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1 **Title: Legacy effect of delayed blood pressure lowering drug treatment in**
2 **middle-aged adults with mildly elevated blood pressure: systematic review and**
3 **meta-analysis**

4

5 **Running title:** Legacy effect of BP lowering drug treatment in primary prevention

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23

24 **Abstract**

25 To investigate if there is evidence for a 'legacy effect' for BP lowering treatment, that
26 is worse health outcomes from not initiating drug treatment at a systolic BP threshold
27 of 140 mmHg in middle-age adults. We systematically reviewed studies comparing
28 the effects of delayed BP treatment (placebo/untreated during the trial or no
29 previous treatment at trial entry) versus early treatment (actively treated during the
30 trial or previous BP treatment at trial entry) on mortality in the short-term (5-year in-
31 trial period) and long-term (≥ 10 years in total period). The data were pooled using
32 Peto ORs. A subgroup analysis by 10-year Framingham risk score was performed.
33 Three studies (ALLHAT, Oslo and PREVEND-IT) involving 4746 participants were
34 included. The results were heavily influenced by the ALLHAT trial. We found no
35 significant difference in all-cause mortality between 'delayed BP' and 'early
36 treatment' in the short-term OR 0.95 (95% CI 0.68- 1.32) or long-term OR 0.90
37 (95%CI 0.78-1.04), with similar results for mortality from cardiovascular disease
38 (CVD). The effects of delayed BP lowering treatment on long-term all-cause and
39 CVD mortality did not vary with baseline risk of CVD. The review showed no clinically
40 adverse 'legacy effect' on mortality or major CVD event from not treating middle-
41 aged adults at a systolic BP threshold of 140 mmHg or over. The results were
42 consistent for all CVD risk subgroups. Although these studies are non-randomised
43 post-hoc analyses, they may allay concerns that early treatment of elevated systolic
44 BP is necessary to prevent CVD events in primary prevention populations.

45 Key words: legacy effect, blood pressure, long-term, all-cause mortality, CVD
46 mortality, primary prevention, cardiovascular disease

47

48 Introduction

49 The effectiveness of blood pressure (BP) lowering drugs to prevent
50 cardiovascular disease (CVD) has been well established in trials of patients with
51 diabetes, the elderly, or those with a systolic BP of ≥ 160 mmHg or over (for example
52 SHEP¹, Syst-Eur² and HYVET³). However, the effects of BP lowering
53 pharmacotherapy in middle-aged adults with mildly elevated BP (defined as systolic
54 BP 140-159 mmHg and/or diastolic BP 90-99 mmHg) are uncertain. A recent
55 systematic review of participants with mildly elevated BP found no statistically
56 significant effect of treatment in this patient group on the incidence of CVD events or
57 mortality (Diao et al ⁴). However, a similar review by the Blood Pressure Lowering
58 Treatment Trialist's Collaboration (BPLTTC)⁵ observed significant reductions in stroke,
59 CVD and all-cause mortality. Although the BPLTTC review included more trials with a
60 larger number of participants, these trials evaluated both less versus more intensive
61 treatments and the addition of new BP treatment to pre-existing medication and so the
62 comparison was not restricted to active treatment versus placebo/no treatment as in
63 the Diao et al review. In line with the findings in the Diao et al review⁴, most of the
64 placebo trials⁶⁻¹² in which previous treatments were not permitted or were withdrawn,
65 did not show substantial effects of active drug treatment on major CVD events,
66 coronary heart disease (CHD), stroke or all-cause mortality within the trial period.

67 Concerns have been raised, however, that the effects of delayed treatment may
68 take longer five years to become evident, and that delaying treatment after a patient
69 reaches a SBP threshold of 140 mmHg could result in irreversible pathological
70 damage. Two systematic reviews^{13, 14} have been conducted of BP lowering trials with
71 a post-trial follow-up of up to ten years and showed a significantly reduced risk of CVD
72 and all-cause mortality in the participants randomly allocated to active treatment.
73 However, these two reviews included patients with pre-existing CVD. Therefore, the
74 'legacy effect' of delayed drug treatment in individuals with mildly elevated SBP without
75 cardiovascular disease remains uncertain. As there are no trials that addressed this
76 specific question, the aim of this review is to investigate if there are any adverse
77 'legacy effects from not initiating drug treatment at a systolic BP threshold of 140
78 mmHg in healthy middle-age adults using post-hoc analyses of existing trials with long-
79 term follow up.

80 **Methods**

81 **Protocol and registration**

82 The review protocol was published in the Journal of Medical Internet Research¹⁵ and
83 can be accessed via <https://www.researchprotocols.org/2017/9/e177/>. The review
84 was registered in PROSPERO International Prospective Register of Systematic
85 Reviews: CRD42017058414

86 **Criteria for considering studies for this review**

87 The current review included randomised controlled trials (RCTs) with at least 1-year
88 post-trial follow-up. Trials including men and non-pregnant women from 30 to 65 years
89 of age, where at least 80% of participants had mildly elevated BP (defined as a systolic
90 BP of 140 – 159 mmHg) and no history of CVD (myocardial infarction, angina pectoris,
91 coronary bypass surgery, coronary angioplasty, stroke, transient ischaemic attack,
92 carotid endarterectomy, surgery for peripheral vascular disease, intermittent
93 claudication or renal failure (creatinine > 1.5 times the upper limit of normal)) at
94 baseline were eligible. We included studies that used a placebo or untreated control
95 comparator or another active BP lowering treatment where it was possible to
96 determine participants who had previously been taking blood pressure lowering
97 treatment (previous treatment) or no pre-existing treatment (treatment naïve). Where
98 trials included participants different to those of interest (e.g. in secondary prevention
99 populations, in participants with moderately or highly elevated BP or older than 65
100 years), we attempted to access data from trial investigators and subsequently
101 included only participants meeting our criteria in the analyses. The primary outcome
102 of the review was all-cause mortality, with secondary outcome of CVD mortality and
103 CVD events (defined as fatal and non-fatal stroke, fatal and non-fatal CHD, fatal and
104 non-fatal heart failure).

105 **Data sources and searches**

106 We searched Medline via Ovid (1946 to Sept 2018), Embase via Ovid (1974 to Sept
107 2018) and the Cochrane Register of Controlled Trials (CENTRAL) (Sept 2018). We
108 combined text word and MeSH/Emtree terms related to BP lowering drug agents with
109 hypertension terms and follow-up studies. We used the Cochrane Highly Sensitive
110 Search Strategy for identifying randomised trials (sensitivity and precision maximising
111 2008 revision) in Medline¹⁶. No language restrictions were applied. The search

112 strategies are provided in Table appendix 1. We modified the search strategy from
113 the published protocol¹⁵ as the planned method of identifying trials and then searching
114 for follow-up studies was considered inadequate to identify potentially eligible RCTs.

115 We searched reference lists of known systematic reviews on post-trial studies of BP
116 lowering drug treatment (Kostis 2010¹³ and Hirakawa 2017¹⁴) and meta-analyses of
117 trials in middle-aged adults with mildly elevated BP^{4, 5, 17, 18}. We contacted
118 corresponding authors of relevant papers regarding any further published or
119 unpublished work.

120 **Study selection**

121 Two reviewers (CH and SS) independently scanned the results of the title and abstract
122 search and any potentially relevant articles were obtained in full text. Two reviewers
123 then screened the full text of potentially relevant articles against the reviews inclusion
124 criteria. Discrepancies were resolved through discussion with a third reviewer.

125 **Data extraction**

126 Data extraction were independently performed by two reviewers (CH and SS). If any
127 disagreement arose, a third reviewer (JD) was consulted. The extraction form included
128 details of study characteristics, participant characteristics, interventions and settings,
129 outcome data, type of analysis used in the studies and follow-up years.

130 **Assessment of risk of bias in included studies**

131 Two review authors (CH and SS) independently assessed risk of bias using the
132 Cochrane Risk of bias in non-randomised and /randomised studies of interventions
133 tools ^{19, 20}. The included ALLHAT study was assessed using the tool for non-
134 randomised studies as data from the original randomised trial was reanalysed to
135 compare non-randomised groups (treatment naïve vs previous treatment) based on
136 data collected at trial baseline. Risk of bias assessment in both non-randomised²¹ and
137 randomised studies²² included consideration of four mutual domains: bias due to
138 deviations from intended interventions, bias due to missing data, bias in measurement
139 of outcomes and bias in selection of the reported. Risk of bias assessment in non-
140 randomised controlled studies required consideration of three further criteria: bias due
141 to confounding, bias in selection of participants into the study and bias in classification
142 of intervention. For randomised studies, risk of bias assessment also included
143 consideration of bias arising from the randomisation process. For the non-randomised

144 studies, each risk of bias domain was assessed as low, moderate, serious or critical
145 risk of bias with a no information response when insufficient data were reported to
146 permit a judgment. For the randomised studies, each risk of bias domain was
147 assessed as low, some concerns and high risk of bias. The domain level judgments
148 provide the basis for an overall risk of bias judgment for each study. An assessment
149 of potential publication bias was not performed due to the small number of included
150 studies.

151 **Data analysis**

152 We compared outcomes in the short-term (average 5-year in-trial period) and long-
153 term (an overall period of at least 10 years cumulative in- and post-trial period)
154 between 'delayed treatment' and 'early treatment' groups. The 'early treatment' group
155 included who had been previously treated with blood pressure lowering treatment at
156 trial entry and the 'delayed treatment' group included participants who were treatment
157 naïve using individual patient data from the trial. This approach has been used
158 previously by Nelson et al²³.

159 Due to the small number of included studies, fixed effect Peto odds ratio (OR) was
160 used to estimate the pooled effects²⁴. As recommended²⁵⁻²⁸, we also used other
161 methods to test the robustness of the results in sensitivity analyses. Heterogeneity of
162 treatment effects in different trials was tested by the I^2 statistic. Statistical
163 heterogeneity was recorded when the p value of the test of heterogeneity was 0.1 or
164 lower or the I^2 value was 0.5 or greater. In a post-hoc analysis of the ALLHAT trial, the
165 effects of 'no previous treatment' versus 'previous treatment' for high BP were
166 estimated using a Cox proportional hazard model. As this analysis was a comparison
167 of non-randomised groups, the two groups were adjusted for an imbalance in baseline
168 characteristics (e.g. age, race, sex, diabetes mellitus, education, body mass index,
169 smoking, aspirin use, randomised group, BP, total cholesterol, serum glucose and
170 creatinine), as per Nelson et al in the ANBP2 study²³. The observed (O), expected
171 event (E) and variance (V) in ALLHAT were estimated from adjusted HR as
172 recommended by Tierney et al²⁹ and then pooled with the corresponding O, E and V
173 in Oslo and PREVEND-IT. The threshold of a significant effect was set at 0.05.

174 We conducted a sub-group analysis based on baseline risk of CVD where data
175 were available. We stratified participants by the baseline estimated 10-year
176 Framingham risk score for fatal and non-fatal CVD events using thresholds of lower

177 than 20% (low risk), 20-30% (moderate risk) and higher than 30% (high risk) over 10
178 years^{30, 31}. We estimated the relative risk for all-cause and CVD mortality in each
179 group and tested for difference between the groups. Data synthesis and analyses were
180 performed in Review Manager 5³². We extracted data based on intention-to-treat
181 principles.

182 **Sensitivity analysis**

183 An analysis restricted to placebo/untreated controlled RCTs was performed to
184 investigate the impact of the observational study on the pooled outcomes. Different
185 statistical methods were also used to check the robustness of the results²⁵⁻²⁸.

186 **Results**

187 **Result of the searches**

188 The database searches identified 6012 records and three articles were identified from
189 other sources (Figure Appendix 1 shows the flowchart of studies). After removal of
190 duplicates 4090 articles were screened. Eighty nine articles were screened in full-text
191 and 3 studies (Oslo, PREVEND-IT and ALLHAT) from 11 articles were included in the
192 review. Aggregate unpublished data from the ALLHAT and individual data of
193 PREVEND-IT trial were provided by the trial investigators.

194 One trial excluded from the review included participants with mildly elevated diastolic
195 BP (90-115 mmHg): USPHS 1977^{33, 34}. Although USPHS did not have a post-trial
196 phase, the trial was followed for up to 10 years. No information on the proportion of
197 participants with mildly elevated systolic BP was reported. Based on the baseline
198 systolic BP 148 ± 15 mmHg, it is likely that less than 80% of participants had systolic BP
199 less than 160 mmHg. The intervention was a combination of a diuretic and rauwolfia
200 serpentine that had limited clinical use in current practice because of the risk of side
201 effects and availability. Thus USPHS was excluded in the current systematic review
202 and meta-analysis.

203 **Characteristics of included studies and risk of bias**

204 The review included published data from the Oslo trial, unpublished aggregate data
205 from the ALLHAT and individual data from the PREVEND-IT. In the ALLHAT trial, we
206 used data based on whether participants had previously been treated with BP lowering
207 agents or not, that is a comparison on a difference in treatment status at baseline
208 between the two groups rather than a randomised comparison. ALLHAT participants

209 were followed for a mean of 4.9 years in the in-trial period and 14 years over the in-
210 and post-trial period. As the original ALLHAT trial ³⁵ reported beneficial effects from
211 BP lowering treatment (e.g. Chlorthalidone 12.5 to 25 mg/d vs amlodipine 2.5 to 10
212 mg/d vs lisinopril 10 to 40mg/d) within the trial period, the majority of participants from
213 all arms of the trials received active treatment in the post-trial phase, so there is likely
214 to be little cross-over between the early treatment and delayed treatment comparison
215 groups. Although some participants in the Oslo trial may have had a diastolic BP
216 exceeding 110 mmHg, nearly 80% of Oslo participants had systolic BP lower than 160
217 mmHg, so we included the published data of this trial. Oslo participants were
218 randomised to active treatment (Hydrochlorothiazide 50 mg) or no active treatment.
219 Oslo reported 10-year³⁶ and 40-year³⁷ follow-up of all-cause mortality and CHD
220 mortality, thus the results of the 40-year study were included in the current review. In
221 PREVEND-IT trial, participants were originally randomised either to active treatment
222 (Fosinopril 20 mg) or placebo. The mean follow-up period ranged from 3.3-4.4 years
223 for the in-trial phase and 9.4-10.7 years for the overall period.

224 The baseline risk for participants in ALLHAT was higher than the other two trials as it
225 included participants with elevated BP and at least one other CVD risk factor (e.g.
226 history of type 2 diabetes, current cigarette smoking, high-density lipoprotein
227 cholesterol of less than 0.91 mmol/L). PREVEND-IT included healthy subjects from
228 the general population with persistent microalbuminuria, and the Oslo trial included
229 men with mildly elevated BP (defined as systolic BP 150-179 mmHg and diastolic BP
230 less than 110 mmHg). More details on the characteristics of the included and excluded
231 studies are provided in Table appendix 2 and 3.

232 The baseline characteristics of the participants included in the review showed no
233 significant differences between study groups in the PREVEND-IT and Oslo trials
234 (Table 1). ALLHAT participants had a higher proportion of patients with diabetes, and
235 contributed to a higher proportion of participants with early treatment having type 2
236 DM. Participants with early treatment in the ALLHAT trial were also more likely to be
237 black, female, non-smoker and had higher estimated 10-year CVD risk scores. We
238 adjusted for these imbalances in multivariable models. Noticeably, Oslo included men
239 only and had higher baseline systolic BP than the other two trials.

240 **Risk of bias (Table 2)**

241 In Table 2, We assessed the ALLHAT data to be at serious risk of bias due to residual
242 confounding as a result of the use of post-hoc non-randomised data from the trial.
243 Although the outcome measurements in the post-trial phase of the PREVEND-IT and
244 Oslo trials were unblinded, the primary outcomes considered in this analysis are
245 generally objective (all-cause and cardiovascular mortality). Thus, the overall risk of
246 bias for the PREVEND-IT and Oslo trials were judged as 'Low risk'. More details on
247 the assessment of the risk of bias in each trial are presented in Table appendix 4.

248 **Short- and long-term all-cause and CVD mortality (Figure 1)**

249 The analyses on short- and long-term all-cause mortality and short-term CVD mortality
250 included 4746 participants from three trials, with 80% originating from the ALLHAT
251 trial. As the Oslo trial separately reported aggregate data for CHD and stroke, these
252 subjects were excluded in the analysis of long-term CVD mortality, leaving 3961
253 participants in the analysis. There were 301 deaths in total and 102 deaths due to CVD
254 recorded in the in-trial period, and 1871 total deaths and 312 CVD deaths during the
255 post-trial period (Table appendix 5).

256 In Figure 1, we observed no statistically significant difference in all-cause mortality in
257 either the short- or long-term (short-term OR 0.95, 95%CI 0.68-1.32; long-term OR
258 0.90, 95%CI 0.78-1.04) for those with delayed BP lowering treatment relative to those
259 with earlier treatment. Similarly, no difference was found for CVD mortality (short-term
260 OR 0.90, 95%CI 0.51-1.59; long-term OR 0.79, 95% CI 0.55-1.14).

261 **CVD events (Figure 1)**

262 Two trials (Oslo and PREVEND-IT) including 934 participants contributed to the
263 analysis of major CVD events in the short-term, with 69 events recorded in the in-trial
264 phase of the Oslo and PREVEND-IT trials. However, only PREVEND-IT (149
265 participants, 19 events) recorded long-term outcomes³⁸. As provided in Figure 1, we
266 found no statistically significant difference in major CVD events for those with delayed
267 drug treatment in either the short or long-term (short-term OR 1.35, 95% 0.83-2.21;
268 long-term OR 1.02, 95% 0.39-2.66).

269 **Subgroup analysis by 10-year Framingham risk score**

270 Data were available to stratify participants in ALLHAT and PREVEND-IT into low,
271 moderate and high risk of CVD. More than half of the included participants were in the
272 high risk group, primarily due to the inclusion criteria of the ALLHAT study. The effects
273 of delayed BP lowering drug treatment were consistent among the three groups

274 (p=0.46 and p=0.79 for the test of subgroup differences in overall all-cause and CVD
275 mortality respectively) (Figure 2 and Figure 3).

276 **Sensitivity analysis**

277 Using different methods (DerSimonian-Laird between-study variance estimator and
278 Wald-type confidence intervals, DerSimonian-Laird between-study variance estimator
279 and Hartung-Knapp-Sidik-Jonkman adjusted confidence intervals, Paule-Mandel
280 between-study variance estimator and Hartung-Knapp-Sidik-Jonkman confidence
281 intervals) to pool the aggregate data did not change the main findings in all-cause and
282 CVD mortality as presented in Table appendix 6.

283 An analysis restricted to the data from the randomised trials only (PREVEND-IT and
284 Oslo), were similar to the main analyses, with no statistically significant difference in
285 for short-term all-cause mortality (OR 0.99, 95% CI 0.43-2.27) or long-term all-cause
286 mortality (OR 0.94, 95% CI 0.70-1.28) or short- or long-term CVD mortality (short-term
287 OR 1.26, 95% CI 0.42 - 3.76; long-term OR 2.23, 95%CI 0.23-21.84) (Table appendix
288 7).

289 A sensitivity analysis adjusting for baseline differences, showed no substantial
290 difference between the adjusted and crude hazard ratio for any outcome (Table
291 appendix 8).

292 **Discussion**

293 The present systematic review and meta-analysis of studies with extended post-trial
294 phase showed no statistically significant difference in all-cause and CVD mortality for
295 participants with 'delayed' drug treatment at a systolic BP threshold of 140 mmHg in
296 middle-aged adults even when the follow-up was extended for more than 10 years.
297 Due to the small number of events in the in-trial period, subgroup analyses were
298 performed only for long-term all-cause and CVD mortality. No heterogeneity of
299 'delayed' treatment effects was found across the low, moderate and high CVD risk
300 subgroups.

301 Our findings are similar to two earlier systematic reviews in middle-aged adults without
302 previous CVD³⁹ and in middle-aged adults both with and without previous CVD¹⁷.
303 Trials in these reviews had follow-up durations of approximately five years, except for
304 the USPHS study³⁴. The USPHS was followed for 7-10 years and did not show any
305 difference in early vs delayed treatment regarding all-cause mortality with a RR 0.51

306 (0.09-2.74). Results from USPHS may not be considered relevant to current
307 populations, however, as this trial used rauwolfia, which is no longer recommended
308 treatment. Similar to our short-term results, the SHEP¹ and Syst-Eur² trials did not
309 record any substantial benefits of 'early' treatment for all-cause or CVD mortality after
310 an in-trial follow-up of five and two years respectively. However, the effects on CVD
311 mortality became statically significant with a HR 0.86 (0.76-0.97) when the SHEP trial
312 was extended to 14 years⁴⁰ and this 'legacy effect' remained significant at the 22-year
313 follow-up⁴¹. The reduction in mortality in Syst-Eur remained non-statistically significant
314 after a total follow-up of 6 years⁴², indicating that a longer time for follow-up is required
315 to observe significant 'delayed benefits'. The SHEP and Syst-Eur trials had a 'placebo'
316 arm when participants experienced 'placebo' run-in or withdrawal phase. However
317 these trials were aimed at the elderly with much higher systolic BP values of 160
318 mmHg or over compared to the participants considered in our review. HOPE-3 trial in
319 intermediate risk participants also observed no statistically significant difference
320 between the effect of an active treatment and placebo in all-cause or CVD mortality
321 and major CVD event after 5.6 years of follow-up.

322 Benefits of 'active treatment' or harms of 'no treatment' may require longer than ten
323 years to become evident, particularly for mortality outcomes in middle-aged adults with
324 mildly elevated BP who are at low CVD risk. This is the group that where treatment
325 with blood pressure lowering medication is not clearly of benefit. We have attempted
326 in this review to determine if treatment can safely be delayed in this treatment group.
327 In this review, the average Framingham risk score was >20%, and so is higher than
328 the low risk patients we would consider where treatment could be delayed. Even in
329 this review, however, no clear evidence of early treatment was observed. The included
330 ALLHAT and Oslo trial³⁷ were extended to 14 and 40 years respectively, with no
331 substantial 'legacy effect' on all-cause or CVD mortality of delayed treatment
332 observed, and we observed consistent results across the low, moderate and high CVD
333 risk subgroups.

334 **Strengths and limitation**

335 This is the first study to systematically review the medical evidence to determine if
336 delaying BP lowering treatment for middle-aged adults with a systolic BP between 140

337 and 159 mmHg results in an increase in all-cause or cardiovascular mortality in the
338 short or long term.

339 In spite of vigorous efforts in accessing individual data to identify eligible participants,
340 only three trials with 4746 participants could be included in the current review. Given
341 the much larger size of ALLHAT trial, the overall results were heavily influenced by the
342 results of this trial. In the ALLHAT trial, information on how long before the start of the
343 trial participants had been on BP lowering treatment was not collected and even if it
344 was, we could not truly know how long someone was hypertensive before it was noted.
345 However, in sensitivity analyses on short- and long-term all-cause mortality, the results
346 of analyses excluding the ALLHAT trial were generally consistent with the overall
347 results.

348 This review did not examine CHD and stroke mortality separately. Given the small
349 number of studies and the potential for CHD and stroke to be affected by different
350 classes of BP lowering medication^{43,44}, we were only able to assess overall and total
351 CVD mortality.

352 The three included trials lacked BP lowering drug treatment information in the post-
353 trial phase except that an equal percentage of participants receiving drug therapy were
354 reported in PREVEND-IT and Oslo trial. Given the 'positive' findings of the original
355 ALLHAT trial, we believe it is likely that a substantial proportion of both arms of the
356 trial would have used BP lowering therapy after the trial period.

357 We used the Peto method for meta-analysis because of the small number of included
358 studies. While it is true that the Peto method is open to bias when including studies
359 with imbalance in the comparison groups, this only becomes apparent in combination
360 with a large treatment effect²⁴. Also, sensitivity analyses using different statistical
361 methods provided similar pooled effects (Appendix 6).

362 One of the barriers to adopting the absolute risk approach for decisions regarding BP
363 lowering treatment is the concern that early treatment of mildly elevated BP is
364 necessary to prevent pathological changes that result in CVD events. Our systematic
365 review and meta-analysis showed no clinically adverse 'legacy effect' on mortality
366 outcomes of not treating middle-aged adults at a systolic BP between 140 and 159
367 mmHg. This study contributes to an area of major concern raised by many clinicians

368 that early treatment of mildly elevated systolic BP is necessary to prevent CVD events
369 in primary prevention population.

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378 **Conflicts of Interest and Source of Funding**

379 C.L.B. Ho is a Ph.D. candidate at Menzies Institute for Medical Research, she has
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381 has served on advisory boards for Sanofi and Bayer in the last 3 years. For the
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383 **References**

- 384 1. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive
385 drug treatment in older persons with isolated systolic hypertension. Final results of
386 the Systolic Hypertension in the Elderly Program (SHEP). *Jama* 1991;265(24):3255-
387 64.
- 388 2. Staessen Jan A, Fagard Robert, Thijs Lutgarde, Celis Hilde, Arabidze Guramy G,
389 Birkenhäger Willem H, et al. Randomised double-blind comparison of placebo and
390 active treatment for older patients with isolated systolic hypertension. *The Lancet*
391 1997;350(9080):757-64.
- 392 3. Beckett Nigel S., Peters Ruth, Fletcher Astrid E., Staessen Jan A., Liu Lisheng,
393 Dumitrascu Dan, et al. Treatment of Hypertension in Patients 80 Years of Age or
394 Older. *New England Journal of Medicine* 2008;358(18):1887-98.
- 395 4. Diao D , Wright JM , Cundiff DK , Gueyffier F. Pharmacotherapy for mild
396 hypertension. *Cochrane Database of Systematic Reviews* 2012;8:CD006742.
- 397 5. Sundström Johan, Arima Hisatomi, Jackson Rod, Turnbull Fiona, Rahimi Kazem,
398 Chalmers John, et al. Effects of blood pressure reduction in mild hypertension: a
399 systematic review and meta-analysis. *Annals of internal medicine* 2015;162(3):184-
400 91.
- 401 6. DREAM Trial Investigators. Effect of ramipril on the incidence of diabetes. *New*
402 *England Journal of Medicine* 2006;355(15):1551-62.
- 403 7. THE AUSTRALIAN THERAPEUTIC TRIAL IN MILD HYPERTENSION. *The*
404 *Lancet* 1980;315(8181):1261-7.
- 405 8. Ho Chau Le Bao, Breslin Monique, Doust Jenny, Reid Christopher M, Nelson
406 Mark R. Effectiveness of blood pressure-lowering drug treatment by levels of
407 absolute risk: post hoc analysis of the Australian National Blood Pressure Study.
408 *BMJ open* 2018;8(3):e017723.
- 409 9. NAVIGATOR Study Group. Effect of valsartan on the incidence of diabetes and
410 cardiovascular events. *New England Journal of Medicine* 2010;362(16):1477-90.
- 411 10. Helgeland Anders. Treatment of mild hypertension: a five year controlled drug
412 trial: the Oslo study. *The American journal of medicine* 1980;69(5):725-32.
- 413 11. Asselbergs Folkert W, Diercks Gilles FH, Hillege Hans L, van Boven Ad J,
414 Janssen Wilbert MT, Voors Adriaan A, et al. Effects of fosinopril and pravastatin on

- 415 cardiovascular events in subjects with microalbuminuria. *Circulation*
416 2004;110(18):2809-16.
- 417 12. Neaton James D, Grimm Richard H, Prineas Ronald J, Stamler Jeremiah,
418 Grandits Greg A, Elmer Patricia J, et al. Treatment of mild hypertension study: final
419 results. *Jama* 1993;270(6):713-24.
- 420 13. Kostis W. J., Thijs L., Richart T., Kostis J. B., Staessen J. A. Persistence of
421 mortality reduction after the end of randomized therapy in clinical trials of blood
422 pressure-lowering medications. *Hypertension* 2010;56(6):1060-8.
- 423 14. Hirakawa Yoichiro, Arima Hisatomi, Rodgers Anthony, Woodward Mark,
424 Chalmers John. Cumulative in-trial and post-trial effects of blood pressure and lipid
425 lowering: systematic review and meta-analysis. *Journal of hypertension*
426 2017;35(5):905-13.
- 427 15. Ho Chau Le Bao, Sanders Sharon, Doust Jenny, Breslin Monique, Reid
428 Christopher M, Nelson Mark Raymond. Legacy Effect of Delayed Blood Pressure-
429 Lowering Pharmacotherapy in Middle-Aged Individuals Stratified by Absolute
430 Cardiovascular Disease Risk: Protocol for a Systematic Review. *JMIR research*
431 *protocols* 2017;6(9).
- 432 16. Lefebvre C, Manheimer E, Glanville J. Chapter 6.4. 11.1 The Cochrane Highly
433 Sensitive Search Strategies for identifying randomized trials in MEDLINE. *Cochrane*
434 *Handbook for Systematic Reviews of Interventions Version*;5(0).
- 435 17. Musini Vijaya M, Gueyffier Francois, Puil Lorri, Salzwedel Douglas M, Wright
436 James M. Pharmacotherapy for hypertension in adults aged 18 to 59 years.
437 *Cochrane Database of Systematic Reviews* 2017(8).
- 438 18. Hoes Arno W, Grobbee Diederick E, Lubsen Jacobus. Does drug treatment
439 improve survival? Reconciling the trials in mild-to-moderate hypertension. 1995.
- 440 19. Higgins Julian P T, Altman Douglas G, Gøtzsche Peter C, Jüni Peter, Moher
441 David, Oxman Andrew D, et al. The Cochrane Collaboration's tool for assessing risk
442 of bias in randomised trials; 2011.
- 443 20. Sterne Jonathan AC, Hernán Miguel A, Reeves Barnaby C, Savović Jelena,
444 Berkman Nancy D, Viswanathan Meera, et al. ROBINS-I: a tool for assessing risk of
445 bias in non-randomised studies of interventions. *Bmj* 2016;355:i4919.
- 446 21. Sterne JAC, Higgins JPT, Elbers RG, Reeves BC and the development group
447 for ROBINS-I. Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I):

- 448 detailed guidance, updated 12 October 2016; 2016 20 April 2019]; Available from:
449 <http://www.riskofbias.info>
- 450 22. Higgins JPT, Sterne JAC, Savović J, Page MJ, Hróbjartsson A, Boutron I, et
451 al. A revised tool for assessing risk of bias in randomized trials In: Chandler J,
452 McKenzie J, Boutron I, Welch V (editors). Cochrane Methods. Cochrane Database of
453 Systematic Reviews 2016(10 (Suppl 1)).
- 454 23. Nelson Mark R. a, Chowdhury Enayet K. b, Doust Jenny c, Reid Christopher
455 M. b d, Wing Lindon M. H. e. Ten-year legacy effects of baseline blood pressure
456 'treatment naivety' in the Second Australian National Blood Pressure study. Journal
457 of Hypertension.
- 458 24. Brockhaus A Catharina, Bender Ralf, Skipka Guido. The Peto odds ratio
459 viewed as a new effect measure. Stat Med 2014;33(28):4861-74.
- 460 25. Bradburn Michael J, Deeks Jonathan J, Berlin Jesse A, Russell Localio A.
461 Much ado about nothing: a comparison of the performance of meta-analytical
462 methods with rare events. Stat Med 2007;26(1):53-77.
- 463 26. IntHout Joanna, Ioannidis John PA, Borm George F. The Hartung-Knapp-
464 Sidik-Jonkman method for random effects meta-analysis is straightforward and
465 considerably outperforms the standard DerSimonian-Laird method. BMC Med Res
466 Methodol 2014;14(1):25.
- 467 27. Efthimiou Orestis. Practical guide to the meta-analysis of rare events.
468 Evidence-based mental health 2018;21(2):72-6.
- 469 28. Kuss O. Statistical methods for meta-analyses including information from
470 studies without any events—add nothing to nothing and succeed nevertheless. Stat
471 Med 2015;34(7):1097-116.
- 472 29. Tierney Jayne F, Stewart Lesley A, Gherzi Davina, Burdett Sarah, Sydes
473 Matthew R. Practical methods for incorporating summary time-to-event data into
474 meta-analysis. Trials 2007;8(1):16.
- 475 30. National Vascular Disease Prevention Alliance. Guidelines for the
476 management of absolute cardiovascular disease risk. 2012.
- 477 31. Nerenberg Kara A., Zarnke Kelly B., Leung Alexander A., Dasgupta Kaberi,
478 Butalia Sonia, McBrien Kerry, et al. Hypertension Canada's 2018 Guidelines for
479 Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults
480 and Children. Can J Cardiol 2018;34(5):506-25.

- 481 32. The Cochrane Collaboration. Review Manager (RevMan) [Computer
482 program], Version 5.3. Copenhagen: The Nordic Cochrane Centre; 2014.
- 483 33. United States Public Health Hospitals Cooperative Study Group. Morbidity
484 and mortality in mild essential hypertension. *Circ Res* 1972;30(31):110-21.
- 485 34. Smith W McFate. Treatment of mild hypertension: results of a ten-year
486 intervention trial. *Circ Res* 1977;40(5 Suppl 1):198-105.
- 487 35. The Allhat Officers and Coordinators for the Allhat Collaborative Research
488 Group. Major outcomes in high-risk hypertensive patients randomized to
489 angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The
490 antihypertensive and lipid-lowering treatment to prevent heart attack trial (allhat).
491 *JAMA* 2002;288(23):2981-97.
- 492 36. Leren Paul, Helgeland Anders. Coronary heart disease and treatment of
493 hypertension some Oslo study data. *The American journal of medicine* 1986;80(2):3-
494 6.
- 495 37. Holme I, Kjeldsen Se. Long-term survival in the randomized trial of drug
496 treatment in mild to moderate hypertension of the Oslo study 1972-3. *Eur J Intern*
497 *Med* [serial online] 2015;26(2):123-6. Available from:
498 [http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/814/CN-](http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/814/CN-01051814/frame.html)
499 [01051814/frame.html](http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/814/CN-01051814/frame.html)
- 500 [https://ac-els-cdn-com.ezproxy.utas.edu.au/S0953620515000321/1-s2.0-](https://ac-els-cdn-com.ezproxy.utas.edu.au/S0953620515000321/1-s2.0-S0953620515000321-main.pdf?_tid=bb06ea32-cd15-11e7-8a97-00000aacb362&acdnt=1511088068_479981dc9deb895a21d5181b3e5dac72)
501 [S0953620515000321-main.pdf?_tid=bb06ea32-cd15-11e7-8a97-](https://ac-els-cdn-com.ezproxy.utas.edu.au/S0953620515000321-main.pdf?_tid=bb06ea32-cd15-11e7-8a97-00000aacb362&acdnt=1511088068_479981dc9deb895a21d5181b3e5dac72)
502 [00000aacb362&acdnt=1511088068_479981dc9deb895a21d5181b3e5dac72.](https://ac-els-cdn-com.ezproxy.utas.edu.au/S0953620515000321-main.pdf?_tid=bb06ea32-cd15-11e7-8a97-00000aacb362&acdnt=1511088068_479981dc9deb895a21d5181b3e5dac72)
- 503 38. Brouwers Frank P, Asselbergs Folkert W, Hillege Hans L, de Boer Rudolf A,
504 Gansevoort Ron T, van Veldhuisen Dirk J, et al. Long-term effects of fosinopril and
505 pravastatin on cardiovascular events in subjects with microalbuminuria: ten years of
506 follow-up of Prevention of Renal and Vascular End-stage Disease Intervention Trial
507 (PREVEND IT). *American heart journal* 2011;161(6):1171-8.
- 508 39. Gueyffier F, Froment A, Gouton M. New meta-analysis of treatment trials of
509 hypertension: improving the estimate of therapeutic benefit. *Journal of human*
510 *hypertension* 1996;10(1):1-8.
- 511 40. Patel Alpesh B, Kostis John B, Wilson Alan C, Shea Michael L, Pressel Sara
512 L, Davis Barry R. Long-term fatal outcomes in subjects with stroke or transient

513 ischemic attack: fourteen-year follow-up of the systolic hypertension in the elderly
514 program. *Stroke* 2008;39(4):1084-9.

515 41. Kostis John B, Cabrera Javier, Cheng Jerry Q, Cosgrove Nora M, Deng
516 Yingzi, Pressel Sara L, et al. Association between chlorthalidone treatment of
517 systolic hypertension and long-term survival. *JAMA* 2011;306(23):2588-93.

518 42. Staessen Jan A, Thijs Lutgarde, Fagard Robert, Celis Hilde, Birkenhäger
519 Willem H, Bulpitt Christopher J, et al. Effects of immediate versus delayed
520 antihypertensive therapy on outcome in the Systolic Hypertension in Europe Trial.
521 *Journal of hypertension* 2004;22(4):847-57.

522 43. Ettehad Dena, Emdin Connor A, Kiran Amit, Anderson Simon G, Callender
523 Thomas, Emberson Jonathan, et al. Blood pressure lowering for prevention of
524 cardiovascular disease and death: a systematic review and meta-analysis. *The*
525 *Lancet* 2016;387(10022):957-67.

526 44. Piepoli Massimo F., Hoes Arno W., Agewall Stefan, Albus Christian, Brotons
527 Carlos, Catapano Alberico L., et al. 2016 European Guidelines on cardiovascular
528 disease prevention in clinical practice The Sixth Joint Task Force of the European
529 Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in
530 Clinical Practice (constituted by representatives of 10 societies and by invited
531 experts) Developed with the special contribution of the European Association for
532 Cardiovascular Prevention & Rehabilitation (EACPR). *European Heart Journal*
533 2016;37(29):2315-81.

534

535 **Figure 1. Forest plot for outcomes during the in-trial and overall follow-up.**

536 CI: Confidence interval, ALLHAT: Antihypertensive and Lipid-Lowering Treatment to
537 Prevent Heart Attack Trial Lipid-Lowering Trial, PREVEND-IT: Prevention of Renal and
538 Vascular Endstage Disease Intervention Trial.

539 **Figure 2. Forest plot for overall all-cause mortality in subgroup by 10-year**
540 **Framingham risk score.**

541 CI: Confidence interval, ALLHAT: Antihypertensive and Lipid-Lowering Treatment to
542 Prevent Heart Attack Trial Lipid-Lowering Trial, PREVEND-IT: Prevention of Renal and
543 Vascular Endstage Disease Intervention Trial.

544 **Figure 3. Forest plot for overall CVD mortality in subgroup by 10-year**
545 **Framingham risk score.**

546 CI: Confidence interval, ALLHAT: Antihypertensive and Lipid-Lowering Treatment to Prevent
547 Heart Attack Trial Lipid-Lowering Trial, PREVEND-IT: Prevention of Renal and Vascular
548 Endstage Disease Intervention Trial.

549

550

551 **Table 1. Baseline characteristics of included participants**

Characteristics	Delayed			Early		
	ALLHAT	PREVEND-IT	Oslo	ALLHAT	PREVEND-IT	Oslo
Number of observations, n	509	70	379	3303	79	406
Age (mean \pm SD, years)	59.5 \pm 2.9	52.3 \pm 8.0	45.2 \pm 2.8	59.5 \pm 2.9	50.3 \pm 8.2	45.3 \pm 2.9
Black, %	34.6*	0	NA	43.6	1.3	NA
Male, %	52.8*	64.3	100	46.3	65.8	100
Current Smoker, %	43.8*	32.9	42.5	34.6	34.2	40.9
BMI (mean \pm SD, kg/m ²) [†]	29.9 \pm 5.9*	28.1 \pm 4.2	NA	31.3 \pm 7.1	27.7 \pm 4.7	NA
Diabetes [†] (%)	41.7*	2.9	0	51.1	2.5	0
SBPs (mean \pm SD, mmHg):	147\pm 7*	147 \pm 6	155 \pm 8	146 \pm 8	148 \pm 6	156 \pm 7
DBPs (mean \pm SD, mmHg):	88\pm7*	84 \pm 8	96 \pm 7	87\pm7	85 \pm 7	97 \pm 7
Fasting Serum Glucose [†] (mmol/L)	7.2\pm 3.5*	5.3 \pm 1.4	6.0 \pm 0.6	7.6 \pm 3.8	5.3 \pm 1.8	6.0 \pm 0.6
Total cholesterol (mmol/L)	5.6 \pm 1.1	6.1 \pm 1.1	7.1 \pm 1.2	5.7 \pm 1.2	6.1 \pm 0.9	7.1 \pm 1.2
HDL-c [†] (mmol/L)	1.2 \pm 0.4	1.0 \pm 0.3	NA	1.2 \pm 0.4	1.0 \pm 0.3	NA
Serum Creatinine [†] (umol/L)	82.2 \pm 27.4	82.4 \pm 14.0	96.9 \pm 13.7	84.0 \pm 27.4	84.8 \pm 14.5	97.2 \pm 14.0
10-year FRS, mean (SD)	27.7 \pm 12.8*	20 \pm 12	NA	34.2 \pm 15.5	21 \pm 16	NA

552 *: p<0.05 for the comparison between the delayed and early treatment groups. ALLHAT:
553 Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Lipid-Lowering Trial,
554 PREVEND-IT: Prevention of Renal and Vascular Endstage Disease Intervention Trial. NA: not available.
555 SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, BMI: Body Mass Index, HDL: High Density
556 Lipoprotein cholesterol, FRS: Framingham Risk Score.

557

558 **Table 2 Risk of bias**

Trial	Risk of bias domain								Overall
	Confounding	Selection of participants into the study	Classification of interventions	Randomisation process	Deviations from intended interventions	Missing data	Measurement of outcomes	Selection of the reported result	
ALLHAT	Serious	Low	Moderate	NA	NI	NI	Low	NA	Serious
PREVEND-IT	NA	NA	NA	Low	Low	Low	Low	Low	Low
Oslo	NA	NA	NA	Low	Low	Low	Low	Low	Low

559 NA – not applicable, NI: No Information. ALLHAT: Antihypertensive and Lipid-Lowering Treatment to

560 Prevent Heart Attack Trial Lipid-Lowering Trial, PREVEND-IT: Prevention of Renal and Vascular

561 Endstage Disease Intervention Trial