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## Effectiveness of Blood Pressure-Lowering Drug Treatment by Levels of Absolute Risk in the Australian National Blood Pressure Study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-017723
Article Type:	Research
Date Submitted by the Author:	12-May-2017
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<b>Primary Subject Heading</b>:	Cardiovascular medicine
Secondary Subject Heading:	General practice / Family practice
Keywords:	cardiovascular disease, antihypertensive drug, absolute cardiovascular risk, primary prevention, Hypertension < CARDIOLOGY

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Word count for text: 3388

**Title:** Effectiveness of Blood Pressure-Lowering Drug Treatment by Levels of Absolute Risk in the Australian National Blood Pressure Study

**Running head:** BP lowering drug treatment by absolute CVD risk.

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## Abstract

**Objectives:** In many current guidelines, blood pressure (BP) lowering drug treatment for primary prevention of cardiovascular disease (CVD) is based on absolute risk. However, in clinical practice, therapeutic decisions are often based on BP levels alone. We sought to investigate which approach was superior by conducting a post-hoc analysis of the Australian National Blood Pressure (ANBP) cohort, a seminal study establishing the efficacy of BP lowering in 'mild hypertensive' persons.

**Design:** a post-hoc subgroup analysis of the ANBP trial.

**Setting and participants:** 3,244 participants aged 35 to 69 years in a community-based randomised placebo controlled trial of blood pressure lowering medication.

**Interventions:** Chlorothiazide 500 mg vs placebo.

**Primary outcome measures:** All-cause mortality and non-fatal events (non-fatal CVD, congestive cardiac failure, renal failure, hypertensive retinopathy or encephalopathy).

## Results

Treatment effects were assessed by hazard ratio, absolute risk reduction and number needed to treat. Participants had an average 5-year CVD risk in the intermediate range ( $10.5 \pm 6.5$ ) with moderately elevated BP (159/103 mmHg) and were middle-aged ( $52 \pm 8$  years). In subgroup analysis, relative and absolute effects did not statistically differ across the three risk groups except the absolute benefit in all-cause mortality. With respect to absolute benefit, drug treatment significantly reduced the number of events in the high-risk group regarding any event with a

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3 Number Needed to Treat of 18 (10, 64), death from any cause with 45 (25, 196) and  
4 major cardiovascular disease events with 23 (12, 193).  
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## 7 **Conclusion**

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10 Our analysis confirms that the benefit of treatment was substantial only in the high-  
11 risk tertile, reaffirming the rationale of treating elevated blood pressure in the setting  
12 of all risk factors rather than in isolation.  
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17 **Key Words:** antihypertensive drug, cardiovascular disease, absolute cardiovascular  
18 risk, primary prevention, hypertension.  
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## 22 **Strengths and limitations of this study**

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25 Our analysis provides further justification that an absolute risk strategy is superior to  
26 management based on the BP level alone in identifying those who are most likely to  
27 benefit from therapy.  
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32 The statistical power of detecting treatment effects was decreased in a post-hoc  
33 subgroup analysis. However the use of multivariate risk score is known to increase  
34 power of detecting heterogeneity in absolute risk benefit.  
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39 Due to the lack of high density lipoprotein cholesterol in the original data set (HDLc),  
40 the HDLc used in the analyses was estimated from the 1980s national survey, but  
41 this method is unlikely to greatly affect the risk stratification because a 0.4 difference  
42 in the HDLc estimate only results in a 1% difference in CVD risk score.  
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## Introduction

For decades, cardiovascular disease (CVD) has remained the main burden of disease in the developed world and now also in the developing world<sup>1,2</sup>. In 2012, CVD was responsible for 17.5 million deaths in the world and more than twenty thousand deaths in Australia<sup>1,3</sup>. Noticeably, nearly 50% of deaths from CVD are attributable to high blood pressure (BP), the commonest modifiable population risk factor<sup>4</sup>. Drug therapy for primary prevention of CVD is now recommended to be based on absolute CVD risk, where BP lowering drug treatment is determined by BP level together with other major CVD risk factors (e.g. sex, age, total cholesterol, high-density lipoprotein cholesterol, diabetes and smoking status) as an integrated score<sup>5-9</sup>. Yet clinicians are reticent to treat systolic BP in those below 140 mmHg as well as not treat those above this figure. There is a paucity of literature on the effects of lowering BP in low to moderate CVD risk individuals with mildly elevated BP (systolic BP from 140 mmHg to 159 mmHg and/or diastolic BP from 90 to 99) and some debate regarding its benefit<sup>10</sup>. Guidelines from the US and Europe focus on BP thresholds and promote early drug treatment due to the potential benefits of earlier intervention and potential adverse effects of delayed intervention<sup>6,7,11-13</sup>. JNC 8 recommends initiating drug treatment at the threshold of 150 mmHg systolic BP or 90 mmHg diastolic BP for the general population at 60 years or older<sup>11</sup>. This revised recommendation has caused controversy amongst clinicians who argue that drug treatments need to be initiated at a lower systolic BP of 140 mmHg, as previously recommended in JNC 7<sup>14</sup>, otherwise patients are exposed to increased risk<sup>15-18</sup>. Specifically, the SPRINT trial<sup>19</sup> reported a significant benefit of intensive treating of lowering BP to a target of 120 mmHg rather than 140 mmHg. However, this benefit was observed in those at high CVD risk without diabetes. In agreement with the

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3 findings from the SPRINT trial, guidelines in Australia <sup>5</sup>, New Zealand <sup>20</sup>, UK <sup>8</sup> and  
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5 Canada <sup>9</sup> based on absolute CVD risk propose to initiate BP lowering treatment as  
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7 soon as possible in high CVD risk individuals, but not in low to moderate risk  
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9 population unless BP persistently exceeds 160/100 mmHg.  
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12 Recently, the HOPE-3 investigators reported a non-significant effect of a  
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14 fixed-dose combination of BP lowering drug treatment in reducing the rate of major  
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16 CVD events in intermediate CVD risk older persons <sup>21</sup>. Similarly, a Cochrane review  
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18 by Diao et al reported no strong benefit of BP treatment in individuals who had grade  
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20 1 hypertension <sup>10</sup>. In contrast, the 2015 Blood Pressure Lowering Treatment Trialists  
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22 Collaboration (BPLTTC) meta-analysis reported a substantial benefit of BP lowering  
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24 drug treatment in grade 1 hypertension in terms of stroke and all-cause mortality <sup>22</sup>.  
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26 However, these stronger treatment effects could reflect differences in the BPLTTC  
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28 sample that included participants who had diabetes and had previously received  
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30 drug treatment. In a 2014 individual patient data meta-analysis, BPLTTC stratified  
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32 the participants by absolute CVD risk at baseline, though the study mixed  
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34 participants who did and did not have a history of CVD <sup>23</sup>.  
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39 Thus, we sought to reanalyse a seminal study used to justify treating  
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41 individuals with 'mildly' elevated BP to see if stratification by baseline CVD risk would  
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43 be a superior method for identifying candidates for BP-lowering medication. In this  
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45 study, we compared the effectiveness of BP lowering drug treatment by a post-hoc  
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47 subgroup analysis of the Australian National Blood Pressure study (ANBP). We  
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49 restricted the analysis group to individuals with no history of CVD or diabetes, and  
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51 who were naïve to BP lowering treatment. We selected this historic study because it  
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53 was placebo controlled and patients in the control arm of the study would not have  
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55 been taking a BP lowering medication unless they had very high levels of BP. Our  
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3 aim was to assess which group of individuals classified by absolute risk benefited  
4 from active treatment vs. placebo for CVD events within this seminal study that  
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7 underwrote the treatment of elevated BP by BP thresholds.  
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## 10 **Methods**

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12 We performed a post-hoc analysis of the Australian National Blood Pressure  
13 (ANBP) study. The study was conducted between 1973 and 1979 and was a  
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15 multicentre, single-blind randomised controlled trial which compared the effects of  
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17 BP lowering drug therapy between individuals who initially received active treatment  
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19 (chlorothiazide) and those who received delayed active treatment or no active  
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21 treatment (placebo). The study intervention has remained applicable in current  
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23 practice when thiazide diuretic is recommended in the majority of patients. At entry,  
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25 all of the eligible participants were not on treatment for hypertension in past three  
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27 months and had no history of CVD or diabetes. In the 1970s, 'mild hypertension'  
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29 was defined as a screening diastolic BP of 95 to 109 mmHg with a systolic BP lower  
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31 than 200 mmHg. 3,931 eligible participants were initially randomised, then 504  
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33 participants were excluded because their BP throughout the study did not meet the  
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35 criteria for starting drug treatment (entry or follow-up diastolic BP higher than 95  
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37 mmHg and/or entry or follow-up systolic BP higher than 200 mmHg). The primary  
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39 endpoints were all-cause mortality and non-fatal events (non-fatal CVD, congestive  
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41 cardiac failure, renal failure, hypertensive retinopathy or encephalopathy)<sup>24</sup>.  
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### 48 *Risk stratification*

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50 The baseline absolute CVD risk was calculated according to the 5-year  
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52 Framingham absolute risk score. The Framingham score was chosen because it is  
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54 currently recommended in the National Vascular Disease Prevention Alliance  
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(NVDPA) guidelines<sup>5</sup> in Australia. The sample was restricted to ages 35 to 74. We also classified all participants with very high BP (systolic BP  $\geq$  180 mmHg and/or diastolic BP  $\geq$  110 mmHg) or total cholesterol ( $>$  7.5 mmol/l) values as high CVD risk regardless of their risk score, as per the guidelines<sup>5</sup>. The ANBP dataset included all variables required for CVD risk calculation except high-density lipoprotein cholesterol (HDLc). The HDLc value was estimated from the Australian National Heart Foundation risk factor prevalence study as this was near contemporaneous with the ANBP<sup>25</sup>. Mean value of HDLc was categorised by age and sex. Missing data of less than 1% in total cholesterol, weight and height were managed by multiple imputation using chained equations.

### *Statistical analysis*

All analyses were based on the modified 'intention to treat' principle. We included participants who prematurely stopped study interventions in all analyses. The differences in baseline characteristics between 'active group' and 'placebo group' were tested by ANOVA test for continuous variables and Chi-square test for categorical variables. Treatment effects were assessed by hazard ratio (HR), absolute risk reduction (ARR) and number needed to treat (NNT). The HRs and corresponding 95% confidence intervals were estimated by Cox proportional hazard model after adjusting for clustering of participants within community-based centers and potential risk factors including baseline characteristics. The proportional assumption was checked by the test for interaction of HR with time. ARR and NNT were estimated from Kaplan-Meier curves at the median of follow-up time (4.4 years)<sup>26</sup>. Tests for interaction of treatment effect over the subgroups were obtained by the Cox regression model for the Hazard ratio and a Cochran's Q test for the absolute risk reduction. The threshold for significance for treatment effect was set at 0.05 for

the main analysis and subgroup analysis. Only one subgroup analysis with related outcomes was conducted, thus multiplicity was not likely to affect our results.

## Results

### Patient characteristics

Table 1 provides baseline characteristics of the participants stratified by the tertile of CVD risk score. On average, study participants had intermediate 5-year CVD risk ( $10.5 \pm 6.5$ ) with moderately elevated BP (159/103 mmHg) and were middle-aged ( $52 \pm 8$ ). The three risk groups were defined as having estimated 5-year CVD risks of less than 6.1%, 6.1 to 17.0% and more than 17.0%. The distribution of baseline characteristics by treatment assignment was not significantly different except for body mass index (BMI) in the total population, the number of smokers in the low-risk group, systolic BP and BMI in the moderate risk group.

Table 1. Baseline characteristics stratified by tertile of baseline CVD risk score.

Group variable	Total	Low ( $<6.1\%$ )	Moderate ( $6.1 - 17.0\%$ )	High ( $>17.0\%$ )
Sample, N	3244	1082	1081	1081
Age, years	$51.7 \pm 8.1$	$46.0 \pm 6.2$	$54.5 \pm 6.5$	$54.6 \pm 8.1$
Male sex, N (%)	2017 (62.2)	567 (52.4)	804 (74.4)	646 (59.8)
Current smoker, N (%)	801 (24.7)	115 (10.6)	352 (32.6)	334 (30.9)
SBP, mmHg	$159.5 \pm 17.5$	$148.4 \pm 12.2$	$157.3 \pm 12.2$	$172.6 \pm 17.9$
DBP, mmHg	$102.9 \pm 6.8$	$100.0 \pm 3.8$	$100.8 \pm 4.4$	$107.9 \pm 8.2$
Total cholesterol, mmol/l	$6.0 \pm 1.1$	$5.5 \pm 0.9$	$6.0 \pm 0.9$	$6.5 \pm 1.3$
BMI, kg/m <sup>2</sup>	$26.6 \pm 3.9$	$26.6 \pm 4.0$	$26.5 \pm 3.6$	$26.7 \pm 4.1$

SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body - mass index.

Approximately one-third of the participants (34.5%) prematurely stopped study treatment due to decisions by clinics, participants' doctors, and the participant themselves, or for unknown reasons (Table 2). Participants' doctors were more likely to stop placebo treatment in all three risk groups, whereas clinics withdrew more BP-lowering drug-randomised participants in the low-risk group and the high-risk group. No substantial difference in baseline characteristics between the two randomised treatment groups was recorded in any risk group.

Table 2. Characteristics of those who prematurely stopped study regimen.

Group variable	Total	Low (<6.1%)	Moderate (6.1-17.0%)	High (>17.0%)
Sample, N	1119	404	346	369
Age, years	51.2 ± 8.3	45.9 ± 6.4	54.1 ± 7.0	54.2 ± 8.5
Male sex, N (%)	626 (55.9)	188 (46.5)	243 (70.2)	195 (52.9)
Current smoker, N (%)	321 (28.7)	58 (14.4)	143 (41.3)	120 (32.5)
SBP, mmHg	159.1 ± 18.1	147.6 ± 12.9	157.0 ± 11.9	173.7 ± 17.7
DBP, mmHg	102.9 ± 6.8	100.0 ± 4.0	100.6 ± 4.2	108.1 ± 8.2
Total cholesterol, mmol/l	6.0 ± 1.1	5.5 ± 0.9	6.0 ± 0.9	6.4 ± 1.3
BMI, kg/m <sup>2</sup>	26.7 ± 4.1	26.7 ± 4.0	26.6 ± 3.9	26.8 ± 4.5
Reason for stopping				
Clinic, N (%)	204 (18.2)	74 (18.3)	75 (21.7)	55 (14.9)
Local doctor, N (%)	287 (25.7)	98 (24.3)	87 (25.1)	102 (27.6)
Participants, N (%)	548 (49.0)	204 (50.5)	162 (46.8)	182 (49.3)
Not known, N (%)	80 (7.2)	28 (6.9)	22 (6.4)	30 (8.1)

SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body - mass index

### Effect of BP lowering drug treatment on total study population

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3 During a median follow-up of 4.4 years (IQR 1.0 – 5.9), 257 major CVD  
4 events (7.9%) were observed, in which ischemic heart disease accounted for 203  
5 events (6.3%), stroke 48 events (1.5%) and congestive heart failure 6 events (0.2%).  
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10 After adjustment for sex, age, BMI, smoking, systolic BP at baseline and study  
11 centers, BP lowering treatment was associated with a 15% reduction in non-fatal  
12 events and a 25% reduction in all-cause mortality (Figure 1). However, the treatment  
13 effects were not statistically significant in our analysis. Similar effects were found in  
14 the secondary endpoints including any events HR 0.82 (0.65 – 1.03), major CVD  
15 events HR 0.83 (0.65 – 1.07) and non-fatal CVD events HR 0.87 (0.67 – 1.13). We  
16 also identified a marginally significant effect in stroke HR 0.55 (0.3 – 1.001).  
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### 26 **Effect of BP lowering drug treatment on 5 year-CVD risk groups**

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28 In the subgroup analysis, the magnitude of relative treatment effect increased  
29 from low to high CVD risk group, though the benefits were not statistically significant  
30 in the high-risk group in terms of all-cause mortality 0.60 (0.26 - 1.40) and major  
31 CVD event with HR 0.76 (0.52 - 1.10).  
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38 The increasing trend for the benefit was also observed when comparing the  
39 absolute treatment effects (absolute risk reduction – ARR) among the three risk  
40 groups. No evidence of heterogeneity was observed except the effect in the major  
41 CVD event. Substantial effects of BP lowering treatment were produced in the high-  
42 risk group regarding any trial endpoints [ARR 5.6 (1.6, 9.6)], all-cause mortality [ARR  
43 2.2 (0.5, 3.9)] and any CVD event [4.3 (0.5, 8.1)] (Table 3). Treating 18 high-risk  
44 participants for 4 years prevented one trial event, treating 45 prevented one death  
45 and treating 23 prevented one CVD event. In contrast, treating low or moderate risk  
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participants needed much higher numbers to prevent one event or possibly caused net harm (Table 3).

Table 3. Effect of treatment by tertile of baseline CVD risk score.

	Event (%)		Adjusted HR (95% CI)*	ARR % (95% CI)	NNT
	Active	Placebo			
<b>Any event</b>					
Low	22 (3.9)	23 (4.4)	0.94 (0.52 - 1.70)	-0.3 (-2.7, 2.1)	-370 (-37, 47)
Moderate	56 (10.9)	67 (11.8)	0.93 (0.65 - 1.33)	1.1 (-2.9, 5.2)	87 (-34, 19)
High	59 (10.7)	75 (14.1)	0.75 (0.53 - 1.06)	<b>5.6 (1.6, 9.6)</b>	<b>18 (10, 64)</b>
p - value	-	-	0.64	0.05	-
<b>All-cause mortality</b>					
Low	6 (1.1)	6 (1.2)	0.96 (0.30-3.01)	-0.5 (-1.6, 0.7)	-213 (-63, 153)
Moderate	10 (2.0)	13 (2.3)	0.81 (0.35 - 1.86)	0.2 (-1.7, 2.1)	476 (-60, 48)
High	9 (1.6)	14 (2.6)	0.60 (0.26 - 1.40)	<b>2.2 (0.5, 3.9)</b>	<b>45 (25, 196)</b>
p - value	-	-	0.78	<b>0.04</b>	-
<b>Non-fatal event</b>					
Low	16 (2.9)	17 (3.3)	0.93 (0.47 - 1.87)	0.2 (-1.9, 2.3)	476 (-52, 43)
Moderate	46 (9.0)	54 (9.5)	0.96 (0.65 - 1.43)	0.9 (-2.8, 4.5)	118 (-35, 22)
High	50 (9.1)	61 (11.5)	0.80 (0.55- 1.16)	3.3 (-0.4, 7.0)	30 (-249, 14)
p - value	-	-	0.77	0.36	-
<b>Major CVD event</b>					
Low	17 (3.0)	18 (3.4)	0.98 (0.50 - 1.91)	0.2 (-1.9, 2.3)	476 (-52, 43)
Moderate	50 (9.8)	58 (10.2)	0.98 (0.67 - 1.43)	0.6 (-3.2, 4.5)	164 (-31, 22)
High	50 (9.1)	64 (12.1)	0.76 (0.52 - 1.10)	<b>4.3 (0.5, 8.1)</b>	<b>23 (12, 193)</b>
p - value	-	-	0.62	0.17	-
<b>Any CHD</b>					
Low	17 (3.0)	14 (2.7)	1.21 (0.59 - 2.48)	-0.4 (-2.4, 1.6)	-256 (-41, 61)
Moderate	39 (7.6)	47 (8.3)	0.93 (0.60 - 1.42)	1.1 (-3.0, 5.1)	94 (-33, 19)

High	41 (7.5)	45 (8.5)	0.90 (0.59 - 1.37)	1.9 (-1.4, 5.3)	52 (-72, 19)
p - value	-	-	0.83	0.47	-

CVD: cardiovascular disease, CHD: coronary heart disease, HR: hazard ratio, CI: confidence interval, ARD: absolute risk difference, NNT: number needed to treat. NNTB: number needed to treat (benefit). NNTH: number needed to treat (harm). p-value indicated p for interaction.

\* Adjusted for age, sex, body-mass index, smoking, screening centres and systolic blood pressure. **Bold** p<0.05

## Discussion

In our post hoc analysis of the ANBP study we found substantial beneficial effects of BP lowering treatment in the high-risk tertile for any trial endpoints and any CVD event with low or moderate risk participants unlikely to benefit. Our study population had an overall moderate 5-year CVD risk (10.5%) and moderately elevated systolic BP (159/103 mmHg) by modern definitions. The ANBP study aimed to treat 'mild hypertension' that was primarily defined by diastolic BP. Some randomised participants were excluded from their analysis because they did not meet the criteria for starting BP lowering drug treatment post randomisation. This would not be seen in modern clinical trials. In our reanalysis we found that BP lowering drug treatment reduced the risk of major CVD events and all-cause mortality, but the effect was not statistically significant. This is likely to be due to reduced power as the cohort was analysed in three groups by tertile of absolute risk rather than two groups by randomised therapy. The original study found a statistically significant reduction in the incidence of CVD mortality and all trial endpoints, using the full dataset and a risk ratio rather than time-to-event analysis<sup>24</sup>.

In our analysis of subgroups defined by CVD risk score, the magnitude of relative treatment effects (relative risk reduction) on all-cause mortality and major CVD events increased across all three CVD risk group from low to high risk, without

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3 statistically significant heterogeneity ( $p = 0.78$  for all-cause mortality and  $p = 0.62$  for  
4 the major CVD event) (Table 3). In terms of absolute benefits, risk reduction linearly  
5 increased across the CVD risk group from low to high risk. BP lowering drug  
6 treatment produced an unclear benefit in the low and intermediate CVD risk group  
7 but a significant benefit in the high CVD risk group. Heterogeneity of absolute  
8 effects across the CVD risk groups was only significant in all-cause mortality  
9 ( $p=0.04$ ).

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19 Regarding the benefit of BP lowering drug treatment in the low to intermediate  
20 CVD risk population, our results from main and subgroup analyses match well with  
21 the study outcomes from the HOPE-3 trial<sup>21</sup> and the Diao review<sup>10</sup>. In the HOPE-3  
22 trial, no benefit of intensive drug treatment was established in the intermediate-risk  
23 persons with HR 0.98 (0.84-1.14) for all-cause mortality and HR 0.92 (0.79 – 1.06)  
24 for major CVD events referred as a first secondary outcome in the paper<sup>21</sup>. At  
25 baseline, the HOPE-3 participants were older (65 years), had a lower level of BP  
26 (138.1/81.9 mmHg) compared to the ANBP participants. This may be due to the 4-  
27 week run-in phase in which all of the HOPE-3 participants received active BP  
28 lowering drug treatment before randomisation and one-fifth of all eligible participants  
29 had previously received drug treatment before the trial. In 2012, Diao et al reviewed  
30 placebo randomised controlled trials in grade 1 hypertension and also found no  
31 beneficial effect of drug treatment with a risk ratio (RR) 0.85 (0.63 – 1.15) for all-  
32 cause mortality and RR 0.97 (0.2 – 1.32) for major CVD events<sup>10</sup>. The participants in  
33 the Diao review were likely to have a lower CVD risk than those in the ANBP and the  
34 HOPE-3 when major CVD events occurred in 2.4% of participants in the placebo  
35 group. Following a similar approach, in 2015, The Blood Pressure Lowering  
36 Treatment Trialists' Collaboration (BPLTTC)<sup>23</sup> reviewed randomised controlled trials  
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3 in grade 1 hypertension but extended to trials comparing active or more intensive  
4 regimen and placebo or less intensive regimen. In line with the findings from the  
5 2015 BPLTTC study, we identified a marginally significant effect on stroke, yet our  
6 effect estimates with an HR 0.75 (0.45 – 1.36) for total deaths and an HR 0.83 (0.65  
7 – 1.07) for major CVD events slightly differed from the 2015 BPLTTC study's results  
8 with an OR 0.78 (0.67-0.92) and an OR 0.86 (0.74-1.01) correspondingly. The  
9 differences in confidence intervals may be due to the difference in sample sizes and  
10 baseline characteristics. It is more likely that the 2015 BPLTTC participants had  
11 higher CVD risk and higher BP value at baseline when about 40% of 15,266  
12 participants had diabetes and about 23% previously received BP lowering drug  
13 treatment. Our study and the 2015 review confirmed the absolute benefits of BP  
14 lowering drug treatment in high CVD risk population in terms of total deaths with  
15 ARR 2.2% (0.5, 3.9, p=0.01) for the ANBP and ARR 1.4% (0.5, 2.2) for the review.  
16 Furthermore, the benefit was also recorded in major CVD event with ARR 4.3% (0.5,  
17 8.1, p=0.03) in the ANBP, whereas the 2015 BPLTTC observed a non-significant  
18 effect with ARR 1.0% (-0.1, 1.9). The difference can be explained in part by the  
19 study design when more than 50% of participants with systolic BP higher than 160  
20 mmHg in eligible studies in the 2015 BPLTTC were excluded. The distribution of  
21 these excluded participants might not be even between active arm and control arm,  
22 thus biasing the treatment effects.

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25 In another subgroup analysis stratified by tertile of baseline systolic BP  
26 (supplement), the mean value of CVD risk varied from low to high corresponding to  
27 the lowest and the highest tertile. The relative treatment benefits were not  
28 statistically significant, but in terms of absolute effects, BP lowering drug treatment  
29 substantially reduced any trial events, all-cause mortality and major CVD events



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3 within the highest tertile. The findings were in line with what we found in the CVD  
4 risk-stratified subgroup when all participants in the highest BP-stratified tertile had  
5 high CVD risk score ( $20.7 \pm 9.5$ ). The substantial absolute benefits recorded in the  
6 highest BP-stratified tertile were more likely to be influenced by baseline CVD risk.  
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## 10 11 12 **Limitations**

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15 There are a number of limitations of our study. Firstly, statistical power is  
16 unavoidably decreased in a post-hoc subgroup analysis. However, the multivariate  
17 risk score used in our analysis has been well validated globally and within the  
18 Australian population<sup>5</sup>. Using such a score for stratification is known to increase  
19 power of detecting heterogeneity in absolute risk benefit over subgroup analyses that  
20 are based on individual risk factors<sup>27</sup>. A prospective study to address the issue of  
21 whether there is an advantage in treating blood pressure by AR is unlikely to be  
22 performed, because of the very large sample size and very long follow-up time  
23 required. Furthermore, placebo controlled contemporary BP lowering drug trials are  
24 not conducted in hypertensive populations due to established efficacy. Therefore,  
25 re-analysis of the early placebo-controlled trials seems to be the most feasible  
26 approach for assessing the effects of delayed versus early drug treatment in  
27 individuals with varying CVD risk together and elevated BP.  
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44 Secondly, the estimation of HDLc from the 1980s national survey may alter  
45 the CVD risk score, but we do not believe this method greatly affected the risk  
46 stratification because a 0.4 difference in the HDL estimate only results in a 0.01  
47 difference in CVD risk score. Furthermore, no association between HDLc and BP  
48 has been observed<sup>28,29</sup>. Also, we performed a sensitivity analysis by using the  
49 GLOBORISK score<sup>30</sup> that does not require HDLc value and is validated in individuals  
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3 over 40 years. The equation for the Australian population was obtained by personal  
4 contact with the author (Peter Ueda, unpublished data, 2016). This analysis  
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6 excluded 471 participants younger than 40 years and confirmed our original findings  
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8 except that the absolute risk reduction in major CVD event is no longer statistically  
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10 significant with ARR 3.4% (-0.4,7.3,  $p = 0.08$ ). This result is likely due to the smaller  
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12 sample size and subsequent number of events. In conclusion, the sensitivity  
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14 analysis supports our main analysis. Thirdly, the paucity of trial endpoints in each  
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16 CVD risk group prevented us from comparing the effects in some specific outcomes  
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18 with respect to stroke and deaths from CVD.  
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23 In conclusion, our research has demonstrated that drug treatment in patients  
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25 with elevated BP is best directed to those at high risk of incident CVD events. This  
26  
27 reinforces the guidelines recommendation to treat based on absolute (or global) CVD  
28  
29 risk, rather than according to BP thresholds alone<sup>5-9</sup>.  
30  
31

### 32 **Competing interests:**

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34  
35 CLBH is a Ph.D. candidate at Menzies Institute for Medical Research, she has  
36  
37 received a Ph.D. scholarship from Merle Weaver Postgraduate Scholarship. JD is  
38  
39 supported by National Health and Medical Research Council Screening and Test  
40  
41 Evaluation Program Grant 633003. CR is supported by a National Health and  
42  
43 Medical Research Council Senior Research Fellowship (1045862). MRN has in the  
44  
45 last 5 years served on an advisory board for AMGEN.  
46  
47

### 48 **Funding:**

49  
50 The ANBP was supported by the National Health and Medical Research Council of  
51  
52 Australia, the Life Insurance Medical Research Fund of Australia and New Zealand,  
53  
54 the Victorian Government, the Clive and Vera Ramaciotti Foundations, and the  
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3 Raine Medical Research Foundation of Western Australia. In the current study, the  
4 researchers gratefully acknowledge the RACGP Foundation and Therapeutic  
5 Guidelines Ltd for their support of this project.  
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10 **Contributors:** MRN is responsible for the study conception and data archive from  
11 the Australian Data Archive. CLBH performed the analysed and drafted the  
12 manuscript. MB, CR, JD provided substantial support on statistical analyses. All  
13 authors made great contribution to the interpretation of data, critically revised the  
14 manuscript and approved the final version.  
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21 **Ethics approval:** This study was approved by the Tasmanian Health and Medical  
22 Human Research Ethics Committee (H0015252).  
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26 **Data sharing statement:** No additional data are available.  
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## 29 **References**

- 30  
31  
32 1. World Health Organisation. The top 10 causes of death [online database].  
33 <http://www.who.int/mediacentre/factsheets/fs310/en/>. Updated May, 2014  
34 Accessed November 13, 2015.  
35  
36  
37  
38 2. Australian Bureau of Statistics. Causes of Death, Australia, 2013;  
39 [http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2013~M](http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2013~Main%20Features~Leading%20Causes%20of%20Death~10001)  
40 [ain%20Features~Leading%20Causes%20of%20Death~10001](http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2013~Main%20Features~Leading%20Causes%20of%20Death~10001). Updated March 7,  
41 2016. Accessed November 30, 2016.  
42  
43  
44  
45  
46  
47 3. Australia Bureau of Statistics. Causes of Death, Australia. 2012.  
48 <http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/3303.0main+features10001201>  
49 2. Updated March 30, 2015. Accessed November 13, 2015.  
50  
51  
52  
53  
54  
55  
56  
57  
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59  
60

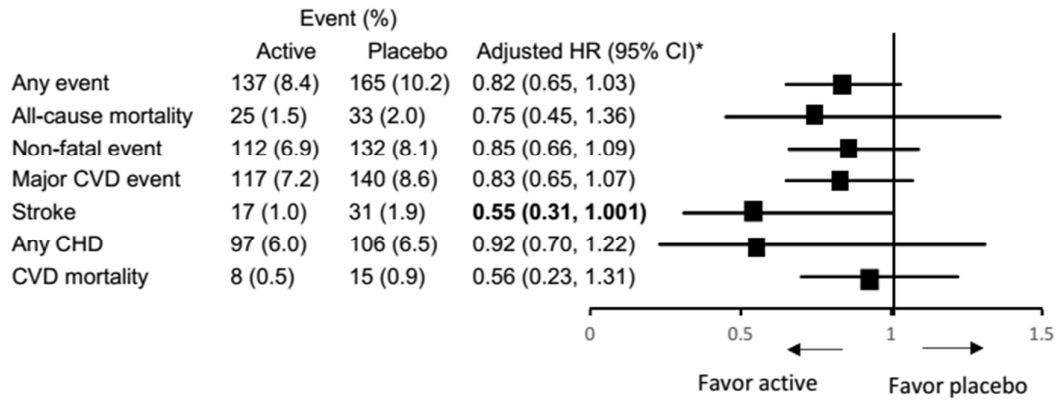
- 1  
2  
3 4. World Health Organisation (WHO). A Global Brief on Hypertension: Silent Killer,  
4  
5 Global Public Health Crisis [Online]. <http://www.thehealthwell.info/node/466541>.  
6  
7 Updated January 4, 2013. Accessed November 13, 2015.
- 8  
9 5. National Vascular Disease Prevention Alliance. *Guidelines for the management*  
10  
11 *of absolute cardiovascular disease*  
12  
13 *risk*. [http://www.cvdcheck.org.au/index.php?option=com\\_content&view=article&id=](http://www.cvdcheck.org.au/index.php?option=com_content&view=article&id=47&Itemid=27)  
14  
15 [47&Itemid=27](http://www.cvdcheck.org.au/index.php?option=com_content&view=article&id=47&Itemid=27). Updated May, 2012. Accessed November 13, 2015.
- 16  
17 6. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the  
18  
19 management of arterial hypertension. *Blood Pressure*. 2013;22(4):193-278.
- 20  
21 7. Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular  
22  
23 disease prevention in clinical practice (version 2012). The Fifth Joint Task Force  
24  
25 of the European Society of Cardiology and Other Societies on Cardiovascular  
26  
27 Disease Prevention in Clinical Practice (constituted by representatives of nine  
28  
29 societies and by invited experts). *Eur. Heart J*. 2012;33(13):1635-1701.
- 30  
31 8. Krause T, Lovibond K, Caulfield M, McCormack T, Williams B. Management of  
32  
33 hypertension: summary of NICE guidance. *BMJ*. 2011;343.
- 34  
35 9. Dasgupta K, Quinn RR, Zarnke KB, et al. The 2014 Canadian Hypertension  
36  
37 Education Program Recommendations for Blood Pressure Measurement,  
38  
39 Diagnosis, Assessment of Risk, Prevention, and Treatment of Hypertension. *Can.*  
40  
41 *J. Cardiol*. 2014;30(5):485-501.
- 42  
43 10. Diao D, Wright J, Cundiff D, Gueyffier F. Pharmacotherapy for mild hypertension.  
44  
45 *Cochrane Database of Systematic Reviews*. 2012;8:CD006742.
- 46  
47 11. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the  
48  
49 management of high blood pressure in adults: report from the panel members  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 appointed to the Eighth Joint National Committee (JNC 8). *Jama*.  
4  
5 2014;311(5):507-520.  
6  
7 12. World Health Organization. International Society of Hypertension Writing Group.  
8  
9 2003 World Health Organization (WHO)/International Society of Hypertension  
10  
11 (ISH) statement on management of hypertension. *Journal of hypertension*.  
12  
13 2003;21(11):1983-1992.  
14  
15 13. Weber MA, Schiffrin EL, White WB, et al. Clinical Practice Guidelines for the  
16  
17 Management of Hypertension in the Community. *The Journal of Clinical*  
18  
19 *Hypertension*. 2014;16(1):14-26.  
20  
21 14. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the joint national  
22  
23 committee on prevention, detection, evaluation, and treatment of high blood  
24  
25 pressure. *Hypertension*. 2003;42(6):1206-1252.  
26  
27 15. Mitka M. Groups spar over new hypertension guidelines. *JAMA*.  
28  
29 2014;311(7):663-664.  
30  
31 16. Guallar E, Laine C. Controversy Over Clinical Guidelines: Listen to the Evidence,  
32  
33 Not the Noise. *Ann. Intern. Med.* 2014;160(5):361-362.  
34  
35 17. Wright JJT, Fine LJ, Lackland DT, Ogedegbe G, Dennison Himmelfarb CR.  
36  
37 Evidence Supporting a Systolic Blood Pressure Goal of Less Than 150 mm Hg in  
38  
39 Patients Aged 60 Years or Older: The Minority ViewSystolic Blood Pressure Goal  
40  
41 for Patients Aged 60 Years or Older. *Ann. Intern. Med.* 2014;160(7):499-503.  
42  
43 18. Zanchetti A. Bottom blood pressure or bottom cardiovascular risk? How far can  
44  
45 cardiovascular risk be reduced? *Journal of hypertension*. 2009;27(8):1509-1520.  
46  
47 19. The SPRINT Research Group. A Randomized Trial of Intensive versus Standard  
48  
49 Blood-Pressure Control. *New England Journal of Medicine*. 2015;373(22):2103-  
50  
51 2116.  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 20. New Zealand Guidelines Group. *The assessment and management of*  
4 *cardiovascular risk*. Wellington, New Zealand Guidelines Group.  
5  
6 [http://www.health.govt.nz/publication/assessment-and-management-](http://www.health.govt.nz/publication/assessment-and-management-cardiovascular-risk)  
7 [cardiovascular-risk](http://www.health.govt.nz/publication/assessment-and-management-cardiovascular-risk). Updated July 8, 2015. Accessed November 13, 2015.  
8  
9
- 10  
11 21. Lonn EM, Bosch J, López-Jaramillo P, et al. Blood-Pressure Lowering in  
12 Intermediate-Risk Persons without Cardiovascular Disease. *New England Journal*  
13 *of Medicine*. 2016;374(21):2009-2020.  
14  
15
- 16 22. The Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of Blood  
17 Pressure Reduction in Mild Hypertension. A Systematic Review and Meta-  
18 analysis. *Ann. Intern. Med.* 2015;162(3):184-191.  
19  
20
- 21 23. The Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure-  
22 lowering treatment based on cardiovascular risk: a meta-analysis of individual  
23 patient data. *The Lancet*. 2014;384(9943):591-598.  
24  
25
- 26 24. The Management Committee. The Australian Therapeutic Trial in Mild  
27 Hypertension. *The Lancet*. 1980;315(8181):1261-1267.  
28  
29
- 30 25. Bennett SA, Magnus P. Trends in cardiovascular risk factors in Australia. Results  
31 from the National Heart Foundation's Risk Factor Prevalence Study, 1980-1989.  
32 *The Medical Journal of Australia*. 1994;161(9):519-527.  
33  
34
- 35 26. Bender R, Kromp M, Kiefer C, Sturtz S. Absolute risks rather than incidence  
36 rates should be used to estimate the number needed to treat from time-to-event  
37 data. *J. Clin. Epidemiol.* 2013;66(9):1038-1044.  
38  
39
- 40 27. Hayward RA, Kent DM, Vijan S, Hofer TP. Multivariable risk prediction can  
41 greatly enhance the statistical power of clinical trial subgroup analysis. *BMC Med.*  
42 *Res. Methodol.* 2006;6(1):1.  
43  
44  
45  
46  
47  
48  
49  
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- 1  
2  
3 28. Hughes K, Leong WP, Sothy SP, Lun KC, Yeo PPB. Relationships between  
4 Cigarette smoking, Blood Pressure and Serum Lipids in the Singapore General  
5 Population. *International Journal of Epidemiology*. 1993;22(4):637-643.  
6  
7  
8  
9 29. Catalano M, Aronica A, Carzaniga G, Seregni R, Libretti A. Serum lipids and  
10 apolipoproteins in patients with essential hypertension. *Atherosclerosis*.  
11 1991;87(1):17-22.  
12  
13  
14  
15 30. Hajifathalian K, Ueda P, Lu Y, et al. A novel risk score to predict cardiovascular  
16 disease risk in national populations (GloboRisk): a pooled analysis of prospective  
17 cohorts and health examination surveys. *Lancet Diabetes  
18 Endocrinol*. 2015;3(5):339-355.  
19  
20  
21  
22  
23  
24  
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Figure. Effect of treatment on the overall study population. CVD: cardiovascular disease, CHD for coronary heart disease. \*Adjusted for age, sex, body-mass index, screening centres, smoking and systolic blood pressure. **Bold** p<0.05



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Effect of treatment on the overall study population. CVD: cardiovascular disease, CHD for coronary heart disease. \*Adjusted for age, sex, body-mass index, screening centres, smoking and systolic blood pressure. Bold p<0.05

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Table 1. Baseline characteristics stratified by tertile of baseline systolic blood pressure

Group variable	1 <sup>st</sup> tertile (113-151 mmHg)	2 <sup>nd</sup> tertile (152 – 165 mmHg)	3rd tertile (166 – 225 mmHg)
Sample, N	1156	1014	1074
Age, years	48.8 ± 7.3	51.4 ± 7.8	55.1 ± 7.8
Male sex, N (%)	803 (69.5)	645 (63.6)	569 (53.0)
Current smoker, N (%)	285 (24.7)	251 (24.8)	265 (24.7)
SBP, mmHg	142.1 ± 7.0	158.2 ± 3.9	179.3 ± 11.7
DBP, mmHg	99.7 ± 4.1	102.7 ± 6.0	106.5 ± 8.0
Total cholesterol, mmol/l	5.9 ± 1.1	6.0 ± 1.1	6.1 ± 1.2
BMI, kg/m <sup>2</sup>	26.7 ± 3.6	26.5 ± 3.7	26.6 ± 4.4
CVD risk (%)	7.9 ± 8.7	12.8 ± 9.6	20.7 ± 9.5

SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body - mass index, CVD: cardiovascular disease.

Table 2. Effect of treatment by tertile of baseline systolic blood pressure.

	Event (%)		Adjusted HR (95% CI)*	ARR % (95% CI)	NNT
	Active	Placebo			
<b>Any event</b>					
113-151 mmHg	34 (5.6)	43 (7.8)	0.71 (0.45 -1.11)	2.5 (-0.7,5.6)	41 (-135, 18)
152 – 165 mmHg	49 (9.8)	46 (9.0)	1.07 (0.71 - 1.61)	-1.2 (-5.0, 2.7)	-87 (-20, 37)
166 – 225 mmHg	54 (10.5)	76 (3.6)	0.73 (0.51-1.03)	<b>4.8 (0.9, 8.8)</b>	<b>21 (11, 112)</b>
p-value	-	-	0.25	0.1	-
<b>All-cause mortality</b>					
113-151 mmHg	5 (0.8)	10 (1.8)	0.49 (0.17-1.46)	0.7 (-0.2, 1.7)	139 (-468, 60)
152 – 165 mmHg	11 (2.2)	8 (1.6)	1.30 (0.51 - 3.28)	-0.9 (-2.7, 0.9)	-110 (-36, 108)
166 – 225 mmHg	9 (1.7)	15 (2.7)	0.64 (0.28 - 1.46)	<b>1.9 (0.3, 3.6)</b>	<b>52 (28, 372)</b>
p – value	-	-	0.26	0.08	-
<b>Non-fatal event</b>					
113-151 mmHg	29 (4.8)	33 (6.0)	0.77 (0.47 - 1.28)	1.2 (-1.7, 1.5)	86 (-59, 25)
152 – 165 mmHg	38 (7.6)	38 (7.4)	1.00 (0.63 - 1.58)	-0.2 (-3.6, 1.7)	-455 (-27, 31)
166 – 225 mmHg	45 (8.7)	61 (10.9)	0.76 (0.52 - 1.13)	2.9 (-0.8, 1.8)	35 (-133, 15)
p – value	-	-	0.58	0.48	-
<b>Major CVD event</b>					
113-151 mmHg	31 (5.1)	35 (6.3)	0.79 (0.48 - 1.28)	1.6 (-1.3, 1.5)	61 (-74, 22)
152 – 165 mmHg	41 (8.2)	40 (7.8)	1.04 (0.67 - 1.61)	-0.4 (-4.0; 3.1)	-227 (-25, 32)
166 – 225 mmHg	45 (8.7)	65 (11.7)	0.73 (0.50 - 1.06)	<b>4.1 (0.4, 7.8)</b>	<b>24 (13, 242)</b>
p - value	-	-	0.39	0.22	-
<b>Any CHD</b>					
113-151 mmHg	30 (5.0)	29 (5.3)	0.93 (0.56 - 1.56)	0.4 (-2.4, 3.1)	286 (-42, 32)
152 – 165 mmHg	29 (5.8)	30 (5.9)	0.95 (0.57-1.59)	-0.1 (-3.1, 2.9)	-1250 (-32, 34)
166 – 225 mmHg	38 (7.4)	47 (8.4)	0.87 (0.57-1.34)	2.0 (-1.4, 5.4)	51 (-71, 19)
p - value	-	-	0.89	0.65	-

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3 CVD: cardiovascular disease, CHD: coronary heart disease, HR: hazard ratio, CI: confidence  
4 interval, ARD: absolute risk difference, NNT: number needed to treat. NNTB: number needed to treat  
5 (benefit). NNTH: number needed to treat (harm).p-value indicated p for interaction.  
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8 \* Adjusted for age, sex, body-mass index, smoking, screening centres and systolic blood pressure.  
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10 **Bold**  $p < 0.05$   
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# BMJ Open

## Effectiveness of Blood Pressure-Lowering Drug Treatment by Levels of Absolute Risk: Post-hoc analysis of the Australian National Blood Pressure Study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-017723.R1
Article Type:	Research
Date Submitted by the Author:	25-Aug-2017
Complete List of Authors:	Ho, Chau; University of Tasmania Menzies Institute for Medical Research, Breslin, Monique; University of Tasmania Menzies Institute for Medical Research Doust, Jenny; Bond University, Faculty of Health Sciences and Medicine Reid, Christopher ; Curtin University, School of Public Health; Monash University, CCRE Therapeutics, School of Public Health and Preventive Medicine Nelson, Mark; University of Tasmania, Menzies Research Institute
<b>Primary Subject Heading</b>:	Cardiovascular medicine
Secondary Subject Heading:	General practice / Family practice
Keywords:	cardiovascular disease, antihypertensive drug, absolute cardiovascular risk, primary prevention, Hypertension < CARDIOLOGY

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**Title:** Effectiveness of Blood Pressure-Lowering Drug Treatment by Levels of Absolute Risk: Post-hoc analysis of the Australian National Blood Pressure Study

**Running head:** BP lowering drug treatment by absolute CVD risk.

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## Abstract

**Objectives:** In many current guidelines, blood pressure (BP) lowering drug treatment for primary prevention of cardiovascular disease (CVD) is based on absolute risk. However, in clinical practice, therapeutic decisions are often based on BP levels alone. We sought to investigate which approach was superior by conducting a post-hoc analysis of the Australian National Blood Pressure (ANBP) cohort, a seminal study establishing the efficacy of BP lowering in 'mild hypertensive' persons.

**Design:** a post-hoc subgroup analysis of the ANBP trial results by baseline absolute risk tertile.

**Setting and participants:** 3,244 participants aged 35 to 69 years in a community-based randomised placebo controlled trial of blood pressure lowering medication.

**Interventions:** Chlorothiazide 500 mg vs placebo.

**Primary outcome measures:** All-cause mortality and non-fatal events (non-fatal CVD, congestive cardiac failure, renal failure, hypertensive retinopathy or encephalopathy).

## Results

Treatment effects were assessed by hazard ratio, absolute risk reduction and number needed to treat. Participants had an average 5-year CVD risk in the intermediate range ( $10.5 \pm 6.5$ ) with moderately elevated BP (mean 159/103 mmHg) and were middle-aged ( $52 \pm 8$  years). In a subgroup analysis, the relative effects (hazard ratio) and absolute effects (absolute risk reduction and number needed to treat) did not statistically differ across the three risk groups except for the absolute

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3 benefit in all-cause mortality ( $p$  for heterogeneity = 0.04). With respect to absolute  
4 benefit, drug treatment significantly reduced the number of events in the high-risk  
5 group regarding any event with a Number Needed to Treat of 18 (10, 64), death from  
6 any cause with 45 (25, 196) and major cardiovascular disease events with 23 (12,  
7 193).

## 14 **Conclusion**

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17 Our analysis confirms that the benefit of treatment was substantial only in the high-  
18 risk tertile, reaffirming the rationale of treating elevated blood pressure in the setting  
19 of all risk factors rather than in isolation.  
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24 **Key Words:** antihypertensive drug, cardiovascular disease, absolute cardiovascular  
25 risk, primary prevention, hypertension.  
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## 28 **Strengths and limitations of this study**

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- 32 • Our analysis provides further justification that an absolute risk strategy is  
33 superior to management based on the BP level alone in identifying those who  
34 are most likely to benefit from therapy.  
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  - 37 • The statistical power to detect treatment effects was limited in this study, and  
38 this is a post-hoc subgroup analysis.  
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  - 41 • Due to the lack of high density lipoprotein cholesterol in the original data set  
42 (HDLc), the HDLc used in the analyses was imputed from a 1980s national  
43 survey. The use of these imputed values is unlikely to greatly affect the risk  
44 stratification.  
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## Introduction

For decades, cardiovascular disease (CVD) has remained the greatest burden of disease in the developed world and now also in the developing world<sup>1,2</sup>. In 2012, CVD was responsible for 17.5 million deaths in the world and more than twenty thousand deaths in Australia<sup>1,3</sup>. Noticeably, nearly 50% of deaths from CVD are attributable to high blood pressure (BP), the commonest modifiable population risk factor<sup>4</sup>. Drug therapy for primary prevention of CVD is now recommended to be based on absolute CVD risk, where BP lowering drug treatment is determined by BP level together with other major CVD risk factors (e.g. sex, age, total cholesterol, high-density lipoprotein cholesterol, diabetes and smoking status) as an integrated score<sup>5-9</sup>. Yet clinicians are reticent to treat systolic BP in those below 140 mmHg at high risk as well as not treating patients at low risk with blood pressure above this threshold. There is a paucity of literature on the effects of lowering BP in low to moderate CVD risk individuals with Grade 1 hypertension (systolic BP from 140 mmHg to 159 mmHg and/or diastolic BP from 90 to 99) and some debate regarding its benefit<sup>10</sup>. Guidelines from the US and Europe focus on BP thresholds and promote early drug treatment due to the potential benefits of earlier intervention and potential adverse effects of delayed intervention<sup>6-8,11-13</sup>. JNC 8<sup>11</sup> recommends initiating drug treatment at the threshold of 150 mmHg systolic BP or 90 mmHg diastolic BP for the general population at 60 years or older. This revised recommendation has caused controversy amongst clinicians who argue that drug treatments need to be initiated at a lower systolic BP of 140 mmHg, as previously recommended in JNC 7<sup>14</sup>, otherwise patients are exposed to increased risk<sup>15-18</sup>. Similarly, the 2016 European Society of Cardiology guidelines recommend considering BP lowering drug treatment when systolic BP is greater than 140 mmHg

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3 and/or diastolic BP is greater than 90 mmHg after a reasonable period of time with  
4 lifestyle choice <sup>7</sup>. Recently, the SPRINT (Systolic Blood Pressure Intervention trial) <sup>19</sup>  
5 reported a significant benefit from intensive treatment to a target BP of 120 mmHg  
6 rather than 140 mmHg. However, this benefit was observed in those at high CVD  
7 risk without diabetes. In agreement with the findings from the SPRINT trial,  
8 guidelines in Australia <sup>5</sup>, New Zealand <sup>20</sup>, UK <sup>8</sup> and Canada <sup>9</sup> recommend BP  
9 lowering medication based on absolute CVD risk, recommending BP lowering  
10 treatment as soon as possible in high CVD risk individuals, but not in the low to  
11 moderate risk population unless BP persistently exceeds 160/100 mmHg.  
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23 Other groups <sup>21</sup> have argued for treatment of patients with grade 1  
24 hypertension even in patients at low risk based on evidence from a meta-analysis by  
25 Thomopolous et al<sup>22</sup> and the HOPE-3 study<sup>23</sup>. In contrast, a Cochrane review by  
26 Diao et al<sup>10</sup> concluded that there was no statistically significant effect of BP treatment  
27 in individuals who had grade 1 hypertension. The 2015 Blood Pressure Lowering  
28 Treatment Trialists Collaboration<sup>24</sup> (BPLTTC) meta-analysis reported a statistically  
29 significant benefit of BP lowering drug treatment in grade 1 hypertension in terms of  
30 stroke and all-cause mortality. However, the effects seen in the BPLTTC analysis  
31 could reflect differences in the BPLTTC sample that included participants who had  
32 diabetes, had a higher baseline risk and had previously received drug treatment. In  
33 another analysis of the BPLTTC individual patient data<sup>25</sup> by absolute CVD risk at  
34 baseline showed a continuously increasing benefit with baseline risk<sup>25</sup>. The BPLTTC  
35 study, however included participants who both did and did not have a history of CVD.  
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51 Thus, we sought to reanalyse a seminal study used to justify treating  
52 individuals with 'mildly' elevated BP to see if stratification by baseline CVD risk would  
53 be a superior method for identifying candidates for BP-lowering medication in a  
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3 treatment-naïve population. In this study, we compared the effectiveness of BP  
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5 lowering drug treatment by a post-hoc subgroup analysis of the Australian National  
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7 Blood Pressure study<sup>26</sup> (ANBP). We restricted the analysis group to individuals with  
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9 no history of CVD or diabetes, and who were naïve to BP lowering treatment. We  
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11 selected this historic study because it was placebo controlled and patients in the  
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13 control arm of the study would not have been taking a BP lowering medication  
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15 previously unless they had very high levels of BP. Our aim was to assess which  
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17 group of individuals classified by absolute risk benefited from active treatment vs.  
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19 placebo for CVD events within this seminal study that underwrote the treatment of  
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21 elevated BP by BP thresholds.  
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## 24 25 **Methods**

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28 We performed a post-hoc analysis of the Australian National Blood Pressure  
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30 study<sup>26</sup>. The study was conducted between 1973 and 1979 and was a multicentre,  
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32 single-blind randomised controlled trial of 3,427 patients which compared the effects  
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34 of BP lowering drug therapy between individuals who initially received active  
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36 treatment (chlorothiazide) and those who received delayed active treatment or no  
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38 active treatment (placebo). The study intervention remains applicable to current  
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40 practice as thiazide diuretic is still one of the first line of blood pressure lowering  
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42 agents<sup>5-9</sup>. The ANBP study enrolled participants who had not been on treatment for  
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44 hypertension in the past three months and had no history of CVD or diabetes. In the  
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46 1970s, 'mild hypertension' was defined as a screening diastolic BP of 95 to 109  
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48 mmHg with a systolic BP lower than 200 mmHg. 3,931 eligible participants were  
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50 initially randomised, then 504 participants were excluded because their BP  
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52 throughout the study did not meet the criteria for starting drug treatment (entry or  
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54 follow-up diastolic BP higher than 95 mmHg and/or entry or follow-up systolic BP  
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3 higher than 200 mmHg). The primary endpoints were all-cause mortality and non-  
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5 fatal events (non-fatal CVD, congestive cardiac failure, renal failure, hypertensive  
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7 retinopathy or encephalopathy)<sup>26</sup>.  
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### 9 10 *Risk stratification*

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12 In this analysis, the baseline absolute CVD risk was calculated according to  
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14 the 5-year Framingham absolute risk score<sup>27</sup>. The Framingham score was chosen  
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16 because it is currently recommended in the National Vascular Disease Prevention  
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18 Alliance (NVDPA) guidelines<sup>5</sup> in Australia. The sample was restricted to 3,244  
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20 participants who were older than 35 years. We also classified all participants with  
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22 very high BP (systolic BP  $\geq$  180 mmHg and/or diastolic BP  $\geq$  110 mmHg) or total  
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24 cholesterol ( $>$  7.5 mmol/l) values as high CVD risk regardless of their risk score, as  
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26 per the Australian guidelines<sup>5</sup>. The ANBP dataset included all variables required for  
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28 CVD risk calculation except high-density lipoprotein cholesterol (HDLc). The HDLc  
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30 value was imputed from the Australian National Heart Foundation risk factor  
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32 prevalence study as this was near contemporaneous with the ANBP<sup>28</sup>. Mean value  
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34 of HDLc was categorised by age and sex. In a sensitivity analysis, a subgroup  
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36 stratified by GLOBORISK score<sup>29</sup> that does not require HDLc value and is validated  
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38 in individuals over 40 years. The equation for the Australian population was  
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40 obtained by personal contact with the author (Peter Ueda, unpublished data, 2016).  
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42 This analysis excluded 471 participants younger than 40 years. Less than 1% of the  
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44 study participants had data missing for total cholesterol, weight and/or height and  
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46 these missing data were managed by multiple imputation using chained equations.  
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### 51 52 *Statistical analysis*

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All analyses were based on the modified 'intention to treat' principle. We included participants who had withdrawn from the study by their group allocation at randomisation in all analyses. The differences in baseline characteristics between 'active group' and 'placebo group' were tested by ANOVA test for continuous variables and Chi-square test for categorical variables. Treatment effects were assessed by hazard ratio (HR), absolute risk reduction (ARR) and number needed to treat (NNT). The HRs and corresponding 95% confidence intervals were estimated by Cox proportional hazard model after adjusting for clustering of participants within community-based centers and potential risk factors including baseline characteristics. The proportional assumption was checked by the test for interaction of HR with time. ARR and NNT were estimated from Kaplan-Meier curves at the median of follow-up time (4.4 years)<sup>30</sup>. Tests for interaction of treatment effect over the subgroups were obtained by the Cox regression model for the Hazard ratio and a Cochran's Q test for the absolute risk reduction. The threshold for significance for treatment effect was set at 0.05 for the main analysis and subgroup analysis. Only one subgroup analysis with related outcomes was conducted, thus multiplicity was not likely to affect our results.

## Results

### Patient characteristics

Table 1 provides baseline characteristics of the participants stratified by the tertile of CVD risk score. On average, study participants had intermediate 5-year CVD risk ( $10.5 \pm 6.5$ ) with moderately elevated BP (mean 159/103 mmHg) and were middle-aged ( $52 \pm 8$ ). The three risk groups were defined as having estimated 5-year CVD risks of less than 6.1%, 6.1 to 17.0% and more than 17.0%. The distribution of

baseline characteristics by treatment assignment was not significantly different except for body mass index (BMI) in the total population, the number of smokers in the low-risk group, systolic BP and BMI in the moderate risk group.

Table 1. Baseline characteristics stratified by tertile of baseline CVD risk score.

Group variable	Total	Low (<6.1 %)	Moderate (6.1 – 17.0%)	High (>17.0%)
Sample, N	3244	1082	1081	1081
Age, years	51.7 ± 8.1	46.0 ± 6.2	54.5 ± 6.5	54.6 ± 8.1
Male sex, N (%)	2017 (62.2)	567 (52.4)	804 (74.4)	646 (59.8)
Current smoker, N (%)	801 (24.7)	<b>115 (10.6)</b>	352 (32.6)	334 (30.9)
SBP, mmHg	159.5 ± 17.5	148.4 ± 12.2	<b>157.3 ± 12.2</b>	172.6 ± 17.9
DBP, mmHg	102.9 ± 6.8	100.0 ± 3.8	100.8 ± 4.4	107.9 ± 8.2
Total cholesterol, mmol/l	6.0 ± 1.1	5.5 ± 0.9	6.0 ± 0.9	6.5 ± 1.3
BMI, kg/m <sup>2</sup>	<b>26.6 ± 3.9</b>	26.6 ± 4.0	<b>26.5 ± 3.6</b>	26.7 ± 4.1

SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body - mass index. **Bold** p<0.05

based on the distribution of baseline characteristics by treatment assignment.

Approximately one-third of the participants (34.5%) prematurely stopped study treatment due to decisions by clinics, participants' doctors, and the participant themselves, or for unknown reasons (Table 2). Participants' doctors were more likely to stop placebo treatment in all three risk groups, whereas clinics withdrew more BP-lowering drug-randomised participants in the low-risk group and the high- risk group. No substantial difference in baseline characteristics between the two randomised treatment groups was recorded in any risk group.

Table 2. Characteristics of those who prematurely stopped study regimen.

Group variable	Total	Low (<6.1%)	Moderate (6.1-17.0%)	High (>17.0%)
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Sample, N	1119	404	346	369
Age, years	51.2 ± 8.3	45.9 ± 6.4	54.1 ± 7.0	54.2 ± 8.5
Male sex, N (%)	626 (55.9)	188 (46.5)	243 (70.2)	195 (52.9)
Current smoker, N (%)	321 (28.7)	58 (14.4)	143 (41.3)	120 (32.5)
SBP, mmHg	159.1 ± 18.1	147.6 ± 12.9	157.0 ± 11.9	173.7 ± 17.7
DBP, mmHg	102.9 ± 6.8	100.0 ± 4.0	100.6 ± 4.2	108.1 ± 8.2
Total cholesterol, mmol/l	6.0 ± 1.1	5.5 ± 0.9	6.0 ± 0.9	6.4 ± 1.3
BMI, kg/m <sup>2</sup>	26.7 ± 4.1	26.7 ± 4.0	26.6 ± 3.9	26.8 ± 4.5
Reason for stopping				
Clinic, N (%)	204 (18.2)	<b>74 (18.3)</b>	75 (21.7)	<b>55 (14.9)</b>
Local doctor, N (%)	287 (25.7)	<b>98 (24.3)</b>	<b>87 (25.1)</b>	<b>102 (27.6)</b>
Participants, N (%)	548 (49.0)	204 (50.5)	162 (46.8)	182 (49.3)
Not known, N (%)	80 (7.2)	28 (6.9)	22 (6.4)	30 (8.1)

SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body - mass index. **Bold**

p<0.05 based on the distribution of baseline characteristics by treatment assignment.

### Effect of BP lowering drug treatment on total study population

During a median follow-up of 4.4 years (IQR 1.0 – 5.9), 257 major CVD events (7.9%) were observed, in which ischemic heart disease accounted for 203 events (6.3%), stroke 48 events (1.5%) and congestive heart failure 6 events (0.2%).

After adjustment for sex, age, BMI, smoking, systolic BP at baseline and study centers, BP lowering treatment was associated with a 15% reduction in non-fatal events and a 25% reduction in all-cause mortality (Figure 1), although the treatment effects were not statistically significant. Similar effects were found in the secondary endpoints including any events HR 0.82 (0.65 – 1.03), major CVD events HR 0.83 (0.65 – 1.07) and non-fatal CVD events HR 0.87 (0.67 – 1.13). We identified a marginally significant effect in stroke HR 0.55 (0.3 – 1.001).

### Effect of BP lowering drug treatment on 5 year-CVD risk groups

In the subgroup analysis, the magnitude of relative treatment effect increased from low to high CVD risk group, though the benefits were not statistically significant in the high-risk group in terms of all-cause mortality 0.60 (0.26 - 1.40) and major CVD event with HR 0.76 (0.52 - 1.10).

The increasing trend for the benefit was also observed when comparing the absolute treatment effects (absolute risk reduction – ARR) among the three risk groups. No evidence of heterogeneity was observed except the effect in the major CVD event. Substantial effects of BP lowering treatment were produced in the high-risk group regarding any trial endpoints [ARR 5.6 (1.6, 9.6)], all-cause mortality [ARR 2.2 (0.5, 3.9)] and any CVD event [4.3 (0.5, 8.1)] (Table 3). Treating 18 high-risk participants for 4 years prevented one trial event, treating 45 prevented one death and treating 23 prevented one CVD event. In contrast, treating low or moderate risk participants needed much higher numbers to prevent one event or possibly caused net harm (Table 3). Also, a sensitivity analysis by using the GLOBORISK score<sup>29</sup> without using HDLc confirmed our original findings except that the absolute risk reduction in major CVD event is no longer statistically significant with ARR 3.4% (-0.4, 7.3, p = 0.08).

Table 3. Effect of treatment by tertile of baseline CVD risk score.

	Active	Placebo	Adjusted HR	ARR %	
	Event (rate per 1000 patient-yr)		(95% CI)*	(95% CI)**	NNT**
Any event					
Low	22 (8.9)	23 (10.0)	0.94 (0.52 - 1.70)	-0.3 (-2.7, 2.1)	-370 (-37, 47)
Moderate	56 (26.1)	67 (28.0)	0.93 (0.65 - 1.33)	1.1 (-2.9, 5.2)	87 (-34, 19)
High	59 (24.8)	75 (33.2)	0.75 (0.53 - 1.06)	<b>5.6 (1.6, 9.6)</b>	<b>18 (10, 64)</b>



p - value	-	-	0.64	0.05	-
<b>All-cause mortality</b>					
Low	6 (2.4)	6 (2.5)	0.96 (0.30-3.01)	-0.5 (-1.6, 0.7)	-213 (-63, 153)
Moderate	10 (4.4)	13 (5.1)	0.81 (0.35 - 1.86)	0.2 (-1.7, 2.1)	476 (-60, 48)
High	9 (3.5)	14 (5.7)	0.60 (0.26 - 1.40)	<b>2.2 (0.5, 3.9)</b>	<b>45 (25, 196)</b>
p - value	-	-	0.78	<b>0.04</b>	-
<b>Non-fatal event</b>					
Low	16 (6.4)	17 (7.4)	0.93 (0.47 - 1.87)	0.2 (-1.9, 2.3)	476 (-52, 43)
Moderate	46 (21.3)	54 (22.2)	0.96 (0.65 - 1.43)	0.9 (-2.8, 4.5)	118 (-35, 22)
High	50 (20.9)	61 (26.6)	0.80 (0.55- 1.16)	3.3 (-0.4, 7.0)	30 (-249, 14)
p - value	-	-	0.77	0.36	-
<b>Major CVD event</b>					
Low	17 (6.8)	18 (7.8)	0.98 (0.50 - 1.91)	0.2 (-1.9, 2.3)	476 (-52, 43)
Moderate	50 (23.2)	58 (24.0)	0.98 (0.67 - 1.43)	0.6 (-3.2, 4.5)	164 (-31, 22)
High	50 (20.9)	64 (28.0)	0.76 (0.52 - 1.10)	<b>4.3 (0.5, 8.1)</b>	<b>23 (12, 193)</b>
p - value	-	-	0.62	0.17	-
<b>Any CHD</b>					
Low	17 (6.8)	14 (6.0)	1.21 (0.59 - 2.48)	-0.4 (-2.4, 1.6)	-256 (-41, 61)
Moderate	39 (17.9)	47 (19.2)	0.93 (0.60 - 1.42)	1.1 (-3.0, 5.1)	94 (-33, 19)
High	41 (17.0)	45 (19.2)	0.90 (0.59 - 1.37)	1.9 (-1.4, 5.3)	52 (-72, 19)
p - value	-	-	0.83	0.47	-

CVD: cardiovascular disease, CHD: coronary heart disease, HR: hazard ratio, CI: confidence interval, ARD: absolute risk difference, NNT: number needed to treat. NNTB: number needed to treat (benefit). NNTH: number needed to treat (harm). p-value indicated p for interaction.

\* Adjusted for age, sex, body-mass index, smoking, screening centres and systolic blood pressure. \*\* As estimated by the Kaplan-Meier curve. **Bold** p<0.05

## Discussion

In our post hoc analysis of the ANBP study we found evidence of benefit from BP lowering treatment in the high-risk tertile for primary trial endpoints of any event

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3 and any CVD event with low or moderate risk participants unlikely to benefit. Our  
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5 study population had an overall moderate 5-year CVD risk (10.5%) and moderately  
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7 elevated systolic BP (mean 159/103 mmHg) by modern definitions. The ANBP study  
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9 aimed to treat 'mild hypertension' that was primarily defined by diastolic BP. Some  
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11 randomised participants were excluded from the original analysis because they did  
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13 not meet the criteria for starting BP lowering drug treatment post randomisation. This  
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15 would not be seen in modern clinical trials. In our reanalysis we found that BP  
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17 lowering drug treatment reduced the risk of major CVD events and all-cause  
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19 mortality, but the effect was not statistically significant. This is likely to be due to  
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21 reduced power as the cohort was analysed by tertile of absolute risk, as well as by  
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23 the two groups of randomised therapy. The original study found a statistically  
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25 significant reduction in the incidence of CVD mortality and all trial endpoints, using  
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27 the full dataset and a risk ratio rather than time-to-event analysis<sup>26</sup>.  
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32 In our analysis of subgroups defined by CVD risk score, the magnitude of  
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34 relative treatment effects (relative risk reduction) on all-cause mortality and major  
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36 CVD events increased across all three CVD risk group from low to high risk, without  
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38 statistically significant heterogeneity ( $p = 0.78$  for all-cause mortality and  $p = 0.62$  for  
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40 the major CVD event) (Table 3). All relative treatment effects in our analysis  
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42 measured by HRs were adjusted by age, sex, body-mass index, smoking, screening  
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44 centres and systolic BP. However, no significant difference was observed between  
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46 adjusted and unadjusted HRs. In terms of absolute benefits, risk reduction linearly  
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48 increased across the CVD risk group from low to high risk. BP lowering drug  
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50 treatment produced an unclear benefit in the low and intermediate CVD risk group  
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52 but a significant benefit in the high CVD risk group. Heterogeneity of absolute  
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3 effects across the CVD risk groups was only significant in all-cause mortality  
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5 (p=0.04).  
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8 Regarding the benefit of BP lowering drug treatment in the low to intermediate  
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10 CVD risk population, our results from main and subgroup analyses match well with  
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12 the study outcomes from the HOPE-3 trial<sup>23</sup> and the Diao review<sup>10</sup>. In the HOPE-3  
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14 trial<sup>23</sup>, no benefit of intensive drug treatment was established in the intermediate-risk  
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16 persons with HR 0.98 (0.84-1.14) for all-cause mortality and HR 0.92 (0.79 – 1.06)  
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18 for major CVD events referred as a first secondary outcome in the paper. At  
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20 baseline, the HOPE-3 participants were older (65 years), and had a lower level of BP  
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22 (138.1/81.9 mmHg) compared to the ANBP participants. One reason for the lower  
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24 blood pressures may be due to the 4-week run-in phase in which all of the HOPE-3  
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26 participants received active BP lowering drug treatment before randomisation and  
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28 one-fifth of all eligible participants had previously received drug treatment before the  
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30 trial. In 2012, Diao et al reviewed placebo randomised controlled trials in grade 1  
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32 hypertension and also found no beneficial effect of drug treatment with a risk ratio  
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34 (RR) 0.85 (0.63 – 1.15) for all-cause mortality and RR 0.97 (0.2 – 1.32) for major  
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36 CVD events<sup>10</sup>. The participants in the Diao review were likely to have a lower CVD  
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38 risk than those in the ANBP and the HOPE-3 trials, with major CVD events occurring  
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40 in only 2.4% of participants in the placebo group. Following a similar approach, in  
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42 2015, The Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC)<sup>24</sup>  
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44 reviewed randomised controlled trials in grade 1 hypertension but extended to trials  
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46 comparing active or more intensive regimens and placebo or less intensive  
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48 regimens. In line with the findings from the 2015 BPLTTC study, we identified a  
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50 marginally significant effect on stroke, yet our effect estimates with an HR 0.75 (0.45  
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52 – 1.36) for total deaths and an HR 0.83 (0.65 – 1.07) for major CVD events slightly  
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3 differed from the 2015 BPLTTC study's results with an OR 0.78 (0.67-0.92) and an  
4 OR 0.86 (0.74-1.01) correspondingly. The differences in confidence intervals may  
5 be due to the difference in sample sizes and baseline characteristics. It is more  
6 likely that the 2015 BPLTTC participants had higher CVD risk and higher BP value at  
7 baseline when about 40% of 15,266 participants had diabetes and about 23% had  
8 previously received BP lowering drug treatment. Our study and the 2015 review  
9 confirm the absolute benefits of BP lowering drug treatment in high CVD risk  
10 population in terms of total deaths with ARR 2.2% (0.5, 3.9,  $p=0.01$ ) for the ANBP  
11 and ARR 1.4% (0.5, 2.2) for the review. Furthermore, the benefit was also recorded  
12 in major CVD event with ARR 4.3% (0.5, 8.1,  $p=0.03$ ) in the ANBP, whereas the  
13 2015 BPLTTC observed a non-significant effect with ARR 1.0% (-0.1, 1.9). The  
14 difference can be explained in part by the study design when more than 50% of  
15 participants with systolic BP higher than 160 mmHg in eligible studies in the 2015  
16 BPLTTC were excluded. The distribution of these excluded participants might not be  
17 even between active arm and control arm, thus biasing the treatment effects.

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36 In another subgroup analysis stratified by tertile of baseline systolic BP  
37 (supplement), the mean value of CVD risk varied from low to high corresponding to  
38 the lowest and the highest tertile. The relative treatment benefits were not  
39 statistically significant, but in terms of absolute effects, BP lowering drug treatment  
40 substantially reduced any trial events, all-cause mortality and major CVD events  
41 within the highest tertile. The findings were in line with what we found in the CVD  
42 risk-stratified subgroup when all participants in the highest BP-stratified tertile had  
43 high CVD risk score ( $20.7 \pm 9.5$ ). However, the heterogeneity of treatment effects  
44 among the three subgroups in analysis by baseline systolic BP was no longer  
45 significant as it was in the subgroup analysis by CVD risk score. Further, the trend of  
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3 lower to higher absolute benefit from low to high risk groups that was seen for CVD  
4 risk was not apparent when groups are defined by BP alone. Thus, in this study,  
5 CVD risk score was better in identifying those who most benefits from BP lowering  
6 drug treatment with regard to all-cause mortality.  
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## 11 **Limitations**

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15 There are a number of limitations of our study. Firstly, statistical power is  
16 unavoidsably decreased in a post-hoc subgroup analysis and the multivariate  
17 Framingham risk score used in our analysis has not been well validated within the  
18 Australian population<sup>31</sup>. However, using a multivariate score for stratification is  
19 known to increase the power to detect heterogeneity in absolute risk benefit over  
20 subgroup analyses that are based on individual risk factors<sup>32</sup>. A prospective study to  
21 address the issue of whether there is an advantage in treating blood pressure by AR  
22 is unlikely to be performed, because of the very large sample size and very long  
23 follow-up time required, particularly in patients at low risk. Therefore, re-analysis of  
24 the early placebo-controlled trials seems to be the most feasible approach for  
25 assessing the effects of delayed versus early drug treatment in individuals with  
26 varying CVD risk together and elevated BP.  
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41 Secondly, the estimation of HDLc from the 1980s national survey may alter the CVD  
42 risk score, but we do not believe this method greatly affected the risk stratification  
43 because a 0.4 difference in the HDL estimate only results in a 0.01 difference in CVD  
44 risk score. Furthermore, no association between HDLc and BP has been observed  
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3 significant, this result is likely due to the smaller sample size and subsequent  
4  
5 number of events. In conclusion, the sensitivity analysis supports our main analysis.  
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8 Thirdly, the paucity of trial endpoints in each CVD risk group prevented us  
9  
10 from comparing the effects in some specific outcomes with respect to stroke and  
11  
12 deaths from CVD.  
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14  
15 In conclusion, our research has demonstrated that drug treatment in patients  
16  
17 with elevated BP is best directed to those at high risk of incident CVD events. This  
18  
19 reinforces the guidelines recommendation to treat based on absolute (or global) CVD  
20  
21 risk, rather than according to BP thresholds alone<sup>5-9</sup>.  
22

#### 23 24 **Competing interests:**

25  
26  
27 CLBH is a Ph.D. candidate at Menzies Institute for Medical Research, she has  
28  
29 received a Ph.D. scholarship from Merle Weaver Postgraduate Scholarship. JD is  
30  
31 supported by National Health and Medical Research Council Screening and Test  
32  
33 Evaluation Program Grant 633003. CR is supported by a National Health and  
34  
35 Medical Research Council Senior Research Fellowship (1045862). MRN has in the  
36  
37 last 5 years served on an advisory board for AMGEN.  
38

#### 39 40 **Funding:**

41  
42 The ANBP was supported by the National Health and Medical Research Council of  
43  
44 Australia, the Life Insurance Medical Research Fund of Australia and New Zealand,  
45  
46 the Victorian Government, the Clive and Vera Ramaciotti Foundations, and the  
47  
48 Raine Medical Research Foundation of Western Australia. In the current study, the  
49  
50 researchers gratefully acknowledge the RACGP Foundation and Therapeutic  
51  
52 Guidelines Ltd for their support of this project.  
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3 **Contributors:** MRN is responsible for the study conception and data archive from  
4 the Australian Data Archive. CLBH performed the analysed and drafted the  
5 manuscript. MB, CR, JD provided substantial support on statistical analyses. All  
6 authors made great contribution to the interpretation of data, critically revised the  
7 manuscript and approved the final version.

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13  
14 **Ethics approval:** This study was approved by the Tasmanian Health and Medical  
15 Human Research Ethics Committee (H0015252).

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19 **Data sharing statement:** No additional data are available.

## 20 21 22 **References**

- 23  
24  
25 1. World Health Organisation. The top 10 causes of death [online database].  
26 <http://www.who.int/mediacentre/factsheets/fs310/en/>. Updated May, 2014 Accessed  
27 November 13, 2015.
- 28  
29  
30  
31  
32 2. Australian Bureau of Statistics. Causes of Death, Australia, 2013;  
33 <http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2013~Main>  
34 <http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2013~Main>  
35 <http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2013~Main>  
36 <http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2013~Main>  
37 <http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2013~Main>  
38 <http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2013~Main>  
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44 <http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2013~Main>  
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47 <http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2013~Main>  
48 <http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2013~Main>  
49 <http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2013~Main>  
50 <http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2013~Main>  
51 <http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2013~Main>  
52 <http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2013~Main>  
53 <http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2013~Main>  
54 <http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2013~Main>  
55 <http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2013~Main>  
56 <http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2013~Main>  
57 <http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2013~Main>  
58 <http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2013~Main>  
59 <http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2013~Main>  
60 <http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2013~Main>
- 41 3. Australia Bureau of Statistics. Causes of Death, Australia. 2012.  
42 <http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/3303.0main+features100012012>.  
43 Updated March 30, 2015. Accessed November 13, 2015.
- 44  
45  
46  
47  
48 4. World Health Organisation (WHO). A Global Brief on Hypertension: Silent Killer,  
49 Global Public Health Crissis [Online]. <http://www.thehealthwell.info/node/466541>.  
50 Updated January 4, 2013. Accessed November 13, 2015.

- 1  
2  
3 5. National Vascular Disease Prevention Allianace. Guidelines for the management  
4 of absolute cardiovascular disease risk.  
5  
6 [http://www.cvdcheck.org.au/index.php?option=com\\_content&view=article&id=47&Itemid=27](http://www.cvdcheck.org.au/index.php?option=com_content&view=article&id=47&Itemid=27). Updated May, 2012. Accessed November 13, 2015.  
7  
8  
9
- 10  
11 6. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the  
12 management of arterial hypertension. *Blood Pressure*. 2013;22(4):193-278.  
13  
14
- 15 7. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016  
16 European Guidelines on cardiovascular disease prevention in clinical practice. The  
17 Sixth Joint Task Force of the European Society of Cardiology and Other Societies on  
18 Cardiovascular Disease Prevention in Clinical Practice (constituted by  
19 representatives of 10 societies and by invited experts). *Eur Heart J*. 2016; 37: 2315–  
20 2381.  
21  
22  
23  
24  
25  
26  
27  
28  
29
- 30 8. Krause T, Lovibond K, Caulfield M, McCormack T, Williams B. Management of  
31 hypertension: summary of NICE guidance. *BMJ*. 2011;343.  
32  
33  
34
- 35 9. Dasgupta K, Quinn RR, Zarnke KB, et al. The 2014 Canadian Hypertension  
36 Education Program Recommendations for Blood Pressure Measurement, Diagnosis,  
37 Assessment of Risk, Prevention, and Treatment of Hypertension. *Can. J. Cardiol*.  
38 2014;30(5):485-501.  
39  
40  
41  
42  
43
- 44 10. Diao D, Wright J, Cundiff D, Gueyffier F. Pharmacotherapy for mild hypertension.  
45 *Cochrane Database of Systematic Reviews*. 2012;8:CD006742.  
46  
47  
48
- 49 11. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the  
50 management of high blood pressure in adults: report from the panel members  
51 appointed to the Eighth Joint National Committee (JNC 8). *Jama*. 2014;311(5):507-  
52 520.  
53  
54  
55  
56  
57  
58  
59



- 1  
2  
3 12. World Health Organization. International Society of Hypertension Writing Group.  
4 2003 World Health Organization (WHO)/International Society of Hypertension (ISH)  
5 statement on management of hypertension. *Journal of hypertension*.  
6  
7 2003;21(11):1983-1992.  
8  
9
- 10  
11  
12 13. Weber MA, Schiffrin EL, White WB, et al. Clinical Practice Guidelines for the  
13  
14 Management of Hypertension in the Community. *The Journal of Clinical*  
15  
16 *Hypertension*. 2014;16(1):14-26.  
17  
18
- 19 14. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the joint national  
20  
21 committee on prevention, detection, evaluation, and treatment of high blood  
22  
23 pressure. *Hypertension*. 2003;42(6):1206-1252.  
24  
25
- 26 15. Mitka M. Groups spar over new hypertension guidelines. *JAMA*.  
27  
28 2014;311(7):663-664.  
29  
30
- 31 16. Guallar E, Laine C. Controversy Over Clinical Guidelines: Listen to the Evidence,  
32  
33 Not the Noise. *Ann. Intern. Med.* 2014;160(5):361-362.  
34  
35
- 36 17. Wright JJT, Fine LJ, Lackland DT, Ogedegbe G, Dennison Himmelfarb CR.  
37  
38 Evidence Supporting a Systolic Blood Pressure Goal of Less Than 150 mm Hg in  
39  
40 Patients Aged 60 Years or Older: The Minority View Systolic Blood Pressure Goal for  
41  
42 Patients Aged 60 Years or Older. *Ann. Intern. Med.* 2014;160(7):499-503.  
43  
44
- 45 18. Zanchetti A. Bottom blood pressure or bottom cardiovascular risk? How far can  
46  
47 cardiovascular risk be reduced? *Journal of hypertension*. 2009;27(8):1509-1520.  
48  
49
- 50 19. The SPRINT Research Group. A Randomized Trial of Intensive versus Standard  
51  
52 Blood-Pressure Control. *New England Journal of Medicine*. 2015;373(22):2103-  
53  
54 2116.  
55  
56  
57  
58  
59  
60

- 1  
2  
3 20. New Zealand Guidelines Group. The assessment and management of  
4 cardiovascular risk. Wellington, New Zealand Guidelines Group.  
5  
6 [http://www.health.govt.nz/publication/assessment-and-management-cardiovascular-](http://www.health.govt.nz/publication/assessment-and-management-cardiovascular-risk)  
7 [risk](http://www.health.govt.nz/publication/assessment-and-management-cardiovascular-risk). Updated July 8, 2015. Accessed November 13, 2015.  
8  
9  
10  
11  
12 21. Morales Salinas A, Coca A, Olsen MH, et al. Clinical Perspective on  
13 Antihypertensive Drug Treatment in Adults With Grade 1 Hypertension and Low-to-  
14 Moderate Cardiovascular Risk: An International Expert Consultation. *Current*  
15 *Problems in Cardiology*. 2017;42(7):198-225.  
16  
17  
18  
19  
20  
21 22. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on  
22 outcome incidence in hypertension: 2. Effects at different baseline and achieved  
23 blood pressure levels—overview and meta-analyses of randomized trials. *Journal of*  
24 *hypertension*. 2014;32(12):2296-2304.  
25  
26  
27  
28  
29  
30  
31 23. Lonn EM, Bosch J, López-Jaramillo P, et al. Blood-Pressure Lowering in  
32 Intermediate-Risk Persons without Cardiovascular Disease. *New England Journal of*  
33 *Medicine*. 2016;374(21):2009-2020.  
34  
35  
36  
37  
38 24. The Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of Blood  
39 Pressure Reduction in Mild Hypertension. A Systematic Review and Meta-analysis.  
40 *Ann. Intern. Med*. 2015;162(3):184-191.  
41  
42  
43  
44  
45 25. The Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure-  
46 lowering treatment based on cardiovascular risk: a meta-analysis of individual patient  
47 data. *The Lancet*. 2014;384(9943):591-598.  
48  
49  
50  
51  
52 26. The Management Committee. The Australian Therapeutic Trial in Mild  
53 Hypertension. *The Lancet*. 1980;315(8181):1261-1267.  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 27. Anderson, K. M., Odell, P. M., Wilson, P. W., & Kannel, W. B. (1991).  
4  
5 Cardiovascular disease risk profiles. *American heart journal*, 121(1), 293-298  
6  
7  
8 28. Bennett SA, Magnus P. Trends in cardiovascular risk factors in Australia. Results  
9  
10 from the National Heart Foundation's Risk Factor Prevalence Study, 1980-1989. *The*  
11  
12 *Medical Journal of Australia*. 1994;161(9):519-527.  
13  
14  
15 29. Hajifathalian K, Ueda P, Lu Y, et al. A novel risk score to predict cardiovascular  
16  
17 disease risk in national populations (GloboRisk): a pooled analysis of prospective  
18  
19 cohorts and health examination surveys. *Lancet Diabetes Endocrinol*.2015;3(5):339-  
20  
21 355.  
22  
23  
24 30. Bender R, Kromp M, Kiefer C, Sturtz S. Absolute risks rather than incidence  
25  
26 rates should be used to estimate the number needed to treat from time-to-event  
27  
28 data. *J. Clin. Epidemiol*. 2013;66(9):1038-1044.  
29  
30  
31 31. Zomer, E., Owen, A., Magliano, D. J., Liew, D., & Reid, C. (2011). Validation of  
32  
33 two Framingham cardiovascular risk prediction algorithms in an Australian  
34  
35 population: the 'old 'versus the 'new 'Framingham equation. *European Journal of*  
36  
37 *Cardiovascular Prevention & Rehabilitation*, 18(1), 115-120.  
38  
39  
40 32. Hayward RA, Kent DM, Vijan S, Hofer TP. Multivariable risk prediction can  
41  
42 greatly enhance the statistical power of clinical trial subgroup analysis. *BMC Med*.  
43  
44 *Res. Methodol*. 2006;6(1):1.  
45  
46  
47 33. Hughes K, Leong WP, Sothy SP, Lun KC, Yeo PPB. Relationships between  
48  
49 Cigarette smoking, Blood Pressure and Serum Lipids in the Singapore General  
50  
51 Population. *International Journal of Epidemiology*. 1993;22(4):637-643.  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 34.Catalano M, Aronica A, Carzaniga G, Seregni R, Libretti A. Serum lipids and  
4 apolipoproteins in patients with essential hypertension. *Atherosclerosis*.

5  
6  
7 1991;87(1):17-22.  
8  
9  
10  
11  
12  
13  
14  
15  
16  
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3 Figure. Effect of treatment in the overall study population. \*Adjusted for age, sex,  
4 body-mass index, screening centers, smoking and systolic blood pressure. **Bold**  
5 **p**<0.05.  
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10 CVD: cardiovascular disease, CHD for coronary heart disease.  
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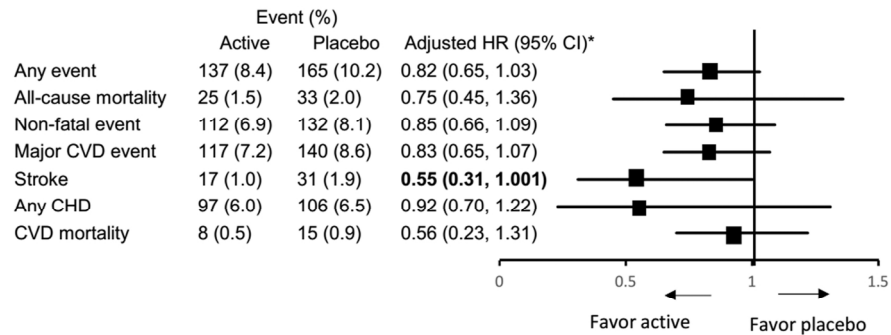


Figure. Effect of treatment in the overall study population. \*Adjusted for age, sex, body-mass index, screening centers, smoking and systolic blood pressure. Bold  $p < 0.05$   
CVD: cardiovascular disease, CHD for coronary heart disease.

162x71mm (300 x 300 DPI)

Table 1. Baseline characteristics stratified by tertile of baseline systolic blood pressure

Group variable	1 <sup>st</sup> tertile (113-151 mmHg)	2 <sup>nd</sup> tertile (152 – 165 mmHg)	3 <sup>rd</sup> tertile (166 – 225 mmHg)
Sample, N	1156	1014	1074
Age, years	48.8 ± 7.3	51.4 ± 7.8	55.1 ± 7.8
Male sex, N (%)	803 (69.5)	645 (63.6)	569 (53.0)
Current smoker, N (%)	285 (24.7)	251 (24.8)	265 (24.7)
SBP, mmHg	142.1 ± 7.0	158.2 ± 3.9	179.3 ± 11.7
DBP, mmHg	99.7 ± 4.1	102.7 ± 6.0	106.5 ± 8.0
Total cholesterol, mmol/l	5.9 ± 1.1	6.0 ± 1.1	6.1 ± 1.2
BMI, kg/m <sup>2</sup>	26.7 ± 3.6	26.5 ± 3.7	26.6 ± 4.4
CVD risk (%)	7.9 ± 8.7	12.8 ± 9.6	20.7 ± 9.5

SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body - mass index, CVD: cardiovascular disease.

Table 2. Effect of treatment by tertile of baseline systolic blood pressure.

	Event (%)		Adjusted HR (95% CI)*	ARR % (95% CI)	NNT
	Active	Placebo			
<b>Any event</b>					
113-151 mmHg	34 (5.6)	43 (7.8)	0.71 (0.45 - 1.11)	2.5 (-0.7, 5.6)	41 (-135, 18)
152 – 165 mmHg	49 (9.8)	46 (9.0)	1.07 (0.71 - 1.61)	-1.2 (-5.0, 2.7)	-87 (-20, 37)
166 – 225 mmHg	54 (10.5)	76 (3.6)	0.73 (0.51-1.03)	<b>4.8 (0.9, 8.8)</b>	<b>21 (11, 112)</b>
p-value	-	-	0.25	0.1	-
<b>All-cause mortality</b>					
113-151 mmHg	5 (0.8)	10 (1.8)	0.49 (0.17-1.46)	0.7 (-0.2, 1.7)	139 (-468, 60)
152 – 165 mmHg	11 (2.2)	8 (1.6)	1.30 (0.51 - 3.28)	-0.9 (-2.7, 0.9)	-110 (-36, 108)
166 – 225 mmHg	9 (1.7)	15 (2.7)	0.64 (0.28 - 1.46)	<b>1.9 (0.3, 3.6)</b>	<b>52 (28, 372)</b>
p – value	-	-	0.26	0.08	-
<b>Non-fatal event</b>					
113-151 mmHg	29 (4.8)	33 (6.0)	0.77 (0.47 - 1.28)	1.2 (-1.7, 1.5)	86 (-59, 25)
152 – 165 mmHg	38 (7.6)	38 (7.4)	1.00 (0.63 - 1.58)	-0.2 (-3.6, 1.7)	-455 (-27, 31)
166 – 225 mmHg	45 (8.7)	61 (10.9)	0.76 (0.52 - 1.13)	2.9 (-0.8, 1.8)	35 (-133, 15)
p – value	-	-	0.58	0.48	-
<b>Major CVD event</b>					
113-151 mmHg	31 (5.1)	35 (6.3)	0.79 (0.48 - 1.28)	1.6 (-1.3, 1.5)	61 (-74, 22)
152 – 165 mmHg	41 (8.2)	40 (7.8)	1.04 (0.67 - 1.61)	-0.4 (-4.0; 3.1)	-227 (-25, 32)
166 – 225 mmHg	45 (8.7)	65 (11.7)	0.73 (0.50 - 1.06)	<b>4.1 (0.4, 7.8)</b>	<b>24 (13, 242)</b>
p - value	-	-	0.39	0.22	-
<b>Any CHD</b>					
113-151 mmHg	30 (5.0)	29 (5.3)	0.93 (0.56 - 1.56)	0.4 (-2.4, 3.1)	286 (-42, 32)
152 – 165 mmHg	29 (5.8)	30 (5.9)	0.95 (0.57-1.59)	-0.1 (-3.1, 2.9)	-1250 (-32, 34)
166 – 225 mmHg	38 (7.4)	47 (8.4)	0.87 (0.57-1.34)	2.0 (-1.4, 5.4)	51 (-71, 19)
p - value	-	-	0.89	0.65	-



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3 CVD: cardiovascular disease, CHD: coronary heart disease, HR: hazard ratio, CI: confidence  
4 interval, ARD: absolute risk difference, NNT: number needed to treat. NNTB: number needed to treat  
5 (benefit). NNTH: number needed to treat (harm).p-value indicated p for interaction.  
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9 \* Adjusted for age, sex, body-mass index, smoking, screening centres and systolic blood pressure.

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11 **Bold** p<0.05  
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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (p1) (b) Provide in the abstract an informative and balanced summary of what was done and what was found (p2-3)
<b>Introduction</b>		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (p4-6)
Objectives	3	State specific objectives, including any prespecified hypotheses (p6)
<b>Methods</b>		
Study design	4	Present key elements of study design early in the paper (p6)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (p6)
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (p6-7) (b) For matched studies, give matching criteria and number of exposed and unexposed (N/A)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (p7)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group (p7)
Bias	9	Describe any efforts to address potential sources of bias (p7)
Study size	10	Explain how the study size was arrived at (N/A because this is a post-hoc analysis of the ANBP)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (p8)
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (p8) (b) Describe any methods used to examine subgroups and interactions (p8) (c) Explain how missing data were addressed (p7) (d) If applicable, explain how loss to follow-up was addressed (p8) (e) Describe any sensitivity analyses (p7)
<b>Results</b>		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (p7 – describe in method section because this was a post-hoc analysis of the ANBP) (b) Give reasons for non-participation at each stage (N/A) (c) Consider use of a flow diagram (N/A)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (p8-9 but not separately describe exposed and unexposed group because there was not enough spaces for describing expose and unexposed in each subgroup (low, moderate and high risk. We mentioned by words in result section). (b) Indicate number of participants with missing data for each variable of interest (No

		<a href="#">because there was only 1% missing data</a>
		(c) Summarise follow-up time (eg, average and total amount) (p8)
Outcome data	15*	Report numbers of outcome events or summary measures over time (p11, p23)
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (not report the unadjusted estimates because there was not enough space. However we mentioned about no significant difference between adjusted and unadjusted estimates on p13)
		(b) Report category boundaries when continuous variables were categorized (p9-10)
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period (p11,12)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (p11, 12, supplementary)
<b>Discussion</b>		
Key results	18	Summarise key results with reference to study objectives (p12-13)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (p15-17)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (p17)
Generalisability	21	Discuss the generalisability (external validity) of the study results (p17)
<b>Other information</b>		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (p17)

\*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

# BMJ Open

## Effectiveness of Blood Pressure-Lowering Drug Treatment by Levels of Absolute Risk: Post-hoc analysis of the Australian National Blood Pressure Study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-017723.R2
Article Type:	Research
Date Submitted by the Author:	07-Dec-2017
Complete List of Authors:	Ho, Chau; University of Tasmania Menzies Institute for Medical Research, Breslin, Monique; University of Tasmania Menzies Institute for Medical Research Doust, Jenny; Bond University, Faculty of Health Sciences and Medicine Reid, Christopher ; Curtin University, School of Public Health; Monash University, CCRE Therapeutics, School of Public Health and Preventive Medicine Nelson, Mark; University of Tasmania, Menzies Research Institute
<b>Primary Subject Heading</b>:	Cardiovascular medicine
Secondary Subject Heading:	General practice / Family practice
Keywords:	cardiovascular disease, antihypertensive drug, absolute cardiovascular risk, primary prevention, Hypertension < CARDIOLOGY

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Word count for text: 4382

**Title:** Effectiveness of Blood Pressure-Lowering Drug Treatment by Levels of Absolute Risk: Post-hoc analysis of the Australian National Blood Pressure Study

**Running head:** BP lowering drug treatment by absolute CVD risk.

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## Abstract

**Objectives:** In many current guidelines, blood pressure (BP) lowering drug treatment for primary prevention of cardiovascular disease (CVD) is based on absolute risk. However, in clinical practice, therapeutic decisions are often based on BP levels alone. We sought to investigate which approach was superior by conducting a post-hoc analysis of the Australian National Blood Pressure (ANBP) cohort, a seminal study establishing the efficacy of BP lowering in 'mild hypertensive' persons.

**Design:** a post-hoc subgroup analysis of the ANBP trial results by baseline absolute risk tertile.

**Setting and participants:** 3,244 participants aged 35 to 69 years in a community-based randomised placebo controlled trial of blood pressure lowering medication.

**Interventions:** Chlorothiazide 500 mg vs placebo.

**Primary outcome measures:** All-cause mortality and non-fatal events (non-fatal CVD, congestive cardiac failure, renal failure, hypertensive retinopathy or encephalopathy).

## Results

Treatment effects were assessed by hazard ratio, absolute risk reduction and number needed to treat. Participants had an average 5-year CVD risk in the intermediate range ( $10.5 \pm 6.5$ ) with moderately elevated BP (mean 159/103 mmHg) and were middle-aged ( $52 \pm 8$  years). In a subgroup analysis, the relative effects (hazard ratio) and absolute effects (absolute risk reduction and number needed to treat) did not statistically differ across the three risk groups except for the absolute

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3 benefit in all-cause mortality ( $p$  for heterogeneity = 0.04). With respect to absolute  
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5 benefit, drug treatment significantly reduced the number of events in the high-risk  
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7 group regarding any event with a Number Needed to Treat of 18 (10, 64), death from  
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9 any cause with 45 (25, 196) and major cardiovascular disease events with 23 (12,  
10  
11 193).

## 12 13 14 **Conclusion**

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17 Our analysis confirms that the benefit of treatment was substantial only in the high-  
18  
19 risk tertile, reaffirming the rationale of treating elevated blood pressure in the setting  
20  
21 of all risk factors rather than in isolation.

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24 **Key Words:** antihypertensive drug, cardiovascular disease, absolute cardiovascular  
25  
26 risk, primary prevention, hypertension.

## 27 28 29 **Strengths and limitations of this study**

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- 32 • Our analysis provides further justification that an absolute risk strategy is  
33 superior to management based on the BP level alone in identifying those who  
34 are most likely to benefit from therapy.
  - 35 • The statistical power to detect treatment effects was limited in this study, and  
36 this is a post-hoc subgroup analysis.
  - 37 • Due to the lack of high density lipoprotein cholesterol in the original data set  
38 (HDLc), the HDLc used in the analyses was imputed from a 1980s national  
39 survey. The use of these imputed values is unlikely to greatly affect the risk  
40 stratification.
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## Introduction

For decades, cardiovascular disease (CVD) has remained the greatest burden of disease in the developed world and now also in the developing world<sup>1,2</sup>. In 2012, CVD was responsible for 17.5 million deaths in the world and more than twenty thousand deaths in Australia<sup>1,3</sup>. Noticeably, nearly 50% of deaths from CVD are attributable to high blood pressure (BP), the commonest modifiable population risk factor<sup>4</sup>. Drug therapy for primary prevention of CVD is now recommended to be based on absolute CVD risk, where BP lowering drug treatment is determined by BP level together with other major CVD risk factors (e.g. sex, age, total cholesterol, high-density lipoprotein cholesterol, diabetes and smoking status) as an integrated score<sup>5-9</sup>. Yet clinicians are reticent to treat systolic BP in those below 140 mmHg at high risk as well as not treating patients at low risk with blood pressure above this threshold. There is a paucity of literature on the effects of lowering BP in low to moderate CVD risk individuals with Grade 1 hypertension (systolic BP from 140 mmHg to 159 mmHg and/or diastolic BP from 90 to 99) and some debate regarding its benefit<sup>10</sup>. Guidelines from the US and Europe focus on BP thresholds and promote early drug treatment due to the potential benefits of earlier intervention and potential adverse effects of delayed intervention<sup>6-8,11-13</sup>. JNC 8<sup>11</sup> recommends initiating drug treatment at the threshold of 150 mmHg systolic BP or 90 mmHg diastolic BP for the general population at 60 years or older. This revised recommendation has caused controversy amongst clinicians who argue that drug treatments need to be initiated at a lower systolic BP of 140 mmHg, as previously recommended in JNC 7<sup>14</sup>, otherwise patients are exposed to increased risk<sup>15-18</sup>. Similarly, the 2016 European Society of Cardiology guidelines recommend considering BP lowering drug treatment when systolic BP is greater than 140 mmHg



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3 and/or diastolic BP is greater than 90 mmHg after a reasonable period of time with  
4 lifestyle choice<sup>7</sup>. Recently, the SPRINT (Systolic Blood Pressure Intervention trial)<sup>19</sup>  
5 reported a significant benefit from intensive treatment to a target BP of 120 mmHg  
6 rather than 140 mmHg. However, this benefit was observed in those at high CVD  
7 risk without diabetes. In agreement with the findings from the SPRINT trial,  
8 guidelines in Australia<sup>5</sup>, New Zealand<sup>20</sup>, UK<sup>8</sup> and Canada<sup>9</sup> recommend BP  
9 lowering medication based on absolute CVD risk, recommending BP lowering  
10 treatment as soon as possible in high CVD risk individuals, but not in the low to  
11 moderate risk population unless BP persistently exceeds 160/100 mmHg.  
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23 Other groups<sup>21</sup> have recommended early drug treatment of grade 1  
24 hypertension even in patients at low risk with the exception of patients with grade 1  
25 “isolated” hypertension, based on a meta-analysis by Thomopolous et al<sup>22</sup> and the  
26 HOPE-3 study<sup>23</sup>. In contrast, a Cochrane review by Diao et al<sup>10</sup> concluded that there  
27 was no statistically significant effect of BP treatment in individuals who had grade 1  
28 hypertension. The 2015 Blood Pressure Lowering Treatment Trialists Collaboration<sup>24</sup>  
29 (BPLTTC) meta-analysis reported a statistically significant benefit of BP lowering  
30 drug treatment in grade 1 hypertension in terms of stroke and all-cause mortality.  
31 However, the effects seen in the BPLTTC analysis could reflect differences in the  
32 BPLTTC sample that included participants who had diabetes, had a higher baseline  
33 risk and had previously received drug treatment. In another analysis of the BPLTTC  
34 individual patient data<sup>25</sup> by absolute CVD risk at baseline showed a continuously  
35 increasing benefit with baseline risk<sup>25</sup>. The BPLTTC study, however included  
36 participants who both did and did not have a history of CVD.  
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53 Thus, we sought to reanalyse a seminal study used to justify treating  
54 individuals with elevated BP to see if stratification by baseline CVD risk would be a  
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3 superior method for identifying candidates for BP-lowering medication in a treatment-  
4 naïve population. In this study, we compared the effectiveness of BP lowering drug  
5 treatment by a post-hoc subgroup analysis of the Australian National Blood Pressure  
6 study<sup>26</sup> (ANBP). We restricted the analysis group to individuals with no history of  
7 CVD or diabetes, and who were naïve to BP lowering treatment. We selected this  
8 historic study because it was placebo controlled and patients in the control arm of  
9 the study would not have been taking a BP lowering medication previously unless  
10 they had very high levels of BP. Our aim was to assess which group of individuals  
11 classified by absolute risk benefited from active treatment vs. placebo for CVD  
12 events within this seminal study that underwrote the treatment of elevated BP by BP  
13 thresholds.

## 24 25 26 27 **Methods**

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29 We performed a post-hoc analysis of the Australian National Blood Pressure  
30 study<sup>26</sup>. The study was conducted between 1973 and 1979 and was a multicentre,  
31 single-blind randomised controlled trial of 3,427 patients which compared the effects  
32 of BP lowering drug therapy between individuals who initially received active  
33 treatment (chlorothiazide) and those who received delayed active treatment or no  
34 active treatment (placebo). The study intervention remains applicable to current  
35 practice as thiazide diuretics (e.g. hydrochlorothiazide) are still first line blood  
36 pressure lowering agents<sup>5-9</sup>. The ANBP study enrolled participants who had not been  
37 on treatment for hypertension in the past three months and had no history of CVD or  
38 diabetes. In the 1970s, 'mild hypertension' was defined as a screening diastolic BP  
39 of 95 to 109 mmHg with a systolic BP lower than 200 mmHg. 3,931 eligible  
40 participants were initially randomised, then 504 participants were excluded because  
41 their BP throughout the study did not meet the criteria for starting drug treatment

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3 (entry or follow-up diastolic BP higher than 95 mmHg and/or entry or follow-up  
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5 systolic BP higher than 200 mmHg). The primary endpoints were all-cause mortality  
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7 and non-fatal events (non-fatal CVD, congestive cardiac failure, renal failure,  
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9 hypertensive retinopathy or encephalopathy) <sup>26</sup>.

### 12 *Risk stratification*

15 In this analysis, the baseline absolute CVD risk was calculated according to  
16 the 5-year Framingham absolute risk score<sup>27</sup>. The Framingham score was chosen  
17 because it is currently recommended in the National Vascular Disease Prevention  
18 Alliance (NVDPA) guidelines <sup>5</sup> in Australia. The sample was restricted to 3,244  
19 participants who were older than 35 years and was stratified by tertile of estimated 5-  
20 year CVD risk score. We also classified all participants with very high BP (systolic  
21 BP  $\geq$  180 mmHg and/or diastolic BP  $\geq$  110 mmHg) or total cholesterol ( $>$  7.5 mmol/l)  
22 values the highest risk tertile regardless of their risk score, as per the Australian  
23 guidelines <sup>5</sup>. The ANBP dataset included all variables required for CVD risk  
24 calculation except high-density lipoprotein cholesterol (HDLc). The HDLc value was  
25 imputed from the Australian National Heart Foundation risk factor prevalence study  
26 as this was near contemporaneous with the ANBP<sup>28</sup>. Mean value of HDLc was  
27 categorised by age and sex. In a sensitivity analysis, we stratified the sample by  
28 GLOBORISK score <sup>29</sup>, a CVD risk score that does not require HDLc value and is  
29 validated in individuals over 40 years. The equation for the Australian population  
30 was obtained by personal contact with the author (Peter Ueda, unpublished data,  
31 2016). This analysis excluded 471 participants younger than 40 years. Less than  
32 1% of the study participants had data missing for total cholesterol, weight and/or  
33 height and these missing data were managed by multiple imputation using chained  
34 equations.

### *Statistical analysis*

All analyses were based on the modified 'intention to treat' principle. We included participants who had withdrawn from the study by their group allocation at randomisation in all analyses. The differences in baseline characteristics between 'active group' and 'placebo group' were tested by ANOVA test for continuous variables and Chi-square test for categorical variables. Treatment effects were assessed by hazard ratio (HR), absolute risk reduction (ARR) and number needed to treat (NNT). The HRs and corresponding 95% confidence intervals were estimated by Cox proportional hazard model after adjusting for clustering of participants within community-based centers and potential risk factors including baseline characteristics. The proportional assumption was checked by the test for interaction of HR with time. ARR and NNT were estimated from Kaplan-Meier curves at the median of follow-up time (4.4 years)<sup>30</sup>. Tests for interaction of treatment effect over the subgroups were obtained by the Cox regression model for the Hazard ratio and a Cochran's Q test for the absolute risk reduction. The threshold for significance for treatment effect was set at 0.05 for the main analysis and subgroup analysis. Only one subgroup analysis with related outcomes was conducted, thus multiplicity was not likely to affect our results.

## **Results**

### **Patient characteristics**

Table 1 provides baseline characteristics of the participants stratified by the tertile of CVD risk score. On average, study participants had intermediate 5-year CVD risk as referred in the NVDPA guideline ( $10.5 \pm 6.5$ ) with moderately elevated BP (mean 159/103 mmHg) and were middle-aged ( $52 \pm 8$ ). The tertiles had estimated

5-year CVD risks of less than 6.1% (low), 6.1 to 17.0% (moderate) and more than 17.0% (high). These values are similar to the thresholds recommended by the Australian NVDPA guideline<sup>5</sup> for low (<10%), moderate (10-15%) and high risk categorisation (>15%). The distribution of baseline characteristics by treatment assignment was not significantly different except for body mass index (BMI) in the total population, the number of smokers in the low-risk group, systolic BP and BMI in the moderate risk group.

Table 1. Baseline characteristics stratified by tertile of baseline CVD risk score.

Group variable	Total	Low (<6.1 %)	Moderate (6.1 – 17.0%)	High (>17.0%)
Sample, N	3244	1082	1081	1081
Randomised to active treatment, N (%)	1622 (50%)	559 (51.7%)	513 (47.5)	550 (50.9)
Age, years	51.7 ± 8.1	46.0 ± 6.2	54.5 ± 6.5	54.6 ± 8.1
Male sex, N (%)	2017 (62.2)	567 (52.4)	804 (74.4)	646 (59.8)
Current smoker, N (%)	801 (24.7)	<b>115 (10.6)</b>	352 (32.6)	334 (30.9)
SBP, mmHg	159.5 ± 17.5	148.4 ± 12.2	<b>157.3 ± 12.2</b>	172.6 ± 17.9
DBP, mmHg	102.9 ± 6.8	100.0 ± 3.8	100.8 ± 4.4	107.9 ± 8.2
Total cholesterol, mmol/l	6.0 ± 1.1	5.5 ± 0.9	6.0 ± 0.9	6.5 ± 1.3
BMI, kg/m <sup>2</sup>	<b>26.6 ± 3.9</b>	26.6 ± 4.0	<b>26.5 ± 3.6</b>	26.7 ± 4.1

SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body - mass index. **Bold** p<0.05

based on the distribution of baseline characteristics by treatment assignment.

Approximately one-third of the participants (34.5%) prematurely stopped study treatment due to decisions by clinics, participants' doctors, and the participant themselves, or for unknown reasons (Table 2). Participants' doctors were more likely to stop placebo treatment in all three risk groups, whereas clinics withdrew more BP-lowering drug-randomised participants in the low-risk group and the high-risk group.

No substantial difference in baseline characteristics between the two randomised treatment groups was recorded in any risk group.

Table 2. Characteristics of those who prematurely stopped study regimen.

Group variable	Total	Low (<6.1%)	Moderate (6.1-17.0%)	High (>17.0%)
Sample, N	1119	404	346	369
Randomised to active treatment, N (%)	531 (47.5)	204 (50.5)	151 (43.6)	176 (47.7)
Age, years	51.2 ± 8.3	45.9 ± 6.4	54.1 ± 7.0	54.2 ± 8.5
Male sex, N (%)	626 (55.9)	188 (46.5)	243 (70.2)	195 (52.9)
Current smoker, N (%)	321 (28.7)	58 (14.4)	143 (41.3)	120 (32.5)
SBP, mmHg	159.1 ± 18.1	147.6 ± 12.9	157.0 ± 11.9	173.7 ± 17.7
DBP, mmHg	102.9 ± 6.8	100.0 ± 4.0	100.6 ± 4.2	108.1 ± 8.2
Total cholesterol, mmol/l	6.0 ± 1.1	5.5 ± 0.9	6.0 ± 0.9	6.4 ± 1.3
BMI, kg/m <sup>2</sup>	26.7 ± 4.1	26.7 ± 4.0	26.6 ± 3.9	26.8 ± 4.5
Reason for stopping				
Clinic, N (%)	204 (18.2)	<b>74 (18.3)</b>	75 (21.7)	<b>55 (14.9)</b>
Local doctor, N (%)	287 (25.7)	<b>98 (24.3)</b>	<b>87 (25.1)</b>	<b>102 (27.6)</b>
Participants, N (%)	548 (49.0)	204 (50.5)	162 (46.8)	182 (49.3)
Not known, N (%)	80 (7.2)	28 (6.9)	22 (6.4)	30 (8.1)

SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body - mass index. **Bold** p<0.05 based on the distribution of baseline characteristics by treatment assignment.

### Effect of BP lowering drug treatment on total study population

During a median follow-up of 4.4 years (IQR 1.0 – 5.9), 257 major CVD events (7.9%) were observed, in which ischemic heart disease accounted for 203 events (6.3%), stroke 48 events (1.5%) and congestive heart failure 6 events (0.2%).

After adjustment for sex, age, BMI, smoking, systolic BP at baseline and study centers, BP lowering treatment was associated with a 15% reduction in non-fatal

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3 events and a 25% reduction in all-cause mortality (Figure 1), although the treatment  
4 effects were not statistically significant. Similar effects were found in the secondary  
5 endpoints including any events HR 0.82 (0.65 – 1.03), major CVD events HR 0.83  
6 (0.65 – 1.07) and non-fatal CVD events HR 0.87 (0.67 – 1.13). We identified a  
7 marginally significant effect in stroke HR 0.55 (0.3 – 1.001).  
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### 13 14 **Effect of BP lowering drug treatment on 5 year-CVD risk groups**

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17 In the subgroup analysis, the magnitude of relative treatment effect increased  
18 from low to high CVD risk group, though the benefits were not statistically significant  
19 in the high-risk group in terms of all-cause mortality 0.60 (0.26 - 1.40) and major  
20 CVD event with HR 0.76 (0.52 - 1.10).  
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26 The increasing trend for the benefit was also observed when comparing the  
27 absolute treatment effects absolute risk reduction – ARR among the three risk  
28 groups. No evidence of heterogeneity was observed except the effect in the major  
29 CVD event. Substantial effects of BP lowering treatment were produced in the high-  
30 risk group regarding any trial endpoints [ARR 5.6 (1.6, 9.6)], all-cause mortality [ARR  
31 2.2 (0.5, 3.9)] and any CVD event [4.3 (0.5, 8.1)] (Table 3). Treating 18 high-risk  
32 participants for 4 years prevented one trial event, treating 45 prevented one death  
33 and treating 23 prevented one CVD event. In contrast, treating low or moderate risk  
34 participants needed much higher numbers to prevent one event or possibly caused  
35 net harm (Table 3). Also, a sensitivity analysis by using the GLOBORISK score<sup>29</sup>  
36 which does not require HDLc was consistent with our original findings, except that  
37 the absolute risk reduction in major CVD event is no longer statistically significant  
38 with ARR 3.4% (-0.4,7.3, p = 0.08).  
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55 Table 3. Effect of treatment by tertile of baseline CVD risk score.  
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	Active	Placebo			
	Event (rate per 1000 patient-yr)		Adjusted HR (95% CI)*	ARR % (95% CI)**	NNT**
<b>Any event</b>					
Low	22 (8.9)	23 (10.0)	0.94 (0.52 - 1.70)	-0.3 (-2.7, 2.1)	-370 (-37, 47)
Moderate	56 (26.1)	67 (28.0)	0.93 (0.65 - 1.33)	1.1 (-2.9, 5.2)	87 (-34, 19)
High	59 (24.8)	75 (33.2)	0.75 (0.53 - 1.06)	<b>5.6 (1.6, 9.6)</b>	<b>18 (10, 64)</b>
p - value	-	-	0.64	0.05	-
<b>All-cause mortality</b>					
Low	6 (2.4)	6 (2.5)	0.96 (0.30-3.01)	-0.5 (-1.6, 0.7)	-213 (-63, 153)
Moderate	10 (4.4)	13 (5.1)	0.81 (0.35 - 1.86)	0.2 (-1.7, 2.1)	476 (-60, 48)
High	9 (3.5)	14 (5.7)	0.60 (0.26 - 1.40)	<b>2.2 (0.5, 3.9)</b>	<b>45 (25, 196)</b>
p - value	-	-	0.78	<b>0.04</b>	-
<b>Non-fatal event</b>					
Low	16 (6.4)	17 (7.4)	0.93 (0.47 - 1.87)	0.2 (-1.9, 2.3)	476 (-52, 43)
Moderate	46 (21.3)	54 (22.2)	0.96 (0.65 - 1.43)	0.9 (-2.8, 4.5)	118 (-35, 22)
High	50 (20.9)	61 (26.6)	0.80 (0.55- 1.16)	3.3 (-0.4, 7.0)	30 (-249, 14)
p - value	-	-	0.77	0.36	-
<b>Major CVD event</b>					
Low	17 (6.8)	18 (7.8)	0.98 (0.50 - 1.91)	0.2 (-1.9, 2.3)	476 (-52, 43)
Moderate	50 (23.2)	58 (24.0)	0.98 (0.67 - 1.43)	0.6 (-3.2, 4.5)	164 (-31, 22)
High	50 (20.9)	64 (28.0)	0.76 (0.52 - 1.10)	<b>4.3 (0.5, 8.1)</b>	<b>23 (12, 193)</b>
p - value	-	-	0.62	0.17	-
<b>Any CHD</b>					
Low	17 (6.8)	14 (6.0)	1.21 (0.59 - 2.48)	-0.4 (-2.4, 1.6)	-256 (-41, 61)
Moderate	39 (17.9)	47 (19.2)	0.93 (0.60 - 1.42)	1.1 (-3.0, 5.1)	94 (-33, 19)
High	41 (17.0)	45 (19.2)	0.90 (0.59 - 1.37)	1.9 (-1.4, 5.3)	52 (-72, 19)
p - value	-	-	0.83	0.47	-

CVD: cardiovascular disease, CHD: coronary heart disease, HR: hazard ratio, CI: confidence interval, ARR: absolute risk difference, NNT: number needed to treat. NNTB: number needed to



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3 treat (benefit). NNTH: number needed to treat (harm). p-value indicated p for interaction.

4 \* Adjusted for age, sex, body-mass index, smoking, screening centres and systolic blood  
5 pressure. \*\* As estimated by the Kaplan-Meier curve. **Bold** p<0.05

## 8 **Discussion**

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11 In our post hoc analysis of the ANBP study we found evidence of benefit from  
12 BP lowering treatment in the high-risk tertile for primary trial endpoints of any event  
13 and any CVD event with low or moderate risk participants unlikely to benefit. Our  
14 study population had an overall moderate 5-year CVD risk (10.5%) and moderately  
15 elevated systolic BP (mean 159/103 mmHg) by modern definitions. The ANBP study  
16 aimed to treat 'mild hypertension' (according to the old definition) that was primarily  
17 defined by diastolic BP. Some randomised participants were excluded from the  
18 original analysis because they did not meet the criteria for starting BP lowering drug  
19 treatment post randomisation. This would not be seen in modern clinical trials. In our  
20 reanalysis we found that BP lowering drug treatment reduced the risk of major CVD  
21 events and all-cause mortality, but the effect was not statistically significant. This is  
22 likely to be due to reduced power as the cohort was analysed by tertile of absolute  
23 risk, as well as by the two groups of randomised therapy. The original study found a  
24 statistically significant reduction in the incidence of CVD mortality and all trial  
25 endpoints, using the full dataset and a risk ratio rather than time-to-event analysis<sup>26</sup>.

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44 In our analysis of subgroups defined by CVD risk score, the magnitude of  
45 relative treatment effects (relative risk reduction) on all-cause mortality and major  
46 CVD events increased across all three CVD risk group from low to high risk, without  
47 statistically significant heterogeneity (p = 0.78 for all-cause mortality and p = 0.62 for  
48 the major CVD event) (Table 3). All relative treatment effects in our analysis  
49 measured by HRs were adjusted by age, sex, body-mass index, smoking, screening  
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3 centres and systolic BP. However, no significant difference was observed between  
4  
5 adjusted and unadjusted HRs. In terms of absolute benefits, risk reduction linearly  
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7 increased across the CVD risk group from low to high risk. BP lowering drug  
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9 treatment produced an unclear benefit in the low and intermediate CVD risk group  
10  
11 but a significant benefit in the high CVD risk group. Heterogeneity of absolute  
12  
13 effects across the CVD risk groups was only significant in all-cause mortality  
14  
15 (p=0.04).  
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19 Regarding the benefit of BP lowering drug treatment in the low to intermediate  
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21 CVD risk population, our results from main and subgroup analyses match well with  
22  
23 the study outcomes from the HOPE-3 trial<sup>23</sup> and the Diao review<sup>10</sup>. In the HOPE-3  
24  
25 trial<sup>23</sup>, no benefit of intensive drug treatment was established in the intermediate-risk  
26  
27 persons with HR 0.98 (0.84-1.14) for all-cause mortality and HR 0.92 (0.79 – 1.06)  
28  
29 for major CVD events referred as a first secondary outcome in the paper. At  
30  
31 baseline, the HOPE-3 participants were older (65 years), and had a lower level of BP  
32  
33 (138.1/81.9 mmHg) compared to the ANBP participants. One reason for the lower  
34  
35 blood pressures may be due to the 4-week run-in phase in which all of the HOPE-3  
36  
37 participants received active BP lowering drug treatment before randomisation and  
38  
39 one-fifth of all eligible participants had previously received drug treatment before the  
40  
41 trial. In 2012, Diao et al reviewed placebo randomised controlled trials in grade 1  
42  
43 hypertension and also found no beneficial effect of drug treatment with a risk ratio  
44  
45 (RR) 0.85 (0.63 – 1.15) for all-cause mortality and RR 0.97 (0.2 – 1.32) for major  
46  
47 CVD events<sup>10</sup>. The participants in the Diao review were likely to have a lower CVD  
48  
49 risk than those in the ANBP and the HOPE-3 trials, with major CVD events occurring  
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51 in only 2.4% of participants in the placebo group. Following a similar approach, in  
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53 2015, The Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC)<sup>24</sup>  
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3 reviewed randomised controlled trials in grade 1 hypertension but extended to trials  
4 comparing active or more intensive regimens and placebo or less intensive  
5 regimens. In line with the findings from the 2015 BPLTTC study, we identified a  
6 marginally significant effect on stroke, yet our effect estimates with an HR 0.75 (0.45  
7 – 1.36) for total deaths and an HR 0.83 (0.65 – 1.07) for major CVD events slightly  
8 differed from the 2015 BPLTTC study's results with an OR 0.78 (0.67-0.92) and an  
9 OR 0.86 (0.74-1.01) correspondingly. The differences in confidence intervals may  
10 be due to the difference in sample sizes and baseline characteristics. It is more  
11 likely that the 2015 BPLTTC participants had higher CVD risk and higher BP value at  
12 baseline when about 40% of 15,266 participants had diabetes and about 23% had  
13 previously received BP lowering drug treatment. Our study and the 2015 review  
14 confirm the absolute benefits of BP lowering drug treatment in high CVD risk  
15 population in terms of total deaths with ARR 2.2% (0.5, 3.9,  $p=0.01$ ) for the ANBP  
16 and ARR 1.4% (0.5, 2.2) for the review. Furthermore, the benefit was also recorded  
17 in major CVD event with ARR 4.3% (0.5, 8.1,  $p=0.03$ ) in the ANBP, whereas the  
18 2015 BPLTTC observed a non-significant effect with ARR 1.0% (-0.1, 1.9). The  
19 difference can be explained in part by the study design when more than 50% of  
20 participants with systolic BP higher than 160 mmHg in eligible studies in the 2015  
21 BPLTTC were excluded. The distribution of these excluded participants might not be  
22 even between active arm and control arm, thus biasing the treatment effects.  
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46 In another subgroup analysis stratified by tertile of baseline systolic BP  
47 (supplement), the mean value of CVD risk varied from low to high corresponding to  
48 the lowest and the highest tertile. The relative treatment benefits were not  
49 statistically significant, but in terms of absolute effects, BP lowering drug treatment  
50 substantially reduced any trial events, all-cause mortality and major CVD events  
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3 within the highest tertile. The findings were in line with what we found in the CVD  
4 risk-stratified subgroup when all participants in the highest BP-stratified tertile had  
5 high CVD risk score ( $20.7 \pm 9.5$ ). However, the heterogeneity of treatment effects  
6 among the three subgroups in analysis by baseline systolic BP was no longer  
7 significant as it was in the subgroup analysis by CVD risk score. Further, the trend of  
8 lower to higher absolute benefit from low to high risk groups that was seen for CVD  
9 risk was not apparent when groups are defined by BP alone. Thus, in this study,  
10 CVD risk score identified those who most benefited from BP lowering drug treatment.  
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## 20 **Limitations**

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23 There are a number of limitations of our study. Firstly, statistical power is  
24 unavoidably decreased in a post-hoc subgroup analysis and the multivariate  
25 Framingham risk score used in our analysis has not been well validated within the  
26 Australian population<sup>31</sup>. However, using a multivariate score for stratification is  
27 known to increase the power to detect heterogeneity in absolute risk benefit over  
28 subgroup analyses that are based on individual risk factors<sup>32</sup>. A prospective study to  
29 address the issue of whether there is an advantage in treating blood pressure by AR  
30 is unlikely to be performed, because of the very large sample size and very long  
31 follow-up time required, particularly in patients at low risk. Therefore, re-analysis of  
32 the early placebo-controlled trials seems to be the most feasible approach for  
33 assessing the effects of delayed versus early drug treatment in individuals with  
34 varying CVD risk together and elevated BP.  
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50 Secondly, the estimation of HDLc from the 1980s national survey may alter the CVD  
51 risk score, but we do not believe this method greatly affected the risk stratification  
52 because a 0.4 difference in the HDL estimate only results in a 0.01 difference in CVD  
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3 risk score. Furthermore, no association between HDLc and BP has been observed  
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5 <sup>33,34</sup>. The sensitivity analysis using GLOBORISK score<sup>29</sup> without HDLc showed  
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7 similar results as our main analysis. Although the ARR is no longer statistically  
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9 significant, this result is likely due to the smaller sample size and subsequent  
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11 number of events. In conclusion, the sensitivity analysis supports our main analysis.  
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15 Thirdly, the paucity of trial endpoints in each CVD risk group prevented us  
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17 from comparing the effects in some specific outcomes with respect to stroke and  
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19 deaths from CVD. In addition, approximately one-third of the participants prematurely  
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21 stopped randomised drug treatment. However, this pattern likely reflects the typical  
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23 situation to occur in actual clinical practice, and this analysis is conducted on an  
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25 intention-to-treat basis, so any difference in the estimate of treatment effect due to  
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27 non-adherence is deliberately retained. Most participants were followed throughout  
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29 the trial, except those with an unknown reason for stopping - loss to follow-up  
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31 (7.2%). An analysis with further adjustment by variable 'premature stopped study  
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33 treatment' did not substantially change our findings, except effects on stroke in  
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35 general population became statistically significant (0.55, 95%CI 0.30-0.99,  
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37  $p=0.05$ ). This is because non-adherence is balanced between the allocated treatment  
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39 groups.  
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44 In conclusion, our research has demonstrated that drug treatment in patients  
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46 with elevated BP is best directed to those at high risk of incident CVD events. This  
47  
48 reinforces the guidelines recommendation to treat based on absolute (or global) CVD  
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50 risk, rather than according to BP thresholds alone <sup>5-9</sup>.  
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53 **Competing interests:**  
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3 CLBH is a Ph.D. candidate at Menzies Institute for Medical Research, she has  
4 received a Ph.D. scholarship from Merle Weaver Postgraduate Scholarship. JD is  
5 supported by National Health and Medical Research Council Screening and Test  
6 Evaluation Program Grant 633003. CR is supported by a National Health and  
7 Medical Research Council Senior Research Fellowship (1045862). MRN has in the  
8 last 5 years served on an advisory board for AMGEN.

### 16 **Funding:**

17  
18 The ANBP was supported by the National Health and Medical Research Council of  
19 Australia, the Life Insurance Medical Research Fund of Australia and New Zealand,  
20 the Victorian Government, the Clive and Vera Ramaciotti Foundations, and the  
21 Raine Medical Research Foundation of Western Australia. In the current study, the  
22 researchers gratefully acknowledge the RACGP Foundation and Therapeutic  
23 Guidelines Ltd for their support of this project.

24  
25 **Contributors:** MRN is responsible for the study conception and data archive from  
26 the Australian Data Archive. CLBH performed the analysed and drafted the  
27 manuscript. MB, CR, JD provided substantial support on statistical analyses. All  
28 authors made great contribution to the interpretation of data, critically revised the  
29 manuscript and approved the final version.

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43 **Ethics approval:** This study was approved by the Tasmanian Health and Medical  
44 Human Research Ethics Committee (H0015252).

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48 **Data sharing statement:** No additional data are available.

### 49 **References**

- 1  
2  
3 1. World Health Organisation. The top 10 causes of death [online database].  
4  
5 <http://www.who.int/mediacentre/factsheets/fs310/en/>. Updated May, 2014 Accessed  
6  
7 November 13, 2015.  
8  
9
- 10 2. Australian Bureau of Statistics. Causes of Death, Australia, 2013;  
11  
12 <http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2013~Main>  
13  
14 [%20Features~Leading%20Causes%20of%20Death~10001](#). Updated March 7,  
15  
16 2016. Accessed November 30, 2016.  
17  
18
- 19 3. Australia Bureau of Statistics. Causes of Death, Australia. 2012.  
20  
21 <http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/3303.0main+features100012012>.  
22  
23 Updated March 30, 2015. Accessed November 13, 2015.  
24  
25
- 26 4. World Health Organisation (WHO). A Global Brief on Hypertension: Silent Killer,  
27  
28 Global Public Health Crissis [Online]. <http://www.thehealthwell.info/node/466541>.  
29  
30 Updated January 4, 2013. Accessed November 13, 2015.  
31  
32
- 33 5. National Vascular Disease Prevention Allianace. Guidelines for the management  
34  
35 of absolute cardiovascular disease risk.  
36  
37 [http://www.cvdcheck.org.au/index.php?option=com\\_content&view=article&id=47&Itemid=27](http://www.cvdcheck.org.au/index.php?option=com_content&view=article&id=47&Itemid=27). Updated May, 2012. Accessed November 13, 2015.  
38  
39  
40  
41  
42
- 43 6. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the  
44  
45 management of arterial hypertension. *Blood Pressure*. 2013;22(4):193-278.  
46  
47
- 48 7. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016  
49  
50 European Guidelines on cardiovascular disease prevention in clinical practice. The  
51  
52 Sixth Joint Task Force of the European Society of Cardiology and Other Societies on  
53  
54 Cardiovascular Disease Prevention in Clinical Practice (constituted by  
55  
56  
57  
58  
59  
60

1  
2  
3 representatives of 10 societies and by invited experts). *Eur Heart J.* 2016; 37: 2315–  
4  
5 2381.

6  
7  
8 8.Krause T, Lovibond K, Caulfield M, McCormack T, Williams B. Management of  
9  
10 hypertension: summary of NICE guidance. *BMJ.* 2011;343.

11  
12  
13 9. Dasgupta K, Quinn RR, Zarnke KB, et al. The 2014 Canadian Hypertension  
14  
15 Education Program Recommendations for Blood Pressure Measurement, Diagnosis,  
16  
17 Assessment of Risk, Prevention, and Treatment of Hypertension. *Can. J. Cardiol.*  
18  
19 2014;30(5):485-501.

20  
21  
22 10.Diao D, Wright J, Cundiff D, Gueyffier F. Pharmacotherapy for mild hypertension.  
23  
24 *Cochrane Database of Systematic Reviews.* 2012;8:CD006742.

25  
26  
27 11. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the  
28  
29 management of high blood pressure in adults: report from the panel members  
30  
31 appointed to the Eighth Joint National Committee (JNC 8). *Jama.* 2014;311(5):507-  
32  
33 520.

34  
35  
36 12. World Health Organization. International Society of Hypertension Writing Group.  
37  
38 2003 World Health Organization (WHO)/International Society of Hypertension (ISH)  
39  
40 statement on management of hypertension. *Journal of hypertension.*  
41  
42 2003;21(11):1983-1992.

43  
44  
45 13. Weber MA, Schiffrin EL, White WB, et al. Clinical Practice Guidelines for the  
46  
47 Management of Hypertension in the Community. *The Journal of Clinical*  
48  
49 *Hypertension.* 2014;16(1):14-26.  
50  
51



- 1  
2  
3 14.Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the joint national  
4  
5 committee on prevention, detection, evaluation, and treatment of high blood  
6  
7 pressure. *Hypertension*. 2003;42(6):1206-1252.  
8  
9
- 10 15. Mitka M. Groups spar over new hypertension guidelines. *JAMA*.  
11  
12 2014;311(7):663-664.  
13
- 14 16. Guallar E, Laine C. Controversy Over Clinical Guidelines: Listen to the Evidence,  
15  
16 Not the Noise. *Ann. Intern. Med.* 2014;160(5):361-362.  
17  
18
- 19 17.Wright JJT, Fine LJ, Lackland DT, Ogedegbe G, Dennison Himmelfarb CR.  
20  
21 Evidence Supporting a Systolic Blood Pressure Goal of Less Than 150 mm Hg in  
22  
23 Patients Aged 60 Years or Older: The Minority ViewSystolic Blood Pressure Goal for  
24  
25 Patients Aged 60 Years or Older. *Ann. Intern. Med.* 2014;160(7):499-503.  
26  
27
- 28 18. Zanchetti A. Bottom blood pressure or bottom cardiovascular risk? How far can  
29  
30 cardiovascular risk be reduced? *Journal of hypertension*. 2009;27(8):1509-1520.  
31  
32  
33
- 34 19. The SPRINT Research Group. A Randomized Trial of Intensive versus Standard  
35  
36 Blood-Pressure Control. *New England Journal of Medicine*. 2015;373(22):2103-  
37  
38 2116.  
39  
40
- 41 20. New Zealand Guidelines Group. The assessment and management of  
42  
43 cardiovascular risk. Wellington, New Zealand Guidelines Group.  
44  
45 <http://www.health.govt.nz/publication/assessment-and-management-cardiovascular->  
46  
47 [risk](http://www.health.govt.nz/publication/assessment-and-management-cardiovascular-).Updated July 8, 2015. Accessed November 13, 2015.  
48  
49
- 50 21. Morales Salinas A, Coca A, Olsen MH, et al. Clinical Perspective on  
51  
52 Antihypertensive Drug Treatment in Adults With Grade 1 Hypertension and Low-to-  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 Moderate Cardiovascular Risk: An International Expert Consultation. *Current*  
4 *Problems in Cardiology*. 2017;42(7):198-225.  
5  
6  
7  
8 22. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on  
9 outcome incidence in hypertension: 2. Effects at different baseline and achieved  
10 blood pressure levels—overview and meta-analyses of randomized trials. *Journal of*  
11 *hypertension*. 2014;32(12):2296-2304.  
12  
13  
14  
15  
16  
17 23. Lonn EM, Bosch J, López-Jaramillo P, et al. Blood-Pressure Lowering in  
18 Intermediate-Risk Persons without Cardiovascular Disease. *New England Journal of*  
19 *Medicine*. 2016;374(21):2009-2020.  
20  
21  
22  
23  
24 24. The Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of Blood  
25 Pressure Reduction in Mild Hypertension. A Systematic Review and Meta-analysis.  
26 *Ann. Intern. Med*. 2015;162(3):184-191.  
27  
28  
29  
30  
31 25. The Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure-  
32 lowering treatment based on cardiovascular risk: a meta-analysis of individual patient  
33 data. *The Lancet*. 2014;384(9943):591-598.  
34  
35  
36  
37  
38 26. The Management Committee. The Australian Therapeutic Trial in Mild  
39 Hypertension. *The Lancet*. 1980;315(8181):1261-1267.  
40  
41  
42  
43 27. Anderson, K. M., Odell, P. M., Wilson, P. W., & Kannel, W. B. (1991).  
44 Cardiovascular disease risk profiles. *American heart journal*, 121(1), 293-298  
45  
46  
47  
48 28. Bennett SA, Magnus P. Trends in cardiovascular risk factors in Australia. Results  
49 from the National Heart Foundation's Risk Factor Prevalence Study, 1980-1989. *The*  
50 *Medical Journal of Australia*. 1994;161(9):519-527.  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 29. Hajifathalian K, Ueda P, Lu Y, et al. A novel risk score to predict cardiovascular  
4 disease risk in national populations (GloboRisk): a pooled analysis of prospective  
5 cohorts and health examination surveys. *Lancet Diabetes Endocrinol.* 2015;3(5):339-  
6 355.  
7  
8  
9  
10  
11  
12 30. Bender R, Kromp M, Kiefer C, Sturtz S. Absolute risks rather than incidence  
13 rates should be used to estimate the number needed to treat from time-to-event  
14 data. *J. Clin. Epidemiol.* 2013;66(9):1038-1044.  
15  
16  
17  
18  
19 31. Zomer, E., Owen, A., Magliano, D. J., Liew, D., & Reid, C. (2011). Validation of  
20 two Framingham cardiovascular risk prediction algorithms in an Australian  
21 population: the 'old' versus the 'new' Framingham equation. *European Journal of*  
22 *Cardiovascular Prevention & Rehabilitation*, 18(1), 115-120.  
23  
24  
25  
26  
27  
28 32. Hayward RA, Kent DM, Vijan S, Hofer TP. Multivariable risk prediction can  
29 greatly enhance the statistical power of clinical trial subgroup analysis. *BMC Med.*  
30 *Res. Methodol.* 2006;6(1):1.  
31  
32  
33  
34  
35 33. Hughes K, Leong WP, Sothy SP, Lun KC, Yeo PPB. Relationships between  
36 Cigarette smoking, Blood Pressure and Serum Lipids in the Singapore General  
37 Population. *International Journal of Epidemiology.* 1993;22(4):637-643.  
38  
39  
40  
41  
42 34. Catalano M, Aronica A, Carzaniga G, Seregini R, Libretti A. Serum lipids and  
43 apolipoproteins in patients with essential hypertension. *Atherosclerosis.*  
44 1991;87(1):17-22.  
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3 Figure 1. Effect of treatment in the overall study population. \*Adjusted for age, sex,  
4 body-mass index, screening centres, smoking and systolic blood pressure. **Bold**  
5 **p**<0.05. CVD for cardiovascular disease, CHD for coronary heart disease.  
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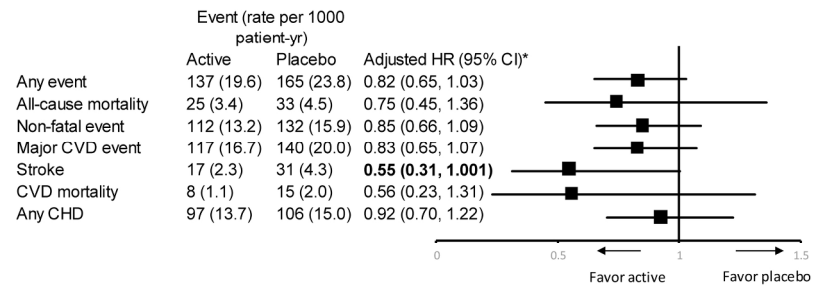


Figure 1. Effect of treatment in the overall study population. \*Adjusted for age, sex, body-mass index, screening centres, smoking and systolic blood pressure. Bold p<0.05. CVD for cardiovascular disease, CHD for coronary heart disease.

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Table 1. Baseline characteristics stratified by tertile of baseline systolic blood pressure

Group variable	1 <sup>st</sup> tertile (113-151 mmHg)	2 <sup>nd</sup> tertile (152 – 165 mmHg)	3 <sup>rd</sup> tertile (166 – 225 mmHg)
Sample, N	1156	1014	1074
Age, years	48.8 ± 7.3	51.4 ± 7.8	55.1 ± 7.8
Male sex, N (%)	803 (69.5)	645 (63.6)	569 (53.0)
Current smoker, N (%)	285 (24.7)	251 (24.8)	265 (24.7)
SBP, mmHg	142.1 ± 7.0	158.2 ± 3.9	179.3 ± 11.7
DBP, mmHg	99.7 ± 4.1	102.7 ± 6.0	106.5 ± 8.0
Total cholesterol, mmol/l	5.9 ± 1.1	6.0 ± 1.1	6.1 ± 1.2
BMI, kg/m <sup>2</sup>	26.7 ± 3.6	26.5 ± 3.7	26.6 ± 4.4
CVD risk (%)	7.9 ± 8.7	12.8 ± 9.6	20.7 ± 9.5

SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body - mass index, CVD: cardiovascular disease.

Table 2. Effect of treatment by tertile of baseline systolic blood pressure.

	Event (%)		Adjusted HR (95% CI)*	ARR % (95% CI)	NNT
	Active	Placebo			
<b>Any event</b>					
113-151 mmHg	34 (5.6)	43 (7.8)	0.71 (0.45 - 1.11)	2.5 (-0.7, 5.6)	41 (-135, 18)
152 – 165 mmHg	49 (9.8)	46 (9.0)	1.07 (0.71 - 1.61)	-1.2 (-5.0, 2.7)	-87 (-20, 37)
166 – 225 mmHg	54 (10.5)	76 (3.6)	0.73 (0.51-1.03)	<b>4.8 (0.9, 8.8)</b>	<b>21 (11, 112)</b>
p-value	-	-	0.25	0.1	-
<b>All-cause mortality</b>					
113-151 mmHg	5 (0.8)	10 (1.8)	0.49 (0.17-1.46)	0.7 (-0.2, 1.7)	139 (-468, 60)
152 – 165 mmHg	11 (2.2)	8 (1.6)	1.30 (0.51 - 3.28)	-0.9 (-2.7, 0.9)	-110 (-36, 108)
166 – 225 mmHg	9 (1.7)	15 (2.7)	0.64 (0.28 - 1.46)	<b>1.9 (0.3, 3.6)</b>	<b>52 (28, 372)</b>
p – value	-	-	0.26	0.08	-
<b>Non-fatal event</b>					
113-151 mmHg	29 (4.8)	33 (6.0)	0.77 (0.47 - 1.28)	1.2 (-1.7, 1.5)	86 (-59, 25)
152 – 165 mmHg	38 (7.6)	38 (7.4)	1.00 (0.63 - 1.58)	-0.2 (-3.6, 1.7)	-455 (-27, 31)
166 – 225 mmHg	45 (8.7)	61 (10.9)	0.76 (0.52 - 1.13)	2.9 (-0.8, 1.8)	35 (-133, 15)
p – value	-	-	0.58	0.48	-
<b>Major CVD event</b>					
113-151 mmHg	31 (5.1)	35 (6.3)	0.79 (0.48 - 1.28)	1.6 (-1.3, 1.5)	61 (-74, 22)
152 – 165 mmHg	41 (8.2)	40 (7.8)	1.04 (0.67 - 1.61)	-0.4 (-4.0; 3.1)	-227 (-25, 32)
166 – 225 mmHg	45 (8.7)	65 (11.7)	0.73 (0.50 - 1.06)	<b>4.1 (0.4, 7.8)</b>	<b>24 (13, 242)</b>
p - value	-	-	0.39	0.22	-
<b>Any CHD</b>					
113-151 mmHg	30 (5.0)	29 (5.3)	0.93 (0.56 - 1.56)	0.4 (-2.4, 3.1)	286 (-42, 32)
152 – 165 mmHg	29 (5.8)	30 (5.9)	0.95 (0.57-1.59)	-0.1 (-3.1, 2.9)	-1250 (-32, 34)
166 – 225 mmHg	38 (7.4)	47 (8.4)	0.87 (0.57-1.34)	2.0 (-1.4, 5.4)	51 (-71, 19)
p - value	-	-	0.89	0.65	-

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3 CVD: cardiovascular disease, CHD: coronary heart disease, HR: hazard ratio, CI: confidence  
4 interval, ARD: absolute risk difference, NNT: number needed to treat. NNTB: number needed to treat  
5 (benefit). NNTH: number needed to treat (harm).p-value indicated p for interaction.  
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9 \* Adjusted for age, sex, body-mass index, smoking, screening centres and systolic blood pressure.

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11 **Bold** p<0.05  
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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (p1) (b) Provide in the abstract an informative and balanced summary of what was done and what was found (p2-3)
<b>Introduction</b>		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (p4-6)
Objectives	3	State specific objectives, including any prespecified hypotheses (p6)
<b>Methods</b>		
Study design	4	Present key elements of study design early in the paper (p6)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (p6)
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (p6-7) (b) For matched studies, give matching criteria and number of exposed and unexposed (N/A)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (p7)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group (p7)
Bias	9	Describe any efforts to address potential sources of bias (p7)
Study size	10	Explain how the study size was arrived at (N/A because this is a post-hoc analysis of the ANBP)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (p8)
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (p8) (b) Describe any methods used to examine subgroups and interactions (p8) (c) Explain how missing data were addressed (p7) (d) If applicable, explain how loss to follow-up was addressed (p8) (e) Describe any sensitivity analyses (p7)
<b>Results</b>		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (p7 – describe in method section because this was a post-hoc analysis of the ANBP) (b) Give reasons for non-participation at each stage (N/A) (c) Consider use of a flow diagram (N/A)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (p8-9 but not separately describe exposed and unexposed group because there was not enough spaces for describing expose and unexposed in each subgroup (low, moderate and high risk. We mentioned by words in result section). (b) Indicate number of participants with missing data for each variable of interest (No

		<a href="#">because there was only 1% missing data</a>
		(c) Summarise follow-up time (eg, average and total amount) (p8)
Outcome data	15*	Report numbers of outcome events or summary measures over time (p11, p23)
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (not report the unadjusted estimates because there was not enough space. However we mentioned about no significant difference between adjusted and unadjusted estimates on p13)
		(b) Report category boundaries when continuous variables were categorized (p9-10)
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period (p11,12)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (p11, 12, supplementary)
<b>Discussion</b>		
Key results	18	Summarise key results with reference to study objectives (p12-13)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (p15-17)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (p17)
Generalisability	21	Discuss the generalisability (external validity) of the study results (p17)
<b>Other information</b>		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (p17)

\*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.