PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effectiveness of Blood Pressure-Lowering Drug Treatment by Levels of Absolute Risk in the Australian National Blood Pressure Study
AUTHORS	Ho, Chau Breslin, Monique Doust, Jenny Reid, Christopher Nelson, Mark

VERSION 1 - REVIEW

REVIEWER	Bernard Waeber
REVIEW RETURNED	05-Jun-2017

GENERAL COMMENTS	Whether it is still justified to base therapeutic decisions on BP levels alone is still debated. This study confirms that it is indeed the case, at lest in patients with highest BPs.It was obviously expected that taking into account global CV risk is a better approach. As pontes out by the authors it is not ethical anymore to carry out a trial to test this important issue by comparing placebo- and a treated patients. This is the reason why the present post-hoc analysis is of interest, although the number patients is too low to get significant results in some important parameters. Comments: Abstract:"In a subgroup analysis, relative and absolute effects did not statistically differ across three risk groups .." ;this has to be introduced. Methods, page 6: "thiazide diuretic is recommended in the majority of patients";This is not correct. I couldn't open the Figure as its dimension in pixels is too large to be converted(must be less than 40 megapixels for my computer). Personally I would prefer the calculation of global risk based on available parameters and forget about HDL-cholesterol. I am ready to believe that it doesn't make any difference if extrapolated values of HDL-C are used rather res values, but the weight of this missing value in the calculation is probably week.

REVIEWER	Alberto Morales-Salinas MD MPH FACC
REVIEW RETURNED	21-Jul-2017

GENERAL COMMENTS	8. Are the references up-to-date and appropriate? I suggest add a) the last version CV Prevention Europ Guidelines (see comments in attached paper) and b) novel and first international consensus about mild HTN with low-moderate CVR (http://dx.doi.org/10.1016/j.cpcardiol.2017.03.001)

	12. Are the study limitations discussed adequately?: a) 5 years framingham RCV score has not been well validated in Australian population. b) The CVR tertiles are not according to the used reference (see the attached paper) c) 1/3 lost follow up d) the following critica bias is not well explaided "withdrew more BP lowering drug-randomised participants in the low-risk group and the high- risk group." The authors should add the variable: withdrew BP lowering drug according to CVR level The author also provided a marked copy with additional comments. Please contact the publisher for full details.

REVIEWER	Yuichiro Yano
REVIEW RETURNED	23-Jul-2017

GENERAL COMMENTS	This is a post-hoc analysis from ANBP, demonstrating the potential effectiveness of BP lowering by the level of absolute risk in young and middle-aged persons. My major concern is how we can compare the effectiveness of BP lowering by the level of individual absolute risk versus individual baseline BP levels. Table 2 shows the effectiveness of BP lowering by the level of individual absolute risk, and Table 3 shows by individual baseline BP; the results appear largely similar between Table 2 and Table 3. The question is, should physicians lower patients' BP by the level of individual absolute risk or by individual baseline BP? In Table 3, please the following information for each BP group: provide event/total number (per 1,000 person-years; 95% CIs) and unadjusted HR. In table 3, study population was divided into the three groups by baseline CVD risk, including age, sex, smoking, BP…..And, authors adjusted for age, sex, smoking, and BP to assess CVD risk across the three groups. This adjustment for what ? What was the target BP by intervention in ANBP ? The high risk group should have intensive BP lowering therapy ?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:
Abstract:"In a subgroup analysis, relative and absolute effects did not statistically differ across three risk groups .." ;this has to be introduced.
-> We revised the statement as following “In a subgroup analysis, 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)”.
Methods, page 6: "thiazide diuretic is recommended in the majority of patients"; This is not correct.
-> We acknowledge that use of thiazide diuretic dramatically declined in recent years. However, together with angiotensin converting enzyme inhibitor, angiotensin receptor blocker, calcium channel blocker, thiazide diuretic has remained the first line of blood pressure lowering therapy. To make it more precise, we revised the statement “The study intervention has remained applicable in current practice when thiazide diuretic is still one of the first line of blood pressure lowering therapy”.
I couldn't open the Figure as its dimension in pixels is too large to be converted (must be less than 40 megapixels for my computer).
-> We explained above.

Personally I would prefer the calculation of global risk based on available parameters and forget about HDL-cholesterol. I am ready to believe that it doesn't make any difference if extrapolated values of HDL-C are used rather res values, but the weight of this missing value in the calculation is probably week.
-> We acknowledge that this is one of our unavoidable limitations.

Reviewer 2:
8. Are the references up-to-date and appropriate? I suggest add a) the last version CV Prevention Europ Guidelines (see comments in attached paper) and b) novel and first international consensus about mild HTN with low-moderate CVR (http://dx.doi.org/10.1016/j.cpcardiol.2017.03.001).
-> a) We added the statement “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” and cited the suggested reference. b) We added the reference in the statement “Other groups 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 and the HOPE-3 study.”
12. Are the study limitations discussed adequately?: a) 5 years framingham RCV score has not been well validated in Australian population. b) The CVR tertiles are not according to the used reference (see the attached paper) c) 1/3 lost follow up d) the following critica bias is not well explaided "withdrew more BP lowering drug-randomised participants in the low-risk group and the high- risk group." The authors should add the variable: withdrew BP lowering drug according to CVR level.
-> a) We have revised the statement as follows: “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”. b) we did not stratify the CVD risk group by the thresholds in the NVDPA guidelines but by the tertile of the total sample to make even numbers of participants in the 3 subgroups and thereby optimise power. Moving the thresholds will not limit our ability to test the aim of the study. We called the groups low, moderate and high risk, but the reviewer is correct that they are not low, moderate and high according to the guidelines. c) 1/3 participants prematurely stopped the randomised regimen, but only 80 (7.2%) participants were lost to follow-up. We applied the intention to treat principles, so the 1/3 was included in the analysis, which reduces the impact of this issue. d) “Participants’ doctors were more likely to recommend stopping 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”. At the time of the original ANBP in 1970s, BP drug treatment was mainly based on doctors’ experience and more focus was put on diastolic BP rather than systolic BP. CVD risk calculation was not in clinical use at that time, so we are unable to provide this suggested variable (withdrew BP lowering drug according to CVR level). In table 2, we described the characteristics of the participants who withdrew from the study according to CVD level.

Reviewer 3:
My major concern is how we can compare the effectiveness of BP lowering by the level of individual absolute risk versus individual baseline BP levels. Table 2 shows the effectiveness of BP lowering by the level of individual absolute risk, and Table 3 shows by individual baseline BP; the results appear largely similar between Table 2 and Table 3. The question is, should physicians lower patients’ BP by the level of individual absolute risk or by individual baseline BP? the results look similar between subgroup by CVD risk and systolic BP. However, in the subgroup by systolic BP, the treatment effects were not significantly different among 3 subgroups whereas a significant heterogeneity was recorded in the subgroup by CVD risk regarding all-cause mortality.
-> We added the statement “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”.
In Table 3, please the following information for each BP group: provide event/total number (per 1,000 person-years; 95% CIs) and unadjusted HR. In table 3, study population was divided into the three groups by baseline CVD risk, including age, sex, smoking, BP…..And, authors adjusted for age, sex, smoking, and BP to assess CVD risk across the three groups. This adjustment for what?
-> We provided incidence rate (patient per year) in table 3. Thank you for your suggestions. We stratified the subgroup by baseline CVD risk but there were some significant differences in characteristics between active group and placebo group (smoking status in low risk group, systolic BP

and BMI in moderate risk group). Thus, we adjusted for those variables in our models. However, there was no significant difference between unadjusted and adjusted results.

What was the target BP by intervention in ANBP ? The high risk group should have intensive BP lowering therapy?
-> In ANBP, the target was to reduce the diastolic to under 80 mmHg for all participants in both active and placebo group. Unfortunately, we do not have the data on the BP values achieved during the trial, so we are not sure if the high risk group had more intensive BP lowering therapy or not.

VERSION 2 – REVIEW

REVIEWER	Alberto Morales Salinas
REVIEW RETURNED	04-Sep-2017

GENERAL COMMENTS	Please take into account some of my former 16 comments/suggestions (see attached file) for updating the study limitations. The author also provided a marked copy with additional comments. Please contact the publisher for full details.

REVIEWER	Yuichiro Yano
REVIEW RETURNED	17-Sep-2017

GENERAL COMMENTS	I have no further comments.

VERSION 2 – AUTHOR RESPONSE

We thank the reviewer for detailed comments on our manuscript. We would like to response to the comments as below.

1. Comment [A2R1]: chlorothiazide 500mg or 50mg?

-> Chlorothiazide 500 mg

2. Comment [A3]: I suggest " Other groups 21 have recommended for early drug treatment of grade 1 hypertension with the exception of patients with grade 1 “isolated” hypertension based on meta-analysis by Thomopolous et al22 andthe HOPE-3 study among other evidences.

-> we revised as ‘Other groups 21 have recommended for 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 meta-analysis by Thomopolous et al22 and the HOPE-3 study among other evidences’. In our study, we would like to raise a concern on treatment based on absolute risk not on hypertension stratification.

3. Comment [A4]: I suggest to eliminate mildly because this trial included patients with moderate and severe HTN too.

->We deleted ‘mildly’.

4. Comment [A5]: Included individuals who received delayed active treatment is placebo group is a bias and It should be recognize as another study limitiations.

-> In this study, we would like to compare the treatment effect between early and delayed BP lowering drug treatment. Thus this is unlikely to be a bias in our study.

5. Comment [A6]: is chlorothiazide available?

-> Hydrochlorothiazide is included in thiazide diuretic group and is dominant in this class in Australia, thus it's still available.

6. Comment [A7]: Diabetes definition should be included

-> In the original publication of ANBP, the authors mentioned diabetes only in their exclusion criteria without further details.

7. Comment [A8]: Highter than 95? it is a contradiction because one of the inclusion criteria is diastolic BP of 95 to 109

-> As reported in the original ANBP, the BP inclusion criteria was assessed at screening visit, however their BP at subsequent clinic visits did not meet the criteria for starting drug treatment. More details are explained in 'The Management Committee. The Australian Therapeutic Trial in Mild Hypertension. The Lancet. 1980;315(8181):1261-1267.

8. Comment [A9]: add definition of low, moderate and high CVR

-> We stratified the participant by the tertile of CVD risk score, not on the risk threshold for low, moderate and high CVR. The definition was added in the 'result' section.

9. Comment [A10]: It is importa to add threshold/definition of mild, moderate/intermediate/high CVR

-> Provided in the manuscript.

10. Comment [A11]: I suggest 1st, 2nd and 3rd tertile instead of low.moderate.high

-> We considered to use 1st, 2nd and 3rd tertile, however, we prefer to use low, moderate and high because it makes the communication easier and our thresholds are likely to be similar to the ones suggested by the NVDPA guideline.

11. Comment [A12]: It should be consider as another study limitation. Premature stoped study treatment is an important confounding variable.

-> 1/3 of the participants did not adhere to study treatment. We added this issue in the 'limitation' section. 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. These participants were still followed throughout the trial, except those with unknown reason for stopping - loss to follow-up (7.2%).

12. Comment [A13]: adjustment should take in to account the "Premature stoped study treatment"

-> We used the 'intention to treat' principle, so any difference in the estimate of treatment effect due to non-adherence is deliberately retained. A sensitivity analysis with further adjustment by 'premature stopped study treatment' did not substantially change our findings, except effects on stroke in general population become 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. I mentioned the analysis with further adjustment by 'prematurely stopped study treatment' as a sensitivity analysis in the 'limitation' section.

13. Comment [A14]: treat mild hypertension (according to the old definition)

-> added as the reviewer's suggestion

14. Comment [A15]: adjustment should take in to account the "Premature stoped study treatment" because it is an important confounding factor.

-> As explained in the comment on p. 10, the treatment effect we are interested in is the ‘intention-to-treat’, including any effects of non-adherence.

15. Comment [A16]: I would like to alert that who were in the subgroup for the upper third of systolic BP (>143.5 mm Hg) and received active treatment (hydrochlorothiazide 12.5 mg and candesartan 16 mg), had significantly lower rates of major cardiovascular outcomes than those in the placebo group

-> Thanks for the reviewer's information. we had a look on such results. in our study, we focus on the treatment effects by absolute CVD risk (not on BP level), particularly in those with mildly or moderately elevated BP.

16. Comment [A17]: Please take into account some of my former 16 comments/suggestions for updating the study limitations.

-> As explained above, due to our research question is on the effectiveness of early versus delayed BP lowering drug treatment by absolute CVD risk, it appears that ‘Including individuals who received delayed active treatment in placebo group is a bias’ is unlikely to be a bias in this study. We added ‘prematurely withdrawal of treatment’ in the ‘limitation’ section.

VERSION 3 – REVIEW

REVIEWER	Alberto Morales-Salinas
REVIEW RETURNED	15-Dec-2017

GENERAL COMMENTS	The authors took into account most of the reviewers' suggestions. The topic of work is interesting. I believe that it can be accepted without modifications, provided that there has been an expert in biostatistics among the reviewers. I also suggest to the magazine that the work be published with critical Editorial on the subject. I am willing to do it together with Richard Kones MD FAHA, FESC (Cardiometabolic Research Institute, Houston, USA)