

## 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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21

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34

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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  $\geq 80$  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  $\geq 80$  years with systolic blood pressure  $< 150$  mmHg and receiving  $\geq 2$   
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  $\infty$ ). 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 disease<sup>1</sup> and the most common  
94 co-morbid condition in older people with multi-morbidity.<sup>2</sup> Antihypertensive treatment has been shown to be  
95 effective at preventing stroke and cardiovascular disease in older high-risk patients<sup>3,4</sup> and approximately half  
96 of individuals aged 80 years or older are prescribed therapy.<sup>5</sup> However, previous trials such as the Systolic  
97 blood PResure INTervention (SPRINT)<sup>4</sup> trial have been shown to represent as few as one third of older  
98 individuals<sup>6</sup> and there is debate about the extent to which these data should be applied to frail patients with  
99 multi-morbidity.<sup>7</sup> 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.<sup>8-10</sup>

102

103 Guidelines recommend using clinical judgement when prescribing in frail older patients,<sup>11,12</sup> emphasising a  
104 personalised approach to care which might include attempts to improve quality of life through  
105 deprescribing.<sup>13-15</sup> 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.<sup>14</sup>

107

108 Very few randomized clinical trials have considered the safety and efficacy of antihypertensive medication  
109 reduction in routine clinical practice.<sup>15</sup> In older patients with multi-morbidity and controlled blood pressure  
110 (<150/90 mmHg), there are advantages and disadvantages to continuing treatment.<sup>8-10</sup> 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.<sup>16</sup>

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  $\geq 80$  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 scale<sup>17</sup> and Montreal Cognitive Assessment  
174 (MoCA)<sup>18</sup> 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.<sup>19</sup> 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.<sup>20</sup> 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 2<sup>nd</sup> and 3<sup>rd</sup> 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<sup>3,4</sup> (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,<sup>21</sup> the Electronic Frailty Index<sup>22</sup> and the Morley FRAIL scale.<sup>23</sup> The Frailty  
193 Index includes 54 items with values ranging from 0 (fit) to 1 (frail).<sup>21</sup> 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.<sup>22</sup>  
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.<sup>23</sup> Quality of life was measured using the EuroQoL 5 Dimensions 5 Levels  
197 questionnaire (EQ-5D-5L).<sup>24</sup> 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).<sup>24</sup> Adverse effects to medication  
200 were captured using the Revised Illness perception questionnaire for hypertension.<sup>25</sup> 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),<sup>26</sup>  
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 20<sup>th</sup> March 2017  
274 and 30<sup>th</sup> 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 9<sup>th</sup>  
281 January 2019 and the study database was locked on 23<sup>rd</sup> 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<sub>adjusted</sub> 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<sub>adjusted</sub> 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,<sup>27-29</sup> had smaller sample sizes,<sup>27,28</sup> examined  
343 younger populations<sup>29</sup> and lacked comparisons with a control group to determine the effect of deprescribing  
344 on outcomes.<sup>27</sup> Longer term studies do exist, but these are observational in nature and do not include a  
345 control group for robust comparison of outcomes.<sup>30</sup> In all but one previous trial,<sup>28</sup> 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.<sup>27,29,31-33</sup> 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.<sup>34,35</sup>

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  $\geq 2$   
353 medications) but with higher baseline blood pressure (148/81 vs 130/69mmHg).<sup>28</sup> 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.<sup>15,28</sup> 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)<sup>3,4,36</sup> do not represent frail patients with multi-morbidity who may be at higher risk of adverse

380 events from polypharmacy.<sup>6,7</sup> 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)<sup>11</sup> and the US American College of Physicians/American Academy of  
383 Family Physicians (2017)<sup>37</sup> 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 guidelines<sup>38</sup> now recommend a target of 130 mmHg (where tolerated), primarily based on the findings of the  
386 SPRINT trial.<sup>4,36</sup> 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.<sup>39</sup> 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<sup>13,14</sup> and clinical care,<sup>15</sup> 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.<sup>3,4,36</sup>

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)  
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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 <sup>a</sup>Participants were required to be aged  $\geq 80$  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 <sup>b</sup>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 <sup>c</sup>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 <sup>d</sup>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 <sup>2</sup> )	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 <sup>a</sup>		
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), <sup>b</sup> (mmol/l)	4.6 (1.2)	4.6 (1.2)
Estimated eGFR	n=241	n=252
Mean (SD), <sup>c</sup> (ml/min per 1.73 m <sup>2</sup> )	61.6 (14.9)	60.4 (14.2)
Montreal Cognitive Assessment score <sup>b</sup>	n=280	n=282
Mean (SD)	24.4 (3.6)	24.0 (4.1)
EQ-5D-5L index <sup>d</sup>	n=279	n=284
Mean (SD)	0.78 (0.17)	0.76 (0.17)
Modified Rankin Scale <sup>e</sup>	n=267	n=273
Score >2, (dependant), (%)	36 (12.8%)	42 (14.6%)
<b>Frailty</b>		
Morley FRAIL scale, <sup>f</sup> 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, <sup>g</sup> mean (SD)	0.14 (0.07)	0.15 (0.07)
Electronic Frailty index (eFI), <sup>h</sup> 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%)
<b>Blood pressure</b>		
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 (%) <sup>i</sup>	n=264	n=261
N (%)	15 (5.3%)	10 (3.5%)
<b>Medical history<sup>j</sup></b>		
Chronic Kidney Disease (%)	83 (29.4%)	103 (35.9%)

Cancer (%)	67 (23.8%)	68 (23.7%)
Cardiac Disease (%) <sup>k</sup>	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) <sup>j</sup>	5.7 (2.7)	6.0 (2.9)
% $\geq 2$ morbidities (%) <sup>j</sup>	278 (98.6%)	282 (98.3%)
<b>Medication prescriptions</b>		
Antihypertensive (%)	282 (100.0%)	287 (100.0%)
ACE inhibitor / Angiotensin II receptor blocker (%) <sup>l</sup>	238 (84.4%)	243 (84.7%)
Calcium channel blockers (%) <sup>l</sup>	199 (70.6%)	191 (66.6%)
Beta blockers (%) <sup>l</sup>	112 (39.7%)	116 (40.4%)
Thiazide & related diuretics (%) <sup>l</sup>	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 <sup>a</sup> Ethnic group was defined according to participant's self-reported ethnicity, using Office for National Statistics  
672 categories.<sup>19</sup> Those identifying as 'White British' or 'White other' were classified as white, all others were classified as  
673 non-white / unknown.

674 <sup>b</sup> Most recently recorded reading from electronic health records.

675 <sup>c</sup> 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 <sup>d</sup> 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 <sup>e</sup> Modified Rankin scale ranges from 0 (no symptoms) to 5 (severe disability).

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

683 <sup>g</sup> The Frailty index includes 54 items and ranges from 0 (fit) to 1 (frail).

684 <sup>h</sup> 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 <sup>i</sup> Orthostatic hypotension defined as a decrease in systolic blood pressure of  $\geq 20$  mmHg within 3 minutes of standing.<sup>40</sup>

687 <sup>j</sup> 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 <sup>k</sup> Cardiac disease defined as the presence of myocardial infarction, coronary heart disease, angina or heart failure.

692 <sup>l</sup> 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

	<b>Medication reduction group</b>	<b>Usual care group</b>	<b>Unadjusted risk difference (97.5% 1-sided CI)</b>	<b>Adjusted risk difference<sup>a</sup> (97.5% 1-sided CI)</b>	<b>Unadjusted relative risk<sup>b</sup> (97.5% 1-sided CI)</b>	<b>Adjusted relative risk<sup>a,b</sup> (97.5% 1-sided CI)</b>	<b>P-value<sup>c</sup></b>
<b>Primary analysis</b>	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
<b>Per protocol analysis<sup>d</sup></b>	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 <sup>a</sup> 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 <sup>b</sup> 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 <sup>c</sup> P-value for non-inferiority for adjusted relative risk.  
699 <sup>d</sup> 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 <sup>b</sup>
	Number analysed	Mean (95% CI)	Number analysed	Mean (95% CI)		
<b>Blood pressure<sup>a</sup></b>						
Systolic (mmHg) <sup>b</sup>	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) <sup>c</sup>	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
<b>Quality of life at 12 weeks<sup>d,e</sup></b>						
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
<b>Frailty at 12 weeks<sup>d,e</sup></b>						
Frailty index	282 <sup>f</sup>	0.137 (0.130 to 0.145)	287 <sup>f</sup>	0.145 (0.136 to 0.152)	-0.00003 (-0.005 to 0.005)	0.77
Electronic frailty index	278 <sup>f</sup>	0.134 (0.126 to 0.141)	285 <sup>f</sup>	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
<b>Post hoc outcomes</b>						
Systolic blood pressure (PP analysis, mmHg) <sup>b,g</sup>	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) <sup>c,g</sup>	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 <sup>f</sup>	-0.68 (-0.74 to -0.61)	283 <sup>f</sup>	-0.05 (-0.08 to -0.01)	-0.63 (-0.70 to -0.56)	<0.001

703 <sup>a</sup> Analyses conducted in the primary analysis population (all available participants), unless otherwise stated.

704 <sup>b</sup> 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 <sup>c</sup> 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 <sup>d</sup> 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 <sup>e</sup> 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 <sup>f</sup> 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 <sup>g</sup>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  
714 algorithm (although this latter action was part of the medication reduction protocol).  
715 <sup>h</sup> 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

	<b>Medication reduction group</b>	<b>Usual care group</b>	<b>Adjusted risk difference<sup>1</sup> (95% CI)</b>	<b>Adjusted risk ratio<sup>a</sup> (95% CI)</b>
<b>Adverse effects<sup>b</sup></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)		
<b>Adverse events<sup>c</sup></b>	n=282	n=287		
At least 1 reported adverse event (%) <sup>c,d</sup>	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 (%) <sup>c</sup>	12 (4.3%)	7 (2.4%)	1.6% (-1.3% to 4.5%)	1.72 (0.68 to 4.29)

718 <sup>a</sup> 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 <sup>b</sup> Ten most commonly reported adverse effects listed as measured by the Revised Illness Perception Questionnaire for Hypertension.<sup>25</sup> 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 <sup>d</sup> 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.