therapeutics letter
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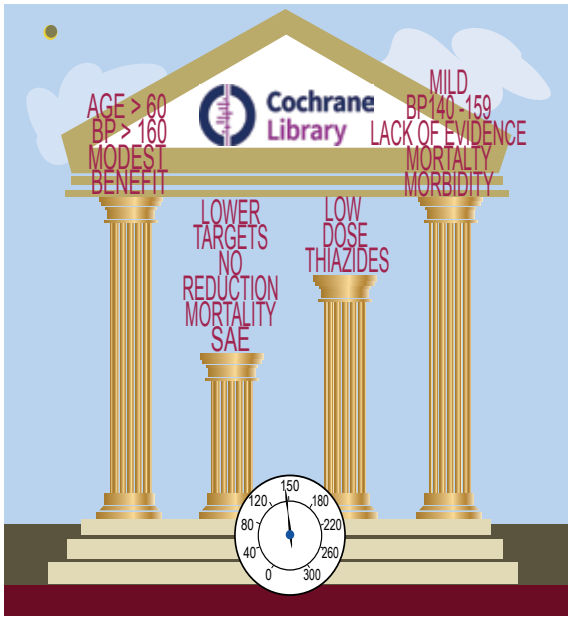
THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

Using Best Evidence for the Management of Hypertension



Elevated blood pressure, commonly referred to as hypertension, is prevalent and has become "big business". As a result much that is written about hypertension is conflicted and influenced by vested interests. It is thus important to know how to find the least biased evidence. Adding to the complexity, the term "evidence" is used in many different ways with many meanings. This Letter uses the term "evidence" to refer to knowledge gleaned from systematic reviews of randomized controlled trials (RCTs) designed to answer the clinical question of interest. We use this approach for 4 practical clinical scenarios that cover over 90% of hypertension management issues in a typical primary care practice. Note that blood pressure measurements in RCTs used multiple readings in a resting state with a rigorous reliable technique.

What is the evidence for drug treatment of moderate to severe hypertension (>160/100) in people ≥ 60 years?

The relevant question is: In an older adult (≥60 years) with a blood pressure >160/100 mmHg does antihypertensive drug treatment reduce mortality or morbidity compared with placebo or no treatment?

This is the question asked in a Cochrane Review published in 2009.[1] The review includes the 13 relevant RCTs, with over 23,000 people. The answer is that drug treatment reduces the outcome most important to patients, total cardiovascular events (fatal and non-fatal stroke, fatal and non-fatal myocardial infarction and fatal and non-fatal congestive heart failure), 5-year relative risk (RR) 0.72 [0.68, 0.77], absolute risk reduction (ARR) 4.3%, NNT=24. This means that approximately 24 people with moderate to severe hypertension must be treated with drugs for 5 years for one person to avoid an adverse cardiovascular event. Serious harms from antihypertensive drugs are not reported in a way that can be analyzed. However, we can be reasonably certain that the benefits of drug treatment outweigh the harms as total mortality (a measure of both benefit and harm) was also reduced: 5-year RR 0.90 [0.84, 0.97], ARR 1.2%, NNT=83.

These findings are relevant to people 60 and over with moderate to severe elevations of BP (>160/100 mmHg), including isolated systolic hypertension. Most patients in this systematic review were primary prevention and treated with stepped care therapy starting with a thiazide. Around 35 to 40% of drug treated patients failed to achieve the blood pressure targets <160/90 mmHg. The evidence was mainly from non-industry funded trials and was judged to be trustworthy (e.g. low risk of bias).

What is the evidence for drug treatment of hypertension in people aged 18 to 59?

A recent Cochrane review[2] suggests that for this age group with mild to moderate hypertension (140-179/90-109) antihypertensive drugs reduce total cardiovascular events: 5-year RR 0.78, [0.67 to 0.91], ARR 0.9%, NNT=122, due primarily to a reduction in stroke. The quality of evidence was, however, low.

What is the evidence for drugs for mild hypertension (140-159/90-99)?

This question was also studied in a Cochrane review.[3] Only one small RCT limited participants to people whose BP was within this range. Therefore the review authors needed to also obtain individual patient data from large trials that included people with mild to moderate hypertension, and analyse only those in the mild hypertension range at baseline. This review was based on 4 RCTs with approximately 7000 people. It failed to find a reduction in

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total cardiovascular events as compared with placebo or no treatment: 5-year RR 0.97 [0.72, 1.32].
This review concluded that antihypertensive drugs for adults (primary prevention) with mild hypertension **have not been proven** to reduce mortality or morbidity in RCTs. More RCTs are needed in this prevalent population to know whether the benefits of treatment exceed the harms. Additionally, 9% of patients discontinued treatment due to adverse effects. If future trials show a benefit, the magnitude is likely to be smaller than for moderate to severe hypertension (e.g. an estimated NNT of 50 to 100 over 5 years at best).

If drug therapy is appropriate, what drug class is the best one to try first?

This question is studied in 5 reviews in the Cochrane Library.[4-8] One review compares first-line drug classes versus placebo[4] and the others compare different drug classes in head-to-head trials. They all come to the same conclusions. There is no evidence that total mortality differs based on the initial drug class used. However, differences exist between the drug classes for serious morbidity. Alpha-blockers and beta-blockers are inferior to other classes of drugs for reducing total cardiovascular events. Initial calcium channel blocker use increases hospitalization and death due to congestive heart failure compared with thiazides, ACE inhibitors and angiotensin receptor blockers. Thiazides reduce stroke as compared with drugs inhibiting the renin angiotensin system. Considering all 5 reviews, low dose thiazides are the best class to try first to reduce overall morbidity in people with hypertension. There is also a recent Cochrane review showing a lack of evidence for starting with combination therapy.[9]

What is the optimal target blood pressure?

Another Cochrane review[10] asked this question: In people with hypertension requiring drug treatment, does attempting to achieve a lower BP target (<135/85 mmHg) as compared to a traditional BP target (<140-160/90-100 mmHg) change mortality and morbidity in RCTs? Trials of different BP targets cannot be blinded. It is therefore important to focus on objective outcomes that measure both benefits and harms: total mortality and total people experiencing at least one serious adverse event (SAE). This review is being updated to include more recent trials including SPRINT.[11,12] The updated analysis shows that in 11 RCTs with over 38,000 participants, lower targets did not reduce total mortality: 5-year RR 0.95 [0.86, 1.05]. Total SAEs (reported in 3 RCTs) were also not reduced: RR 1.03 [0.99, 1.08].
The conclusions from this updated analysis (like the original review) are that BP targets less than the traditional target of <140-160/90-100 mmHg **do not result in** lower total mortality and total SAEs. Benefits of lower BP targets **have not been proven** to outweigh the harms in any population, including diabetes.[13] In managing hypertension, BP targets should be those used in most RCTs: <160 mmHg systolic and <90 mmHg diastolic. It is important to appreciate that even these targets cannot be achieved in at least a third of patients.

Conclusions

- Antihypertensive drug treatment modestly reduces mortality and morbidity in people ≥ 60 with moderate to severe hypertension (>160/100).
- **Low-dose thiazide diuretics are the best drug class for starting therapy.**
- In mild hypertension (140-159/90-99) antihypertensive drugs have not been proven to reduce mortality and morbidity.
- **Blood pressure treatment targets should be those used in RCTs (<140-160/90-100), as lower BP targets have not been shown to have a net health benefit.**

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The draft of this Therapeutics Letter was submitted for review to 75 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

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