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Should All Studies Swim in the Same Pool?

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Meta-analyses have become increasingly popular since they were introduced in medical literature during the 80s and 90s, with publication rates increasing exponentially over time. Now, detailed instructions on how to design, conduct, and report meta-analyses are readily available, most notably from the Cochrane Collaboration. (1) The most important step in the meta-analysis process is the underlying systematic review of the published literature. An accurately performed systematic review ensures that all available evidence is considered and critically appraised before it is analyzed, which is essential for the meta-analysis to be valid.

The meta-analysis itself is a statistical method for pooling results from different studies. Instead of simply calculating the average treatment effect across studies, each study is assigned a weight corresponding roughly to its number of participants and events. This, the simplest form of meta-analysis, is often called fixed-effects model because it does not take differences between trials into account. When included studies differ to some extent, the overall estimate needs to be adjusted for between-study variability, requiring more sophisticated models. A variety of such models is available, commonly referred to as random-effects models.

The real challenge is when multiple studies, with different patient populations and interventions, are available within the scope of the proposed research question. Due to the portfolio of available drug classes, several agents within each class, several doses for each agent, the wide range of co-morbidities, and the extraordinary change in population blood pressure over time, evaluation of antihypertensive treatment is probably one of the most complex situations where meta-analysis could be applied. Nevertheless, it is one of the most important situations to be evaluated systematically, because the array of available studies invite to selective citing of studies supporting specific notions.

When deciding how to analyze data, a critical question is if the included studies best answer the proposed question together, or subdivided to some extent. Some authors have used the approach of randomized controlled trials, where the primary analysis contains all study participants, and subgroup analyses are performed to explore possible interactions. However, randomized controlled trials and meta-analyses differ on one very important point. All study participants in a trial are recruited to answer the same question, fulfilling the same eligibility criteria, and receiving the same intervention or control. Studies included in a meta-analysis are likely to have asked different research questions, having different eligibility criteria, interventions, controls, and follow-up. Whereas participants in trials are "pooled by design", trials in meta-analyses are not.

Thus, before trials are pooled in a meta-analysis, analysts need to carefully consider potential clinical heterogeneity between studies, as well as possible modifiers of treatment effect. Are trials with different drugs or drug classes included in the analysis; if so, is it possible that they differ with respect to the effect on blood pressure or cardiovascular events? How the answers to these questions affect the statistical analysis plan depends on the research question, but readers should be aware that when trials are pooled it is assumed that differences are negligible.

Once trials have been pooled in a meta-analysis, it cannot be fully accounted for by subgroup/interaction analyses. This is because the power to detect clinically important interactions in meta-analyses is extremely poor, especially when subgroups include few trials or when heterogeneity is present within subgroups. Thus, negative subgroup/interaction analyses should be interpreted with great caution, and not necessarily as "no difference between subgroups" if such an interaction is suspected from a clinical or pathophysiological point of view.(1)

For systematic reviews of antihypertensive treatment at different blood pressure levels, different analytical

strategies have resulted in very different conclusions, depending on how co-morbidities have been handled. For example, some reviews have included heart failure trials and trials in the acute phase after myocardial infarction.(2,3) In such trials, patients generally have low blood pressure due to failure of the left ventricle. At the same time, several antihypertensive drug classes (such as inhibitors of the renin-angiotensin system, beta-blockers and diuretics) have important effects not related to blood pressure lowering, affecting cardiovascular mortality and morbidity. Thus, what appears to be a consistent effect of blood pressure lowering across blood pressure levels is actually an effect of blood pressure lowering in the upper end of the blood pressure spectrum and an effect of heart failure treatment in the lower end of the spectrum, which happens to be statistically similar in terms of effect size.

Even if heart failure trials are excluded from the analyses, different systematic reviews come to different conclusions about the effect of treatment at different blood pressure levels, largely dependent on how analyses are pooled or sub-grouped. For example, one analysis, pooling primary and secondary preventive trials, found treatment effect to be similar across blood pressure levels. (4) Other analyses, splitting primary and secondary preventive trials, have found attenuated treatment effect at lower blood pressure levels in primary prevention, as well as differences between primary and secondary preventive trials. (5)

In the end, which analysis to trust depends on whether one can accept the assumption that treatment effects are similar across the pooled trials. We hope that this paper has illustrated some of the potential problems with broad analytical approaches, missing differences between subgroups. In the end, who likes it when the pool is too crowded?

References

1. Higgins JPT. Cochrane Handbook for Systematic Reviews of Interventions [electronic resource]. Wiley. doi: 10.1002/9780470712184

2. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *British Medical Journal* 2009; 338: 34. doi: 10.1136/bmj.b1665

3. 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. doi: 10.1001/jamacardio.2017.1421

4. 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. doi: 10.1016/S0140-6736(15)01225-8

5. 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. doi: 10.1001/jamainternmed.2017.6015

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