Επίκαιρο άρθρο
Ξένου συγγραφέα

Meta-analyses of blood pressure lowering trials: Separating the wheat from the chaff

M. Brunström

ABSTRACT

Systematic reviews and meta-analyses are often considered the pillar of evidence-based medicine, and have therefore had considerable impact on clinical medicine in the last several decades. The quality of any meta-analysis depends crucially on the underlying systematic review. In this review, special considerations of importance to the field of hypertension treatment are discussed, including how the research question should guide which studies are included in the review, and how the analytical approach should take into consideration possible differences between trials. Indeed, the field of hypertension is fertile soil for systematic reviews and meta-analyses, with its hundreds of clinical trials. But with this great opportunity comes the problem of potentially biased reviews and the need for clinicians to be able to separate the wheat from the chaff.

Key-words: Systematic reviews, meta-analyses, hypertension, hypertension treatment

INTRODUCTION

Meta-analyses are frequently recognized as the highest level of evidence for clinical research questions about treatment effect. This is particularly true for the field of hypertension research, where they have had major impact on clinical practice guidelines for the last few decades[1,2]. The reason for this is probably the vastness of data available from hundreds of trials assessing the effect of BP lowering treatment. Although this is indeed fertile soil to gain new insights from already published data, interpretation of large meta-analyses, including many and often diverse original trials, may be complex. This article aims to provide some guidance on how to critically appraise systematic reviews and meta-analyses of the effects of blood pressure lowering interventions on clinical outcomes, building on a recently published comprehensive review on the topic[3], and a lecture held at the 32nd ESH meeting in Milan, 24th of June 2023.

Systematic review vs. meta-analysis

The terms systematic review and meta-analysis are often used interchangeably. However, it is important to know the distinction between these terms to be able to critically appraise any publication reporting the results of a meta-analysis, as the validity often depends on the underlying work not presented in figures or abstracts. Whereas a systematic review starts with a clearly defined research question, for which the available literature is systematically assessed to retrieve all available evidence, which is then critically appraised and reported transparently, the meta-analysis is barely a statistical method used to calculate a weighted average effect estimate (Table 1)[4]. Although such summary estimates can be of great importance in clinical decision making, they tell us nothing about the quality of the underlying evidence and the selection process from which trials have been included. If the data included in a meta-analysis are not representative of the totality of the evidence, or if original studies are of poor quality, effect estimates may indeed be seriously misleading.

✉ **Correspondence:** **Mattias Brunström** • MD PhD, Department of Public Health and Clinical Medicine, Umeå University, Sweden • E-mail: mattias.brunstrom@umu.se

Table 1. Generic systematic review process.

Research question => eligibility criteria
Comprehensive literature search
Transparent selection process
Risk of bias assessment
Data synthesis
Meta-analysis
Certainty and quality of evidence (GRADE)
Interpretation

Selection of trials

The results of a meta-analysis are only as reliable as the trials included in the analysis. Thus, the eligibility criteria for trials play a crucial role in any systematic review, and thus also when critically appraising a systematic review and meta-analysis[3,4]. Importantly, inclusion criteria should be specific for the research question under study. For example, if the research question is about the effect of BP lowering, it is reasonable to include trials aiming to achieve a BP difference between treatment arms during follow-up. This may include trials comparing any antihypertensive agent against placebo and trials comparing different BP targets[5,6]. Some review authors have also included trials comparing two or more agents against each other (Table 2)[7]. This has been a matter of intense debate, however, because such trials are generally designed to achieve as little BP difference as possible between treatment arms, aiming to investigate BP independent effects of different drugs or drug classes[8]. Although some BP differences may occur anyway, they are not likely to drive major differences in clinical outcomes. Including such studies in a meta-analysis of treatment effects of BP lowering thus puts the analysis at risk of bias; where some studies may contribute to the results primarily through BP lowering, others are likely to affect outcomes through other mechanisms.

In addition to study design features, one needs to consider for whom the research question is relevant, and if results from trials in other patient groups are likely to be generalizable to the target group.[3] For example, a systematic review of the effect of BP lowering treatment in people with diabetes should ideally only include people with diabetes, or at least trials in which the majority of patients had diabetes at baseline[9]. On the other hand, if the research question is about possible differences in treatment effect between people with diabetes and people without diabetes, only trials including both patient groups and presenting data on these patient groups separately will contribute meaningfully[10]. Trials without participants with diabetes may only provide indirect evidence, and including such trials puts the analysis at risk of bias due to possible design differences between participants with and without diabetes.

Analytical approach

As mentioned previously, a meta-analysis is a weighted average of the included trials[3,4]. Weighting builds on standard errors within trials, which depends largely on the number of events. In its simplest form, often referred to as the fixed-effects model, the weight given to each trial is proportional to the inverse variance, i.e. the larger number of events, the more weight. Importantly, this makes the assumption that differences between trials are non-random, or in other words, that all included trials estimate the same true effect (fixed-effects). This assumption rarely holds in the

Table 2. Design features of clinical hypertension trials.

Study type	Comparative trials	Placebo-controlled trials	Target trials
General design	One agent or class of agents versus another agent or class of agents with the same treatment target	One agent or a combination of agents versus placebo, sometime with similar BP target	Different BP targets, often with similar treatment strategies
General purpose	Investigate BP independent effects between agents or classes of agents	Investigate the effect of an agent or combination of agents on clinical outcomes	Investigate the effect of different BP targets and/or a certain BP difference between treatment arms
Appropriate use in meta-analyses	Research questions about effect of specific agents or classes of agents; not questions about the effect of BP lowering; not questions about thresholds or targets	Research questions about the effect of BP lowering; questions about thresholds or targets; questions about the effect of specific agents or classes of agents in the context of network meta-analyses	Research questions about the effect of BP lowering; questions about thresholds or targets; not questions about specific agents or classes of agents

very diverse setting of BP lowering meta-analyses – we can simply expect results from trials in different patient groups, testing different agents or classes of agents, to be different, and thus a statistical method taking between-trial differences into account is needed. This is the rationale for random-effects meta-analysis, a group of statistical models with the common feature that they consider between-study variance when assigning trial weights, thus loosing the assumption about similarity between studies[3,4].

Perhaps even more important than the statistical method is how trials are grouped before they are entered into the analysis. Can we assume that all trials included in the systematic review approximate the same effect, or may there be important differences? A common example is treatment effect across blood pressure levels. If the effect is assumed to be the same in different patient groups, it will look as if treatment is similarly effective in all circumstances[11]. However, if one separates trials in people with established CVD from those in people free of disease at baseline, another pattern may appear[6,12]. Importantly, this needs to be considered beforehand, based on previous knowledge, because the power of detecting differences between subgroups in a meta-analysis, once pooled, is very poor.

A particular problem in hypertension research is that most of the treatment effect is mediated through BP lowering. As the magnitude of BP lowering differs between trials, it may be expected that the effect on clinical outcomes will differ as well. The question is if and how this should be handled analytically.

In principle, there are three ways to move forward in this situation[3]. Firstly, one could accept differences between studies, accounting for it using random-effects model, possibly with additional modifications to reduce the risk of false positive findings[13]. Secondly, one could be very strict in defining the eligibility criteria, excluding trials with small BP differences[14]. Thirdly, one may standardize the results to a certain BP reduction[7,11,15].

Standardization deserves specific mentioning because several highly cited meta-analyses in our field have used this approach[7,11,15]. Without getting too mathematical, the principle is to adjust the effect estimate in each trial according to its BP reduction, as if all trials reduced BP to a similar extent. As an example, if you have a trial with 5 mmHg BP reduction and a 10% relative risk reduction in CVD (relative risk 0.9), this may be standardized to 10 mmHg BP reduction according to the formula $RR^{10/deltaSBP} = 0.9^{10/5} = 0.9^2 = 0.81$. This perhaps seems reasonable at first, but when used on trials with very small BP differences between treatment arms, the problem is obvious[16]. In the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study, participants were randomized to losartan or atenolol, resulting in a 1.2 mmHg differences between treatment arms during follow-up[17]. The relative risk for stroke was 25% lower in the losartan group, which was generally interpreted as if losartan is superior to atenolol in terms of stroke prevention. When LIFE is included in a meta-analysis standardized to a larger BP reduction, e.g. 5 mmHg as applied by the Blood Pressure Lowering Treatment Trialists Collaboration (BPLTTC)[7], its effect estimates becomes completely unrealistic. A relative risk of 0.75 and a BP differences of 1.2 mmHg gives us the calculation $0.75^{5/1.2} = 0.75^{4.2} = 0.3$, which means 5 mmHg BP reduction would cause a 70% risk reduction for stroke.

Interpretation of recent meta-analyses

The points described above are not only crucial for designing future systematic reviews and meta-analyses in hypertension, but has major implications for the interpretation of existing systematic reviews. Table 3 shows how three major systematic reviews of treatment effect across BP levels have handled trial design, statistical methods in general and differences in BP lowering between trials in particular[6,7,12].

As is evident from the table, there are substantial differences between systematic reviews of BP lowering in terms of methodological considerations. Importantly, these methodological differences are of greater importance to the results of the meta-analyses than the difference in trial-level data versus individual-patient data, which is often emphasized by the BPLTTC group[7,8].

CONCLUSION

When assessing the quality of any meta-analysis, the importance of also assessing the underlying systematic review cannot be emphasized enough. As a clinician it is important to critically consider if the research question posed in the review corresponds to the clinical question you are asking. Furthermore, the research question should guide the selection of trials and the analytical approach, considering study type, comorbidities, differences and similarities between studies in terms of intervention, control and follow-up, and choice of statistical methods. What makes perfect sense from a statistical point of view, may very well be un-

Table 3. Methodological considerations in meta-analyses of BP lowering.

Authors	Study type	Patients	Statistics	BP diff between trials
BPLTTC	Comparative + placebo-controlled + target trials	Primary prevention and established cardiovascular disease separately	One-stage Cox model (fixed)	Standardized to 5 mmHg
Brunström et al.	Placebo-controlled + target trials	Primary prevention, coronary artery disease, stroke, and other cardiovascular disease separately	Random-effects (Knapp-Hartung modification)	Accepted
Thomopoulos et al.	Placebo-controlled + target trials	Low vs high risk	Random-effects model	Accepted and standardized results from meta-analysis

BPLTTC = Blood Pressure Lowering Treatment Trialists Collaboration.

reasonable for a clinician, considering clinical variables which may be obscure to the statistician. Systematic reviews and meta-analyses are important tools to synthesize clinical research and guide treatment, but as clinicians we must be able to critically appraise these tools, to separate the wheat from the chaff.

REFERENCES

1. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2017.
2. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: *J Hypertens* 2018; 36(10): 1953-2041.
3. Brunström M, Thomopoulos C, Carlberg B, Kreutz R, Mancia G. Methodological Aspects of Meta-Analyses Assessing the Effect of Blood Pressure-Lowering Treatment on Clinical Outcomes. *Hypertension* 2022; 79(3): 491-504.
4. Higgins J, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions. 2nd ed. Chichester (UK): John Wiley & Sons, 2019.
5. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension. 1. Overview, meta-analyses, and meta-regression analyses of randomized trials. *Journal of Hypertension* 2014; 32(12): 2285-95.
6. Brunström M, Carlberg B. Association of Blood Pressure Lowering With Mortality and Cardiovascular Disease Across Blood Pressure Levels: A Systematic Review and Meta-analysis. *JAMA Intern Med* 2018; 178(1): 28-36.
7. Collaboration BPLTT. 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. *Lancet* 2021; 397(10285): 1625-36.
8. 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. *J Hypertens* 2022; 40(5): 839-46.
9. Brunström M, Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses. *BMJ* 2016; 352: i717.
10. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment on outcome incidence in hypertension: 10 - Should blood pressure management differ in hypertensive patients with and without diabetes mellitus? Overview and meta-analyses of randomized trials. *J Hypertens* 2017; 35(5): 922-44.
11. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 2016; 387(10022): 957-67.
12. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment on outcome incidence. 12. Effects in individuals with high-normal and normal blood pressure: overview and meta-analyses of randomized trials. *J Hypertens* 2017; 35(11): 2150-60.
13. Cornell JE, Mulrow CD, Localio R, et al. Random-Effects Meta-analysis of Inconsistent Effects: A Time for Change. *Annals of Internal Medicine* 2014; 160(4): 267-70.
14. Bundy JD, Li C, Stuchlik P, et al. Systolic Blood Pressure Reduction and Risk of Cardiovascular Disease and Mortality: A Systematic Review and Network Meta-analysis. *JAMA Cardiol* 2017; 2(7): 775-81.
15. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood Pressure Lowering in Type 2 Diabetes A Systematic Review and Meta-analysis. *JAMA* 2015; 313(6): 603-15.
16. Brunström M, Carlberg B. Standardization according to blood pressure lowering in meta-analyses of antihypertensive trials: comparison of three methodological approaches. *J Hypertens* 2018; 36(1): 4-15.
17. Dahlof B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; 359(9311): 995-1003.