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Effect of Antihypertensive Medication Reduction vs Usual Care on Short-term Blood Pressure Control in Patients With Hypertension Aged 80 Years and Older

The OPTIMISE Randomized Clinical Trial

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IMPORTANCE Deprescribing of antihypertensive medications is recommended for some older patients with polypharmacy and multimorbidity when the benefits of continued treatment may not outweigh the harms.

OBJECTIVE This study aimed to establish whether antihypertensive medication reduction is possible without significant changes in systolic blood pressure control or adverse events during 12-week follow-up.

DESIGN, SETTING, AND PARTICIPANTS The Optimising Treatment for Mild Systolic Hypertension in the Elderly (OPTIMISE) study was a randomized, unblinded, noninferiority trial conducted in 69 primary care sites in England. Participants, whose primary care physician considered them appropriate for medication reduction, were aged 80 years and older, had systolic blood pressure lower than 150 mm Hg, and were receiving at least 2 antihypertensive medications were included. Participants enrolled between April 2017 and September 2018 and underwent follow-up until January 2019.

INTERVENTIONS Participants were randomized (1:1 ratio) to a strategy of antihypertensive medication reduction (removal of 1 drug [intervention], n = 282) or usual care (control, n = 287), in which no medication changes were mandated.

MAIN OUTCOMES AND MEASURES The primary outcome was systolic blood pressure lower than 150 mm Hg at 12-week follow-up. The prespecified noninferiority margin was a relative risk (RR) of 0.90. Secondary outcomes included the proportion of participants maintaining medication reduction and differences in blood pressure, frailty, quality of life, adverse effects, and serious adverse events.

RESULTS Among 569 patients randomized (mean age, 84.8 years; 276 [48.5%] women; median of 2 antihypertensive medications prescribed at baseline), 534 (93.8%) completed the trial. Overall, 229 (86.4%) patients in the intervention group and 236 (87.7%) patients in the control group had a systolic blood pressure lower than 150 mm Hg at 12 weeks (adjusted RR, 0.98 [97.5% 1-sided CI, 0.92 to ∞]). Of 7 prespecified secondary end points, 5 showed no significant difference. Medication reduction was sustained in 187 (66.3%) participants at 12 weeks. Mean change in systolic blood pressure was 3.4 mm Hg (95% CI, 1.1 to 5.8 mm Hg) higher in the intervention group compared with the control group. Twelve (4.3%) participants in the intervention group and 7 (2.4%) in the control group reported at least 1 serious adverse event (adjusted RR, 1.72 [95% CI, 0.7 to 4.3]).

CONCLUSIONS AND RELEVANCE Among older patients treated with multiple antihypertensive medications, a strategy of medication reduction, compared with usual care, was noninferior with regard to systolic blood pressure control at 12 weeks. The findings suggest antihypertensive medication reduction in some older patients with hypertension is not associated with substantial change in blood pressure control, although further research is needed to understand long-term clinical outcomes.

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Visual Abstract

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High blood pressure is the leading modifiable risk factor for cardiovascular disease[1] and the most common comorbid condition in older people with multimorbidity.[2] Antihypertensive treatment prevents stroke and cardiovascular disease in older high-risk patients,[3,4] and approximately half of individuals aged 80 years or older are prescribed therapy.[5] However, previous trials such as the Systolic Blood Pressure Intervention (SPRINT)[4] trial have been shown to represent as few as one-third of older individuals in the general population,[6] and there is debate about the extent to which these data should be applied to frail patients with multimorbidity.[7] Evidence from observational studies suggests that lower blood pressure and multiple antihypertensive prescriptions may be harmful in some older patients with polypharmacy and multimorbidity.[8-10]

Guidelines recommend using clinical judgement when prescribing in frail older patients,[11,12] emphasizing a personalized approach to care that might include attempts to improve quality of life through deprescribing.[13-15] However, these guidelines are largely based on expert opinion and are vague on how to achieve medication reduction due to a lack of evidence, highlighting the need for research in this area.[14]

Few randomized clinical trials have considered the safety and efficacy of antihypertensive medication reduction in routine clinical practice.[15] In older patients with multimorbidity and controlled blood pressure (<150/90 mm Hg), there are advantages and disadvantages to continuing treatment.[8-10] For patients whose physicians determine that potential risks of continuing treatment outweigh benefits, there is no evidence to guide medication reduction. This trial examined a structured approach to antihypertensive medication reduction in older patients with multimorbidity and controlled systolic hypertension prescribed 2 or more antihypertensives. The trial aimed to establish whether partial medication reduction is possible without clinically significant changes in blood pressure control, frailty, quality of life, adverse effects, serious adverse events, and change in systolic and diastolic blood pressure after 12 weeks of follow-up.

Key Points

Question Among older adults taking multiple antihypertensive medications, is a strategy of antihypertensive medication reduction noninferior to usual care with regard to short-term blood pressure control?

Findings In this randomized clinical trial that included 569 patients aged 80 years and older, the proportion with systolic blood pressure lower than 150 mm Hg at 12 weeks was 86.4% in the intervention group and 87.7% in the control group (adjusted relative risk, 0.98), a difference that met the noninferiority margin of a relative risk of 0.90.

Meaning The findings suggest antihypertensive medication reduction can be achieved without substantial change in blood pressure control in some older patients with hypertension.

Methods

The study protocol can be found in Supplement 1. The statistical analysis plan can be found in Supplement 2. The protocol for this trial has also been published in detail elsewhere.[16]

Study Design

The Optimising Treatment for Mild Systolic Hypertension in the Elderly (OPTIMISE) trial used a primary care-based, randomized, unblinded, parallel group, noninferiority design. Participants were individually randomized (1:1 ratio) to a strategy of antihypertensive medication reduction (intervention group) or usual care (control group) and followed up for 12 weeks. The study was approved by an NHS Research Ethics Committee (South Central-Oxford A; ref 16/SC/0628) and the Medicines and Healthcare Products Regulatory Agency (MHRA; ref 21584/0371/001-0001). All participants provided written informed consent.

Participants and Setting

This study was conducted in primary care sites across South and Central England. Participants were aged 80 years and older, had a baseline systolic blood pressure lower than 150 mm Hg, and were prescribed 2 or more antihypertensive treatments for at least 12 months. Detailed inclusion and exclusion criteria are provided in eTable 1 in Supplement 3. At the beginning of the trial, primary care physicians who conducted recruitment were educated about the latest guidelines and evidence from randomized clinical trials. The generalizability of these trials was discussed and physicians were asked to only enroll patients who, in their opinion, might potentially benefit from medication reduction due to 1 or more of the following existing characteristics: polypharmacy, comorbidity, nonadherence or dislike of medicines, or frailty. This clinical judgement was considered important given the current lack of evidence as to who should be targeted for medication reduction. Patients with a history of heart failure due to left ventricular dysfunction or myocardial infarction or stroke in the preceding 12 months, secondary hypertension, or lacking in capacity to consent were excluded. Participants were identified from searches of electronic health records in participating sites and sent letters of invitation. Those expressing an interest attended a screening appointment.

Randomization and Masking

The screening appointment comprised a study explanation by the primary care physician, obtainment of informed consent, and eligibility assessment. Participants underwent baseline assessments and were randomized (1:1 ratio) to one of the 2 study groups using a nondeterministic minimization algorithm, with minimization designed to balance site and baseline SBP via a fully validated web-based password-protected system. The first 3 participants were allocated using simple randomization with subsequent participants allocated with a probability at 0.8 to ensure balance across the groups.

Investigators and participants were unaware of treatment allocation prior to consent and baseline assessments.

The trial used an unblinded design with patients and investigators not masked to randomization group. Prespecified statistical analyses were performed blind to participant allocation.

Procedures

Participating primary care physicians reviewed each patient's medication regimen prior to baseline and decided which antihypertensive drug would be removed if the participant was randomized to the medication reduction group of the trial. Primary care physicians were given a medication reduction algorithm (eFigure 1 in Supplement 3) to assist with this decision. Since combination pills for antihypertensive treatment are rarely used in the United Kingdom, no specific guidance was given on how these should be handled. Following medication reduction, primary care physicians were asked to follow a safety monitoring algorithm (eFigure 2 in Supplement 3) including through the 4-week follow-up. They were asked to reinstate treatment if systolic blood pressure was found to be above 150 mm Hg or diastolic blood pressure was above 90 mm Hg for more than 1 week, adverse events occurred, or signs of accelerated hypertension developed. All participants randomized to the medication reduction group were given the option to self-monitor their blood pressure. Some participants chose to accept this offer, but rates of self-monitoring among the intervention group were not recorded systematically. All other clinical care continued as usual.

Participants who were randomized to the control group followed usual clinical care, in which they continued to take all antihypertensive medications as prescribed, with no medication changes mandated. All participants were followed-up at 12 weeks. All data were collected by a research facilitator or nurse in clinics held at baseline, 4-week safety visit (for the intervention group only), and 12-week follow-up. At baseline, assessments of functional independence were undertaken using the Modified Rankin scale,[17] and cognitive function was assessed using the Montreal Cognitive Assessment.[18] The ethnicity of each participant was recorded at baseline to better characterize the sample population. Ethnicity was self-determined by the participant using a questionnaire containing standard fixed ethnic categories.[19] For analysis, those identifying as *White British* or *White other* were classified as white, and all other participants were classified as *nonwhite/unknown*.

Outcome Measures

The primary outcome was the relative risk of systolic blood pressure control (<150 mm Hg; defined by UK National Institute for Health and Care Excellence as the target blood pressure for those older than 80 years) between groups at 12-week follow-up. Blood pressure was measured using the clinically validated BpTRU blood pressure monitor.[20] Readings were taken in the left arm, using an appropriately sized cuff, after participants had been seated for at least 5 minutes of rest. Systolic blood pressure was estimated from the mean of the second and third readings.

All prespecified secondary outcomes are reported in this article, with the exception of one to determine how the baseline characteristics of the study population relate to those of previous trials[3,4] (which will be reported separately). Secondary outcomes were the proportion of participants in the intervention group who maintained medication reduction and between-group differences in frailty, quality of life, adverse effects, serious adverse events, and change in systolic and diastolic blood pressure over 12 weeks. Frailty was defined using the Frailty index (54 items; range, 0 [fit] to 1 [frail]),[21] the Electronic Frailty Index (36 items; range, 0 [fit] to 1 [frail]; estimated using data from electronic health records),[22] and the Morley FRAIL scale (5 components; range, 0 [robust health] to 4 [frail]; captured via questionnaire).[23] Quality of life was measured using the EuroQoL 5 Dimensions 5 Levels questionnaire (EQ-5D-5L).[24] Data from this questionnaire were analyzed using the cross-walk approach, which translates the scores for the 5 EQ-5D-5L items into a single index value and visual analogue scale (VAS; range, 0 [worst health] to 100 [best health]).[24] Adverse effects to medication were captured using the Revised Illness Perception Questionnaire for hypertension.[25] Adverse effects included 24 symptoms, and these were summed to give the number of symptoms reported. Serious adverse events were defined as those resulting in death or considered life threatening, required inpatient hospitalization or prolonged existing hospitalization, resulted in persistent or significant disability or incapacity, or were classified as other medical events considered to be serious because they put the participant at risk of one of the previously mentioned consequences or required intervention to prevent occurrence.

Further post hoc outcomes were specified after viewing the initial results to better understand the effect of the medication reduction intervention. These were mean difference in change in number of antihypertensive medication prescriptions, the proportion of patients with no increase in systolic blood pressure during follow-up, mean difference in health resource use (primary care consultations and hospital attendance), and difference in adverse events (nonserious) during 12-week follow-up. To better understand any observed differences in adverse events, each event was categorized by the treating clinician as to whether or not it was possibly related to medication reduction and classified by the research team according to definitions of disease (online version, International Classification of Diseases, 11th Revision).

Statistical Analysis

A sample size of 540 participants was prespecified for the trial, assuming that 100% of participants in the usual care group, and 96% of those in the medication reduction group would have systolic blood pressure lower than 150 mm Hg at 12-week follow-up. Calculations assumed a 0.90 noninferiority margin, 90% power, 2.5% 1-sided level of significance, 10% loss to follow-up, and a 10% dilution effect due to crossover between groups. Due to the lack of evidence defining noninferiority, the margin of 0.90 was chosen to inform future physician-patient discussions about medication reduction; under these assumptions, if noninferiority was demonstrated, it would suggest that for every 10 patients who have their medication reduced, 9 would still have controlled blood pressure at 12-week follow-up.

The primary analysis population was defined as all participants for whom data were available, and participants were analyzed according to groups to which they were randomly allocated, regardless of deviation from protocol. The prespecified analysis for the primary outcome planned a generalized linear mixed-effects model with baseline systolic blood pressure as a fixed effect and primary care site as a random effect. However, due to convergence problems at the time of analysis, we omitted site from the model and fitted a robust Poisson regression model adjusting for baseline systolic blood pressure. In addition, to account for missing data in the analysis, a logistic regression model was used to explore associations between baseline characteristics and availability of the primary outcome. Covariates found to be related to missingness were adjusted in the primary analysis, including sex, Montreal Cognitive Assessment score, EQ-5D-5L Index, and the Frailty Index. Six missing baseline EQ-5D-5L scores and 10 missing baseline EQ-5D VAS scores were replaced with the overall mean of respective variables at baseline. Model diagnostics were checked and satisfied (eFigure 3 in Supplement 3). Noninferiority was assumed if the lower limit of the CI around the adjusted relative risk (RR) of participants with controlled blood pressure was above 0.90. Adjusted risk differences (RD_s) were also calculated and reported using a robust Poisson model with identity link function.

Secondary analyses used descriptive statistics to examine the proportion of participants in the intervention group who maintained medication reduction throughout the 12-week follow-up period (overall and by drug class). Further analyses comparing the adjusted mean difference in change in blood pressure, antihypertensive medications, quality of life (estimated from the EQ-5D-5L using the crosswalk value set),[26] frailty, and health resource use at 12 weeks were analyzed by means of linear mixed-effects models, adjusting for the baseline level of the outcome and baseline systolic blood pressure, with primary care site fitted as a random effect. The difference in adverse effects and serious adverse events between the intervention and usual care groups was analyzed using a robust Poisson model with adjustment for baseline systolic blood pressure; site was not included in the model for the same reason as the analysis of the primary outcome.

A per-protocol analysis of the primary outcome was performed, excluding patients from the intervention group who did not reduce treatment or who had medication reinstated during follow-up (although this latter action was part of the medication reduction protocol). A post hoc analysis of mean difference in change in blood pressure between groups, corrected for baseline, was performed in the per-protocol population. Prespecified subgroup analyses of systolic blood pressure control, change in systolic blood pressure, and maintenance of medication reduction were conducted by different levels of baseline frailty, functional independence, cognitive function, number of medications, and number of comorbidities. Each potential moderator was dichotomized, and an interaction term with treatment group was fitted to the primary and secondary analysis models to obtain the *P* value for interaction. Post hoc subgroup analyses by baseline systolic blood pressure were performed for the RR of systolic blood pressure control, maintenance of medication reduction, and mean difference in change in blood pressure at 12-week follow-up. Further post hoc analyses examined the primary outcome (systolic blood pressure control) defined as below 140 mm Hg and below 130 mm Hg.

Sensitivity analyses of the primary outcome were undertaken to examine missing data and outlying systolic blood pressure values. Significance thresholds were set at 2.5% (1-sided) for noninferiority and 5% (2-sided) for superiority. Because of potential for type I error due to multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory. All data were analyzed using Stata version 15.1 (StataCorp).

Results

A total of 69 primary care sites participated from Central and Southern England. Between March 20, 2017, and September 30, 2018, 6194 patients were invited by post to participate in the trial, and 739 attended a screening appointment (**Figure**). Of these, 569 participants (77.0%) provided informed consent and were randomized. The characteristics of participants in the trial were broadly similar to those of the general population (eTable 3 in Supplement 3).

Two hundred eighty-two participants (49.6%) were randomized to the medication reduction intervention and 287 participants (50.4%) were randomized to usual care (Figure). Follow-up was completed on January 9, 2019, and the study database was locked on May 23, 2019. Data on the primary outcome were available in 534 participants (Figure). Participants were well matched for all variables at baseline (**Table 1**; eTable 4 in Supplement 3).

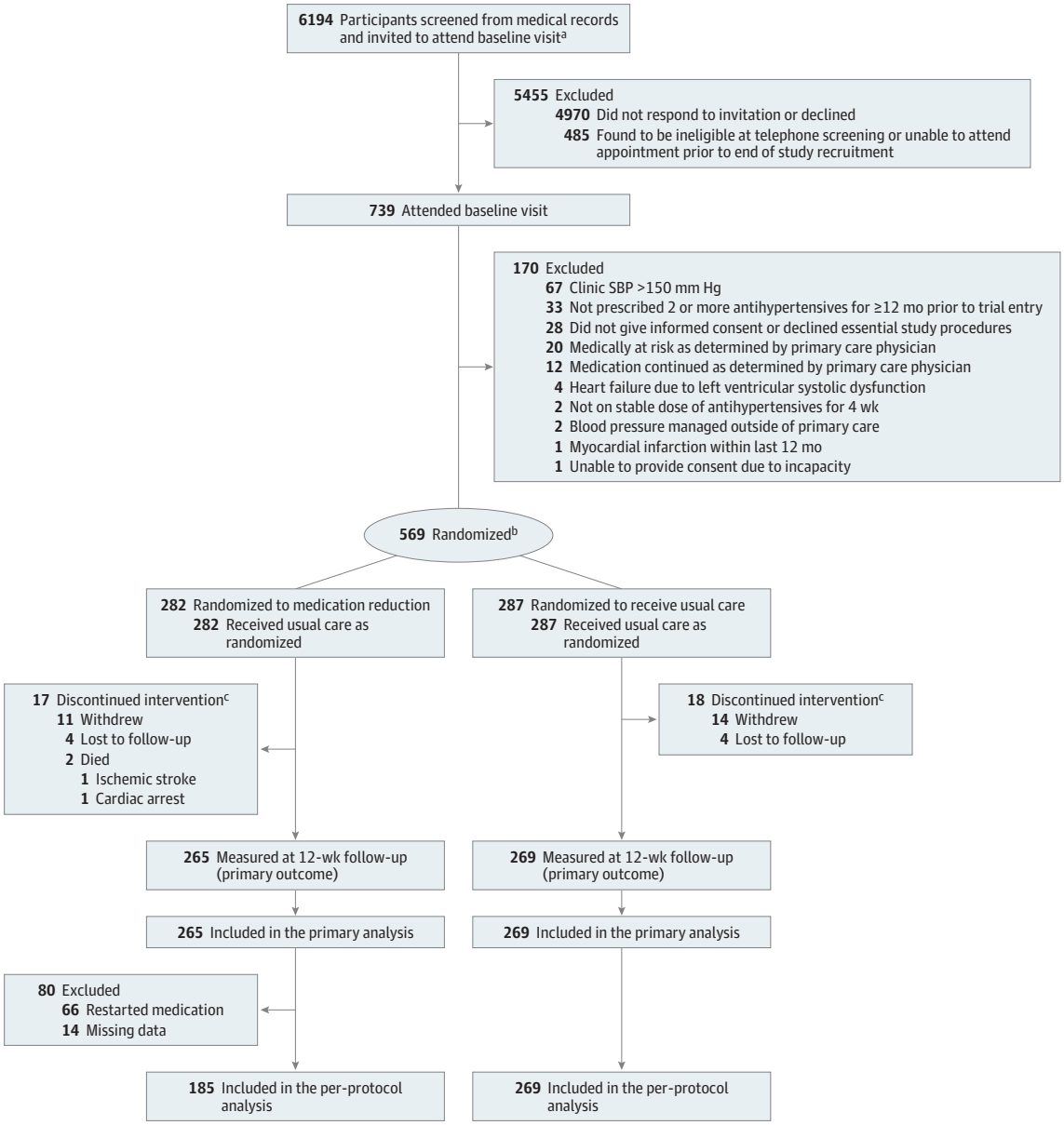
Primary Outcome

Overall, 229 (86.4%) patients in the medication reduction group and 236 (87.7%) patients in the usual care group had a systolic blood pressure lower than 150 mm Hg at 12-week follow-up (adjusted RR, 0.98 [97.5% CI, 0.92 to ∞]; **Table 2**). The 97.5% 1-sided CI for this adjusted RR was greater than 0.9, indicating that medication reduction was noninferior to usual care. These findings were robust to sensitivity analyses examining the effect of missing data and outlying blood pressure values (eTable 5 in Supplement 3). Results were not materially different in the per-protocol population (Table 2).

Secondary Outcomes

Medication reduction was maintained in 187 (66.3%) participants in the intervention group (eTable 6 in Supplement 3). Mean (SD) systolic blood pressure at baseline was 129.4 (13.1) mm Hg in the medication reduction group and 130.5 (12.3) mm Hg in the usual care group (Table 1). At 12 weeks, mean systolic blood pressure was 133.7 (95% CI, 131.7 to 135.6) mm Hg in the medication reduction group and 130.8 (95% CI, 128.9 to 132.7) mm Hg in the usual care group,

Figure. Recruitment, Randomization, and Analysis Population



[a] Participants were required to be aged 80 years or older with controlled systolic blood pressure at baseline (<150 mm Hg) and prescribed 2 or more antihypertensive treatments for at least 12 months. Patients with a history of heart failure due to left ventricular dysfunction or myocardial infarction or stroke in the preceding 12 months, secondary hypertension, or lacking in capacity to consent were excluded.

[b] Participants were allocated to one of the 2 study groups using a nondeterministic minimization algorithm, minimized for site and baseline systolic blood pressure. The first 3 participants were allocated using simple randomization with subsequent participants allocated with a probability at 0.8 to ensure balance across the groups.

[c] A notes review was conducted in a further 25 patients (11 in the medication reduction group and 14 in the usual care group) who did not attend 12-week follow-up to obtain data available in the electronic health record (eg, medical history, prescriptions).

meaning that the change in systolic blood pressure at 12 weeks was 3.4 mm Hg (95% CI, 1.0 to 5.8 mm Hg; **Table 3**) higher in the medication reduction group compared with usual care after correcting for baseline blood pressure. Mean (SD) diastolic blood pressure at baseline was 68.4 (9.1) mm Hg in the medication reduction group and 70.1 (8.4) mm Hg in the usual care group (Table 1), and at 12 weeks, it was 70.9 (95% CI, 69.6 to 72.1) mm Hg in the medication reduction group and 69.7 (95% CI, 68.5 to 70.8) mm Hg in the usual care group. The adjusted mean difference in change in diastolic blood pressure corrected for baseline was 2.2 mm Hg (95% CI, 0.9 to 3.6 mm Hg). There were no statistically significant differences between groups in frailty, quality of life (Table 3), adverse effects, or serious adverse events at follow-up (**Table 4**).

Table 1. Baseline Demographics and Clinical Characteristics

	No. (%)[a]	
	Medication reduction group (n = 282)	Usual care group (n = 287)
Age, mean (SD), y	84.6 (3.3)	85.0 (3.5)
>85 y	131 (46.5)	143 (49.8)
Women	131 (46.5)	145 (50.5)
Men	151 (53.5)	142 (29.5)
BMI, mean (SD)[b]	27.2 (4.2) [n = 270]	28.0 (4.3) [n = 264]
Underweight, BMI<18.5	1 (0.4)	2 (0.8)
Normal, BMI ≥18.5 to ≤30	213 (78.9)	183 (69.3)
Overweight, BMI>30	56 (20.7)	79 (29.9)
Race/ethnicity[c]		
White	278 (98.6)	278 (96.9)
Other	4 (1.4)	9 (3.1)
Undergraduate or postgraduate degree obtained	44 (15.6)	39 (13.6)
Current smoker	3 (1.1)	5 (1.7)
Reported alcohol consumption every week	98 (34.8)	108 (37.6)
Total cholesterol, mean (SD), mmol/L[d]	177.6 (46.3) [n = 252]	177.6 (46.3) [n = 259]
Estimated GFR, mean (SD), mL/min per 1.73 m^2	61.6 (14.9) [n = 241]	60.4 (14.2) [n = 252]
Montreal Cognitive Assessment, mean (SD), score[e]	24.4 (3.6) [n = 280]	24.0 (4.1) [n = 282]
EQ-5D-5L index, mean (SD), score[f]	0.78 (0.17) [n = 279]	0.76 (0.17) [n = 284]
Modified Rankin Score >2[g]	36 (13.5) [n = 267]	42 (15.4) [n = 273]
Frailty		
Morley FRAIL scale, mean (SD)[h]	0.77 (0.99)	0.95 (1.07)
0	155 (55.0)	134 (46.7)
1	58 (20.6)	68 (23.7)
2	50 (17.7)	55 (19.2)
3	17 (6.0)	26 (9.1)
4	2 (0.7)	4 (1.4)
Frailty index, mean (SD)[i]	0.14 (0.07)	0.15 (0.07)
Electronic Frailty index[j]	0.14 (0.07)	0.15 (0.07)
Mean (SD)		
Fit	121 (42.9)	109 (38.0)
Mild	132 (46.8)	143 (49.8)
Moderate	27 (9.6)	32 (11.1)
Severe	2 (0.7)	3 (1.0)
Blood pressure		
Systolic, mean (SD), mm Hg	129.4 (13.1)	130.5 (12.3)
Diastolic, mean, (SD), mm Hg	68.4 (9.1)	70.1 (8.4)
History of high blood pressure, mean (SD), y	16.8 (8.9) [n = 269]	16.3 (9.0) [n = 276]
Standing systolic blood pressure, mean (SD), mm Hg	128.7 (15.5) [n = 264]	131.8 (16.2) [n = 261]
Orthostatic hypotension[k]	15 (5.7) [n = 264]	10 (3.8) [n = 261]
Medical history[l]		
Chronic kidney disease	83 (29.4)	103 (35.9)
Cancer	67 (23.8)	68 (23.7)
Cardiac disease[m]	61 (21.6)	61 (21.3)
Diabetes	48 (17.0)	53 (18.5)
Atrial fibrillation	45 (16.0)	45 (15.7)
Transient ischemic attack	27 (9.6)	22 (7.7)
Stroke	23 (8.2)	22 (7.7)
Peripheral vascular disease	6 (2.1)	9 (3.1)
No. of morbidities, mean (SD)[l]	5.7 (2.7)	6.0 (2.9)
No. with ≥ 2 morbidities[l]	278 (98.6)	282 (98.3)

(continued)

Table 1. Baseline Demographics and Clinical Characteristics (continued)

	No. (%)[a]	
	Medication reduction group (n = 282)	Usual care group (n = 287)
Prescribed medications		
Antihypertensive	282 (100.0)	287 (100.0)
ACE inhibitor/angiotensin II receptor blocker[n]	238 (84.4)	243 (84.7)
Calcium channel blocker[n]	199 (70.6)	191 (66.6)
β-blocker[n]	112 (39.7)	116 (40.4)
Thiazide and related diuretics[n]	109 (38.7)	111 (38.7)
Statin	97 (34.4)	92 (32.1)
Antiplatelet	58 (20.6)	53 (18.5)
Total antihypertensives, median (IQR)	2 (2-3)	2 (2-3)
Total noncardiovascular medications, median (IQR)	1 (1-2)	1 (1-2)
Total prescribed medications, median (IQR)	4 (3-7)	4 (3-7)

Abbreviations: BMI, body mass index; EQ-5D-5L, EuroQoL 5 Dimensions 5 Levels questionnaire; GFR, glomerular filtration rate; IQR, interquartile range.

SI conversion factor: To convert cholesterol to mmol/L, multiply by 0.0259.

[a] Values are reported as No. (%) unless otherwise indicated.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Ethnic group was defined according to each participant's self-reported ethnicity, using Office for National Statistics categories.[19] Those identifying as *white British* or *white other* were classified as white; all other participants were classified as *nonwhite/unknown* (termed as *other*)—4 in the medication reduction group (1 African, 2 Caribbean, 1 unknown) and 9 in the usual care group (1 Indian, 1 Pakistani, 1 Chinese, 1 Asian other, 1 Caribbean, 2 black/African/Caribbean, 2 unknown).

[d] Most recently recorded reading from electronic health records.

[e] Score ranges between 0 and 30 with lower scores representing greater impairment. A score of 26 or greater is considered to be normal.

[f] The EQ-5D-5L assesses 5 aspects of health: mobility, self-care, activities, discomfort, and anxiety/depression. EQ-5D-5L index scores were generated using crosswalk approach, which translates the scores for the 5 EQ-5D-5L items into a single index value. The index value ranges from −0.594 (worse than death) to 1 (full health).

[g] Modified Rankin Score ranges from 0 (no symptoms), 1 (no significant disability, able to carry out prestroke activities), 2 (slight disability, unable to carry out prestroke activities but able to look after self without daily help), 3 (moderate disability, requiring some external help but able to walk without assistance of another individual), 4 (moderately severe disability; unable to walk or attend to bodily functions without assistance of another individual), to 5 (severe disability; bedridden, incontinent, requires continuous care).[27]

[h] Morley FRAIL scale consists of 5 components (fatigue, resistance, ambulation, weight-loss, and illness), and ranges from 0 (fit) to 4 (frail).

[i] The Frailty index includes 54 items and ranges from 0 (fit) to 1 (frail).

[j] The Electronic Frailty Index has 36 items and is estimated from electronic health records. The index ranges from 0 to 1 (fit, 0-0.12; mild, >0.12-0.24; moderate, >0.24-0.36; severe, >0.36-1.0).

[k] Orthostatic hypotension is defined as a decrease in systolic blood pressure of at least 20 mm Hg within 3 minutes of standing.[28]

[l] Individual conditions listed represent the 8 most common, thought to be associated with high blood pressure. Conditions recorded and included in the total morbidity count are listed in eTable 2 in Supplement 3. These included 49 conditions relating to cardiovascular disease and risk factors and also chronic diseases and conditions resulting in physical and cognitive impairment.

[m] Cardiac disease is defined as the presence of myocardial infarction, coronary heart disease, angina, or heart failure.

[n] The sum of percentages for all antihypertensive medication classes may exceed 100% since participants had to be taking more than 1 antihypertensive medication to be eligible for the trial.

Table 2. Primary Outcome Difference in the Proportion of Patients With Clinically Acceptable Systolic Blood Pressure Lower Than 150 mm Hg at 12 Weeks

	Group, No. (%)		RD, % (97.5% 1-sided CI)		RR (97.5% 1-sided CI)[a]		
	Medication reduction	Usual care	Unadjusted	Adjusted[b]	Unadjusted	Adjusted[b]	*P* value[c]
Primary analysis, No.	265	269					
SBP <150 mm Hg	229 (86.4)	236 (87.7)	−1.3 (−7.0 to ∞)	−1.5 (−7.4 to ∞)	0.98 (0.92 to ∞)	0.98 (0.92 to ∞)	.01
Per-protocol analysis, No.[d]	185	269					
SBP <150 mm Hg	161 (87.0)	236 (87.7)	−0.7 (−6.9 to ∞)	−1.6 (−8.1 to ∞)	0.99 (0.92 to ∞)	0.98 (0.92 to ∞)	.007

Abbreviations: EQ-5D-5L, EuroQoL 5 Dimensions 5 Levels questionnaire; RD, risk difference; RR, relative risk; SBP, systolic blood pressure.

[a] The margin for noninferiority was set at 0.90 for RR. A lower bound of the CI that did not exceed this margin indicated noninferiority.

[b] Indicates adjustment for baseline SBP, sex, cognitive function (Montreal Cognitive Assessment score), and EQ-5D-5L Index and Frailty Index (both of which were predictive of missingness, eTable 13 in Supplement 3).

[c] Indicates a *P* value for noninferiority for adjusted RR.

[d] A total of 187 participants maintained medication reduction. However, 2 did not have blood pressure measured at follow-up and therefore were excluded from the per-protocol analysis. Of those who did have blood pressure measured (n = 265), 80 participants were not taking fewer medications at follow-up and therefore were excluded from the per-protocol analysis. Sixty-six of these 80 participants had medications reinstated during follow-up based on the study safety monitoring algorithm (eFigure 2 in Supplement 3).

Subgroup Analyses

There were no statistically significant interactions between the randomized group and prespecified subgroups in systolic blood pressure control, change in blood pressure, or maintenance of medication reduction by subgroups (eFigures 4 and 5 and eTable 6 in Supplement 3).

Table 3. Secondary Outcomes and Post Hoc Outcomes at 12 Weeks

	Medication reduction group		Usual care group			
	No. analyzed	Mean (95% CI)	No. analyzed	Mean (95% CI)	Adjusted mean difference (95% CI)	*P* value[a]
SBP[b,c]	265	133.7 (131.7 to 135.6)	269	130.8 (128.9 to 132.7)	3.4 (1.0 to 5.8)	.005
DBP[b,d]	265	70.9 (69.6 to 72.1)	269	69.7 (68.5 to 70.8)	2.2 (0.9 to 3.6)	.001
Quality of life at 12 weeks[e,f]						
EQ-5D-5L index	260	0.79 (0.77 to 0.81)	263	0.79 (0.77 to 0.81)	−0.01 (−0.03 to 0.01)	.50
EQ-5D-5L VAS	259	78.5 (76.6 to 80.4)	259	78.3 (76.5 to 80.1)	−0.76 (−2.86 to 1.33)	.47
Frailty at 12 weeks[e,f]						
Frailty index	282[g]	0.137 (0.130 to 0.145)	287[g]	0.145 (0.136 to 0.152)	−0.00003 (−0.005 to 0.005)	.77
Electronic frailty index	278[g]	0.134 (0.126 to 0.141)	285[g]	0.140 (0.132 to 0.148)	0.001 (−0.003 to 0.005)	.77
Morley frailty score	265	0.74 (0.62 to 0.86)	269	0.83 (0.71 to 0.96)	0.01 (−0.10 to 0.12)	.88
Post hoc outcomes						
SBP (per-protocol analysis, mm Hg)[c,h]	185	134.4 (132.1 to 136.7)	269	130.8 (128.9 to 132.7)	4.9 (2.4 to 7.5)	<.001
DBP (per-protocol analysis, mm Hg)[d,h]	185	71.6 (70.2 to 73.1)	269	69.7 (68.5 to 70.8)	3.4 (1.8 to 4.9)	<.001
Change in antihypertensive prescriptions	276[g]	−0.68 (−0.74 to −0.61)	283[g]	−0.05 (−0.08 to −0.01)	−0.63 (−0.70 to −0.56)	<.001

Abbreviation: DBP, diastolic blood pressure; EQ-5D-5L, EuroQoL 5 Dimensions 5 Levels questionnaire; SBP, systolic blood pressure; VAS, visual analog scale.

[a] *P* values are given for superiority, in contrast to Table 2 (in which they are given for noninferiority).

[b] Analyses conducted in the primary analysis population (all available participants) unless otherwise stated.

[c] Adjusted for baseline SBP, sex, cognitive function (Montreal Cognitive Assessment score), and EQ-5D-5L Index and Frailty Index (both of which were predictive of missingness, eTable 13 in Supplement 3) with a random effect for primary care site.

[d] Adjusted for baseline SBP and DBP, sex, cognitive function Montreal Cognitive Assessment score, and EQ-5D-5L Index and Frailty Index (both of which were predictive of missingness, eTable 13 in Supplement 3) with a random effect for primary care site.

[e] Adjusted for baseline level of the outcome; baseline SBP fitted as a fixed effect. Six missing baseline EQ-5D-5L scores and 10 missing baseline EQ-5D VAS scores were replaced with the overall mean of the covariate at baseline.

[f] See Table 1 for definitions of quality of life and frailty indices. The EQ-5D-5L VAS has values between 0 (worst health) and 100 (best health).

[g] The number analyzed includes all participant for whom data could be collected from the electronic health record and therefore exceeds the numbers (265 and 269) who underwent 12-week face-to-face follow-up.

[h] The per-protocol population excluded patients from the intervention group who did not reduce treatment or who had medication reinstated during follow-up as part of the safety algorithm (although this latter action was part of the medication reduction protocol).

Post Hoc Outcomes

Three participants in the intervention group did not reduce medications while 2 increased treatment (eTable 7 in Supplement 3). Participants in the medication reduction group were taking 0.6 fewer antihypertensive medications than the usual care group at 12-week follow-up (Table 3). A total of 101 participants (38.1% [95% CI, 32.2% to 44.2%]) in the medication reduction group had no increase in systolic blood pressure at 12-week follow-up vs 64 participants (34.6% [95% CI, 27.8% to 41.9%]) in the per-protocol population (eFigure 6 in Supplement 3). When analyses were restricted to those patients who maintained medication reduction throughout follow-up (per-protocol population), a greater increase in systolic and diastolic blood pressure was seen in the intervention group (Table 3). There was no statistically significant difference in systolic blood pressure control or mean difference in blood pressure by baseline systolic blood pressure level (eFigures 4 and 5 in Supplement 3). There was no statistically significant difference in maintenance of medication reduction by baseline blood pressure (eTable 8 in Supplement 3). However, the RR of blood pressure control was reduced when thresholds defining control were reduced to lower than 150 mm Hg (eTable 9 in Supplement 3).

The number of patients experiencing at least 1 adverse event was significantly higher in the medication reduction group (adjusted RR, 1.28 [95% CI, 1.06 to 1.54]; Table 4). A total of 65 (27% of those occurring in the intervention group) adverse events were considered possibly related to withdrawal of treatment. More adverse events related to the circulatory system were reported in the medication reduction group, but this was not observed for serious cardiovascular events (eTables 10 and 11 in Supplement 3). Participants in the medication reduction group attended significantly more health care appointments during follow-up than the usual care group (eTable 12 in Supplement 3).

Discussion

In this noninferiority randomized clinical trial among older patients treated with multiple antihypertensive medications, a strategy of antihypertensive medication reduction, compared with usual care, demonstrated noninferiority with regard to the proportion of patients with systolic blood pressure lower than 150 mm Hg at 12 weeks. However, systolic blood pressure was increased in the medication reduction group, and therefore, potential benefits of reducing medication need to be balanced against possible harms from increased risk of cardiovascular disease in the longer term.

In contrast with the present study, previous antihypertensive deprescribing trials have only attempted medication

Table 4. Most Commonly Reported Adverse Effects, Adverse Events, and Serious Adverse Events

	Medication reduction group	Usual care group	Adjusted risk difference (95% CI)[a]	Adjusted risk ratio (95% CI)[a]
Adverse effects, No.[b]	264	266		
Stiff joints	124 (47.0)	130 (48.9)	5.1 (−3.3 to 13.4)	1.05 (0.89 to 1.23)
Pain	108 (40.9)	124 (46.6)	−3.7 (−12.1 to 4.6)	0.90 (0.75 to 1.08)
Fatigue	107 (40.5)	119 (44.7)	−4.6 (−12.8 to 3.6)	0.93 (0.78 to 1.11)
Loss of strength	77 (29.2)	95 (35.7)	−5.6 (−13.2 to 1.9)	0.81 (0.64 to 1.01)
Breathlessness	77 (29.2)	88 (33.1)	−2.1 (−8.8 to 4.6)	0.96 (0.77 to 1.20)
Sleep difficulties	77 (29.2)	85 (32.0)	−0.4 (−7.4 to 6.6)	0.97 (0.77 to 1.22)
Pins and needles	78 (30.0)	65 (24.4)	2.8 (−2.9 to 8.6)	1.20 (0.93 to 1.51)
Sore eyes	57 (21.6)	72 (27.1)	−5.5 (−12.1 to 1.0)	0.89 (0.67 to 1.17)
Dizziness	54 (20.5)	57 (21.4)	−3.2 (−2.7 to 9.1)	1.08 (0.80 to 1.46)
Impotence	47 (17.8)	53 (20.0)	−2.1 (−7.0 to 2.9)	0.93 (0.70 to 1.24)
≥1 Reported adverse effect	234 (88.6)	246 (92.5)	−3.5 (−8.6 to 1.5)	0.96 (0.91 to 1.02)
No. of adverse effects, median (IQR)	4 (2 to 6)	4 (2 to 7)		
Adverse events, No.[c]	282	287		
≥1 Reported adverse event[c,d]	139 (49.3)	113 (39.4)	10.0 (1.9 to 18.1)	1.28 (1.06 to 1.54)
No. of adverse events, median (IQR)	0 (0 to 1)	0 (0 to 1)		
≥1 Reported serious adverse event[e]	12 (4.3)	7 (2.4)	1.6 (−1.3 to 4.5)	1.72 (0.68 to 4.29)

Abbreviation: IQR, interquartile range.

[a] Adjusted for baseline systolic blood pressure and baseline adverse effects for adverse effect outcomes. The reporting of adverse effects and adverse events involved classifying the number into a binary variable in which 0 indicates no reported adverse effect or event and 1 indicates at least 1 reported adverse effect or event.

[b] Ten most commonly reported adverse effects listed as measured by the Revised Illness Perception Questionnaire for Hypertension.[25] The denominator in each group reflects the number of participants completing this questionnaire at follow-up.

[c] Adverse events were those reported by the participant or observed by the investigator during trial follow-up, which were then assessed for relatedness by the local primary care physician and did not result in hospitalization or death.

[d] Post hoc outcome not included in protocol or statistical analysis plan and specified after seeing initial results.

[e] Serious adverse events were those reported by the treating physician during trial follow-up, defined as those resulting in death or considered life threatening, required inpatient hospitalization or prolonged existing hospitalization, resulted in persistent or significant disability/incapacity or other medical events considered to be serious because they jeopardized the participant or required intervention to prevent one of the above consequences. The number of serious adverse events are reported as follows (per intervention group; control group): hospitalization (2; 4), fall (2; 1), acute coronary syndrome (1; 0), arrhythmia (1; 0), gastrointestinal hemorrhage (1; 0), hip arthroplasty (1; 0), inguinal hernia repair (1; 0), ischaemic stroke (1; 0), myocardial infarction (0; 1), peripheral ischemia (0; 1), pneumonia (1; 0), sepsis (0;1), somnolence (1; 0), transurethral bladder resection (1; 0), urinary tract infection (0; 1) and wound dehiscence (0; 1).

reduction in 32% to 68% of participants,[29-31] had smaller sample sizes,[29,30] examined younger populations,[31] and lacked comparisons with a control group to determine the effect of deprescribing on outcomes.[29] Longer-term studies do exist, but these are observational in nature and do not include a control group for robust comparison of outcomes.[32] In all but 1 previous trial,[30] medication reduction was part of a medication review but not specifically mandated, and patients could have only been taking a single antihypertensive at trial entry.[29,31,33-35] Mandating medication reduction in this trial, while ensuring all participants continued some antihypertensive treatment, may have reduced clinical inertia by the treating physician compared with previous work.[36,37]

The only other trial that has examined the effect of antihypertensive medication reduction on blood pressure in older patients examined individuals prescribed fewer antihypertensives (61.5% vs 100% prescribed ≥2 medications) but with higher baseline blood pressure (148/81 mm Hg vs 130/69 mm Hg).[30] Initial medication reduction was achieved in 67.8% of participants, but the number having therapy reinstated at 16-week follow-up was not reported. Medication reduction in that trial resulted in a larger increase in systolic blood pressure (7.4-mm Hg increase in all patients available for analysis and 11.1-mm Hg increase in the per-protocol population) than was observed in the present study. This is likely due to the medication reduction algorithm used, in which antihypertensive medications were iteratively stopped until a maximum increase in systolic blood pressure of 20 mm Hg was reached.

Proponents of deprescribing suggest potential benefits could be an increased quality of life, reduced adverse effects, and a reversal of cognitive decline.[15,30] However, these potential benefits might be expected to happen over the longer term and are yet to be demonstrated in robust randomized clinical trials. This study was unable to demonstrate short-term benefits but was not powered to detect significant differences in adverse effects or quality of life. These should be studied in a longer-term context.

This trial described a structured approach to antihypertensive medication reduction and provides evidence relevant to routine clinical practice. It showed that antihypertensive medication reduction can be achieved (in the

short-term) in some patients with multimorbidity and polypharmacy, who were selected by their primary care physician to potentially benefit from medication reduction. Of those following the medication reduction and monitoring algorithms, a similar proportion had systolic blood pressure lower than 150 mm Hg at follow-up compared with those not reducing medication, and two-thirds were taking fewer antihypertensive medications after 12 weeks. This resulted in participants in the medication reduction group taking 0.6 fewer antihypertensives than those not reducing medication at follow-up. This reduction was modest, and further studies should explore whether greater medication reduction (ie, removal of multiple medications) can be achieved without affecting blood pressure control at follow-up.

Previous trials of blood pressure lowering in older adults (such as SPRINT and the Hypertension in the Very Elderly Trial)[3,4,38] do not represent frail patients with multimorbidity who may be at higher risk of adverse events from polypharmacy.[6,7] As a result, there is divergence in international guidelines as to what is an appropriate target for blood pressure in people older than 80 years. The UK National Institute for Health and Care Excellence (updated in 2019)[11] and the US American College of Physicians/American Academy of Family Physicians (2017)[39] define the threshold for systolic blood pressure control as lower than 150 mm Hg—the threshold used in this study. In contrast, American Heart Association/American College of Cardiology guidelines[40] now recommend a target of 130 mm Hg (where tolerated), primarily based on the findings of the SPRINT trial.[4,38] What this trial has shown is that withdrawal of a blood pressure agent is associated with a small rise in blood pressure in patients older than 80 years with multimorbidity, mild frailty, polypharmacy, or a combination of these characteristics. The threshold at which such medication reduction is contemplated will depend on the guideline being used. Post hoc analyses of the current study suggested that lower thresholds for blood pressure control would have resulted in worse control from drug withdrawal, presumably because primary care physicians were less likely to reintroduce therapy at such lower thresholds because this was not specified in the study protocol.

Although the patient population in this study was generalizable to primary care, this trial did not establish whether or not medication reduction should be attempted (in terms of clinical outcomes) or who should be targeted with such an intervention. The 3.4-mm Hg increase in systolic blood pressure and the 2.2-mm Hg increase in diastolic blood pressure observed following medication reduction suggest caution should be exercised when adopting this approach in routine clinical practice. Studies in populations with less multimorbidity have suggested that medication reduction might not result in an increase in cardiovascular events, provided blood pressure remains controlled, although this was attributed to greater use of nonpharmacological interventions.[41] It is unclear whether an increased risk of cardiovascular disease is as important in an older population in which there are competing risks from other conditions.

Deprescribing of antihypertensive drugs (and other medications) is increasingly being promoted in clinical guidelines[13,14] and clinical care,[15] despite a lack of robust evidence from randomized clinical trials. This study is an important step to addressing this evidence gap and highlights the short-term effects, which could be important to informing decision making between patients and physicians considering antihypertensive medication reduction. Future trials should explore the long-term effects of medication reduction, particularly focusing on frailer patients with multimorbidity who have not been studied in previous trials.[3,4,38]

Limitations

This study has several limitations. First, participants were selected based on the primary care physician's view that they might benefit from medication reduction, and approximately 1 in 10 of those invited by post were enrolled. Despite this, included participants were representative of the general population in primary care in terms of age and blood pressure, with similar levels of morbidity and frailty (eTable 3 Supplement 3). The trial was designed to minimize bias using a web-based randomization algorithm and allocation concealment prior to consent and choice of medication to reduce. Follow-up was achieved in 94% of participants, limiting the likelihood of attrition bias.

Second, the unblinded design meant patients and investigators were aware of the treatment allocation and study end points. However, blood pressure measurement was undertaken using an automatic sphygmomanometer, which required minimal input from the investigator, and therefore, the potential for bias in ascertainment of the primary outcome was low. Knowledge of taking fewer medications may have led participants in the medication reduction group to report fewer adverse effects at follow-up, but no significant differences between groups were observed.

Third, participants in the medication reduction group attended at least 1 additional appointment during follow-up (the 4-week safety visit) compared with usual care, explaining most of the increased consultation rate. This may also explain the significantly higher incidence of adverse events seen in this group, particularly given that only one-fourth of the events were considered possibly related to medication reduction.

Fourth, 13 participants in the usual care group reduced their antihypertensive medication during follow-up. We did not robustly measure whether individuals were adherent to their remaining medications in either group, and this could have affected the proportion of participants with systolic blood pressure lower than 150 mm Hg at follow-up.

Fifth, the decision to design the trial with a short period of follow-up (12 weeks) was made for ethical reasons to demonstrate the short-term effects of medication reduction on blood pressure and adverse events prior to embarking on a larger study with longer follow-up. This meant the study was underpowered to make reliable comparisons of adverse events between groups, and as a result, the long-term benefits and harms of antihypertensive medication reduction remain unknown.

Sixth, the noninferiority margin was determined based on opinion of likely meaningfulness for physician and patient discussions and not prior evidence.

Conclusions

Among older patients treated with multiple antihypertensive medications, a strategy of antihypertensive medication reduction, compared with usual care, was noninferior with regard to the proportion of patients with systolic blood pressure lower than 150 mm Hg at 12 weeks. The findings suggest antihypertensive medication reduction can be achieved without substantial change in blood pressure control in some older patients with hypertension, although further research is needed to understand long-term clinical outcomes.

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