

All in on ARBs

Is it time to fold the ACEIs?

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Abstract

Objective To summarize the efficacy and safety of angiotensin II receptor blockers (ARBs) compared to angiotensin-converting enzyme inhibitors (ACEIs) in primary hypertension and other compelling indications, focusing on cardiovascular and renal outcomes.

Quality of evidence Relevant randomized controlled trials and systematic reviews were identified through the MEDLINE, Embase, and Cochrane Central Register of Controlled Trials databases. Additional clinical evidence was manually retrieved from the PubMed database.

Main message Inhibitors of the renin-angiotensin-aldosterone system are cornerstone therapies in the management of primary hypertension with or without comorbidities. ACEIs have traditionally been preferred by many clinicians due to their long-standing use, robust efficacy, and low cost. However, current evidence supports comparable efficacy between ARBs and ACEIs in managing primary hypertension, cardiovascular disease, heart failure, chronic kidney disease, and diabetes. Importantly, ARBs consistently demonstrate a more favourable safety profile in head-to-head trials, particularly in reducing cough and angioedema. With most agents now available as generics, ARBs are also cost comparable. That said, in patients with stage 3 to 5 chronic kidney disease, limited evidence suggests that ACEIs may confer superior renoprotective benefits. In 2022, approximately 11.3% of Canadians were prescribed an ACEI, compared with only 7.7% prescribed an ARB. These findings suggest a disconnect between current prescribing patterns and current evidence, warranting reconsideration of ARBs as a preferred first-line option in many patients.

Conclusion While ARBs and ACEIs demonstrate comparable cardiovascular and renal efficacy across hypertension and other compelling indications, ARBs show a substantially better safety profile in head-to-head comparisons, supporting their broader use in clinical practice.

Editor's key points

- ▶ Despite comparable efficacy and superior safety, angiotensin-converting enzyme inhibitors (ACEIs) remain more commonly prescribed than angiotensin II receptor blockers (ARBs), likely due to greater familiarity and longer market presence.
- ▶ ARBs demonstrate similar effectiveness to ACEIs across most compelling indications, while offering a superior safety profile and similar cost aside from ramipril.
- ▶ Evidence directly comparing ACEIs and ARBs in nondiabetic chronic kidney disease is limited, reducing certainty in that population.
- ▶ Much of the head-to-head evidence between ACEIs and ARBs originates from 3-arm trials that also evaluate combination therapy.

Points de repère du rédacteur

- ▶ En dépit d'une efficacité comparable et d'un profil d'innocuité supérieur, les antagonistes du récepteur de l'angiotensine II (ARA) demeurent moins souvent prescrits que les inhibiteurs de l'enzyme de conversion de l'angiotensine (IECA), probablement en raison de la plus grande popularité et d'une présence plus longue sur le marché de ces derniers.
- ▶ Il a été démontré que les ARA avaient une efficacité semblable à celle des IECA pour la plupart des indications les plus impérieuses, tout en offrant un profil de sécurité supérieur et des coûts similaires, sauf en ce qui concerne le ramipril.
- ▶ Les données probantes comparant directement les IECA et les ARA dans les cas de néphropathie chronique non diabétique sont limitées, ce qui réduit la certitude dans cette population.
- ▶ La majorité des données probantes dans des comparaisons directes entre les IECA et les ARA proviennent d'essais dans 3 groupes qui évaluaient aussi une thérapie combinée.

En faveur des ARA

Est-ce le temps de mettre les IECA de côté?

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Résumé

Objectif Résumer l'efficacité et l'innocuité des antagonistes des récepteurs de l'angiotensine II (ARA) par rapport à celles des inhibiteurs de l'enzyme de conversion de l'angiotensine (IECA) dans les cas d'hypertension primaire et d'autres indications importantes, en insistant sur les issues cardiovasculaires et rénales.

Qualité des données Des revues systématiques et des essais contrôlés randomisés pertinents ont été recensés dans les bases de données MEDLINE, Embase et du Cochrane Central Register of Controlled Trials. D'autres données cliniques probantes ont été extraites manuellement de la base de données PubMed.

Message principal Les inhibiteurs du système rénine-angiotensine-aldostérone constituent des thérapies fondamentales dans la prise en charge de l'hypertension primaire avec ou sans comorbidités. Les IECA ont traditionnellement été privilégiés par de nombreux cliniciens en raison de leur utilisation de longue date, de leur efficacité robuste et de leur coût peu élevé. Par ailleurs, des données probantes actuelles étayaient une efficacité comparable entre les ARA et les IECA dans la prise en charge de l'hypertension primaire, de la maladie cardiovasculaire, de l'insuffisance cardiaque, de la néphropathie chronique et du diabète. Avant tout, les ARA démontrent uniformément un profil de sécurité plus favorable dans des essais de comparaison directe, en particulier pour réduire la toux et l'angioœdème. Étant donné que la plupart des agents sont maintenant disponibles sous formes génériques, les ARA sont aussi comparables sur le plan des coûts. Cela étant, chez les patients atteints d'une néphropathie chronique de stade 3 à 5, des données probantes limitées portent à croire que les IECA procureraient des bienfaits supérieurs sur le plan de la protection rénale. En 2022, environ 11,3 % des Canadiens ont reçu une prescription d'IECA par rapport à seulement 7,7 % à qui on a prescrit un ARA. Ces constatations mettent l'accent sur une déconnexion entre les habitudes actuelles de pratique et les données probantes récentes, ce qui mériterait de reconsidérer les ARA comme une option de première intention à privilégier chez de nombreux patients.

Conclusion Si les ARA et les IECA démontrent une efficacité cardiovasculaire et rénale comparable pour l'hypertension et d'autres indications impérieuses, les ARA ont un profil de sécurité considérablement meilleur dans des comparaisons directes, ce qui étaye une utilisation plus généralisée dans la pratique clinique.

Inhibitors of the renin-angiotensin-aldosterone system (RAAS) are fundamental therapies in the management of primary hypertension across multiple guidelines.¹⁻⁴ Among these, angiotensin-converting enzyme inhibitors (ACEIs) have traditionally been preferred as first-line agents owing to their well-established efficacy, long history of use, and low cost.⁵ In contrast, angiotensin II receptor blockers (ARBs) are often positioned as alternatives, typically reserved for patients who are intolerant to ACEIs. This clinical mindset has persisted over time and is reflected in the recently published 2025 Hypertension Canada guidelines,¹ which position ARBs as equivalent but not superior to ACEIs for initial therapy.

In 2022, approximately 11.3% of Canadians were prescribed an ACEI, compared with only 7.7% prescribed an ARB.⁶ There is growing consensus that ARBs offer comparable cardiovascular and renal protection while offering a more favourable safety profile.¹⁻⁴ With the widespread availability of generics, cost is no longer a barrier to their use. As such, it is timely to re-evaluate the role of ACEIs as the default RAAS inhibitor in primary care.

This clinical review summarizes the best available evidence comparing ARBs and ACEIs in adults with primary hypertension, with a focus on cardiovascular and renal outcomes. In addition, we explore their relative benefits in other compelling indications. Safety, tolerability, and cost considerations are also discussed to promote evidence-based prescribing decisions.

Quality of evidence

The MEDLINE, Embase, and Cochrane Central Register of Controlled Trials databases were searched for comparative, head-to-head randomized controlled trials (RCTs) and systematic reviews (SRs) evaluating ACEIs versus (vs) ARBs in adults with primary hypertension and common comorbidities (Supplementary Data, available from **CFPlus***). Eligible studies reported clinically meaningful cardiovascular or renal outcomes. Safety outcomes were also assessed. Additional studies were identified through grey literature searches using the PubMed database, Google, and the references of included papers.

Main message

Are ARBs as effective as ACEIs in managing primary hypertension?

Bottom line: In adults with primary hypertension, ARBs and ACEIs show no significant differences in all-cause mortality, cardiovascular and renal outcomes, or blood pressure (BP) control (level of evidence I).

Evidence: Of the 5 SRs found, 2 directly compared ACEIs and ARBs across several clinically meaningful

outcomes in patients with primary hypertension. Two were excluded for not focusing on head-to-head comparisons, and 1 was excluded as it was an outdated version of a retained meta-analysis.

A 2014 Cochrane review evaluated 9 RCTs (11,007 participants) directly comparing ARBs and ACEIs in individuals with primary hypertension, defined as a BP above 140/90 mm Hg.⁷ Eligible trials had a minimum duration of 1 year. The SR showed no difference between ARBs and ACEIs in all-cause mortality (5 RCTs, 10,248 participants; 11.1% vs 11.6%; risk ratio [RR]=0.98; 95% confidence interval [CI] 0.88 to 1.10), cardiovascular mortality (4 RCTs, 9747 participants; 6.9% vs 7.1%; RR=0.98; 95% CI 0.85 to 1.13), and cardiovascular events (3 RCTs, 5499 participants; 19.1% vs 17.9%; RR=1.07; 95% CI 0.96 to 1.19).⁷

A more inclusive SR, primarily of RCTs with at least 12 weeks of follow-up, found no difference in long-term BP control (70 RCTs, 7 non-RCTs; 26,170 participants) or monotherapy success (26 RCTs, 3 non-RCTs; 16,609 participants).⁸ Low-quality evidence also suggested similar efficacy for all-cause mortality and cardiovascular events.

No renal outcomes were evaluated in either SR. In a post hoc analysis of the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), the largest study included in the Cochrane review, no difference was observed between telmisartan and ramipril among patients with hypertension (11,780 participants) for the primary renal outcome of dialysis, doubling of serum creatinine level, or death.⁹

Additionally, a large multinational cohort study supports comparable efficacy for myocardial infarction (MI), stroke, heart failure (HF), and composite cardiovascular events.¹⁰

Comments: Several key trials in patients with HF or MI, namely Optimal Therapy in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL),¹¹ the Losartan Heart Failure Survival Study (ELITE II),¹² and Valsartan in Acute Myocardial Infarction (VALIANT),¹³ were excluded from the Cochrane review because hypertension subgroup data could not be extracted. ONTARGET,¹⁴ which compared telmisartan and ramipril in high-cardiovascular-risk patients, was also excluded from the cardiovascular events analysis for this reason. As for other outcomes, a large proportion of the sample size in the meta-analysis was drawn from the ONTARGET trial, potentially limiting the generalizability of the findings.⁷

Do ARBs offer comparable cardiovascular protection to ACEIs in patients with cardiovascular disease?

Bottom line: In adults with cardiovascular disease (CVD), ARBs and ACEIs demonstrate no significant differences in all-cause mortality, cardiovascular outcomes, and hospitalizations (level of evidence I).

Evidence: No SRs of RCTs were found directly comparing ACEIs and ARBs in patients with CVD, but 3 major industry-funded RCTs addressed this question.^{11,13,14}

*Supplementary Data are available from <https://www.cfp.ca>. Go to the full text of the article online and click on the **CFPlus** tab.

ONTARGET compared telmisartan and ramipril in high-risk patients, of whom 74.5% had established CVD (15,627 participants). Over a median follow-up of 56 months, subgroup analysis found no differences in composite outcomes of cardiovascular death, MI, stroke, or hospitalizations for HF.¹⁴

The VALIANT trial involved adults post-MI with left ventricular dysfunction, HF, or both (9818 participants). After 24 months, valsartan and captopril showed no difference in all-cause mortality (19.9% vs 19.5%), cardiovascular mortality (16.8% vs 16.9%), and hospitalizations for MI or HF (18.7% vs 19.3%). Valsartan was noninferior in both intent-to-treat and per-protocol analyses. Subgroup analyses demonstrated similar results regardless of HF status, with a trend favouring valsartan in patients without HF (7743 participants).¹³

The OPTIMAAL trial involved adults post-MI with HF (5477 participants). After 2.7 years, losartan and captopril showed no difference in all primary outcomes, including all-cause mortality (18.2% vs 16.4%), sudden cardiac death or resuscitated cardiac arrest (8.7% vs 7.4%), and myocardial reinfarction (14.0% vs 13.9%). Prespecified secondary outcomes showed no differences, aside from cardiovascular death, which was significantly higher with losartan (15.3% vs 13.3%; relative risk=1.17; 95% CI 1.01 to 1.34; number needed to harm=50). Subgroup analysis suggested similar efficacy regardless of HF status, but a trend favouring captopril in patients without HF (1060 participants).¹¹

Comments: Although a substantial number of patients in the OPTIMAAL and VALIANT trials had HF,^{11,13} subgroup analyses showed consistent results regardless of HF status, suggesting comparable efficacy between ACEIs and ARBs in CVD. A meta-analysis would likely improve the generalizability of our findings.

How do ARBs compare to ACEIs in reducing morbidity and mortality in patients with HF with reduced ejection fraction?

Bottom line: In adults with HF with reduced ejection fraction (HFrEF), ARBs and ACEIs demonstrate no significant differences in mortality, cardiovascular events, or hospitalizations (level of evidence I).

Evidence: At least 2 SRs evaluated RCTs directly comparing ACEIs and ARBs in patients with HFrEF.^{15,16} One focused on all-cause and cardiovascular mortality (minimal study duration of 12 months), while the other, a Cochrane review (minimal study duration of 4 weeks) also included other clinically meaningful outcomes. Both incorporated the ELITE II trial,¹² a large comparative study in HF.

In both reviews, ARBs and ACEIs offered similar reductions in all-cause mortality (11% to 17% vs 13% to 17%) and cardiovascular mortality (12% to 15% vs 11% to 15%).^{15,16} The Cochrane review found no differences in MI or stroke based on data from Evaluation of Losartan in the Elderly Study (ELITE)¹⁷ and ELITE II.^{12,15}

Hospitalization rates were also comparable. In 3 RCTs (N=4310), there were no differences between ARBs and ACEIs in all-cause hospitalizations (36.5% vs 37.6%) or HF-related hospitalizations (14.8% vs 15.6%).¹⁶

Comments: The SRs differed in their definition of HFrEF. The Cochrane review used an ejection fraction threshold of 40%, aligning with current practice, while the second meta-analysis used 45%. Most of the data included in the second review originated from the VALIANT trial, as opposed to the Cochrane review, which did not include them. This may impede the generalizability of the second SR. However, the impact on clinical interpretation is likely minimal given the consistency of findings across both studies.

Are ARBs as effective as ACEIs in chronic kidney disease?

Bottom line: In adults with chronic kidney disease (CKD), with or without diabetes, ARBs and ACEIs show similar efficacy in all-cause mortality and cardiovascular or renal outcomes. However, based on very limited data, ACEIs may offer superior renal benefits in stage 3 to 5 CKD (level of evidence I).

Evidence: Two network meta-analyses (44 to 119 RCTs; 42,319 to 64,768 participants) compared ACEIs and ARBs for a minimum duration of 6 months in patients with CKD.^{18,19} One focused on stage 3 to 5 non-dialysis CKD.¹⁸ Head-to-head comparisons were limited.

All-cause mortality was similar in general CKD in pairwise (odds ratio [OR]=1.02; 95% CI 0.36 to 2.91) and network (OR=0.90; 95% CI 0.69 to 1.17) analyses.¹⁹ In stage 3 to 5 CKD, ACEIs were significantly superior in network analysis (OR=0.76; 95% CI 0.66 to 0.91), but not pairwise (OR=1.60; 95% CI 0.15 to 16.75).¹⁸

For cardiovascular mortality, no difference was found in general CKD per both pairwise (OR=0.61; 95% CI 0.10 to 3.71) and network (OR=0.80; 95% CI 0.56 to 1.14) analyses.¹⁹ In advanced CKD, ACEIs significantly reduced cardiovascular mortality in network analysis (OR=0.63; 95% CI 0.46 to 0.86), but not pairwise (OR=1.00; 95% CI 0.41 to 2.46).¹⁸

Cardiovascular event rates were comparable in both studies (OR=1.09; 95% CI 0.91 to 1.31 and OR=0.88; 95% CI 0.73 to 1.07). Pairwise analyses showed no differences.^{18,19}

In general, kidney failure rates were similar between ACEIs and ARBs in pairwise (4 RCTs, 717 participants; 17.0% vs 15.9%) and network (OR=0.89; 95% CI 0.66 to 1.19) analyses.¹⁹ In stage 3 to 5 CKD, ACEIs significantly reduced renal events in both pairwise (OR=0.71; 95% CI 0.52 to 0.97) and network analyses (OR=0.71; 95% CI 0.52 to 0.96).¹⁸

A post hoc ONTARGET analysis, not included in either meta-analysis, found no renal outcome differences among patients with an estimated glomerular filtration rate of less than 60 mL/min/1.73 m².⁹ A separate meta-analysis (12 RCTs, 131 to 3290 participants) focusing on albuminuria found no renal or cardiovascular differences between ACEIs and ARBs.²⁰

Comments: These findings are largely based on indirect comparisons, which limit the strength of the evidence. While the available data suggest that ACEIs may be more effective in reducing renal outcomes in people with stage 3 to 5 CKD, this should be interpreted with caution. Subgroup analyses in nondiabetic CKD were limited. As a result, the presented data do not account for diabetes as a comorbidity.

What is the comparative efficacy of ARBs vs ACEIs in patients with diabetes mellitus?

Bottom line: In adults with diabetes, ARBs and ACEIs demonstrate no significant differences in all-cause mortality, cardiovascular outcomes, or renal outcomes (level of evidence I).

Evidence: A 2024 Cochrane review assessing cardiovascular and renal outcomes in patients with diabetes and albuminuria included 109 RCTs of at least 6 months' duration, of which 24 directly compared ARBs with ACEIs. Among these, 15 RCTs (1739 participants) found no difference in all-cause mortality (3.4% vs 3.1%), 13 RCTs (1606 participants) found no significant difference in cardiovascular death (1.1% vs 1.0%), and 3 RCTs (867 participants) found no significant difference in kidney failure (2.9% vs 5.5%). Albuminuria-related outcomes were also similar after 1 year. In 6 RCTs (612 participants), all-cause withdrawal rates were comparable (15% vs 17.3%).²¹

A 2016 network meta-analysis of 71 RCTs of at least 12 months' duration studying patients with diabetes supports these findings. In pairwise analysis, 5 RCTs (13,480 participants) showed no difference between ACEIs and ARBs in major cardiovascular outcomes (18.1% vs 16.5%), 3 RCTs (10,976 participants) found no difference in composite renal outcomes (13.9% vs 13.1%), and 6 RCTs (13,670 participants) showed no difference in all-cause mortality (14.5% vs 13.8%).²²

Comments: The 2024 Cochrane review graded the evidence as low quality, largely due to unclear allocation concealment and lack of blinding in many included trials.²¹ Additionally, the low event rates necessitated the use of composite outcomes, which assume all components are equally influenced by treatment.

Are ARBs better tolerated than ACEIs?

Bottom line: ARBs demonstrate a significantly better safety profile than ACEIs, particularly for cough, angioedema, and withdrawals due to adverse events (WDAEs) (level of evidence I).

Evidence: At least 1 meta-analysis (9 RCTs, 11,007 participants) assessed WDAEs. Over a mean duration of 4.1 years, ARBs showed significantly fewer WDAEs (9.5% vs 11.3%; number needed to treat [NNT]=55), mainly due to ACEI-related cough.⁷

A separate SR (7 RCTs, 34,381 participants, minimal duration of 8 weeks) including major trials (ELITE,

Table 1. Approximate 90-day costs of ACEIs and ARBs

GENERIC NAME	APPROXIMATE 90-DAY COST, \$*
ACEIs	
• Ramipril	10
• Perindopril	25
ARBs	
• Valsartan	20
• Telmisartan	20
• Candesartan	20

ACEI—angiotensin-converting enzyme inhibitor, ARB—angiotensin II receptor blocker.
*Excluding pharmacists' professional fees. Cost may vary between provinces. Data from Manitoba Health.²⁵

ONTARGET, OPTIMAAL, VALIANT) reported lower angioedema risk with ARBs (0.19% vs 0.44%; NNT=400).²³

A meta-analysis involving 81 RCTs directly comparing ARBs and ACEIs found a significantly lower rate of cough among 64,997 participants (1.8% vs 6.5%; NNT=22).²⁴

Are ARBs a cost-effective alternative to ACEIs in the management of hypertension and related comorbidities?

Bottom line: Historically, ACEIs were developed and approved earlier than ARBs, leading to earlier patent expirations and broader availability of low-cost generics. This cost advantage contributed to their favourable role as a first-line RAAS inhibitor. However, with many ARBs now available in generic form, cost is no longer a substantial barrier to their use in primary hypertension (Table 1).²⁵

Conclusion

Given robust head-to-head evidence demonstrating comparable efficacy and a more favourable safety profile, ARBs represent a compelling first-line option for most indications, except possibly in CKD. Future studies should focus on patients with renal failure as data in this population are scarce (level of evidence I). Furthermore, in patients with long-standing ACEI therapy and no safety concerns, a switch is likely not necessary (level of evidence I).

With costs now largely equivalent due to generic availability, a shift toward ARB prescribing may improve adherence, minimize adverse effects, and better align clinical practice with current evidence. Ramipril may be better suited for patients with financial challenges (level of evidence I).

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Contributors

All authors contributed to conducting the literature review and to preparing the manuscript for submission.

Competing interests

None declared

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This article has been peer reviewed.

Can Fam Physician. 2026 Mar;72(3):167-72.

doi: [10.46747/cfp.7203167](https://doi.org/10.46747/cfp.7203167)