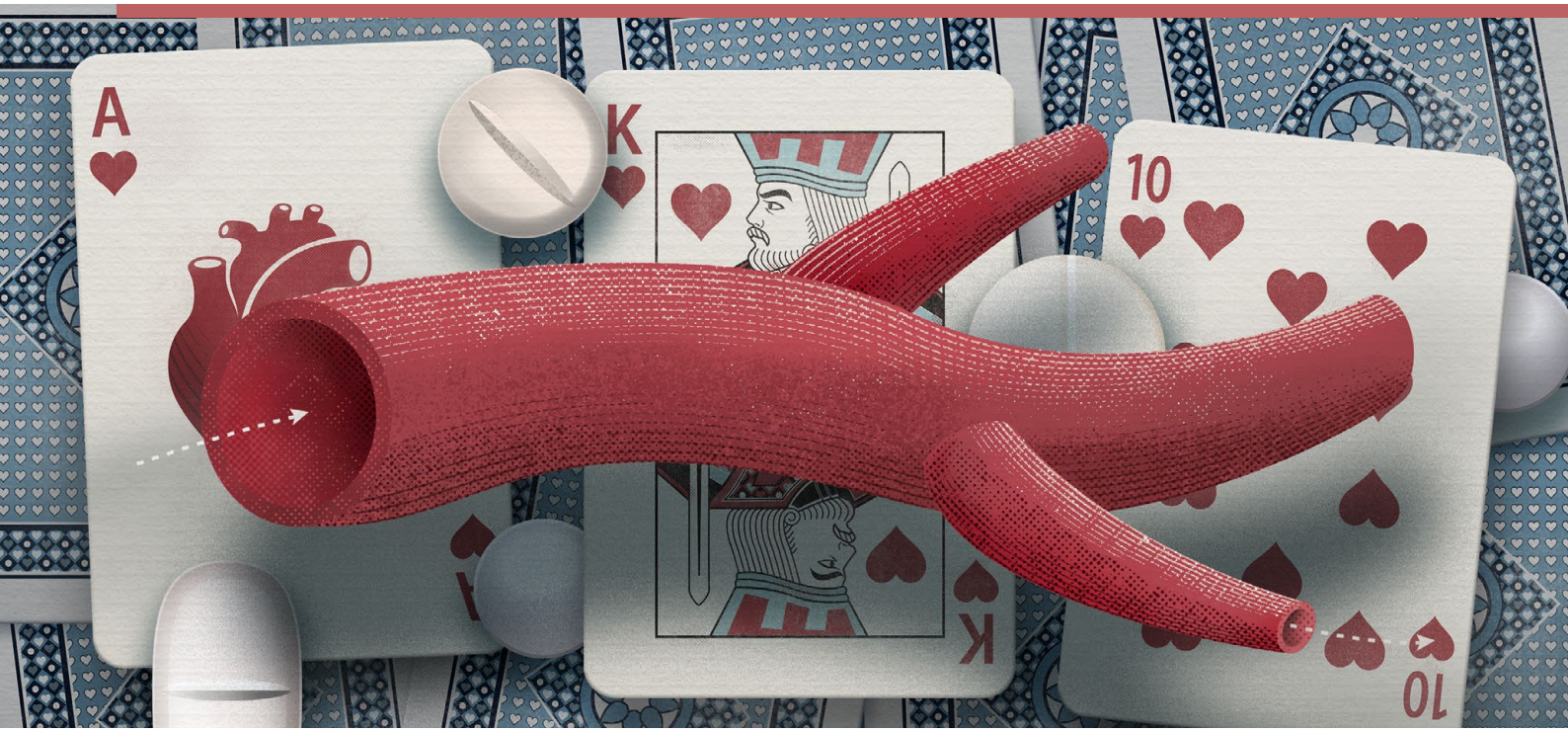


Prescribing ACE inhibitors: time to reconsider old habits

Prescribers in New Zealand are highly reliant on cilazapril as their "go-to" ACE inhibitor, but this prescribing is out of step with many other countries where cilazapril is infrequently used, such as Australia and the United Kingdom. From 1 May, 2021, cilazapril will no longer be funded for new patients. While cilazapril may be prescribed by endorsement to existing patients, this should be used as an opportunity to proactively switch patients to another ACE inhibitor, angiotensin II receptor blocker (ARB) or another medicine. Guidelines that recommend use of an ACE inhibitor support the use of any medicine in this class (or often also an ARB) as they are regarded as having similar benefits and risks.

KEY PRACTICE POINTS:

- In New Zealand, approximately 60% of people taking angiotensin-converting enzyme (ACE) inhibitors are still being prescribed cilazapril. The high use of cilazapril in New Zealand, and low use internationally, leaves New Zealand vulnerable to supply issues.
- From 1 May, 2021, cilazapril will no longer be funded for new patients. Prescribers will need to endorse any new prescriptions for cilazapril for patients who were taking this medicine prior to 1 May, 2021, but ultimately all patients will need to switch to a different ACE inhibitor, angiotensin II receptor blocker (ARB) or another medicine.
- A range of funded ACE inhibitors are available:
  - The benefits and risks associated with ACE inhibitors are similar across the class
  - Most ACE inhibitors can be taken as once-daily tablets; when changing treatment, patients can discontinue one ACE inhibitor and initiate another the following day
  - Contraindications, cautions and medicines interactions are similar for all ACE inhibitors
- ARBs are a first-line alternative to ACE inhibitors, with comparable outcomes for treating hypertension, chronic kidney disease and diabetic nephropathy, and are often better tolerated

This is a revision of a previously published article. What's new for this update:

- Change to cilazapril funding status – no longer funded for new patients, existing patients must have prescriptions endorsed (from 1 May, 2021)
- Cilazapril with hydrochlorothiazide has been discontinued
- ARBs are a first-line alternative to ACE inhibitors for many indications

Use of cilazapril in New Zealand is still very high

Approximately half a million people in New Zealand are prescribed an angiotensin-converting enzyme (ACE) inhibitor, and of these, approximately 60% are still being prescribed cilazapril, despite recommendations in 2018 to consider switching due to potential supply issues.[1,2] Although a range of ACE inhibitors are funded, familiarity means cilazapril remains a favoured choice by many clinicians. However, there is only one manufacturer of the active pharmaceutical ingredient for cilazapril internationally, increasing our vulnerability to supply issues; global manufacturing and shipping issues due to the COVID-19 pandemic have further emphasised this risk. Cilazapril is used infrequently or not at all in other countries such as Australia and the United Kingdom.[3,4] Perindopril and lisinopril (both fully funded in New Zealand) are among the most frequently prescribed ACE inhibitors overseas.[4,5]

The funding status of cilazapril is changing

To reduce the reliance on cilazapril in the New Zealand market, and therefore protect against supply issues, PHARMAC has developed a multi-year plan to proactively manage switching people to an alternative treatment. From 1 May, 2021, cilazapril will no longer be funded for new patients. Consider whether patients already taking cilazapril can be switched to another ACE inhibitor or to an angiotensin II receptor blocker (ARB) at their next prescription renewal (see: "Could this patient take an angiotensin II receptor blocker (ARB) instead of an ACE inhibitor?"). Any patient who is unable to change immediately will need to have their prescription for cilazapril endorsed after 1 May, 2021.

Medicine changes are often associated with increased burden on primary care and potentially increased costs to patients. The timeframe for this change (i.e. cilazapril is still currently available if needed) allows practices to establish a strategy for managing the switch in a way that minimises extra demand on prescribers.

For further information, see: **https://pharmac.govt.nz/medicine-funding-and-supply/medicine-notices/cilazapril/**

ACE inhibitors are prescribed for a variety of indications

ACE inhibitors are generally prescribed in primary care for:

- Hypertension; either an ACE inhibitor, ARB, calcium channel blocker (CCB) or thiazide diuretic are recommended as first-line options*. An ACE inhibitor or ARB is preferred for patients with, or at high risk of, diabetes.[6]
- Heart failure with reduced ejection fraction; an ACE inhibitor is typically initiated alongside a diuretic and beta blocker.[7,8] ACE inhibitors may be used in some patients with heart failure with preserved ejection fraction, e.g. patients with concurrent hypertension.
- Following a myocardial infarction in order to reduce the risk of heart failure, re-infarction and cardiovascular mortality; lisinopril and perindopril are approved for this indication.[9,10]
- Chronic kidney disease; either an ACE inhibitor or ARB are recommended first-line (unapproved indication for both classes)[11]
- Diabetic nephropathy[12]; either an ACE inhibitor or ARB are recommended first-line (unapproved indication for most ACE inhibitors† and all ARBs)

* In people of African or Caribbean ethnicity with type 2 diabetes, an ARB is preferred to an ACE inhibitor due to a risk of angioedema; for those without diabetes, a CCB is recommended first-line[6]

† Captopril is approved for the treatment of diabetic nephropathy in type 1 diabetes, but is only funded in a liquid formulation for children aged under 12 years.

There are a range of funded ACE inhibitors

ACE inhibitors funded in New Zealand are: cilazapril, enalapril, lisinopril, perindopril and quinapril (Table 1). Captopril is available in an oral liquid formulation subsidised for children aged < 12 years. A funded combination formulation of quinapril with hydrochlorothiazide is also available; the cilazapril with hydrochlorothiazide combination formulation has been discontinued (see link below).

If guidelines recommend prescribing an ACE inhibitor, any of these options can be used as ACE inhibitors are generally recommended as a class, without specifying individual medicines.[6,7,9,13] In fact, there is more evidence in support of ACE inhibitors such as enalapril, lisinopril and perindopril, rather than cilazapril, as these are the medicines used in clinical trials which form the basis of guideline recommendations. This is an important point to highlight to patients who may be concerned about switching medicines.

For further information on the discontinuation of cilazapril with hydrochlorothiazide, see: **https://pharmac.govt.nz/medicine-funding-and-supply/medicine-notices/cilazapril/cilazapril-with-hydrochlorothiazide-discontinuation/**

No differences between adverse effects

There is no evidence of any difference in effectiveness or rates of adverse effects between ACE inhibitors when used for heart failure or hypertension. The available research has found that differences are not statistically significant, findings are not consistent or patient risk factors that affect morbidity and mortality have not been taken into account.[14–18]

Other factors that can influence prescribing decisions, such as medicines interactions, contraindications, and dose reductions in renal impairment, are similar for all members of the ACE inhibitor class.[10]

Titration and dosing are similar

Most of the subsidised ACE inhibitors are available in three tablet sizes, allowing for titration and adjustments to dosing (Table 1). All ACE inhibitors require titration to effect over the same timeframe.[10]

Once-daily medicines are recommended where possible to make dosing and adherence simpler for patients. Once-daily dosing is possible with any of the funded ACE inhibitors, although quinapril and enalapril are usually dosed twice daily in patients with chronic heart failure and quinapril may be dosed twice daily in some patients with hypertension.[10]

Combination tablets containing quinapril are available in two different doses, allowing for greater flexibility in dosing of the ACE inhibitor component of a combination tablet.

A guide for initiating and titrating ACE inhibitors for patients with heart failure is available from: **http://www.saferx.co.nz/assets/Documents/c4aeb520bc/ACE_Inhibitor_titration.pdf**

Table 1: Funded ACE inhibitors and ARBs, available tablet strength and recommended doses.[10] N.B. For further information on ARBs, see: "Could this patient take an angiotensin II receptor blocker (ARB) instead of an ACE inhibitor?"

Tablet strength		Diuretic combination tablets	Patients with hypertension		Patients with heart failure	
			Starting dose†	Typical maintenance dose†	Starting dose†	Typical maintenance dose†
ACE inhibitors						
Cilazapril*	0.5 mg 2.5 mg 5.0 mg		0.5–1.0 mg, once daily	2.5–5 mg, once daily	0.5 mg, once daily	5 mg, once daily
Enalapril‡	5 mg 10 mg 20 mg		5 mg, once daily	20 mg, once daily	2.5 mg, once daily	10 mg, twice daily**
Lisinopril	5 mg 10 mg 20 mg		2.5–10 mg, once daily	20 mg, once daily	2.5 mg, once daily	20 mg, once daily
Perindopril	2 mg 4 mg		2–4 mg, once daily	4–8 mg, once daily	2 mg, once daily	8 mg, once daily§
Quinapril‡	5 mg 10 mg 20 mg	quinapril 10 mg + hydrochlorothiazide 12.5 mg quinapril 20 mg + hydrochlorothiazide 12.5 mg	2.5–10 mg, once daily	20–40 mg, daily in one or two divided doses	2.5 mg, twice daily	10 mg, twice daily**
ARBs						
Candesartan	4 mg 8 mg 16 mg 32 mg		4–8 mg, once daily	8 mg, once daily	4 mg, once daily	32 mg, once daily
Losartan	12.5 mg 25 mg 50 mg 100 mg	losartan 50 mg + hydrochlorothiazide 12.5 mg	25–50 mg, once daily	50 mg, once daily	12.5 mg, once daily	150 mg, once daily

* From 1 May, 2021, endorsement will be required for funded treatment; new patients will not be able to be initiated on cilazapril

† Starting and maintenance doses depend on the condition being treated and the patient's response to treatment. All ACE inhibitors are titrated at the same rate. Lower doses are recommended for patients with renal impairment for most ACE inhibitors, and lower initial doses for older patients; see NZF for further details: **www.nzf.org.nz/nzf_1240** Lower ARB doses are recommended for patients with hepatic or renal impairment, and lower initial doses for patients aged over 75 years; see NZF for further details: **www.nzf.org.nz/nzf_1240**

** Can be once daily if tolerated

‡ Higher doses, e.g. 40 mg daily, may be indicated for some patients, such as for those with co-existing hypertension

§ N.B. this dose is recommended in the NZF, but is not specified in the manufacturers datasheet.

Changing between ACE inhibitors or between an ACE inhibitor and ARB

When changing treatment, patients can discontinue one ACE inhibitor and initiate a different ACE inhibitor or an ARB at a comparable dose (Table 1) the following day. Although ACE inhibitors are regarded as clinically equivalent, individual patients may respond differently. Patients should ideally be followed up one to two weeks after initiating a new ACE inhibitor; assess blood pressure, creatinine and electrolytes and enquire about symptoms of adverse effects, such as hypotension or cough.[19]

Patient information sheets for subsidised ACE inhibitor and ARB medicines are available from:

- The NZF: **www.nzf.org.nz/nzf_70421**
- Health Navigator: **https://www.healthnavigator.org.nz/medicines/a/ace-inhibitors/** and **https://www.healthnavigator.org.nz/medicines/a/angiotensin-receptor-blockers-arbs/**

Prescribing points for ACE inhibitors

All ACE inhibitors should be started at a low dose and titrated to effect over a number of weeks, with the same rate of titration regardless of which ACE inhibitor is prescribed.[20] Consider lower initial dosing in patients at increased risk of adverse effects, such as older, frail people.

The same contraindications apply to all ACE inhibitors. They are contraindicated in pregnancy (as are ARBs) and can cause fetal malformations from exposure in the first trimester.[10] In females of childbearing age, discuss contraception options and whether another treatment option may be more appropriate, e.g. a CCB for patients with hypertension. There is limited data on the use of ACE inhibitors in breast-feeding.[10] ACE inhibitors should not be used in patients with a known hypersensitivity, e.g. a previous episode of angioedema while using an ACE inhibitor (see "Adverse effects" below)*.[10]

The same risks of medicine interactions apply to all ACE inhibitors, and there is no reason to favour one over another on the basis of co-prescribed medicines.[10]

In patients with renal impairment, lower initial and maximum doses are recommended for all ACE inhibitors; see NZF for details: **www.nzf.org.nz/nzf_1240.**

In patients with hepatic impairment, the pharmacodynamic response and blood levels of ACE inhibitors may be altered. ACE inhibitors should be initiated at low doses with careful monitoring in these patients.[21]

* Patients who experience angioedema while using an ACE inhibitor may be able to use an ARB without a recurrence of angioedema (see: "Could this patient take an angiotensin receptor blocker (ARB) instead of an ACE inhibitor?")

Monitoring for adverse effects

Monitoring patients for the development of adverse effects is recommended during initiation of treatment, after adjusting doses or changing the type of ACE inhibitor (Table 2). After the maximum tolerated dose has been reached, the frequency of monitoring can be reduced, guided by the condition being treated, co-morbidities and the patient's risk of developing hypotension or renal impairment.[6] For example, patients with heart failure may require follow-up after two weeks if their clinical condition changes, but patients with stable hypertension and a stable medicine regimen may only require follow-up every six months or more.[7]

Table 2: Recommended monitoring for patients taking ACE inhibitors[19, 22]

Monitoring recommended	Prior to initiation	One to two weeks after dose adjustments or changing ACE	After titration to maximum tolerated dose
■ Measure blood pressure	✓	✓	Depending on patient characteristics; at least annually
■ Ask patients about symptoms of hypotension or adverse effects	–	✓	
■ Request tests for: – Creatinine – Electrolytes	✓	✓	

A dry, irritating cough is the most common adverse effect associated with the use of any ACE inhibitor. In a meta-analysis of approximately 200,000 people taking enalapril, the incidence of cough was 11%, with 3% of people withdrawing from treatment due to cough.[23] Clinical trials have found rates of cough were two and half times higher in people of Asian ethnicity compared to European ethnicity.[23] In patients who find the cough problematic, temporarily withdrawing treatment and then re-challenging with the same or another ACE inhibitor is an option, but in practice patients are often switched to an ARB (See: "Could this patient take an angiotensin II receptor blocker (ARB) instead of an ACE inhibitor?").

A decline in renal function is associated with the use of ACE inhibitors and ARBs. Blocking the effects of angiotensin II, either through the use of ACE inhibitors or ARBs, reduces glomerular pressure and causes a reduction in glomerular filtration rate due to dilation of the efferent (post-glomerular) blood vessels.[24] Some degree of increase in serum creatinine is likely, however, changes may resolve with continued treatment and withdrawing the ACE inhibitor is not always necessary (Table 3). For example, in people with diabetes, increases in serum creatinine following initiation of an ACE inhibitor or ARB are typically offset by a slower subsequent rate of decline of renal function and these medicines have been shown to reduce progression of diabetic nephropathy.[25] Most patients will not have increases in serum creatinine that necessitate withdrawal of treatment. In the United Kingdom, for example, only approximately 2% of people initiating an ACE inhibitor or ARB had an increase of creatinine levels of 30% or more in the two months after initiation.[26]

Combined use of ACE inhibitors or ARBs with other medicines which influence renal function, such as non-steroidal anti-inflammatory medicines (NSAIDs) or diuretics, can increase the risk of acute kidney injury.

For further information on avoiding the risk of acute kidney injury when prescribing ACE inhibitors or ARBs, see: "Avoiding the triple whammy in primary care: ACE inhibitor/ARB + diuretic + NSAID", available from: **www.bpac.org.nz/2018/triple-whammy.aspx**

The use of ACE inhibitors can increase serum potassium levels. Monitoring potassium levels is recommended, with management depending on the extent of change. In clinical trials, 1–5% of people using an ACE inhibitor had their serum potassium level increase to > 5.5 mmol/L.[27, 28] A typical increase is around 0.1–0.2 mmol/L, which does not require intervention.[24] To minimise the risk of hyperkalaemia while taking an ACE inhibitor, advise patients to avoid other medicines which cause an elevation of potassium levels, such as NSAIDs, and salt substitutes high in potassium, e.g. Lo Salt.[20]

Table 3: An example of testing and monitoring for adverse effects in patients taking ACE inhibitors for heart failure; thresholds for intervention may differ in local guidance [19, 20]

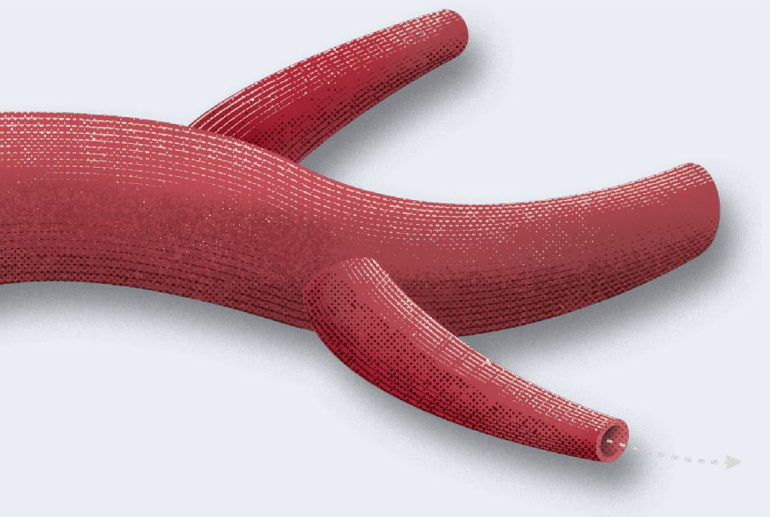
Decision point	Extent of increase		Action
Prior to reducing dose or withdrawing treatment consider other causes of increased creatinine or potassium levels, such as other medicines or foods which influence potassium levels or renal function, or re-testing potassium as haemolysis can cause higher readings[29]			
Mild creatinine or potassium elevation	Creatinine	▪ > 50% to < 100% higher than baseline (before an ACE inhibitor was initiated) ***OR*** ▪ > 266 micromol/L to < 310 micromol/L	Reduce the dose of ACE inhibitor by half
	Potassium	▪ Above reference range but <5.9 mmol/L	
Moderate to severe creatinine or potassium elevation	Creatinine	▪ >100% above baseline level ***OR*** ▪ > 310 micromol/L	Discontinue ACE inhibitor treatment Consider discussing treatment options with a nephrologist or cardiologist
	Potassium	▪ > 5.9 mmol/L	

A bpac[nz] clinical audit on the safe and effective use of ACE inhibitors is available from: **www.bpac.org.nz/Audits/ace-inhibitors.aspx**

Are there long-term risks associated with ACE inhibitors?

The association between antihypertensives and cancer has been debated for many years. Some studies have reported increased risks, while others have reported no association or decreased risk. The most recent meta-analysis data has shown no increased risk of lung (or any other) cancer with antihypertensive treatment, including ACE inhibitors, even with long-term treatment.[36]

A 2018 large population-based cohort study from the United Kingdom found a 14% increase in the relative risk of lung cancer associated with ACE inhibitor use compared with ARBs; the risk was highest in those who had been taking ACE inhibitors for more than ten years.[37] However, due to the nature of the dataset the authors were unable to adjust for confounding factors such as such as family history of lung cancer, exposure to environmental pollutants such as radon or asbestos, socioeconomic status and diet.[37] The authors also acknowledged the potential detection bias that may have come from persistent cough as an adverse effect of ACE inhibitor treatment, prompting more diagnostic investigations than in those prescribed ARBs.[37] The conclusion was that further research was needed, and that for the individual patient, the potential small increase in lung cancer risk should be balanced against the known benefits of ACE inhibitor treatment.[37, 38] Subsequently, a yet to be published 2021 meta-analysis of 31 randomised control trials including over 250,000 people found that antihypertensive treatment, including ACE inhibitors, did not increase the risk of lung (or any other) cancer; there was also no indication that the duration of treatment influenced risk.[36] This analysis was reported as "late breaking research" at the ESC Congress 2020 and is expected to be published in Lancet Oncology soon.



Angioedema is a rare but potentially serious adverse effect which can be fatal. It can occur at any time, including in patients who have been taking ACE inhibitors for years.[23] Clinical trials have found angioedema occurs in approximately 0.3% of people, with approximately 20% of these cases being life-threatening and affecting the upper respiratory tract and larynx.[23] Patients who develop angioedema should stop taking an ACE inhibitor immediately; most patients can be cautiously switched to an ARB (see: "Could this patient take an angiotensin II receptor blocker (ARB) instead of an ACE inhibitor?").[20]

Could this patient take an angiotensin II receptor blocker (ARB) instead of an ACE inhibitor?

ARBs block the binding of angiotensin II to angiotensin type 1 (AT1) receptors.[10] In New Zealand, losartan and candesartan are fully funded ARBs and both can be prescribed without restriction in primary care (Table 1). Sacubitril + valsartan, a neprilysin inhibitor in combination with an ARB, is available fully funded with Special Authority approval for the treatment of patients with chronic heart failure with reduced ejection fraction.

Choosing an ACE inhibitor or ARB

ACE inhibitor *first-line*	**Either ACE inhibitor or ARB *first-line***
Conditions where an ACE inhibitor should be used first-line (except for those requiring treatment with sacubitril + valsartan), with an ARB as a second-line option for patients who develop adverse effects:	Conditions where evidence and guidelines suggest either medicine class can be used first-line as they are equally effective:
■ Heart failure*[7, 8] ■ Following a myocardial infarction[9]	■ Hypertension, including people with type 2 diabetes[6] ■ Chronic kidney disease[11] ■ Diabetic nephropathy*[30]

* Unapproved indication for ARB, except sacubitril + valsartan

Combination ACE and ARB treatment is not recommended

An ARB and ACE inhibitor should not be used in combination for patients with hypertension, following a myocardial infarction or with diabetic nephropathy, as combination treatment results in increased rates of adverse events with no additional benefit.[6, 9] For some patients with chronic heart failure an ACE inhibitor and ARB may be used combination, however, this regimen would typically be initiated in secondary care.[20] N.B. Use of sacubitril + valsartan with an ACE inhibitor is contraindicated.

Patients are much less likely to experience cough with an ARB

A common adverse effect of ACE inhibitors is the development of cough. This is thought to occur due to increases in bradykinin levels with ACE inhibition, which does not occur when ARBs are used.[23] The incidence of cough in patients taking ARBs is approximately 65–75% lower than in patients taking ACE inhibitors.[31, 32] Other than a reduced incidence of cough with ARBs, the overall rate of adverse effects in clinical trials of ACE inhibitors or ARBs is the same.[33]

N.B. Avoidance of cough as an adverse symptom may be particularly desirable in the current environment of the global COVID-19 pandemic.

Monitoring is the same for patients taking ACE inhibitors or ARBs

Like ACE inhibitors, ARBs are associated with changes in renal function and the same monitoring advice for measuring serum creatinine and electrolytes in patients taking ACE inhibitors applies for patients being treated with ARBs.[10] Angioedema is also a rare adverse effect associated with ARB use, but occurs approximately half as often compared to patients taking ACE inhibitors.[34] If patients have previously experienced angioedema while taking an ACE inhibitor, an ARB could be initiated with caution; available evidence suggests approximately 10% or fewer patients who have angioedema while taking an ACE inhibitor have a recurrence of angioedema while taking an ARB.[35]

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References

1. Pharmacuetical Management Agency (PHARMAC). Top 20 medicines by prescriptions. 2020. Available from: https://pharmac.govt.nz/about/what-we-do/accountability-information/year-in-review/top-20-medicines-groups-by-prescription-volume/ (Accessed Mar, 2021).
2. Ministry of Health. Pharmaceutical Claims Collection. 2021.
3. Pharmacuetical Management Agency (PHARMAC). Over-reliance in cardiovascular treatment – a supply risk that needs to change. 2017. Available from: : https://pharmac.govt.nz/medicine-funding-and-supply/medicine-notices/cilazapril/over-reliance-in-cardiovascular-treatment-a-supply-risk-that-needs-to-change (Accessed Mar, 2021).
4. NHS Business Services Authority. Prescription Cost Analysis (PCA) data. 2018. Available from: www.nhsbsa.nhs.uk/prescription-data/dispensing-data/prescription-cost-analysis-pca-data (Accessed Dec, 2020).
5. Australian Government Department of Health. Pharmaceutical Benefits Scheme (PBS), expenditure and prescriptions report 1 July 2018 to 30 June 2019. 2019. Available from: https://www.pbs.gov.au/info/statistics/expenditure-prescriptions/pbs-expenditure-and-prescriptions-report
6. National Institute for Health and Care Excellence (NICE). Hypertension in adults: diagnosis and management. 2019. Available from: https://www.nice.org.uk/guidance/ng136 (Accessed Dec, 2020).
7. National Institute for Health and Care Excellence (NICE). Chronic heart failure in adults: diagnosis and management. 2018. Available from: https://www.nice.org.uk/guidance/ng106 (Accessed Dec, 2020).
8. Atherton JJ, Sindone A, De Pasquale CG, et al. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Guidelines for the prevention, detection, and management of heart failure in Australia 2018. Heart, Lung and Circulation 2018;27:1123–208. doi:10.1016/j.hlc.2018.06.1042
9. National Institute for Health and Care Excellence (NICE). Acute coronary syndromes. 2020. Available from: https://www.nice.org.uk/guidance/ng185 (Accessed Dec, 2020).
10. New Zealand Formulary (NZF). NZF v105. Available from: www.nzf.org.nz (Accessed Mar, 2021).
11. National Institute for Health and Care Excellence (NICE). Chronic kidney disease in adults: assessment and management. 2014. Available from: https://www.nice.org.uk/guidance/cg182/chapter/recommendations#terms-used-in-this-guideline (Accessed Mar, 2021).
12. American Diabetes Association. 11. Microvascular complications and foot care: standards of medical care in diabetes - 2020. Diabetes Care 2020;43:S135–51. doi:10.2337/dc20-S011

13. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. European Heart Journal 2018;39:3021–104. doi:10.1093/eurheartj/ehy339
14. Chitnis AS, Aparasu RR, Chen H, et al. Effect of certain angiotensin-converting enzyme inhibitors on mortality in heart failure: A multiple-propensity analysis. Research in Social and Administrative Pharmacy 2012;8:145–56. doi:10.1016/j.sapharm.2011.03.001
15. Svanström H, Pasternak B, Melbye M, et al. Use of different types of angiotensin converting enzyme inhibitors and mortality in systolic heart failure. International Journal of Cardiology 2015;182:90–6. doi:10.1016/j.ijcard.2014.12.092
16. Fröhlich H, Henning F, Täger T, et al. Comparative effectiveness of enalapril, lisinopril, and ramipril in the treatment of patients with chronic heart failure: a propensity score-matched cohort study. European Heart Journal - Cardiovascular Pharmacotherapy 2018;4:82–92. doi:10.1093/ehjcvp/pvx013
17. Chang C-H, Lin J-W, Caffrey JL, et al. Different angiotensin-converting enzyme inhibitors and the associations with overall and cause-specific mortalities in patients with hypertension. American Journal of Hypertension 2015;28:823–30. doi:10.1093/ajh/hpu237
18. Hernandez AF, Harrington RA. Comparative effectiveness of angiotensin-converting-enzyme inhibitors: Is an ACE always an ace? Canadian Medical Association Journal 2008;178:1316–9. doi:10.1503/cmaj.080370
19. Waitemata District Health Board. Guide for initiation and up-titration of ACE inhibitors for patients with heart failure. 2017. Available from: http://www.saferx.co.nz/assets/Documents/c4aeb520bc/ACE_Inhibitor_titration.pdf (Accessed Mar, 2021).
20. Scottish Intercollegiate Guidelines Network (SIGN). SIGN 147 Management of chronic heart failure. 2016. Available from: https://www.sign.ac.uk/assets/sign147.pdf (Accessed Dec, 2020).
21. LeBlanc JM, Dasta JF, Pruchnicki MC, et al. Impact of disease states on the pharmacokinetics and pharmacodynamics of angiotensin-converting enzyme inhibitors. The Journal of Clinical Pharmacology 2006;46:968–79. doi:10.1177/0091270006290333
22. Al-Naher A, Wright D, Devonald MAJ, et al. Renal function monitoring in heart failure - what is the optimal frequency? A narrative review: Frequency of renal monitoring in heart failure. Br J Clin Pharmacol 2018;84:5–17. doi:10.1111/bcp.13434
23. Messerli FH, Bangalore S, Bavishi C, et al. Angiotensin-converting enzyme inhibitors in hypertension. Journal of the American College of Cardiology 2018;71:1474–82. doi:10.1016/j.jacc.2018.01.058
24. Sica DA. Angiotensin-converting enzyme inhibitors side effects--physiologic and non-physiologic considerations. J Clin Hypertens (Greenwich) 2004;6:410–6. doi:10.1111/j.1524-6175.2004.02866.x
25. St. Peter WL, Odum LE, Whaley-Connell AT. To RAS or not to RAS? The evidence for and cautions with renin-angiotensin system inhibition in patients with diabetic kidney disease. Pharmacotherapy 2013;33:496–514. doi:10.1002/phar.1232
26. Schmidt M, Mansfield KE, Bhaskaran K, et al. Serum creatinine elevation after renin-angiotensin system blockade and long term cardiorenal risks: cohort study. BMJ 2017;356:j791. doi:10.1136/bmj.j791
27. Makani H, Bangalore S, Desouza KA, et al. Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomised trials. BMJ 2013;346:f360. doi:10.1136/bmj.f360
28. Phillips CO, Kashani A, Ko DK, et al. Adverse Effects of Combination Angiotensin II Receptor Blockers Plus Angiotensin-Converting Enzyme Inhibitors for Left Ventricular Dysfunction: A Quantitative Review of Data From Randomized Clinical Trials. Arch Intern Med 2007;167:1930. doi:10.1001/archinte.167.18.1930
29. Kyle C. Sonic Pathology Handbook.
30. American Diabetes Association. 11. Microvascular Complications and Foot Care: Standards of Medical Care in Diabetes—2021. Dia Care 2021;44:S151–67. doi:10.2337/dc21-S011
31. Pfeffer MA, McMurray JJV, Velazquez EJ, et al. Valsartan, Captopril, or Both in Myocardial Infarction Complicated by Heart Failure, Left Ventricular Dysfunction, or Both. N Engl J Med 2003;349:1893–906. doi:10.1056/NEJMoa032292
32. Telmisartan, Ramipril, or Both in Patients at High Risk for Vascular Events. N Engl J Med 2008;358:1547–59. doi:10.1056/NEJMoa0801317
33. Li EC, Heran BS, Wright JM. Angiotensin converting enzyme (ACE) inhibitors versus angiotensin receptor blockers for primary hypertension. Cochrane Database of Systematic Reviews 2014; [Epub ahead of print]. doi:10.1002/14651858.CD009096.pub2
34. Makani H, Messerli FH, Romero J, et al. Meta-analysis of randomized trials of angioedema as an adverse event of renin–angiotensin system inhibitors. The American Journal of Cardiology 2012;110:383–91. doi:10.1016/j.amjcard.2012.03.034
35. Haymore BR, Yoon J, Mikita CP, et al. Risk of angioedema with angiotensin receptor blockers in patients with prior angioedema associated with angiotensin-converting enzyme inhibitors: a meta-analysis. Annals of Allergy, Asthma & Immunology 2008;101:495–9. doi:10.1016/S1081-1206(10)60288-8
36. European Society of Cardiology. Large study finds no link between blood pressure medication and cancer. 2020. Available from: https://www.escardio.org/The-ESC/Press-Office/Press-releases/Large-study-finds-no-link-between-blood-pressure-medication-and-cancer (Accessed Mar, 2021).
37. Hicks BM, Filion KB, Yin H, et al. Angiotensin converting enzyme inhibitors and risk of lung cancer: population based cohort study. BMJ 2018;363:k4209. doi:10.1136/bmj.k4209
38. Cronin-Fenton D. Angiotensin converting enzyme inhibitors and lung cancer. BMJ 2018;:k4337. doi:10.1136/bmj.k4337

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