Category: Therapeutics

Study type: Systematic review and meta-analysis

Author's declarative title (30 words): Blood pressure lowering treatment lowers mortality and cardiovascular disease risk, but whether effects differ at an arbitrary threshold of 140 mmHg systolic blood pressure requires further research.

Citation: 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**:28-36

Commentary (800 words)

Context (80-120 words)

Favourable vascular health outcomes associated with blood pressure (BP) lowering treatment are well-established. Using evidence from randomised controlled trials (RCTs), clinical guidelines support initiating treatment in patients with elevated BP usually set at systolic/diastolic BP≥140/≥85 mmHg. Over the years, increasing evidence suggests beneficial effects of BP lowering treatment at baseline BP below these thresholds.[1-3] However, in this current meta-analysis, methods used in earlier studies[1-2] were questioned, and aimed to re-examine differential effects of BP lowering treatment on mortality and cardiovascular disease (CVD) by baseline systolic BP (SBP).[4]

Methods (100-150 words)

This meta-analysis included BP lowering treatment trials (vs placebo or each other with different BP targets) on all-cause mortality, CVD mortality, major cardiovascular events (MACE), coronary heart disease (CHD), stroke, heart failure, and end-stage renal disease (ESRD).[4] Trial-level risk estimates were extracted from published articles, and, for each outcome, results were summarised as relative risks (RR) with their confidence intervals (CI) by baseline SBP, without any correction for multiple testing. Separate meta-analyses were conducted for 'preventive' trials (<50% of participants with established CVD at baseline) and other trials (>50% of participants with established CHD, stroke or mixed CVD). The rationale for this stratification (without testing for heterogeneity) was not pre-specified. Heterogeneity and risk of bias were assessed, and results reported according to PRISMA guidelines. There was neither an a priori registration nor a published protocol.

Findings (75-100 words)

Seventy-four RCTs were included, reporting on 306,273 participants (40% women) with mean age=63.6 years. Of these studies, 51 were classified as preventive trials (N=192,795), and the rest as CHD (12 studies), stroke (6 studies) or mixed CVD trials (5 studies). In the 'preventive' trials, treatment was associated with beneficial effects for all outcomes (except ESRD) for baseline SBP 140-159 mmHg and ≥160 mmHg, but not
<140 mmHg (interaction between treatment groups and baseline SBP significant only for CVD mortality, MACE and heart failure outcomes). For 'CHD' and 'poststroke' trials, results were not stratified according to baseline SBP (only overall effects were presented). For 'CHD' trials, MACE, CHD, stroke and heart failure, but not all-cause and CVD mortality, risks were reduced; for 'poststroke' trials, no significant associations were found with any outcome.

Commentary (250-300 words)

For the main research question, only findings from the preventive trials are relevant, showing treatment to reduce SBP by 6.6 mmHg on average, but beneficial effects were limited to baseline SBP≥140 mmHg (risks varied by type of outcome), a finding that is in contrast to earlier reports which showed efficacy in patients with baseline SBP<140 mmHg[1-3] and the recently published recommendation to initiate treatment in adults with BP≥130/80 mmHg and increased background CVD risk.[5] Differences in the methods could account for this inconsistency. Classifying RCTs arbitrarily into preventative and non-preventative trials implies

that treatment effects differ between studies involving CVD and non-CVD populations, which was not justified statistically. Intensity of BP lowering was not accounted for, giving similar weight to treatment effects regardless of the absolute reduction in BP.

A closer inspection of the data suggests that some findings might be more consistent with earlier studies than they appear to be. In the 'preventive' trials, statistical interaction between treatment groups and baseline SBP was not significant for CHD and stroke outcomes (Figure 1), suggesting similar risk reductions across baseline SBP, a finding consistent with earlier reports.[1-3] The RRs by baseline SBP were not calculated for 'CHD' trials because of the narrow range of mean SBP (129-141 mmHg). For these RCTs, demonstrable treatment benefits were suggested at baseline SBP (mostly) <140 mmHg for most vascular outcomes.

Meta-analyses are important in summarising available evidence of treatment effects, but relying on published data may insufficiently overcome substantial between-study differences for answering questions these trials were not originally designed to answer. To overcome these limitations, an individual participant data meta-analysis is needed to resolve this controversy on differential effects of BP lowering treatment by baseline BP.

Implications for practice (50 words)
The overall evidence suggests that it is reasonable to initiate BP lowering treatment based on BP thresholds lower than that previously recommended, but the background risk of the individual, and other personal circumstances and preferences, need to be considered.

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References (Max 8)

1. Wright JT, Williamson JD, Whelton PK, *et al*. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;**373**:2103-2106.
2. 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**:957-967.
3. Xie X, Atkins E, Lv Jet al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta- analysis. Lancet 2016;387:435-443.
4. 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**:28-36.
5. 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. *J Am Coll Cardiol* 2017;pii:S0735-1097(17)41519-1.

Competing interests
None