The Blood Pressure Lowering Treatment Trialists' Collaboration: methodological clarifications of recent reports

Milad Nazarzadeh[1,2]*, Dexter Canoy[1,2,3], Zeinab Bidel[1,2], Emma Copland[1,2], Kazem Rahimi[1,2,3], Koon Teo[4], Barry R Davis[5], John Chalmers[6], Carl J. Pepine[7], Mark Woodward[6,8]

1 Deep Medicine, Oxford Martin School, University of Oxford, UK

2 Nuffield Department of Women's and Reproductive Health, Medical Science Division, University of Oxford, UK

3 NIHR Oxford Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

4 Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada

5 The University of Texas School of Public Health, Houston, Texas, USA

6 The George Institute for Global Health, University of New South Wales, Sydney, Australia

7 Department of Medicine, University of Florida, Gainesville, Florida, USA

8 The George Institute for Global Health, School of Public Health, Imperial College London, London, UK

*** Correspondence to**: Milad Nazarzadeh, Deep Medicine, Nuffield Department of Women's and Reproductive Health, University of Oxford, Oxford, OX1 2BQ, UK, Email: milad.nazarzadehlarzjan@wrh.ox.ac.uk

Abstract

Epidemiological evidence has consistently shown that people with higher systolic or diastolic blood pressure are at greater risk of cardiovascular diseases. However, there has been limited randomised evidence to determine the role of blood pressure level at treatment initiation in the reduction of cardiovascular diseases risk. The extent to which other characteristics of individuals, such as prior disease history, age or sex, should be taken into account has also been controversial. Furthermore, effects on less commonly reported efficacy and safety outcomes remain underexplored. The Blood Pressure Lowering Treatment Trialists Collaboration (BPLTTC) has collected individual-level participant data from 52 randomised clinical trials (RCTs), with more than 360 000 participants, and is now the largest source of individual-level data from RCTs of blood pressure-lowering treatment. This resource provides an unprecedented opportunity to address major areas of uncertainty relating to stratified efficacy and safety of antihypertensive therapy. Recent reports have demonstrated the power of pooled analyses of the BPLTTC dataset in filling long-standing gaps in our knowledge. However, there have been some misconceptions regarding the methods underpinning the recent reports, which we clarify in this paper.

Introduction

Individual participant data (IPD) meta-analyses are particularly powerful for investigation of stratified treatment effects. In addition to being able to verify the information and standardise rules and definitions across trials, the use of IPD can more efficiently and accurately utilise previously collected information. For instance, a conventional aggregate-data meta-analysis might group all participants from a trial into a single category of systolic blood pressure (SBP) based on the mean value of SBP across the whole trial dataset. Thus, an individual with an SBP of 118 mm Hg at baseline will contribute information to the category of SBP 130 -140 mm Hg when the mean SBP in the trial cohort falls into this range. By contrast, access to IPD will use the individuals' actual characteristics and assign them to the correct category. In addition, one can simultaneously group individuals based on multiple characteristics (e.g., age and BP) for investigation of clinically important subgroup effects. Thus, with the use of IPD, a participant's information is characterised more accurately, statistical power for subgroup analyses or less common outcomes is increased, and bias resulting from 'ecological fallacy' is mitigated.[1]

The Blood Pressure Lowering Treatment Trialists Collaboration (BPLTTC) currently holds IPD from 52 randomised clinical trials (RCTs), with 363 684 participants.[2] This is the largest known source of IPD from RCTs and provides an opportunity to investigate the heterogeneity of treatment effects among important, but underrepresented, patient groups as well as impacts on outcomes that were not often or consistently reported in individual trials. Kreutz et al., raise concerns regarding the interpretation of recent BPLTTC publications.[3] Their central criticism is that our conclusions have been exaggerated due to several methodological limitations. This view is not shared by other experts who have felt the findings were to be expected. Our conclusion that the baseline BP is not a key determinant of treatment effects is judged by Kreutz et al., to be only hypothesis-generating but confirmatory by others.[4] In the context of such vastly differing judgements, we welcome the opportunity to clarify several misunderstandings of our methodological approach and their implications. This will help readers to better appreciate the value of the BPLTTC findings to inform clinical decisions.

Trial selection process and impact on statistical power

IPD meta-analyses at the scale of BPLTTC are resource-intensive. In an overview protocol paper, we described the approach taken for trial selection, data collection and harmonisation, as well as analyses and reporting.[2] Eligible large-scale trials meeting the pre-specified definitions are identified and investigators and sponsors are invited to join the collaboration. To avoid selection bias, no eligible study is excluded at this stage. For each project, all analyses are pre-specified, except for sensitivity or supplementary analyses that become necessary during peer-review. The BPLTTC data collection effort is an ongoing process. Some potentially eligible RCTs can not be included due to difficulty in contacting relevant investigators, or their inability or unwillingness to share their data. This is to be expected in any voluntary collaborative project.

A key concern related to missing eligible trials is that this could reduce statistical power, and eventually lead to type 2 errors.[5] A superficial comparison of tabular meta-analyses of published information with the BPLTTC IPD meta-analyses might lead to such an impression, but these concerns are unfounded. This is because IPD meta-analyses are much more efficient in making use of information than traditional meta-analyses that use aggregate group-level information. For instance, a large-scale tabular meta-analysis based on 123 trials and 613 815 participants ranked only four trials with 8 428 participants into its lowest baseline BP category (SBP <130 mm Hg).[6] No trial had a mean BP category of 120 mm Hg, which lead to considerable ambiguity and hampered the comprehensive categorising of participants by BP. By contrast, a recent BPLTTC analysis based on 48 trials, included 45 848 participants with SBP <130 mm Hg.[7] The total number of primary events (the key measure of statistical power) in the groups with normal or mildly elevated BP (SBP <130 mm Hg) was 5 702 in BPLTTC, which is 5.3 times higher than the 1 072 in the earlier tabular meta-analysis.[6,7] Because of this, for the first time, the BPLTTC has enabled meaningful assessments of effects, not only across a wide range of baseline BP but also through the simultaneous grouping of individuals based on other features, such as prevalent cardiovascular disease (CVD), atrial fibrillation, age, drug classes or time since

randomisation.[7–10] Thus, despite the inclusion of a smaller number of trials, the statistical power of the IPD meta-analysis to examine stratified treatment effects is superior.

Risk of bias due to missing several trials

But, could missing information from some trials have biased study findings in a particular direction? Several lines of evidence speak against this, as well. First, identification of trials is not biased and contacting investigators to request inclusion of their trial data has not been related to testing a particular hypothesis. Second, the overall findings of effects of BP lowering per unit of BP reduction are similar to what has been reported in 'larger' tabular meta-analyses where only published group-level information of more trials was used. For instance, Ettehad et al., found that a 10-mm Hg reduction in SBP reduces the risk of major CVD by 20%,[6] which corresponds well to the IPD BPLTTC meta-analyses estimate of a 10% relative risk reduction for a decrement of 5 mm Hg SBP.[7] Third, the potential for data acquisition bias is routinely investigated by the BPLTTC research group using funnel plots and Egger's regression test, and as reported, no evidence of such bias has been identified. [7,8,11]

Inclusion of head-to-head drug comparison trials and the issue of differing intensities of blood pressure lowering

The BPLTTC aims to investigate stratified effects of BP-lowering, as well as effects by specific drug classes on a range of outcomes. As specified in the protocol, trials are eligible if they compare one drug against a placebo, different intensities of pharmacological BP reduction (i.e., trials in which groups with different BP treatment targets were compared), or one versus another drug. [2] Therefore, eligible studies fall into one of the following three categories: placebo-controlled trials, intensity-comparison trials, or head-to-head drug comparison trials. In an earlier report, we found that the SBP reductions after the first 12 months were -5.1 mm Hg (95% CIs -5.3 to -5.0), -11.2 mm Hg (95% CIs -11.4 to -11.0) and -1.4 mm Hg (95% CIs -1.5 to -1.3) in these three categories of trials, respectively.[12]

Some might argue that head-to-head trials should have been excluded from the analyses because of the low achieved and potentially 'unintentional BP reduction' in those trials.[3]

This would, however, create methodological challenges that outweigh any potential benefits. For instance, few would disagree that the Heart Outcomes Prevention Evaluation (HOPE) study has been a BP-lowering trial, but it was originally designed to assess whether the inhibition of the angiotensin-converting enzyme (not BP reduction) would prevent events related to ischaemia and atherosclerosis. The HOPE investigators reported that 'only a small part of the benefit could be attributed to a reduction in blood pressure'.[13] In this context, was the 3 mm Hg SBP reduction observed in the HOPE study intentional or unintentional? There is also a related challenge of defining what is a worthwhile BP reduction. For example, if a certain amount of BP reduction is required for trials to be included in the BPLTTC, what should that minimal threshold be? A difference in SBP between treatment arms of 1 mm Hg, 5 mm Hg or another value? Should the threshold apply to all types of trials or only those that compared a single drug vs another one? For instance, the DIABHYCAR trial was a placebo-controlled trial and achieved a 1.54 mm Hg SBP reduction (95% confidence interval [CI] 0.34 to 2.75) over the course of the study.[14] Should this trial have been excluded? More importantly, what would be the biological or clinical justification for setting any threshold? Observational epidemiology, Mendelian randomisations and meta-regression of RCTs have not provided any justification for the adoption of a minimum threshold.[6,15–18] Therefore, it seems that inclusion of trials based on an arbitrary threshold of BP reduction or intention in BP-lowering would have been far less defensible and more prone to selection bias than including all trials a priori. The inclusion of head-to-head trials also offers the advantage of being able to investigate the effect of drug classes where at least some of the effect could be mediated through pathways other than BP-lowering.[8,10,11]

The trade-off that such an inclusive approach has is that studies with very little difference in BP between arms could introduce random error and hence bias the overall findings towards the null. Instead of excluding them from the outset, we have adopted several strategies to mitigate this risk and quantify their effects. First, our main analyses were additionally weighted by the achieved intensity of BP reduction in each trial. Assuming that treatment effects are proportional to the intensity of BP reduction, one can re-scale the effects from the different studies and express them as a per unit change in BP reduction. This 'standardisation' enables comparison of like-with-like when primary hypotheses are

concerned with the BP-mediated effects. In practical terms, this means that everything else being equal, trials with very little BP reduction between treatment arms are given a proportionately lower weight than when no standardisation is applied. Second, to quantify whether the findings could have been affected by inclusion of 'low-information' studies, in which the BP differences between the treatment groups was small, we typically report sensitivity analyses excluding them. To date, we have found no evidence that their exclusion would have changed the study conclusions. Furthermore, excluding such trials would inevitably lead to the loss of information and increase in the widths of confidence intervals overall and in subgroups, which underscores the value of including such trials.

Impact of specific studies included in the analyses

Of course, the value of the systematic approach taken by BPLTTC is that any 'unique' features of individual trials become less relevant and the tyranny of selecting single trials for comparison with the collective evidence is made obsolete. But suppose that certain studies have slipped through the scrutiny of bias assessment by researchers, reviewers, and editors. How can readers be reassured that no particular study is causing bias? For instance, concerns were raised about the inclusion of the Systolic Blood Pressure Intervention Trial (SPRINT) in a recent BPLTTC report[7], with speculation that a 'non-marginal fraction of the findings' belonged to this study.[3] To address this concern, we have reported an extensive sensitivity analysis where one trial was excluded at a time[7]. This showed no evidence that any particular trial dominated the study findings. This is to be expected given that the BPLTTC dataset has far greater power in comparison to any individual trial included in it. However, if there were some residual concerns, those should have been dealt with unequivocally with this sensitivity analysis.

Impact of specific studies not included in the analyses

But what about the omission of specific trials? Could their inclusion have changed the BPLTTC study results? Again, the strength of meta-analyses based on systematic reviews is that subjective, potentially biased, views of researchers in selecting studies that favour a particular interpretation is reduced. Therefore, if the sample size of individuals included in meta-analyses is large, any random omission of individual studies should not matter.

Kreutz et al. seem particularly concerned about the HOPE-3 trial, for which data has not been shared with the BPLTTC.[3] HOPE-3 had an overall neutral finding, with an average SBP reduction of 6.0 mm Hg between treatment arms, and there was no clear evidence of a beneficial effect (hazard ratio 0.93, CI 0.79 to 1.10).[19] While these overall findings are entirely consistent with the BPLTTC effect estimates, a subgroup analysis reported by the HOPE-3 investigators was suggestive of a beneficial effect among those in the top third of SBP but no effect or potentially a harmful effect in the two bottom thirds (SBP <143.5 mm Hg).[19]

Statistical literature is rich with examples of unreliable subgroup analyses of underpowered studies. Many trials have reported clinically significant subgroup effects that have later been proven to be erroneous. For example, some trials revealed no preventive effect for BP-lowering treatment on the prevention of CVD in women versus men[20,21], or in elderly people[22], which were refuted in subsequent trials.[23–25] The comparison of HOPE-3 subgroup results to the BPLTTC findings adds only one more to this list. Participants in the bottom two thirds of SBP in HOPE-3 contributed only a total of 300 events to the analyses. By contrast, the recent BPLTTC report without the inclusion of the HOPE-3 trial contained 14 times as many events just in the primary prevention population cohort who had an SBP of 139 mm Hg or lower at baseline (4 412 major CVD events) and provided no evidence to reject the null hypothesis of homogeneity of effects by baseline BP categories (p=1.0). Thus, this suggests that the suggestive heterogeneity of effect in HOPE-3 is likely to have been due to chance, or factors other than baseline BP.

We would argue that the findings from large-scale, comprehensive IPD meta-analysis by BPLTTC provide a more reliable set of findings, and supersedes the clinical hypothesis generated by HOPE-3 and any other individual studies that BP reduction has quantitatively or even qualitatively different effects on relative risk, such that they can be rejected.

Analytical approaches and selection of blood pressure categories

In addition to the issues pertaining to study selection, the findings from IPD meta-analyses, like any other study, might depend on the analytical approaches chosen. The BPLTTC

followed established epidemiological methods, which were all pre-specified and approved by the Steering Committee before data release for analyses. For specific projects, this also applies to such things as stratification thresholds and the number of categories according to BP, age or other phenotypes investigated.

It has been argued that since the greatest uncertainty of BP-mediating effects is in patients with BP <140 mm Hg, participants with a BP greater than that value should have been excluded from our analyses.[3] One issue with this approach is that it is debatable as to how to define the cut-off for exclusion. Observational studies and RCTs that have generated the hypothesis of the existence of an optimal BP have mostly been inconsistent about that optimum (i.e., the nadir of the J-shape association). [6,15–18] Furthermore, from the statistical point of view, it makes more sense to investigate the variation of treatment effects across the full spectrum of BP available, rather than a truncated section of it. Indeed, it could be argued that the likelihood of detecting heterogeneous treatment effects would only increase when more patients and categories are introduced. Thus, the absence of such evidence, without an arbitrary and potentially biased exclusion of certain participants, is a key strength, and not a weakness, of the BPLTTC approach.

Selecting just a few strata from the BPLTTC report (e.g., the three lowest BP categories[3]) brings additional statistical problems. One classic mistake in the interpretation of trial results is to ignore the p-value for interaction to make inferences about subgroup effects. This goes against statistical recommendations where, in the absence of a heterogeneous treatment effect, one should accept the overall effect across all groups as the best estimate of effect in any subgroup investigated. [25,26] The fact that interpretation of findings by simply inspecting the treatment effects in subgroups can be misleading is evident from the BPLTTC paper that stratified patients by CVD status and BP. Although there was no statistical evidence of heterogeneity by BP, the CIs in several patient subgroups, when considered in isolation, did span the line of parity of treatment effects.[7] For instance, the hazard ratio in the subgroup of no prior CVD and baseline SBP 140-149 was 0.95 and the lower boundary of CI was 1.03. Ignoring the test for interaction would lead to the conclusion that treatment is ineffective in this patient group, which is clearly inaccurate.

Calculation of mean blood pressure differences for effect standardisation

Another misunderstanding about the BPLTTC studies is the meaning and impact of standardisation of studies according to the intensity of achieved BP reduction. It has been suggested that events during the first 12 months should have been ignored given that BP measurements during the first 12 months were dismissed for the estimation of the intensity of BP reduction for each trial.[3] We are unclear why the lack of congruency of periods for measuring BP change and clinical outcomes would bias or invalidate our study findings. But we note that the method was consistently applied to all studies. In addition, in an earlier study, we showed that BP differences were marginally smaller when the whole duration of trials was considered than when the first 12 months were dismissed.[12] Thus, if one would include the difference from the whole trial duration and re-scale the findings back to a 5 mm Hg difference, the average treatment effect per unit of BP reduction would be expected to be only stronger. More importantly, we reported a sensitivity analysis without any BP standardisation and the conclusions remain the same.[7–9]

Applicability of the trial findings to particular at-risk groups

A key strength of the BPLTTC is that it did not restrict inclusion to any particular at-risk groups and, as described earlier, there is no evidence to suggest that trial inclusion is biased in any direction. This comprehensive approach renders the study findings widely applicable. However, there may be some concerns about the 'extremely high cardiovascular risk' of individuals included in the BPLTTC and the applicability of the findings to a wide range of primary prevention populations with a much lower risk.[3]

There are several arguments against this point of view. First, even if a particular patient group has been heavily underrepresented (e.g., with very low risk of CVD), then the conclusion might be that treatment effects are uncertain in that group, rather than to claim that baseline BP as the key feature for selecting patients should be upheld in that group. Indeed, in the recent BPLTTC report, there was no variation in absolute risk reductions by baseline BP either, which only confirms the poor discriminatory power of a single risk factor, like BP.[7] Second, average risk is not necessarily an indicator of the range of risk in the

population. This was shown in an earlier BPLTTC report, in which the range of CVD risk was substantial and the group with the lowest CVD risk had a 5-year risk of major CVD of <5%.[27] Third, in the presence of high internal validity, the trial findings are broadly applicable to populations, irrespective of average event rates.[28,29] This is also supported by an earlier BPLTTC study which rejected the hypothesis that relative treatment effects vary by baseline risk of CVD.[30] Indeed, a risk-based approach dominated alternative strategies based on age or BP for the selection of individuals for treatment[27]

A similar argument can be made against concerns about the applicability of the findings to those who have not previously been given BP-lowering medications.[3] There is no evidence to suggest that BP reduction would lead to materially different effects in those with or without previous use of antihypertensive therapy.[27] We are not even aware as to why the heterogeneity of relative risk reductions by current BP values should differ when individuals have not received treatment before. Indeed, the conduct of causal inference is more straightforward in this healthy population and therefore the commonly reported J-shape association observed in high-risk populations has not been a concern among those without prior disease and treatment.[31] Therefore, in the absence of any evidence against the core conclusion of the recent BPLTTC studies, they are applicable to low- and high-risk patients, irrespective of a prior history of antihypertensive medication use.

The strength of randomised comparisons of medical interventions lies in their ability to provide unbiased estimates of relative treatment effects. Internal validity, as a prerequisite, must be satisfied in order to attain this goal. The valid evaluation of the causal link may be broadly generalisable if the internal validity is high, and the participants do not have to be representative of those to whom the new findings would be applied.[29] Unlike population-based national surveys, that aim to identify the incidence, prevalence or other measures of absolute risk in a particular representative population, RCTs are rarely sampled for population representativeness. Indeed, there are good statistical and pragmatic reasons why RCTs should actively deviate from a representative sample and focus on particular risk groups or oversample individuals with particular features; however, such intricacies are outside the scope of this article. Thus, to select the best therapies, clinicians rely on the findings of internally valid investigations, often RCTs conducted in different nations on

patients who have different characteristics, comorbidities, ethnicities and lifestyles. Of course, the price for achieving a high internal validity in RCTs is their limited external validity or generalisability to underrepresented groups.

Conclusions

In order to delve into the delicate terrain of knowledge, scientists frequently navigate the conflict between scepticism and constructive exploration. In this paper, we welcomed the criticism by Kreutz et al.,[3] as an impetus to clarify some of the methodological issues pertaining to IPD meta-analyses and the work by the BPLTTC. We have shown that the previously presented study methodology and results are robust and unbiased. Earlier reports have not supported the role of BP-based strategies for selection of individuals for BP-lowering treatment. They have also shown the lack of discriminatory power of BP in various age groups, in those with or without prior CVD and those with or with atrial fibrillation. However, when single factors do not affect either relative or absolute risk reductions, we should not infer that everyone requires drug therapy, or that everyone will benefit to the same degree from treatment. Medical interventions incur costs and have side effects. Therefore, some thresholds need to be defined for selection of those who are most likely to benefit from treatment. While work of the BPLTTC will continue to identify groups of individuals who are most likely to benefit from treatment, the best evidence to date suggests that BP-based thresholds are not as efficient as risk-based thresholds. Where that risk threshold is to be set will depend on several factors and might vary from region to region depending on the availability of resources and priorities. In the meantime, clinicians should not completely dismiss initiating BP lowering simply because a specific patient's BP level is normal when the patient could benefit from major CVD risk reduction in the future. To identify individuals who are candidates for BP-lowering medications, multivariable risk stratification based on demographic characteristics, clinical risk of outcomes, and even genetic risk scores are likely to be necessary. As with any therapeutic decisions, other essential aspects such as patient preferences, additional medical expenditures and physician visits, risk of adverse effects and subsequent non-compliance should be taken into account. It is critical to consider both the benefits and harms to arrive at fair judgments about the best treatment.

Conflict of interests

Nazarzadeh (grant number: FS/19/36/34346), Rahimi (grant number: PG/18/65/33872) and Canoy (grant number: PG/18/65/33872) are supported by the British Heart Foundation. Rahimi, Canoy and Bennett are supported by the National Institute of Health Research (NIHR) Oxford Biomedical Research Centre. Rahimi received support from the Oxford Martin School and UKRI Global Challenge Research Fund Grant Ref: ES/P011055/1, and reports personal fees from the BMJ Heart and PLOS Medicine outside the submitted work. Chalmers reports research grants and personal fees from Servier for the ADVANCE and PROGRESS trials, and grants from the National Health and Medical Research Council of Australia for these two trials. Woodward is supported by the Australian National Health and Medical Research Council (Investigator Grant APP1174120 and Program Grant APP1149987) and personal funding from Amgen, Kyowa Kirin and Freeline outside the current work.

References

1 Riley RD, Steyerberg EW. Meta-analysis of a binary outcome using individual participant data and aggregate data. *Research Synthesis Methods* 2010; 1:2–19.

2 Rahimi K, Canoy D, Nazarzadeh M, Salimi-Khorshidi G, Woodward M, Teo K, *et al.* Investigating the stratified efficacy and safety of pharmacological blood pressure-lowering: An overall protocol for individual patient-level data meta-analyses of over 300 000 randomised participants in the new phase of the Blood Pressure Lowering Treatm. *BMJ Open* 2019; 9:28698.

3 Kreutz R, Brunström M, Thomopoulos C, Carlberg B, Mancia G. Do recent meta-analyses truly prove that treatment with blood pressure lowering drugs is beneficial at any blood pressure value, no matter how low? - A critical review. *Journal of hypertension* 2022.

4 Wald N. Blood pressure meta-analysis. *Lancet* 2022; In press.

5 Greenland S, Senn SJ, Rothman KJ, Carlin JB, Poole C, Goodman SN, *et al.* Statistical tests, P values, confidence intervals, and power: a guide to misinterpretations. *European Journal of Epidemiology 2016 31:4* 2016; 31:337–350.

6 Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, *et al.* Blood pressure lowering for prevention of cardiovascular disease and death: A systematic review and meta-analysis. *The Lancet* 2016; 387:957–967.

7 The Blood Pressure Lowering Treatment Trialists' Collaboration. Pharmacological blood pressure lowering for primary and secondary prevention of cardiovascular disease across different levels of blood pressure: an individual participant-level data meta-analysis. *The Lancet* 2021; 397:1625–1636.

8 Pinho-Gomes AC, Azevedo L, Copland E, Canoy D, Nazarzadeh M, Ramakrishnan R, *et al.* Blood pressure-lowering treatment for the prevention of cardiovascular events in patients with atrial fibrillation: An individual participant data meta-analysis. *PLoS Medicine* 2021; 18:e1003599.

9 Blood Pressure Lowering Treatment Trialists' Collaboration. Age-stratified and blood-pressure-stratified effects of blood-pressure-lowering pharmacotherapy for the prevention of cardiovascular disease and death: an individual participant-level data meta-analysis. *Lancet* 2021; 0. doi:10.1016/S0140-6736(21)01921-8

10 Copland E, Canoy D, Nazarzadeh M, Bidel Z, Ramakrishnan R, Woodward M, *et al.* Antihypertensive treatment and risk of cancer: an individual participant data meta-analysis. *The Lancet Oncology* 2021; 22:558–570.

11 Nazarzadeh M, Bidel Z, Canoy D, Copland E, Wamil M, Majert J, *et al.* Blood pressure lowering and risk of new-onset type 2 diabetes: an individual participant data meta-analysis. *The Lancet* 2021; 398:1803–1810.

12 Canoy D, Copland E, Nazarzadeh M, Ramakrishnan R, Pinho-Gomes A-C, Salam A, *et al.* Effect of antihypertensive drug treatment on long-term blood pressure reduction: An individual patient-level data meta-analysis of 352,744 Participants from 51 large-scale randomised clinical trials. *Heart* Published Online First: 2022. doi:10.1136/heartjnl-2021-320171

13 The Heart Outcomes Prevention Evaluation Study. Effects of an Angiotensin-Converting–Enzyme Inhibitor, Ramipril, on Cardiovascular Events in High-Risk Patients. *New England Journal of Medicine* 2000; 342:145–153.

14 Marre M, Lievre M, Chatellier G, Mann JFE, Passa P, Ménard J. Effects of low dose ramipril on cardiovascular and renal outcomes in patients with type 2 diabetes and raised excretion of urinary albumin: randomised, double blind, placebo controlled trial (the DIABHYCAR study). *BMJ* 2004; 328:495.
15 Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *The Lancet* 2002; 360:1903–1913.
16 Zhou B, Bentham J, Di Cesare M, Bixby H, Danaei G, Cowan MJ, *et al.* Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants. *Lancet* 2017; 389:37.
17 Malik R, Georgakis MK, Vujkovic M, Damrauer SM, Elliott P, Karhunen V, *et al.* Relationship between Blood Pressure and Incident Cardiovascular Disease: Linear and Nonlinear Mendelian Randomization Analyses. *Hypertension* 2021; :2004–2013.
18 Czernichow S, Zanchetti A, Turnbull F, Barzi F, Ninomiya T, Kengne A-P, *et al.* The effects of blood pressure reduction and of different blood pressure-lowering regimens on major cardiovascular events according to baseline blood pressure: meta-analysis of randomized trials. *Journal of hypertension* 2011; 29:4–16.
19 Lonn EM, Bosch J, López-Jaramillo P, Zhu J, Liu L, Pais P, *et al.* Blood-Pressure Lowering in Intermediate-Risk Persons without Cardiovascular Disease. *New England Journal of Medicine* 2016; 374:2009–2020.
20 Raymond Hoffenberg S, M Ledingham PJ, Taylor PJ, Miall WE, Greenberg G, Brennan PJ, *et al.* MRC trial of treatment of mild hypertension: principal results. Medical Research Council Working Party. *Br Med J (Clin Res Ed)* 1985; 291:97–104.
21 Anastos K, Charney P, Charon RA, Cohen E, Jones CY, Marte C, *et al.* Hypertension in women: What is really known? The women's caucus, working group on women's health of the society of general internal medicine. *Annals of Internal Medicine* 1991; 115:287–293.
22 Amery A, Birkenhäger W, Brixko P, Bulpitt C, Clement D, de Leeuw P, *et al.* Influence of antihypertensive drug treatment on morbidity and mortality in patients over the age of 60 years. European Working Party on High blood pressure in the Elderly (EWPHE) results: sub-group analysis on entry stratification. Journal of hypertension. Supplement. 1986; 4(6): S642-7.
23 Gueyffier F, Boutitie F, Boissel JP, Pocock S, Coope J, Cutler J, *et al.* Effect of antihypertensive drug treatment on cardiovascular outcomes in women and men. A meta-analysis of individual patient data from randomized, controlled trials. The INDANA Investigators. *Annals of internal medicine* 1997; 126:761–767.
24 Gueyffier F, Bulpitt C, Boissel JP, Schron E, Ekbom T, Fagard R, *et al.* Antihypertensive drugs in very old people: a subgroup meta-analysis of randomised controlled trials. INDANA Group. *Lancet* 1999; 353:793–796.
25 Rothwell PM. Subgroup analysis in randomised controlled trials: importance, indications, and interpretation. *The Lancet* 2005; 365:176–186.
26 Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in Medicine — Reporting of Subgroup Analyses in Clinical Trials. *New England Journal of Medicine* 2007; 357:2189–2194.
27 Karmali KN, Lloyd-Jones DM, van der Leeuw J, Goff DC, Yusuf S, Zanchetti A, *et al.* Blood pressure-lowering treatment strategies based on cardiovascular risk versus blood pressure: A meta-analysis of individual participant data. *PLoS Medicine* 2018;

15:e1002538.
28 Elwood JM. Commentary: On representativeness. *International Journal of Epidemiology* 2013; 42:1014–1015.
29 Rothman KJ, Gallacher JEJ, Hatch EE. Why representativeness should be avoided. *International Journal of Epidemiology* 2013; 42:1012–1014.
30 Sundström J, Arima H, Woodward M, Jackson R, Karmali K, Lloyd-Jones D, *et al.* Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. *The Lancet* 2014; 384:591–598.
31 Rahimi K, Emdin CA, MacMahon S. The Epidemiology of Blood Pressure and Its Worldwide Management. *Circulation Research* 2015; 116:925–935.