ORIGINAL ARTICLE

Functional Status and Antihypertensive Therapy in Older Adults: A New Perspective on Old Data

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BACKGROUND
Functional status may be useful for identifying older adults who benefit from lower blood pressure. We examined whether functional status modifies the effect of antihypertensive treatment among older adults.

METHODS
Post hoc analyses of the Systolic Hypertension in the Elderly Program (SHEP), a randomized trial of antihypertensive therapy vs. placebo (1985–1991) in 4,736 adults aged 60 years or older with isolated systolic hypertension. Outcomes were all-cause death, cardiovascular (CV) death, myocardial infarction (MI), stroke, falls, and symptoms of hypotension. The effect modifier of interest was functional status, assessed by self-reported physical ability limitation (PAL).

RESULTS
Among persons with no PAL, those receiving treatment had a lower rate of death, CV death, and MI compared with placebo (4.0, 2.9, and 4.2 per 1,000 person-years lower, respectively). In contrast, among persons with a PAL, those receiving treatment had a higher rate of death, CV death, and MI compared with placebo (8.6, 5.3, and 2.7 per 1,000 person-years higher, respectively). These patterns persisted in Cox models, although interaction terms did not reach statistical significance. Treatment remained protective for stroke regardless of functional status. The rate of falls associated with treatment differed by functional status; incidence-rate ratio = 0.81, 95% confidence interval (CI) = (0.66, 0.99), and 1.32, 95% CI = (0.87, 2.00) in participants without and with a PAL, respectively, in models adjusted for demographics and baseline blood pressure (*P*-value for interaction, 0.04).

CONCLUSIONS
Functional status may modify the effect of antihypertensive treatment on MI, mortality, and falls, but not stroke, in older adults. Functional status should be examined in other trial settings.

Keywords: antihypertensives; blood pressure; falls; functional status; hypertension.

doi:10.1093/ajh/hpv177

An estimated 66% and 79% of community-dwelling US adults aged 65–79 and 80 years or older, respectively, are taking at least 1 antihypertensive medication.[1]However it remains unclear whether blood pressure lowering is beneficial for all older adults,[2–8] and the appropriate blood pressure target for those older than 60 years continues to be an issue of active debate.[9–11]

The missing piece of the current discussion is that chronologic age may not be the optimal tool for classifying older adults into meaningful risk categories. Measures of health status may be more useful than age for identifying those older adults who benefit from lower blood pressure targets and those who do not. Observational studies have shown that the relationship between high blood pressure and outcomes is modified by functional status.[12–14] More specifically, it has been shown that lower blood pressure is beneficial among those who are robust, but higher blood pressure is beneficial among poor-functioning older adults. However, few data exist on whether effects of pharmacologic intervention to lower blood pressure vary by functional status among older persons in a clinical trial setting.

In the present study, we evaluated whether functional status modifies the effect of antihypertensive treatment among participants in the Systolic Hypertension in the Elderly Program (SHEP). Although SHEP was conducted nearly 3 decades ago, it is the only placebo-controlled trial of antihypertensive therapy in US older adults, and remains the basis for treating isolated systolic hypertension in this population. An advantage of using SHEP data is that antihypertensive therapy was not widely used among older adults at the time of the trial, so the placebo group had a low prevalence of medication use. Therefore, although this is a post hoc analysis, blood pressure lowering among the treated group can be attributed primarily to the intervention.

METHODS

Study design and participants

Detailed methods for the SHEP have been previously described.[15,16] SHEP was a randomized, double-blind, placebo-controlled trial that investigated the efficacy of

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Initially submitted July 3, 2015; date of first revision July 30, 2015; accepted for publication October 19, 2015; online publication November 4, 2015.

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antihypertensive treatment on the primary endpoint of fatal and nonfatal stroke. Participants were 4,736 adults aged 60 years or older with isolated systolic hypertension (systolic blood pressure (SBP) 160–219 mm Hg and diastolic blood pressure (DBP) <90 mm Hg). Participants were randomized to receive placebo or active stepped-care treatment (chlorathalidone ± atenolol), with the goal of achieving the lower of 2 potential targets: SBP < 160 mm Hg or a 20 mm Hg reduction from baseline. Stepped care escalated treatment for participants that did not attain SBP goals. The sequence of stepped care was 12.5 mg/day chlorthalidone, then 25 mg/day chlorthalidone, followed by addition of 25 mg/day atenolol, then 50 mg/day atenolol. Reserpine (0.05 mg/day then 0.10 mg/day) could be substituted at step 2 if atenolol was contraindicated. Participants were followed for an average of 4.5 years.[15]

Variables

Outcomes of interest for this study were stroke, myocardial infarction (MI), all-cause death, cardiovascular (CV) death, and self-reported falls and symptoms of hypotension (defined as imbalance, lightheadedness, or passing out). Other variables included age, sex, race (White, Black, or other), current smoking status, and body mass index. Additionally, blood samples were collected for determination of baseline fasting serum glucose, serum creatinine, triglycerides, and total and high-density lipoprotein cholesterol. Low-density lipoprotein was calculated from total cholesterol, high-density lipoprotein cholesterol, and triglyceride levels. A trained interviewer also obtained a baseline Center for Epidemiologic Studies Depression Scale (CES-D) score. Baseline physical ability limitation (PAL) was defined as present if a person answered "no" to 1 or more of the following questions: "are you able to do heavy work around the house, like washing windows, walls or floors without help?" "are you able to walk up and down stairs to the second floor without help?" or "are you able to walk half a mile without help? That's about eight ordinary blocks." This measure was chosen from the available physical function variables in SHEP based on the strength of its association with all-cause mortality in a classification and regression tree analysis. Blood pressure was measured by trained staff using standardized techniques and recorded as the average of 2 seated readings.[15]

Analyses

We compared baseline characteristics of participants in the treatment and placebo groups, by PAL, using chi-square tests or *t*-tests as appropriate. We then described the total event count, incidence rate in treatment and placebo groups, and rate difference for death, CV death, MI and stroke, across strata of PAL. Hazard ratios (HRs) were computed using Cox proportional hazards regression models, and the proportional hazards assumption was verified using Schoenfeld residuals. First, we computed the unadjusted HR. Since it is possible that stratification by PAL could compromise randomization, we took a conservative approach and also presented a secondary model, adjusted for age, sex, race, and baseline SBP and DBP.

The relationship between treatment and adverse events across strata of PAL was also examined, using negative binomial regression models. Adjusted incidence-rate ratios were obtained by including the same sets of covariates in negative binomial regression models that were used in Cox proportional hazards models, as described above. All analyses were performed using Stata 12.0 (College Station, TX), according to intention-to-treat principles.

RESULTS

A total of 545 participants (11.9%) reported having at least 1 PAL (Table 1). Compared to those with no PAL, participants with a PAL were more likely to be older, female, or Black. They also had higher baseline SBP and slightly lower baseline DBP, greater values for body mass index, high-density lipoprotein cholesterol, and CES-D score, and lower values for triglycerides, compared to those with no limitation. Among those without a PAL, there was a small difference in DBP levels across treatment groups.

The proportion of participants experiencing death, CV death, MI, or stroke during the study period was higher among those with a PAL, compared to those with no PAL (Table 2). The mortality rate difference associated with treatment varied by functional status. Among persons with no PAL, those receiving treatment had a lower mortality rate than the placebo group. In contrast, among persons with a PAL, those receiving active treatment had a higher mortality rate than the placebo group. This pattern persisted in Cox proportional hazards models, where treatment was associated with a lower adjusted risk of death among those with no PAL (HR = 0.82, 95% confidence interval (CI) = (0.66, 1.00)) but not in those with a PAL (HR = 1.22, 95% CI = (0.79, 1.88)), (*P*-value for treatment and ability limitation interaction = 0.10). Similarly, treatment resulted in lower CV death rates than placebo among those without a PAL, but higher rates among those with a PAL. In adjusted Cox proportional hazards models, treatment was protective against CV death for those with no PAL (HR = 0.71, 95% CI = (0.51, 0.98)), but not for those with a PAL (HR = 1.27, 95% CI = (0.71, 2.28)), (*P*-value for interaction = 0.08). Results suggested a similar pattern for treatment effect by PAL for MI; among persons with no PAL, those on treatment had a lower rate of MI, whereas among persons with a PAL, those on treatment had a higher rate of MI. In Cox proportional hazards models, treatment was associated with a lower adjusted risk of MI among those with no PAL (HR = 0.57, 95% CI = (0.40, 0.81)) unlike in those with a PAL (HR=1.25, 95% CI = (0.54, 2.89)), (*P*-value for interaction = 0.08). In contrast to our findings for all-cause death, CV death, and MI, treatment remained protective for stroke regardless of functional status.

The association between treatment and falls varied across categories of functional status (Table 3). Treatment was associated with a decreased adjusted risk of falls among those without a PAL (incidence-rate ratios = 0.81, 95% CI = (0.66, 0.99)), but an increased, although not statistically significant, risk of falls among those with a PAL (incidence-rate ratios = 1.32, 95% CI = (0.87, 2.00)), (*P*-value for interaction, 0.04). There was no association between treatment and symptoms of hypotension in either physical ability group.

Table 1. Participant characteristics by physical ability limitation and randomization group

Variable	Physical ability limitation: Absent			Physical ability limitation: Present			
	Treated (*N* = 2,046)	Placebo (*N* = 2,002)	*P*-value[a]	Treated (*N* = 258)	Placebo (*N* = 287)	*P*-value[a]	*P*-value[b]
Age (years)—mean ± SD	71.7 ± 6.4	71.6 ± 6.4	0.75	76.2 ± 7.2	75.9 ± 7.3	0.60	<0.001
Female sex—*n* (%)	1,094 (53)	1,084 (54)	0.67[c]	204 (79)	226 (79)	0.93[c]	<0.001[c]
Race—*n* (%)			0.58[c]			0.08[c]	<0.001[c]
White	1,634 (80)	1,621 (81)		186 (72)	192 (67)		
Black	260 (13)	233 (12)		60 (23)	88 (31)		
Other	152 (7)	148 (7)		12 (5)	7 (2)		
Blood pressure (mm Hg)—mean ± SD							
Systolic	170.2 ± 9.3	169.8 ± 9.0	0.09	172.5 ± 11.2	172.0 ± 10.3	0.54	<0.001
Diastolic	77.1 ± 9.5	76.5 ± 9.8	0.05	74.7 ± 10.7	74.9 ± 9.8	0.76	<0.001
Current smoker—*N* (%)	256 (13)	255 (13)	0.83[c]	33 (13)	41 (14)	0.62[c]	0.52[c]
Body mass index (kg/m^2) – mean ± SD	27.5 ± 4.8	27.4 ± 4.9	0.67	28.3 ± 6.2	28.9 ± 6.5	0.30	<0.001
Fasting serum glucose (mg/dl)—mean ± SD	107.8 ± 33.2	108.8 ± 32.8	0.35	108.8 ± 37.6	109.7 ± 37.7	0.77	0.53
Serum creatinine (mg/dl)—mean ± SD	1.0 ± 0.2	1.0 ± 0.2	0.43	1.0 ± 0.3	1.0 ± 0.3	0.77	0.31
Triglycerides (mg/dl)—mean ± SD	158.0 ± 96.5	161.1 ± 98.9	0.33	148.5 ± 88.9	145.2 ± 77.5	0.66	0.01
Cholesterol (mg/dl)—mean ± SD							
Total	237.5 ± 43.9	236.1 ± 44.0	0.33	236.2 ± 56.4	233.1 ± 40.8	0.47	0.29
Low-density lipoprotein	152.0 ± 40.3	150.9 ± 39.5	0.38	150.4 ± 43.5	148.2 ± 39.4	0.56	0.25
High-density lipoprotein	53.7 ± 15.0	53.1 ± 14.3	0.17	54.6 ± 14.2	55.9 ± 15.4	0.35	0.01
CES-D total score	23.7 ± 5.0	23.7 ± 5.1	0.84	27.5 ± 7.4	27.0 ± 7.3	0.43	<0.001
History of CVD—*n* (%)	134 (7)	124 (6)	0.64[c]	19 (7)	25 (9)	0.57[c]	0.13[c]

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; CVD, cardiovascular disease.
[a]*P*-value within physical ability limitation groups. [b]*P*-value across physical ability limitation groups. [c]*P*-value from chi-square test; all other *P*-values are from *t*-test.

DISCUSSION

In this *post hoc* analysis of data from the SHEP trial, the benefit and harms of antihypertensive therapy appear to be modified by the presence of PAL. Among persons with self-reported PAL, those on treatment had higher rates of all-cause mortality, CV mortality, MI, and falls compared to those on placebo. However, treatment remained protective for stroke regardless of functional status. These findings suggest that functional ability should be examined in other trial settings to determine whether it can be used to guide treatment decision making.

This study builds on previous observational research that has shown measures of functional status modify the relationship between blood pressure and health outcomes among community-dwelling older adults. Recent studies have reported effect modification by gait speed, Activities of Daily Living limitation, and physical and cognitive function measures; in these studies, lower blood pressure was protective among participants with good health status, whereas the association was null or even harmful among participants with poor health status.[12–14,17] Only one previous study has examined whether there are differential treatment effects by functional status in older adults. In a *post hoc* analysis of the Hypertension in the Very Elderly Trial (HYVET), a placebo-controlled trial of antihypertensive medication use among adults aged 80 and older, the authors found no evidence that frailty attenuated the positive effect of antihypertensive medication.[18] There are several potential explanations for these apparently conflicting findings. First, functional status among the HYVET participants was measured using a frailty index, whereas the present study used self-reported ability limitation. Prior literature has reported a differential effect of blood pressure lowering by disability status, but not walking speed,[14] so it is possible that the measure used to define poor functional or frailty status could affect the results. Second, HYVET had a lower prevalence of comorbid health conditions compared with community-dwelling octogenarians, so it is possible that the study included a healthier than average population.[19] Finally, although SHEP and HYVET used

Table 2. Treatment effects on morbidity and mortality, by physical ability limitation

	Physical ability limitation	
	Absent (*N* = 4,048)	**Present (*N* = 545)**
Death		
Events—*n* (%)[a]	357 (8.8)	45 (8.3)
Mortality rate per 1,000 person-years		
Treatment	18.1	40.3
Placebo	22.1	31.7
Rate difference	−4.0	8.6
HR (95% CI)—unadjusted[b]	0.82 (0.67, 1.01)	1.27 (0.83, 1.95)
HR (95% CI)—adjusted[b]	0.82 (0.66, 1.00)	1.22 (0.79, 1.88)
CV Death		
Events—*n* (%)	150 (3.7)	46 (8.4)
Mortality rate per 1,000 person-years		
Treatment	7.0	22.4
Placebo	9.9	17.1
Rate difference	−2.9	5.3
HR (95% CI)—unadjusted[c]	0.71 (0.51, 0.98)	1.31 (0.73, 2.34)
HR (95% CI)—adjusted[c]	0.71 (0.51, 0.98)	1.27 (0.71, 2.28)
MI		
Events—*n* (%)[a]	135 (3.3)	22 (4.0)
Incidence rate per 1,000 person-years		
Treatment	5.6	11.0
Placebo	9.8	8.3
Rate difference	-4.2	2.7
HR (95% CI)—unadjusted[d]	0.57 (0.40, 0.81)	1.33 (0.57, 3.07)
HR (95% CI)—adjusted[d]	0.57 (0.40, 0.81)	1.25 (0.54, 2.89)
Stroke		
Events—*n* (%)[a]	211 (5.2)	45 (8.3)
Incidence rate per 1,000 person-years		
Treatment	9.5	17.5
Placebo	14.9	22.1
Rate difference	−5.4	-4.6
HR (95% CI)—unadjusted[e]	0.64 (0.49, 0.84)	0.79 (0.44, 1.44)
HR (95% CI)—adjusted[e]	0.64 (0.49, 0.85)	0.80 (0.44, 1.46)

Abbreviation: HR, hazard ratio.

Adjusted models include age, sex, race, baseline SBP and DBP.

[a]*P*-values from chi-square test for death $P < 0.001$; MI $P = 0.40$; and stroke $P = 0.004$. [b]*P*-values for interaction: unadjusted, $P = 0.07$; adjusted model, $P = 0.10$. [c]*P*-values for interaction: unadjusted, $P = 0.07$; adjusted model, $P = 0.08$. [d]*P*-values for interaction: unadjusted, $P = 0.07$; adjusted model, $P = 0.08$. [e]*P*-values for interaction: unadjusted, $P = 0.53$; adjusted model, $P = 0.48$.

diuretics as the primary class of medication for the intervention the secondary drug was a beta-blocker in SHEP and an angiotensin converting enzyme inhibitor in HYVET. It is possible that the presence of an interaction by functional status may differ by the treatment used. However, the evidence from observational studies of the differential effect of lower blood pressure across functional status has been confirmed in a variety of populations using a range of different antihypertensive medications. Our finding of an attenuated treatment effect for MI but not stroke aligns with other work that has suggested the presence of a J-shaped relationship between blood pressure and coronary heart disease.[2,20,21]

Current US guidelines recommend initiation of blood pressure lowering treatment when SBP exceeds 150 mm Hg in patients older than 60 years, and some recommend treatment to a target of 140 mm Hg.[11] In addition, early

Table 3. Treatment effects on adverse events, by physical ability limitation

	Physical ability limitation Absent (*N* = 4,048)	Physical ability limitation Present (*N* = 545)	*P*-value for Interaction
Falls			
Events—*n*	441	117	
IRR (95% CI)—unadjusted	0.83 (0.68, 1.02)	1.32 (0.87, 2.01)	0.05
IRR (95% CI)—adjusted	0.81 (0.66, 0.99)	1.32 (0.87, 2.00)	0.04
Imbalance/lightheaded/pass out			
Events—*n*	3,841	876	
IRR (95% CI)—unadjusted	1.00 (0.90, 1.11)	0.95 (0.77, 1.17)	0.75
IRR (95% CI)—adjusted	1.00 (0.91, 1.11)	0.96 (0.78, 1.18)	0.78

Abbreviation: IRR, incidence-rate ratio.
Adjusted model includes age, sex, race, baseline SBP, and DBP.

findings from the Systolic Blood Pressure Intervention Trial (SPRINT) suggest that intensive blood pressure lowering to <120 mm Hg may be beneficial for adults older than 50 years.[22] In contrast, the threshold for blood pressure lowering treatment in SHEP was 160 mm Hg. Despite this higher initiation threshold, we found that some SHEP participants may experience better outcomes with placebo than active treatment. The possibility that functionally impaired older adults may do better without treatment, even with the high baseline blood pressures required for entry into SHEP, is a substantial warning flag that warrants further research, given the current lower thresholds for blood pressure treatment. Pending analyses investigating the subgroup of SPRINT participants older than 75 years, and potential effect modification by functional status, will provide additional knowledge on this salient topic. Randomized trials of de-intensification or discontinuation of antihypertensive medications could also offer further insight into this area. A recent study has set the stage for such trials by examining the effect of antihypertensive medication discontinuation on cognitive function, and future work may draw on this methodology.[23,24]

Several potential mechanisms may explain the differing effects of antihypertensive treatment by functional status. For example, it is possible that elevated blood pressure represents a protective mechanism that allows adequate perfusion of vital organs such as the heart and brain among some older adults.[25,26] It is also possible that poorly functioning older persons may be more vulnerable to adverse effects of antihypertensive medications.[27] Additionally, recent studies have highlighted the potential increase in fall risk among persons on antihypertensives, which could initiate a cascade of events ending in morbidity or mortality.[28–30]

Our results should be interpreted in the context of several limitations. The findings presented here were *post hoc* analyses of a subgroup of participants in SHEP. Examining subsets of trial participants introduces the potential for latent confounding; however, the lack of statistically significant differences between treated and control participants within PAL groups (Table 1) provides support for the idea that randomization was not significantly compromised. Second, we examined self-reported ability limitation as a measure of functional status, due to its association with all-cause mortality in a classification and regression tree analysis. Poor functional status may be a marker of frailty status; however, the components of the frailty phenotype were not available in SHEP, therefore we could not compare the relative importance of frailty status. Inherent heterogeneity of poor-functioning older adults, as well as the small sample size of the PAL group, contributed to imprecise estimates for the effect of treatment in those with a PAL, limiting the ability to determine the extent to which these findings were due to sampling variability. Future research may overcome similar limitations by purposefully oversampling older adults and collecting information about functional status, as in the SPRINT.[31] Another limitation of the present study is that using a single measure of self-reported health status may lead to misclassification of functional status. Lastly, the use of thiazides ± beta-blocker as the blood pressure lowering treatment in SHEP does not reflect current standard treatment practices. However, other observational research supports the hypothesis that functional limitation modifies the effect of blood pressure lowering among modern cohorts of older adults, who use antihypertensive medications which likely do reflect current treatment practices.[12–14]

Given the rising prevalence and treatment of hypertension,[32,33] optimal use of antihypertensive medications among older adults will continue to be an important public health issue. Older adults with poor functional status represent a vulnerable population with elevated risk of morbidity and mortality, and any treatment-related risks could exacerbate this poor health. Our findings are a warning flag that highlights the need for more research on this topic, especially given current blood pressure guidelines, which are lower than SHEP-era targets. Randomized controlled trials of antihypertensive medication discontinuation among frail older adults could provide valuable information to inform clinical decision making.

ACKNOWLEDGMENTS

This research was supported by the National Institute on Aging, NIH (K01AG039387, R01AG046206). This manuscript was prepared using SHEP research materials obtained from the NHLBI Biologic Specimen and Data Repository Information Coordinating Center and do not necessarily reflect the opinions or views of the SHEP or the NHLBI.

DISCLOSURE

The authors declared no conflict of interest.

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