

Effect of antihypertensive medication reduction vs usual care on short-term blood pressure control in patients with hypertension aged 80 years and older

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

3

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39 **Key points**

40

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

44

45 **Findings:** In this randomized clinical trial that included 569 patients aged ≥ 80 years, the proportion of
46 patients with systolic blood pressure < 150 mm Hg at 12 weeks was 86.4% in the intervention group and
47 87.7% in the control group (Adjusted RR 0.98), a difference that met the non-inferiority margin of a relative
48 risk of 0.90.

49

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

52 **Abstract**

53

54 **Importance:** Deprescribing of antihypertensive medications is recommended for some older patients with
55 polypharmacy and multi-morbidity where the benefits of continued treatment may not outweigh the harms.

56 **Objective:** This study aimed to establish whether antihypertensive medication reduction is possible without
57 significant changes in systolic blood pressure control or adverse events during a 12-week follow-up period.

58 **Design, Setting, and Participants:** The OPTimising Treatment for MIld Systolic hypertension in the Elderly
59 (OPTIMISE) study was a randomized, unblinded, non-inferiority trial conducted in 69 primary care sites in
60 England. Participants were aged ≥ 80 years with systolic blood pressure < 150 mmHg and receiving ≥ 2
61 antihypertensive medications, whose primary care physician considered them appropriate for medication
62 reduction. Participants were enrolled between April 2017 and September 2018 and followed-up until January
63 2019.

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

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

72 **Results:** Among 569 patients who were randomized (mean age, 84.8; 276 (48.5%) women; median of 2
73 antihypertensive medications prescribed at baseline), 534 (93.8%) completed the trial. Overall, 229 (86.4%)
74 patients in the intervention group and 236 (87.7%) patients in the control group had a systolic blood pressure
75 of < 150 mmHg at follow-up (Adjusted RR 0.98, 97.5% 1-sided CI 0.92 to ∞). Of seven pre-specified
76 secondary endpoints, five showed no significant difference. Medication reduction was sustained in 187
77 (66.3%) participants at 12 weeks. Mean change in systolic blood pressure was 3.4 mmHg (95% CI 1.1 to 5.8
78 mmHg) higher in the intervention group compared to control. Twelve (4.3%) participants in the intervention
79 group and 7 (2.4%) in the control group reported at least one serious adverse event (adjusted RR 1.72,
80 95%CI 0.7 to 4.3).

81 **Conclusions and relevance:** Among older patients treated with multiple antihypertensive medications, a
82 strategy of medication reduction, compared with usual care, was non-inferior with regard to systolic blood
83 pressure control at 12 weeks. The findings suggest antihypertensive medication reduction can be achieved in
84 some older patients with hypertension, without substantial change in blood pressure control, although further
85 research is needed to understand long-term clinical outcomes.

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

87

88 **Abstract word count:** 415 words

89

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

92 **Introduction**

93 High blood pressure is the leading modifiable risk factor for cardiovascular disease¹ and the most common
94 co-morbid condition in older people with multi-morbidity.² Antihypertensive treatment has been shown to be
95 effective at preventing stroke and cardiovascular disease in older high-risk patients^{3,4} and approximately half
96 of individuals aged 80 years or older are prescribed therapy.⁵ However, previous trials such as the Systolic
97 blood PResure INTervention (SPRINT)⁴ trial have been shown to represent as few as one third of older
98 individuals⁶ and there is debate about the extent to which these data should be applied to frail patients with
99 multi-morbidity.⁷ Evidence from observational studies suggests that lower blood pressure and multiple
100 antihypertensive prescriptions may be harmful in some older patients with polypharmacy and multi-
101 morbidity.⁸⁻¹⁰

102

103 Guidelines recommend using clinical judgement when prescribing in frail older patients,^{11,12} emphasising a
104 personalised approach to care which might include attempts to improve quality of life through
105 deprescribing.¹³⁻¹⁵ However, these guidelines are largely based on expert opinion and are vague on how to
106 achieve medication reduction due to a lack of evidence, highlighting the need for research in this area.¹⁴

107

108 Very few randomized clinical trials have considered the safety and efficacy of antihypertensive medication
109 reduction in routine clinical practice.¹⁵ In older patients with multi-morbidity and controlled blood pressure
110 (<150/90 mmHg), there are advantages and disadvantages to continuing treatment.⁸⁻¹⁰ For those who decide
111 that potential risks of continuing treatment outweigh benefits, there is no evidence to guide medication
112 reduction. This trial examined a structured approach to antihypertensive medication reduction in older
113 patients with multi-morbidity and controlled systolic hypertension prescribed, two or more antihypertensives.
114 The trial aimed to establish whether partial medication reduction is possible without clinically significant
115 changes in blood pressure control, frailty, quality of life, adverse effects, serious adverse events, and change
116 in systolic and diastolic blood pressure after 12 weeks of follow-up.

117

118 **Methods**

119 The study protocol can be found in supplement 1. The statistical analysis plan can be found in supplement 2.
120 The protocol for this trial has also been published in detail elsewhere.¹⁶

121

122 *Study design*

123 The OPTimising Treatment for MIld Systolic hypertension in the Elderly (OPTIMISE) trial used a primary
124 care based, randomized, unblinded, parallel group, non-inferiority design. Participants were individually
125 allocated (1:1 allocation ratio) to a strategy of antihypertensive medication reduction (intervention) or usual
126 care (control) and followed-up for 12 weeks. The study was approved by an NHS Research Ethics
127 Committee (South Central - Oxford A; ref 16/SC/0628) and the Medicines and Healthcare products
128 Regulatory Agency (MHRA; ref 21584/0371/001-0001). All participants gave written informed consent.

129

130 *Participants and setting*

131 This study was conducted in primary care sites from across South and Central England. Participants were
132 aged ≥ 80 years, with systolic blood pressure at baseline < 150 mmHg and prescribed two or more
133 antihypertensive treatments for at least 12 months. Detailed inclusion and exclusion criteria are provided in
134 eTable 1. Recruiting primary care physicians were educated about the latest guidelines and evidence from
135 randomized clinical trials at the beginning of the trial as part of the study training. The generalizability of
136 these trials was discussed and they were asked to only enrol patients whom in their opinion might potentially
137 benefit from medication reduction due to existing polypharmacy, co-morbidity, non-adherence or dislike of
138 medicines and/or frailty. This clinical judgement was considered important given the current lack of
139 evidence as to who should be targeted for medication reduction. Patients with a history of heart failure due to
140 left ventricular dysfunction or myocardial infarction/stroke in the preceding 12 months, secondary
141 hypertension or lacking in capacity to consent were excluded. Participants were identified from searches of
142 electronic health records in participating sites and sent letters of invitation. Those expressing an interest
143 attended a screening appointment.

144

145 *Randomisation and masking*

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

150 (Sortition®). The first three participants were allocated using simple randomisation with subsequent
151 participants allocated with a probability at 0.8 to ensure balance across the groups.

152 Investigators and participants were unaware of treatment allocation prior to consent and baseline
153 assessments. The trial used an unblinded design with patients and investigators not masked to randomisation
154 group. Pre-specified statistical analyses were performed blind to participant allocation.

155

156 *Procedures*

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

168

169 Those allocated to control followed usual clinical care, where they continued to take all antihypertensive
170 medications as prescribed with no medication changes mandated. All participants were followed-up at 12
171 weeks. All data were collected by a research facilitator or nurse in clinics held at baseline, 4-week (safety –
172 intervention group only) and 12-week follow-up. Assessments of functional independence and cognitive
173 function were undertaken at baseline using the Modified Rankin scale¹⁷ and Montreal Cognitive Assessment
174 (MoCA)¹⁸ respectively. The ethnicity of each participant was recorded at baseline to better characterise the
175 sample population. Ethnicity was self-determined by the participant using a questionnaire containing
176 standard fixed ethnic categories.¹⁹ For analysis, those identifying as 'White British' or 'White other' were
177 classified as white, all others were classified as non-white / unknown.

178

179 *Outcome measures*

180 The primary outcome was the relative risk of systolic blood pressure control (<150 mmHg; defined by UK
181 National Institute for Health and Care Excellence as the target blood pressure for those aged over 80 years)
182 between groups at 12-week follow-up. Blood pressure was measured using the clinically validated BpTRU
183 blood pressure monitor.²⁰ Readings were taken in the left arm, using an appropriately sized cuff, after
184 participants had been seated for at least five minutes of rest. Systolic blood pressure was estimated from the
185 mean of the 2nd and 3rd readings.

186

187 All pre-specified secondary outcomes are reported in this article, with the exception of one to determine how
188 the baseline characteristics of the study population relate to those of previous trials^{3,4} (which will be reported
189 separately). Secondary outcomes were the proportion of participants in the intervention group who
190 maintained medication reduction and between-group differences in frailty, quality of life, adverse effects,
191 serious adverse events, and change in systolic and diastolic blood pressure over 12 weeks. Frailty was
192 defined using the Frailty index,²¹ the Electronic Frailty Index²² and the Morley FRAIL scale.²³ The Frailty
193 Index includes 54 items with values ranging from 0 (fit) to 1 (frail).²¹ The Electronic Frailty Index has 36
194 items and ranges between 0 (fit) to 1 (frail) and was estimated using data from electronic health records.²²
195 The Morley FRAIL scale has 5 components and the scale ranges from 0 (robust health) to 4 (frail) and was
196 captured via questionnaire.²³ Quality of life was measured using the EuroQoL 5 Dimensions 5 Levels
197 questionnaire (EQ-5D-5L).²⁴ Data from this questionnaire were analysed using the cross-walk approach
198 which translates the scores for the five EQ-5D-5L items into a single index value and visual analogue scale
199 (VAS) which has values between 0 (worst health) and 100 (best health).²⁴ Adverse effects to medication
200 were captured using the Revised Illness perception questionnaire for hypertension.²⁵ Adverse effects
201 included 24 symptoms and these were summed to give the number of symptoms reported. Serious adverse
202 events were defined as those resulting in death or considered life-threatening, required inpatient
203 hospitalization or prolonged existing hospitalization, resulted in persistent or significant disability/incapacity
204 or were classed as 'other medical events' considered to be serious because they put the participant at risk of
205 one of the above consequences or required intervention to prevent them from occurring.

206

207 Further post hoc outcomes were specified after viewing the initial results to better understand the effect of
208 the medication reduction intervention. These were mean difference in change in number of antihypertensive
209 medication prescriptions, the proportion of patients with no increase in systolic blood pressure during follow-
210 up, mean difference in health resource use (primary care consultations and hospital attendance) and
211 difference in adverse events (non-serious) during 12-week follow-up. To better understand any observed
212 differences in adverse events, each event was categorised by the treating clinician as to whether or not it was
213 possibly related to medication reduction and classified by the research team according to ICD-11 definitions
214 of disease.

215

216 *Statistical analysis*

217 A sample size of 540 participants was pre-specified for the trial, assuming that 100% of participants in the
218 usual care group, and 96% of those in the medication reduction group would have systolic blood pressure
219 <150 mmHg at 12-week follow-up. Calculations assumed a 0.90 non-inferiority margin, 90% power, 2.5% 1-
220 sided level of significance, 10% loss to follow-up and a 10% dilution effect due to cross-over between
221 groups. Due to the lack of evidence defining non-inferiority, the margin of 0.90 was chosen to inform future
222 physician-patient discussions about medication reduction: if non-inferiority was demonstrated, it would
223 suggest that for every ten patients who have their medication reduced, nine would still have controlled blood
224 pressure at 12 week follow-up.

225

226 The primary analysis population was defined as all participants for whom data were available and were
227 analysed according to the groups they were randomly allocated to, regardless of deviation from protocol. The
228 pre-specified analysis for the primary outcome planned a generalised linear mixed effects model with
229 baseline systolic blood pressure as a fixed effect and primary care site as a random effect. However, due to
230 convergence problems at the time of analysis, we omitted site from the model and fitted a robust Poisson
231 regression model adjusting for baseline systolic blood pressure. In addition, to account for missing data in
232 the analysis, a logistic regression model was used to explore associations between baseline characteristics
233 and availability of the primary outcome. Covariates found to be predictive of missingness were adjusted in
234 the primary analysis, including gender, MoCA Score, EQ-5D-5L Index and the Frailty Index. Six missing
235 baseline EQ-5D-5L and ten missing baseline EQ-5D VAS scores were replaced with the overall mean of

236 respective variables at baseline. Model diagnostics were checked and satisfied (eFigure 3). Non-inferiority
237 was assumed if the lower limit of the confidence interval around the adjusted relative risk (RR_{adjusted}) of
238 participants with controlled blood pressure was above 0.90. Adjusted risk differences (RD_{adjusted}) were also
239 calculated and reported, using robust Poisson model with identity link function.

240

241 Secondary analyses used descriptive statistics to examine the proportion of participants in the intervention
242 group who maintained medication reduction throughout the 12-week follow-up period (overall and by drug
243 class). Further analyses comparing the adjusted mean difference in change in blood pressure,
244 antihypertensive medications, quality of life (estimated from the EQ-5D-5L using the crosswalk value set),²⁶
245 frailty and health resource use at 12 weeks, were analysed by means of linear mixed effects models,
246 adjusting for the baseline level of the outcome and baseline systolic blood pressure, with primary care site
247 fitted as a random effect. The difference in adverse effects and serious adverse events between the
248 intervention and usual care groups was analysed using a robust Poisson model with adjustment for baseline
249 systolic blood pressure; site was not included in the model for the same reason as the analysis of the primary
250 outcome. Because of potential for type 1 error due to multiple comparisons, findings for analyses of
251 secondary endpoints should be interpreted as exploratory.

252

253 A per-protocol analysis of the primary outcome was performed, excluding patients from the intervention
254 group who did not reduce treatment or who had medication reinstated during follow-up (although this latter
255 action was part of the medication reduction protocol). A post hoc analysis of mean difference in change in
256 blood pressure between groups, corrected for baseline, was performed in the per-protocol population. Pre-
257 specified subgroup analyses of systolic blood pressure control, change in systolic blood pressure and
258 maintenance of medication reduction were conducted by different levels of baseline frailty, functional
259 independence, cognitive function, number of medications and number of co-morbidities. Each potential
260 moderator was dichotomised and an interaction term with treatment group was fitted to the primary and
261 secondary analysis models to obtain the P value for interaction. Post hoc subgroup analyses by baseline
262 systolic blood pressure were performed for the relative risk of systolic blood pressure control, maintenance
263 of medication reduction and mean difference in change in blood pressure at 12-week follow-up. Further post

264 hoc analyses examined the primary outcome (systolic blood pressure control) defined as <140 mmHg and
265 <130 mmHg.

266

267 Sensitivity analyses of the primary outcome were undertaken to examine missing data and outlying systolic
268 blood pressure values (see supplement 3). All data were analysed using Stata statistical software (version
269 15.1, College Station TSL, StataCorp, 2017). Significance thresholds were set at 5% (2-sided) for superiority
270 and 2.5% (1-sided) for non-inferiority.

271

272 **Results**

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

278

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

284

285 *Primary outcome*

286 Overall, 229 (86.4%) patients in the medication reduction group and 236 (87.7%) patients in the usual care
287 group had a systolic blood pressure of <150 mmHg at 12-week follow-up (RR_{adjusted} 0.98, 97.5% CI 0.92 to
288 ∞, Table 2). The 97.5% 1-sided confidence interval for this adjusted relative risk was greater than 0.9,
289 indicating that medication reduction was non-inferior to usual care. These findings were robust to sensitivity
290 analyses examining the effect of missing data and outlying blood pressure values (eTable 5). Results were
291 not materially different in the per-protocol population (Table 2).

292

293 *Secondary outcomes*

294 Medication reduction was maintained in 187 (66.3%) participants in the intervention group (eTable 6). Mean
295 systolic blood pressure at baseline was 129.4 (SD 13.4) mmHg in the intervention group and 130.5 (SD 12.3)
296 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
297 128.9 to 132.7) mmHg in the intervention and control groups respectively, meaning that the change in
298 systolic blood pressure at 12-weeks was 3.4 mmHg (95% CI 1.0 to 5.8 mmHg; table 3) higher in the
299 medication reduction group compared to usual care after correcting for baseline blood pressure. Mean
300 diastolic blood pressure at baseline was 68.4 (SD 9.1) mmHg in the intervention group and 70.1 (SD 8.4)
301 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
302 70.8) mmHg in the intervention and control groups respectively. The adjusted mean difference in change in
303 diastolic blood pressure corrected for baseline was 2.2 mmHg (95% CI 0.9 to 3.6 mmHg). There were no
304 statistically significant differences between groups in frailty, quality of life (Table 3), adverse effects or
305 serious adverse events at follow-up (Table 4).

306

307 *Subgroup analyses*

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

311

312 *Post hoc outcomes*

313 Three participants in the intervention group did not reduce medications whilst two increased treatment
314 (eTable 7). Participants in the medication reduction group were taking 0.6 fewer antihypertensive
315 medications than the usual care group at 12-week follow-up (Table 3). A total of 101 participants (38.1%,
316 95% CI 32.2% to 44.2%) in the medication reduction group had no increase in systolic blood pressure at 12-
317 week follow-up (34.5%, 95% CI 27.8% to 42.9% in the per-protocol population; eFigure 6). When analyses
318 were restricted to those patients who maintained medication reduction throughout follow-up (per-protocol
319 population), a greater increase in systolic and diastolic blood pressure was seen in the intervention group
320 (Table 3). There was no statistically significant difference in systolic blood pressure control or mean
321 difference in blood pressure by baseline systolic blood pressure level (eFigures 4 and 5). There was no

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

325

326 The number experiencing at least one adverse event was significantly higher in the medication reduction
327 group (RR_{adjusted} 1.28, 95% CI 1.06 to 1.54; Table 4). A total of 27% of adverse events were considered
328 “possibly related” to withdrawal of treatment. More adverse events related to the circulatory system were
329 reported in the medication reduction group, but this was not observed for serious cardiovascular events
330 (eTables 10 and 11). Participants in the medication reduction group attended significantly more healthcare
331 appointments during follow-up than the usual care group (eTable 12).

332

333 **Discussion**

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

340

341 In contrast to the present study, previous antihypertensive deprescribing trials have only attempted
342 medication reduction in between 32% to 68% of participants,²⁷⁻²⁹ had smaller sample sizes,^{27,28} examined
343 younger populations²⁹ and lacked comparisons with a control group to determine the effect of deprescribing
344 on outcomes.²⁷ Longer term studies do exist, but these are observational in nature and do not include a
345 control group for robust comparison of outcomes.³⁰ In all but one previous trial,²⁸ medication reduction was
346 part of a medication review but not specifically mandated and patients could have only been taking a single
347 antihypertensive at trial entry.^{27,29,31-33} Mandating medication reduction in this trial whilst ensuring all
348 participants continued some antihypertensive treatment may have reduced clinical inertia by the treating
349 physician compared to previous work.^{34,35}

350

351 The only other trial that has examined the effect of antihypertensive medication reduction on blood pressure
352 in older patients examined individuals prescribed fewer antihypertensives (61.5% vs 100% prescribed ≥ 2
353 medications) but with higher baseline blood pressure (148/81 vs 130/69mmHg).²⁸ Initial medication
354 reduction was achieved in 67.8% of participants but the number having therapy reinstated at 16 week follow-
355 up was not reported. Medication reduction in that trial resulted in a larger increase in systolic blood pressure
356 (7.4 mmHg in all patients available for analysis and 11.1 mmHg in the per-protocol population) than was
357 observed in the present study. This is likely due to the medication reduction algorithm employed in which
358 antihypertensive medications were iteratively stopped until a maximum increase in systolic blood pressure of
359 20 mmHg was reached.

360

361 Proponents of deprescribing suggest potential benefits could be an increased quality of life, reduced adverse
362 effects and a reversal of cognitive decline.^{15,28} However, these potential benefits might be expected to happen
363 over the longer term and are yet to be demonstrated in robust randomized clinical trials. This study was
364 unable to demonstrate short term benefits, but was not powered to detect significant differences in adverse
365 effects or quality of life. These should be studied in a longer term context.

366

367 This trial described a structured approach to antihypertensive medication reduction and provides evidence
368 relevant to routine clinical practice. It showed that antihypertensive medication reduction can be achieved (in
369 the short-term) in some patients with multi-morbidity and polypharmacy, who were selected by their primary
370 care physician to potentially benefit from medication reduction. Of those following the medication reduction
371 and monitoring algorithms, a similar proportion had systolic blood pressure < 150 mmHg at follow-up
372 compared to those not reducing medication, and two thirds were taking fewer antihypertensive medications
373 after 12 weeks. This resulted in participants in the medication reduction group taking 0.6 fewer
374 antihypertensives than those not reducing medication at follow-up. This reduction was modest and further
375 studies should explore whether greater medication reduction (i.e. removal of multiple medications) can be
376 achieved without affecting blood pressure control at follow-up.

377

378 Previous trials of blood pressure lowering in older adults (such as SPRINT and the Hypertension in the Very
379 Elderly Trial)^{3,4,36} do not represent frail patients with multi-morbidity who may be at higher risk of adverse

380 events from polypharmacy.^{6,7} As a result, there is divergence in international guidelines as to what is an
381 appropriate target for blood pressure in people over the age of 80. The UK National Institute for Health and
382 Care Excellence (updated in 2019)¹¹ and the US American College of Physicians/American Academy of
383 Family Physicians (2017)³⁷ define the threshold for systolic blood pressure control as <150 mmHg – the
384 threshold used in this study. In contrast, American Heart Association/American College of Cardiology
385 guidelines³⁸ now recommend a target of 130 mmHg (where tolerated), primarily based on the findings of the
386 SPRINT trial.^{4,36} What this trial has shown is that withdrawal of a blood pressure agent is associated with a
387 small rise in blood pressure in patients over the age of 80 with multi-morbidity, mild frailty, and/or
388 polypharmacy. The threshold at which such medication reduction is contemplated will depend upon the
389 guideline being used. Post hoc analyses of the current study suggested that lower thresholds for blood
390 pressure control would have resulted in worse control from drug withdrawal, presumably because primary
391 care physicians were less likely to reintroduce therapy at such lower thresholds because this was not
392 specified in the study protocol.

393

394 Although the population was generalizable to primary care, this trial did not establish whether or not
395 medication reduction should be attempted (in terms of clinical outcomes) or who should be targeted with
396 such an intervention. The 3.4/2.2 mmHg increase in blood pressure observed following medication reduction
397 suggests caution should be exercised when adopting this approach in routine clinical practice. Studies in
398 populations with less multi-morbidity have suggested that medication reduction might not result in an
399 increase in cardiovascular events provided blood pressure remains controlled, although this was attributed to
400 greater use of non-pharmacological interventions.³⁹ It is unclear whether an increased risk of cardiovascular
401 disease is as important in an older population where there are competing risks from other conditions.

402

403 Deprescribing of antihypertensive drugs (and other medications) is increasingly being promoted in clinical
404 guidelines^{13,14} and clinical care,¹⁵ despite a lack of robust evidence from randomized clinical trials. This
405 study is an important step to addressing this evidence gap and highlights the short term effects, which could
406 be important to informing decision making between patients and physicians considering antihypertensive
407 medication reduction. Future trials should explore the long term effects of medication reduction, particularly
408 focussing on frailer patients with multi-morbidity who have not been studied in previous trials.^{3,4,36}

409

410 *Limitations*

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

418

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

425

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

430

431 Fourth, thirteen participants in the usual care group reduced their antihypertensive medication during follow-
432 up. We did not robustly measure whether individuals were adherent to their remaining medications in either
433 group and this could have affected the proportion of participants with systolic blood pressure <150 mmHg at
434 follow-up.

435

436 Fifth, the decision to design the trial with a short period of follow-up (12 weeks) was made for ethical
437 reasons to demonstrate the short-term effects of medication reduction on blood pressure and adverse events

438 prior to embarking on a larger study with longer follow-up. This meant the study was underpowered to make
439 reliable comparisons of adverse events between groups and so the long-term benefits and harms of
440 antihypertensive medication reduction remain unknown.

441

442 *Conclusions*

443 Among older patients treated with multiple antihypertensive medications, a strategy of antihypertensive
444 medication reduction, compared with usual care, was non-inferior with regard to the proportion of patients
445 with systolic blood pressure <150 mmHg at 12 weeks. The findings suggest antihypertensive medication
446 reduction can be achieved without substantial change in blood pressure control in some older patients with
447 hypertension, although further research is needed to understand long-term clinical outcomes.

448 **Contributors**

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

453

454 **Declaration of interests**

455 The authors declare no conflicts of interest.

456

457 **Ethics and approvals**

458 The study was approved by an NHS Research Ethics Committee (South Central - Oxford A; ref 16/SC/0628)
459 and the Medicines and Healthcare products Regulatory Agency (MHRA; ref 21584/0371/001-0001). All
460 participants gave written informed consent.

461

462 **Data Sharing Statement**

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

465

466 **Access to Data and Data Analysis**

467 JS and RJMcM had full access to all the data in the study and take responsibility for the integrity of the data
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- 652

653 **Figure legends**

654

655 **Figure 1.** Recruitment, randomization, and analysis population

656

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

661 ^b Participants were allocated to one of the two study groups using a non-deterministic minimisation
662 algorithm, minimised for site and baseline SBP. The first three participants were allocated using simple
663 randomisation with subsequent participants allocated with a probability at 0.8 to ensure balance across the
664 groups

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

668 ^d Reasons for death were ischemic stroke and cardiac arrest.

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)

671 ^a Ethnic group was defined according to participant's self-reported ethnicity, using Office for National Statistics
672 categories.¹⁹ Those identifying as 'White British' or 'White other' were classified as white, all others were classified as
673 non-white / unknown.

674 ^b Most recently recorded reading from electronic health records.

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

677 ^d The EQ-5D-5L assesses five aspects of health: mobility, self-care, activities, discomfort, and anxiety / depression. EQ-
678 5D-5L index scores were generated using crosswalk approach which translates the scores for the five EQ-5D-5L items
679 into a single index value. The index value ranges from -0.594 (worse than death) to 1 (full health).

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

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

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

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

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

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

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

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

694 SD=standard deviation.

695 **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

696 ^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).
697 ^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.
698 ^c P-value for non-inferiority for adjusted relative risk.
699 ^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.
700 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-
701 six of these 80 participants had medications reinstated during follow-up based on the study safety monitoring algorithm (eFigure 2).

702 **Table 3.** Secondary outcomes at 12 weeks

	Medication reduction group		Usual care group		Adjusted mean difference (95% CI)	P Value ^b
	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

703 ^a Analyses conducted in the primary analysis population (all available participants), unless otherwise stated.

704 ^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
705 13) with a random effect for primary care site.

706 ^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
707 missingness, eTable 13) with a random effect for primary care site.

708 ^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
709 were replaced with the overall mean of the covariate at baseline.

710 ^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).

711 ^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
712 followed up face-to-face at 12 weeks.

713 ^gThe 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
714 algorithm (although this latter action was part of the medication reduction protocol).
715 ^h P-values are given for superiority, in contrast to Table 2, where they are given for non-inferiority.
716 PP=Per-protocol; SD=standard deviation.

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

	Medication reduction group	Usual care group	Adjusted risk difference¹ (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 (%) ^c	12 (4.3%)	7 (2.4%)	1.6% (-1.3% to 4.5%)	1.72 (0.68 to 4.29)

718 ^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
719 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.

720 ^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
721 number of participants completing this questionnaire at follow-up.

722 ° 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
723 physician and did not result in hospitalisation or death.
724 ^d Post hoc outcome not included in protocol or statistical analysis plan and specified after seeing initial results.
725 ° 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
726 hospitalisation or prolonged existing hospitalisation, resulted in persistent or significant disability/incapacity or ‘other medical events’ considered to be serious because they
727 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),
728 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
729 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
730 (0,1).
731 IQR = Interquartile range.