New perspectives on cardiovascular risk prediction in old age

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Chapter 4

Low blood pressure predicts increased mortality in very old age even without heart failure: the Leiden 85-plus Study

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ABSTRACT

Aims

To investigate whether low systolic blood pressure is predictive for increased mortality risk in 90-year-old subjects without heart failure, defined by low levels of NT-proBNP, as well as in 90-year-old subjects with high levels of NT-proBNP.

Methods and results

This study was embedded in the Leiden 85-plus Study, an observational population-based prospective study. All 90-year-old participants (n = 267) were included between 2002 and 2004 and followed up for mortality for at least 5 years. Differences in mortality risks were compared between participants with low systolic blood pressure (≤150 mmHg) and high systolic blood pressure (>150 mmHg) within strata of low NT-proBNP (<284 pg/mL for women and >306 pg/mL for men = lowest tertile) vs. high NT-proBNP (middle and highest tertile) at age 90 years. During maximal follow-up of 7.2 years, 212 participants (79%) died. Among participants with low NT-proBNP, low systolic blood pressure gave a two-fold increased risk (hazard ratio 2.0, 95% confidence interval 1.1–3.4) compared with participants with high systolic blood pressure. For participants with high NT-proBNP, low systolic blood pressure provided a 1.7 increased mortality risk (95% confidence interval 1.2–2.3) compared with high systolic blood pressure.

Conclusion

Low systolic blood pressure is predictive for increased mortality risk in 90-year-old subjects, irrespective of the NT-proBNP level. Therefore, the absence or presence of heart failure as determined by NT-proBNP does not influence the prognostic value of low systolic blood pressure with regard to mortality in the oldest old.

INTRODUCTION

High systolic blood pressure is an established risk factor for cardiovascular disease and mortality in middle-aged persons. In contrast, observational data on the predictive relationship between systolic blood pressure and mortality in very old age are less consistent.[1-4] One large meta-analysis showed that high systolic blood pressure predicts increased mortality risk in all age groups, but also that this relationship was considerably attenuated with age.[1] Others, especially observational studies in exclusively elderly populations, have shown that not high, but low systolic blood pressure predicts increased mortality.[2-4] To date, it remains unknown which mechanism(s) are responsible for this 'inversion of risk prediction'.

A plausible explanation is that (subclinical) heart failure may, at least in part, underlie this 'inversion of risk prediction'.[2,4-7] Prolonged and uncontrolled hypertension can lead to heart failure that might lower blood pressure.[8] Indeed, patients with heart failure tend to have lower blood pressure values. Our group previously reported that very old subjects with low systolic blood pressure have an impaired cardiac function.[5] Therefore, we hypothesized that in very old subjects without heart failure, low systolic blood pressure is not predictive for increased mortality risk compared with those with high systolic blood pressure, but, instead, still follows the usual pattern (low systolic blood pressure associated with low risk, and high systolic blood pressure associated with high risk).

Diagnosing heart failure in old age is challenging. Symptoms and signs in combination with NT-proBNP reliably identify the presence or absence of heart failure in the vast majority of patients.[9] NT-proBNP alone is a sensitive but not highly specific marker of heart failure. The negative predictive value of low levels of NT-proBNP is robust, and low levels of NT-proBNP are reported to exclude heart failure.[10-12] Also, within the Leiden 85-plus Study, it was shown that low NT-proBNP levels exclude echocardiographic abnormalities in very old age.[13]

The present study investigates the predictive relationship between systolic blood pressure and mortality in a population-based cohort of nonagenarians without heart failure as evidenced by low levels of NT-proBNP, as well as in nonagenarians with high levels of NT-proBNP.

METHODS

Study population

The Leiden 85-plus Study is a prospective population-based study in 85-year-old inhabitants of the city of Leiden (The Netherlands). The study design and characteristics of the cohort have been described in detail.[14,15] Between September 1997 and September 1999,

705 people in the 1912–1914 birth cohort reached the age of 85 years and were eligible to participate in the study. No exclusion criteria were used. Fourteen people died before enrolment; a total of 599 (87%) people gave informed consent and were enrolled. Of the 599 participants enrolled in the study at age 85 years, 295 died before the age of 90, and 37 refused further participation or refused blood sampling. Thus, for the present study, 'baseline measurements at age 90 years', including systolic blood pressure and NT-proBNP levels, were available for 267 participants, all 'included' between 2002 and 2004. Participants were visited by a research nurse at their place of residence to collect information on socio-demographic characteristics, as well as a venous blood sample. The Medical Ethics Commission of the Leiden University Medical Center approved the study, and all participants gave informed consent. The investigation conforms with the principles outlined in the Declaration of Helsinki.

Blood pressure and blood pressure categories

At age 90, blood pressure was measured twice with an interval of 2 weeks. Blood pressure was measured using a mercury sphygmomanometer, in the seating position after at least 5 min rest without having performed vigorous exercise during the preceding 30 min. The systolic value was measured at the onset of phase 1 of the Korotkoff sounds. For the analysis, we used the mean of the two systolic values at age 90 years.

Systolic blood pressure values were divided into two categories, 'low' and 'high' systolic blood pressure. Low systolic blood pressure was defined as a systolic blood pressure ≤ 150 mmHg, and high systolic blood pressure was defined as a systolic blood pressure >150 mmHg. This cut-off was based on the target value used in studies assessing the risks and benefits of treating hypertension in individuals aged ≥ 80 years.[16]

N-terminal pro brain natriuretic peptide and categories of heart failure

Serum levels of NT-proBNP were measured for all participants at age 90 in one batch using the NT-proBNP assay of Roche Diagnostics (Mannheim, Germany) on a Roche Modular E-17 automated immunoanalyser. The within-run coefficient of variation was ≤ 2% and total variation was ≤ 6% at all levels measured (400–13 500 pg/mL). Low levels of NT-proBNP can be used to rule out the diagnosis of heart failure.[10-12] Since clinical cut-offs for NT-proBNP in very old age are still the subject of debate,[12] in the present study we used gender-specific tertiles of NT-pro-BNP levels. Heart failure was considered absent in all participants in the lowest NT-proBNP tertile (NT-proBNP <284 pg/mL for women and <306 pg/mL for men). Heart failure was considered to be probably present in the participants in the middle and highest NT-proBNP tertile (NT-proBNP ≥ 284 pg/mL for women and ≥ 306 pg/mL for men).

Other clinical characteristics

Each participant's general practitioner (or, if applicable, nursing home physician) was interviewed annually about the participant's medical history, using standardized questionnaires, including questions on present and past cardiovascular[17] and non-cardiovascular morbidities.

Mortality

All participants were followed for mortality from age 90 years onwards. Dates of death were obtained from municipality records, with the censoring date 31 December 2009 (until ages 95–97 years). Specific data on cause of death were obtained from Statistics Netherlands, where all national death certificates are coded according to the International Classification of Diseases and Related Disorders, 10th revision (ICD-10).[18] Causes of death were divided into two groups: cardiovascular mortality (ICD codes I00–I99) and non-cardiovascular mortality (all other ICD codes).

Statistical analysis

Participants were divided into two groups based on the NT-proBNP levels (lowest gender-specific tertile vs. middle and highest gender-specific tertile). Baseline summary characteristics are reported as mean with standard deviation (SD) for continuous variables and as numbers with percentage for categorical variables. Distributions of categorical clinical characteristics were compared using X^2 tests, and continuous data were compared using independent t-tests. Time to event curves were constructed with the Kaplan–Meier method and compared using log rank test. Hazard ratios (HR) and corresponding 95% confidence intervals (CIs) were calculated with Cox proportional hazard models. The analysis of the mortality risk for the lowest tertile NT-proBNP compared with the middle/highest tertiles NT-proBNP was adjusted for the continuous systolic blood pressure value. The analysis of the mortality risk for low systolic blood pressure compared with high systolic blood pressure was adjusted for the continuous NT-proBNP value. The HRs for the two NT-proBNP groups were calculated with Cox proportional hazard models, containing the systolic blood pressure category (low or high) as a categorical variable. These HRs were adjusted for sex only, because the present study focused on the question of whether the predictive value of low systolic blood pressure for mortality in very old age is dependent on the presence of (subclinical) heart failure and not on in-depth aetiology.[19] All participants were 90 years of age, so no adjustment for age was made. HRs per increase in SD for systolic blood pressure at age 90 years and NT-proBNP at age 90 years, respectively, were also analysed with Cox proportional hazard models. In the additional model, the HRs were adjusted for the use of antihypertensive medication and history of diabetes, cardiac morbidity, other vascu-

lar morbidity, non-cardiovascular morbidity (including history of COPD, malignancies, arthritis, Parkinson's disease, and hip fracture), and hypertension. To explore whether the predicted difference in mortality risk was attributable to terminally ill patients, participants who died within 3 months after baseline were excluded in an additional sensitivity analysis. To evaluate the influence of the choice to combine the middle and highest tertile of NT-proBNP in the analyses, the analyses were repeated including only the lowest and highest tertile of NT-proBNP in the analyses.

Data analysis was performed using SPSS 17 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Study population

Table 1 presents the baseline characteristics according to NT-proBNP values. At age 90 years, < 30% of the participants were male, and almost 40% of the participants were institutionalized. Half of the study population had a history of cardiac morbidity, and almost half of the population used antihypertensive drugs. At age 90, mean systolic blood pressure was 152 mmHg (range 105–203 mmHg). There was no difference in systolic blood pressure at age 90 between participants with high NT-proBNP and those with low NT-proBNP. Participants with high NT-proBNP more often had a history of cardiac disease compared with those with low NT-proBNP (56% vs. 36%, P = 0.002). There were no differences in other clinical and socio-demographic characteristics between participants with low and high NT-proBNP (P ≥0.05).

Mortality

During maximal follow-up of 7.2 years (median 3.6), 212 (79%) of the 267 participants died from age 90 years onwards. Participants with high NT-proBNP had a 2.9 increased mortality risk (95% CI 2.1–4.0) compared with those with low NT-proBNP, adjusted for the continuous systolic blood pressure value at age 90 years (HR 2.5, 95% CI 1.7–3.5 when adjusted for the use of antihypertensive medication and concomitant diseases mentioned in Table 1). A 1 SD increase in NT-proBNP (1915 pg/mL) was associated with an increased mortality risk (HR 1.39, 95% CI 1.25–1.55). Participants with low systolic blood pressure had a 1.6-fold increased mortality risk (95% CI 1.2–2.1) compared with participants with high systolic blood pressure, adjusted for the continuous NT-proBNP value at age 90; and HR 2.0 (95% CI 1.4–2.7) when adjusted for the use of antihypertensive medication and concomitant diseases mentioned in Table 1. A 1 SD increase in systolic blood pressure (18 mmHg) was associated with a decreased mortality risk (HR 0.77, 95% CI 1.25–1.55).

Table 1. Baseline sociodemographic and clinical characteristics at age 90 years, according to N-terminal pro-brain natriuretic peptide (NT-proBNP) value (n=276)

		NT-proBNP[a]	
	Overall (n=267)	Low (n=90)	High (n=177)
Sociodemographics			
Male (%)	73 (27%)	25 (28%)	48[b] (27%)
Institutionalized (%)	100 (38%)	32 (36%)	68[b] (38%)
Primary school only (%)	167 (63%)	55 (61%)	112[b] (64%)
State pension only (%)	41 (15%)	10 (11%)	31[b] (18%)
Systolic blood pressure (SD)	152 (18)	152 (17)	151[c] (18)
History of (non)cardiovascular comorbidity			
Cardiac morbidity[d] (%)	131 (49%)	32 (36%)	99[e] (56%)
Other vascular morbidity[f] (%)	44 (17%)	15 (17%)	29[b] (16%)
Non-cardiovascular morbidity[g] (%)	170 (64%)	55 (61%)	115[b] (65%)
Hypertension (missing n=5) (%)	145 (55%)	44 (50%)	101[b] (58%)
Use of antihypertensive drugs (missing n=46) (%)	104 (47%)	30 (41%)	74[b] (50%)
Diabetes	47 (18%)	11 (13%)	36 [b] (21%)

SD, standard deviation.

[a] Low NT-proBNP <284 pg/mL for women and <306 pg/mL for men; high NT-proBNP ≥284 pg/mL for women and ≥306 pg/mL for men.

[b] X^2 $P \geq 0.05$.

[c] *t*-test $P \geq 0.05$.

[d] Presence of a medical history of myocardial infarction, angina pectoris, arrhythmias, or heart failure.

[e] X^2 $P = 0.002$.

[f] Including history of stroke and peripheral arterial disease.

[g] Including history of chronic obstructive pulmonary disease, malignancies, arthritis (including arthrosis, rheumatoid arthritis and polymyalgia rheumatica), Parkinson's disease, and hip fracture.

Figure 1 presents the Kaplan–Meier analysis of time to all-cause mortality depending on the systolic blood pressure at age 90 years for those in the low and high NT-proBNP category. It shows that low systolic blood pressure was associated with an increased cumulative all-cause mortality compared with high systolic blood pressure, in both the low and high NT-proBNP categories. In participants with low and in participants with high NT-proBNP, those with low systolic blood pressure had an increased all-cause mortality risk compared with participants with high systolic blood pressure (Table 2). The same was seen after analysis of the data with full adjustments for the use of antihypertensive medication and a range of concomitant diseases (HR 2.6, 95% CI 1.3–5.3 in participants with low NT-proBNP and low systolic blood pressure compared with those with low NT-proBNP and high systolic blood pressure, and HR 2.1, 95% CI 1.5–3.1 in participants with high NT-pro-BNP and low systolic blood pressure compared with those with high NT-proBNP and high systolic blood pressure). When the same analysis was carried out

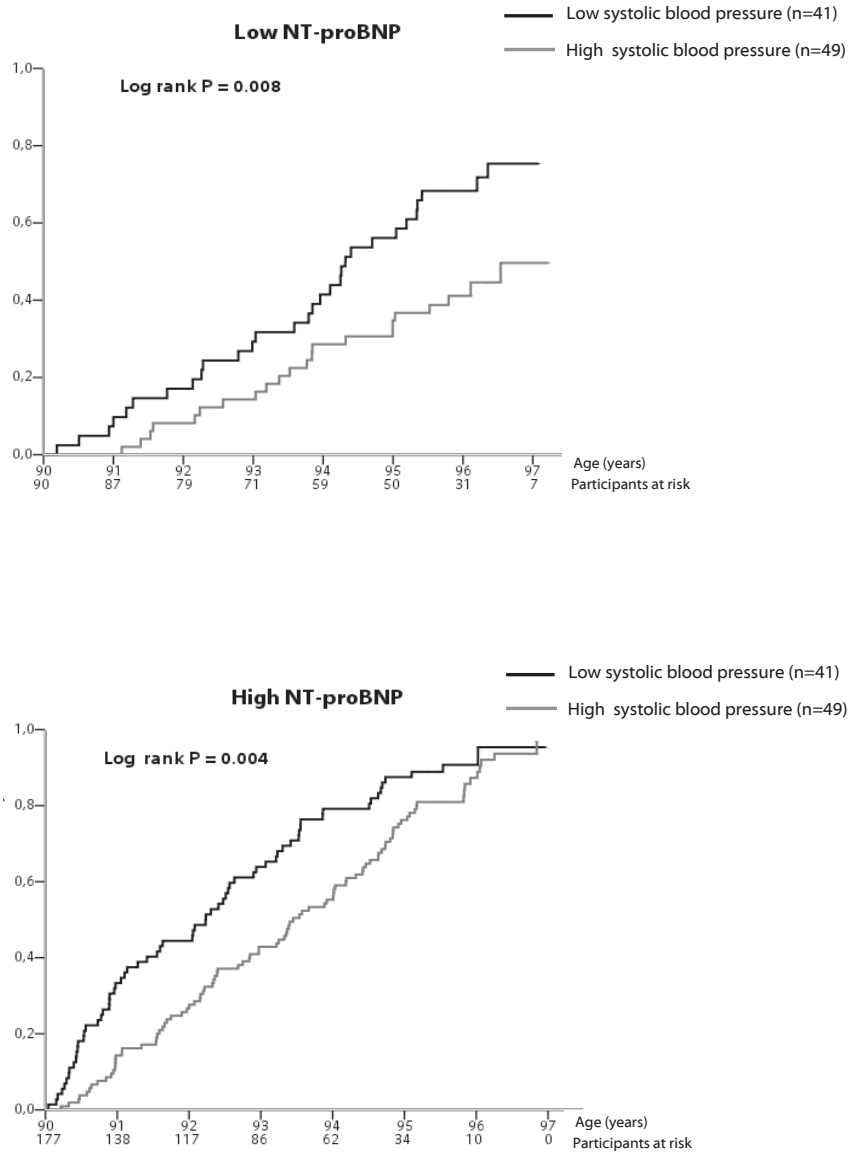

Figure 1. Cumulative all-cause mortality depending on the systolic blood pressure at age 90 years for (a) participants from age 90 years onwards with low NT-proBNP(<284 pg/mL for women and <306 pg/mL for men); and (b) for participants with high NT-proBNP (≥284 pg/mL for women and ≥306 pg/mL for men)

for cause-specific mortality, the same risk patterns were observed for cardiovascular and non-cardiovascular mortality (Table 2).

When participants who died within 3 months after baseline were excluded, similar increased mortality risks were seen. In both those with low and those with high NT-proBNP, low systolic blood pressure still predicted increased mortality risk (HR 1.9, 95% CI 1.0–3.3 and HR 1.6, 95% CI 1.1–2.2, respectively).

When the analyses were repeated including only the lowest and the highest NT-proBNP tertile, the same results emerged (data not shown).

Table 2. Mortality in low/high N-terminal pro-brain natriuretic peptide categories, depending on systolic blood pressure at age 90 years (n=267)

	Cumulative 5-year mortality		
	Low systolic blood pressure[a] (93/113)[b]	High systolic blood pressure (116/154)[b]	HR (95% CI)[c]
All-cause mortality[d]			
Low NT-proBNP[e]	30/41	22/49	2.0 (1.1-3.4)
High NT-proBNP[e]	66/72	94/105	1.7 (1.2-2.3)
Cardiovascular mortality			
Low NT-proBNP	9/40	6/49	2.5 (0.9-7.2)
High NT-proBNP	22/72	35/101	1.4 (0.8-2.4)
Non-cardiovascular mortality			
Low NT-proBNP	20/40	16/49	1.7 (0.9 -3.3)
High NT-proBNP	44/72	58/104	1.8 (1.2 -2.6)

CI, confidence interval; HR, hazard ratio.

[a] Low systolic blood pressure ≤150 mmHg; high systolic blood pressure >150 mmHg.

[b] Number of deceased/total.

[c] Sex-adjusted hazard ratios (95% CI); hazard ratios express risk of mortality associated with low blood pressure compared to high blood pressure (as a reference category).

[d] Complete cause-specific mortality data were missing for five participants.

[e] Low NT-proBNP <284 pg/mL for women and <306 pg/mL for men; high NT-proBNP ≥284 pg/mL for women and ≥306 pg/mL for men.

DISCUSSION

This study shows that, in nonagenarians, low systolic blood pressure defined as ≤ 150 mmHg is predictive for an almost doubled mortality compared with high systolic blood pressure, in those without (subclinical) heart failure based on low NT-proBNP levels as well as in those with high NT-proBNP levels. Therefore, we could not confirm the hypothesis that impaired cardiac function with concomitant low systolic blood pressure, in part, underlies the association between low blood pressure and increased mortality. The potential clinical relevance of these findings, after replication in another cohort,

may become clearer when alternative explanations for the observed inversion of risk prediction of low systolic blood pressure in very old age have been studied.

Strengths and limitations of study

The use of tertiles of NT-proBNP could potentially introduce misclassification. At age 90 years, heart failure was considered absent based on low NT-proBNP values, but, vice versa, no explicit diagnosis of heart failure was made based on higher NT-proBNP values. The level of the lowest tertile in the present study (<284 pg/mL for women and <306 pg/mL for men) is, however, in line with cut-off points used to exclude heart failure in earlier studies.[10,12,13] Also, there was no difference in the predictive value of low systolic blood pressure in the analysis adjusted for the continuous NT-proBNP value, confirming that the chosen cut-off value did not influence our results. Misclassification by using tertiles of NT-proBNP is therefore minimal.

We chose the cut-off value of 150 mmHg for high systolic blood pressure at age 90 years. This could be seen as an arbitrary choice. However, this value is based on the target value of systolic blood pressure used in the 2011 revision of the Dutch Guideline on Cardiovascular Risk Management,[20] as well as studies assessing the risks/benefits of treating hypertension in individuals aged ≥ 80 years,[16] indicating that this cut-off value may be clinically more relevant than the formal cut-off value of 140 mmHg as incorporated in the World Health Organization (WHO) definition of hypertension.[21] This was supported by the fact that there was no difference in the predictive value of high NT-proBNP in the analysis adjusted for the continuous systolic blood pressure value.

It may be considered a limitation of the present study that only participants aged 90 years were evaluated. Since our study population was a selection of strong survivors, we cannot extrapolate our conclusions to younger people. Still, our general population-based study is well suited to show the 'proof of principle' of our research question. Nevertheless, replication in other, preferably larger, study populations is warranted.

Comparison with other studies

The relationship between high NT-proBNP and increased mortality risk, as well as the relationship between low systolic blood pressure and increased mortality risk described in the present study are in line with earlier observational studies in the elderly population showing that high (NT-pro)BNP[22-25] and low systolic blood pressure[2-4] are each associated with an increased mortality risk. The present study shows that, in nonagenarians, low systolic blood pressure remains associated with a doubled mortality risk even when (subclinical) heart failure is ruled out and regardless of the use of antihypertensive medication and concomitant diseases. To our knowledge, no other study has analysed

the association between low systolic blood pressure and increased mortality in participants in whom heart failure was excluded based on their NT-proBNP level.

Implications

Although the present study was not aimed at investigating aetiological mechanisms behind the observed associations, it is tempting to hypothesize that the increased all-cause mortality risk associated with low systolic blood pressure as well as the increased all-cause mortality risk associated with heart failure are two unrelated phenomena. This finding warrants additional studies on the underlying mechanism(s). Also, instead of focusing on a monocausal explanation (e.g. heart failure,[5] atrophy of the brain, or chronic hypoperfusion), low systolic blood pressure in very old age could also be a marker of an underlying syndrome that is associated with increased mortality (such as general wasting, inflammation, and sarcopenia). Also, the 'inversion of risk prediction' of high blood pressure in old age is not a unique phenomenon. In old age, high cholesterol[26] and obesity[27] are no longer risk factors for mortality, and in some studies have even been shown to be associated with better survival. These paradoxical observations have also been referred to as 'reverse epidemiology', 'inverse epidemiology', or 'risk factor paradox'. In chronic dialysis patients, the reverse epidemiology of high blood pressure,[28] high body mass index,[29] and high serum cholesterol or serum creatinine concentration[29] has also been described. The same reverse epidemiology was observed in other chronic diseases such as chronic heart failure,[30] advanced COPD,[31] and rheumatoid arthritis.[32]

Conclusion

In conclusion, the present study shows that in very old age, low systolic blood pressure is associated with an almost doubled mortality risk, even when there is no evidence of underlying heart failure. Thus, heart failure does not underlie the 'inversion of risk prediction' of systolic blood pressure in very old age. Future studies are needed to replicate these findings, and to gain more insight into the aetiological mechanisms and clinical implications.

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