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Published in:
Age and Ageing

DOI:
10.1093/ageing/afq080

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Received 25 November 2009; accepted in revised form 14 May 2010

Age and Ageing 2010; **39:** 603–609
doi: 10.1093/ageing/afq080
Published electronically 9 July 2010

Lower blood pressure associated with higher mortality in elderly diabetic patients (ZODIAC-12)

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Abstract

Objective: to investigate the relationship between blood pressure over time and mortality in elderly patients with type 2 diabetes mellitus (T2DM).
Design: prospective observational cohort study.
Setting: primary care, Zwolle, The Netherlands.
Subjects: patients with T2DM aged 60 years and older (n = 881). The cohort was divided into two age categories: 60–75 years and older than 75 years.

Methods: updated means for systolic, diastolic and pulse pressures were calculated after a median follow-up time of 9.8 years. These values were used as time-dependent covariates in a Cox proportional hazard model. Main outcome measures were all-cause and cardiovascular mortality.

Results: all of the blood pressure measures were inversely related to all-cause mortality in elderly diabetic patients (>75 years). Furthermore, these relationships were specifically found in elderly patients treated with antihypertensive medication at baseline. A decrease of 10 mm Hg in systolic blood pressure, diastolic blood pressure and pulse pressure led to a mortality increase of 20% [95% confidence interval (95% CI): 12–27%], 26% [95% CI: 12%–38%] and 20% [95% CI: 10%–29%], respectively. In the low age group (60–75 years), no relationship was found between blood pressure and mortality.

Conclusions: blood pressure is a marker for mortality in elderly T2DM patients; however, the relationship is inverse.

Keywords: *diabetes mellitus type 2, elderly, mortality, blood pressure, observational studies*

Introduction

Hypertension increases the already high risk for cardiovascular disease in patients with type 2 diabetes mellitus (T2DM) [1, 2]. Although many large randomised controlled trials have shown that blood pressure control is beneficial for patients with T2DM, the level of evidence for aggressive treatment as recommended by the various international guidelines is low [3–5]. Recent studies have shown that targeting for a systolic blood pressure lower than the standard target (<140 mm Hg) does not provide additional benefit [6–8].

Aggressive treatment is even more controversial in old age, since several epidemiological population studies and one meta-analysis of randomised controlled trials suggest an inverse relationship between mortality risk and blood pressure in elderly subjects from the general population [9–16]. Although a few hypertension trials included patients older than 75 years, no separate analyses were performed for this age group. A recent study has shown that in patients over the age of 80 without heart failure for whom antihypertensive therapy was considered indicated, a reduction in blood pressure resulted in improved cardiovascular morbidity as well as cardiovascular and all-cause mortality [17]. However, this study included healthy elderly patients and only a small subgroup of patients with T2DM. As a consequence, data from this study cannot be generalised to elderly diabetic patients who have higher rates of functional disability and coexisting illnesses than those without T2DM [18, 19].

To our knowledge, the relationship between blood pressure and mortality in (elderly) diabetic patients has been described only once before in a cohort study from Finland in which an inverse relationship was reported [20]. To add to the body of evidence, we analysed the all-cause and cardiovascular mortality risk in association with blood pressure and pulse pressure over time in a cohort of elderly diabetic patients.

Methods

This study is part of the ZODIAC (Zwolle Outpatient Diabetes project Integrating Available Care) study; the design and details of which have been presented elsewhere [21]. In this project, general practitioners are assisted by hospital-based nurses specialised in diabetes in their care of patients with T2DM. The patients consult with the nurses once per year. In the first year (1998) of the ZODIAC study, 1,664 patients were assessed for eligibility. A total of 338 patients were already treated in the secondary care for their diabetes. Another 57 patients were excluded because of a very short life expectancy (including patients with active cancer) or insufficient cognitive abilities. Eventually, 1,269 eligible patients were invited to participate. Of those, 1,143 patients agreed to participate in the study. For the present study, we selected all patients aged 60 years and older (n = 881). Baseline data, collected in 1998 and 1999, consisted of a full medical history including macrovascular complications, medication use and tobacco consumption. Laboratory and physical assessment data, such as lipid profile, creatinine levels, the presence of albuminuria, blood pressure, weight and height, were collected annually. Blood pressure was measured twice with a Welch Allyn Sphygmomanometer in the supine position after at least 5 min of rest. For each visit, the mean blood pressure of two recordings was calculated. Early 2009, the life status and cause of death were retrieved from records maintained by the hospital and the general practitioners.

The cohort of 881 patients was divided into two age groups: 60–75 years (low age group) and older than 75 years (high age group). Updated means for systolic blood pressure, diastolic blood pressure and pulse pressure were calculated for each individual from baseline to the end of follow-up by averaging the baseline values with the mean annual values. This technique is similar to the one used in the United Kingdom Prospective Diabetes Study [22]. For example, at 2 years the updated mean of systolic blood pressure is the average of baseline, 1- and 2-year values. Eleven baseline variables were selected for their possible confounding effects on the relationship between blood pressure and mortality: gender, smoking (yes or no), body mass index, duration of diabetes, serum creatinine level, cholesterol-HDL ratio, macrovascular complications (yes or no), albuminuria (yes or no), the use of lipid lowering and antihypertensive medications (yes or no) and age. Patients were considered to have macrovascular complications when they had a previous history of angina pectoris, myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, stroke or transient ischaemic attack.

Continuous variables are represented as a mean (± standard deviation) for the normally distributed values and as a median (interquartile range) for the non-normally distributed values. Normality was evaluated using Q–Q plots and histograms. Nominal variables are represented as total number (percentage). A Cox proportional hazard model was used to investigate the relationship between the updated means of the different blood pressure measures, as time-dependent covariates, and mortality with adjustment for the selected confounders. The model was used for both age groups. Analyses were repeated in strata according to the baseline use of antihypertensive medication (yes or no). All hazard ratios (HRs) refer to a pressure increase of 10 mm Hg. For Kaplan–Meier curves, the baseline systolic blood pressure values were categorised into three different groups (<140, 140–169 and ≥170 mm Hg). The assumption of proportional hazards was checked by inspecting the Schoenfeld residual plots for the baseline predictor variables and the log(−log(S(t))) plots for different categories of the baseline predictors. No substantial deviations from the plots were observed. All analyses were performed with SPSS version 15.0.1 software (SPSS Inc., Chicago, IL, USA) and Stata version 10 (StataCorp, College Station, TX, USA).

Results

The baseline characteristics of the study population are shown in Table 1. The median age [interquartile range] at baseline was 80 years [77–83] in the high age group (>75 years) and 69 [65–72] in the low age group (60–75 years). During a median follow-up time of 9.8 years, 267 patients (81.9%) in the high age group and 198 patients (35.7%) in the low age group had died. Cause of death was not known for 19 patients (2.2%), and 19 patients were lost to follow-up (2.2%). The proportion of deaths attributable to cardiovascular factors was 42.7% in the high age group and 41.9% in the low age group. In the high age group, the mortality rate for patients with a systolic blood pressure <140 mm Hg was 89.7% compared to 76.9% in the group with a blood pressure ≥170 mm Hg (Figure 1). In the low age groups, these proportions were 37.0 and 39.6%, respectively.

Table 1. Baseline characteristics

	60–75 Years	>75 Years
Characteristic	*n* = 555	*n* = 326
Age (years)	69 (65–72)	80 (77–83)
Male sex	230 (41%)	118 (36%)
Body mass index (kg/m^2)	29.0 (4.6)	27.7 (4.4)
Systolic blood pressure (mm Hg)	158.2 (25.1)	156.0 (24.0)
Diastolic blood pressure (mm Hg)	84.8 (11.2)	81.5 (10.8)
Pulse pressure (mm Hg)	73.5 (20.2)	74.6 (18.9)
Current smoking	85 (15%)	31 (10%)
Albuminuria present	245 (44%)	181 (56%)
Cholesterol-HDL ratio	5.3 (1.5)	4.9 (1.6)
HbA1c (%)	7.5 (1.4)	7.4 (1.2)
Macrovascular complications present	208 (37%)	149 (46%)
Receiving antihypertensive treatment	277 (50%)	197 (60%)
- ACE-inhibitor	128 (23.1%)	84 (25.8%)
- Beta-blocker	119 (21.4%)	59 (18.1%)
Receiving lipid lowering treatment	80 (14%)	15 (5%)
Duration of T2DM (years)	6 (3–12)	8 (4–13)
Serum creatinine (μmol/l)	92 (82–104)	98 (86–117)

Data are means (± SD), medians (interquartile range) or *n* (%).

All-cause and cardiovascular mortality

Table 2 presents the HRs for systolic blood pressure, diastolic blood pressure and pulse pressure for all-cause and cardiovascular mortality. The updated means for all blood pressure measures in the high age group were inversely related to all-cause mortality. After adjusting for confounders, the mortality risk increased by 15% [95% confidence interval (95% CI): 9–21%] and 22% [95% CI: 10–32%] for every 10 mm Hg decrease in systolic and diastolic pressures, respectively. The mortality risk was 15% [95% CI: 7–22%] higher per 10 mm Hg decrease in pulse pressure after adjusting for the selected confounders. There was no significant relationship between cardiovascular mortality and blood pressure in the high age group. In the low age group, the associations between blood pressure and mortality, both all-cause and cardiovascular mortality, were also not significant.

Baseline use of antihypertensive medication

After adjusting for confounders, systolic blood pressure was inversely related to both all-cause and cardiovascular mortality in the group of elderly patients (>75 years) who received antihypertensive medication at baseline ($HR_{\text{all-cause}}$ 0.80 [95% CI: 0.73–0.88], $HR_{\text{cardiovascular}}$ 0.86 [95% CI: 0.75–0.98]). For elderly patients, who did not use antihypertensive medication, the HRs were 0.95 [95% CI: 0.84–1.08] and 1.02 [95% CI: 0.84–1.23] for all-cause and cardiovascular mortality, respectively. For diastolic blood pressure and pulse pressure, the results were comparable: for elderly patients who received antihypertensive medication, the HRs for all-cause mortality were 0.74 [95% CI: 0.62–0.88] and 0.80 [95% CI: 0.71–0.90], respectively.

Low blood pressure before death

Low blood pressure seen in patients close to death could account for the inverse relationship between blood pressure and mortality in our group of elderly patients. To examine this, we performed an additional analysis in which we excluded the deaths early in follow-up and an analysis in which we excluded the last blood pressure value before death. The relationships between blood pressure and mortality in these analyses did not relevantly change (data not shown).

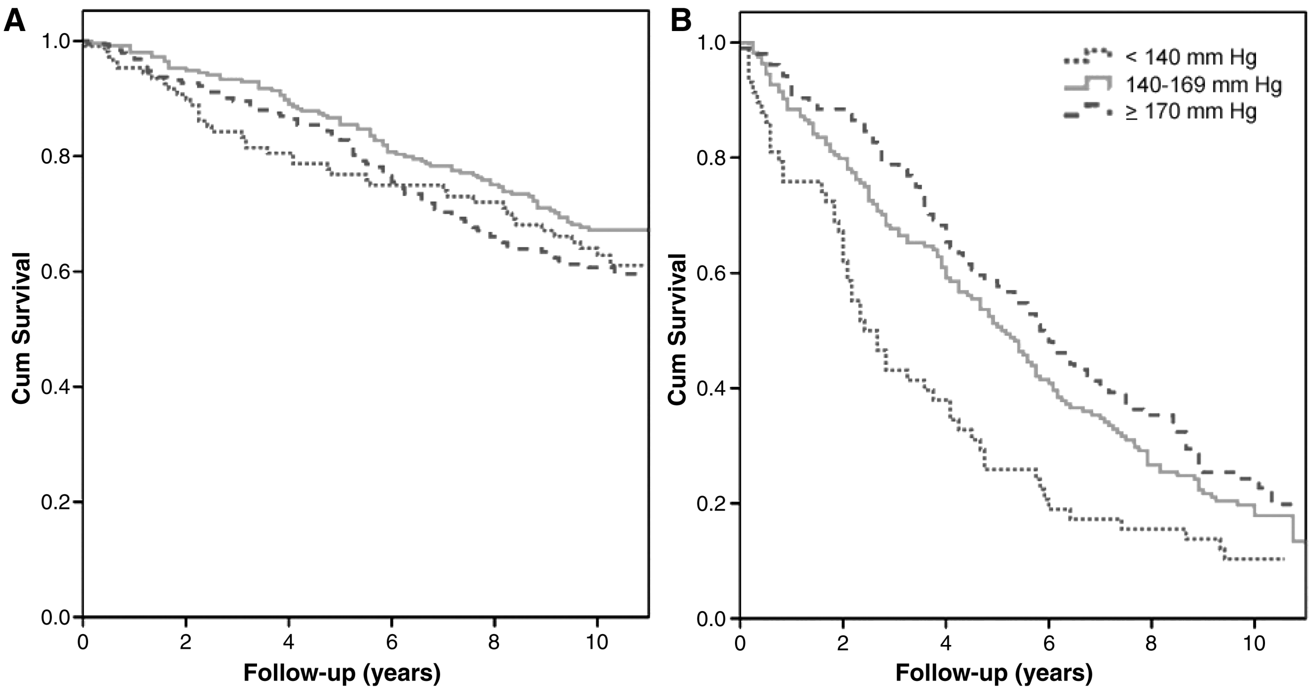

Figure 1. Kaplan–Meier curve; systolic blood pressure and all-cause mortality in both the low (A) and high (B) age groups.

Table 2. Hazard ratios for all-cause and cardiovascular mortality

Blood pressure variable	60–75 Years		>75 Years	
	All-cause mortality	Cardiovascular mortality	All-cause mortality	Cardiovascular mortality
Systolic blood pressure				
Unadjusted for confounders	1.03 (0.95–1.10)	0.95 (0.85–1.07)	0.86 (0.80–0.91)	0.90 (0.82–0.99)
Adjusted for confounders	1.01 (0.93–1.09)	0.92 (0.82–1.05)	0.85 (0.79–0.91)	0.90 (0.81–1.00)
Diastolic blood pressure				
Unadjusted for confounders	0.94 (0.80–1.12)	0.84 (0.65–1.08)	0.75 (0.65–0.86)	0.87 (0.71–1.07)
Adjusted for confounders	1.04 (0.89–1.22)	0.90 (0.70–1.16)	0.78 (0.68–0.90)	0.91 (0.74–1.13)
Pulse pressure				
Unadjusted for confounders	1.06 (0.97–1.17)	0.98 (0.85–1.14)	0.86 (0.79–0.93)	0.89 (0.78–1.00)
Adjusted for confounders	0.99 (0.90–1.10)	0.90 (0.77–1.06)	0.85 (0.78–0.93)	0.88 (0.77–1.01)

The hazard ratios (95% confidence interval) refer to a pressure increase of 10 mm Hg. Gender, smoking (yes or no), body mass index, duration of diabetes, serum creatinine level, cholesterol-HDL ratio, macrovascular complications (yes or no), albuminuria (yes or no), the use of lipid lowering and antihypertensive medications (yes or no) and age were selected as potential confounders.

Discussion

In this prospective observational study, lower blood pressure was related to higher all-cause and cardiovascular mortality rates in elderly T2DM patients (>75 years) who were using antihypertensive medication at baseline. A decrease of 10 mm Hg in systolic blood pressure, diastolic blood pressure and pulse pressure was associated with an increase in mortality risk of 20, 26 and 20%, respectively. Remarkably, these relationships did not exist in the elderly patients who did not receive antihypertensive treatment at baseline. We also observed another important finding: there was no relationship between blood pressure and mortality in the low age group (60–75 years).

A recent meta-analysis showed that the all-cause mortality risk is not reduced by hypertension treatment in very elderly patients from the general population [23]. Furthermore, several epidemiological studies have described an inverse relationship between blood pressure and mortality in elderly subjects [10–16]. To our knowledge, only the study by Rönnback *et al.* showed such an inverse relationship in elderly diabetic patients [20]. Where this study used the baseline blood pressure values in their analyses, we used the different measures of blood pressure as time-dependent covariates. This allowed us to correct for changes in blood pressure over time and even, to some extent, for the imprecision inherent to a single blood pressure measurement. Rönnback *et al.* selected patients in primary care using a single selection criterion: T2DM, as did we. As a result, both of these study populations are more representative of typical type 2 diabetic patients than the populations studied in other hypertension trials.

It is important to emphasise that the associations found between blood pressure and mortality do not imply causality. Because of the observational nature of our study, we can only speculate about the underlying mechanisms. However, it is interesting to generate hypotheses about the role of antihypertensive medication. There are many possible explanations why the inverse relationship was only found for elderly patients treated with antihypertensive medication at baseline. Firstly, excessive lowering of diastolic blood pressure could play a role. In the Systolic Hypertension in the Elderly Program, a decrease of diastolic blood pressure in the active treatment group was related to an increased risk of cardiovascular disease [24]. More recently, results of the International Verapamil SR-trandolapril trial showed that a systolic blood pressure below 115 mm Hg was associated with increased mortality [7].

Secondly, side effects of antihypertensive medication may be a possible confounder. For example, orthostatic hypotension, a possible manifestation of autonomic neuropathy, has been described as an independent predictor of all-cause mortality [25]. Its prevalence increases with age; moreover, it is more prevalent in patients with diabetes [26, 27]. Because data on orthostatic hypotension have not been collected in our study, we can only hypothesise about its possible effect.

Thirdly, the existing co-morbidities and the general frailty of elderly patients have been suggested as the explanation for the inverse relationship between blood pressure and mortality in elderly patients in the general population [28]. One could hypothesise that congestive heart failure causes the inverse relationship in our study. Patients with heart failure tend to have lower blood pressure values, and perhaps the prevalence of heart failure in our study cohort was higher in the patients using antihypertensives at baseline. Both cardiovascular disease and diabetes mellitus are important risk factors for the development of heart failure [29]. In our model, we included previous macrovascular complications as a covariate. Furthermore, when we excluded the last blood pressure value before death and the data associated with the initial deaths in our study, the results were not different. Therefore, it is less plausible that co-morbidity (e.g. heart failure) and frailty are the only explanations for the inverse relationship observed.

The above-mentioned explanations for the inverse relationship in the high age group may also account for the absence of a relationship in the low age group. However, many large randomised controlled trials have included diabetic patients aged 60–75 years. Data from these trials have been reviewed in a meta-analysis, which showed beneficial effects of hypertension treatment [30]. In our opinion, it is more likely that our findings are a result of the lower mortality rate in this age group, which prevents us from drawing definite conclusions.

Our main challenge is to identify the applicability of our results into daily practice. Although no causality was proven or implied for this observational relationship, these results do raise questions about the necessity for aggressive treatment of hypertension in elderly diabetic patients; moreover, they are highly suggestive that hypertension treatment is harmful. This study and data from recent studies indicate that there is no evidence for the ever decreasing target value for systolic blood pressure in both elderly and diabetic patients [6–8, 23].

We are not recommending against the initiation of antihypertensive treatment in elderly diabetic patients. Nevertheless, we need to realise that elderly patients exhibit widely heterogeneous health status, ranging from healthy to frail [18]. Physicians caring for elderly diabetic patients should take co-morbidity and the estimated life expectancy into account when setting treatment goals for the individual patient. In order to make valid recommendations concerning the treatment of hypertension in elderly patients with T2DM and the optimum target level for blood pressure, a randomised controlled trial or a meta-analysis concerning this specific population is necessary.

Key points

- No randomised controlled hypertension trials have been performed in a cohort of elderly patients with T2DM.
- Blood pressure was inversely related to mortality in diabetic patients >75 years; no relationship was found in younger patients.
- The inverse relationship was specifically found in elderly patients treated with antihypertensive medication at baseline.
- The results of this study are suggestive that hypertension treatment is harmful in elderly diabetic patients.
- A randomised controlled trial or meta-analysis concerning this specific population is necessary.

Conflicts of interest

We declare that we have no (financial) conflicts of interest.

Funding

This study had no external funding source.

Ethical approval

The ZODIAC study and the informed consent procedure were approved by the local medical ethics committee of the Isala Clinics, Zwolle, The Netherlands. Verbal informed consent was obtained for all patients by the participating diabetes specialist nurses and the consent was documented in the patients' records. According to Dutch law, written informed consent was not necessary for this type of study in 1998. All data were analysed anonymously.

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Received 27 November 2009; accepted in revised form 5 May 2010

Age and Ageing 2010; **39:** 609–616
doi: 10.1093/ageing/afq071
Published electronically 23 June 2010

The effect of treatment based on a diuretic (indapamide) ± ACE inhibitor (perindopril) on fractures in the Hypertension in the Very Elderly Trial (HYVET)

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These results were presented as a poster during the European Society of Hypertension meeting 12–16 June 2009.

Abstract

Background: fractures may have serious implications in an elderly individual, and fracture prevention may include a careful choice of medications.
Design: the Hypertension in the Very Elderly Trial (HYVET) was a double-blind placebo-controlled trial of a thiazide-like diuretic (indapamide 1.5 mg SR) with the optional addition of the angiotensin-converting enzyme (ACE) inhibitor (perindopril 2–4 mg). Fracture was a secondary end point of the trial.
Setting: HYVET recruited participants from Eastern and Western Europe, China, Australasia, and Tunisia.
Subjects: all participants were ≥80 years of age and hypertensive.
Methods: participants were randomised to receive a thiazide-like diuretic (indapamide 1.5 mg SR) ± ACE inhibitor (perindopril 2–4 mg) or matching placebos. Incident fractures were validated and analysed based on time to first fracture.
Results: there were 3,845 participants in HYVET and a total 102 reported fractures (42 in the active and 60 in the placebo group). When taking only validated first fractures, 90 were included in the analyses (38 in the active and 52 in the placebo group). Cox proportional hazard regression, adjusted for key baseline risk factors, resulted in a point estimate of 0.58 (95% CI 0.33–1.00, P=0.0498).
Conclusions: despite the lowering of blood pressure, treatment with a thiazide-like diuretic and an ACE inhibitor does not increase and may decrease fracture rate.

Keywords: *fractures, bone, aged, antihypertensive agents, elderly*