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Systolic Blood Pressure Trajectory, Frailty, and All-Cause Mortality >80 Years of Age

Cohort Study Using Electronic Health Records

Editorial, see p 2369

BACKGROUND: Clinical trials show benefit from lowering systolic blood pressure (SBP) in people ≥80 years of age, but nonrandomized epidemiological studies suggest lower SBP may be associated with higher mortality. This study aimed to evaluate associations of SBP with all-cause mortality by frailty category >80 years of age and to evaluate SBP trajectories before death.

METHODS: A population-based cohort study was conducted using electronic health records of 144 403 participants ≥80 years of age registered with family practices in the United Kingdom from 2001 to 2014. Participants were followed for ≤5 years. Clinical records of SBP were analyzed. Frailty status was classified using the e-Frailty Index into the categories of fit, mild, moderate, and severe. All-cause mortality was evaluated by frailty status and mean SBP in Cox proportional-hazards models. SBP trajectories were evaluated using person months as observations, with mean SBP and antihypertensive treatment status estimated for each person month. Fractional polynomial models were used to estimate SBP trajectories over 5 years before death.

RESULTS: During follow-up, 51 808 deaths occurred. Mortality rates increased with frailty level and were greatest at SBP <110 mm Hg. In fit women, mortality was 7.7 per 100 person years at SBP 120 to 139 mm Hg, 15.2 at SBP 110 to 119 mm Hg, and 22.7 at SBP <110 mm Hg. For women with severe frailty, rates were 16.8, 25.2, and 39.6, respectively. SBP trajectories showed an accelerated decline in the last 2 years of life. The relative odds of SBP <120 mm Hg were higher in the last 3 months of life than 5 years previously in both treated (odds ratio, 6.06; 95% confidence interval, 5.40–6.81) and untreated (odds ratio, 6.31; 95% confidence interval, 5.30–7.52) patients. There was no evidence of intensification of antihypertensive therapy in the final 2 years of life.

CONCLUSIONS: A terminal decline of SBP in the final 2 years of life suggests that nonrandomized epidemiological associations of low SBP with higher mortality may be accounted for by reverse causation if participants with lower blood pressure values are closer, on average, to the end of life.

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Clinical Perspective

What Is New?

- Clinical trials suggest that antihypertensive treatment for octogenarians may reduce mortality and cardiovascular events, but nonrandomized epidemiological studies generally associate low blood pressure with higher mortality in older adults.
- This article presents data for 144 403 people >80 years of age living in the United Kingdom.
- The sample was classified by frailty level and antihypertensive treatment status.
- Longitudinal analysis of patients' blood pressure records revealed that a terminal decline occurs in systolic blood pressure in the 24 months before death, not accounting for changes in antihypertensive treatment.

What Are the Clinical Implications?

- Clinicians may be concerned by epidemiological analyses which suggest that lower systolic blood pressure may be associated with higher mortality in older adults.
- Recognition that systolic blood pressure may enter a phase of terminal decline in the last 24 months of life suggests that reverse causation may account for nonrandomized epidemiological associations of lower SBP with higher mortality because participants with low blood pressure values may, on average, be closer to the end of life.

Blood pressure increases with age, and older people have a higher prevalence of hypertension.[1,2] Elevated systolic blood pressure (SBP) may be the most important risk factor for cardiovascular disease in older people.[3] Recently, several large clinical trials[4–9] have suggested that use of antihypertensive medications to lower blood pressure may reduce cardiovascular events and mortality in older adults. In HYVET (Hypertension in the Very Elderly Trial)[6] of antihypertensive therapy >80 years of age, lowering blood pressure was associated with 30% reduction in stroke, 21% reduction in all-cause mortality, and 64% reduction in heart failure. In SPRINT (Systolic Blood Pressure Intervention Trial),[7] in people ≥75 years of age, management of SBP to a target of <120 mm Hg was associated with 34% reduction in cardiovascular events and 33% reduction in all-cause mortality. These results from clinical trials have prompted renewed interest in delivering more intensive management of SBP among very old people.

Several nonrandomized epidemiological studies have raised concerns about the safety of intensive lowering of SBP in people ≥80 years of age. In the Umea cohort study of people >85 years of age, baseline SBP of <120 mm Hg was associated with substantially higher mortality than any other blood pressure category.[10] An association of higher blood pressure with lower mortality has been reported in other cohort studies of people >75[11,12] or >85 years of age.[13] These observational findings have led to the suggestion that high blood pressure may not be a risk factor for mortality >85 years of age.[14] The paradoxical association between lower SBP with increased mortality has sometimes been explained in terms of patients' frailty, which may confound the association of low SBP with mortality in old age.[12] Evidence suggests that SBP levels tend to decline as frailty status increases among very old patients,[15] supporting future investigations into the modifying effect of frailty on the association of SBP with mortality. Frail older adults might also be at risk of adverse outcomes from antihypertensive treatment,[16] but if they are underrepresented in trial samples, then the results of clinical trials might not be generalizable to wider community-dwelling populations.[17,18] In an analysis of NHANES data (National Health and Nutrition Examination Survey), Odden et al[19] found evidence of effect modification according to frailty level in terms of walking speed. In fit persons >65 years of age, elevated SBP was associated with greater mortality, whereas in frail participants, higher blood pressure was associated with lower mortality risk.

This study aimed to investigate the reasons for conflicting results from nonrandomized studies and clinical trials concerning the prognostic significance of SBP in older adults. We conducted longitudinal analyses of primary care electronic health records data for a large cohort of adults ≥80 years of age in the United Kingdom. Participants were classified according to frailty level using a previously reported measure.[20] We aimed to evaluate whether the association of SBP with mortality was consistent at different levels of frailty, comparing participants according to antihypertensive treatment status. We also compared SBP trajectories for participants who died with those who did not die during 5 years' follow-up.

METHODS

Patient Involvement and Data Source

This study used data from the Clinical Practice Research Datalink (CPRD). The CPRD is 1 of the world's largest databases of primary care electronic health records, including ≈7% of UK general practices, with anonymized data collected from 1990 to present. The registered active population of ≈5 million is generally representative of the UK population in terms of age and sex.[21] Data collected into CPRD comprise clinical diagnoses, records of blood pressure and other clinical measurements, prescriptions, results of investigations, and referrals to specialist services. The protocol for this study received scientific and ethical approval from the Independent Scientific Advisory Committee for CPRD Studies (ISAC Protocol 13_151). The CPRD has broad National Research Ethics Service Committee ethics approval for observational

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research studies. All data were fully anonymized, and individual consent was not obtained. MG had full access to all the data in the study and takes responsibility for its integrity and the data analysis.

Study Design and Participants

This research was part of a wider study of aging in the CPRD population. For this we drew a random sample of participants who had their 80th, 85th, 90th, 95th, and 100th birthdays while registered in CPRD between 1990 and 2014, including ≤50 000 each of men and women, with replacement, in each age group. There were <50 000 men and 50 000 women eligible in the older age groups, and after accounting for participants sampled in >1 age group, the total sample comprised 299 495 participants. This procedure enhanced representation of older ages in the sample. Participants entered the analysis at the age they were sampled, and all analyses were adjusted for age and calendar year. To focus on a more recent period, the present analysis was restricted to 183 425 participants who were registered between January 1, 2001, and December 31, 2009, with latest follow-up at December 31, 2014. After excluding participants who did not have ≥1 valid blood pressure records during follow-up, 144 403 (79%) participants ≥80 years of age had ≥1 blood pressure records.

Main Measures

The study analyzed blood pressure measurements recorded into participants' electronic health records at consultations in primary care. For each participant, we calculated the mean of all systolic and diastolic records recorded within the first 5 years of follow-up. Participants were divided according to their mean SBP values into the categories <110, 110 to 119, 120 to 139, 140 to 159, and ≥160 mm Hg. Antihypertensive drug prescriptions recorded during the first year of follow-up were analyzed to determine whether participants were treated with antihypertensive medications, which were further classified into drugs acting on the renin-angiotensin system, including angiotensin-converting enzyme inhibitors and angiotensin receptor-blocking drugs; β-blockers; calcium channel blockers; and thiazide diuretics.[22] A further category of other antihypertensive drugs was defined, including centrally acting drugs, α-blockers, and vasodilators.

Clinical records were used to determine smoking status,[23] classified into nonsmoker, current smoker, or ex-smoker. Body mass index was categorized into underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥30.0 kg/m^2). Serum total cholesterol values were grouped into the categories <3.0, 3.0 to 3.9, 4.0 to 4.9, 5.0 to 5.9, and ≥ 6.0 mmol/L. Indicator variables were included for participants with no values recorded. The prevalence of comorbidity at the start of the study was determined from analysis of Read medical codes and drug product codes for diabetes mellitus, coronary heart disease, stroke, cancer, chronic obstructive pulmonary disease, musculoskeletal, and connective tissue diseases and nervous system diseases. Multiple morbidity was coded into the categories none, 1 to 2, 3 to 4, and ≥5. An index of frailty status was calculated for each participant using a previously published 36-item electronic Frailty Index (eFI).[20] The eFI was defined based on a cumulative deficit model, which accounts for the number of deficits present in an individual.[15] The eFI score was calculated by the presence or absence of individual deficits as a proportion of the total possible based on medical diagnoses recorded during the first 12 months of follow-up. Categories of fit, mild, moderate, and severe frailty were defined according to Clegg et al,[20] but the assessment of quantitative traits (including blood pressure values) and polypharmacy (including antihypertensive medications) were omitted from the assessment of frailty because these were key exposures for this study. Deaths from any cause were obtained from CPRD records. Records were censored after 5 years of follow-up or when participants' CPRD record ended.

Statistical Analysis

Baseline characteristics of study participants were described. Time-to-event analyses were conducted to evaluate the association of mean SBP with death from any cause. Mortality rates per 100 person years were estimated as measures of absolute risk, whereas adjusted hazard ratios were estimated using the Cox proportional-hazards model as measures of relative risk. The age at which participants were sampled was included as a stratification variable. In the model, SBP category was the exposure of interest, with SBP 120 to 139 mm Hg as reference. Analyses were conducted separately by sex, frailty category, and antihypertensive treatment status. Models were adjusted for age, comorbidity (including coronary heart disease, stroke, cancer, chronic obstructive pulmonary disorder, musculoskeletal disorders, digestive disorders, nervous system disorders, and dementia), total cholesterol category, and smoking status. For participants receiving antihypertensive medications, analyses were further adjusted for the number of classes of antihypertensive drugs prescribed and type of drug class. Schoenfeld residuals were evaluated to test the proportional-hazards assumption, which was not violated.

To evaluate blood pressure trajectories, we analyzed blood pressure records for the same sample of participants. We estimated the mean SBP value for each participant month for 60 months from 5 years before to death or end of study, including all SBP values recorded up to the date of death. We also evaluated antihypertensive drug prescribing over time and classified each participant month as treated or not treated with antihypertensive drugs. We also estimated the number of antihypertensive drug classes prescribed in each participant month. We used scatter plots, with lowess lines, to compare changes in mean SBP values over time for participants who died by the end of the study and participants who remained alive. We fitted second-order fractional polynomial models using mean SBP values for each participant and each month as observations. Models were adjusted for age, sex, calendar year, and frailty category. Robust variance estimates were used to account for clustering of observations by participant. Models were fitted using the mfp command in Stata version 14 (StataCorp LP). Predicted values and their confidence intervals were estimated using the fracpred command. Logistic regression models were fitted using generalized estimating equations and robust variance estimates to estimate the relative odds of SBP <120 mm Hg by quarter up to the date of death.

RESULTS

Baseline Characteristics

Baseline characteristics of 144 403 eligible participants by mean SBP category are shown in Table 1. There were 4389 (3.0%) participants with SBP <110 mm Hg and 9381 (6.4%) with SBP 110 to 119 mm Hg. There were 17 983 (12.5%) with SBP ≥160 mm Hg. Increasing frailty was generally associated with lower blood pressure. In those with SBP <110 mm Hg, 22% were fit, 28% had moderate frailty, and 12% had severe frailty. In participants with SBP ≥160 mm Hg, 42% were fit, 16% had moderate frailty, and 4% had severe frailty. Diagnoses of coronary heart disease, stroke, and dementia were more frequent among those with lower SBP values. Dementia was diagnosed in 12% of participants with SBP <120 mm Hg but only 2% of those with SBP ≥160 mm Hg. Serum total cholesterol values were generally lower in those with lower SBP, but there was no clear trend in cigarette smoking. Use of antihyperten-

Table 1. Baseline Characteristics of the Study Cohort, by Systolic Blood Pressure Category

Characteristics	Systolic Blood Pressure Category (mm Hg)				
	<110	110–119	120–139	140–159	≥160
N	4389	9381	53 931	58 719	17 983
Women	2186 (50)	4686 (50)	28 250 (52)	34 453 (59)	12 252 (68)
Age, y	88.0 (5.4)	87.1 (5.4)	85.8 (5.2)	85.1 (4.9)	85.6 (4.9)
Frailty					
Fit	957 (22)	2192 (23)	15 197 (28)	21 129 (36)	7519 (42)
Mild	1658 (38)	3680 (39)	22 017 (41)	23 581 (40)	6821 (38)
Moderate	1244 (28)	2479 (26)	12 369 (23)	10 843 (18)	2850 (16)
Severe	530 (12)	1030 (11)	4348 (8)	3166 (5)	793 (4)
Comorbidity at entry					
Coronary heart disease	1555 (35)	3332 (36)	15 890 (29)	12 870 (22)	3253 (18)
Stroke	545 (12)	1180 (13)	5637 (10)	4465 (8)	1236 (7)
Cancer	964 (22)	2044 (22)	11 045 (20)	11 264 (19)	3108 (17)
Chronic obstructive pulmonary disorder	1040 (24)	2022 (22)	11 142 (21)	10 789 (18)	2932 (16)
Musculoskeletal	2988 (68)	6527 (70)	39 093 (72)	42 096 (72)	12 208 (68)
Digestive	2592 (59)	5477 (58)	31 240 (58)	32 200 (55)	8823 (49)
Nervous system	3077 (70)	6650 (71)	39 057 (72)	41 781 (71)	12 103 (67)
Dementia	710 (16)	1342 (14)	4500 (8)	2377 (4)	516 (3)
Total cholesterol, mmol/L	4.4 (1.1)	4.5 (1.2)	4.8 (1.2)	5.1 (1.2)	5.4 (1.2)
Diastolic blood pressure, mm Hg	63 (10)	69 (10)	74 (10)	79 (10)	84 (12)
Smoking status					
Nonsmoker	1340 (31)	3445 (37)	22 759 (42)	27 304 (47)	8211 (46)
Current smoker	517 (12)	1351 (14)	8359 (16)	8624 (15)	2189 (12)
Ex-smoker	732 (17)	1904 (20)	12 030 (22)	12 522 (21)	3281 (18)
Not recorded	1800 (41)	2681 (29)	10 783 (20)	10 269 (17)	4302 (24)
Antihypertensive medications*	2141 (49)	4898 (52)	31 912 (59)	37 258 (63)	11 264 (63)
Renin angiotensin system medications†	1476 (69)	3064 (63)	17 136 (54)	18 297 (49)	5531 (49)
Beta-blockers†	676 (32)	1745 (36)	10 764 (34)	12 578 (34)	4308 (38)
Calcium channel blockers†	482 (23)	1425 (29)	12 633 (40)	16 091 (43)	4704 (42)
Diuretics†	332 (16)	1021 (21)	10 502 (33)	17 320 (46)	5943 (53)
Other antihypertensive†	86 (4)	287 (6)	2591 (8)	4075 (11)	1701 (15)

Values are mean±SD or n (%).
*Drugs prescribed in first 12 months of patients' record.
†Percentage of participants treated with antihypertensive drugs.

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Table 2. Number of Deaths and Mortality Rates per 100 Person Years for Patients Not Treated With Antihypertensive Medications, by Systolic Blood Pressure and Frailty Category

Frailty Category	Systolic Blood Pressure Category (mm Hg)				
	<110	110–119	120–139	140–159	≥160
Fit					
n	672	1478	8463	10350	3807
Mean age, y	88.2	86.9	85.5	84.6	84.8
Deaths	413	703	2696	2248	833
Rate	20.3	13.4	8.0	5.1	5.3
Mild					
n	846	1742	8510	7491	2080
Mean age, y	88.8	88.3	86.8	86.0	86.7
Deaths	608	1046	3607	2326	685
Rate	28.6	19.6	11.8	8.1	9.0
Moderate					
n	540	941	3860	2832	672
Mean age, y	89.3	88.5	87.7	87.5	88.3
Deaths	432	631	1892	1203	309
Rate	40.3	25.5	15.3	12.6	14.7
Severe					
n	190	322	1186	788	160
Mean age, y	89.1	88.7	88.4	88.1	88.4
Deaths	162	233	713	409	87
Rate	47.9	32.3	20.7	18.0	22.5

Table 3. Number of Deaths and Mortality Rates per 100 Person Years for Patients Treated With Antihypertensive Medications, by Systolic Blood Pressure and Frailty Category

Frailty Category	Systolic Blood Pressure Category (mm Hg)				
	<110	110–119	120–139	140–159	≥160
Fit					
n	285	714	6734	10779	3712
Mean age, y	87.5	86.3	84.5	83.9	84.6
Deaths	185	355	2064	2307	917
Rate	22.7	15.2	7.7	5.1	6.3
Mild					
n	812	1938	13507	16090	4741
Mean age, y	87.5	86.1	85.1	84.7	85.6
Deaths	599	1036	4864	4322	1506
Rate	31.9	16.7	9.7	6.8	8.7
Moderate					
n	704	1538	8509	8011	2178
Mean age, y	86.8	86.6	85.9	85.6	86.5
Deaths	522	942	3696	2717	848
Rate	33.8	21.9	12.7	9.3	11.6
Severe					
n	340	708	3162	2378	633
Mean age, y	87.6	86.7	86.6	86.5	87.1
Deaths	267	469	1643	1020	293
Rate	39.6	25.2	16.8	13.1	16.1

sive medications was generally more frequent in those with higher SBP values.

Mortality and SBP

There were 51 808 deaths during follow-up. Tables 2 and 3 presents mortality rates per 100 person years by frailty, SBP category, and antihypertensive treatment status. Mortality increased with increasing frailty category. At each level of frailty, mortality rates were lowest among participants with SBP 140 to 159 mm Hg, whereas for participants with SBP 100 to 119 mm Hg, mortality rates were more than twice as high, and for participants with SBP <110 mm Hg, mortality was >3 times as high. The results were similar among those who were treated with antihypertensive medications and those who were not on treatment. The data reveal that 340/7221 (5%) of treated patients with severe frailty and 285/22 224 (1%) of fit patients had SBP records <110 mm Hg.

To address confounding and the influence of antihypertensive treatment, adjusted hazard ratios for the association of SBP category with mortality were estimated separately by antihypertensive treatment status for men and women and for each frailty category (Table 4 and 5). Analyses were adjusted for diastolic blood pressure, age and comorbidity, total cholesterol, and smoking status. In men and women, there was a greater relative hazard for SBP 110 to 119 or <110 mm Hg compared with SBP 120 to 139 mm Hg as a reference category. This association was observed in both participants treated with antihypertensive drugs and untreated participants. Hazard ratios were higher for SBP <110 mm Hg than for SBP 110 to 119 mm Hg. Hazard ratios for a given SBP category were generally consistent across frailty categories. Hazard ratios were generally lower for SBP 140 to 159 mm Hg than the reference category. SBP ≥160 mm Hg was not generally associated with higher relative hazard, except in men with severe frailty. When 10 mm Hg SBP categories were used for analysis of the sample as a single group, the hazard ratio for SBP 130 to 139 mm Hg, compared with 120 to 129 mm Hg as reference, was 0.82 (0.79–0.84).

Table 4. Association of Systolic Blood Pressure Category With All-Cause Mortality for Patients Not Treated With Antihypertensive Medications, by Frailty Category, Sex, and Antihypertensive Treatment

Systolic Blood Pressure Category (mm Hg)	Fit		Mild		Moderate		Severe	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Men								
<110	1.71 (1.42 to 2.05)	<0.001	1.96 (1.66–2.30)	<0.001	2.05 (1.69–2.47)	<0.001	1.78 (1.21–2.64)	0.004
110–119	1.29 (1.13–1.47)	<0.001	1.47 (1.31 to 1.65)	<0.001	1.58 (1.36–1.84)	<0.001	1.39 (1.06–1.82)	0.015
120–139	Reference		Reference		Reference		Reference	
140–159	0.83 (0.76–0.90)	<0.001	0.85 (0.78–0.92)	<0.001	0.88 (0.77–1.00)	0.052	1.28 (1.01–1.61)	0.039
≥160	0.87 (0.76–0.99)	0.029	1.01 (0.87–1.17)	0.876	1.15 (0.91–1.46)	0.239	2.32 (1.57–3.45)	<0.001
Women								
<110	1.63 (1.35–1.95)	<0.001	1.61 (1.38–1.88)	<0.001	2.11 (1.77–2.53)	<0.001	2.00 (1.55–2.58)	<0.001
110–119	1.26 (1.10–1.44)	0.001	1.24 (1.12–1.39)	<0.001	1.43 (1.25–1.64)	<0.001	1.47 (1.20–1.82)	<0.001
120–139	Reference		Reference		Reference		Reference	
140–159	0.73 (0.67–0.80)	<0.001	0.80 (0.74–0.87)	<0.001	0.90 (0.82–0.99)	0.039	0.85 (0.72–1.01)	0.062
≥160	0.82 (0.72–0.92)	0.001	0.81 (0.72–0.92)	0.001	0.93 (0.79–1.11)	0.423	0.79 (0.56–1.11)	0.176

Values are adjusted for age, diastolic blood pressure, comorbidity, total cholesterol, smoking, and antihypertensive treatment. CI indicates confidence interval; and HR, hazard ratio.

SBP Trajectories

To clarify the association of SBP with mortality, we plotted the mean of SBP values recorded by month from 5 years before death or end of study (Figure 1). Data are presented for 144 403 participants in total. There was a mean of 16 970 (range 10 610–26 464) participants contributing data in any single month. Individual participants contributed data in a mean of 7 months (range 1–58 months). Figure 1, Left shows that mean SBP values declined over time. This decline was more rapid among participants who died than in those who did not die during the study. In the last 12 to 24 months of life, the decline in SBP accelerated, with SBP values being ≈15 mm Hg lower at the end of the period than at the beginning. SBP values were initially higher in participants who were treated with antihypertensive medications, but a terminal decline in SBP values before death was observed in both treated and untreated participants.

Fractional polynomial models were fitted separately for participants who died or did not die by antihypertensive treatment status (Figure 1, Right, and Table I in the online-only Data Supplement). Fractional polynomial models were adjusted for sex, age, frailty category, and calendar year. The fractional polynomial plots (Figure 1, Right) confirm an accelerated decline in SBP in the last 24 months of life. In a logistic regression analysis, the relative odds of SBP <120 mm Hg were higher in the last 3 months of life than 5 years previously in both treated (odds ratio, 6.06; 95% confidence interval, 5.40–6.81) and untreated patients (odds ratio, 6.31; 95% confidence interval, 5.30–7.52). (Figure I in the online-only Data Supplement).

Additional Information and Sensitivity Analyses

Table 6 shows data for blood pressure recording and antihypertensive therapy for deceased and surviving participants by year. Participants who died during the 5-year study period necessarily had shorter overall follow-up than those who survived. The proportion of participants with ≥1 blood pressure readings in each year was generally slightly higher among surviving participants than those who died ($P<0.001$). Surviving participants also tended to have more frequent blood pressure readings than those who died. We noted that the number of blood pressure readings available for analysis was associated

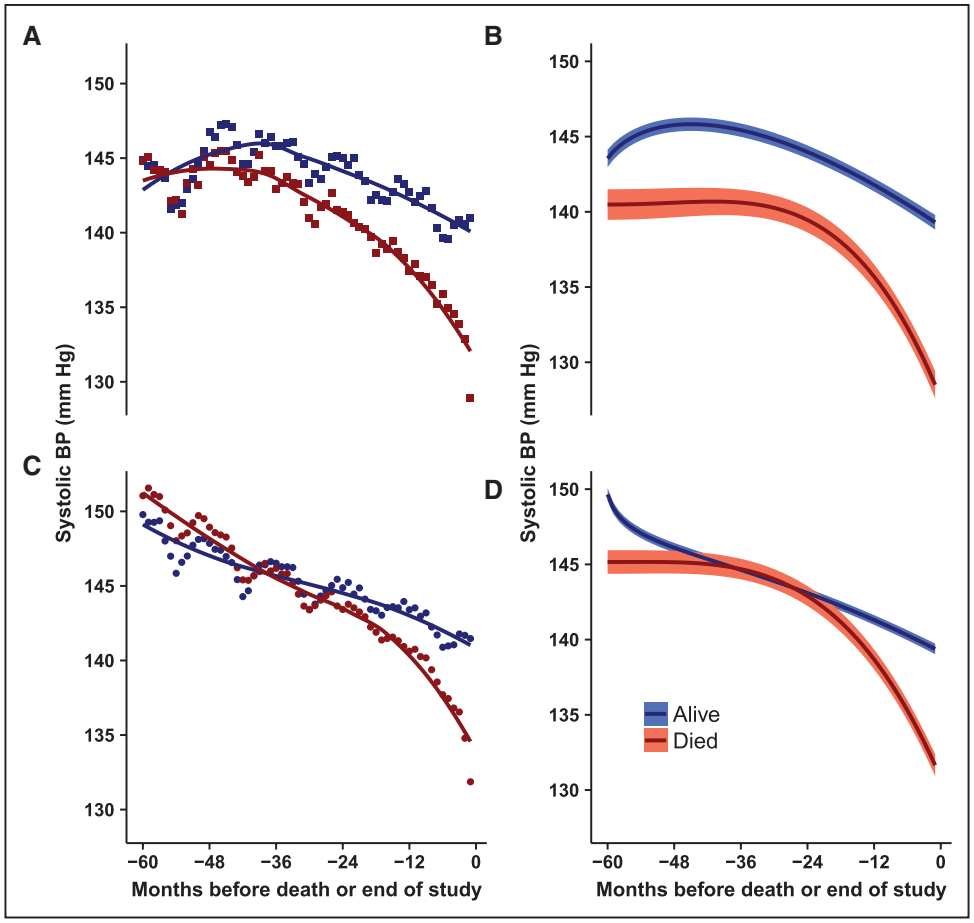

Figure 1. Trajectory of systolic blood pressure during 60 months before death (red) or end of study (blue). **Left,** Mean SBP by month: (**A**) squares, not treated; (**C**) circles, treated with antihypertensive medications. **Right,** Predictions (95% confidence intervals) from multiple fractional polynomial model adjusted for age, sex, calendar year, and frailty category: (**B**) not treated; (**D**) treated with antihypertensive medications.

with both the mean SBP category and the level of frailty (Table II in the online-only Data Supplement). Among fit participants, the median number of BP readings per participant year ranged from 0.8 to 1.8, whereas for participants with severe frailty, the median number of BP readings per year ranged from 2.3 to 3.0. However, SBP trajectories were similar for participants who had had either more, less than, or equal to the mean number of 7 participant months with SBP values recorded (Figure II in the online-only Data Supplement). There was no evidence that patients who died received more intense antihypertensive therapy. Surviving participants included a slightly lower proportion not prescribed antihypertensive drugs, with higher proportions prescribed ≥2 classes of antihypertensive drugs ($P<0.001$). Antihypertensive drug prescribing increased over the period ($P<0.001$), but there was only weak evidence for a difference in trend according to whether patients survived ($P=0.042$). There was no evidence for intensification of antihypertensive therapy in the final months of life. When participants who died within 6 months of study entry were excluded from the analysis, there was no difference in interpretation (Table III in the online-only Data Supplement).

DISCUSSION

Main Findings

In this large cohort of individuals ≥80 years of age, SBP <120 mm Hg was associated with greater risk of mortality in both men and women when compared with SBP of 120 to 139 mm Hg. The level of frailty was classified from data recorded into primary care electronic health records. Mortality was higher in more frail participants, whereas the association of SBP <120 mm Hg with mortality was consistently observed at each level of frailty. The proportion of treated patients with SBP <110 mm Hg increased with frailty level, which might indicate overtreatment in some cases. Longitudinal analysis of participants' blood pressure records revealed a secular decline in SBP,[24] but participants who die experience an accelerated decline in SBP in the final 24 months of life. These last months of life are associated with greatly increased

Table 5. Association of Systolic Blood Pressure Category With All-Cause Mortality for Patients Treated With Antihypertensive Medications, by Frailty Category, Sex, and Antihypertensive Treatment

Systolic Blood Pressure Category (mm Hg)	Fit		Mild		Moderate		Severe	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Men								
<110	2.02 (1.54–2.66)	<0.001	2.51 (2.16–2.91)	<0.001	2.00 (1.71–2.33)	<0.001	1.62 (1.25–2.09)	<0.001
110–119	1.54 (1.30–1.83)	<0.001	1.45 (1.32–1.60)	<0.001	1.44 (1.29–1.61)	<0.001	1.31 (1.11–1.53)	0.001
120–139	Reference		Reference		Reference		Reference	
140–159	0.78 (0.71–0.85)	<0.001	0.83 (0.78–0.88)	<0.001	0.89 (0.82–0.96)	0.004	0.89 (0.77–1.03)	0.112
≥160	0.98 (0.85–1.13)	0.748	1.04 (0.94–1.16)	0.436	1.18 (1.01–1.37)	0.028	1.21 (0.90–1.63)	0.212
Women								
<110	1.86 (1.39–2.47)	<0.001	1.98 (1.67–2.35)	<0.001	2.34 (1.98–2.77)	<0.001	1.98 (1.53–2.56)	<0.001
110–119	1.48 (1.23–1.79)	<0.001	1.46 (1.30–1.63)	<0.001	1.55 (1.38–1.75)	<0.001	1.44 (1.24–1.70)	<0.001
120–139	Reference		Reference		Reference		Reference	
140–159	0.76 (0.70–0.84)	<0.001	0.79 (0.74–0.84)	<0.001	0.81 (0.75–0.87)	<0.001	0.80 (0.72–0.89)	<0.004
≥160	0.85 (0.75–0.96)	0.011	0.91 (0.83–1.00)	0.068	0.95 (0.86–1.06)	0.401	0.97 (0.82–1.15)	0.733

odds of low SBP recordings. These observations may account for the discrepancy between clinical trial results, which provide evidence of benefit from blood pressure lowering, as compared with nonrandomized studies, which generally associate lower SBP with higher mortality. Randomization will ensure that comparison groups are, on average, similar with respect to underlying risk of mortality; in nonrandomized studies, reverse causation may apply if lower SBP values are accounted for by proximity to death. Changes in SBP before death were generally similar in participants who were treated or not treated with antihypertensive drugs. Analysis of blood pressure recording and prescription of antihypertensive drugs revealed no evidence to suggest that there might be intensification of antihypertensive therapy to account for lower blood pressure before death. Participants who survived to the end of the study period had more frequent blood pressure recordings and were more likely to be treated with multiple antihypertensive drug classes.

Strengths and Limitations

The study has the strengths of a large sample of older adults with comprehensive data for medical diagnoses and drug treatment. The eligibility criteria were unrestricted, and the sample may have included nonambulatory patients as well as those with dementia or living in nursing homes. These groups of patients are often excluded from clinical trials. Blood pressure measurements were recorded in clinical practice using possibly nonstandardized methods, with no regularity of measurements over time in individual participants. Blood pressure measurements in the clinic may be higher than usual ambulatory values[25] and may also be appreciably higher than those recorded in clinical trials. In SPRINT, a 5-minute rest period was observed for all BP measurements.[7,26] We did not have information concerning resting time, position, cuff size, device type, number of measurements, or whether orthostatic BP measurements were recorded. Despite these limitations, analysis of measurements routinely recorded in primary care may closely resemble those encountered by physicians in their usual practice.

The effect of misclassification of blood pressure will generally be to reduce the strength of reported associations. We did not have sufficient data concerning the dosage of antihypertensive medications. It may also be noted that, although information on prescription might be available, we cannot guarantee administration of the drugs. There were also missing and possibly misclassified values for important covariates, including smoking, which might lead to bias. There is no consensus on the definition of the frailty syndrome, and different operational tools have been used to measure this condition.[27] Studies comparing different models suggest that most

Table 6. Changes in Blood Pressure and Antihypertensive Therapy 5 Years Before Death

Years Before Death or End of Study	At Risk in Year, n	With ≥1 Blood Pressure Reading in Year, n (%)	Mean Number of Months With Blood Pressure Readings*	Systolic Blood Pressure, Mean (SD)	Number of Antihypertensive Drug Classes Prescribed in Year				
					0	1	2	3	4+
Alive									
–5	70954	52379 (74)	2.5	145.4 (17)	27759 (39)	18402 (26)	15793 (22)	7140 (10)	1860 (3)
–4	76716	58513 (76)	2.5	144.3 (17)	28096 (37)	20333 (27)	17884 (23)	8104 (11)	2299 (3)
–3	82816	65181 (79)	2.4	142.9 (17)	29221 (35)	22627 (27)	19691 (24)	8808 (11)	2469 (3)
–2	88879	72285 (81)	2.4	141.5 (17)	30492 (34)	24982 (28)	21202 (24)	9545 (11)	2658 (3)
–1	92554	77463 (84)	2.3	139.6 (17)	31168 (34)	26697 (29)	22320 (24)	9831 (11)	2538 (3)
Died†									
–5	8131	4147 (51)	1.8	144.5 (20)	3612 (44)	2332 (29)	1513 (19)	529 (7)	145 (2)
–4	18309	11567 (63)	2.1	142.7 (19)	7646 (42)	5494 (30)	3557 (19)	1299 (7)	313 (2)
–3	29425	20556 (70)	2.1	140.6 (19)	11795 (40)	9077 (31)	5875 (20)	2169 (7)	509 (2)
–2	39830	31258 (78)	2.1	138.3 (20)	15418 (39)	12724 (32)	8047 (20)	2977 (7)	664 (2)
–1	43133	36679 (85)	2.3	133.6 (19)	16153 (37)	14074 (33)	8970 (21)	3212 (7)	724 (2)

Values are n (%), except where indicated.

*Mean number of months in year with blood pressure values were recorded for participants with 1 or more readings.

†Person-time was eligible for analysis from January 1, 2010, to December 3, 2014. Participants who died during this period necessarily had shorter duration of follow-up overall.

tools used to assess frailty are strongly associated with adverse outcomes, including mortality.[28,29] The Frailty phenotype[30] and the eFI[31] are the 2 most widely used frailty models. We used a deficit accumulation model to assess frailty, whereas the Frailty Phenotype includes physical measures of frailty, such as walking speed, grip strength, low physical activity, and weight loss. Studies comparing these models have shown that they both predict adverse outcomes, but different frailty models might not necessarily identify the same individuals as frail.[32] It is also important to emphasize that physical measures may be difficult to complete in the very old because of their poor health and possible inability to participate.[33] The eFI is based on clinical diagnoses and records of age-related impairments that impact physical and mental functioning. We assumed that items not recorded were absent, but clinical records may sometimes have low sensitivity for age-related impairments, especially when these are in their early stages. For example, the prevalence of clinical dementia diagnosis in this sample is almost certainty an underestimate of the condition's true prevalence. Both the Frailty phenotype and the deficit accumulation approach may predict adverse outcomes, but there may be differential classification of individuals.[34] We did not have data concerning gait speed or other objective physical function measures, and it should be noted that lack of objective measures of functional problems, including cognitive function, may be a limitation of the eFI. However, assessment of physical function across different primary care practices might result in bias from misclassification. The eFI addresses activity limitations and cognitive functioning through the analysis of physician recorded diagnostic codes. We excluded blood pressure measurements from estimation of the eFI, but we did not exclude clinical diagnoses of hypotension, hypertension, and dizziness, which contribute to the 36 deficits contained in the eFI. This finding implies that hypertensive individuals may be classified as slightly more frail, but we analyzed frailty in broad categories as recommended by the scale developers. We compared SBP trajectories of participants who died with those who survived to the end of the study, but associations might be diminished if the surviving patients were also nearing the end of their lives. During the period of study, there were changes in antihypertensive drug utilization in this population, with declining use of diuretics and increasing use of drugs acting on the renin-angiotensin system and calcium channel blockers.[24] Secular declines also occurred in SBP[24] and mortality.[35] More people are living to older ages but often with greater comorbidity.[36] We caution that associations might differ in future periods of time.

Comparison With Previous Research

In HYVET[6] of antihypertensive therapy >80 years of age, blood pressure lowering was associated with substantial

reduction in stroke, all-cause mortality, and heart failure. In SPRINT[7] in people ≥75 years of age, management of SBP to a target of <120 mm Hg was associated with reduction in cardiovascular events and all-cause mortality. To address concerns that the trial samples may not have been representative, each of these clinical trials conducted analyses to show that the main findings were consistent across frailty categories.[17,18]

Several previous observational studies showed a negative association of increased blood pressure and mortality in the very old.[2,13,14,37,38] A report from EPESE (the Established Populations for Epidemiological Studies of the Elderly)[13] found that in younger elderly individuals 65 to 84 years of age, there was a positive association between SBP and mortality even after adjusting for comorbidities, whereas in men ≥85 years of age, higher SBP was associated with lower mortality. In women ≥85 years of age, there was no association between SBP and mortality.[13] Rastas et al[39] found that SBP <140 mm Hg was associated with higher all-cause mortality in all men and women after adjusting for confounders. In the Umea 85+ study, low SBP was associated with greater mortality even after adjustment for preexisting comorbidity and frailty.[10,39] Although it has been suggested that the association between low blood pressure and mortality might be an indicator of a greater disease burden and a marker of poor health, our results show that low SBP is associated with mortality even in fit participants. The results from a population study by Nilsson et al[40] in those ≥80 years of age showed that low SBP was associated with an increased risk of cognitive decline irrespective of frailty status. In the PARTAGE study (Predictive Values of Blood Pressure and Arterial Stiffness in Institutionalized Very Aged Population) of institutionalized older adults ≥80 years of age, there was effect modification from antihypertensive treatment. Participants with low SBP (<130 mm Hg) receiving ≥2 antihypertensive drugs were at increased risk of mortality compared with the group receiving either 1 or no antihypertensive drugs. This study included an institutional sample that may differ from our community dwelling sample, and differing definitions of antihypertensive treatment were used.[41] Analysis of NHANES data suggested that the association of lower BP with greater mortality was most evident in frail participants.[19] In the present study, mortality rates were elevated for lower blood pressures at all levels of frailty. These differences might be explained by differing participant selection and choice of frailty classification. Considering the totality of evidence, a systematic review suggested that less aggressive treatment would be an optimal approach in treating hypertension in older adults.[42] A review exploring the management of hypertension in those ≥80 years of age suggested that individualized treatment plans should be designed when treating frail older adults.[43]

Kalantar-Zadeh et al[44] noted that lower SBP values have been associated with higher mortality in patients with heart failure and end-stage renal failure[45] and offered several explanations for this finding. People who live to advanced ages or advanced disease states are necessarily highly selected with the consequence that survivor bias may contribute to patterns of association that differ from those observed in the general population.[44] The temporal pattern of exposure may also be important if higher blood pressure confers a short-term survival advantage in the final months of life.[44] Deteriorating nutritional status, accompanied by chronic inflammation, may also tend to lower blood pressure levels at the end of life.[44]

Our results suggest that a substantial decline in blood pressure may be a recognizable feature of the final stages of life, at least in the final 2 years, with lower SBP often being a marker of proximity to death. Accelerated functional decline before death was noted by Diehr et al[46] in data from the Cardiovascular Health Study. This decline is sometimes referred to as terminal decline or terminal drop.[47] Terminal decline has been described previously with respect to cognitive function[48] and subjective health measures[49] but not blood pressure.

CONCLUSIONS

In nonrandomized data for people >80 years of age, SBP <120 mm Hg is associated with higher mortality irrespective of frailty status, sex, or antihypertensive treatment. This association may be explained in part by a terminal decline of SBP, which is observed in the final 2 years of life. These observations may account for the discrepancy between randomized and nonrandomized studies of SBP and mortality in people >80 years of age. Reverse causation may apply if lower SBP values result from proximity to death. The present data may not provide an explanation for BP-outcome associations <2 years before death. Whether the observation of more favorable outcomes with higher SBP for >2 years before death is true or confounded remains uncertain. Consequently, it may be inadvisable to base blood pressure treatment recommendations on nonrandomized data for effectiveness outcomes. We noted SBP values <110 mm Hg in a minority of treated patients, which suggests that reducing the intensity of antihypertensive therapy may sometimes be important in this age group.

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DISCLOSURES

None.

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FOOTNOTES

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Systolic Blood Pressure Trajectory, Frailty, and All-Cause Mortality >80 Years of Age: Cohort Study Using Electronic Health Records

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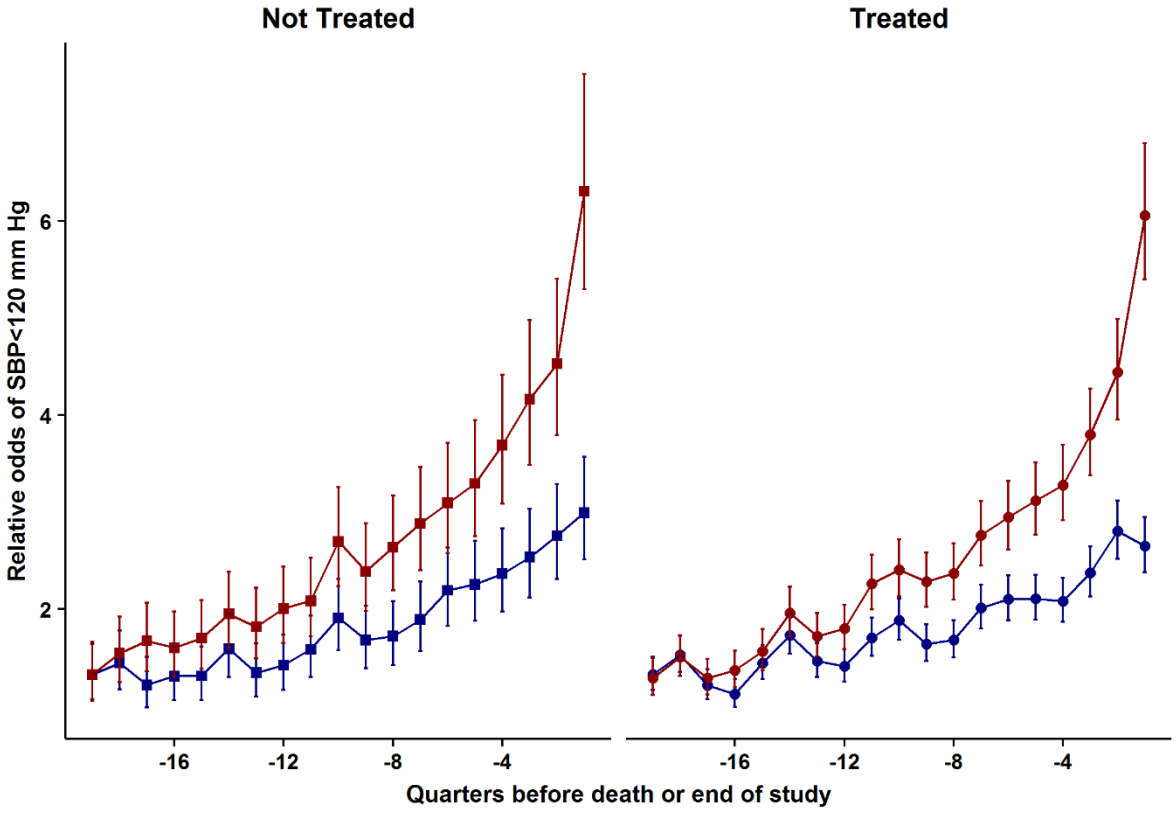
SUPPLEMENTARY MATERIAL

Supplementary Table 1: Estimates from multiple fractional polynomial (FP) models.

Status	Antihypertensive medications	Powers selected		Coefficients for month before end	
		First	Second	First term	Second term
Died	Not treated	-0.5	3	2.56 (0.59)	-0.05 (0.002)
Alive	Not treated	0	2	-0.55 (0.09)	-0.19 (0.008)
Died	Treated	3	3	0.02 (0.02)	-0.05 (0.01)
Alive	Treated	0	2	-1.10 (0.06)	-0.14 (0.005)

Coefficients for month before death or end of study were adjusted for age and calendar year (both as second-degree FP) and frailty category and gender.

Supplementary Figure 1: Relative odds of SBP 120 mm Hg by quarter before death or end of study by antihypertensive treatment status. Left panel, not treated with antihypertensive drugs; right panel, treated with antihypertensive drugs.



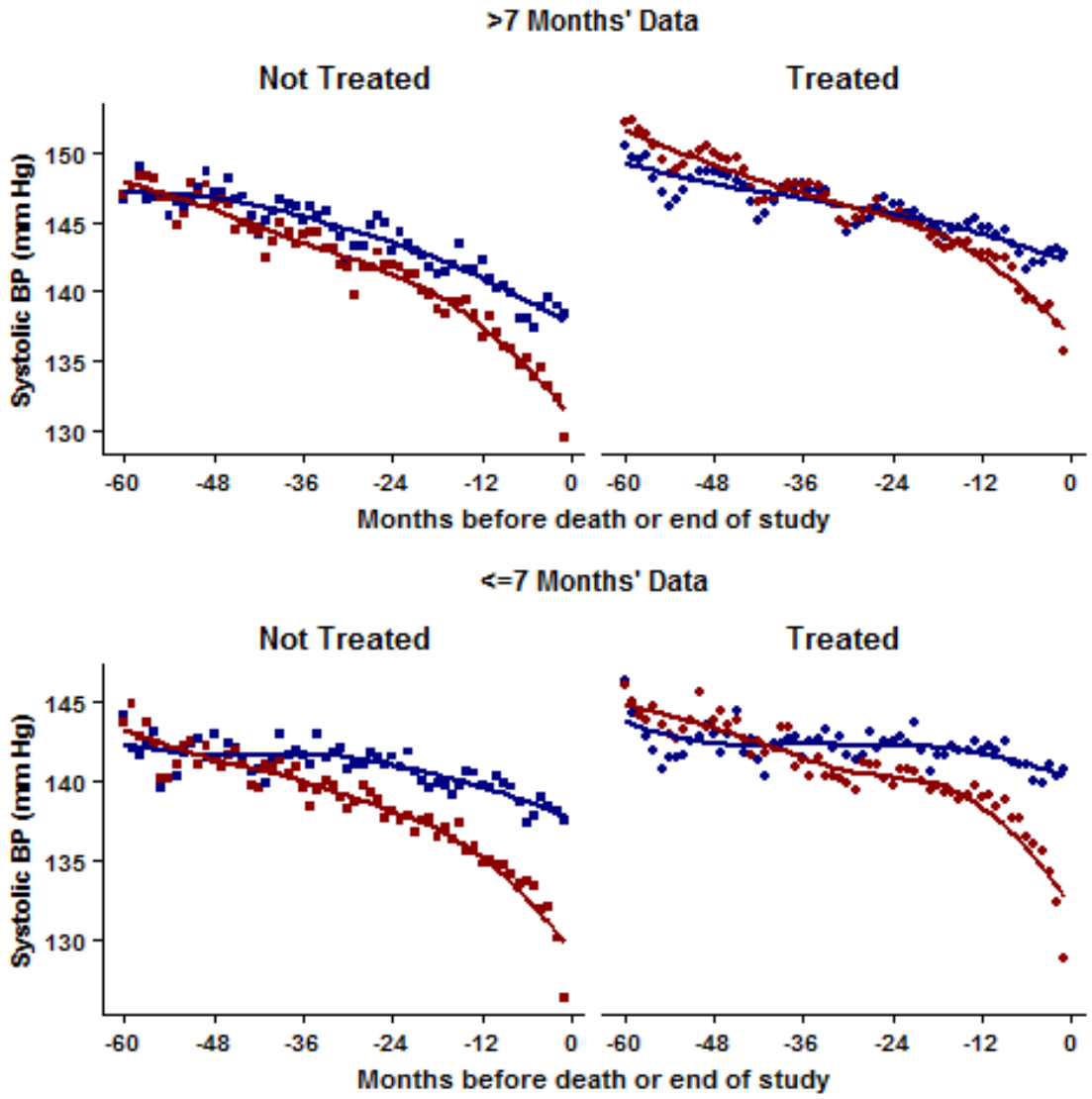
Figures are odds ratios (95% confidence intervals). Red symbols, participants who died; blue symbols, participants who did not die.

Supplementary Table 2. Rate of BP recordings by frailty and systolic blood pressure categories.

	Systolic BP category (mm Hg)				
Frailty category	**<110**	**110-119**	**120-139**	**140-159**	**≥160**
Fit	0.84	1.00	1.20	1.67	1.80
Mild	1.44	1.54	1.75	2.20	2.60
Moderate	1.92	1.94	2.00	2.55	2.82
Severe	2.34	2.32	2.40	2.73	3.04

Figures are median number of BP readings per patient year.

Supplementary Figure 2: Systolic blood pressure trajectories by level of BP recording.



Figures were plotted for participants with more than the mean, or less than or equal to the mean number of participant months contributing data.

Supplementary Table 3: Association of SBP category with all-cause mortality by frailty category, gender and anti-hypertensive treatment. Participants that died within six months of study entry were excluded.

	SBP category (mm Hg)	'Fit'		'Mild frailty'		'Moderate frailty'		'Severe frailty'	
		HR (95% CI)	P value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
					Not Treated with Antihypertensive Medications				
Men	<110	1.66 (1.38 to 2.00)	<0.001	1.86 (1.57 to 2.20)	<0.001	2.03 (1.66 to 2.47)	<0.001	1.90 (1.25 to 2.87)	0.003
	110-119	1.27 (1.11 to 1.45)	<0.001	1.46 (1.30 to 1.65)	<0.001	1.60 (1.37 to 1.88)	<0.001	1.45 (1.10 to 1.93)	0.008
	120-139	Reference		Reference		Reference		Reference	
	140-159	0.82 (0.76 to 0.89)	<0.001	0.83 (0.76 to 0.91)	<0.001	0.86 (0.75 to 0.98)	0.023	1.17 (0.92 to 1.49)	0.191
	≥160	0.86 (0.75 to 0.97)	0.018	0.98 (0.85 to 1.14)	0.842	1.09 (0.85 to 1.40)	0.494	2.11 (1.31 to 3.17)	<0.001
Women	<110	1.49 (1.23 to 1.80)	<0.001	1.53 (1.31 to 1.79)	<0.001	2.03 (1.68 to 2.45)	<0.001	1.99 (1.51 to 2.61)	<0.001
	110-119	1.24 (1.07 to 1.42)	0.002	1.23 (1.10 to 1.37)	<0.001	1.41 (1.22 to 1.62)	<0.001	1.38 (1.11 to 1.72)	0.003
	120-139	Reference		Reference		Reference		Reference	
	140-159	0.72 (0.66 to 0.79)	<0.001	0.78 (0.72 to 0.84)	<0.001	0.90 (0.82 to 1.00)	0.050	0.82 (0.69 to 0.97)	0.020
	≥160	0.81 (0.72 to 0.92)	0.001	0.78 (0.69 to 0.88)	<0.001	0.89 (0.75 to 1.06)	0.198	0.77 (0.54 to 1.10)	0.149
					Treated with Antihypertensive Medications				
Men	<110	1.93 (1.46 to 2.55)	<0.001	2.38 (2.05 to 2.77)	<0.001	1.97 (1.68 to 2.31)	<0.001	1.58 (1.21 to 2.06)	0.001
	110-119	1.55 (1.30 to 1.85)	<0.001	1.45 (1.32 to 1.60)	<0.001	1.47 (1.31 to 1.65)	<0.001	1.35 (1.15 to 1.60)	<0.001
	120-139	Reference		Reference		Reference		Reference	
	140-159	0.78 (0.71 to 0.85)	<0.001	0.82 (0.76 to 0.87)	<0.001	0.88 (0.80 to 0.95)	0.002	0.86 (0.74 to 1.00)	0.049
	≥160	0.95 (0.82 to 1.10)	0.501	1.02 (0.91 to 1.14)	0.724	1.14 (0.98 to 1.32)	0.094	1.17 (0.86 to 1.57)	0.317
Women	<110	1.86 (1.38 to 2.50)	<0.001	2.14 (1.81 to 2.54)	<0.001	2.24 (1.88 to 2.66)	<0.001	1.95 (1.50 to 2.54)	<0.001
	110-119	1.46 (1.21 to 1.77)	<0.001	1.51 (1.34 to 1.69)	<0.001	1.51 (1.33 to 1.70)	<0.001	1.43 (1.21 to 1.68)	<0.001
	120-139	Reference		Reference		Reference		Reference	
	140-159	0.76 (0.70 to 0.84)	<0.001	0.80 (0.75 to 0.85)	<0.001	0.81 (0.75 to 0.87)	<0.001	0.77 (0.69 to 0.86)	<0.001
	≥160	0.84 (0.74 to 0.95)	0.007	0.91 (0.83 to 1.00)	0.059	0.94 (0.85 to 1.05)	0.304	0.91 (0.76 to 1.09)	0.313

Figures are hazard ratios (HR) and 95% confidence intervals adjusted for age, diastolic blood pressure, comorbidity, total cholesterol, smoking and anti-hypertensive treatment.