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Effect of antihypertensive medication reduction vs usual care on short-term blood pressure control in patients aged ≥ 80 years with hypertension: the OPTIMISE randomized clinical trial

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Key points

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

Findings: In this randomized clinical trial that included 569 patients aged ≥80 years, the proportion of patients with systolic blood pressure <150 mm Hg at 12 weeks was 86.4% in the intervention group and 87.7% in the control group (Adjusted RR 0.98), a difference that met the non-inferiority 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.

Abstract

Importance: Deprescribing of antihypertensive medications is recommended for some older patients with polypharmacy and multi-morbidity where 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 a 12-week follow-up period.

Design, Setting, and Participants: The OPtimising Treatment for MIld Systolic hypertension in the Elderly (OPTIMISE) study was a randomized, unblinded, non-inferiority trial conducted in 69 primary care sites in England. Participants were aged ≥80 years with systolic blood pressure <150mmHg and receiving ≥2 antihypertensive medications, whose primary care physician considered them appropriate for medication reduction. Participants were enrolled between April 2017 and September 2018 and followed-up until January 2019.

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

Main outcomes: The primary outcome was systolic blood pressure <150 mmHg at 12-week follow-up. The pre-specified non-inferiority margin was a relative risk (RR) of 0.90 (intervention:control). Secondary outcomes included the proportion of participants in the intervention group maintaining medication reduction and between group differences in systolic and diastolic blood pressure, frailty, quality of life, adverse effects and serious adverse events.

Results: Among 569 patients who were randomized (mean age, 84.8; 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 of <150 mmHg at follow-up (Adjusted RR 0.98, 97.5% 1-sided CI 0.92 to ∞). Of seven pre-specified secondary endpoints, five 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 mmHg (95% CI 1.1 to 5.8 mmHg) higher in the intervention group compared to control. Twelve (4.3%) participants in the intervention group and 7 (2.4%) in the control group reported at least one 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 non-inferior with regard to systolic blood pressure control at 12 weeks. The findings suggest antihypertensive medication reduction can be achieved in some older patients with hypertension, without substantial change in blood pressure control, although further research is needed to understand long-term clinical outcomes.

Trial registration: EudraCT:2016-004236-38; ISRCTN:97503221.

Abstract word count: 415 words

Keywords: Randomized clinical trial, non-inferiority, blood pressure, deprescribing, medication discontinuation, medication withdrawal, adverse events, primary care, aged, multi-morbidity , frailty

Introduction

High blood pressure is the leading modifiable risk factor for cardiovascular disease[1] and the most common co-morbid condition in older people with multi-morbidity.[2] Antihypertensive treatment has been shown to be effective at preventing 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[6] and there is debate about the extent to which these data should be applied to frail patients with multi-morbidity.[7] Evidence from observational studies suggests that lower blood pressure and multiple antihypertensive prescriptions may be harmful in some older patients with polypharmacy and multi-morbidity.[8-10]

Guidelines recommend using clinical judgement when prescribing in frail older patients,[11,12] emphasising a personalised approach to care which 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]

Very few randomized clinical trials have considered the safety and efficacy of antihypertensive medication reduction in routine clinical practice.[15] In older patients with multi-morbidity and controlled blood pressure (<150/90 mmHg), there are advantages and disadvantages to continuing treatment.[8-10] For those who decide 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 multi-morbidity and controlled systolic hypertension prescribed, two 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.

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, non-inferiority design. Participants were individually allocated (1:1 allocation ratio) to a strategy of antihypertensive medication reduction (intervention) or usual care (control) 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 gave written informed consent.

Participants and setting

This study was conducted in primary care sites from across South and Central England. Participants were aged ≥80 years, with systolic blood pressure at baseline <150 mmHg and prescribed two or more antihypertensive treatments for at least 12 months. Detailed inclusion and exclusion criteria are provided in eTable 1. Recruiting primary care physicians were educated about the latest guidelines and evidence from randomized clinical trials at the beginning of the trial as part of the study training. The generalizability of these trials was discussed and they were asked to only enrol patients whom in their opinion might potentially benefit from medication reduction due to existing polypharmacy, co-morbidity, non-adherence or dislike of medicines and/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/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.

Randomisation and masking

The screening appointment comprised: a study explanation by the primary care physician, informed consent and eligibility assessment. Participants underwent baseline assessments and were allocated (1:1 allocation ratio) to one of the two study groups using a non-deterministic minimization algorithm, with minimization designed to balance site and baseline SBP, via a fully validated, web-based, password protected system

(Sortition®). The first three participants were allocated using simple randomisation 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 randomisation group. Pre-specified 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 would be removed if the participant was randomised to the medication reduction group of the trial. Primary care physicians were given a medication reduction algorithm (eFigure 1, supplement 3) to assist with this decision. Since combination pills for antihypertensive treatment are rarely used in the UK, 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, supplement 3) including 4-week follow-up. They were asked to reinstate treatment if blood pressure was found to be above 150 (systolic) or 90 (diastolic) mmHg for more than one week, adverse events occurred or signs of accelerated hypertension developed. All participants randomised to medication reduction were given the option to self-monitor their blood pressure. Some 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.

Those allocated to control followed usual clinical care, where 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 – intervention group only) and 12-week follow-up. Assessments of functional independence and cognitive function were undertaken at baseline using the Modified Rankin scale[17] and Montreal Cognitive Assessment (MoCA)[18] respectively. The ethnicity of each participant was recorded at baseline to better characterise 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, all others were classified as non-white / unknown.

Outcome measures

The primary outcome was the relative risk of systolic blood pressure control (<150 mmHg; defined by UK National Institute for Health and Care Excellence as the target blood pressure for those aged over 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 five minutes of rest. Systolic blood pressure was estimated from the mean of the 2nd and 3rd readings.

All pre-specified 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,[21] the Electronic Frailty Index[22] and the Morley FRAIL scale.[23] The Frailty Index includes 54 items with values ranging from 0 (fit) to 1 (frail).[21] The Electronic Frailty Index has 36 items and ranges between 0 (fit) to 1 (frail) and was estimated using data from electronic health records.[22] The Morley FRAIL scale has 5 components and the scale ranges from 0 (robust health) to 4 (frail) and was 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 analysed using the cross-walk approach which translates the scores for the five EQ-5D-5L items into a single index value and visual analogue scale (VAS) which has values between 0 (worst health) and 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/incapacity or were classed as 'other medical events' considered to be serious because they put the participant at risk of one of the above consequences or required intervention to prevent them from occurring.

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 (non-serious) during 12-week follow-up. To better understand any observed differences in adverse events, each event was categorised by the treating clinician as to whether or not it was possibly related to medication reduction and classified by the research team according to ICD-11 definitions of disease.

Statistical analysis

A sample size of 540 participants was pre-specified 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 <150 mmHg at 12-week follow-up. Calculations assumed a 0.90 non-inferiority margin, 90% power, 2.5% 1-sided level of significance, 10% loss to follow-up and a 10% dilution effect due to cross-over between groups. Due to the lack of evidence defining non-inferiority, the margin of 0.90 was chosen to inform future physician-patient discussions about medication reduction: if non-inferiority was demonstrated, it would suggest that for every ten patients who have their medication reduced, nine 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 were analysed according to the groups they were randomly allocated to, regardless of deviation from protocol. The pre-specified analysis for the primary outcome planned a generalised 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 predictive of missingness were adjusted in the primary analysis, including gender, MoCA Score, EQ-5D-5L Index and the Frailty Index. Six missing baseline EQ-5D-5L and ten 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). Non-inferiority was assumed if the lower limit of the confidence interval around the adjusted relative risk ($RR_{adjusted}$) of participants with controlled blood pressure was above 0.90. Adjusted risk differences ($RD_{adjusted}$) were also calculated and reported, using 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 analysed 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 analysed 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. Because of potential for type 1 error due to multiple comparisons, findings for analyses of secondary endpoints should be interpreted as exploratory.

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. Pre-specified 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 co-morbidities. Each potential moderator was dichotomised 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 relative risk 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 <140 mmHg and <130 mmHg.

Sensitivity analyses of the primary outcome were undertaken to examine missing data and outlying systolic blood pressure values (see supplement 3). All data were analysed using Stata statistical software (version 15.1, College Station TSL, StataCorp, 2017). Significance thresholds were set at 5% (2-sided) for superiority and 2.5% (1-sided) for non-inferiority.

Results

A total of 69 primary care sites participated from Central and Southern England. Between 20th March 2017 and 30th September 2018, 6,194 patients were invited by post to participate in the trial and 739 attended a screening appointment (Figure 1). Of these, 569 participants (77.0%) provided informed consent and were randomised to the trial. The characteristics of participants in the trial were broadly similar to those of the general population (eTable 3).

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

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 of <150 mmHg at 12-week follow-up ($RR_{adjusted}$ 0.98, 97.5% CI 0.92 to ∞, Table 2). The 97.5% 1-sided confidence interval for this adjusted relative risk was greater than 0.9, indicating that medication reduction was non-inferior to usual care. These findings were robust to sensitivity analyses examining the effect of missing data and outlying blood pressure values (eTable 5). 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). Mean systolic blood pressure at baseline was 129.4 (SD 13.4) mmHg in the intervention group and 130.5 (SD 12.3) mmHg in the control group. At 12 weeks it was 133.7 (95% CI 131.7 to 135.6) mmHg and 130.8 (95% CI 128.9 to 132.7) mmHg in the intervention and control groups respectively, meaning that the change in systolic blood pressure at 12-weeks was 3.4 mmHg (95% CI 1.0 to 5.8 mmHg; table 3) higher in the medication reduction group compared to usual care after correcting for baseline blood pressure. Mean diastolic blood pressure at baseline was 68.4 (SD 9.1) mmHg in the intervention group and 70.1 (SD 8.4) mmHg in the control group and at 12 weeks 70.9 (95% CI 69.6 to 72.1) mmHg and 69.7 (95% CI 68.5 to 70.8) mmHg in the intervention and control groups respectively. The adjusted mean difference in change in diastolic blood pressure corrected for baseline was 2.2 mmHg (95% CI 0.9 to 3.6 mmHg). 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).

Subgroup analyses

There was no evidence of any interaction effects between the randomised group and pre-specified subgroups in systolic blood pressure control, change in blood pressure or maintenance of medication reduction by subgroups (eFigures 4 and 5; eTable 6, supplement 3).

Post hoc outcomes

Three participants in the intervention group did not reduce medications whilst two increased treatment (eTable 7). 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 (34.5%, 95% CI 27.8% to 42.9% in the per-protocol population; eFigure 6). 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). There was no

statistically significant difference in maintenance of medication reduction by baseline blood pressure (eTable 8). However, the relative risk of blood pressure control was reduced when thresholds defining control were reduced to lower than 150 mmHg (eTable 9).

The number experiencing at least one adverse event was significantly higher in the medication reduction group ($RR_{adjusted}$ 1.28, 95% CI 1.06 to 1.54; Table 4). A total of 27% of 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). Participants in the medication reduction group attended significantly more healthcare appointments during follow-up than the usual care group (eTable 12).

Discussion

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

In contrast to the present study, previous antihypertensive deprescribing trials have only attempted medication reduction in between 32% to 68% of participants,[27-29] had smaller sample sizes,[27,28] examined younger populations[29] and lacked comparisons with a control group to determine the effect of deprescribing on outcomes.[27] Longer term studies do exist, but these are observational in nature and do not include a control group for robust comparison of outcomes.[30] In all but one previous trial,[28] 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.[27,29,31-33] Mandating medication reduction in this trial whilst ensuring all participants continued some antihypertensive treatment may have reduced clinical inertia by the treating physician compared to previous work.[34,35]

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 vs 130/69mmHg).[28] 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 mmHg in all patients available for analysis and 11.1 mmHg in the per-protocol population) than was observed in the present study. This is likely due to the medication reduction algorithm employed in which antihypertensive medications were iteratively stopped until a maximum increase in systolic blood pressure of 20 mmHg was reached.

Proponents of deprescribing suggest potential benefits could be an increased quality of life, reduced adverse effects and a reversal of cognitive decline.[15,28] 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 multi-morbidity 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 <150 mmHg at follow-up compared to 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 (i.e. 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)[3,4,36] do not represent frail patients with multi-morbidity 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 over the age of 80. 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)[37] define the threshold for systolic blood pressure control as <150 mmHg – the threshold used in this study. In contrast, American Heart Association/American College of Cardiology guidelines[38] now recommend a target of 130 mmHg (where tolerated), primarily based on the findings of the SPRINT trial.[4,36] What this trial has shown is that withdrawal of a blood pressure agent is associated with a small rise in blood pressure in patients over the age of 80 with multi-morbidity, mild frailty, and/or polypharmacy. The threshold at which such medication reduction is contemplated will depend upon 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 population 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 3.4/2.2 mmHg increase in blood pressure observed following medication reduction suggests caution should be exercised when adopting this approach in routine clinical practice. Studies in populations with less multi-morbidity 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 non-pharmacological interventions.[39] It is unclear whether an increased risk of cardiovascular disease is as important in an older population where 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 focussing on frailer patients with multi-morbidity who have not been studied in previous trials.[3,4,36]

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 one in ten 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). The trial was designed to minimise bias using a web-based randomisation 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 both patients and investigators were aware of the treatment allocation and study endpoints. However, blood pressure measurement was undertaken using an automatic sphygmomanometer, which required minimal input from the investigator and so 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 intervention group attended at least one additional appointment during follow-up (the 4-week safety visit) compared to 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 quarter were considered possibly related to medication reduction.

Fourth, thirteen 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 <150 mmHg 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 so the long-term benefits and harms of antihypertensive medication reduction remain unknown.

Conclusions

Among older patients treated with multiple antihypertensive medications, a strategy of antihypertensive medication reduction, compared with usual care, was non-inferior with regard to the proportion of patients with systolic blood pressure <150 mmHg 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.

Contributors

JS and RJMcM conceived, designed and secured funding for the study with JBu, ML, GAF, CH, FDRH, SJ, PL, JM, RAP, MW and LMY. ET was the trial manager. RF, JMo and LMY conducted the statistical analysis. JS wrote the first draft. All authors reviewed and edited the manuscript. JS and RJMcM are co-chief investigators and will act as guarantors for this work.

Declaration of interests

The authors declare no conflicts of interest.

Ethics and approvals

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 gave written informed consent.

Data Sharing Statement

Data sharing statement: See supplement 4. Requests for sharing of de-identified individual participant data and a data dictionary defining each field in the set will be considered by the corresponding author.

Access to Data and Data Analysis

JS and RJMcM had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Figure legends

Figure 1. Recruitment, randomization, and analysis population

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

[b] Participants were allocated to one of the two study groups using a non-deterministic minimisation algorithm, minimised for site and baseline SBP. The first three participants were allocated using simple randomisation 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 (e.g. medical history, prescriptions).

[d] Reasons for death were ischemic stroke and cardiac arrest.

669 **Tables**

670 **Table 1**. Baseline Demographics and Clinical Characteristics

	Medication reduction group (n=282)	**Usual care group (n=287)**
Age (years), mean (SD)	84.6 (3.3)	85.0 (3.5)
Age >85 years (%)	131 (46.5%)	143 (49.8%)
Female (%)	131 (46.5%)	145 (50.5%)
Male (%)	151 (53.5%)	142 (29.5%)
Body mass index (BMI)	n=270	n=264
Mean (SD), (kg/m^2)	27.2 (4.2)	28.0 (4.3)
Underweight, BMI < 18.5 (%)	1 (0.4%)	2 (0.8%)
Normal, 18.5 ≥ BMI ≤ 30 (%)	213 (78.9%)	183 (69.3%)
Overweight, BMI > 30 (%)	56 (20.7%)	79 (29.9%)
Ethnicity[a]		
White (%)	278 (98.6%)	278 (96.9%)
Non-white (%)	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%)
Alcohol consumption (% reporting drinking alcohol every week)	98 (34.8%)	108 (37.6%)
Total cholesterol	n=252	n=259
Mean (SD),[b] (mmol/l)	4.6 (1.2)	4.6 (1.2)
Estimated eGFR	n=241	n=252
Mean (SD),[c] (ml/min per 1.73 m^2)	61.6 (14.9)	60.4 (14.2)
Montreal Cognitive Assessment score[b]	n=280	n=282
Mean (SD)	24.4 (3.6)	24.0 (4.1)
EQ-5D-5L index[d]	n=279	n=284
Mean (SD)	0.78 (0.17)	0.76 (0.17)
Modified Rankin Scale[e]	n=267	n=273
Score >2, (dependant), (%)	36 (12.8%)	42 (14.6%)
Frailty		
Morley FRAIL scale,[f] mean (SD)	0.77 (0.99)	0.95 (1.07)
FRAIL scale = 0	155 (55.0%)	134 (46.7%)
FRAIL scale = 1	58 (20.6%)	68 (23.7%)
FRAIL scale = 2	50 (17.7%)	55 (19.2%)
FRAIL scale = 3	17 (6.0%)	26 (9.1%)
FRAIL scale = 4	2 (0.7%)	4 (1.4%)
Frailty index,[g] mean (SD)	0.14 (0.07)	0.15 (0.07)
Electronic Frailty index (eFI),[h] mean (SD)	0.14 (0.07)	0.15 (0.07)
Fit (eFI 0-0.12; %)	121 (42.9%)	109 (38.0%)
Mild (eFI >0.12-0.24; %)	132 (46.8%)	143 (49.8%)
Moderate (eFI >0.24-0.36; %)	27 (9.6%)	32 (11.1%)
Severe (eFI >0.36; %)	2 (0.7%)	3 (1.0%)
Blood pressure		
Systolic blood pressure (mmHg), mean (SD)	129.4 (13.1)	130.5 (12.3)
Diastolic blood pressure (mmHg), mean (SD)	68.4 (9.1)	70.1 (8.4)
History of high blood pressure	n=269	n=276
Mean (SD), (years)	16.8 (8.9)	16.3 (9.0)
Standing systolic blood pressure	n=264	n=261
Mean (SD), (mmHg)	128.7 (15.5)	131.8 (16.2)
Orthostatic hypotension (%)[i]	n=264	n=261
N (%)	15 (5.3%)	10 (3.5%)
Medical history[j]		
Chronic Kidney Disease (%)	83 (29.4%)	103 (35.9%)

Cancer (%)	67 (23.8%)	68 (23.7%)
Cardiac Disease (%)[k]	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%)
Number of morbidities, mean (SD)[j]	5.7 (2.7)	6.0 (2.9)
% ≥2 morbidities (%)[j]	278 (98.6%)	282 (98.3%)
Medication prescriptions		
Antihypertensive (%)	282 (100.0%)	287 (100.0%)
ACE inhibitor / Angiotensin II receptor blocker (%)[l]	238 (84.4%)	243 (84.7%)
Calcium channel blockers (%)[l]	199 (70.6%)	191 (66.6%)
Beta blockers (%)[l]	112 (39.7%)	116 (40.4%)
Thiazide & related diuretics (%)[l]	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 to 3)	2 (2 to 3)
Total non-cardiovascular medications, median (IQR)	1 (1 to 2)	1 (1 to 2)
Total prescribed medications, median (IQR)	4 (3 to 7)	4 (3 to 7)

[a] Ethnic group was defined according to 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 others were classified as non-white / unknown.

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

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

[d] The EQ-5D-5L assesses five 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 five EQ-5D-5L items into a single index value. The index value ranges from -0.594 (worse than death) to 1 (full health).

[e] Modified Rankin scale ranges from 0 (no symptoms) to 5 (severe disability).

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

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

[h] The Electronic Frailty Index has 36 items and is estimated from electronic health records. The index ranges from 0 (fit) to 1 (frail).

[i] Orthostatic hypotension defined as a decrease in systolic blood pressure of ≥20 mmHg within 3 minutes of standing.[40]

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

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

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

SD=standard deviation.

Table 2. Primary outcome difference in the proportion of patients with clinically acceptable systolic blood pressure <150 mmHg at 12 weeks

	Medication reduction group	Usual care group	Unadjusted risk difference (97.5% 1-sided CI)	Adjusted risk difference[a] (97.5% 1-sided CI)	Unadjusted relative risk[b] (97.5% 1-sided CI)	Adjusted relative risk[a,b] (97.5% 1-sided CI)	P-value[c]
Primary analysis	n=265	n=269					
Systolic blood pressure <150 mmHg	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 ∞)	0.01
Per protocol analysis[d]	n=185	n=269					
Systolic blood pressure <150 mmHg	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 ∞)	0.007

[a] Adjusting for baseline systolic blood pressure, gender, cognitive function (MoCA Score), EQ-5D-5L Index and Frailty Index (which were predictive of missingness, eTable 13).

[b] The margin for non-inferiority was set at 0.90 for RR. A lower bound of the CI that did not exceed this margin indicated non-inferiority.

[c] P-value for non-inferiority for adjusted relative risk.

[d] A total of 187 participants maintained medication reduction. However, two did not have blood pressure measured at follow-up and so 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 so 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).

Table 3. Secondary outcomes at 12 weeks

	Medication reduction group		Usual care group		Adjusted mean difference (95% CI)	P Value[h]
	Number analysed	Mean (95% CI)	Number analysed	Mean (95% CI)		
Blood pressure[a]						
Systolic (mmHg)[b]	265	133.7 (131.7 to 135.6)	269	130.8 (128.9 to 132.7)	3.4 (1.0 to 5.8)	0.005
Diastolic (mmHg)[c]	265	70.9 (69.6 to 72.1)	269	69.7 (68.5 to 70.8)	2.2 (0.9 to 3.6)	0.001
Quality of life at 12 weeks[d,e]						
EQ-5D-5L index	260	0.79 (0.17)	263	0.79 (0.77 to 0.81)	-0.01 (-0.03 to 0.01)	0.50
EQ-5D-5L visual analogue scale	259	78.5 (15.7)	259	78.3 (76.5 to 80.1)	-0.76 (-2.86 to 1.33)	0.47
Frailty at 12 weeks[d,e]						
Frailty index	282[f]	0.137 (0.130 to 0.145)	287[f]	0.145 (0.136 to 0.152)	-0.00003 (-0.005 to 0.005)	0.77
Electronic frailty index	278[f]	0.134 (0.126 to 0.141)	285[f]	0.140 (0.132 to 0.148)	0.001 (-0.003 to 0.005)	0.77
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)	0.88
Post hoc outcomes						
Systolic blood pressure (PP analysis, mmHg)[b,g]	185	134.4 (132.1 to 136.7)	269	130.8 (128.9 to 132.7)	4.9 (2.4 to 7.5)	<0.001
Diastolic blood pressure (PP analysis, mmHg)[c,g]	185	71.6 (70.2 to 73.1)	269	69.7 (68.5 to 70.8)	3.4 (1.8 to 4.9)	<0.001
Change in Antihypertensive prescriptions	276[f]	-0.68 (-0.74 to -0.61)	283[f]	-0.05 (-0.08 to -0.01)	-0.63 (-0.70 to -0.56)	<0.001

[a] Analyses conducted in the primary analysis population (all available participants), unless otherwise stated.
[b] Adjusted for baseline systolic blood pressure, and gender, Montreal Cognitive Assessment score, EQ-5D-5L Index and Frailty Index (which were predictive of missingness, eTable 13) with a random effect for primary care site.
[c] Adjusted for baseline systolic and diastolic blood pressure, and gender, Montreal Cognitive Assessment score, EQ-5D-5L Index and Frailty Index (which were predictive of missingness, eTable 13) with a random effect for primary care site.
[d] Adjusted for baseline level of the outcome, baseline systolic blood pressure fitted as a fixed effect. Six missing baseline EQ-5D-5L and ten missing baseline EQ-5D VAS scores were replaced with the overall mean of the covariate at baseline.
[e] See Table 1 for definitions of quality of life and frailty indices. The EQ-5D-5L visual analogue scale (VAS) has values between 0 (worst health) and 100 (best health).
[f] 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 were followed up face-to-face at 12 weeks.

[g]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).

[h] P-values are given for superiority, in contrast to Table 2, where they are given for non-inferiority.

PP=Per-protocol; SD=standard deviation.

Table 4. Most commonly reported adverse effects, adverse events, and serious adverse events

	Medication reduction group	Usual care group	Adjusted risk difference[1] (95% CI)	Adjusted risk ratio[a] (95% CI)
Adverse effects[b]	n=264	n=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)
At least 1 reported adverse effect (%)	234 (88.6%)	246 (92.5%)	-3.5% (-8.6% to 1.5%)	0.96 (0.91 to 1.02)
Number of adverse effects, median (IQR)	4 (2 to 6)	4 (2 to 7)		
Adverse events[c]	n=282	n=287		
At least 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)
Number of adverse events, median (IQR)	0 (0 to 1)	0 (0 to 1)		
At least 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)

[a] Adjusted for baseline systolic blood pressure and baseline adverse effects for adverse effect outcomes. The reporting of adverse effects/adverse events involved classifying the number into a binary variable – where 0 indicates no reported adverse effect/adverse event and 1 indicates at least 1 reported adverse effect/adverse 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 hospitalisation 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 hospitalisation or prolonged existing hospitalisation, resulted in persistent or significant disability/incapacity or 'other medical events' considered to be serious because they jeopardised the participant or required intervention to prevent one of the above consequences. Serious adverse events per intervention, control group: Hospitalisation (2,4), Fall (2,1), Acute coronary syndrome (1,0), Arrhythmia (1,0), gastrointestinal haemorrhage (1,0), Hip arthroplasty (1,0), Inguinal hernia repair (1,0), Ischaemic stroke (1,0), myocardial infarction (0,1), Peripheral ischaemia (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).

IQR = Interquartile range.