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# ANTIHYPERTENSIVE MEDICATIONS AND PHYSICAL FUNCTION IN OLDER PERSONS

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## Abstract

**Background—**To further inform benefits and risks of medications on physical function in aging populations, we have evaluated the associations of antihypertensive (antiHTN) class and number used with skeletal muscle function, mobility, sedentary time, and symptoms in older persons.

**Methods—**Using baseline data from the Lifestyle Interventions and Independence in Elder (LIFE) study (N=1567, mean age 78.9 years) and multivariable models, we evaluated cross-sectional associations of antiHTN class and number used with physical measures and symptom questionnaires. AntiHTN class included diuretics, angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), calcium channel blockers (CCB), and beta blockers (BB). Physical measures included respiratory muscle weakness (maximal inspiratory pressure), grip weakness (dynamometer), impaired lower extremity proximal muscle strength (chair stands), impaired balance (three-stage test), slow gait (400m walk), mobility impairment (Short Physical Performance Battery), and high sedentary time (accelerometry). Symptoms included dyspnea and fatigue. Covariates included clinical characteristics and non-antiHTNs.

**Results—**Use of any antiHTN was highly prevalent (n=1248 [79.6%]). In the antiHTN subgroup, each antiHTN class was well represented (ranging 36.6%–62.7%) and included use of three or more antiHTNs (32.0%). In adjusted models, the only statistically significant associations were use of BB and three or more antiHTNs with high sedentary time: odds ratios (95% confidence intervals) 1.44 (1.12, 1.85) and 1.52 (1.04, 2.23), respectively.

**Conclusion—**Use of BB and three or more antiHTNs yielded 44% and 52% increased odds of accelerometry-defined high sedentary time, respectively. Notably, high sedentary time is a risk

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factor for adverse health outcomes. Thus, future work should evaluate whether high sedentary time mitigates benefits or increases risks, regarding antiHTN use in aging populations.

**Keywords**

antihypertensive; skeletal muscle; mobility; sedentary; dyspnea

## INTRODUCTION

The United States population aged ≥65 years was 50.9 million in 2017.[1] In national surveys, this older age group commonly reports impaired mobility (22%), described as serious difficulty in walking or climbing stairs.[1,2] Thus, identifying modifiable factors that impair mobility has clinical value, as these establish preventive and therapeutic interventions. Because aging leads to changes in pharmaco-kinetics and -dynamics, and increased polypharmacy,[3–5] identifying medication-associated adverse effects on mobility, including impaired skeletal muscle function, physical inactivity, and symptom limitations, should be a high priority.

Medications that lower blood pressure, termed antihypertensives (antiHTNs), are often used in older persons but benefits and risks may vary by clinical setting.[5–15] For example, antiHTNs classified as a diuretic, angiotensin converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), and dihydropyridine calcium channel blocker (CCB) decrease left ventricular preload (intravascular volume) and/or afterload (systemic vascular resistance).[6–8] Other antiHTNs classified as a non-dihydropyridine CCB and beta blocker (BB) decrease heart rate and cardiac contractility, thus also decreasing myocardial oxygen ($O_2$) consumption.[6,8] These medication effects frequently benefit clinical settings that include heart failure (HF) and coronary heart disease (CHD). However, in the absence of established cardiovascular (CV) disease or in response to using multiple antiHTNs, the medication effects may instead decrease the perfusion of skeletal muscle, due to a reduced cardiac output or impaired distribution of systemic blood flow, and may be especially limiting during physical activity.[6–15]

Decreased perfusion of skeletal muscle reduces $O_2$ delivery, limiting aerobic cellular respiration and, in turn, decreasing metabolic and physiologic capacity.[11] Metabolically, the skeletal muscle generates less adenosine triphosphate (energy), leading to increased lactate production and carbon dioxide ($CO_2$) flux to the lung (buffering of lactate by bicarbonate).[11] Physiologically, skeletal muscle function decreases and ventilatory demand increases, impairing mobility and increasing dyspnea and fatigue.[11–15] Alternatively, the predominant physiology may be reduced endurance, simply manifested by low physical activity across the daytime period.[1,11]

Older persons are at increased risk of having reductions in skeletal muscle function.[11–20] Specifically, the aging skeletal muscle undergoes reductions in capillarization, myoglobin, glycogen, and mitochondrial volume and enzyme activity, each potentially limiting aerobic cellular respiration — these changes are additionally exacerbated by age-related declines in physical activity.[11,18,19] Moreover, aging decreases sympathetic modulation of cardiac

function and the Windkessel effect of the aorta, each potentially decreasing perfusion of skeletal muscle and limiting aerobic cellular respiration.[16,17,19]

Therefore, using baseline data on 1567 older persons from the Lifestyle Interventions and Independence for Elders (LIFE) study,[21] we have evaluated cross-sectional associations of antiHTN class and number used with physical function, including performance measures of skeletal muscle function and mobility, objective measures of physical activity, and the symptoms of dyspnea and fatigue. In our analyses, we included potential confounders and also evaluated whether CV disease is an effect modifier of the association between antiHTNs and mobility. Given that older persons have high rates of impaired mobility and medication use, our results will further inform the benefits and risks of antiHTNs in aging populations.

## METHODS

### Study Population

The LIFE study was a multicenter randomized controlled trial, conducted in 2010–2014.[21] The trial compared a physical activity intervention with health education in 1635 community-dwelling persons, aged 70–89 years.[21] Eligibility criteria included sedentary status (<20 minutes/week of regular physical activity and <125 minutes/week of moderate physical activity in past month) and impaired lower extremity function (Short Physical Performance Battery [SPPB] score <10, but able to walk 400 meters in ≤15 minutes without assistance).[21–23] The Institutional Review Boards of each participating center approved all procedures.[21]

Our current study reports on the baseline evaluation of LIFE participants, prior to the physical activity intervention.

### Demographic and Clinical Characteristics

Age, gender, race, body mass index (BMI), never-smoker status, blood pressure (seated), and comorbidities were recorded at baseline. Comorbidities included: stage 2 HTN (systolic ≥140 or diastolic ≥90), diabetes mellitus (self-reported, physician-diagnosed or use of diabetes medication), CV disease (self-reported, physician-diagnosed myocardial infarction [MI], HF, stroke, or peripheral artery disease, or electrocardiogram-defined silent MI), lung disease (forced expiratory volume in 1-second [$FEV_1$] < lower limit of normal [LLN]), arthritis (self-reported, physician-diagnosed), hip fracture (self-reported, physician-diagnosed), and depression (Center for Epidemiologic Studies Depression [CES-D], short form score ≥6).[21,24,25]

### Medications

AntiHTN use was determined by visual inspection of all prescription and nonprescription medications taken in the previous 2 weeks. AntiHTNs were then coded to reflect four medication classes: diuretic, ACEi or ARB, CCB, or BB.[6] When taken as a combination pill, components were assigned separately to the respective antiHTN class. We note that these antiHTN classes are the most commonly used medications for hypertension treatment in the

United States,[26] and that use of multiple antiHTN classes has therapeutic implications, e.g. combining two antiHTN classes is associated with an approximate five-fold greater blood pressure reduction, as compared with doubling the dose of one antiHTN.[27] In addition, we included ACEi and ARB in the same class, because the underlying mechanisms of action (renin-angiotensin system) and clinical indications for ACEi and ARB are similar and because simultaneous use of ACEi and ARB has no additional benefit and potentially harmful.[28]

All other non-antiHTN medications, prescribed and nonprescribed, were categorized by Anatomical Therapeutic Chemical (ATC) codes, using the RxNorm drug database.[29,30]

### Skeletal Muscle Function

Respiratory muscle strength was evaluated by the maximal inspiratory pressure (MIP), using a Magnehelic 2000–200 pressure gauge (Dwyer Instruments, Michigan City, IN). Based on reference equations,[20] participants had respiratory muscle weakness if the highest measured MIP in cm H2O was <LLN, i.e. <5$^{th}$ percentile distribution.

Grip strength in kg was evaluated in the dominant hand, using the Jamar Handheld Dynamometer (Bolingbrook, IL).[21] The highest measured grip strength was then compared with thresholds for grip weakness, specific to gender and BMI.[31]

As a surrogate measure of lower extremity proximal muscle strength,[14,19,32–34] the time required to complete five chair stands was evaluated — participants were instructed to rise from a chair, stand up straight, and return to seated position, as quickly as possible, five times. Using the SPPB protocol,[23] time-to-complete five chair stands was scored on a scale of 0–4 points. In the current study, a score of 0–2 points established impaired chair stands, based on ≥13.7 seconds to complete task, or unable to complete task, or unable to rise from a seated position without the use of arms.

### Mobility Measures

Balance was evaluated by testing of side-by-side, semi-tandem, and tandem stands. Using the SPPB protocol,[23] participants with normal balance achieved a total score of 4 points, one point each for side-by-side and semi-tandem, and two points for tandem. For the current study, 0–2 points established impaired balance.

Gait speed was recorded during a 400m walk test (400MWT), performed over a 40-meter course at participant's usual walking pace. Gait speed <0.8 meters/second defined slow.[35]

SPPB total score was a composite measure of mobility, including time to walk 4 meters at usual pace, time to complete five chair stands, and three increasingly difficult standing balance maneuvers (side-by-side, semi-tandem, and tandem).[22,23] SPPB total scores ≤7 established moderate-to-severe mobility impairment, henceforth simply termed mobility impairment.[22,23]

### Sedentary Time

Sedentary time was measured by accelerometry, using the ActiGraph GT3X (Pensacola, FL), and defined by percent of wear-time with activity <100 counts/minute (approximated sitting time),[36] averaged across a minimum of 3 days. Participants in the highest quartile were classified as having high sedentary time.[24]

### Symptoms

Dyspnea was evaluated by the American Thoracic Society (ATS) questionnaire, which graded severity on a scale of 0–5.[37] ATS grade ≥2 established moderate-to-severe dyspnea, henceforth simply termed dyspnea.[37] ATS grade ≥2 included a yes response to "Do you have to walk slower than people of your age on the level because of breathlessness?" This level of dyspnea is associated with adverse health outcomes and occurs at a low exertional workload.[37,38]

Fatigue was evaluated by Modified Exercise-induced Feeling Inventory (MEFI), which graded severity based on a scale of 0–5.[30] MEFI rating ≥3 established fatigue as occurring "good bit- to all-of-the-time during the past week".[39]

### Statistical Analysis

Baseline characteristics were first summarized as means and standard deviations or counts and percentages, overall and stratified by use of any antiHTN.

Next, using multivariable logistic regression models, adjusted odds ratios (ORs) with 95% confidence intervals (95%CIs) were calculated as measures of association between predictor variables and binary (yes/no) outcomes. In the first set of models, indicator variables were created to reflect use of the four classes of antiHTNs: diuretic, ACEi or ARB, CCB, and BB. In the second set of models, indicator variables reflected number of antiHTNs, categorized as one, two, and three or more, with those not taking any of the four antiHTN classes as the referent group. In both sets of models, nine binary outcomes were included: skeletal muscle function, i.e., respiratory and grip weakness and impaired chair stands; mobility measures, i.e., impaired balance, slow gait, and mobility impairment (SPPB ≥7); accelerometry-defined high sedentary time; and symptoms (dyspnea and fatigue). In the multivariable models, covariates identified a priori as clinically plausible confounders were additionally included: age, female gender, non-white race, obesity (BMI ≥30), never-smoker, comorbidities, and non-antiHTN medications. Model goodness of fit was assessed by the Hosmer-Lemeshow measure and additional goodness of fit tests for logistic regression were implemented in a SAS macro by Kuss.[40] Residual analysis and influence statistics were also examined.

For reasons discussed earlier, an exploratory analysis evaluated whether CV disease was an effect modifier of the association between antiHTNs and the outcome of mobility impairment. Specifically, interaction terms crossing antiHTN class and number used with CV disease were added to respective logistic regression models.

SAS version 9.4 software (SAS Institute Inc, Cary, NC) was used for all analyses.

Lastly, to account for missing data, including accelerometry (n=276 [17.6%]), $FEV_1$ (n=211 [13.5%]), MIP (n=207 [13.2%]), grip strength (n=87 [5.6%]), depression (n=77 [4.9%]), dyspnea (n=72 [4.6%]), smoking (n=24 [1.5%]), and fatigue (n=9 [<1%]), multiple imputation was used. Indicator variables for missing values were created and logistic regression models identified the explanatory variables associated with missingness or any of the nine outcomes. A total of 39 variables were identified and 20 datasets imputed, using fully conditional specification of logistic and discriminant models for categorical variables and a linear regression model for continuous variables.[41] PROC MI procedure in SAS (SAS/STAT version 14.3, SAS Institute Inc, Cary NC) was used to impute values and the PROC MIANALYZE procedure subsequently combined the coefficients from separate models, using Rubin's rules to obtain the final model coefficients.[42]

## RESULTS

Table 1 summarizes the characteristics of our study sample (N=1567). Overall, mean age was 78.9 years, 67.3% were female, 23.4% were non-white, 45.8% were obese, and 51.7% were never-smokers. Blood pressure (seated) averaged a systolic of 127.6 and diastolic of 68.2, and included 16 participants (1.0%) with a systolic <90. Comorbidities and medications were prevalent and included established CV disease (30.0%) and use of antiHTNs (79.6%). As to outcomes, a substantial proportion had weakness (respiratory 14.2%, grip 39.6%), impaired chair stands (79.8%) and balance (43.0%), slow gait (60.4%), mobility impairment (44.9%), high sedentary time (26.0%), dyspnea (43.1%), and fatigue (18.0%).

Table 1 also summarizes baseline characteristics by use of any antiHTN. Relative to no antiHTN, the use of any antiHTN had substantially greater representation of non-whites (25.6% vs. 14.7%), obesity (49.1% vs. 32.6%), diabetes (32.1% vs. 14.4%), and established CV disease (33.7% vs. 15.4%), but only modestly greater prevalence of slow gait (61.9% vs. 54.9%), high sedentary time (27.0% vs. 21.9%), and dyspnea (44.4% vs. 37.9%). Notably, participants in the antiHTN group frequently used all four antiHTN classes (ranged 36.6% to 62.7%) and multiple antiHTNs (65.0%), and had similar blood pressure readings as the no antiHTN group. Appendix A provides additional results on frequency distributions for the various combinations of antiHTN classes.

Tables 2 and 3 report adjusted ORs with 95%CIs for having respiratory and grip weakness, impaired chair stands and balance, slow gait speed, and mobility impairment, stratified by antiHTN class and number used, respectively. Results showed no statistically significant associations between antiHTNs and the stated outcomes of interest.

Table 4 reports adjusted ORs with 95%CIs for having high sedentary time, dyspnea, and fatigue, stratified by antiHTN class and number used, respectively. Results showed statistically significant associations between use of a BB and three or more antiHTNs and the outcome of high sedentary time: adjusted ORs (95%CIs) 1.44 (1.12, 1.85) and 1.52 (1.04, 2.23), respectively. Otherwise, no statistically significant associations were found between antiHTNs and the outcomes of dyspnea and fatigue.

Table 5 reports exploratory results on effect modification by CV disease of associations between anti-HTNs, including class and number used, and mobility impairment. Results showed no statistically significant effect modification: P-values for interaction all >.05. Although interactive effects were not statistically significant, the results nonetheless showed that use of antiHTNs, when evaluated as one, two, three or more vs. none, consistently yielded two-fold higher adjusted ORs for mobility impairment in those with established CV disease, as compared with those not having CV disease.

To further inform the results of Table 5, Appendix B reports frequency distributions that result from cross-tabulation of anti-HTN class and number used with CV disease and mobility impairment. For several subgroups, sample sizes were <100 participants, suggesting reduced statistical power.

## DISCUSSION

We have evaluated antiHTNs in a large sample of community-dwelling older persons, using data from the LIFE study. We found that antiHTNs were highly prevalent, including each of the four antiHTN classes of interest and use of multiple antiHTNs. Thus, the LIFE study provides a unique opportunity to evaluate the cross-sectional associations of antiHTN class and number used with physical function, including performance measures of skeletal muscle function and mobility, objective measures of physical activity, and the symptoms of dyspnea and fatigue.

In adjusted models, our results show that use of BB (50.1% of antiHTN group) and three or more antiHTNs (32.0% of antiHTN group) yield statistically significant increases of 44% and 52% in the odds of having accelerometry-defined high sedentary time, respectively. These results raise concerns regarding the potential effects of medications on physical activity. For example, in the LIFE study, the intervention group attended only 63% of scheduled physical activity sessions (interquartile range: 50–83%).[43] Future work in the LIFE study should therefore evaluate whether antiHTNs reduced participation in physical activity sessions. This line of research may also inform the role of medications as factors underlying the high rate of physical inactivity in the general population of older persons. National surveys of older persons report that 82.6% do not participate in regular physical activity and 39% take five or more prescription medications.[5,44] Moreover, recent research has recommended a triple antiHTN regimen in the management of mild-to-moderate hypertension.[45]

Ultimately, the clinical impact of high sedentary time is on health status. In particular, the accelerometry-based activity threshold for establishing sedentary time is <100 counts/min, which approximates sitting time, a defining component of sedentary behavior.[46,47] In prior work, increased sedentary time was associated with adverse health outcomes, including type 2 diabetes mellitus, metabolic syndrome, CV disease, cancer, hospitalization, and death.[47–49] Future work should therefore evaluate whether high sedentary time mitigates the benefits or increases the risks of antiHTNs on health outcomes.[10]

In the current study, additional results did not inform the mechanisms that potentially underlie the associations between antiHTNs and high sedentary time. Specifically, we found no statistically significant associations between antiHTNs and the outcomes of impaired skeletal muscle function and mobility, or dyspnea and fatigue. Given these null results and our cross-sectional design, future work should evaluate the longitudinal associations between antiHTNs and high sedentary time, including analyses that account for residual confounding by disease severity and for mediation by other factors such as orthostasis, dizziness, fear of falls, or a cardiac limitation (e.g. submaximal heart rate). If longitudinal associations are confirmed, but a mediating factor is not established, an alternative mechanism may be that antiHTNs predominantly reduce skeletal muscle endurance, manifested simply as low physical activity across the daytime period (rather than poor performance on a one-time test of skeletal muscle function).[1,11]

In the Introduction section, we postulated that patients with established CV disease are more likely to benefit from the effects of antiHTNs on intravascular volume, systemic vascular resistance, and myocardial oxygen consumption.[6–8] Our results, however, showed no statistically significant effect modification by CV disease on associations between antiHTNs and mobility impairment (SPPB ≤7), but these analyses were limited by the small sample sizes of subgroups. Despite the lack of statistical significance, our results nonetheless show that use of antiHTNs, when evaluated as one, two, and three or more vs. none, consistently yielded two-fold higher odds of mobility impairment in those who had established CV disease, as compared with those who did not. These results suggest that antiHTNs may have greater adverse effects on mobility in those with established CV disease (high sedentary time could be a mediating factor), but may also reflect residual confounding by the adverse effects of more severe forms of CV disease on mobility. Regardless of mechanisms, the implication of these exploratory results remains that patients who have established CV disease and are on antiHTNs should be evaluated for impaired mobility, as measured by a composite of chair stands, balance, and gait speed (SPPB).[22,23]

The current study has strengths: well-established cohort of older persons at increased risk of medication-related adverse effects; performance measures of skeletal muscle function and mobility; objective measures of physical activity; and the patient-centered outcomes of dyspnea and fatigue.[3–5,20–24,32–39] In addition, we evaluated commonly used antiHTN classes. Based on a recent survey of hypertension treatment in the United States, the most commonly used antiHTN classes were: ACEi (29%), thiazide-like diuretic (24%), ARB (22%), CCB (21%), and BB (19%).[26]

We acknowledge, however, several limitations. First, as discussed earlier, our cross-sectional design precludes establishing causal associations and concerns remain regarding residual confounding by differences in disease severity. Second, we only evaluated antiHTN class and number used. Additional strategies would be to evaluate adverse effects specific to antiHTN class combinations and to the intensity of antiHTN treatment, i.e., potentially reflected by a lower systolic blood pressure and higher antiHTN dose — in the SPRINT trial, for example, hypertension treatment began with two or three antiHTN classes and adverse effects were more frequent in the intensive antiHTN group.[10] Third, although a strong rational exists for including ACEi and ARB in the same class (see Methods), their

effects on skeletal muscle function may differ.[50] Fourth, our results on effect modification are exploratory, as sample sizes became substantially smaller when cross-tabulating subgroups. Fifth, we report multiple comparisons, increasing the chance of false-positives.[51] Lastly, the LIFE study required all participants be sedentary and have impaired lower extremity function, limiting generalizability of results.[21–23] To address these limitations, future work would require a longitudinal design, including objective measures of disease severity, larger subgroups to evaluate antiHTN class combinations and intensity of antiHTN treatment, and additional enrollment of participants who are not sedentary or physically impaired at baseline.

In conclusion, based on cross-sectional data from the LIFE study, we have shown that older persons who use a BB and three or more antiHTNs have an adjusted 44% and 52% increased odds of having accelerometry-defined high sedentary time, respectively. Since high sedentary time is a risk factor for adverse health outcomes, future work should evaluate whether high sedentary time mitigates benefits or increases risks, regarding antiHTN use in aging populations.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## ACKNOWLEDGMENTS

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## Highlights

- Uniquely evaluated antihypertensives in a large elderly cohort (LIFE study)
- Use of any antihypertensive was prevalent, including beta-blockers and ≥3 medications
- Beta-blockers and ≥3 antihypertensives were associated with high sedentary time
- High sedentary time may mitigate benefits or increase risks of antihypertensives

**Table 1.**

Baseline characteristics of participants, overall and by use of antiHTN medication

| Characteristic | All N=1567 [a] | AntiHTN Medication [b] | |
|---|---|---|---|
| | | Yes N=1248 | No N=319 |
| | Mean ± SD or No. (%) [c] | | |
| Age | 78.9 ± 5.2 | 78.9 ± 5.2 | 78.9 ± 5.4 |
| Female | 1055 (67.3) | 833 (66.7) | 222 (69.6) |
| Non-white | 366 (23.4) | 319 (25.6) | 47 (14.7) |
| BMI (kg/m$^2$) | 30.2 ± 5.9 | 30.7 ± 5.8 | 28.3 ± 6.0 |
| BMI ≥30 | 717 (45.8) | 613 (49.1) | 104 (32.6) |
| Never-smoker | 810 (51.7) | 641 (51.4) | 169 (53.0) |
| *Blood pressure (mmHg)* | | | |
| Systolic | 127.6 ± 18.0 | 128.0 ± 18.4 | 125.9 ± 16.7 |
| Diastolic | 68.2 ± 10.2 | 67.8 ± 10.3 | 69.6 ± 9.6 |
| Systolic <90 | 16 (1.0) | 14 (1.1) | 2 (0.6) |
| *Comorbidities* | | | |
| HTN stage 2 [d] | 375 (23.9) | 307 (24.6) | 68 (21.3) |
| Diabetes mellitus [e] | 446 (28.5) | 400 (32.1) | 46 (14.4) |
| CV Disease [f] | 470 (30.0) | 421 (33.7) | 49 (15.4) |
| Lung disease [g] | 280 (17.9) | 228 (18.3) | 52 (16.3) |
| Arthritis [h] | 307 (19.6) | 249 (20.0) | 58 (18.2) |
| Hip fracture [h] | 67 (4.3) | 45 (3.6) | 22 (6.9) |
| Depression [i] | 411 (26.2) | 326 (26.1) | 85 (26.8) |
| *Medications* | | | |
| AntiHTN | 1248 (79.9) | 1248 (100) | None |
| Diuretic | 676 (43.1) | 676 (54.2) | |
| ACEi or ARB | 782 (49.9) | 782 (62.7) | |
| CCB | 457 (29.2) | 457 (36.6) | |
| BB | 625 (39.9) | 625 (50.1) | |
| Number used | 1.6 ± 1.2 | 2.0 ± 1.0 | |
| One | 437 (27.9) | 437 (35.0) | |
| Two | 412 (26.3) | 412 (33.0) | |
| Three or more | 399 (25.5) | 399 (32.0) | |
| Non-antiHTN: number used | 3.8 ± 2.8 | 4.2 ± 2.7 | 2.4 ± 2.4 |
| *Skeletal muscle function* | | | |
| MIP (cm $H_2O$) [j] | 59.2 ± 22.6 | 59.4 ± 22.5 | 58.4 ± 22.8 |
| Respiratory muscle weakness | 222 (14.2) | 179 (14.3) | 43 (13.5) |

| Characteristic | All N=1567 [a] | AntiHTN Medication [b] | |
|---|---|---|---|
| | | Yes N=1248 | No N=319 |
| | Mean ± SD or No. (%) [c] | | |
| Grip strength (kg) [k] | 24.4 ± 10.0 | 24.5 ± 9.8 | 24.2 ± 10.7 |
| Grip weakness | 620 (39.6) | 501 (40.1) | 120 (37.6) |
| Chair stand score [l] | 1.6 ± 1.0 | 1.6 ± 1.0 | 1.6 ± 1.0 |
| Impaired [m] | 1250 (79.8) | 989 (79.2) | 261 (81.8) |
| *Mobility* | | | |
| Balance score [n] | 2.7 ± 1.1 | 2.7 ± 1.1 | 2.8 ± 1.1 |
| Impaired [o] | 674 (43.0) | 552 (44.2) | 122 (38.2) |
| Gait speed (meters/second) [p] | 0.77 ± 0.16 | 0.76 ± 0.16 | 0.79 ± 0.16 |
| Slow gait [q] | 947 (60.4 | 772 (61.9) | 175 (54.9) |
| Mobility impairment [r] | 703 (44.9) | 568 (45.5) | 135 (42.3) |
| High sedentary time [s] | 407 (26.0) | 337 (27.0) | 70 (21.9) |
| Dyspnea [t] | 675 (43.1) | 554 (44.4) | 121 (37.9) |
| Fatigue [u] | 283 (18.0) | 232 (18.6) | 51 (16.0) |

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; AntiHTN, antihypertensive; ARB, angiotensin receptor blocker; ATS, American Thoracic Society; BB, beta blocker; BMI, body mass index; CCB, calcium channel blocker; CES-D, Center for Epidemiologic Studies Depression scale; CHD, coronary heart disease; CV, cardiovascular; $FEV_1$, forced expiratory volume in 1-second; HF, heart failure; HTN, hypertension; LIFE, Lifestyle Interventions and Independence for Elder study; LLN, lower limit of normal; MEFI, Modified Exercise-induced Feeling Inventory; MI, myocardial infarction; MIP, maximal inspiratory pressure; PAD, peripheral artery disease; SD, Standard Deviation; SPPB, Short Physical Performance Battery; 400MWT, 400m walk test.

[a] Of the original sample of 1635 LIFE participants, 2 were excluded due to missing antiHTN medication and 66 were excluded due to missing spirometry or MIP testing.

[b] Any classified as a diuretic, ACEi, ARB, CCB, or BB.

[c] Column percent, using imputed data (see Methods).

[d] Blood pressure: systolic ≥140 or diastolic ≥90.

[e] Self-reported, physician-diagnosed or use of diabetes medication.

[f] Self-reported, physician-diagnosed MI, HF, stroke, or PAD, or silent MI on electrocardiogram.

[g] $FEV_1$ Z-score < −1.64 (< LLN).

[h] Self-reported, physician-diagnosed

[i] CES-D ≥6.

[j] Measured by MIP in cm $H_2O$: MIP values <LLN established respiratory muscle weakness.

[k] By dynamometer in dominant hand: threshold for grip weakness stratified by gender and BMI.

[l] Score range of 0–4 points, based on time to complete five chair stands.

[m] Score of 0–2 points on five chair stands.

[n] Score range of 0–4 points on testing of side-by-side, semi-tandem, and tandem stands.

[o] Score of 0–2 points on testing of side-by-side, semi-tandem, and tandem stands.

[p] Recorded during 400MWT at participant's usual pace

[q] Gait speed <0.8 meters/second on 400MWT was defined as slow.

[r] SPPB total score ≤7 defined mobility impairment (moderate-to-severe).

[s] Percentage of accelerometry wear-time with activity <100 counts/min. High sedentary time was defined by highest quartile of participants with accelerometry activity <100 counts/min.

[t] ATS grade ≥2 (moderate-to-severe).

[u] MEFI rating ≥3.

**Table 2.**

Adjusted odds ratio (OR) for respiratory and grip weakness, and impaired chair stands, stratified by antiHTN class and number used, respectively [a]

| AntiHTN | Respiratory Weakness [b] Adjusted OR (95%CI) [e] | Grip Weakness [c] Adjusted OR (95%CI) [e] | Impaired Chair Stands [d] Adjusted OR (95%CI) [e] |
|---|---|---|---|
| Class [f] | | | |
| Diuretic | 0.85 (0.61, 1.19) | 1.00 (0.79, 1.26) | 0.89 (0.68, 1.16) |
| ACEi or ARB | 1.09 (0.78, 1.52) | 0.91 (0.72, 1.15) | 1.17 (0.89, 1.53) |
| CCB | 1.07 (0.76, 1.53) | 0.77 (0.60, 0.99) | 0.84 (0.64, 1.11) |
| BB | 1.07 (0.76, 1.50) | 1.02 (0.81, 1.29) | 0.95 (0.73, 1.24) |
| Number used [g] | | | |
| One | 1.18 (0.74, 1.88) | 0.90 (0.65, 1.25) | 0.88 (0.60, 1.29) |
| Two | 1.39 (0.85, 2.27) | 0.83 (0.59, 1.16) | 0.72 (0.49, 1.06) |
| Three or more | 1.00 (0.59, 1.69) | 0.80 (0.56, 1.14) | 0.98 (0.65, 1.47) |

Abbreviations: ACEi, angiotensin converting enzyme; AntiHTN, antihypertensive; ARB, angiotensin receptor blocker; BB, beta blocker; CCB, calcium channel blocker; BMI, body mass index; CI, confidence interval; LLN, lower limit of normal; SPPB, Short Physical Performance Battery.

[a] Because some characteristics had >5% missing data, multiple imputation was applied (see Statistical Analysis section).

[b] Maximal inspiratory pressure (cm H2O) <LLN.

[c] Threshold values for establishing weakness are stratified by gender and BMI.

[d] Scores of 0–2 points on five chair stands, specifically a time ≥13.7 seconds to complete the task or unable to rise from the chair without use of the participant's arms.

[e] Adjusted for age, female gender, non-white race, obesity (BMI ≥30), never-smoker, comorbidities, and non-antiHTN medications.

[f] Comparisons were between medication regimens that included a specified antiHTN class (e.g. diuretic) vs. medication regimens that did not include the specified antiHTN class (e.g. diuretic).

[g] Comparison is use of one, two, or three or more antiHTN medications vs. no antiHTN medication, respectively.

**Table 3.**

Adjusted odds ratio (OR) for impaired balance, slow gait speed and mobility impairment, stratified by antiHTN class and number used, respectively [a]

| AntiHTN | Impaired Balance [b] Adjusted OR (95%CI) [e] | Slow Gait Speed [c] Adjusted OR (95%CI) [e] | Mobility Impairment [d] Adjusted OR (95%CI) [e] |
|---|---|---|---|
| Class [f] | | | |
| Diuretic | 1.04 (0.84, 1.30) | 1.17 (0.94, 1.47) | 1.13 (0.91, 1.41) |
| ACEi or ARB | 0.91 (0.73, 1.14) | 1.05 (0.84, 1.32) | 0.96 (0.77, 1.19) |
| CCB | 1.18 (0.93, 1.49) | 1.23 (0.96, 1.56) | 0.96 (0.76, 1.22) |
| BB | 1.15 (0.92, 1.43) | 0.97 (0.78, 1.22) | 1.20 (0.97, 1.50) |
| Number used [g] | | | |
| One | 1.34 (0.98, 1.82) | 0.93 (0.69, 1.27) | 1.10 (0.81, 1.50) |
| Two | 1.06 (0.77, 1.46) | 1.14 (0.83, 1.58) | 0.82 (0.59, 1.13) |
| Three or more | 1.34 (0.96, 1.86) | 1.20 (0.86, 1.68) | 1.37 (0.99, 1.91) |

Abbreviations: ACEi, angiotensin converting enzyme; AntiHTN, antihypertensive; ARB, angiotensin receptor blocker; BB, beta blocker; CCB, calcium channel blocker; BMI, body mass index; CI, confidence interval; SPPB, Short Physical Performance Battery; 400MWT, 400m walk test.

[a] Because some characteristics had >5% missing data, multiple imputation was applied (see Statistical Analysis section).

[b] Scores of 0–2 points on testing of side-by-side, semi-tandem, and tandem stands.

[c] 400-MWT gait speed < 48 meters/minute (< 0.8 meters/second).

[d] SPPB total score ≤7 (moderate-to-severe).

[e] Adjusted for age, gender, race, obesity (BMI ≥30), smoking status, comorbidities, and non-antiHTN medications.

[f] Comparisons were between medication regimens that included a specified antiHTN class (e.g. diuretic) vs. medication regimens that did not include the specified antiHTN class (e.g. diuretic).

[g] Comparison is use of one, two, or three or more antiHTN medications vs. no antiHTN medication, respectively.

**Table 4.**

Adjusted odds ratio (OR) for high sedentary time, dyspnea, and fatigue, stratified by antiHTN class and number used, respectively [a]

| AntiHTN | High Sedentary Time [b] Adjusted OR (95%CI) [e] | Dyspnea [c] Adjusted OR (95%CI) [e] | Fatigue [d] Adjusted OR (95%CI) [e] |
|---|---|---|---|
| Class [f] | | | |
| Diuretic | 1.03 (0.78, 1.35) | 1.03 (0.82, 1.30) | 0.72 (0.53, 0.97) |
| ACEi or ARB | 1.00 (0.75, 1.34) | 1.11 (0.88, 1.40) | 0.90 (0.67, 1.21) |
| CCB | 0.93 (0.70, 1.24) | 1.06 (0.83, 1.36) | 1.07 (0.78, 1.47) |
| BB | 1.44 (1.12, 1.85) | 1.12 (0.89, 1.41) | 1.20 (0.89, 1.61) |
| Number used [g] | | | |
| One | 1.15 (0.80, 1.67) | 0.96 (0.69, 1.34) | 1.11 (0.73, 1.69) |
| Two | 0.96 (0.66, 1.42) | 1.08 (0.77, 1.51) | 1.14 (0.74, 1.76) |
| Three or more | 1.52 (1.04, 2.23) | 1.20 (0.85, 1.70) | 0.81 (0.51, 1.28) |

Abbreviations: ACEi, angiotensin converting enzyme; AntiHTN, antihypertensive; ARB, angiotensin receptor blocker; ATS, American Thoracic Society; BB, beta blocker; CCB, calcium channel blocker; BMI, body mass index; CI, confidence interval; MEFI, Modified Exercise-induced Feeling Inventory; SPPB, Short Physical Performance Battery.

[a] Because some characteristics had >5% missing data [Statistical Analysis section]), multiple imputation was applied.

[b] Highest quartile in percent of accelerometry wear-time with activity <100 counts/minute (approximated sitting time).

[c] ATS grade ≥2 (moderate-to-severe).

[d] MEFI rating ≥3 established fatigue as occurring “good bit- to all-of-the-time during the past week”.

[e] Adjusted for age, female gender, non-white race, obesity (BMI ≥30), never-smoker, comorbidities, and non-antiHTN medications.

[f] Comparisons were between medication regimens that included a specified antiHTN class (e.g. diuretic) vs. medication regimens that did not include the specified antiHTN class (e.g. diuretic).

[g] Comparison is use of one, two, or three or more antiHTN medications vs. no antiHTN medication, respectively.

**Table 5.**

Modification by CV disease of the associations of anti-HTN class and number used with mobility impairment, stratified by antiHTN class and number used, respectively [a]

| AntiHTN | Mobility Impairment [b] Adjusted OR (95%CI) [c] | | P-Value for Interaction |
|---|---|---|---|
| | No CV Disease [d] | Have CV Disease [e] | |
| Class [f] | | | |
| Diuretic | 1.03 (0.79, 1.35) | 1.40 (0.94, 2.07) | .192 |
| ACEi or ARB | 0.86 (0.66, 1.13) | 1.23 (0.82, 1.83) | .220 |
| CCB | 0.96 (0.72, 1.29) | 0.97 (0.65, 1.45) | .995 |
| BB | 1.20 (0.92, 1.57) | 1.23 (0.84, 1.82) | .981 |
| Number used [g] | | | |
| One | 0.96 (0.68, 1.36) | 2.00 (0.95, 4.21) | .147 |
| Two | 0.70 (0.48, 1.02) | 1.46 (0.70, 3.03) | .140 |
| Three or more | 1.14 (0.77, 1.68) | 2.64 (1.28, 5.44) | .077 |

Abbreviations: ACEi, angiotensin converting enzyme; AntiHTN, antihypertensive; ARB, angiotensin receptor blocker; BB, beta blocker; CCB, calcium channel blocker; BMI, body mass index; CI, confidence interval; CV, cardiovascular; OR, Odds Ratio; SPPB, Short Physical Performance Battery.

[a] Because some characteristics had >5% missing data, multiple imputation was applied (see Statistical Analysis section).

[b] SPPB total score ≤7 (moderate-to-severe).

[c] Adjusted for age, female gender, non-white race, obesity (BMI ≥30), never-smoker, comorbidities (except CV disease), and non-antiHTN medications.

[d] Absence of established CV disease was defined by not having any of the following: self-reported, physician-diagnosed MI, HF, stroke, or PAD, or adjudicated silent MI on electrocardiogram.

[e] Presence of established CV disease was defined by having any of the following: self-reported, physician-diagnosed MI, HF, stroke, or PAD, or adjudicated silent MI on electrocardiogram.

[f] Comparisons were between medication regimens that included a specified antiHTN class (e.g. diuretic) vs. medication regimens that did not include the specified antiHTN class (e.g. diuretic).

[g] Comparison is use of one, two, or three or more antiHTN medications vs. no antiHTN medication, respectively.