

Cochrane for Clinicians

Putting Evidence Into Practice

Thiazide Diuretics vs. Other Antihypertensive Drug Classes

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Clinical Question

Are thiazide and thiazide-like diuretics more effective than other first-line antihypertensive drug classes in reducing mortality or cardiovascular events in patients with hypertension?

Evidence-Based Answer

There is no mortality benefit in using thiazide or thiazide-like diuretics compared with other first-line antihypertensive drug classes; however, these diuretics most likely reduce cardiovascular events (number needed to treat [NNT] = 100; 95% CI, 63 to 333) and heart failure (NNT = 84; 95% CI, 66 to 125) compared with calcium channel blockers.¹ (Strength of Recommendation [SOR]: B, based on inconsistent or limited-quality patient-oriented evidence.) Thiazide and thiazide-like diuretics reduce stroke risk compared with angiotensin-converting enzyme (ACE) inhibitors (NNT = 167; 95% CI, 100 to 1,000). (SOR: B, based on inconsistent or limited-quality patient-oriented evidence.) Thiazides are associated with fewer withdrawals and drug discontinuations due to adverse effects compared with beta blockers, calcium channel blockers, ACE inhibitors, and alpha blockers.

Practice Pointers

The primary goal of hypertension treatment is to reduce morbidity and mortality, myocardial infarction, stroke, and renal failure while minimizing the risk of harm from medical intervention.² The ideal blood pressure target for treatment continues to be debated. The 2014 Eighth Joint National Committee guidelines and 2017 American College of Cardiology/American Heart Association guidelines agree

on the drug classes that should be used as first-line therapy.^{3,4} Among the three main classes of first-line antihypertensives, thiazide or thiazide-like diuretics may have advantages over calcium channel blockers and ACE inhibitors.

This Cochrane review assessed 20 trials with more than 90,000 participants between 50 and 75 years of age.¹ Participants had comorbidities, including type 2 diabetes mellitus; the trials lasted an average of five years. Cardiovascular events were a composite clinical end point referring to myocardial infarction, stroke, or death. Most trials in this review used chlorthalidone.

This review found that, compared with ACE inhibitors, thiazides and thiazide-like diuretics resulted in little to no difference in total mortality, cardiovascular events, coronary heart disease, or heart failure. Thiazide and thiazide-like diuretics decreased the risk of stroke compared with ACE inhibitors (NNT = 167; 95% CI, 100 to 1,000). Fewer patients receiving these diuretics discontinued their regimen than patients receiving ACE inhibitors (NNT = 100; 95% CI, 71 to 167). The data comparing thiazide diuretics to angiotensin receptor blockers or renin inhibitors were inadequate.

Compared with calcium channel blockers, thiazide and thiazide-like diuretics did not reduce total mortality, strokes, or coronary heart disease. They reduced total cardiovascular events (NNT = 100; 95% CI, 63 to 333) and likely reduced heart failure (NNT = 83; 95% CI, 66 to 125).

The results of this review are consistent with recommendations from current guidelines that thiazide diuretics be considered first—as opposed to alpha blockers or beta blockers—for the reduction of total cardiovascular events, stroke, and heart failure.^{3,4} This review did not evaluate differences between the diuretics hydrochlorothiazide, chlorthalidone, indapamide, or metolazone (loop diuretic). Previous guidelines have recommended chlorthalidone because of its longer half-life and proven cardiovascular disease reduction.⁴

The practice recommendations in this activity are available at <https://www.cochrane.org/CD008161>.

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These are summaries of reviews from the Cochrane Library. This series is coordinated by Corey D. Fogleman, MD, assistant medical editor.

A collection of Cochrane for Clinicians published in *AFP* is available at <https://www.aafp.org/afp/cochrane>.

CME This clinical content conforms to AAFP criteria for CME. See CME Quiz on page 205.

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Direct Oral Anticoagulants vs. Conventional Anticoagulants for the Treatment of VTE

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Clinical Question

Are direct oral anticoagulants better than conventional anticoagulants (e.g., warfarin) for the treatment of venous thromboembolism (VTE)?

Evidence-Based Answer

Direct oral anticoagulants are as effective as conventional anticoagulants at preventing recurrent deep venous thrombosis (DVT) or pulmonary embolism (PE) and reducing all-cause mortality. Direct oral anticoagulants slightly decrease the likelihood of major bleeding compared with conventional anticoagulants in the treatment of VTE (number needed to treat [NNT] = 123 for direct thrombin inhibitors; NNT = 156 for oral factor Xa inhibitors).^{1,2} (Strength of Recommendation: A, based on consistent, good-quality patient-oriented evidence.)

Practice Pointers

VTE is when a blood clot forms in a vein. The most common types are PE and DVT. An estimated 300,000 to 600,000 cases of PE occur annually in the United States.³ Due to the life-threatening nature of VTE, effective anticoagulation is essential for treatment and mortality reduction. Conventional therapy uses unfractionated heparin, low-molecular-weight heparin, fondaparinux, and vitamin K antagonists. More recently developed anticoagulants include two forms of direct oral anticoagulants: thrombin inhibitors and Xa inhibitors. Direct oral anticoagulants have several preferable characteristics compared with conventional therapy, including a more predictable effect, less frequent monitoring or redosing, and fewer drug interactions.⁴ The authors of these Cochrane reviews sought to assess the safety and effectiveness of direct oral anticoagulants vs. conventional therapies.

Two updated Cochrane reviews initially published in 2015 examined treatments for PE and DVT.^{1,2} One Cochrane review examined therapeutic options for PE and included 10 randomized controlled trials (RCTs) with 13,073 patients.² The other Cochrane review was broader, examined treatments for DVT, and included 21 RCTs with 30,895 patients.¹

Every study from the Cochrane on PE treatment is included in the Cochrane on DVT treatment, except for one RCT that involved 114 patients.^{1,2} Both reviews examined outcomes among patients treated with oral direct thrombin inhibitors (e.g., dabigatran [Pradaxa]) or oral factor Xa inhibitors (e.g., rivaroxaban [Xarelto], apixaban [Eliquis]), compared with patients treated with conventional anticoagulants. Studies that lasted at least three months and excluded intramuscular or intravenous anticoagulation were performed in multiple countries, including the United States. The primary outcomes examined were recurrent or new VTE. The secondary outcomes included all-cause mortality and adverse effects such as major bleeding.^{1,2}

There were no differences in recurrent VTE or all-cause mortality between direct oral anticoagulants and conventional anticoagulants in the treatment of DVT or PE. The rates for these outcomes were very low in each respective arm, estimating 3 to 30 outcomes per every 1,000 patients treated.

In the Cochrane review examining the treatment of patients with DVT, there was a difference in the risk of major bleeding events favoring oral direct thrombin inhibitors (odds ratio [OR] = 0.58; 95% CI, 0.38 to 0.89; number needed to harm [NNH] = 123) and oral factor Xa inhibitors (OR = 0.63; 95% CI, 0.45 to 0.89; NNH = 156) over conventional anticoagulants.¹ The Cochrane review describing the treatment of patients with PE found no difference in the risk of major bleeding.²

The 2021 CHEST guidelines recommend direct oral anticoagulants over conventional therapy in the general patient population.⁵ Direct oral anticoagulants are as effective as conventional therapies, may decrease major bleeding events, and should be considered first-line therapy for patients with VTE.^{1,2}

The practice recommendations in this activity are available at <https://www.cochrane.org/CD010956> and <https://www.cochrane.org/CD010957>.

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the U.S. Army, the U.S. Department of Defense, or the U.S. government.

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