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ORIGINAL RESEARCH ARTICLE

Hypotension Under Antihypertensive Treatment and Incident Hospitalizations of Nursing Home Residents

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Abstract

Background and Objective Hypertension is the most prevalent chronic disease in older adults. Antihypertensive drug use increases with aging. In some studies, hypotension developing under antihypertensive medication use has been indicated as a potential risk factor for morbidity and mortality in older adults. Our objective was to assess the relationship between hypotension under antihypertensive treatment and incident hospitalization of nursing home residents.

Methods We detailed blood pressure measurements of the previous 1-year period that were noted regularly at 2-week intervals and studied their mean values. The systolic blood pressure (SBP) and diastolic blood pressure (DBP) thresholds to define low SBP (≤ 110 mm Hg) and DBP (≤ 65 mm Hg) were derived from our previous study. We noted demographics, number of co-morbidities and regular medications, mobility status, and nutritional assessment via the Mini Nutritional Assessment Short Form.

Results We included 253 participants (66% male, mean age 75.7 ± 8.7 years). The prevalence of low SBP (≤ 110 mmHg) and low DBP (≤ 65 mmHg) was 34.8% and 15.8%, respectively. Among residents, 4% were bedridden, 15.8% wheelchair bound, 14.5% needing assistance for reduced mobility, and 62.7% were ambulatory. At a median of 15 months of follow-up, hospitalization incidence from any cause was 50.8% ($n = 134$). Incident hospitalization was more common in the group that had low DBP (odds ratio = 3.06; 95% confidence interval 1.02–9.15; $p = 0.04$) after adjusting for age, number of comorbidities and medications, mobility status, and nutritional status. Low SBP was not associated with hospitalization.

Conclusions The low DBP (≤ 65 mm Hg) during the previous year was associated with incident hospitalization of nursing home residents after adjustment for several factors. These findings indicate that lower DBP may be a causative factor for incident hospitalization. We need further studies to explore whether a correction of diastolic hypotension may decrease the hospitalization risk in this vulnerable population.

1 Introduction

Hypertension is the most prevalent chronic disease in older adults globally [1–3]. While there was a reluctance to treat hypertension because of concerns about vital organ hypoperfusion, recent studies on the treatment of hypertension in older adults indicated the benefit of treatment of hypertension in older age as well [4, 5]. Consequently, antihypertensive medications became often prescribed at a higher rate in older adults [6].

Key Points

Among older adults receiving hypertension treatment in a nursing home, systolic hypotension (≤ 110 mmHg) and diastolic hypotension (≤ 65 mmHg) were present in about one third and 15% of the residents, respectively; which indicates prevalent overtreatment.

Low diastolic blood pressure was associated with a higher risk of incident hospitalization after adjustment for several confounding factors.

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Older adults encompass a spectrum, from robust individuals with complete independence in functionality to those who are frail, disabled, and totally dependent. Currently, frailty is considered as a factor that may alter the benefits of hypertension treatment [7]. Previous studies revealed different recommendations for the treatment of hypertension in frail older adults, some suggesting higher blood pressure (BP) targets or a deleterious effect of antihypertensive treatment in frail patients, [8–14] while some others, i.e., the SPRINT trial, suggested lower targets and beneficial effects [5, 15].

However, the studies that claim the inclusion of frail older adults are being criticized for their inadequate frailty assessment [16, 17]. We and others have recently shown that hypotension under antihypertensive treatment might lead to increased mortality among vulnerable nursing home (NH) residents [18, 19]. The treatment of hypertension in frail older adults to a lowered target BP has been challenged by the experts in the field. In our recent study, we showed that a systolic BP $\leq$ 110 mm Hg and DBP $\leq$ 65 mm Hg were associated with mortality after several adjustments in NH residents [20]. We needed to report the analysis of associations of low BP with hospitalization in this study because hospitalization and mortality are different entities, which have some common risk factors but also uncommon risk factors. Furthermore, it was not feasible to analyze and discuss the findings of both hospitalization and mortality in the same paper and hospitalization risk and mortality risk have their own significance in an individual's life course. In a recent study, intensive antihypertensive treatment was reported to be associated with an increased hospitalization risk [21]. In view of these findings, the debate on the treatment of hypertension seems unresolved. In this study, we aimed to examine whether the hypotension under antihypertensive treatment was associated with incident hospitalization of NH residents in order to provide data for this still unresolved issue.

2 Methods

2.1 Population and Setting

This study was performed by using some of the data of our recently reported study on the association of low SBP and DBP with mortality in NH residents [18]. This was a single-center observational longitudinal study that was undertaken in the most populated NH in the country including a total of 592 residents aged $\geq$ 60 years. From those, 253 residents were taking antihypertensive medications and all of them accepted to be involved in the study. We completed the basal evaluation between June 2014 and February 2015.

2.2 Measurements

We recorded the data regarding age (years), sex, mobility status (i.e., ambulatory, need assistance for ambulation, wheelchair bound, or bedridden), number of co-morbidities and medications, and antihypertensive medications. Mobility status was considered as independent if the resident was ambulatory and dependent if he/she needed assistance for reduced mobility or was wheelchair bound or bedridden. We obtained the information by reviewing the patients' medical records and also from NH physicians and nurses during face-to-face interviews. A list of chronic diseases can be found in the methodology of our previously published paper [18]. We noted the number of long-term medications used including vitamin supplements and over-the-counter medications. Considering a combination of antihypertensive medications, we regarded each antihypertensive agent as a separate prescription. We evaluated nutrition by the Mini Nutritional Assessment Short Form (MNA-SF), which is a validated instrument in older adults. A MNA-SF score of $<$ 8 was considered as undernourished, 8–11 as at risk of undernutrition, and $\geq$ 12 as well nourished.

Blood pressures of the residents were measured at 2-week intervals by registered NH nurses by use of a manual aneroid sphygmomanometer (ERKA brand). Blood pressure was measured at 9 a.m. and 9 p.m., approximately 2–3 h after meals and/or caffeine intake in a sitting position for ambulatory participants after a minimum of 5 min of resting and in the supine position for bedridden participants. At the first visit, we recorded 26 consecutive BP measurements of each participant undertaken in the previous 1-year period. In that way, we computed mean values of the previous 1-year systolic and DBP measurements. There were no missing variables. We followed the participants for subsequent hospitalization for any cause.

We obtained ethics approval from the local ethics committee of our university hospital. We performed this study in line with the guidelines of the Declaration of Helsinki. We received written informed consent from all participants and/or their proxies.

2.3 Statistical Analysis

We investigated the variables for normality by using visual (histograms and probability plots) and analytical methods. Numerical variables were given as mean $\pm$ standard deviation for normally distributed variables and as median (minimum–maximum) for skew-distributed continuous variables. We showed categorical variables with numbers and frequencies. Two groups were compared with an independent sample *t* test or the Mann–Whitney *U* test when necessary. The Chi-square test with Yates correction and Fisher's exact test

was used for 2 × 2 contingency tables when appropriate for non-numerical data. The cut-off values of SBP and DBP in relation to mortality were determined by a receiver operating characteristic analysis in our previous study in the same residents [24]. A multivariate binary logistic regression with subsequent hospitalization as the outcome variable was performed. We outlined the results as odds ratio and 95% confidence interval. We performed statistical analyses by use of SPSS version 21.0 (SPSS Statistics; IBM, Armonk, NY, USA) and MedCalc Statistical Software version 15.2 (MedCalc Software Ltd, Ostend, Belgium). A p value < 0.05 determined statistical significance.

3 Results

We included 253 residents (mean age: 75.7 ± 8.7 years); 66% (n = 167) were male, 34% (n = 86) were female. Regarding their mobility status, 4% were bedridden, 15.8% wheelchair bound, 14.5% in need of assistance for reduced mobility, and 62.7% (n = 159) were ambulatory. The residents had a median number of seven chronic diseases and a median number of ten daily drugs. Among them, the median number of antihypertensive drugs was two. We evaluated if the residents were hospitalized at a mean follow-up time of 14.3 ± 5.2 months (median: 15 months). In the follow-up, 50.8% (n = 134) of the residents needed hospitalization.

3.1 Factors Related to the Presence of Low SBP and Low DBP

Of all 253 residents, 34.8% had low SBP (≤ 110 mm Hg) and 15.8% (n = 40) had low DBP (≤ 65 mm Hg). The comparison of residents with higher and low SBP respectively is given in Table 1 and those with higher and low DBP respectively is given in Table 2. The presence of low SBP was more common in male than in female patients (40.7% [n = 68] vs 23.2% [n = 20], respectively; p = 0.006). In residents with low SBP, nutritional status was worse (p = 0.006). However, although incident hospitalization was more common in those with low SBP (56.8% [n = 50] vs 47.3% [n = 78]), this finding did not reach statistical significance (p = 0.1) [Table 1]. However, there was no difference regarding age (years), mobility status, the total number of diseases, number of drugs, and the number of antihypertensive drugs between the SBP groups (Table 1). Regarding low DBP, it was also more common in male than in female patients (19.2% vs 9.3%, respectively; p = 0.006). The total number of drugs was higher in residents with low DBP than residents with high DBP (median numbers 12 (4–19) vs 10 (2–19) respectively; p = 0.04). Additionally, incident hospitalization was more common in residents with low DBP (70% vs 46.9%, p = 0.007) [Table 2].

3.2 Multivariate Binary Logistic Regression Analyses for Factors Related to the Incident Hospitalization

3.2.1 Analysis for Association of Low DBP with Incident Hospitalization

We created two different models to analyze factors related to incident hospitalization (Table 3). In both models, the dependent factor was incident hospitalization. In Model 1, the independent variables were age, total number of comorbidities and drugs, the presence of a mobility problem, and low DBP. In the second model (Model 2), we added the nutritional status in addition to the variables

Table 1 Comparison of residents who have low SBP with residents who have higher SBP (univariate analyses)

	Higher SBP (n = 165)	Low SBP (n = 88)	p value
Age (years)[b]	75.6 ± 8.3	76 ± 9.2	0.7
Sex[a] (male/female) [%]	77.3/22.7%	60.0/40.0%	0.006
Mobility status[c] (independent/dependent) [%]	66/34%	56.6/43.4%	0.2
Total number of diseases[b]	7.4 ± 2.8 [7 (1–17)]	8 ± 2.4 [8 (3–13)]	0.1
Total number of drugs[b]	10.1 ± 3.6 [10 (2–19)]	10.2 ± 3.3 [10 (3–19)]	0.7
Number of antihypertensive drugs[b]	2.2 ± 1.1 [2 (1–6)]	2.0 ± 1.1 [2 (1–5)]	0.3
MNA-SF score[a,b]	12.0 ± 2.3 [13 (3–14)]	11.1 ± 2.3 [11 (5–14)]	0.006
Hospitalization [% (n)]	47.3% (78)	56.8% (50)	0.1

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MNA-SF Mini Nutritional Assessment Short Form, *SBP* systolic blood pressure

[a]Significant differences present between the groups

[b]Data are given as (mean ± standard deviation) and [median (minimum–maximum)] as appropriate

[c]Mobility status: independent: ambulatory; dependent: need assistance for ambulation, wheelchair bound or bedridden

Table 2 Comparison of residents who have low DBP with residents who have higher DBP (univariate analyses)

	Higher DBP ($n = 213$)	Low DBP ($n = 40$)	p value
Age (years)[b]	75.6 ± 8.5	76.2 ± 9.4	0.7
Sex[a] (male/female) [%]	63.4/36.6%	80.0/20.0%	0.006
Mobility status[c] (independent/dependent) [%]	63.6/36.4%	57.6/42.4%	0.5
Total number of diseases[b]	7 (1–17)	8 (3–12)	0.1
Total number of drugs[a,b]	10 (2–19)	12 (4–19)	0.04
Number of antihypertensive drugs[b]	2 (1–6) 2 (1–5)	0.3	
MNA-SF score[b]	11.8 ± 2.4	11.3 ± 2.3	0.3
Hospitalization[a] [%, (*n*)]	46.9% (100)	70% (28)	0.007

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DBP diastolic blood pressure, *MNA-SF* Mini Nutritional Assessment Short Form

[a]Significant differences present between the groups

[b]Data are given as (mean ± standard deviation) and [median (minimum–maximum)] as appropriate

[c]Mobility status: independent: ambulatory; dependent: need assistance for ambulation, wheelchair bound or bedridden

in Model 1. In both models, the presence of low DBP was related to incident hospitalization (in Model 1 and Model 2; odds ratio = 2.56, 3.06, 95% confidence interval 1.05–6.22, 1.02–9.15, respectively; $p = 0.04$ in both models). The other factors related to incident hospitalization were the number of total medications in both models, and nutritional status, in Model 2.

Table 3 Multivariate binary logistic regression analyses to determine the factors that predict incident hospitalization including and revealing low DBP as an independent associated factor

	Odds ratio	95% confidence interval	p value
Model 1			
Age	0.99	0.96–1.03	0.75
Total number of diseases	0.94	0.82–1.08	0.44
Total number of drugs[a]	1.21	1.08–1.36	0.001
Mobility problem	1.21	0.64–2.29	0.54
Low DBP[a]	2.56	1.05–6.22	0.04
Model 2			
Age	0.99	0.95–1.03	0.71
Total number of diseases	0.91	0.78–1.06	0.23
Total number of drugs[a]	1.27	1.14–1.44	< 0.001
Mobility problem	0.94	0.46–1.92	0.87
MNA-SF[a]	0.83	0.71–0.97	0.02
Low DBP[a]	3.06	1.02–9.15	0.04

Outcome variable was hospitalization in the follow-up. Covariates were age (years), mobility status, total number of diseases, total number of drugs, MNA-SF score, and presence of low DBP

Mobility status: independent: ambulatory; dependent: need assistance for ambulation, wheelchair bound or bedridden

DBP diastolic blood pressure, *MNA-SF* Mini Nutritional Assessment Short Form

[a]Significant association

3.2.2 Analysis for Association of Low SBP with Incident Hospitalization

Again, we created two models for low SBP, which were similar to those we studied in the analysis for low DBP. In both models, the presence of low SBP was not associated with incident hospitalization. The only factors related to incident hospitalization were the number of medications and the presence of a mobility problem. Model 2 for low SBP versus incident hospitalization is given in Table 4.

4 Discussion

In this study performed in 253 NH residents receiving antihypertensive treatment aged 75.7 ± 8.7 years, the presence of low DBP (≤ 65 mm Hg) was independently associated with incident hospitalization within a period of 15 months after adjustment for several factors, i.e., age, total number of co-morbidities and medications, mobility status, and nutritional status. Frailty, functional status, and disability have the potential to change the benefits and harms of the treatment of a specific disease. Accordingly, different targets are commonly recommended while treating chronic internal diseases, for example, diabetes mellitus. It is well known that frail older adults are vulnerable to medication-related side effects [22]. In addition, frailty is linked to limited life expectancy and this may reduce the benefit from antihypertensive treatment [23].

Table 4 Multivariate binary logistic regression analyses to determine the factors that predict incident hospitalization including low SBP among independent factors

	Odds ratio	95% confidence interval	*p* value
Age	0.99	0.96–1.03	0.86
Total number of diseases	0.92	0.79–1.07	0.30
Total number of drugs[a]	1.27	1.12–1.45	< 0.001
Mobility problem[a]	0.84	0.73–0.99	0.04
MNA-SF	1.21	0.61–2.40	0.58
Low SBP	0.93	0.46–1.87	0.84

Outcome variable was hospitalization in the follow-up. Covariates were age (years), mobility status, total number of diseases, total number of drugs, MNA-SF score, and presence of low SBP

Mobility status: independent: ambulatory; dependent: need assistance for ambulation, wheelchair bound or bedridden

MNA-SF Mini Nutritional Assessment Short Form, *SBP* systolic blood pressure

[a]Significant association

Consequently, we argue whether strict treatment of hypertension in frail individuals is beneficial and consider that this even may be hazardous. Accordingly, some recent trials included frailer older adults and their results indicated that frail individuals may not benefit from strict antihypertensive treatment [9–11]. Moreover, some trials indicated that there are hazardous consequences of the treatment of hypertension in frail individuals [10–12]. Correspondingly, the European Geriatric Medicine Society and European Society of Hypertension worked together to produce an expert opinion and proposed that frailty should be considered while managing hypertension in older adults [24]. They recommended to apply a simple practical evaluation of frailty status [24]. However, the recently performed SPRINT trial suggested that lower SBP targets, as low as < 120 mm Hg, in older adults and frailty did not affect the benefit or harm gained by such BP control [15]. This study triggered a modification of antihypertensive targets by the consensus committees defining a lower target BP in older adults [25, 26]. Nevertheless, from a geriatrics point of view, the SPRINT trial has been appraised as including only ambulatory community-dwelling older adults [16]. The exclusion criteria were extensive encompassing unintentional weight loss, expected survival < 3 years, significant heart or renal failure, or the use of too many medications, which are considerably prevalent in older age, particularly in frail older adults. Hence, frailer older individuals were excluded. Another significant point was that in slow walkers, study outcomes (i.e., composite outcome of nonfatal myocardial infarction, acute coronary syndrome not resulting in a myocardial infarction, nonfatal stroke, nonfatal acute decompensated heart failure and death from cardiovascular causes, and all-cause mortality) did not indicate the benefit of intensive treatment compared with the standard treatment group ($p = 0.05$ and $p = 0.3$, respectively) [5].

HYVET (HYpertension in the Very Elderly Trial) is another cornerstone study specifically designed in very old patients with a specific emphasis on frailty [27]. HYVET authors did not find an interaction between frailty and antihypertensive treatment. Noteworthy, in that trial, frailty was evaluated by the Frailty Index. However, the relationship between hypertension and mortality varied according to the frailty categories whereby frailty was identified by walking speed [10, 14], and not by the Frailty Index. SHEP trial data have also been re-analyzed to check if functional status modified the outcomes of antihypertensive treatment in older individuals [13]. We suggest that the Frailty Index, rather than being a reliable marker of frailty, represents a long checklist of clinical conditions and diseases, and it mainly indicates the burden of co-morbidities instead of the patient's functionality or vulnerability [28].

Some studies, in line with the findings of the present study, urged the clinicians to be watchful whilst treating frail older adults with antihypertensive treatments. In a longitudinal Partage study involving 1127 participants, Benetos et al. evaluated all-cause mortality in institutionalized individuals aged > 80 years. In that study, BP was measured with assisted self-measurements during 3 consecutive days. A significant interaction between low SBP (designated as < 130 mm Hg) and treatment with two or more antihypertensives was reported, which resulted in a higher risk of mortality. Subsequently, they drew attention to questioning the safety of using a combination of antihypertensive medications in frail older adults already having SBP < 130 mm Hg [19]. In a recent study from the Netherlands performed in 244 patients aged 85 year or more from a population-based cohort study, all-cause mortality was higher in those with lower BP receiving antihypertensive treatments [29]. Most recently, in this same cohort, we questioned the benefit of too low BP in frail NH residents in terms of mortality [18]. At a median follow-up period of 40 months, we showed that low SBP (≤ 110 mm Hg) and DBP (≤ 65 mm Hg) were associated with mortality after adjustments with several confounders [18]. The possible hospitalization risk associated with the application of more intensive antihypertensive treatment has been analyzed in 255,670 NH residents [21]. In that study, the authors presented the number and intensity of antihypertensive treatments rather than the BP values obtained by the use of antihypertensive medications. They stated that increased intensity of antihypertensive treatment was associated with an increase in hospitalization, which is in line with the increased risk of incident hospitalization with attainment of low DBP (≤ 65 mm Hg) in NH residents found in our study. In this current study, it was remarkable

that the relationship between low DBP and incident hospitalization was independent from the higher age, mobility status as a proxy of functionality, nutritional status, and the number of co-morbidities or drugs. Moreover, the odds ratio of low DBP was highest among the all predictors of incident hospitalization (odds ratio = 3.06 for low DBP); 1.27 for number of medications, 0.83 (in favor of better nutrition) for the MNA-SF score. Likewise, in another vulnerable subset of older adults, Anderson et al. studied the association between the intensification of antihypertensive regimens at hospital discharge and clinical outcomes in a propensity-matched cohort [30]. They included 4056 hospitalized hypertensive older adults and they showed that prescription of intensified antihypertensive medications at discharge was associated with an increased risk of readmission and serious adverse events within 30 days. Most recently, Albasri et al. studied the association between antihypertensive treatment and adverse events in their systematic review and meta-analysis including the randomized controlled trials of adults receiving antihypertensive medications. Remarkably, they reported an association with both severe (acute kidney injury, syncope) and mild adverse events (hyperkalemia, hypotension). They urged clinicians to inform patients about the initiation and continuation of antihypertensive medications, especially in those at higher risk of harm including the older adults with those characteristics [31]. In their recent review on hypertension management in nursing homes, Vu et al. also indicated that observational studies with patients more representative of NH residents suggest harms associated with more intensive BP treatment [32].

It is worth mentioning that, in this study, low SBP was present in 35% and low DBP in 16%, hence BP was very low in a large number of participants. While the current literature does not support reducing BP too much especially in frail older adults, the attained lower BP values in many settings is probably owing to the lack of personalized treatment decision making by means of comprehensive geriatric evaluations and because of the extrapolation of the lower BP goals valid in younger adults to the older population, which is a common practice in many settings [33–35]

This study has several limitations and strengths. The first limitation concerns the fact that the study was performed in a single center. In addition, the participants were NH residents who were likely to be frail but we did not have a formal evaluation of frailty status. However, we did assess the mobility status, being dependent or independent in mobility, as a proxy marker for functional status and physical frailty. Almost 40% of the participants had some dependency. The number of participants was 253, which was not very high, owing to the fact it was a single-center study. Considering that hypertension is prevalent in older adults, i.e., more than 50% of the older adults, this number may be considered as low and should be noted as a limitation. Nevertheless, this figure is comparable to the recent reports studying the benefit/harm of antihypertensive drug use in older adults receiving antihypertensive treatments [29]. A manual BP measurement device was used that is prone to measurement error and inter-individual variances, albeit measurements were performed by skilled NH nurses. It is a common practice to round the BP values during the use of non-automatic devices and therefore these measurements do not reflect the precise BP values. However, use of manual devices was also preferred in some other similar studies in the literature [29] and is a general limitation where non-automated devices are used. Another point, we recorded the SBP and DBP values of the previous 1-year period and have no follow-up data on BP measurements in the observation period. We were not permitted to manage the treatment because of the institutional regulations. In the study period, the institutional physicians did not change. Hence, it is unlikely that the BP management differed in the follow-up. Nevertheless, we do not have complete data on the BP course and this should be considered as a limitation.

The strengths of the present study are that we recorded the mean of BP measurements obtained from 26 consecutive measurements of the previous 1-year period, which were measured regularly at 2-week intervals. This is a particular strength because in the reports that examine associations between low BP and incident adverse events, the BP measurements were recorded at the beginning of the study as well but less frequently and for a shorter time period (e.g., 18 times in only 3 consecutive days or only two times recorded at 2 weeks apart) [19, 29]. The present study has a higher number of BP measurements across a much longer time period.

Another limitation of this study is its observational nature. Therefore, one cannot definitely conclude that lower BP resulted in deterioration of the health status and caused hospitalization. Clinical deterioration might have resulted in lower BP as well. However, one of the inclusion criteria of our study was receiving antihypertensive treatment. Hence, while clinical deterioration might have resulted in lower BP, receiving antihypertensive treatment should be certainly another factor for lower BP. Hence, we suggest that our study indicates some indirect evidence that lower BP attained by pharmacologic treatment of hypertension has some contribution to the clinical deterioration and hospitalization. This issue might have been addressed by performing an analysis on the relationship between the risk of hospitalization and trends in BP (decrease in BP over time) in the hospitalized patients. However, in our data, we did not have details of each measured BP values of the residents but the mean BP values of the previous 1 year determined by the average of 26 consecutive measurements. Therefore, we did not have the chance to perform such an analysis. As an additional output, analysis of the relationship

between BP variability and incident hospitalization could have contributed to understanding risk factors for future hospitalizations, as it is reported as a prognostic impact in previous studies. As noted above, we did not have details of each measured BP value of the residents and hence could not perform such an analysis either.

5 Conclusions and Implications

We showed that the presence of low DBP ($\leq$ 65 mm Hg) during the previous 1-year period was associated with incident hospitalization after adjustment with several factors. Because of the longitudinal design of the study, these results indicate that lower DBP may be a causative factor for incident hospitalization. We cannot comment whether the prevention of low DBP through a reduction in antihypertensive medications can decrease hospitalization needs. Randomized trials and rigorous observational studies to examine the effects of de-intensification of antihypertensive medications in complex older populations are required.

Declarations

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Conflicts of interest/competing interests GB, BI, AT, CK, MAK, and MP have no conflicts of interest that are directly relevant to the contents of this study.

Ethics approval This study was approved by the ethical committees at all participating sites and was conducted in accordance with the Declaration of Helsinki.

Consent to participate Informed consent was obtained from every patient and/or their parent or legal representative.

Consent for publication Not applicable.

Availability of data and material Anonymized data will be shared at the request of any qualified investigator.

Code availability Not applicable.

Authors' contributions GB designed and conceptualized the study, coordinated and supervised the data collection, carried out the data analyses, and drafted the manuscript. AT, BI, CK,MAK, and MP designed and conceptualized the study, and coordinated and supervised the data collection. GB, AT, BI, CK, MAK, and MP were involved in the acquisition of data. All authors critically revised the manuscript for important intellectual content. All authors approved the final manuscript for submission and agree to be accountable for all aspects of the work.

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