codes 1-1, 1-2, 1-3, 4-1, 4-2, 4-3, 5-1, 5-2 and 5-3) [20]. The presence of chronic disease was defined as a previous history of diabetes, Parkinson's disease, chronic obstructive pulmonary disease, arthrosis, or malignancies. Angiotensin converting enzyme inhibitors, angiotensin-1 receptor blockers, thiazide diuretics, dihydropyridin calcium channel blockers or β-blockers with the exclusion of sotacor, were classified as antihypertensive drugs.

Baseline blood pressure categories

According to national and international guidelines, we categorized the participants for both systolic and diastolic blood pressure in three clinically relevant groups, namely a systolic blood pressure lower than 140 mmHg (normal blood pressure), 140-159 mmHg (hypertension stage 1) and 160 mmHg and over (hypertension stage 2) [21]. For diastolic blood pressure we used lower than 70 mmHg (low blood pressure), 70-89 mmHg (normal blood pressure) and 90 mmHg and over (hypertension stage 1 and 2) [7,21].

Statistical analysis

Distributions of categorical clinical characteristics were compared with chi-squared tests, and continuous data were compared with independent t-tests. Mortality risks and 95% confidence intervals for participants with hypertension versus those without a history of hypertension were estimated in a Cox proportional-hazards model. We adjusted the mortality risks for gender, number of used antihypertensive medications and the presence of cardiovascular disease, because these determinants were differently distributed in the participants with and without a history of hypertension. The association between all-cause mortality and systolic and diastolic blood pressure was first visualized by use of Kaplan- Meier analyses, and differences were tested by log-rank tests. Mortality risks and 95% confidence intervals depending on systolic and diastolic blood pressure were estimated in a Cox proportional-hazards model. We adjusted the mortality risks for gender, use of antihypertensive medication and the presence of cardiovascular disease. To estimate the absolute risks of mortality, mortality rates and corresponding 95% confidence intervals were calculated by life tables for strata of systolic and diastolic blood pressure. All analyses were performed with SPSS version 12.01 (SPSS Inc., Chicago, Illinois, USA).

Results

Of the 705 eligible participants, 14 died before they could be enrolled and 92 refused to participate, resulting in a cohort of 599 participants (87% response). In the present analyses we included only the 571 participants for whom two measurements of blood pressure at baseline were available.

At baseline, 224 participants (39.2%) had a history of hypertension according to the medical records of their general practitioner or nursing home doctor. The history of hypertension was equally distributed for gender and education (Table 1). There were no differences in daily functioning (both ADL and IADL), cognitive function and the presence of chronic diseases for those with and without a history of hypertension (Table 1). Participants with a history of hypertension more often had a history of cardiovascular disease compared to participants without a history

of hypertension (71 versus 58%, chi-squared P ≤ 0.001). Some 62% (n=138) of the participants with a history of hypertension used one or more antihypertensive drugs. Specific medications that were used included (combinations of) β-blockers (n=57, 41%), thiazide diuretics (n=55, 40%), dihydropyridin calcium channel blockers (n=36, 26%), angiotensin converting enzyme inhibitors and angiotensin-1 receptor blockers (n=45, 33%). Of the participants without a history of hypertension, some 20% used one or more of the aforementioned drugs for other diagnosis, as was verified by the general practitioners.

For participants with a history of hypertension, the mean baseline systolic blood pressure was 157.3 mmHg [standard deviation (SD) 18.3] versus 153.7 mmHg (SD 19.1) in those without a history of hypertension (independent t-test, P = 0.03). In total, 210 participants (36.8 %) had a systolic blood pressure at age 85 of 160 mmHg or higher. The mean diastolic blood pressure at age 85 was 77.0 mmHg (SD 9.9) in participants with a history of hypertension versus 75.8 mmHg (SD 9.2) in those without a history of hypertension (independent t-test, P = 0.01). In total, 48 participants (8.4 %) had a mean diastolic blood pressure above 90 mmHg at age 85.

Table 1 Clinical characteristics at baseline of 571 participants at age 85 years, according to a history of hypertension.

	History of Hypertension	
	Present (*n*=224)	Absent (*n*=347)
Females	160 (71%)	221 (64%)
Low education (%)	151 (68%)	219 (64%)
ADL independency (%)	105 (47%)	154 (45%)
IADL independency (%)	56 (25%)	91 (26%)
Cognitive function		
MMSE > 27 points (%)	78 (35%)	124 (36%)
MMSE < 19 points (%)	34 (15%)	58 (17%)
Mean systolic blood pressure (SD) (mmHg)	157.3 (18.3)*	153.7 (19.1)
Mean diastolic blood pressure (SD) (mmHg)	77.0 (9.9)*	75.8 (9.2)
History of chronic disease (%) †	131 (59%)	200 (58%)
History of cardiovascular disease (%) ‡	160 (71%)**	200 (58%)

ADL, basic activities of daily livibg; IADL, instrumental activities of daily living; MMSE, Mini -Mental State Examination; SD, standard deviation. * independent t-test $P \leq 0.03$, **chi-squared, $P \leq 0.001$, † Including diabetes, Parkinson's disease, chronic obstructive pulmonary disease, arthrosis (including rheumatoid arthritis and polymyalgia rheumatica), and malignancies. ‡ Including cerebrovascular accident, angina pectoris, myocardial infarction, peripheral vascular disease or an electrocardiogram revealing myocardial ischaemia or infarction.

During a median follow-up of 4.2 years, 290 participants died. One hundred and nineteen participants died from cardiovascular causes and 164 from non-cardiovascular causes; causes of death could not be obtained for 7 participants. Participants with a history of hypertension did not have an increased all-cause mortality risk compared to those without a history of hypertension [adjusted relative risk (RR) 1.19, 95% confidence interval (CI) 0.91-1.55], but they did have a 1.6-fold increased cardiovascular mortality risk (95% CI 1.06-2.40). There was no association between a history of hypertension at age 85 years and non-cardiovascular mortality (Table 2).

Table 2 Mortality risks depending on history of hypertension at age 85 years.

	History of hypertension	
	Present (*n*=224)	Absent * (*n*=347)
All causes († 290)	1.17 (0.90-1.53)	1
Cardiovascular († 119)	1.54 (1.03-2.32)	1
Non-cardiovascular († 164)	0.97 (0.68-1.39)	1

Mortality risks and corresponding 95% confidence intervals were estimated with Cox proportional hazards model adjusted for gender, number of antihypertensive medications and presence of cardiovascular disease. † Observed Number of deaths; * Reference category; *n* = number of participants.

Figure 1 presents the cumulative mortality depending on categories of systolic and diastolic blood pressure at baseline. A significantly gradual inverse relation appeared between all-cause mortality and systolic blood pressure. Participants (n=129) with a diastolic blood pressure at baseline below 70 mmHg had a higher all-cause mortality compared to those in the other two categories of diastolic blood pressure.

Table 3 presents the all-cause mortality risks dependent on categories of systolic and diastolic blood pressure at baseline, adjusted for gender, number of antihypertensive medications and presence of cardiovascular disease. Compared to participants with a systolic blood pressure between 140 and 159 mmHg and a diastolic blood pressure between 70 and 89 mmHg (reference group) a 2.3-fold increased mortality risk was found for participants with a blood pressure lower than 140/70 mmHg (95% CI 1.61-3.38).

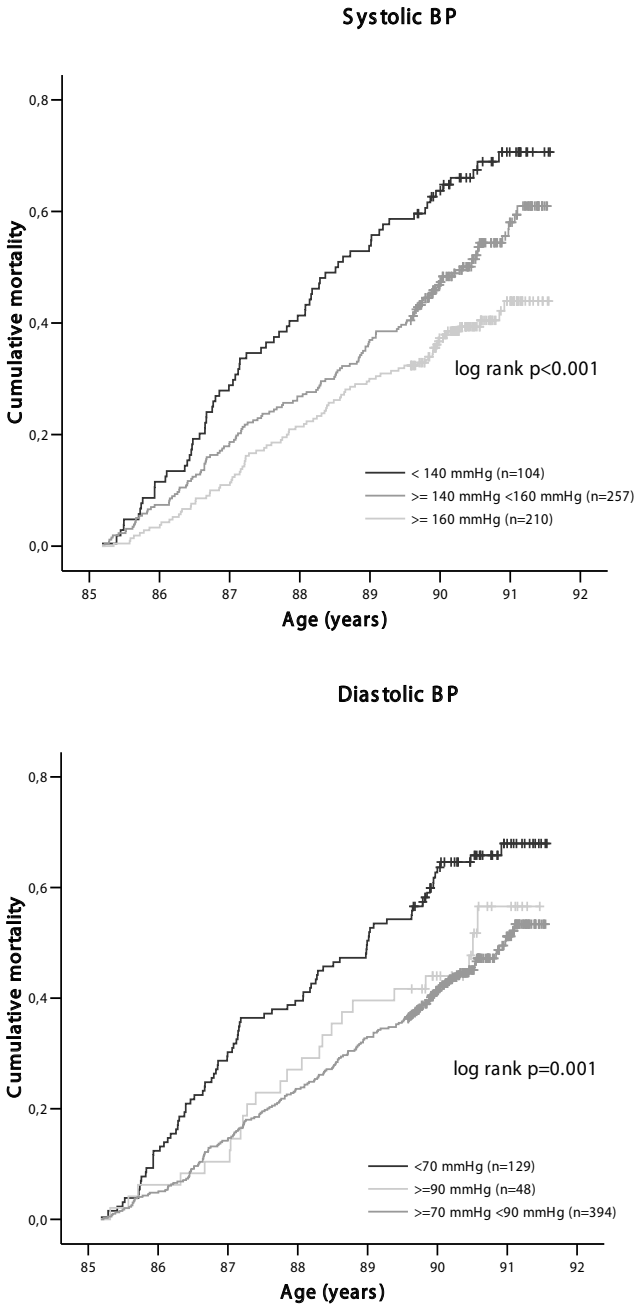

Figure 1: Cumulative all cause mortality depending on systolic and diastolic blood pressure at age 85.

Table 3: Number of participants rates (number of deaths) and relative risks (RR) for all cause mortality dependent on categories of systolic and diastolic blood pressure at baseline.

	Systolic BP (mmHg)		
Diastolic BP (mmHg)	< 140	140 - 159	≥ 160
< 70			
No. participants (no. deaths)	48 (40)	68 (37)	13 (7)
RR (95% CI)	2.33 (1.61-3.38)	1.04 (0.71-1.53)	1.14 (0.52-2.46)
70 – 89			
No participants (no. deaths)	56 (31)	180 (93)	158 (58)
RR (95% CI)	1.19 (0.79-1.79)	1*	0.66 (0.47-0.92)
≥ 90			
No participants (no. deaths)	0	9 (6)	39 (18)
RR (95% CI)		1.65 (0.72-3.78)	0.82 (0.50-1.36)

BP, blood pressure. Mortality risks and corresponding 95% confidence intervals (CI) were estimated with Cox proportional-hazards model adjusted for gender, number of antihypertensive medications and presence of cardiovascular disease. *, Reference category.

To investigate whether poor general health might be confounding this result an additional adjustment for the presence of chronic diseases, MMSE, ADL and IADL was performed. The increased mortality risk for participants with a blood pressure lower than 140/70 mmHg remained significant (RR 1.51, 95% CI 1.03-2.23). For participants with a systolic blood pressure equal to and higher than 160 mmHg and a diastolic blood pressure between 70 and 89 mmHg, a survival benefit was found compared to the reference group (RR 0.66, CI 0.47-0.92). However, after the additional adjustment for poor general health, this survival benefit disappeared (RR 0.73, 95% CI 0.52-1.02).

The absolute mortality rates dependent on blood pressure at age 85 stratified for the history of hypertension are presented in Table 4. In both strata, all-cause mortality was highest for participants with low blood pressure (systolic blood pressure below 140 mmHg or diastolic blood pressure below 70 mmHg) and most pronounced in participants with a history of hypertension and a low systolic blood pressure. In the group of participants with a systolic blood pressure lower than 140 mmHg, participants with a history of hypertension had a significant higher all-cause mortality rate (29.1 per 100 person years, 95% CI 19.4-38.9) compared to those without a history of hypertension (14.6 per 100 person years, 95% CI 9.9-19.3).

Table 4 Absolute mortality rates dependent on blood pressure at baseline stratified for a history of hypertension at age 85 years.

		History of hypertension			*History of hypertension*	
	Systolic BP	Present	Absent	*Diastolic BP*	Present	Absent
All cause	*< 140*	29.1 (19.4-38.9)*	14.6 (9.9-19.3)	*< 70*	19.6 (12.1-27.1)	17.5 (13.0-21.9)
	140-159	13.1 (9.2-16.9)	12.5 (10.0-15.1)	*70-89*	11.7 (9.2-14.3)	9.9 (8.0-11.9)
	≥ 160	8.6 (6.0-11.3)	9.2 (6.4-11.9)	*≥ 90*	11.2 (4.9-17.6)	12.7 (4.8-20.6)
Cardiovascular	*< 140*	12.0 (5.7-18.3)	6.3 (3.2- 9.4)	*< 70*	9.8 (4.5-15.1)	6.0 (3.4-8.7)
	140-159	7.1 (4.3-10.0)*	3.4 (2.1-4.7)	*70-89*	5.9 (4.1-7.8) *	3.5 (2.4-4.7)
	≥ 160	4.4 (2.5-6.3)	4.1 (2.3-6.0)	*≥ 90*	4.7 (0.1-8.8)	4.2 (0.0-8.4)
Non-cardiovascular	*< 140*	17.1 (9.6-24.7)*	7.9 (4.4-11.4)	*< 70*	9.8 (4.5-15.1)	10.8 (5.5-14.4)
	140-159	5.6 (3.1-8.2)	8.6 (6.5-10.7)*	*70-89*	5.5 (4.2-7.8)	6.1 (4.6-7.6)
	≥ 160	4.0 (2.2-5.8)	5.0 (3.0-7.1)	*≥ 90*	6.6 (1.7-11.4)	8.5 (2.6-14.3)

BP blood pressure in mmHg. Data are presented as number of deaths per 100 observed person years at risk and corresponding 95% confidence intervals. * $P < 0.05$, present versus absent history of hypertension within stratum of blood pressure.

Within the participants with blood pressures lower than 140/70 mmHg at baseline, the amount of cardiovascular disease was not uniformly divided. Of the 48 participants, 16 had a positive history of hypertension. Cardiovascular disease was present in 14 (87.5%) participants with a history of hypertension compared to 18 (56.3%) of the 32 participants without a history of hypertension (chi squared, P = 0.03).

Discussion

The main finding of this prospective population-based study was, that at the age of 85 years and over, high blood pressure was not associated with increased mortality, independently of the history of hypertension. Moreover, subjects with low systolic and diastolic blood pressure had an increased mortality risk.

Except for the lowest range of blood pressures, we did not find a relationship between blood pressure and mortality in participants aged 85 years and over, despite the fact that a history of hypertension remained a risk factor for cardiovascular mortality in this age group. This is different from reports in younger age groups, where those with the highest blood pressure are at the highest mortality risk [1,10-13,22]. The finding that low blood pressure is associated with an increased mortality risk in the oldest old corroborates with earlier results from the Leiden 85-plus Study and other reports [4-6,8,23,24].

The crude results from both cohorts of the Leiden 85-plus Study are similar. Both studies showed a higher mortality for participants in the low blood pressure group. However, in the present study the higher mortality was especially apparent for the participants with a history of hypertension. Secondly, in the present study systolic and diastolic blood pressure were analysed together in blood pressure categories according to international guidelines [21]. This was done because a low diastolic blood pressure in the presence of a high systolic blood pressure might have a different aetiology and thus prognosis, e.g. high atherosclerotic burden, than the same low diastolic blood pressure with a low systolic blood pressure, e.g. heart failure [25]. This was confirmed by the finding that a low diastolic blood

pressure is only harmful in the presence of a low systolic blood pressure in the very old.

How can we explain the results? Hypertension is a well-known risk factor for heart failure. Possibly, longstanding hypertension leads to preclinical heart failure that might lower actual blood pressure and therefore could be partly responsible for our finding [26]. Nevertheless, it cannot be excluded that blood pressure-lowering therapy contributed to the inverse relation between low blood pressure and mortality risk.

The strength of the present study is that it seems to reflect the history of elderly individuals with different levels of blood pressure, given the population-based character, the 87% enrolment of the 85-year-olds and the small number of individuals who were lost to follow-up. Its weakness is that it relies on a baseline assessment of blood pressure. Another possible weakness might be the lack of uniformity for a positive history of hypertension. It could be that the general practitioners used variable criteria for a former diagnosis of hypertension. Moreover, because of the observational nature of the data, we cannot exclude that residual confounding is at play and therefore we are not able to draw final conclusions on causality.

From the present study, the clear message is that in the oldest old, blood pressure is not a predictor for mortality, again except for those participants with a blood pressure lower than 140/70 mmHg. Our finding supports the general clinical feeling that at old age a blood pressure lower than 140/70 mmHg is relatively rare; in the present cohort only 8.4 % of the participants had blood pressures lower than 140/70 mmHg. This is in sharp contrast to younger age groups where these ranges of blood pressures are considered to be normal. The finding that blood pressures higher than 140/70 mmHg are found not to be associated with mortality risk in the oldest old might have important clinical implications. Moreover, a blood pressure below 140/70 mmHg in the general population of oldest old identifies a new high-risk subgroup. The therapeutic consequences of these findings are unknown and have to be explored in future. The fact that a history of hypertension remains a risk factor for cardiovascular mortality in old age, independent of the current blood pressure, further complicates clinical decision-making.

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