



THERAPEUTICS INITIATIVE

Evidence Based Drug Therapy

Clinical Hypertension Pearls from The Cochrane Library

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The Cochrane Library's 2010 impact factor of 6.186 ranks amongst the top 10 general and internal medical journals (155 journals).

This Letter highlights 5 Cochrane systematic reviews about hypertension, which provide clear clinical evidence to direct patient care.

First-line drugs for hypertension

Published on July 8, 2009, this review reports the evidence from all randomized controlled trials (RCTs) comparing one of the 6 major drug classes, given first as part of stepped care therapy, with placebo or no treatment. It addresses the question: Which class of drugs is the best to give first-line for the management of patients with hypertension?¹

Findings: The review includes 24 RCTs involving 58,040 people. First-line low-dose thiazides reduce coronary heart disease events, ARR 1.1% [0.6, 1.5], whereas high-dose thiazides do not, ARR 0% [- 0.4, 0.5]. First-line low-dose thiazides (19,874 people) reduce mortality, ARR 1.2% [0.3, 2.0] and total cardiovascular (CV) events, ARR 3.9% [3.1, 4.7]. First-line beta-blockers (19,313 people) reduce total CV events, ARR 0.8% [0.2, 1.4], but not mortality. First-line angiotensin converting enzyme (ACE) inhibitors (6002 people) reduce mortality, ARR 2.3% [0.7, 3.8] and total CV events, ARR 4.8% [3.0, 6.6]. First-line calcium channel blockers (4,695 people) reduce total CV



events, ARR 2.3% [1.1, 3.5], but not mortality. There were no trials for other classes.

Conclusion: First-line low-dose thiazides reduce all morbidity and mortality outcomes. First-line ACE inhibitors and calcium channel blockers (CCBs) may be similarly effective but the evidence is less robust (wider confidence intervals). First-line high-dose thiazides and first-line beta-blockers are inferior to first-line low-dose thiazides. **Clinical implications:** The evidence of benefit for first-line low-dose thiazides is mostly in a primary prevention population, is of a magnitude that is meaningful and is unlikely to be overturned. Fortunately, thiazides are also inexpensive. The data for ACE inhibitors is mostly from a secondary prevention population (people with hypertension in the HOPE trial²), the explanation for the numerically higher ARRs.

Beta-blockers for hypertension

Published on-line on January 21, 2009, this review reports on all RCTs comparing first-line beta-blockers with placebo, no treatment or with other first-line classes of antihypertensive drugs.³

Findings: This review includes 13 RCTs involving 91,561 people. It confirms that as compared with placebo or no treatment, beta-blockers do not reduce mortality, but do reduce CV events, ARR 0.6% [0.1, 1.2]. In the head-to-head comparisons beta-blockers **increase** mortality as compared with thiazides, CCBs and renin-angiotensin system (RAS) inhibitors, ARI 0.6% [0.2, 1.0] and also **increase** total CV events as compared with thiazides, CCBs and RAS inhibitors, ARI 1.1% [0.6, 1.6].

Conclusion: The available evidence does not support the use of beta-blockers as first-line drugs in the treatment of hypertension. This conclusion is based on the relatively weak effect of beta-blockers to reduce stroke and the absence of an effect on coronary heart disease when compared with placebo or no treatment. More importantly, it is based on the trend towards worse outcomes in comparison with CCBs, RAS inhibitors, and thiazide diuretics. Most of the evidence for these conclusions comes from trials where atenolol was the beta-blocker used (75% of beta-blocker participants in this review).

Clinical implications: The inferior mortality and morbidity outcomes with beta-blockers make them at best a fourth-line option for hypertension. More RCTs are needed to know whether these worse outcomes are limited to atenolol or to all beta-blockers.⁶

Calcium channel blockers versus other classes of drugs for hypertension

Published on August 4, 2010, this review reports on all RCTs comparing first-line CCBs with other anti-hypertensive drugs.⁴

Findings: The review includes 18 RCTs involving 141,807 people. Mortality was not different between first-line CCBs and any other first-line antihypertensive class. CCBs reduced total CV events as compared with beta-blockers, ARR 1.5% [0.7, 2.1] but **increased** total CV events as compared with thiazides, ARI 1.0% [0.1, 1.9]. CCBs **increased** congestive heart failure as compared with thiazides, ARI 1.7% [1.1, 2.3], ACE inhibitors, ARI 1.1% [0.4, 1.8] and angiotensin receptor blockers (ARBs), ARI 1.0% [0.3, 1.8], but decreased stroke as compared with ACE inhibitors, ARR 0.6% [0.1, 1.2] and ARBs, ARR 0.6% [0.1, 1.1]

Conclusion: Thiazide diuretics are preferred first-line over CCBs to optimize reduction of cardiovascular events. The review does not distinguish between CCBs, ACE inhibitors or ARBs, but does provide evidence supporting the use of CCBs over beta-blockers. Many of the differences found in the current review are not robust and further trials might change the conclusions.

The draft of this Therapeutics Letter was submitted for review to 60 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

References

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Clinical implications: CCBs are a second or third-line option for hypertension. When CCBs are used for hypertension, physicians should advise patients that congestive heart failure is a potential adverse effect.

Treatment Blood Pressure Targets for Hypertension

Published on-line on July 8, 2009, this review reports on all RCTs comparing lower BP targets $\leq 135/85$ mmHg with standard targets $\leq 140 - 160/90 - 100$ mmHg.⁵

Findings: The review includes 7 RCTs involving 20,089 people with elevated blood pressure. Attempting to achieve "lower targets" instead of "standard targets" did not change total mortality, RR 0.99 [0.86-1.15], myocardial infarction, RR 0.90 [0.74-1.09], stroke, RR 0.99 [0.79-1.25], congestive heart failure, RR 0.88 [0.59-1.32], major cardiovascular events, RR 0.94 [0.83-1.07], or end-stage renal disease, RR 1.01 [0.81-1.27].

Conclusion: Treating patients to lower than standard BP targets, $\leq 140-160/90-100$ mmHg, does not reduce mortality or morbidity.

Clinical implications: Attempting to lower BP to less than the standard targets has not been shown in RCTs to be beneficial in general patients with elevated blood pressure, nor in hypertensive patients with diabetes or chronic renal disease.

Relaxation therapies for the management of primary hypertension in adults

Published on-line on January 21, 2009, this review reports on all RCTs comparing relaxation therapies with no active treatment, or sham therapy.⁷

Findings: The review included 25 RCTs involving 1,198 people with elevated blood pressure. In the 9 RCTs with adequate blinding, relaxation did not reduce systolic blood pressure significantly, compared with no treatment: -3.2 mmHg [-7.7 to 1.40]. Similarly in 15 trials comparing relaxation with sham therapy, the reduction in systolic blood pressure was not significant, -3.5 mmHg [-7.1 to 0.2].

Conclusion: In view of the poor quality of included trials and unexplained variation between trials, the evidence in favour of a causal association between relaxation and blood pressure reduction is weak. Some of the apparent benefit of relaxation was probably due to aspects of treatment unrelated to relaxation.

Clinical implications: Interventions designed to promote relaxation, such as biofeedback, cognitive behavioral therapy, meditation, yoga, or progressive muscle relaxation therapy, have not been proven to lower blood pressure.

RR – relative risk ARR – absolute risk reduction
ARI – absolute risk increase

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