Title: Blood pressure targets: comparing lower versus standard for people with hypertension

Commentary on:

Arguedas JA, Leiva V, Wright JM. Blood pressure targets in adults with hypertension. Cochrane Database of Systematic Reviews 2020, Issue 12. Art. No.: CD004349. DOI: 10.1002/14651858.CD004349.pub3.

Key Points

- Lower blood pressure targets (≤ 135/85 mm Hg) compared to standard targets (≤140/90 mm Hg) do not reduce mortality or serious adverse events.
- Lower blood pressure targets may reduce the risk of myocardial infarction and congestive heart failure.
- For hypertensive patients, the benefit of achieving a lower rather than standard blood pressure target may not outweigh the harms associated with pharmacological therapy.

Introduction

Hypertension is a common condition that affects approximately 1.39 billion adults worldwide (31.1% of the adult population) (Mills et al. 2020; Mills et al. 2016). Hypertension has a significant clinical and economic impact on the patient and healthcare providers (Sakima et al. 2019). It is currently the leading preventable risk factor for cardiovascular disease and all-cause mortality worldwide (GBD, 2018). Intensive treatment that lowers blood pressure has been shown to reduce rates of major cardiovascular events, morbidity and mortality from all causes (Wright et al. 2015). Pharmacological reduction of blood pressure is recognised as one of the most effective interventions for at-risk populations (Blood Pressure Lowering Treatment Trialists' Collaboration, 2021). However, there has been some dispute as to whether target blood pressure as the goal of pharmacological therapy (antihypertensive medication), should be a 'standard target' of ≤140/ 90 mm Hg (Systolic Blood Pressure/ Diastolic Blood Pressure) or a 'lower target' of ≤135/85 mm Hg (Whelton et al. 2018; Arguedas et al. 2020). Aiming for lower blood pressure targets may hold benefits for some older patient populations, but greater usage of antihypertensive medication may increase adverse events such as renal failure and increase patient/healthcare costs (Das et al. 2021). The Cochrane systematic review by Arguedas et al. (2020) aimed to determine if a lower targeted blood pressure may reduce mortality and morbidity compared to standard targeting. The aim of this commentary is to critically appraise the methods used in the Cochrane systematic review and consider the importance of the findings for clinical practice.

Methods

This Cochrane systematic review undertook a comprehensive search of six databases from inception to 2019, including the Cochrane Hypertension Specialised Register, US National Institutes of Health Ongoing Trials Register, Cochrane Central Register of Controlled Trials, Embase, World Health Organization International Clinical Trials Registry, and MedLine. Additional citation lists were searched, not limited by language. Only randomised controlled trials (RCTs) which included patients who were adults (>18 years) with elevated blood pressure were included. Trials were included if patients were randomised to a "lower" target Systolic Blood Pressure /Diastolic Blood Pressure (≤ 135/85 mm Hg) compared with a "standard" target blood pressure (≤ 140/90 mm Hg) and excluded if treatment targets were higher than the “standard” targets.

A comprehensive screening, data extraction and assessment of bias (RoB method described in the Cochrane Handbook; Higgins et al., 2019) were undertaken by two reviewers independently, with arbitration by a third reviewer. An overall level of evidence quality for each outcome (rating of certainty) was given using the grading of recommendations assessment, development and evaluation (GRADE). The primary outcomes assessed were all-cause mortality plus cardiovascular and non-cardiovascular mortality, total serious adverse events, cardiovascular serious adverse events and all other serious adverse events. The secondary outcomes assessed were systolic blood pressure (SBP) achieved, diastolic blood pressure (DBP) achieved, withdrawals due to adverse events and number of antihypertensive drugs needed per patient. A meta-analysis was undertaken using risk ratio (RR) and a fixed-effect model to combine outcomes across trials. Subgroup analysis was undertaken for systolic targets and diastolic targets to separate the data for each target.

Results

This review found that there was no evidence of difference between a lower blood pressure target (≤135/85 mm Hg) compared to a standard blood pressure target (≤140/ 90 mm Hg) for total mortality (GRADE certainty: High), total serious adverse events (GRADE certainty: Moderate), non-cardiovascular (GRADE certainty: Not reported) and end-stage renal disease (GRADE certainty: Not reported). A clinically significant reduction was found for a lower blood pressure target compared to a standard blood pressure target for risk of myocardial infarction (number of patients needed to treat for an additional beneficial outcome [NNTB] = 137 over 3.7 years, GRADE certainty: Low) and congestive heart failure (NNTB = 167 over 3.7 years, GRADE certainty: Low). There was a notable but small reduction in risk of stroke for a lower blood pressure target compared to a standard blood

pressure target (0.6% fewer to 0% fewer, GRADE certainty: Low). There was an increased risk of other serious adverse events for a lower blood pressure target compared to a standard blood pressure target (number of patients needed to treat to produce one additional harm) = 33 over 4 years, GRADE certainty: Low).

Commentary

Using the AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews 2) critical appraisal tool for systematic reviews (Shea et al. 2017), this review satisfied 15 out of 16 criteria. The one criterion lacking related to the impact of publication bias, presumably non-applicable due to the number of included studies (lack of statistical power). Overall, it was judged that this Cochrane systematic review provided an accurate and comprehensive summary of the results from available studies that address the research question. That said, the findings from this review were limited by the fact that the trials were not blinded to blood pressure target and for the most part attempts were not made to decrease performance and detection bias (e.g., blinding individuals measuring blood pressure and adjudicating outcomes). Furthermore, a key trial which had a decisive influence on the reduction detected in congestive heart failure and myocardial infarction, was assessed to have a high risk of bias (Wright et al. 2015).

Some clinical guidelines exist that promote tighter BP control (ADA, 2016; Flack & Adekola 2020; Garber et al. 2019) however, these lower targets are not supported by evidence, as synthesised in this review (Arguedas et al. 2020). The findings suggest that lower blood pressure targets do not reduce mortality or serious adverse events compared to standard targets. For the outcome of total mortality, the review authors have high certainty that the true effect is similar to the estimated effect. This review did identify a small reduction in risk of myocardial infarction, congestive heart failure and risk of stroke for lower blood pressure targets, however this was based on low certainty evidence and the analysis highlighted an increased risk of serious adverse events for interventions that adopted a lower blood pressure target. As such, the benefits of lower versus standard targets may not outweigh the harms associated with the intervention. In light of these findings, it is important for health care professionals to promote standard blood pressure targets (≤140/90 mm Hg) and discourage lower targets (≤ 135/85 mm Hg) when treating patients with hypertension.

Serious adverse events identified in this review were explored further in two of the larger included studies. Events such as hypotension, syncope and bradycardia were attributed to blood pressure medications. To help reduce the use of medications, non-pharmacological interventions such as lifestyle modifications can be used before starting medication therapy or in combination after

(Mahmood et al. 2019). Such modifications require a multi-factorial approach including quality nutrition, regular physical activity, attainment of normal body weight, cessation of smoking and alcohol, and reduction of salt (Mahmood et al. 2019; Verma et al. 2021). It is recommended by NICE guidelines that lifestyle advice is offered to people with suspected or diagnosed hypertension on a periodic basis including healthy diet, regular exercise, reduction of alcohol, salt and excessively caffeine-rich products (NICE 2019).

This review included participants between the ages of 20 to 80 and patients with different medical histories including diabetes, stroke and atrial fibrilation. It is not clear what impact lower blood pressure targets would have on different groups of people of different ages and backgrounds. Indeed, one recent observational study suggested that normalised blood pressure values (<140/90 mmHg) during anti-hypertensive treatment may be associated with an increased risk of mortality in patients over 80 years old or patients over 70 with a previous cardiovascular event (Douros et al. 2019). Future research should focus on the identification of specific types of patient who might benefit or be at a detriment from lower blood pressure targets with subsequent evaluation in a randomised controlled trial.

CPD reflective questions

- What are the main limitations of the systematic review presented?
- What advice can be given on lifestyle modifications to reduce blood pressure?
- In future research on blood pressure targets, what type of patients should be identified?

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