

## Cost-effectiveness of antihypertensive deprescribing in primary care

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DOI:

[10.1161/HYPERTENSIONAHA.121.18726](https://doi.org/10.1161/HYPERTENSIONAHA.121.18726)

### Document Version

Peer reviewed version

### Citation for published version (Harvard):

Jowett, S, Kodabuckus, S, Ford, GA, Hobbs, R, Lown, M, Mant, J, Payne, R, McManus, R, Sheppard, J & OPTiMISE investigators 2022, 'Cost-effectiveness of antihypertensive deprescribing in primary care: a Markov modelling study using data from the OPTiMISE trial', *Hypertension*, vol. 79, no. 5, pp. 1122-1131. <https://doi.org/10.1161/HYPERTENSIONAHA.121.18726>

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1 **Cost-effectiveness of antihypertensive deprescribing in primary care: a Markov**  
2 **modelling study using data from the OPTiMISE trial**

3

4 **Running title:** Cost-effectiveness of antihypertensive deprescribing

5

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## OPTiMISE Economic Evaluation

- 26 **Word count:** 6,541 (max 6,000)
- 27 **Tables:** 3
- 28 **Figures:** 2
- 29 **References:** 54

30 **Abstract**

31 **Background:** Deprescribing of antihypertensive medications for older patients with normal  
32 blood pressure is recommended by some clinical guidelines, where the potential harms of  
33 treatment may outweigh the benefits. This study aimed to assess the cost-effectiveness of this  
34 approach.

35 **Methods:** A Markov patient-level simulation was undertaken to model the effect of  
36 withdrawing one antihypertensive compared to usual care, over a life-time horizon. Model  
37 population characteristics were estimated using data from the OPTiMISE antihypertensive  
38 deprescribing trial and the effects of blood pressure changes on outcomes were derived from  
39 the literature. Health-related quality of life was modelled in Quality-Adjusted Life Years  
40 (QALYs) and presented as costs per QALY gained.

41 **Results:** In the base-case analysis, medication reduction resulted in lower costs than usual  
42 care (mean difference £185), but also lower QALYs (mean difference 0.062) per patient over  
43 a life-time horizon. Usual care was cost-effective at £2,975 per QALY gained (more costly,  
44 but more effective). Medication reduction resulted more heart failure and stroke/TIA events  
45 but fewer adverse events. Medication reduction may be the preferred strategy at a  
46 willingness-to-pay of £20,000/QALY, where the baseline absolute risk of serious drug-  
47 related adverse events was  $\geq 7.7\%$  a year (compared to 1.7% in the base-case).

48 **Conclusions:** Although there was uncertainty around many of the assumptions underpinning  
49 this model, these findings suggest that antihypertensive medication reduction should not be  
50 attempted in many older patients with controlled systolic blood pressure. For populations at  
51 high risk of adverse effects, deprescribing may be beneficial, but a targeted approach would  
52 be required in routine practice.

53

54 **Word count:** 250 (250 max)

- 55 **Key words:** blood pressure; medication withdrawal, hypertension, older adults, general  
56 practice; cost utility analysis

57 **Introduction**

58 Hypertension is the leading risk factor for cardiovascular disease,<sup>1</sup> the commonest cause of  
59 morbidity and mortality worldwide.<sup>2</sup> Antihypertensive treatment has been shown to be very  
60 effective at preventing cardiovascular disease (CVD) across many different populations,  
61 including those with advancing age.<sup>3, 4</sup> However, most randomised controlled trials focusing  
62 on older people<sup>5, 6</sup> do not include those patients with significant frailty and multi-morbidity  
63 who are prescribed many medications to treat their conditions.<sup>7</sup> As a result, clinical  
64 guidelines<sup>8, 9</sup> recommend caution when prescribing antihypertensive treatment in these older  
65 adults, due to a lack of evidence on efficacy and concerns about the potential for drug related  
66 harm.<sup>10</sup>

67  
68 Increasingly, deprescribing of antihypertensive medications is being encouraged in patients  
69 with controlled blood pressure,<sup>11, 12</sup> where the potential harms of treatment<sup>10</sup> may outweigh  
70 the benefits. It is also seen as a mechanism to reduce polypharmacy, since the most common  
71 co-morbidity in older people is hypertension<sup>13</sup> and most patients will need multiple  
72 antihypertensive medications to control their blood pressure.<sup>14</sup> Indeed, it has been suggested  
73 that ‘deprescribing’ treatment prescriptions which no longer provide benefit could be cost-  
74 saving for healthcare providers.<sup>15</sup> However, there is very little evidence to support the  
75 practice of deprescribing antihypertensives.<sup>16</sup>

76  
77 The OPTimising Treatment for MIld Systolic hypertension in the Elderly (OPTiMISE) trial  
78 sought to address this evidence gap through a randomised, open label, non-inferiority trial of  
79 antihypertensive deprescribing (withdrawal of one antihypertensive) versus usual care.<sup>17</sup> In  
80 569 participants aged 80 years or older, antihypertensive deprescribing was shown to be  
81 possible with no difference in the proportion of participants with controlled systolic blood

82 pressure (<150 mmHg) between groups at 12-week follow-up. There were also no differences  
83 in serious adverse events or health-related quality of life, although blood pressure did  
84 increase modestly (3/2 mmHg) in the deprescribing group.<sup>17</sup> Whilst this trial suggested that  
85 antihypertensive deprescribing was safe in the short-term, the long-term impacts on clinical  
86 outcomes remain unknown, as do the cost implications of this strategy if it were to be  
87 adopted in routine clinical practice.

88

89 The present study aimed to extrapolate results from the OPTiMISE trial to assess the longer-  
90 term cost-effectiveness of antihypertensive deprescribing from a National Health Service  
91 (NHS)/Personal Social Services (PSS) perspective, using a Markov model with individual  
92 patient level simulation.

93

## 94 **Methods**

### 95 *Study design*

96 A Markov patient-level simulation was undertaken in TreeAge 2019 (TreeAge Software, Inc.,  
97 Williamstown, MA, USA) to model the two treatment strategies (usual care and withdrawal  
98 of one antihypertensive agent). This type of Markov model tracks the costs and consequences  
99 of individual patients passing through the model, with characteristics (taken from OPTiMISE  
100 patient-level data)<sup>17</sup> free to vary between patients. The model was run over a life-time  
101 (maximum of 20 years) time horizon to capture all relevant long-term costs and  
102 consequences, with a three month time cycle.

103

### 104 *Patient level data collection*

105 Full details of the OPTiMISE trial have been published elsewhere.<sup>17, 18</sup> Briefly, this was a  
106 randomised controlled trial assessing a strategy of antihypertensive medication reduction

107 (withdrawal of one drug) compared with usual care where no medication changes were  
108 mandated. Eligible patients were aged  $\geq 80$  years with systolic blood pressure  $< 150$  mmHg  
109 and receiving  $\geq 2$  antihypertensive medications, whose primary care physician considered  
110 them appropriate for medication reduction due to increasing frailty and/or multi-morbidity.

111

112 The primary outcome of the trial was to determine whether a reduction in medication could  
113 be achieved with a proportion of participants maintaining clinically safe blood pressure levels  
114 (defined as a systolic blood pressure  $< 150$  mmHg) that was non-inferior to that achieved by  
115 the usual care group, over 12-weeks follow-up. Data were collected on prescribed  
116 antihypertensives, quality of life (EQ-5D-5L), number of cardiovascular comorbidities and all  
117 variables required for the calculation of 10-year cardiovascular risk using the QRisk2  
118 algorithm.<sup>19</sup>

119

#### 120 *Study population*

121 Patients in the model had characteristics (age, sex, cardiovascular risk) created by randomly  
122 sampling the trial patient-level data by means of a uniform distribution. These characteristics  
123 affected their probability of subsequent model events. The model was run with a large  
124 number of simulated patients (100,000) to account for inter-patient variability and to  
125 adequately model a representative clinical population.

126

#### 127 *Model comparators and costs*

128 In keeping with the original trial intervention, patients receiving the medication reduction  
129 strategy had a 4-week follow-up safety appointment and treatment was reinstated if systolic  
130 blood pressure was found to be above 150 mmHg for more than one week, adverse events  
131 occurred or signs of accelerated hypertension developed. Both strategies included the cost of

132 ongoing primary care consultations (assumed to be an average of 0.8 per 3 months [included  
133 regardless of whether or not they were related to hypertension management)<sup>20</sup> and  
134 antihypertensive prescriptions (eTable 1). The medication reduction strategy also included  
135 the cost of the 4-week safety appointment, and an additional visit if treatment was reinstated.  
136 Costs of modelled clinical events (detailed in the Model Structure) including initial acute care  
137 costs and long-term care were obtained from previously published work, expert opinion and  
138 standard reference costs (eTable 1). Costs are reported in 2017/2018 prices (reflecting the  
139 trial timeframe) and inflated where applicable using the New Health Services Index.<sup>21</sup>

140

#### 141 *Model Structure and Assumptions*

142 Within each 3-month time cycle, a patient had a risk of suffering a cardiovascular event, an  
143 antihypertensive-related serious or minor adverse event, or death (eFigure 1). Possible  
144 cardiovascular events were coronary heart disease (stable angina, acute coronary syndrome,  
145 myocardial infarction), heart failure, stroke and transient ischemic attack (TIA).  
146 Antihypertensive-related adverse events were acute kidney injury, hospitalised and non-  
147 hospitalised falls, hypotension, syncope, bradycardia and electrolyte imbalance. Ten-year  
148 cardiovascular risk was calculated for each individual patient using the QRisk2 algorithm.<sup>19</sup>  
149 In the absence of robust published estimates in this older population, an assumption of greater  
150 CVD risk was applied to those with CVD conditions by applying a multiplier of 1.5, based on  
151 expert clinical opinion. The distribution of coronary heart disease and stroke/TIA events was  
152 dependent on age and gender<sup>22</sup> and heart failure risk was dependent on age.<sup>23</sup> The risk of  
153 minor and serious adverse events (serious falls, acute kidney injury) from antihypertensive  
154 treatment were obtained from SPRINT data in those aged 75 and over (table 1).<sup>24</sup>

155

156 Patients who suffered a non-fatal cardiovascular event or serious antihypertensive-related  
157 adverse event transitioned to a post-event health state with an adjusted mortality risk.  
158 Additional clinical events or medication changes were not modelled.

159

160 The impact of changes in blood pressure was taken from a meta-analysis of blood pressure  
161 lowering trials, focussing on patients aged over 80 (table 1).<sup>4</sup> These were applied as a relative  
162 risk, taking into account the mean difference in systolic blood pressure observed in the  
163 OPTiMISE trial (3.4 mmHg higher in the intervention group),<sup>17</sup> using log-linear  
164 interpolation. In the base-case analysis, it was assumed that the 12 week differences were  
165 maintained over the patient life-time. A half-cycle correction was applied to model costs and  
166 outcomes. Future costs and outcomes were discounted at an annual rate of 3.5% as  
167 recommended by NICE.<sup>25</sup> All model assumptions are summarised in eTable 2.

168

#### 169 *Model Outcomes*

170 Health-related quality of life outcomes were modelled in Quality-Adjusted Life Years  
171 (QALYs), taking into account quality of life and survival. Utility scores for health states are  
172 detailed in table 1. Initial quality of life was estimated as the overall mean EQ-5D-5L index<sup>26</sup>  
173 at baseline taken from the OPTiMISE trial,<sup>17</sup> calculated using the NICE-recommended  
174 crosswalk algorithm.<sup>27</sup> Utility values for long-term CVD events and serious adverse effects of  
175 treatment were applied multiplicatively to baseline utility scores. Disutilities for TIA and  
176 minor side effects were assumed to last for one month and were subtracted from utility scores  
177 for one time cycle. Utility decrements for acute kidney injury were applied every 3 months  
178 for life. Gender-specific life tables were used to determine the probability of death at  
179 different ages, with adjustment to avoid double counting of circulatory deaths.<sup>28,29</sup>

180

181 *Analysis*

182 A cost-utility analysis from an National Health Service/Personal Social Services perspective  
183 was undertaken to estimate Incremental Cost-Effectiveness Ratios (ICERs). An ICER was  
184 calculated as the difference in costs divided by the difference in QALYs of two strategies,  
185 with results presented as cost per QALY gained. The cost-effectiveness of an intervention  
186 was considered in relation to the lower NICE threshold of £20,000 per QALY.<sup>30</sup> Probabilistic  
187 Sensitivity Analysis (PSA) was undertaken to assess parameter uncertainty.<sup>31</sup> Beta  
188 distributions were attached to probabilities and utilities, and gamma distributions were  
189 attached to costs. Log normal distributions were used for the relative risks associated with the  
190 change in systolic blood pressure from the intervention and mortality. The model was run for  
191 1,000 iterations across 100,000 patients and the results are expressed as a Cost-Effectiveness  
192 Acceptability Curve (CEAC).<sup>32</sup> Additional analysis was undertaken to estimate the number of  
193 disease events in each category per 100,000 patients.

194

195 *Deterministic Sensitivity Analyses*

196 Analyses to evaluate the impact of changing model assumptions and values were undertaken  
197 to assess model robustness.<sup>31</sup> Whilst all parameter values were tested, focus was placed on  
198 areas of greatest uncertainty (in the underlying data), which could have the largest impact on  
199 the study results. The following scenarios were explored:

200 1. Threshold analyses examining:

- 201 • the minimum baseline risk of serious adverse events required for usual care to exceed  
202 the £20,000/QALY threshold for cost-effectiveness.
- 203 • the minimum additional ‘utility’ required to result in quality of life improvements in  
204 those patients reducing medications.

205 2. Sensitivity analyses examining:

- 206       • alternative values for the relative risk of cardiovascular and medication-related  
207       adverse events (using the upper and lower 95% confidence intervals [table 1] or a  
208       relative risk of 1).
- 209       • the effect of halving the risk of all cardiovascular events.
- 210       • using the lower 95% confidence interval of the increase in systolic blood pressure  
211       with the intervention (1 mm Hg).
- 212       • the effect of reducing the length of time the difference in blood pressure is sustained  
213       (ranging from 1 year to 10 years).
- 214       • the effect of reducing the time horizon to 5 years.
- 215    3. Sub-group analyses examining the results by level of frailty<sup>33</sup> (fit or frail) and number of  
216       cardiovascular disease co-morbidities at baseline (none, 1, 2+).

217

## 218 **Results**

### 219 *Cost-effectiveness of medication reduction*

220 In the base-case analysis, medication reduction resulted in lower costs than usual care (mean  
221 difference £185), but also lower QALYs (mean difference 0.062) per patient over a life-time  
222 time horizon (table 2). The Incremental Cost-Effectiveness Ratio (ICER) for usual care was  
223 £2,975 per QALY gained (more costly, but more effective), meaning that usual care was  
224 highly cost-effective at the £20,000/QALY threshold. The probabilistic sensitivity analyses  
225 showed that usual care was the most cost-effective option in 99.0% of iterations at the  
226 £20,000/QALY threshold, and 99.7% at £30,000/QALY, with almost all replications of the  
227 model in the western half of the plane (fewer QALYs for medication reduction; figures 1 and  
228 2).

229

230 Medication reduction was estimated to result in an increase in the number of heart failure,  
231 stroke and TIA events, with between 684-2,739 events occurring per 100,000 population  
232 over the life-time (20 year) time horizon (table 3). However, medication reduction was  
233 associated with fewer adverse events and coronary heart disease events (due to competing  
234 risks where patients were more likely to die before experiencing a CHD event) (table 3).

235

### 236 *Sensitivity analyses*

237 Using a willingness-to-pay of £20,000/QALY in the threshold analyses, medication reduction  
238 may be the preferred strategy (as the ICER for usual care exceeds £20,000/QALY), where the  
239 baseline absolute risk of serious drug-related adverse events was greater than 7.7% a year for  
240 each individual in the model (compared with the base-case value of 1.7%; table 2).

241 Additional threshold analyses demonstrated that patients had to gain more than 0.017 of  
242 utility per year from having their medication reduced (compared with the base-case value of  
243 0) for this intervention to become the preferred strategy (table 2). Both analyses assume that  
244 decision makers are willing to forgo small QALY gains in order to reduce costs.

245

246 Assuming medication reduction conferred no additional risk (RR=1) for cardiovascular  
247 disease simultaneously resulted in usual care no longer being cost-effective, with an ICER of  
248 £178,631 per QALY (eTable 3). Usual care was still cost-effective when applying the upper  
249 and lower 95% confidence intervals of the relative risks of cardiovascular events. Applying  
250 the same approach for the adverse events did not change the findings of the primary analysis  
251 and in some cases usual care became dominant (eTable 3).

252

253 When the model time horizon was reduced to 5 years, maintaining antihypertensive  
254 prescription (usual care) remained cost-effective. The results were also robust when reducing

255 the timeframe of the effect of the intervention (in terms of increased blood pressure) from  
256 life-time to 1 year through to 10 years, halving absolute cardiovascular risk, and when using  
257 the lower 95% confidence interval of the observed systolic blood pressure change (eTable 4).  
258 Usual care was also estimated to be cost-effective in subgroup analyses by frailty and number  
259 of cardiovascular conditions present at baseline (eTable 5). Sensitivity analysis examining the  
260 remaining parameter values had no effect on the model findings.

261

## 262 **Discussion**

### 263 *Main findings*

264 The primary finding of this study was that usual care, compared with antihypertensive  
265 deprescribing, was more expensive (due to higher medication costs) but results in more  
266 QALYs, and has an ICER of £2,975 per QALY. This indicates that usual care of continuation  
267 of antihypertensive drugs is highly cost-effective compared to deprescribing. The lower  
268 QALYs associated with the antihypertensive deprescribing strategy occurred due to a  
269 projected increase in cardiovascular events (particularly heart failure) caused by a modest  
270 sustained increase in systolic blood pressure. Antihypertensive deprescribing was only the  
271 preferred strategy when patients were assumed to have a high baseline risk of serious adverse  
272 events (e.g. were at high risk of falling or experiencing acute kidney injury in the next year).

273

274 Many of the model inputs had considerable uncertainty or required assumptions to be made,  
275 due to a lack of evidence in this older population. Based on currently available data, these  
276 findings suggest that antihypertensive medication reduction should not be attempted in most  
277 older patients with controlled systolic blood pressure. In some specific populations at  
278 particularly high risk of adverse drug events, antihypertensive deprescribing may carry some

279 benefits so a targeted approach may be needed if deprescribing is to be adopted in routine  
280 clinical practice.

281

282 *Strengths and weaknesses*

283 The present analyses were informed by robust data from a pragmatic randomised controlled  
284 trial comparing antihypertensive deprescribing with usual care in a primary care setting.

285 Participants recruited to this trial were representative of the general population aged 80 years  
286 and older registered at practices in primary care.<sup>17</sup> This trial was limited to just 12 weeks of

287 follow-up, meaning that the long-term effects of antihypertensive deprescribing had to be

288 modelled on the basis of observed differences in blood pressure. For the base case analysis,

289 such differences were assumed to be sustained over a lifetime which may not reflect

290 experience in routine practice, although sensitivity analyses shortening the period in which a

291 blood pressure difference existed from 1-10 years did not affect the primary findings of the

292 analysis. This short period of follow-up in the trial meant that estimates of treatment safety

293 and efficacy had to be taken from previous treatment *intensification* trials which are likely

294 (and by design of OPTiMISE) to have recruited a different population to that considered for

295 *deprescribing*.<sup>7, 10</sup> Estimates of cardiovascular disease risk (which drove the observed

296 differences in QALYs) were based on the best available cardiovascular risk score (QRISK2),

297 which was not developed or validated for individuals aged 85 years or older.<sup>19</sup> Also, whilst

298 the OPTiMISE trial recruited a population of patients similar to the general older population

299 in primary care,<sup>7</sup> based on the sample size of the trial there may be some uncertainty around

300 some of the parameters included in the model such as age and baseline cardiovascular risk.

301 Changing these values in a sensitivity analysis did not alter the primary findings.

302

303 Ninety-eight percent of OPTiMISE trial participants were living with multiple long-term  
304 conditions which could carry competing risks eclipsing future cardiovascular disease events.  
305 These could not be taken into account in the present analysis due to a lack of evidence. The  
306 present model was complex, requiring a number of assumptions related to the risk of CVD  
307 and adverse events for which there is little evidence in this population. This meant it was not  
308 possible to add further complexity relating to treatment changes following cardiovascular  
309 events, terminal care costs or the impact of recurring events which often occur in real world  
310 practice. Such uncertainty, and reliance on data from antihypertensive *intensification* trials  
311 may have favoured cost-effectiveness of the usual care strategy.

312

### 313 *Findings in the context of existing literature*

314 To our knowledge, this is the first study to examine the cost-effectiveness of antihypertensive  
315 deprescribing in older adults aged 80 years and above. Indeed, few studies have examined the  
316 cost-effectiveness of deprescribing of any medication classes in routine clinical practice.<sup>34, 35</sup>  
317 Two analyses based on data from the Developing Pharmacist-Led Research to Educate and  
318 Sensitize Community Residents to the Inappropriate Prescriptions Burden in the Elderly (D-  
319 PRESCRIBE) trial<sup>36</sup> examined the cost-effectiveness of nonsteroidal anti-inflammatory drugs  
320 (NSAID)<sup>34</sup> and sedatives.<sup>35</sup> In contrast to the present analyses, these studies found  
321 deprescribing of these medications to be a cost-effective intervention, both in terms of saving  
322 money and increasing health related quality of life. Although our analysis found  
323 antihypertensive deprescribing to be cost saving too, it is possible that the disutility from  
324 adverse events related to NSAID and sedative prescribing is higher than that from  
325 antihypertensives, resulting in fewer QALYs gained from stopping antihypertensive  
326 treatment. This was supported by sensitivity analyses which suggested that an increasing  
327 disutility associated with antihypertensive treatment prescription would have resulted in

328 deprescribing becoming preferred strategy. However, such a gain was not observed in the  
329 original trial over 3 months of follow-up.<sup>17</sup> Indeed, there was no significant difference in EQ-  
330 5D-5L index between the two trial arms and a change of the magnitude modelled in this  
331 sensitivity analysis was outside the 95% confidence interval for the observed difference.

332

### 333 *Implications for clinical practice*

334 Although based on data with some uncertainty, this study suggests that antihypertensive  
335 deprescribing may not be cost-effective in older patients aged 80 years and older, and  
336 therefore should not be attempted in patients with controlled systolic blood pressure as a  
337 routine policy. This is important for guideline and policy makers, who are increasingly  
338 encouraging physicians to think about deprescribing chronic medications where the benefits  
339 of treatment no longer outweigh the harms.<sup>11, 37, 38</sup> Sensitivity analyses conducted here were  
340 able to identify scenarios where this might occur, notably, in those with a high risk of  
341 medication related adverse events. However, it is currently difficult to determine who these  
342 patients might be in routine practice. For other treatments, such as anticoagulants, tools exist  
343 which can help physicians quantify an individual's risk of bleeding which may be increased  
344 by treatment.<sup>39</sup> Similar tools predicting adverse events related to antihypertensive treatment  
345 would help target deprescribing at those most likely to benefit, although this requires further  
346 research. In the interim, for physicians wishing to reduce antihypertensives prescriptions in  
347 older patients under their care, tools such as the electronic frailty index<sup>33</sup> or QAdmissions  
348 score<sup>40</sup> may be considered as a proxy to determine higher risk patients.

349

### 350 **Perspectives**

351 The present analysis found that deprescribing of antihypertensive medication in older adults  
352 was cost saving, but resulted in fewer quality adjusted life years gained when compared to

353 usual care. Although sensitivity analyses suggested that such a strategy may be preferred  
354 when targeted at individuals at high risk of adverse events, the lack of robust data regarding  
355 the underlying risk in this population, and the long-term effects of deprescribing preclude  
356 firm recommendations being drawn. Whilst reducing polypharmacy in the elderly may still  
357 be a desirable policy, these data suggest that it may be better to attempt withdrawal of  
358 medications that don't reduce major clinical events.

359

360 **Acknowledgements**

361 The authors acknowledge the OPTiMISE investigators (listed in the supplementary appendix)  
362 for their contributions to the original trial and thank the patients who participated in the trial.

363

364 **Sources of Funding**

365 This work received joint funding from the National Institute for Health Research (NIHR)  
366 Oxford Collaboration for Leadership in Applied Health Research and Care (CLAHRC) at  
367 Oxford Health NHS Foundation Trust (ref: P2-501) and the NIHR School for Primary Care  
368 Research (SPCR; ref 335). JS now receives funding from the Wellcome Trust/Royal Society  
369 via a Sir Henry Dale Fellowship (ref: 211182/Z/18/Z). FDRH reports personal fees from  
370 NOVARTIS and grants from Boehringer Ingelheim and Pfizer outside of the submitted work.  
371 RJMcM and JM are NIHR Senior Investigators. JM reports personal fees from BMS/Pfizer,  
372 outside the submitted work. The views expressed are those of the author(s) and not  
373 necessarily those of the NIHR or the Department of Health and Social Care.

374

375 This research was funded in part, by the Wellcome Trust [ref: 211182/Z/18/Z]. For the  
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378

379 **Disclosures**

380 The authors declare no conflicts of interest.

381

382 **Data sharing**

383 Individuals wishing to use the data in this study should contact the corresponding author.

384

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550 **Novelty and Significance**

551 *What Is New?*

- 552       • This is the first study to examine the cost-effectiveness of antihypertensive  
553       medication reduction in older adults.
- 554       • This analysis found that reducing antihypertensive medication in older adults was cost  
555       saving, but resulted in fewer quality adjusted life years gained when compared to  
556       usual care.
- 557       • Medication reduction was found to be the preferred strategy at a willingness-to-pay of  
558       £20,000/QALY only where the baseline absolute risk of serious drug-related adverse  
559       events was high (7.7% a year or greater).

560 *What Is Relevant?*

- 561       • For most older patients with controlled systolic blood pressure, antihypertensive  
562       medication reduction was not a cost-effective treatment strategy.
- 563       • In some specific populations at high risk of adverse events, antihypertensive  
564       medication reduction may carry potential benefits, so a targeted approach may be  
565       needed if this strategy is to be adopted in routine clinical practice.

566 *Clinical/Pathophysiological Implications?*

567 Despite some uncertainty regarding model inputs, due to a lack of evidence in this older  
568 population, these findings suggest that antihypertensive medication reduction should not be  
569 attempted in most older patients with controlled systolic blood pressure. Further research is  
570 required to understand the risks and benefit of antihypertensive medication reduction in older  
571 people at high risk of adverse effects from blood pressure lowering.

572

573

## Tables and figures

Table 1. Model Parameters

| Parameter   | Model estimate   | Source   |
|---|--|--|
| <b>Patient characteristics</b>                                    |  |  |
| Mean age in years   | 84.8   | Sheppard <i>et al.</i> , 2020 <sup>17</sup>                                |
| Sex (% male)  | 51.5%  | as above   |
| No previous CVD   | 42.9%  | as above   |
| 1 previous CVD event  | 29.5%  |  |
| 2+ previous CVD events  | 27.6%  |  |
| Systolic BP increase (mm Hg) at 12 weeks compared with Usual Care | 3.4 (95% CI 1.0 to 5.8)  | as above   |
| Proportion maintaining reduced treatment reduction at 12 weeks    | 66.3%  | as above   |
| <b>Mortality and risk of cardiovascular disease</b>               |  |  |
| Probability of non-cardiovascular death                           | Age and sex dependent  | England and Wales 2016-2018 lifetables without CVD death <sup>28, 29</sup> |
| 10 year CVD risk (QRISK2): Range                                  | Patient specific   | Sheppard <i>et al.</i> , 2020; <sup>17</sup> QRisk2 <sup>19</sup>          |
| Ratio of 10 year CVD risk CHD:Cerebrovascular                     | 50:50  | Assumption   |
| Proportion of cerebrovascular events (stroke, TIA)                | M, 75-84: 81.1%, 18.9%<br>M, 85+: 95.6%, 4.4%<br>F, 75-84: 82.6%, 17.4%<br>F, 85+: 85.2%, 14.8%                              | Ward <i>et al.</i> , 2007 <sup>22</sup>                                    |
| Proportion of CHD events (MI, ACS, SA)                            | M, 75-84: 37.2%, 18.7%, 44.1%<br>M, 85+: 37.5%, 19.4%, 43.1%<br>F, 75-84: 35.8%, 11.9%, 52.3%<br>F, 85+: 37.7%, 10.9%, 51.3% | as above   |
| 1-year risk of HF (HF) event                                      | 80-84: 2.23%<br>85-89: 3.58%<br>90+: 5.36%   | Conrad <i>et al.</i> , 2018 <sup>23</sup>                                  |
| 1-year risk of SAEs related to antihypertensives                  | 1.74%  | Williamson <i>et al.</i> , 2016 <sup>24</sup>                              |
| Ratio of serious fall:AKI   | 0.52:0.48  | as above   |
| 1-year risk of non-serious adverse event                          | 13.7%  | as above   |
| <b>Relative risks with a reduction in medication</b>              |  |  |
| Coronary heart disease  | 1.009 (95% CI 0.896-1.135)   | Thomopoulos <i>et al.</i> , 2018 <sup>4</sup>                              |
| Stroke/TIA  | 1.108 (95% CI 1.047-1.177)   | as above   |

|  |                            |   |
|--|----------------------------|---|
| Heart failure                                | 1.290 (95% CI 1.134-1.472) | as above  |
| Serious fall/AKI                             | 0.685 (95% CI 0.343-1.366) | as above  |
| Minor adverse events                         | 0.685 (95% CI 0.343-1.366) | as above  |
| <b>Standardized Mortality Rate (SMR)</b>     |                            |   |
| Myocardial infarction                        | 2.68                       | Brønnum-Hansen <i>et al.</i> , 2001 <sup>41</sup> |
| Acute coronary syndrome                      | 2.19                       | NICE guidelines, 2010 <sup>42</sup>               |
| Stable angina                                | 1.95                       | Rosengren <i>et al.</i> , 1998 <sup>43</sup>      |
| Stroke                                       | 2.72                       | Brønnum-Hansen <i>et al.</i> , 2001 <sup>41</sup> |
| Transient ischemic attack                    | 1.40                       | Dennis <i>et al.</i> , 1990 <sup>44</sup>         |
| Heart failure                                | 2.17                       | de Guili <i>et al.</i> , 2005 <sup>45</sup>       |
| Serious fall (hip fracture)                  | 1.49                       | Finnes <i>et al.</i> , 2013 <sup>46</sup>         |
| Acute kidney injury                          | 1.18                       | Bihorac <i>et al.</i> , 2009 <sup>47</sup>        |
| <b>Quality of life multipliers</b>           |                            |   |
| Utility for initial health state (no events) | 0.769                      | Sheppard <i>et al.</i> , 2020 <sup>17</sup>       |
| Stroke                                       | 0.629                      | Ward <i>et al.</i> , 2007 <sup>22</sup>           |
| MI   | 0.778                      | Jiang and You, 2017 <sup>48</sup>                 |
| ACS  | 0.77                       | Ward <i>et al.</i> , 2007 <sup>22</sup>           |
| SA   | 0.88                       | as above  |
| HF   | 0.68                       | Cooper <i>et al.</i> , 2008 <sup>49</sup>         |
| Serious fall                                 | 0.797                      | Hiligsmann <i>et al.</i> , 2008 <sup>50</sup>     |
| <b>Quality of life decrements</b>            |                            |   |
|  | <b>Annual decrement</b>    |   |
| TIA  | 0.103                      | Meckley <i>et al.</i> , 2010 <sup>51</sup>        |
| AKI  | 0.15                       | Nisula <i>et al.</i> , 2013 <sup>52</sup>         |
| Hypotension                                  | 0.0290                     | Ademi <i>et al.</i> , 2017 <sup>53</sup>          |
| Syncope                                      | 0.1                        | Bress <i>et al.</i> , 2017 <sup>54</sup>          |
| Bradycardia                                  | 0.1                        | as above  |
| Electrolyte abnormalities                    | 0.1                        | as above  |
| Non-serious fall                             | 0.1                        | as above  |

BP=blood pressure; CVD=cardiovascular; CHD=coronary heart disease; SAE=serious adverse event; TIA=Transient Ischaemic Attack; MI=Myocardial Infarction; ACS=Acute Coronary Syndrome; SA=Stable Angina; HF=Heart failure; AKI=Acute kidney injury; NICE= National Institute for Health and Care Excellence;

**Table 2.** Results of base-case and threshold cost-effectiveness analyses

| Analysis  | Strategy           | Costs per patient | Incremental cost | QALYs gained | Incremental QALYs | ICER (£/QALY) | Interpretation  |
|---|--------------------|-------------------|------------------|--------------|-------------------|---------------|---|
| <b>Base-case analysis</b>   | Reduced medication | £4,560            |                  | 3.343        |                   |               | Usual care is cost-effective. The reduced medication strategy is not cost-effective (cost savings not worth loss of QALYs)                      |
|   | Usual Care         | £4,745            | £185             | 3.405        | 0.062             | 2,975         |   |
| <b>Threshold analysis:</b> Absolute risk of SAEs = 7.7% per year*<br>Willingness to pay = £20,000/QALY                                  | Reduced medication | £7,275            |                  | 3.301        |                   |               | Usual care no longer the preferred strategy if risk >7.7% per year. Cost savings worth the loss of QALYs with reduced medication.               |
|   | Usual Care         | £8,069            | £794             | 3.340        | 0.039             | 20,613        |   |
| <b>Threshold analysis:</b> Additional utility given to patients reducing medication = 0.017 per year. Willingness to pay = £20,000/QALY | Reduced medication | £4,560            |                  | 3.396        |                   |               | Usual care no longer the preferred strategy if additional utility >0.017 per year Cost savings worth the loss of QALYs with reduced medication. |
|   | Usual Care         | £4,745            | £185             | 3.405        | 0.009             | 21,302        |   |

QALYs: Quality Adjusted Life Years; ICER: Incremental Cost-Effectiveness Ratio

\*Absolute risk of SAEs in the base-case was 1.74% per year

**Table 3.** Estimated incidence of outcome events in the base-case analysis over the life-time time horizon

| Outcome event type                 | Outcome events per 100,000 patients |            |                            |
|------------------------------------|-------------------------------------|------------|----------------------------|
|                                    | Medication reduction                | Usual care | Difference between groups* |
| Heart failure                      | 22,160                              | 19,421     | 2,739                      |
| Coronary heart disease             | 18,177                              | 18,606     | -429                       |
| Stroke/Transient ischemic attack   | 19,376                              | 18,692     | 684                        |
| Serious drug-related adverse event | 4,938                               | 6,376      | -1,438                     |
| Minor drug-related adverse event   | 39,859                              | 51,568     | -11,709                    |

\*Positive integer indicates more events in the medication reduction group

**Figure legends**

**Figure 1.** Cost-effectiveness plane for medication reduction versus usual care

QALY=quality adjusted life years

**Figure 2.** Cost-effectiveness acceptability curve for medication reduction versus usual care

Probability that usual care is cost effective at £20,000/QALY=99.0%

QALY=quality adjusted life year