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Treatment of Hypertension in Complex Older Adults: How Many Medications Are Needed?

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Abstract

Background: Many older adults with hypertension receive multiple antihypertensives. It is unclear whether treatment with several antihypertensive classes results in greater cardiovascular benefits than fewer antihypertensive classes. **Objectives:** We investigated (a) the longitudinal associations between treatment with ≥ 3 versus 1-2 classes and death and major adverse cardiovascular events (MACE) and (b) whether these associations varied by the presence of mobility disability. **Methods:** We included 6,011 treated hypertensive adults ≥65 from the Medical Expenditure Panel Survey (MEPS), a nationally representative community sample. Times to MACE and death were compared between those receiving ≥3 versus 1-2 classes using multivariable proportional hazards regression. We used inverse probability of treatment weighting to account for indication and contraindication bias. **Results:** There were no significant differences in the risk of mortality (hazard ratio [HR] = 0.96, p = .769) or MACE (HR = 1.10, p = .574) between the exposure groups, and there were no significant exposure × mobility disability interactions. **Discussion:** We found no benefit of ≥3 versus 1-2 antihypertensive classes in reducing mortality and cardiovascular events in a representative cohort of older adults, raising concern about the added benefit of additional antihypertensives in the real world.

Keywords

hypertension treatment, cardiovascular outcomes, antihypertensive medications, older adults

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Introduction

Hypertension affects approximately 65% of U.S. adults ≥65 years (Gillespie & Hurvitz, 2013), and 36.3% of them are treated with ≥ 3 antihypertensives (Ritchey et al., 2016) to reduce cardiovascular risk (James et al., 2014). Clinical trials support mortality and cardiovascular benefits of antihypertensives in relatively healthy older adults (Amery et al., 1985; Beckett et al., 2008; Dahlof et al., 1991; Musini, Tejani, Bassett, & Wright, 2009; SHEP Cooperative Research Group, 1991; Staessen et al., 1997). The recent Systolic Blood Pressure Intervention Trial (SPRINT) extended this evidence base to show greater cardiovascular benefit with more stringent blood pressure control (Williamson et al., 2016; Wright et al., 2015).

However, it remains unclear whether these benefits extend to complex older adults, that is, those with multiple conditions and functional disabilities. These complex patients have been largely excluded from clinical trials or have been significantly unrepresented (Jadad, To, Emara, & Jones, 2011; Van Spall, Toren, Kiss, & Fowler, 2007; Zulman et al., 2011). As these individuals have reduced life expectancies (DuGoff, Canudas-Romo, Buttorff, Leff, & Anderson, 2014; Inouye et al., 1998; Torisson, Stavenow, Minthon, & Londos, 2017), they may not obtain the same benefits from treatments. In fact, observational studies have suggested that there may be less potential for benefit outside of highly controlled clinical trials. Data from a representative cohort in the United Kingdom demonstrated diminishing associations between blood pressure and stroke with increasing age (Rapsomaniki et al., 2014). Other studies of the oldest old have found either no effect or a protective effect of hypertension on mortality (Molander, Lovheim, Norman, Nordstrom, & Gustafson, 2008; van Bemmel, Gussekloo, Westendorp, & Blauw, 2006), possibly reflecting increased risk of death from other causes.

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Complex older patients face significant tradeoffs between benefits and harms when adding medications. Treatment with more antihypertensives may result in greater cardiovascular risk reduction, but also may increase the risk of medication-related harms. Antihypertensive treatment has been associated with increased risk of serious fall injuries, especially among those with a history of falls (Tinetti, Han, Lee, et al., 2014) and decreased physical endurance (Agostini et al., 2007). More aggressive treatment has been associated with incident chronic kidney disease (Beddhu et al., 2018) and the composite of hypotension, syncope, electrolyte abnormalities, acute kidney injury, and injurious falls (Krishnaswami et al., 2018) in clinical trial data.

The general population may be even more susceptible to adverse effects than clinical trial participants. In the Irish Longitudinal Study on Aging (TILDA), those meeting SPRINT eligibility criteria had five fold greater rates of falls and syncope than observed in SPRINT (Sexton et al., 2017), raising questions about the generalizability of harms noted in a well-monitored clinical trial setting to routine practice. Clinicians and patients need compelling evidence of benefits that outweigh harms to justify adding more antihypertensives.

In this study, we aimed to determine whether there is evidence of greater benefit of treatment with ≥ 3 versus 1-2 antihypertensive classes in a representative sample of older adults. We specifically compared the risks of cardiovascular events and death between those on ≥ 3 versus 1-2 classes using data from the nationally representative Medical Expenditure Panel Survey (MEPS). We also specifically investigated whether the associations between the exposure and outcomes varied by the presence of mobility disability, a measure of both chronic disease burden (Collins et al., 2018) and risk for death (Perera, Studenski, Chandler, & Guralnik, 2005; Studenski et al., 2011).

Methods

Study Sample

This study included 6,011 hypertensive participants aged ≥65 years from five consecutive panels of enrollees in the MEPS, enrolled from 2008 to 2013. MEPS is a representative sample of the U.S. civilian, noninstitutionalized population, sponsored by the Agency for Health Care Research and Quality (AHRQ) and the Centers for Disease Control and Prevention (CDC). Participants were interviewed using computer-assisted personal interviewing five times over approximately 2.5 years. MEPS collected detailed information on demographic characteristics, medical conditions, prescription medications, functional status, vital status, and health care utilization (Agency for Healthcare Research and Quality, 2009). As these data were publicly available and de-identified, this study was exempted from review by the Yale Institutional Review Board.

Hypertension was defined by self-report of diagnosis by a health professional of "hypertension, also called high blood pressure" at one or more medical encounter. As most older adults with hypertension are treated (Nwankwo, Yoon, Burt, & Gu, 2013), untreated patients were not included in this study.

Exposure—Antihypertensive Medication Use

During each interview, the interviewer reviewed pharmacy receipts or inspected medication containers. Participants were asked to report the month and year of each medication initiation. Medications were assumed to have been continuously prescribed from the reported initiation date until the end of follow up. When the initiation date was missing or unknown for medications reported in Rounds 1 through 3, initiation was assumed to be the start of Year 1. For Rounds 4 and 5, when the initiation date was missing or unknown, initiation was assumed to be the start of Year 2. Prescribed medications were grouped into classes (WHO Collaborating Centre for Drug Statistics Methology, 2018) using the National Library of Medicine RxNorm database (U.S. National Library of Medicine, 2018). We included 16 discrete antihypertensive classes including both agents recommended by the Eight Joint National Committee as initial agents (James et al., 2014) including dihydropyridine calcium channel blockers, nondihydropyridine calcium channel blockers, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), thiazide diuretics, as well as several other classes: nonselective beta-blockers, selective beta-blockers, nonselective alpha-blockers, alpha-1 blockers, loop diuretics, aldosterone antagonists, other K-sparing diuretics, nitrates, renin inhibitors, imidazoline receptor antagonists, and arterial vasodilators.

Antihypertensive exposure category was operationalized as a time-dependent measure with two categories, 1-2 or ≥3 classes. As the Eight Joint National Committee Hypertension Guidelines (JNC 8) recommend using only one class of calcium channel blockers and choosing either an ACE inhibitor or an ARB, clinicians may prescribe, at maximum, three recommended initial drugs before turning to other agents (James et al., 2014). As such, ≥3 classes were identified as our greater exposure group, similar to prior work (Agostini et al., 2007; Tinetti, Han, McAvay, et al., 2014).

Outcomes

The primary outcomes of this study were all-cause mortality and major adverse cardiovascular events (MACE). At each follow up, each participant or an informed household member provided information about all hospital and emergency encounters since the previous round, approximately every 6 months. Death dates were ascertained by report of an informed household member at the time of regularly scheduled follow up. MEPS staff

transposed all utilization reported by participants or an informed household member into Clinical Classification Software (CCS) and International Classification of Disease–Version 9 (ICD-9) codes (Healthcare Cost and Utilization Project, 2011; Medicode (Firm), 1996). We defined MACE to include acute myocardial infarctions and acute strokes. Acute myocardial infarctions were defined by ICD9 410 or CCS 100 and acute strokes by ICD9 codes 430-434 or CCS 109.

Covariates

Demographic characteristics included age, gender, race, marital status, education (≤11 years vs ≥12 years), household income (< 200% vs ≥200% of the poverty line), prescription drug insurance and current smoking. Comorbid conditions included cancer, cardiovascular diseases (coronary heart disease, angina, and myocardial infarction), chronic obstructive pulmonary disease (COPD), diabetes, stroke or transient ischemic attack, cardiac arrhythmia, and heart failure. Self-reported duration of treatment with antihypertensives was grouped into less than or equal to 1 year, 2 to 5 years, 6 to 10 years, >10 years or unknown. Similar to the primary exposure variable, treatment with statins and total prescribed nonantihypertensive medications were based on a brown-bag review by MEPS staff at each survey round.

The main measure of geriatric vulnerability in this study was mobility disability (defined by any difficulty walking three blocks). This was chosen for two reasons. First, mobility is both strongly associated with chronic disease burden (Collins et al., 2018) and risk for death (Perera et al., 2005; Studenski et al., 2011). Second, mobility disability is more common in community-dwelling populations (as in the MEPS study) than disability in activities of daily living (ADL; Kaye, 2013). Other geriatrics impairments included self-reported difficulty with vision, hearing, cognition (confusion, memory loss, difficulty making decisions, or requiring supervision for safety), and ADL disability (needing help or supervision for bathing, dressing, or getting around the house).

Quality of life measures included perceived health measured by a 5-point Likert-type scale, SF-12 summary score for general health (Ware, Kosinski, & Keller, 1996), and self-reported social limitation.

Statistical Analysis

Baseline patient characteristics were compared between those receiving ≥3 antihypertensive classes and those receiving 1-2, with frequencies and percentages listed for categorical variables and means and standard deviations for continuous variables. To address indication and contraindication bias, we created a propensity score using logistic regression with the antihypertensive exposure category at baseline as the binary outcome. Baseline variables included in the propensity model were selected based on likely association with both the likelihood of being assigned to a given treatment category and the ultimate study outcomes of MACE and death (Brookhart et al., 2006). These variables included age; race; marital status; history of smoking, cancer, diabetes, myocardial infarction, angina, coronary heart disease, cardiac arrhythmia, or heart failure; statin use; duration of antihypertensive treatment; number of other medications; perceived health status, SF-12 mental health composite score; difficulty walking three blocks; and limitation in social activities.

We then used multivariable Cox proportional hazards regression to model the association between treatment with ≥3 antihypertensive classes versus 1-2 and time to each outcome. Models were adjusted for the probability of receiving ≥3 versus 1-2 classes using Inverse Probability of Treatment Weighting (IPTW) (Austin & Stuart, 2015). We assessed the prespecified interaction of antihypertensive exposure category × mobility disability to determine whether the benefits of using ≥3 classes differed by mobility disability.

Multivariable models were adjusted for the following confounders: age, coronary heart disease, cancer, congestive heart failure (CHF), cognitive limitation, COPD, diabetes, general health (SF-12), medical coverage, number of other medications, race, sex, smoking, stroke, and use of statins.

Data missingness was minimal. Assuming missingness at random, we employed multiple imputation (five replicates) using SAS/STAT PROC MI and MIANALYZE (SAS Institute). We systematically assessed model assumptions with cumulative sums of martingale residuals (Lin, Wei, & Ying, 1993). Analysis was completed using SAS version 9.4 (SAS Institute, Cary, NC). For all analyses, a p value of .05 was used to denote statistical significance.

Sensitivity Analyses

To assess the potential bias from the competing risk of death in this study sample, we also used the hazard of subdistribution method of Fine and Gray for the MACE, myocardial infarction, and stroke analysis (Fine & Gray, 1999). To assess whether exposure reclassification during the study affected our results, we performed a sensitivity analysis in which participants who were reclassified were excluded.

Results

The study population comprised 6,011 hypertensive individuals aged ≥65 years receiving at least one antihypertensive class. Baseline characteristics stratified by the exposure category are in Table 1 with and without weighting by the inverse probability of receiving ≥3 versus 1-2 classes. Approximately, 39% received ≥3% and 61% received 1-2 classes. Participant mean age was

Table 1. Baseline Characteristics of Study Sample by Antihypertensive Exposure Category Before and After Inverse Probability of Treatment Weighting.

	Unweighted, % (*n*) or *M* ± *SD*		Weighted by inverse probability of exposure category, % or *M* ± *SD*	
	1-2 Classes (*n* = 3,668)	≥3 Classes (*n* = 2,343)	1-2 Classes (*n* = 3,668)	≥3 Classes (*n* = 2,343)
Demographics				
Female	57.2 (2,099)	58.4 (1,369)	57.4	58.8
Age	73.9 ± 6.55	74.6 ± 6.42	74.2 ± 6.60	74.3 ± 6.44
Non-White	32.0 (1,172)	36.5 (855)	34.2	33.4
Married	52.2 (1,914)	46.6 (1,092)	49.8	49.2
Education ≤12 years	29.7 (1,088)	32.4 (760)	31.2	30.8
Low income	16.0 (586)	17.9 (419)	16.7	17.2
Prescription drug coverage	28.2 (1,033)	26.3 (615)	27.2	26.7
Current smoker	9.3 (341)	7.1 (167)	8.6	8.1
Past medical history				
Arrhythmia	4.9 (181)	6.7 (156)	5.7	5.7
Coronary artery disease	23.9 (875)	39.8 (933)	27.5	28.2
Heart failure	1.0 (37)	3.1 (73)	1.8	1.8
Stroke	12.9 (473)	18.1 (425)	14.4	15.8
Diabetes mellitus	28.1 (1,031)	39.4 (931)	32.6	32.9
Cancer	11.7 (429)	13.7 (322)	12.9	12.4
COPD	9.5 (350)	10.3 (241)	10.6	9.0
Treatment with statin	46.3 (1,697)	54.8 (1,283)	50.1	48.6
#Other medications	2.8 + 2.78	3.6 + 3.07	3.2 ± 3.05	3.1 ± 2.84
Geriatric impairments				
Visual impairment	24.7 (907)	26.6 (623)	25.6	25.9
Hearing impairment	28.9 (1,059)	29.9 (701)	29.3	29.3
Cognitive impairment	12.1 (443)	13.7 (321)	12.0	13.3
Mobility disability	21.0 (770)	29.9 (702)	24.5	24.8
ADL disability[a]	6.7 (244)	7.9 (186)	7.8	6.5

Note. ADL = activities of daily living. COPD = Chronic Obstructive Pulmonary Disease.
[a]ADL disability defined as needing help or supervision for any of the following tasks: bathing, dressing, or getting around the house.

74.1 years, 57.7% were female, and 33.7% were non-White. At baseline, participants receiving ≥3 classes were more likely to have diabetes, coronary artery disease, cardiac arrhythmia, and stroke, as well as more likely to receive a statin than participants receiving 1-2 classes. The prevalence of hearing, visual, and cognitive impairment, and disabilities in both ADL and mobility at baseline were similar in both groups; however, a greater percentage of participants on ≥3 classes had mobility impairment compared with those on 1-2 classes. Weighting by the inverse probability of receiving ≥3 versus 1-2 classes resulted in well-balanced exposure groups with all propensity score adjusted standardized differences less than 0.1 (not presented).

Median follow up was 1.8 years. During follow up, 242 (4.0%) patients died, and 156 experienced at least one MACE (2.6%), 94 experienced a myocardial infarction (1.6%), and 87 (1.4%) experienced a stroke (myocardial infarction and stroke *n* and frequency not mutually exclusive). The mortality rate was 3.6% (133 deaths) among those on 1-2 classes and 4.7% (109 deaths) among those on ≥3 classes. Among patients with no mobility disability at baseline, there were no significant differences in all-cause mortality and MACE between those receiving ≥3 and those receiving 1-2 classes. Similarly, among those with mobility disability at baseline, there were no significant differences in between those receiving between those receiving ≥3 versus 1-2 classes (Figure 1).

Multivariable models weighted by the inverse probability of a given exposure category are presented in Table 2. When adjusted for age, sex, race, cognitive impairment, smoking status, comorbidities, and the number of other medications, there remained no differences in the risk of all-cause mortality (hazard ratio [HR] = 0.96 [0.73-1.26], $p = .769$) between those receiving ≥3 and those receiving 1-2 classes. The lack of benefit was evident in those without mobility disability (HR = 0.78 [0.49-1.23], $p = .276$) and those with mobility disability (HR=1.00 [0.72-1.37], $p = .989$). Similarly, in the adjusted model, there were no differences in the risk of MACE between those receiving ≥3 and those receiving 1-2 classes (HR 1.10 [0.79-1.54], $p = .574$). Again, this lack of benefit was demonstrated in those without mobility disability (HR = 1.15 [0.79-1.53], $p = .571$) and in those with mobility disability (HR=1.13 [0.74-1.74],

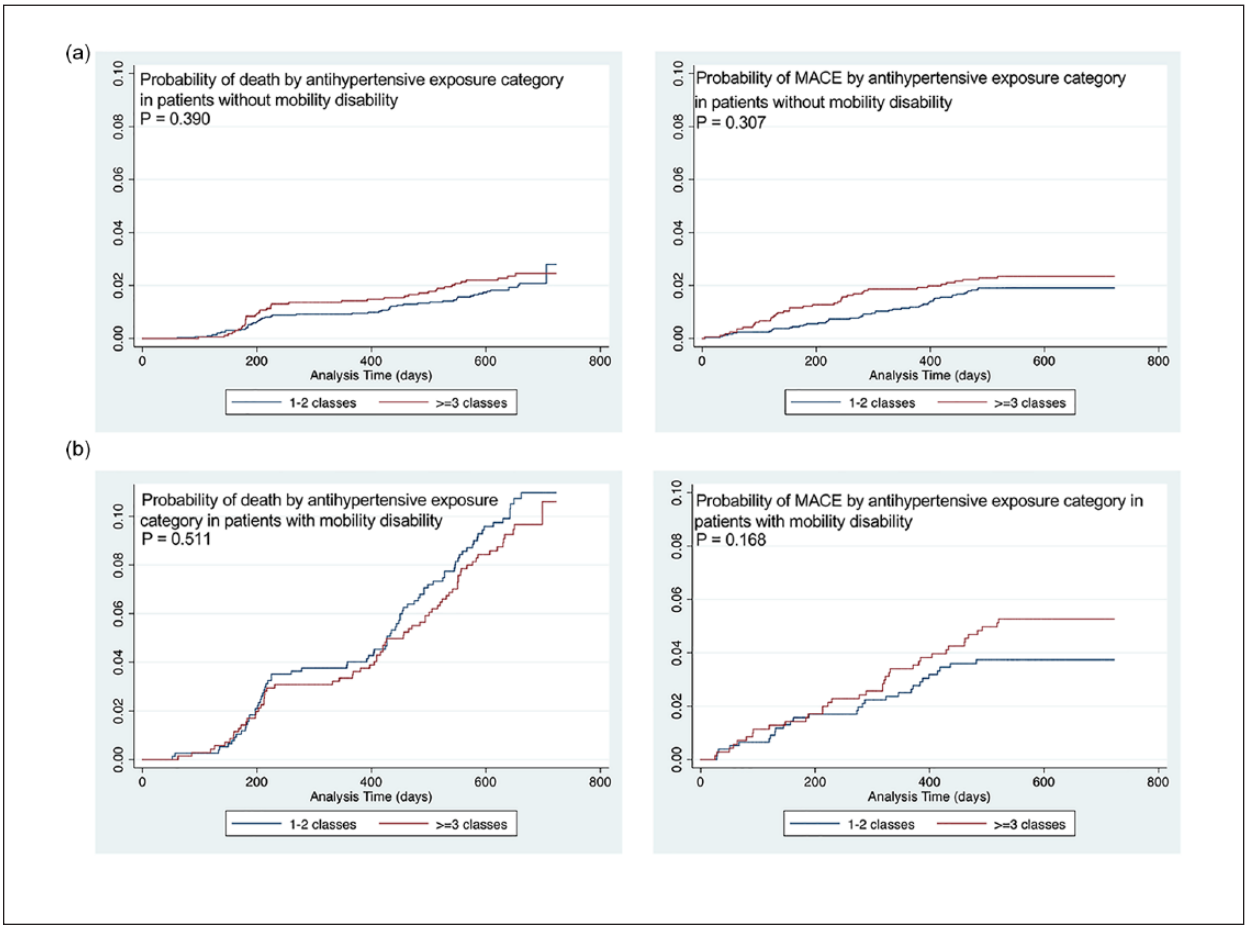

Figure 1. Unadjusted probabilities of death and major adverse cardiovascular event in patients: (a) without mobility disability and (b) with mobility disability.

p = .573). Of note, there were no significant treatment by mobility disability, treatment by sex, and treatment by cognitive impairment interactions.

Results similarly demonstrated no differences between those receiving ≥3 and those receiving 1-2 classes for the secondary outcomes of myocardial infarction and stroke (Table 2). Results for the myocardial infarction, stroke, and MACE analyses were similar when calculated from the Fine and Gray models of the hazard of the subdistribution to account for the competing risk of death (Online Appendix A). Results for the primary outcomes of death and MACE were also similar when participants whose exposure category changed during follow up were excluded (Online Appendix B).

Discussion

We found no benefit of ≥3 versus 1-2 antihypertensive classes in reducing mortality and cardiovascular events in this representative cohort of community-dwelling older adults. We did not find a significant interaction of antihypertensive exposure category and mobility disability, a strong predictor of risk for both outcomes. Almost 40% of our study sample were receiving ≥3 classes, similar to previous report (Tinetti, Han, Lee, et al., 2014). This underscores the need to understand whether the benefits of multiple antihypertensives extend to older adults in the presence of vulnerability factors such as functional impairment.

Although nonsignificant, the point estimate of the hazard ratio for mortality suggests a possible benefit of ≥3 classes among those without mobility disability, HR = 0.78 (95% confidence interval [CI] = [0.49-1.23]). This is consistent with the assertion that the healthiest older adults, similar to those in clinical trials, may benefit from additional agents. Despite no overall difference in MACE between the exposure groups, there was a trend toward a reduced stroke risk (HR = 0.77 [95% CI = 0.48-1.23]) and increased myocardial infarction risk with ≥3 classes versus 1-2 classes (HR = 1.40 [95% CI = 0.87-2.24]). It is likely that our study was underpowered for these secondary outcomes. However, the fact that the point estimates of the effects for stroke and myocardial infarction are opposite in direction merits further investigation.

Numerous clinical trials have studied antihypertensive treatment in older adults, but few have compared varying numbers of prescribed agents. In fact, most of the studies which established the mortality and cardiovascular benefit of antihypertensive treatment compared

Table 2. Adjusted Risk of Death and MACE, Overall and Stratified by the Presence of Mobility Disability.

	Overall *N* = 6,011		No mobility disability *N* = 4,539		Mobility disability *N* = 1,472	
	HR [95% CI]	*p* value	HR [95% CI]	*p* value	HR [95% CI]	*p* value
Death	0.96 [0.73, 1.26]	.769	0.78 [0.49, 1.23]	.276	1.00 [0.72, 1.37]	.989
MACE	1.10 [0.79, 1.54]	.564	1.10 [0.79, 1.53]	.574	1.13 [0.74, 1.74]	.567
Myocardial infarction	1.40 [0.87, 2.24]	.164	1.40 [0.73, 2.68]	.311	1.58 [0.82, 3.06]	.170
Stroke	0.77 [0.48, 1.23]	.273	0.87 [0.41, 1.86]	.723	0.78 [0.44, 1.35]	.370

Note. All models adjusted for age, sex, race, coronary heart disease, stroke, cancer, heart failure, chronic obstructive pulmonary disease, diabetes, total number of other medications, mobility disability (unstratified models only), cognitive impairment, smoking status, statin use, prescription drug coverage, and SF-12 general health. MACE = major adverse cardiovascular events; HR = hazard ratio; CI = confidence interval.

treatment to placebo in patients with relatively high untreated blood pressures (i.e., ≥160 mmHg) (Beckett et al., 2008; Dahlof et al., 1991; Staessen et al., 1997). Given the pretreatment blood pressures in these trials, the treatment goals were generally 140 to 150 mmHg systolic, similar to the target noted in the JNC8 guidelines for treating hypertension in older adults. At present, >80% of older adults with hypertension are treated and as such (Gu, Burt, Dillon, & Yoon, 2012), the question of the optimal number of classes of antihypertensives is apropos.

The recent SPRINT trial found reduced cardiovascular events and mortality with more aggressive treatment, in contrast to the findings of our study (Williamson et al., 2016). One possible reason for this discrepancy is that SPRINT excluded several groups which could be expected to have competing risk of death from other causes such as those with symptomatic heart failure, advanced chronic kidney disease and diabetes, as well as patients with perceived life expectancy <3 years (Wright et al., 2015). Our sample, derived with a nationally representative survey, includes numerous individuals with cognition and mobility impairments as well as a significant proportion with diabetes or a prior stroke. These comorbid chronic conditions and geriatric vulnerabilities may decrease the potential for benefit with more aggressive therapy.

Our results are concordant with several observational studies based on samples more representative of the general population of community-dwelling older adults. One study using the Medicare Current Beneficiary Survey found a mortality benefit with both 1-2 prescribed antihypertensives and ≥3 antihypertensives when compared with no treatment (Tinetti, Han, McAvay, et al., 2014). While not compared statistically, the magnitude of mortality risk reductions were similar between those on ≥ 3 and 1-2 antihypertensives (HR = 0.72 for ≥ 3 and HR = 0.79 for 1-2). In studies of the relationship between measured blood pressure and mortality and cardiovascular risk, the presence of functional and mobility impairments attenuated the potential for risk reduction with lower blood pressure. In the large, multicenter Atherosclerosis Risk in Communities cohort, hypertension was not associated with mortality in patients 65 and older with functional disabilities (Windham et al., 2017). Similarly, National Health and Nutrition Examination Survey data revealed results with no association between hypertension and mortality in older adults with slowed gait (Odden, Peralta, Haan, & Covinsky, 2012).

This study has notable strengths. The study population is drawn from a nationally representative survey and includes a sizable proportion of patients with multiple chronic conditions and functional impairments. MEPS contains detailed information about their chronic conditions, daily function, mobility, as well as medication prescriptions over time. We used a robust statistical method, that is, weighting by the inverse probability of a receiving ≥3 versus 1-2 antihypertensives, to account for indication and contraindication bias (Austin & Stuart, 2015). We also addressed the potential competing risk of death in our MACE analysis using the subdistribution methodology of Fine and Gray (1999).

When interpreting our results, one must consider their limitations. One key limitation is the lack of dosage information available in MEPS. Current JNC8 guidelines support several titration strategies including adding new agents before reaching the maximal dose on the first (James et al., 2014). While dosage certainly impacts the degree of blood pressure reduction, others have found that combining antihypertensives results in approximately five-fold-greater blood-pressure reduction when compared with doubling the dose of one antihypertensive (Wald, Law, Morris, Bestwick, & Wald, 2009). This supports our choice to use the number of classes of antihypertensives as the basis of our exposure measure. The lack of blood pressure measurements and information about medication adherence in MEPS are other key limitations. Patients on ≥3 classes may have had particularly severe hypertension or have been nonadherent to treatment. While the mortality rate was slightly greater in those receiving ≥3 agents, it is much lower at 4.7% than would be expected if this group were significantly enriched with participants with resistant hypertension or significant nonadherence. We also

likely lacked the statistical power to detect an interaction between antihypertensive exposure category and mobility disability. Finally, outcome ascertainment relies on self-report. When compared with claims data, MEPS participants accurately reported hospitalizations but underreported emergency department visits (Zuvekas & Olin, 2009). Underreporting of emergency visits is unlikely to have affected our results, as myocardial infarctions and strokes almost universally result in hospitalization.

Clinicians caring for hypertensive older adults face a decisional challenge in selecting the appropriate number of antihypertensives. While clinical trials suggest modest benefit with greater lowering of blood pressure, there is considerable uncertainty about the real-world effects in older adults. The negative results described here, notably discordant with clinical trial evidence, suggest that the benefits and harms in many clinical trials may not accurately reflect outcomes in clinical practice. This calls attention to the need for inclusion of complex older adults, that is, those with functional impairments and multiple coexisting chronic conditions, in future clinical trials.

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The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplemental Material

Supplemental material for this article is available online.

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