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The Devil is in the Details

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Meta-Analyses and systematic reviews have been traditionally placed at the top of the hierarchy for evidence pyramid because they increase the power to detect differences, provide greater precision of treatment effects and can investigate consistency of effect across groups. As such, over the past decade there has been an explosion of meta-analyses – with almost 18,000 meta-analyses published in 2017 alone. However, this enthusiasm for meta-analyses must be tempered with cautious optimism. As eloquently discussed in the accompanying paper by Drs. Brunström and Carlberg, some important methodological decisions in designing and executing meta-analysis rely on personal judgement and expertise and therefore can introduce personal bias and strongly influence conclusions (1). Authors and consumers of meta-analyses need to be aware of these potential sources of bias arising in the selection of patient populations, trials and outcomes when designing and interpreting findings from meta-analyses (2). Here we will illustrate the influence of study selection and outcomes with three recent examples of meta-analyses purporting to investigate the same question, "What are the optimal blood pressure targets for high risk persons with hypertension?"

The first meta-analysis published in 2018 by the Cochrane Goup compared blood pressure targets (≤ 135/85 mmHg) with standard blood pressure targets (≤ 140 to 160/90 to 100 mmHg) in people with hypertension and a history of cardiovascular disease (3). The Cochrane Group updated this meta-analysis in response to multiple guidelines commenting on blood pressure targets in high-risk individuals. Although guideline recommendations refer to high-risk individuals (4), the authors restricted their analysis to only patients with established cardiovascular disease defined as those with a history of myocardial infarction, angina, stroke, peripheral arterial disease. Although angina was included, other cardiovascular risk equivalents were not: diabetes and chronic kidney disease (5) for example. The Cochrane Group analyzed patients regardless of age or baseline blood pressure. Based on these criteria, the authors included evidence from six RCTs (9,484 patients) (AASK 2002; ACCORD BP 2010; HOT 1998; Past BP 2016; SPRINT 2015; SPS3 2013) (6-11) with only small subsets of individual patient data being drawn from each of these trials with the exception of including the majority of patient data from the SPS3 study (11). Perhaps not surprising, the pooling of these small groups, even among trials that did not pre-specify CVD subgroups, yielded no significant differences in reduction of total mortality or total cardiovascular events with more intensive blood pressure lowering (≤ 135/85 mmHg) compared with more relaxed BP targets (≤ 140 to 160/90 to 100 mmHg).

The second meta-analysis was published in 2017 as the basis for the 2017 American Association of Family Physicians hypertension guidelines recommendations for target blood pressures in the elderly (12). This meta-analysis also aimed to investigate intensive vs. less intensive blood pressure lowering but restricted to patients 60 years or older and further stratified by baseline blood pressure (< 160 mmHg SBP and ≥ 160 mmHg). In contrast to the Cochrane study, this meta-analysis included patients with cardiac disease but excluded patients with prior cerebrovascular disease. The outcomes examined included total mortality, stroke, and cardiac events (narrowly defined as myocardial infarction or sudden cardiac death). These outcomes also differ from the Cochrane review and did not include heart failure, arguably one of the most salient endpoints in the management of hypertension. Six RCTs (41,491 patients) were included: ACCORD BP 2010, Cardio-Sis 2009, HOT 1998, SPRINT 2015, JATOS 2008, VALISH 2010 (7, 8, 10, 13-15). The target SBP of less than 140 mmHg was not significantly different from a less strict target for mortality (RR: 0.93, 95%CI 0.75-1.14), stroke 0.86 (0.64-1.07) or cardiac events (0.91, 95%CI: 0.77-1.04). Heterogeneity was generally low within these pooled comparisons.

In a meta analysis conducted by the ACC/AHA guideline group (16), the authors included 15 RCTs and specifically 9 trials evaluating SBP target <130 mmHg for the intensive target: SPS3, SPRINT, MDRD 2005, AASK

2006, REIN-2 2005, Asayama K et al. 2012, Schrier RW et al. 2014, Cardio-Sis 2009, and ACCORD 2010 (7, 10, 11, 13, 17-21). This patient population included high-risk patients with diabetes, chronic kidney disease, stroke and cardiovascular disease. This meta-analysis evaluated a broader number of endpoints including: total mortality, cardiovascular mortality, composite major cardiovascular events, myocardial infarction, stroke, heart failure, and renal outcomes. Here, intensive BP lowering was associated with significant reductions in major cardiovascular events (RR: 0.84; 95% CI: 0.73 to 0.99) and stroke (RR: 0.82; 95% CI: 0.70 to 0.96) but not total mortality or heart failure.

From these three meta-analyses, which conclusion is true? There have been at least 8 systematic reviews and meta-analyses published on this topic in the last few years and most of the differences in conclusions arise from the variability in selection of studies and outcomes. Certainly, authors and readers will have differing opinions on the appropriateness of combining different RCTs and patient populations. As the entirety of the available data on blood pressure targets are diverse, differences in non-random selection of studies and outcomes, the starting point of a meta-analysis, can significantly influence the conclusions. Although when selection is too broad, the risk of increased statistical and clinical heterogeneity increases. When selecting too narrowly, the heightened power of a meta-analysis is attenuated, diminishing the probability of detecting differences that exist. Although one may argue that narrow comparability is essential to avoid comparing apples with oranges, one of the methodological advantages of meta-analysis over large single RCTs is the ability to address a broader question and formally assess generalizability. Michael Borenstein (22) stated meta-analysis ask "questions about fruit, for which both apples and oranges (and indeed pears and melons) contribute valuable information." A number of solutions may help to mitigate issues of selection and outcome reporting bias including appropriately ensuring relevant patient populations are included, registering meta analysis protocols, inclusion of primary endpoints from the primary RCTs, and robust sensitivity analyses to examine narrow subgroups after broader examination (1, 22). Indeed, the devil is in the details.

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