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

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

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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 ± 6.5) with moderately elevated BP (159/103 mmHg) and were middle-aged (52 ± 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

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

Conclusion

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

Key Words: antihypertensive drug, cardiovascular disease, absolute cardiovascular risk, primary prevention, hypertension.

Strengths and limitations of this study

Our analysis provides further justification that an absolute risk strategy is superior to management based on the BP level alone in identifying those who are most likely to benefit from therapy.

The statistical power of detecting treatment effects was decreased in a post-hoc subgroup analysis. However the use of multivariate risk score is known to increase power of detecting heterogeneity in absolute risk benefit.

Due to the lack of high density lipoprotein cholesterol in the original data set (HDLc), the HDLc used in the analyses was estimated from the 1980s national survey, but this method is unlikely to greatly affect the risk stratification because a 0.4 difference in the HDLc estimate only results in a 1% difference in CVD risk score.

Introduction

For decades, cardiovascular disease (CVD) has remained the main burden of disease in the developed world and now also in the developing world [1,2]. In 2012, CVD was responsible for 17.5 million deaths in the world and more than twenty thousand deaths in Australia[1,3]. Noticeably, nearly 50% of deaths from CVD are attributable to high blood pressure (BP), the commonest modifiable population risk factor [4]. 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 [5-9]. 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 [10]. 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 [6,7,11-13]. 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[11]. 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 [14], otherwise patients are exposed to increased risk [15-18]. Specifically, the SPRINT trial[19] 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

findings from the SPRINT trial, guidelines in Australia [5], New Zealand [20], UK [8] and Canada [9] based on absolute CVD risk propose to initiate BP lowering treatment as soon as possible in high CVD risk individuals, but not in low to moderate risk population unless BP persistently exceeds 160/100 mmHg.

Recently, the HOPE-3 investigators reported a non-significant effect of a fixed-dose combination of BP lowering drug treatment in reducing the rate of major CVD events in intermediate CVD risk older persons [21]. Similarly, a Cochrane review by Diao et al reported no strong benefit of BP treatment in individuals who had grade 1 hypertension[10]. In contrast, the 2015 Blood Pressure Lowering Treatment Trialists Collaboration (BPLTTC) meta-analysis reported a substantial benefit of BP lowering drug treatment in grade 1 hypertension in terms of stroke and all-cause mortality [22]. However, these stronger treatment effects could reflect differences in the BPLTTC sample that included participants who had diabetes and had previously received drug treatment. In a 2014 individual patient data meta-analysis, BPLTTC stratified the participants by absolute CVD risk at baseline, though the study mixed participants who did and did not have a history of CVD [23].

Thus, we sought to reanalyse a seminal study used to justify treating individuals with 'mildly' elevated BP to see if stratification by baseline CVD risk would be a superior method for identifying candidates for BP-lowering medication. In this study, we compared the effectiveness of BP lowering drug treatment by a post-hoc subgroup analysis of the Australian National Blood Pressure study (ANBP). We restricted the analysis group to individuals with no history of CVD or diabetes, and who were naïve to BP lowering treatment. We selected this historic study because it was placebo controlled and patients in the control arm of the study would not have been taking a BP lowering medication unless they had very high levels of BP. Our

aim was to assess which group of individuals classified by absolute risk benefited from active treatment vs. placebo for CVD events within this seminal study that underwrote the treatment of elevated BP by BP thresholds.

Methods

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

Risk stratification

The baseline absolute CVD risk was calculated according to the 5-year Framingham absolute risk score. The Framingham score was chosen because it is currently recommended in the National Vascular Disease Prevention Alliance

(NVDPA) guidelines [5] in Australia. The sample was restricted to ages 35 to 74. We also classified all participants with very high BP (systolic BP ≥ 180 mmHg and/or diastolic BP ≥ 110 mmHg) or total cholesterol (> 7.5 mmol/l) values as high CVD risk regardless of their risk score, as per the guidelines [5]. 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[25]. 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-basedcenters 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) [26]. 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 ± 6.5) with moderately elevated BP (159/103 mmHg) and were middle-aged (52± 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)	115 (10.6)	352 (32.6)	334 (30.9)
SBP, mmHg	159.5 ± 17.5	148.4 ± 12.2	157.3 ± 12.2	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/m2	26.6 ± 3.9	26.6 ± 4.0	26.5 ± 3.6	26.7 ± 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/m2	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

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). However, the treatment effects were not statistically significant in our analysis. 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 also 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).

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

	Event (%)				
	Active	Placebo	Adjusted HR (95% CI)*	ARR % (95% CI)	NNT
Any event					
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)	**5.6 (1.6, 9.6)**	**18 (10, 64)**
p - value	-	-	0.64	0.05	-
All-cause mortality					
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)	**2.2 (0.5, 3.9)**	**45 (25, 196)**
p – value	-	-	0.78	**0.04**	-
Non-fatal event					
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	-
Major CVD event					
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)	**4.3 (0.5, 8.1)**	**23 (12, 193)**
p - value	-	-	0.62	0.17	-
Any CHD					
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 [24].

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

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

Regarding the benefit of BP lowering drug treatment in the low to intermediate CVD risk population, our results from main and subgroup analyses match well with the study outcomes from the HOPE-3 trial [21] and the Diao review [10]. In the HOPE-3 trial, no benefit of intensive drug treatment was established in the intermediate-risk persons with HR 0.98 (0.84-1.14) for all-cause mortality and HR 0.92 (0.79 – 1.06) for major CVD events referred as a first secondary outcome in the paper [21]. At baseline, the HOPE-3 participants were older (65 years), had a lower level of BP (138.1/81.9 mmHg) compared to the ANBP participants. This may be due to the 4-week run-in phase in which all of the HOPE-3 participants received active BP lowering drug treatment before randomisation and one-fifth of all eligible participants had previously received drug treatment before the trial. In 2012, Diao et al reviewed placebo randomised controlled trials in grade 1 hypertension and also found no beneficial effect of drug treatment with a risk ratio (RR) 0.85 (0.63 – 1.15) for all-cause mortality and RR 0.97 (0.2 – 1.32) for major CVD events[10]. The participants in the Diao review were likely to have a lower CVD risk than those in the ANBP and the HOPE-3 when major CVD events occurred in 2.4% of participants in the placebo group. Following a similar approach, in 2015, The Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) [23] reviewed randomised controlled trials

in grade 1 hypertension but extended to trials comparing active or more intensive regimen and placebo or less intensive regimen. In line with the findings from the 2015 BPLTTC study, we identified a marginally significant effect on stroke, yet our effect estimates with an HR 0.75 (0.45 – 1.36) for total deaths and an HR 0.83 (0.65 – 1.07) for major CVD events slightly differed from the 2015 BPLTTC study's results with an OR 0.78 (0.67-0.92) and an OR 0.86 (0.74-1.01) correspondingly. The differences in confidence intervals may be due to the difference in sample sizes and baseline characteristics. It is more likely that the 2015 BPLTTC participants had higher CVD risk and higher BP value at baseline when about 40% of 15,266 participants had diabetes and about 23% previously received BP lowering drug treatment. Our study and the 2015 review confirmed the absolute benefits of BP lowering drug treatment in high CVD risk population in terms of total deaths with ARR 2.2% (0.5, 3.9, p=0.01) for the ANBP and ARR 1.4% (0.5, 2.2) for the review. Furthermore, the benefit was also recorded in major CVD event with ARR 4.3% (0.5, 8.1, p=0.03) in the ANBP, whereas the 2015 BPLTTC observed a non-significant effect with ARR 1.0% (-0.1, 1.9). The difference can be explained in part by the study design when more than 50% of participants with systolic BP higher than 160 mmHg in eligible studies in the 2015 BPLTTC were excluded. The distribution of these excluded participants might not be even between active arm and control arm, thus biasing the treatment effects.

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

within the highest tertile. The findings were in line with what we found in the CVD risk-stratified subgroup when all participants in the highest BP-stratified tertile had high CVD risk score (20.7 ± 9.5). The substantial absolute benefits recorded in the highest BP-stratified tertile were more likely to be influenced by baseline CVD risk.

Limitations

There are a number of limitations of our study. Firstly, statistical power is unavoidably decreased in a post-hoc subgroup analysis. However, the multivariate risk score used in our analysis has been well validated globally and within the Australian population [5]. Using such a score for stratification is known to increase power of detecting heterogeneity in absolute risk benefit over subgroup analyses that are based on individual risk factors[27]. A prospective study to address the issue of whether there is an advantage in treating blood pressure by AR is unlikely to be performed, because of the very large sample size and very long follow-up time required. Furthermore, placebo controlled contemporary BP lowering drug trials are not conducted in hypertensive populations due to established efficacy. Therefore, re-analysis of the early placebo-controlled trials seems to be the most feasible approach for assessing the effects of delayed versus early drug treatment in individuals with varying CVD risk together and elevated BP.

Secondly, the estimation of HDLc from the 1980s national survey may alter the CVD risk score, but we do not believe this method greatly affected the risk stratification because a 0.4 difference in the HDL estimate only results in a 0.01 difference in CVD risk score. Furthermore, no association between HDLc and BP has been observed [28,29]. Also, we performed a sensitivity analysis by using the GLOBORISK score[30] that does not require HDLc value and is validated in individuals

over 40 years. The equation for the Australian population was obtained by personal contact with the author (Peter Ueda, unpublished data, 2016). This analysis excluded 471 participants younger than 40 years and 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). This result is likely due to the smaller sample size and subsequent number of events. In conclusion, the sensitivity analysis supports our main analysis. Thirdly, the paucity of trial endpoints in each CVD risk group prevented us from comparing the effects in some specific outcomes with respect to stroke and deaths from CVD.

In conclusion, our research has demonstrated that drug treatment in patients with elevated BP is best directed to those at high risk of incident CVD events. This reinforces the guidelines recommendation to treat based on absolute (or global) CVD risk, rather than according to BP thresholds alone [5-9].

Competing interests:

CLBH is a Ph.D. candidate at Menzies Institute for Medical Research, she has received a Ph.D. scholarship from Merle Weaver Postgraduate Scholarship. JD is supported by National Health and Medical Research Council Screening and Test Evaluation Program Grant 633003. CR is supported by a National Health and Medical Research Council Senior Research Fellowship (1045862). MRN has in the last 5 years served on an advisory board for AMGEN.

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

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

Data sharing statement: No additional data are available.

References

1. World Health Organisation. The top 10 causes of death [online database]. http://www.who.int/mediacentre/factsheets/fs310/en/. Updated May, 2014 Accessed November 13, 2015.
2. Australian Bureau of Statistics. Causes of Death, Australia, 2013; http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2013~Main%20Features~Leading%20Causes%20of%20Death~10001. Updated March 7, 2016. Accessed November 30, 2016.
3. Australia Bureau of Statistics. Causes of Death, Australia. 2012. http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/3303.0main+features100012012. Updated March 30, 2015. Accessed November 13, 2015.

4. World Health Organisation (WHO). A Global Brief on Hypertension: Silent Killer, Global Public Health Crissis [Online]. http://www.thehealthwell.info/node/466541. Updated January 4, 2013. Accessed November 13, 2015.
5. National Vascular Disease Prevention Allianace. *Guidelines for the management of absolute cardiovascular disease risk.*http://www.cvdcheck.org.au/index.php?option=com_content&view=article&id=47&Itemid=27.Updated May, 2012. Accessed November 13, 2015.
6. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension. *Blood Pressure.* 2013;22(4):193-278.
7. Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur. Heart J.* 2012;33(13):1635-1701.
8. Krause T, Lovibond K, Caulfield M, McCormack T, Williams B. Management of hypertension: summary of NICE guidance. *BMJ.* 2011;343.
9. Dasgupta K, Quinn RR, Zarnke KB, et al. The 2014 Canadian Hypertension Education Program Recommendations for Blood Pressure Measurement, Diagnosis, Assessment of Risk, Prevention, and Treatment of Hypertension. *Can. J. Cardiol.* 2014;30(5):485-501.
10. Diao D, Wright J, Cundiff D, Gueyffier F. Pharmacotherapy for mild hypertension. *Cochrane Database of Systematic Reviews.* 2012;8:CD006742.
11. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members

appointed to the Eighth Joint National Committee (JNC 8). *Jama.* 2014;311(5):507-520.

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

20. New Zealand Guidelines Group. *The assessment and management of cardiovascular risk.* Wellington, New Zealand Guidelines Group. http://www.health.govt.nz/publication/assessment-and-management-cardiovascular-risk.Updated July 8, 2015. Accessed November 13, 2015.

21. Lonn EM, Bosch J, López-Jaramillo P, et al. Blood-Pressure Lowering in Intermediate-Risk Persons without Cardiovascular Disease. *New England Journal of Medicine.* 2016;374(21):2009-2020.

22. The Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of Blood Pressure Reduction in Mild Hypertension. A Systematic Review and Meta-analysis. *Ann. Intern. Med.* 2015;162(3):184-191.

23. The Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. *The Lancet.* 2014;384(9943):591-598.

24. The Management Committee. The Australian Therapeutic Trial in Mild Hypertension. *The Lancet.* 1980;315(8181):1261-1267.

25. Bennett SA, Magnus P. Trends in cardiovascular risk factors in Australia. Results from the National Heart Foundation's Risk Factor Prevalence Study, 1980-1989. *The Medical Journal of Australia.* 1994;161(9):519-527.

26. Bender R, Kromp M, Kiefer C, Sturtz S. Absolute risks rather than incidence rates should be used to estimate the number needed to treat from time-to-event data. *J. Clin. Epidemiol.* 2013;66(9):1038-1044.

27. Hayward RA, Kent DM, Vijan S, Hofer TP. Multivariable risk prediction can greatly enhance the statistical power of clinical trial subgroup analysis. *BMC Med. Res. Methodol.* 2006;6(1):1.

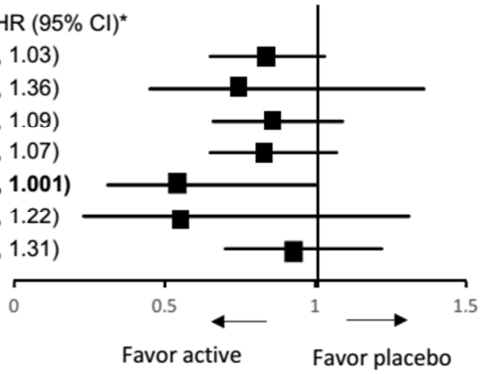
28. Hughes K, Leong WP, Sothy SP, Lun KC, Yeo PPB. Relationships between Cigarette smoking, Blood Pressure and Serum Lipids in the Singapore General Population. *International Journal of Epidemiology.* 1993;22(4):637-643.

29. Catalano M, Aronica A, Carzaniga G, Seregni R, Libretti A. Serum lipids and apolipoproteins in patients with essential hypertension. *Atherosclerosis.* 1991;87(1):17-22.

30. Hajifathalian K, Ueda P, Lu Y, et al. A novel risk score to predict cardiovascular disease risk in national populations (Globorisk): a pooled analysis of prospective cohorts and health examination surveys. *Lancet Diabetes Endocrinol.2015;*3(5):339-355.

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

	Event (%)		
	Active	Placebo	Adjusted HR (95% CI)*
Any event	137 (8.4)	165 (10.2)	0.82 (0.65, 1.03)
All-cause mortality	25 (1.5)	33 (2.0)	0.75 (0.45, 1.36)
Non-fatal event	112 (6.9)	132 (8.1)	0.85 (0.66, 1.09)
Major CVD event	117 (7.2)	140 (8.6)	0.83 (0.65, 1.07)
Stroke	17 (1.0)	31 (1.9)	**0.55 (0.31, 1.001)**
Any CHD	97 (6.0)	106 (6.5)	0.92 (0.70, 1.22)
CVD mortality	8 (0.5)	15 (0.9)	0.56 (0.23, 1.31)



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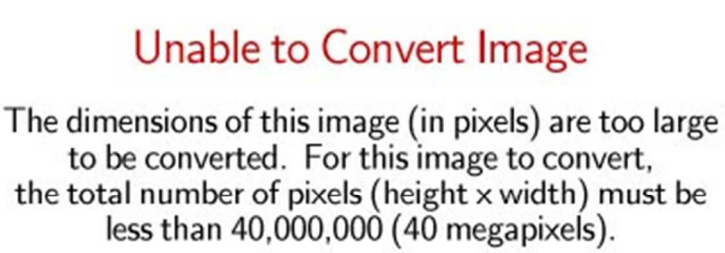

Effect of treatment on the overall study population. CVD: cardiovascular disease, CHD for coronary heart disease. *Adjusted for age, sex, body-mass index, screening centres, smoking and systolic blood pressure. Bold $p<0.05$

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

Group variable	1st tertile (113-151 mmHg)	2nd 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/m2	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 (%)				
	Active	Placebo	Adjusted HR (95% CI)*	ARR % (95% CI)	NNT
Any event					
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)	**4.8 (0.9, 8.8)**	**21 (11, 112)**
p-value	-	-	0.25	0.1	-
All-cause mortality					
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)	**1.9 (0.3, 3.6)**	**52 (28, 372)**
p – value	-	-	0.26	0.08	-
Non-fatal event					
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	-
Major CVD event					
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)	**4.1 (0.4, 7.8)**	**24 (13, 242)**
p - value	-	-	0.39	0.22	-
Any CHD					
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	-

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 $p<0.05$

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

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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 ± 6.5) with moderately elevated BP (mean 159/103 mmHg) and were middle-aged (52 ± 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

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

Conclusion

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

Key Words: antihypertensive drug, cardiovascular disease, absolute cardiovascular risk, primary prevention, hypertension.

Strengths and limitations of this study

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

Introduction

For decades, cardiovascular disease (CVD) has remained the greatest burden of disease in the developed world and now also in the developing world [1,2]. In 2012, CVD was responsible for 17.5 million deaths in the world and more than twenty thousand deaths in Australia[1,3]. Noticeably, nearly 50% of deaths from CVD are attributable to high blood pressure (BP), the commonest modifiable population risk factor [4]. 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 [5-9]. 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 [10]. 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 [6-8,11-13]. JNC 8[11] 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 [14], otherwise patients are exposed to increased risk [15-18]. Similarly, the 2016 European Society of Cardiology guidelines recommend considering BP lowering drug treatment when systolic BP is greater than 140 mmHg

and/or diastolic BP is greater than 90 mmHg after a reasonable period of time with lifestyle choice [7]. Recently, the SPRINT (Systolic Blood Pressure Intervention trial) [19] reported a significant benefit from intensive treatment to a target BP of 120 mmHg rather than 140 mmHg. However, this benefit was observed in those at high CVD risk without diabetes. In agreement with the findings from the SPRINT trial, guidelines in Australia [5], New Zealand [20], UK [8] and Canada [9] recommend BP lowering medication based on absolute CVD risk, recommending BP lowering treatment as soon as possible in high CVD risk individuals, but not in the low to moderate risk population unless BP persistently exceeds 160/100 mmHg.

Other groups [21] have argued for treatment of patients with grade 1 hypertension even in patients at low risk based on evidence from a meta-analysis by Thomopolous et al[22] and the HOPE-3 study[23]. In contrast, a Cochrane review by Diao et al[10] concluded that there was no statistically significant effect of BP treatment in individuals who had grade 1 hypertension. The 2015 Blood Pressure Lowering Treatment Trialists Collaboration[24] (BPLTTC) meta-analysis reported a statistically significant benefit of BP lowering drug treatment in grade 1 hypertension in terms of stroke and all-cause mortality. However, the effects seen in the BPLTTC analysis could reflect differences in the BPLTTC sample that included participants who had diabetes, had a higher baseline risk and had previously received drug treatment. In another analysis of the BPLTTC individual patient data[25] by absolute CVD risk at baseline showed a continuously increasing benefit with baseline risk[25]. The BPLTTC study, however included participants who both did and did not have a history of CVD.

Thus, we sought to reanalyse a seminal study used to justify treating individuals with 'mildly' elevated BP to see if stratification by baseline CVD risk would be a superior method for identifying candidates for BP-lowering medication in a

treatment-naïve population. In this study, we compared the effectiveness of BP lowering drug treatment by a post-hoc subgroup analysis of the Australian National Blood Pressure study[26] (ANBP). We restricted the analysis group to individuals with no history of CVD or diabetes, and who were naïve to BP lowering treatment. We selected this historic study because it was placebo controlled and patients in the control arm of the study would not have been taking a BP lowering medication previously unless they had very high levels of BP. Our aim was to assess which group of individuals classified by absolute risk benefited from active treatment vs. placebo for CVD events within this seminal study that underwrote the treatment of elevated BP by BP thresholds.

Methods

We performed a post-hoc analysis of the Australian National Blood Pressure study[26]. The study was conducted between 1973 and 1979 and was a multicentre, single-blind randomised controlled trial of 3,427 patients which compared the effects of BP lowering drug therapy between individuals who initially received active treatment (chlorothiazide) and those who received delayed active treatment or no active treatment (placebo). The study intervention remains applicable to current practice as thiazide diuretic is still one of the first line of blood pressure lowering agents[5-9]. The ANBP study enrolled participants who had not been on treatment for hypertension in the past three months and had no history of CVD or diabetes. In the 1970s, 'mild hypertension' was defined as a screening diastolic BP of 95 to 109 mmHg with a systolic BP lower than 200 mmHg. 3,931 eligible participants were initially randomised, then 504 participants were excluded because their BP throughout the study did not meet the criteria for starting drug treatment (entry or follow-up diastolic BP higher than 95 mmHg and/or entry or follow-up systolic BP

higher than 200 mmHg). The primary endpoints were all-cause mortality and non-fatal events (non-fatal CVD, congestive cardiac failure, renal failure, hypertensive retinopathy or encephalopathy) [26].

Risk stratification

In this analysis, the baseline absolute CVD risk was calculated according to the 5-year Framingham absolute risk score[27]. The Framingham score was chosen because it is currently recommended in the National Vascular Disease Prevention Alliance (NVDPA) guidelines [5] in Australia. The sample was restricted to 3,244 participants who were older than 35 years. We also classified all participants with very high BP (systolic BP ≥ 180 mmHg and/or diastolic BP ≥ 110 mmHg) or total cholesterol (> 7.5 mmol/l) values as high CVD risk regardless of their risk score, as per the Australian guidelines [5]. The ANBP dataset included all variables required for CVD risk calculation except high-density lipoprotein cholesterol (HDLc). The HDLc value was imputed from the Australian National Heart Foundation risk factor prevalence study as this was near contemporaneous with the ANBP[28]. Mean value of HDLc was categorised by age and sex. In a sensitivity analysis, a subgroup stratified by GLOBORISK score [29] that does not require HDLc value and is validated in individuals over 40 years. The equation for the Australian population was obtained by personal contact with the author (Peter Ueda, unpublished data, 2016). This analysis excluded 471 participants younger than 40 years. Less than 1% of the study participants had data missing for total cholesterol, weight and/or height and these missing data 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 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-basedcenters 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) [30]. 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 ± 6.5) with moderately elevated BP (mean 159/103 mmHg) and were middle-aged (52± 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)	**115 (10.6)**	352 (32.6)	334 (30.9)
SBP, mmHg	159.5 ± 17.5	148.4 ± 12.2	**157.3 ± 12.2**	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/m2	**26.6 ± 3.9**	26.6 ± 4.0	**26.5 ± 3.6**	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
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/m2	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. **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[29] 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)	**5.6 (1.6, 9.6)**	**18 (10, 64)**

p - value	-	-	0.64	0.05	-
All-cause mortality					
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)	**2.2 (0.5, 3.9)**	**45 (25, 196)**
p – value	-	-	0.78	**0.04**	-
Non-fatal event					
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	-
Major CVD event					
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)	**4.3 (0.5, 8.1)**	**23 (12, 193)**
p - value	-	-	0.62	0.17	-
Any CHD					
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

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 (mean 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 the original 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 by tertile of absolute risk, as well as by the two groups of 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 [26].

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 statistically significant heterogeneity ($p = 0.78$ for all-cause mortality and $p = 0.62$ for the major CVD event) (Table 3). All relative treatment effects in our analysis measured by HRs were adjusted by age, sex, body-mass index, smoking, screening centres and systolic BP. However, no significant difference was observed between adjusted and unadjusted HRs. In terms of absolute benefits, risk reduction linearly increased across the CVD risk group from low to high risk. BP lowering drug treatment produced an unclear benefit in the low and intermediate CVD risk group but a significant benefit in the high CVD risk group. Heterogeneity of absolute

effects across the CVD risk groups was only significant in all-cause mortality (p=0.04).

Regarding the benefit of BP lowering drug treatment in the low to intermediate CVD risk population, our results from main and subgroup analyses match well with the study outcomes from the HOPE-3 trial [23] and the Diao review[10]. In the HOPE-3 trial[23], no benefit of intensive drug treatment was established in the intermediate-risk persons with HR 0.98 (0.84-1.14) for all-cause mortality and HR 0.92 (0.79 – 1.06) for major CVD events referred as a first secondary outcome in the paper. At baseline, the HOPE-3 participants were older (65 years), and had a lower level of BP (138.1/81.9 mmHg) compared to the ANBP participants. One reason for the lower blood pressures may be due to the 4-week run-in phase in which all of the HOPE-3 participants received active BP lowering drug treatment before randomisation and one-fifth of all eligible participants had previously received drug treatment before the trial. In 2012, Diao et al reviewed placebo randomised controlled trials in grade 1 hypertension and also found no beneficial effect of drug treatment with a risk ratio (RR) 0.85 (0.63 – 1.15) for all-cause mortality and RR 0.97 (0.2 – 1.32) for major CVD events[10]. The participants in the Diao review were likely to have a lower CVD risk than those in the ANBP and the HOPE-3 trials, with major CVD events occurring in only 2.4% of participants in the placebo group. Following a similar approach, in 2015, The Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) [24] reviewed randomised controlled trials in grade 1 hypertension but extended to trials comparing active or more intensive regimens and placebo or less intensive regimens. In line with the findings from the 2015 BPLTTC study, we identified a marginally significant effect on stroke, yet our effect estimates with an HR 0.75 (0.45 – 1.36) for total deaths and an HR 0.83 (0.65 – 1.07) for major CVD events slightly

differed from the 2015 BPLTTC study's results with an OR 0.78 (0.67-0.92) and an OR 0.86 (0.74-1.01) correspondingly. The differences in confidence intervals may be due to the difference in sample sizes and baseline characteristics. It is more likely that the 2015 BPLTTC participants had higher CVD risk and higher BP value at baseline when about 40% of 15,266 participants had diabetes and about 23% had previously received BP lowering drug treatment. Our study and the 2015 review confirm the absolute benefits of BP lowering drug treatment in high CVD risk population in terms of total deaths with ARR 2.2% (0.5, 3.9, p=0.01) for the ANBP and ARR 1.4% (0.5, 2.2) for the review. Furthermore, the benefit was also recorded in major CVD event with ARR 4.3% (0.5, 8.1, p=0.03) in the ANBP, whereas the 2015 BPLTTC observed a non-significant effect with ARR 1.0% (-0.1, 1.9). The difference can be explained in part by the study design when more than 50% of participants with systolic BP higher than 160 mmHg in eligible studies in the 2015 BPLTTC were excluded. The distribution of these excluded participants might not be even between active arm and control arm, thus biasing the treatment effects.

In another subgroup analysis stratified by tertile of baseline systolic BP (supplement), the mean value of CVD risk varied from low to high corresponding to the lowest and the highest tertile. The relative treatment benefits were not statistically significant, but in terms of absolute effects, BP lowering drug treatment substantially reduced any trial events, all-cause mortality and major CVD events within the highest tertile. The findings were in line with what we found in the CVD risk-stratified subgroup when all participants in the highest BP-stratified tertile had high CVD risk score (20.7 ± 9.5). However, the heterogeneity of treatment effects among the three subgroups in analysis by baseline systolic BP was no longer significant as it was in the subgroup analysis by CVD risk score. Further, the trend of

lower to higher absolute benefit from low to high risk groups that was seen for CVD risk was not apparent when groups are defined by BP alone. Thus, in this study, CVD risk score was better in identifying those who most benefits from BP lowering drug treatment with regard to all-cause mortality.

Limitations

There are a number of limitations of our study. Firstly, statistical power is unavoidably decreased in a post-hoc subgroup analysis and the multivariate Framingham risk score used in our analysis has not been well validated within the Australian population[31]. However, using a multivariate score for stratification is known to increase the power to detect heterogeneity in absolute risk benefit over subgroup analyses that are based on individual risk factors[32]. A prospective study to address the issue of whether there is an advantage in treating blood pressure by AR is unlikely to be performed, because of the very large sample size and very long follow-up time required, particularly in patients at low risk. Therefore, re-analysis of the early placebo-controlled trials seems to be the most feasible approach for assessing the effects of delayed versus early drug treatment in individuals with varying CVD risk together and elevated BP.

Secondly, the estimation of HDLc from the 1980s national survey may alter the CVD risk score, but we do not believe this method greatly affected the risk stratification because a 0.4 difference in the HDL estimate only results in a 0.01 difference in CVD risk score. Furthermore, no association between HDLc and BP has been observed [33,34]. The sensitivity analysis using GLOBORISK score[29] without HDLc observed similar results with our main analysis. Although the ARR is no longer statistically

significant, this result is likely due to the smaller sample size and subsequent number of events. In conclusion, the sensitivity analysis supports our main analysis.

Thirdly, the paucity of trial endpoints in each CVD risk group prevented us from comparing the effects in some specific outcomes with respect to stroke and deaths from CVD.

In conclusion, our research has demonstrated that drug treatment in patients with elevated BP is best directed to those at high risk of incident CVD events. This reinforces the guidelines recommendation to treat based on absolute (or global) CVD risk, rather than according to BP thresholds alone [5-9].

Competing interests:

CLBH is a Ph.D. candidate at Menzies Institute for Medical Research, she has received a Ph.D. scholarship from Merle Weaver Postgraduate Scholarship. JD is supported by National Health and Medical Research Council Screening and Test Evaluation Program Grant 633003. CR is supported by a National Health and Medical Research Council Senior Research Fellowship (1045862). MRN has in the last 5 years served on an advisory board for AMGEN.

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

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

Data sharing statement: No additional data are available.

References

1. World Health Organisation. The top 10 causes of death [online database]. http://www.who.int/mediacentre/factsheets/fs310/en/. Updated May, 2014 Accessed November 13, 2015.

2. Australian Bureau of Statistics. Causes of Death, Australia, 2013; http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2013~Main%20Features~Leading%20Causes%20of%20Death~10001. Updated March 7, 2016. Accessed November 30, 2016.

3. Australia Bureau of Statistics. Causes of Death, Australia. 2012. http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/3303.0main+features100012012. Updated March 30, 2015. Accessed November 13, 2015.

4. World Health Organisation (WHO). A Global Brief on Hypertension: Silent Killer, Global Public Health Crissis [Online]. http://www.thehealthwell.info/node/466541. Updated January 4, 2013. Accessed November 13, 2015.

5. National Vascular Disease Prevention Allianace. Guidelines for the management of absolute cardiovascular disease risk. http://www.cvdcheck.org.au/index.php?option=com_content&view=article&id=47&Itemid=27.Updated May, 2012. Accessed November 13, 2015.

6.Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension. Blood Pressure. 2013;22(4):193-278.

7. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts). Eur Heart J. 2016; 37: 2315–2381.

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

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

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

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

12. World Health Organization. International Society of Hypertension Writing Group. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. Journal of hypertension. 2003;21(11):1983-1992.

13. Weber MA, Schiffrin EL, White WB, et al. Clinical Practice Guidelines for the Management of Hypertension in the Community. The Journal of Clinical Hypertension. 2014;16(1):14-26.

14.Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension. 2003;42(6):1206-1252.

15. Mitka M. Groups spar over new hypertension guidelines. JAMA. 2014;311(7):663-664.

16. Guallar E, Laine C. Controversy Over Clinical Guidelines: Listen to the Evidence, Not the Noise. Ann. Intern. Med. 2014;160(5):361-362.

17.Wright JJT, Fine LJ, Lackland DT, Ogedegbe G, Dennison Himmelfarb CR. Evidence Supporting a Systolic Blood Pressure Goal of Less Than 150 mm Hg in Patients Aged 60 Years or Older: The Minority ViewSystolic Blood Pressure Goal for Patients Aged 60 Years or Older. Ann. Intern. Med. 2014;160(7):499-503.

18. Zanchetti A. Bottom blood pressure or bottom cardiovascular risk? How far can cardiovascular risk be reduced? Journal of hypertension. 2009;27(8):1509-1520.

19. The SPRINT Research Group. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. New England Journal of Medicine. 2015;373(22):2103-2116.

20. New Zealand Guidelines Group. The assessment and management of cardiovascular risk. Wellington, New Zealand Guidelines Group. http://www.health.govt.nz/publication/assessment-and-management-cardiovascular-risk.Updated July 8, 2015. Accessed November 13, 2015.

21. Morales Salinas A, Coca A, Olsen MH, et al. Clinical Perspective on Antihypertensive Drug Treatment in Adults With Grade 1 Hypertension and Low-to-Moderate Cardiovascular Risk: An International Expert Consultation. Current Problems in Cardiology. 2017;42(7):198-225.

22. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 2. Effects at different baseline and achieved blood pressure levels–overview and meta-analyses of randomized trials. Journal of hypertension. 2014;32(12):2296-2304.

23. Lonn EM, Bosch J, López-Jaramillo P, et al. Blood-Pressure Lowering in Intermediate-Risk Persons without Cardiovascular Disease. New England Journal of Medicine. 2016;374(21):2009-2020.

24. The Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of Blood Pressure Reduction in Mild Hypertension. A Systematic Review and Meta-analysis. Ann. Intern. Med. 2015;162(3):184-191.

25. The Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. The Lancet. 2014;384(9943):591-598.

26. The Management Committee. The Australian Therapeutic Trial in Mild Hypertension. The Lancet. 1980;315(8181):1261-1267.

27. Anderson, K. M., Odell, P. M., Wilson, P. W., & Kannel, W. B. (1991). Cardiovascular disease risk profiles. American heart journal, 121(1), 293-298

28. Bennett SA, Magnus P. Trends in cardiovascular risk factors in Australia. Results from the National Heart Foundation's Risk Factor Prevalence Study, 1980-1989. The Medical Journal of Australia. 1994;161(9):519-527.

29. Hajifathalian K, Ueda P, Lu Y, et al. A novel risk score to predict cardiovascular disease risk in national populations (Globorisk): a pooled analysis of prospective cohorts and health examination surveys. Lancet Diabetes Endocrinol.2015;3(5):339-355.

30. Bender R, Kromp M, Kiefer C, Sturtz S. Absolute risks rather than incidence rates should be used to estimate the number needed to treat from time-to-event data. J. Clin. Epidemiol. 2013;66(9):1038-1044.

31. Zomer, E., Owen, A., Magliano, D. J., Liew, D., & Reid, C. (2011). Validation of two Framingham cardiovascular risk prediction algorithms in an Australian population: the ‘old ’versus the ‘new ‘Framingham equation. European Journal of Cardiovascular Prevention & Rehabilitation, 18(1), 115-120.

32. Hayward RA, Kent DM, Vijan S, Hofer TP. Multivariable risk prediction can greatly enhance the statistical power of clinical trial subgroup analysis. BMC Med. Res. Methodol. 2006;6(1):1.

33. Hughes K, Leong WP, Sothy SP, Lun KC, Yeo PPB. Relationships between Cigarette smoking, Blood Pressure and Serum Lipids in the Singapore General Population. International Journal of Epidemiology. 1993;22(4):637-643.

34.Catalano M, Aronica A, Carzaniga G, Seregni R, Libretti A. Serum lipids and apolipoproteins in patients with essential hypertension. Atherosclerosis. 1991;87(1):17-22.

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.

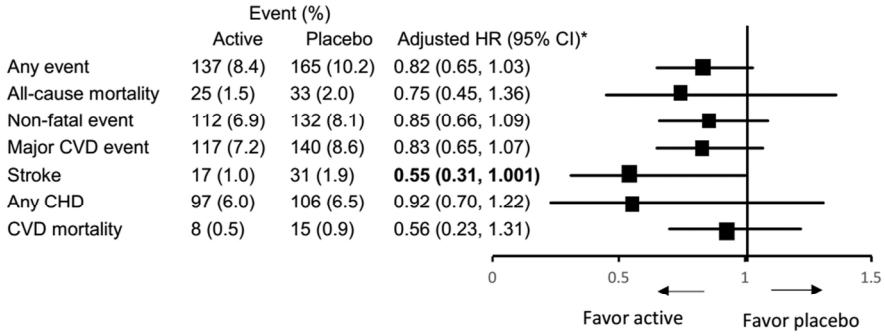

Figure. Effect of treatment in the overall study population. *Adjusted for age, sex, body-mass index, screening centers, smoking and systolic blood pressure. Bold p<0.05
CVD: cardiovascular disease, CHD for coronary heart disease.

162x71mm (300 x 300 DPI)

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

Group variable	1st tertile (113-151 mmHg)	2nd 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/m2	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 (%)				
	Active	Placebo	Adjusted HR (95% CI)*	ARR % (95% CI)	NNT
Any event					
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)	**4.8 (0.9, 8.8)**	**21 (11, 112)**
p-value	-	-	0.25	0.1	-
All-cause mortality					
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)	**1.9 (0.3, 3.6)**	**52 (28, 372)**
p – value	-	-	0.26	0.08	-
Non-fatal event					
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	-
Major CVD event					
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)	**4.1 (0.4, 7.8)**	**24 (13, 242)**
p - value	-	-	0.39	0.22	-
Any CHD					
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	-

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

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	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)
Introduction		
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)
Methods		
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)
Results		
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

		because there was only 1% missing data)
		(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)
Discussion		
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)
Other information		
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

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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 ± 6.5) with moderately elevated BP (mean 159/103 mmHg) and were middle-aged (52 ± 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

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

Conclusion

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

Key Words: antihypertensive drug, cardiovascular disease, absolute cardiovascular risk, primary prevention, hypertension.

Strengths and limitations of this study

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

Introduction

For decades, cardiovascular disease (CVD) has remained the greatest burden of disease in the developed world and now also in the developing world [1,2]. In 2012, CVD was responsible for 17.5 million deaths in the world and more than twenty thousand deaths in Australia[1,3]. Noticeably, nearly 50% of deaths from CVD are attributable to high blood pressure (BP), the commonest modifiable population risk factor [4]. 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 [5-9]. 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 [10]. 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 [6-8,11-13]. JNC 8[11] 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 [14], otherwise patients are exposed to increased risk [15-18]. Similarly, the 2016 European Society of Cardiology guidelines recommend considering BP lowering drug treatment when systolic BP is greater than 140 mmHg

and/or diastolic BP is greater than 90 mmHg after a reasonable period of time with lifestyle choice [7]. Recently, the SPRINT (Systolic Blood Pressure Intervention trial) [19] reported a significant benefit from intensive treatment to a target BP of 120 mmHg rather than 140 mmHg. However, this benefit was observed in those at high CVD risk without diabetes. In agreement with the findings from the SPRINT trial, guidelines in Australia [5], New Zealand [20], UK [8] and Canada [9] recommend BP lowering medication based on absolute CVD risk, recommending BP lowering treatment as soon as possible in high CVD risk individuals, but not in the low to moderate risk population unless BP persistently exceeds 160/100 mmHg.

Other groups [21] have recommended early drug treatment of grade 1 hypertension even in patients at low risk with the exception of patients with grade 1 "isolated" hypertension, based on a meta-analysis by Thomopolous et al[22] and the HOPE-3 study[23]. In contrast, a Cochrane review by Diao et al[10] concluded that there was no statistically significant effect of BP treatment in individuals who had grade 1 hypertension. The 2015 Blood Pressure Lowering Treatment Trialists Collaboration[24] (BPLTTC) meta-analysis reported a statistically significant benefit of BP lowering drug treatment in grade 1 hypertension in terms of stroke and all-cause mortality. However, the effects seen in the BPLTTC analysis could reflect differences in the BPLTTC sample that included participants who had diabetes, had a higher baseline risk and had previously received drug treatment. In another analysis of the BPLTTC individual patient data[25] by absolute CVD risk at baseline showed a continuously increasing benefit with baseline risk[25]. The BPLTTC study, however included participants who both did and did not have a history of CVD.

Thus, we sought to reanalyse a seminal study used to justify treating individuals with elevated BP to see if stratification by baseline CVD risk would be a

superior method for identifying candidates for BP-lowering medication in a treatment-naïve population. In this study, we compared the effectiveness of BP lowering drug treatment by a post-hoc subgroup analysis of the Australian National Blood Pressure study[26] (ANBP). We restricted the analysis group to individuals with no history of CVD or diabetes, and who were naïve to BP lowering treatment. We selected this historic study because it was placebo controlled and patients in the control arm of the study would not have been taking a BP lowering medication previously unless they had very high levels of BP. Our aim was to assess which group of individuals classified by absolute risk benefited from active treatment vs. placebo for CVD events within this seminal study that underwrote the treatment of elevated BP by BP thresholds.

Methods

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

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

Risk stratification

In this analysis, the baseline absolute CVD risk was calculated according to the 5-year Framingham absolute risk score[27]. The Framingham score was chosen because it is currently recommended in the National Vascular Disease Prevention Alliance (NVDPA) guidelines [5] in Australia. The sample was restricted to 3,244 participants who were older than 35 years and was stratified by tertile of estimated 5-year CVD risk score. We also classified all participants with very high BP (systolic BP ≥ 180 mmHg and/or diastolic BP ≥ 110 mmHg) or total cholesterol (> 7.5 mmol/l) values the highest risk tertile regardless of their risk score, as per the Australian guidelines [5]. The ANBP dataset included all variables required for CVD risk calculation except high-density lipoprotein cholesterol (HDLc). The HDLc value was imputed from the Australian National Heart Foundation risk factor prevalence study as this was near contemporaneous with the ANBP[28]. Mean value of HDLc was categorised by age and sex. In a sensitivity analysis, we stratified the sample by GLOBORISK score [29], a CVD risk score that does not require HDLc value and is validated in individuals over 40 years. The equation for the Australian population was obtained by personal contact with the author (Peter Ueda, unpublished data, 2016). This analysis excluded 471 participants younger than 40 years. Less than 1% of the study participants had data missing for total cholesterol, weight and/or height and these missing data 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 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-basedcenters 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) [30]. 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 ± 6.5) with moderately elevated BP (mean 159/103 mmHg) and were middle-aged (52± 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[5] 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)	**115 (10.6)**	352 (32.6)	334 (30.9)
SBP, mmHg	159.5 ± 17.5	148.4 ± 12.2	**157.3 ± 12.2**	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/m2	**26.6 ± 3.9**	26.6 ± 4.0	**26.5 ± 3.6**	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/m2	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. **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[29] which does not require HDLc was consistent with 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			
	Event (rate per 1000 patient-yr)		Adjusted HR (95% CI)*	ARR % (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)	**5.6 (1.6, 9.6)**	**18 (10, 64)**
p - value	-	-	0.64	0.05	-
All-cause mortality					
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)	**2.2 (0.5, 3.9)**	**45 (25, 196)**
p – value	-	-	0.78	**0.04**	-
Non-fatal event					
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	-
Major CVD event					
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)	**4.3 (0.5, 8.1)**	**23 (12, 193)**
p - value	-	-	0.62	0.17	-
Any CHD					
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 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 (mean 159/103 mmHg) by modern definitions. The ANBP study aimed to treat 'mild hypertension' (according to the old definition) that was primarily defined by diastolic BP. Some randomised participants were excluded from the original 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 analyses by tertile of absolute risk, as well as by the two groups of 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 [26].

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 statistically significant heterogeneity (p = 0.78 for all-cause mortality and p = 0.62 for the major CVD event) (Table 3). All relative treatment effects in our analysis measured by HRs were adjusted by age, sex, body-mass index, smoking, screening

centres and systolic BP. However, no significant difference was observed between adjusted and unadjusted HRs. In terms of absolute benefits, risk reduction linearly increased across the CVD risk group from low to high risk. BP lowering drug treatment produced an unclear benefit in the low and intermediate CVD risk group but a significant benefit in the high CVD risk group. Heterogeneity of absolute effects across the CVD risk groups was only significant in all-cause mortality (p=0.04).

Regarding the benefit of BP lowering drug treatment in the low to intermediate CVD risk population, our results from main and subgroup analyses match well with the study outcomes from the HOPE-3 trial [23] and the Diao review[10]. In the HOPE-3 trial[23], no benefit of intensive drug treatment was established in the intermediate-risk persons with HR 0.98 (0.84-1.14) for all-cause mortality and HR 0.92 (0.79 – 1.06) for major CVD events referred as a first secondary outcome in the paper. At baseline, the HOPE-3 participants were older (65 years), and had a lower level of BP (138.1/81.9 mmHg) compared to the ANBP participants. One reason for the lower blood pressures may be due to the 4-week run-in phase in which all of the HOPE-3 participants received active BP lowering drug treatment before randomisation and one-fifth of all eligible participants had previously received drug treatment before the trial. In 2012, Diao et al reviewed placebo randomised controlled trials in grade 1 hypertension and also found no beneficial effect of drug treatment with a risk ratio (RR) 0.85 (0.63 – 1.15) for all-cause mortality and RR 0.97 (0.2 – 1.32) for major CVD events[10]. The participants in the Diao review were likely to have a lower CVD risk than those in the ANBP and the HOPE-3 trials, with major CVD events occurring in only 2.4% of participants in the placebo group. Following a similar approach, in 2015, The Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) [24]

reviewed randomised controlled trials in grade 1 hypertension but extended to trials comparing active or more intensive regimens and placebo or less intensive regimens. In line with the findings from the 2015 BPLTTC study, we identified a marginally significant effect on stroke, yet our effect estimates with an HR 0.75 (0.45 – 1.36) for total deaths and an HR 0.83 (0.65 – 1.07) for major CVD events slightly differed from the 2015 BPLTTC study's results with an OR 0.78 (0.67-0.92) and an OR 0.86 (0.74-1.01) correspondingly. The differences in confidence intervals may be due to the difference in sample sizes and baseline characteristics. It is more likely that the 2015 BPLTTC participants had higher CVD risk and higher BP value at baseline when about 40% of 15,266 participants had diabetes and about 23% had previously received BP lowering drug treatment. Our study and the 2015 review confirm the absolute benefits of BP lowering drug treatment in high CVD risk population in terms of total deaths with ARR 2.2% (0.5, 3.9, p=0.01) for the ANBP and ARR 1.4% (0.5, 2.2) for the review. Furthermore, the benefit was also recorded in major CVD event with ARR 4.3% (0.5, 8.1, p=0.03) in the ANBP, whereas the 2015 BPLTTC observed a non-significant effect with ARR 1.0% (-0.1, 1.9). The difference can be explained in part by the study design when more than 50% of participants with systolic BP higher than 160 mmHg in eligible studies in the 2015 BPLTTC were excluded. The distribution of these excluded participants might not be even between active arm and control arm, thus biasing the treatment effects.

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

within the highest tertile. The findings were in line with what we found in the CVD risk-stratified subgroup when all participants in the highest BP-stratified tertile had high CVD risk score (20.7 ± 9.5). However, the heterogeneity of treatment effects among the three subgroups in analysis by baseline systolic BP was no longer significant as it was in the subgroup analysis by CVD risk score. Further, the trend of lower to higher absolute benefit from low to high risk groups that was seen for CVD risk was not apparent when groups are defined by BP alone. Thus, in this study, CVD risk score identified those who most benefited from BP lowering drug treatment.

Limitations

There are a number of limitations of our study. Firstly, statistical power is unavoidably decreased in a post-hoc subgroup analysis and the multivariate Framingham risk score used in our analysis has not been well validated within the Australian population[31]. However, using a multivariate score for stratification is known to increase the power to detect heterogeneity in absolute risk benefit over subgroup analyses that are based on individual risk factors[32]. A prospective study to address the issue of whether there is an advantage in treating blood pressure by AR is unlikely to be performed, because of the very large sample size and very long follow-up time required, particularly in patients at low risk. Therefore, re-analysis of the early placebo-controlled trials seems to be the most feasible approach for assessing the effects of delayed versus early drug treatment in individuals with varying CVD risk together and elevated BP.

Secondly, the estimation of HDLc from the 1980s national survey may alter the CVD risk score, but we do not believe this method greatly affected the risk stratification because a 0.4 difference in the HDL estimate only results in a 0.01 difference in CVD

risk score. Furthermore, no association between HDLc and BP has been observed [33,34]. The sensitivity analysis using GLOBORISK score[29] without HDLc showed similar results as our main analysis. Although the ARR is no longer statistically significant, this result is likely due to the smaller sample size and subsequent number of events. In conclusion, the sensitivity analysis supports our main analysis.

Thirdly, the paucity of trial endpoints in each CVD risk group prevented us from comparing the effects in some specific outcomes with respect to stroke and deaths from CVD. In addition, approximately one-third of the participants prematurely stopped randomised drug treatment. However, this pattern likely reflects the typical situation to occur in actual clinical practice, and this analysis is conducted on an intention-to-treat basis, so any difference in the estimate of treatment effect due to non-adherence is deliberately retained. Most participants were followed throughout the trial, except those with an unknown reason for stopping - loss to follow-up (7.2%). An analysis with further adjustment by variable 'premature stopped study treatment' did not substantially change our findings, except effects on stroke in general population became statistically significant (0.55, 95%CI 0.30-0.99, p=0.05).This is because non-adherence is balanced between the allocated treatment groups.

In conclusion, our research has demonstrated that drug treatment in patients with elevated BP is best directed to those at high risk of incident CVD events. This reinforces the guidelines recommendation to treat based on absolute (or global) CVD risk, rather than according to BP thresholds alone [5-9].

Competing interests:

CLBH is a Ph.D. candidate at Menzies Institute for Medical Research, she has received a Ph.D. scholarship from Merle Weaver Postgraduate Scholarship. JD is supported by National Health and Medical Research Council Screening and Test Evaluation Program Grant 633003. CR is supported by a National Health and Medical Research Council Senior Research Fellowship (1045862). MRN has in the last 5 years served on an advisory board for AMGEN.

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

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

Data sharing statement: No additional data are available.

References

1. World Health Organisation. The top 10 causes of death [online database]. http://www.who.int/mediacentre/factsheets/fs310/en/. Updated May, 2014 Accessed November 13, 2015.

2. Australian Bureau of Statistics. Causes of Death, Australia, 2013; http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2013~Main%20Features~Leading%20Causes%20of%20Death~10001. Updated March 7, 2016. Accessed November 30, 2016.

3. Australia Bureau of Statistics. Causes of Death, Australia. 2012. http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/3303.0main+features100012012. Updated March 30, 2015. Accessed November 13, 2015.

4. World Health Organisation (WHO). A Global Brief on Hypertension: Silent Killer, Global Public Health Crissis [Online]. http://www.thehealthwell.info/node/466541. Updated January 4, 2013. Accessed November 13, 2015.

5. National Vascular Disease Prevention Allianace. Guidelines for the management of absolute cardiovascular disease risk. http://www.cvdcheck.org.au/index.php?option=com_content&view=article&id=47&Itemid=27.Updated May, 2012. Accessed November 13, 2015.

6.Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension. Blood Pressure. 2013;22(4):193-278.

7. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by

representatives of 10 societies and by invited experts). Eur Heart J. 2016; 37: 2315–2381.

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

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

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

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

12. World Health Organization. International Society of Hypertension Writing Group. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. Journal of hypertension. 2003;21(11):1983-1992.

13. Weber MA, Schiffrin EL, White WB, et al. Clinical Practice Guidelines for the Management of Hypertension in the Community. The Journal of Clinical Hypertension. 2014;16(1):14-26.

14.Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension. 2003;42(6):1206-1252.

15. Mitka M. Groups spar over new hypertension guidelines. JAMA. 2014;311(7):663-664.

16. Guallar E, Laine C. Controversy Over Clinical Guidelines: Listen to the Evidence, Not the Noise. Ann. Intern. Med. 2014;160(5):361-362.

17.Wright JJT, Fine LJ, Lackland DT, Ogedegbe G, Dennison Himmelfarb CR. Evidence Supporting a Systolic Blood Pressure Goal of Less Than 150 mm Hg in Patients Aged 60 Years or Older: The Minority ViewSystolic Blood Pressure Goal for Patients Aged 60 Years or Older. Ann. Intern. Med. 2014;160(7):499-503.

18. Zanchetti A. Bottom blood pressure or bottom cardiovascular risk? How far can cardiovascular risk be reduced? Journal of hypertension. 2009;27(8):1509-1520.

19. The SPRINT Research Group. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. New England Journal of Medicine. 2015;373(22):2103-2116.

20. New Zealand Guidelines Group. The assessment and management of cardiovascular risk. Wellington, New Zealand Guidelines Group. http://www.health.govt.nz/publication/assessment-and-management-cardiovascular-risk.Updated July 8, 2015. Accessed November 13, 2015.

21. Morales Salinas A, Coca A, Olsen MH, et al. Clinical Perspective on Antihypertensive Drug Treatment in Adults With Grade 1 Hypertension and Low-to-

Moderate Cardiovascular Risk: An International Expert Consultation. Current Problems in Cardiology. 2017;42(7):198-225.

22. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 2. Effects at different baseline and achieved blood pressure levels–overview and meta-analyses of randomized trials. Journal of hypertension. 2014;32(12):2296-2304.

23. Lonn EM, Bosch J, López-Jaramillo P, et al. Blood-Pressure Lowering in Intermediate-Risk Persons without Cardiovascular Disease. New England Journal of Medicine. 2016;374(21):2009-2020.

24. The Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of Blood Pressure Reduction in Mild Hypertension. A Systematic Review and Meta-analysis. Ann. Intern. Med. 2015;162(3):184-191.

25. The Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. The Lancet. 2014;384(9943):591-598.

26. The Management Committee. The Australian Therapeutic Trial in Mild Hypertension. The Lancet. 1980;315(8181):1261-1267.

27. Anderson, K. M., Odell, P. M., Wilson, P. W., & Kannel, W. B. (1991). Cardiovascular disease risk profiles. American heart journal, 121(1), 293-298

28. Bennett SA, Magnus P. Trends in cardiovascular risk factors in Australia. Results from the National Heart Foundation's Risk Factor Prevalence Study, 1980-1989. The Medical Journal of Australia. 1994;161(9):519-527.

29. Hajifathalian K, Ueda P, Lu Y, et al. A novel risk score to predict cardiovascular disease risk in national populations (Globorisk): a pooled analysis of prospective cohorts and health examination surveys. Lancet Diabetes Endocrinol.2015;3(5):339-355.

30. Bender R, Kromp M, Kiefer C, Sturtz S. Absolute risks rather than incidence rates should be used to estimate the number needed to treat from time-to-event data. J. Clin. Epidemiol. 2013;66(9):1038-1044.

31. Zomer, E., Owen, A., Magliano, D. J., Liew, D., & Reid, C. (2011). Validation of two Framingham cardiovascular risk prediction algorithms in an Australian population: the 'old 'versus the 'new 'Framingham equation. European Journal of Cardiovascular Prevention & Rehabilitation, 18(1), 115-120.

32. Hayward RA, Kent DM, Vijan S, Hofer TP. Multivariable risk prediction can greatly enhance the statistical power of clinical trial subgroup analysis. BMC Med. Res. Methodol. 2006;6(1):1.

33. Hughes K, Leong WP, Sothy SP, Lun KC, Yeo PPB. Relationships between Cigarette smoking, Blood Pressure and Serum Lipids in the Singapore General Population. International Journal of Epidemiology. 1993;22(4):637-643.

34.Catalano M, Aronica A, Carzaniga G, Seregni R, Libretti A. Serum lipids and apolipoproteins in patients with essential hypertension. Atherosclerosis. 1991;87(1):17-22.

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.

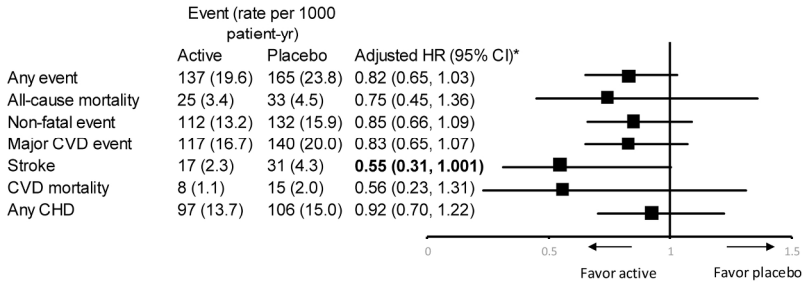

Figure 1. Effect of treatment in the overall study population. *Adjusted for age, sex, body-mass index, screening centres, smoking and systolic blood pressure. Bold p<0.05. CVD for cardiovascular disease, CHD for coronary heart disease.

209x148mm (300 x 300 DPI)

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

Group variable	1st tertile (113-151 mmHg)	2nd 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/m2	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 (%)				
	Active	Placebo	Adjusted HR (95% CI)*	ARR % (95% CI)	NNT
Any event					
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)	**4.8 (0.9, 8.8)**	**21 (11, 112)**
p-value	-	-	0.25	0.1	-
All-cause mortality					
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)	**1.9 (0.3, 3.6)**	**52 (28, 372)**
p – value	-	-	0.26	0.08	-
Non-fatal event					
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	-
Major CVD event					
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)	**4.1 (0.4, 7.8)**	**24 (13, 242)**
p - value	-	-	0.39	0.22	-
Any CHD					
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	-

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

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	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)
Introduction		
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)
Methods		
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)
Results		
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

		because there was only 1% missing data)
		(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)
Discussion		
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)
Other information		
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.