

## 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. Cilazapril is to be delisted at the end of 2023. All patients should be switched to another ACE inhibitor, angiotensin II receptor blocker (ARB) or another medicines). Guidelines that recommend the use of an ACE inhibitor support the use of any medicine in this class (or often also an ARB) as they are often 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 and delisted from end of 2023
- 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.<sup>1,2</sup> 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.<sup>3,4</sup> Perindopril and lisinopril (both fully funded in New Zealand) are among the most frequently prescribed ACE inhibitors overseas.<sup>4,5</sup>

## 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 is no longer 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 was unable to change immediately still needs to have their prescription for cilazapril endorsed after 1 May, 2021. Cilazapril will be delisted at the end of 2023.

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-notice/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.<sup>6</sup>
- Heart failure with reduced ejection fraction; an ACE inhibitor is typically initiated alongside a diuretic and beta blocker.<sup>7,8</sup> 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.<sup>9,10</sup>
- Chronic kidney disease; either an ACE inhibitor or ARB are recommended first-line (unapproved indication for both classes)<sup>11</sup>
- Diabetic nephropathy<sup>12</sup>; either an ACE inhibitor or ARB are recommended first-line (unapproved indication for most ACE inhibitors<sup>†</sup> 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<sup>6</sup>

† 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: enalapril, lisinopril, perindopril, quinapril, ramipril\* and cilazapril<sup>†</sup> (Table 1). Captopril is available in an oral liquid formulation subsidised for children aged < 12 years. The cilazapril with hydrochlorothiazide combination formulation has been discontinued, and the quinapril with hydrochlorothiazide combination branded Accuretic<sup>‡</sup> was withdrawn in New Zealand on 30 June, 2022, due to a contamination issue (see links below). Any patients currently taking Accuretic should be switched to a suitable alternative, as clinically appropriate, such as losartan + hydrochlorothiazide, or any concurrent use of an ACE inhibitor or ARB with a thiazide or thiazide-like diuretic.


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.<sup>6,7,9,13</sup> 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.

\* Funded from 1 December, 2022

† To be delisted by end of 2023

‡ To be delisted by 1 February, 2023

 For further information on the discontinuation of cilazapril with hydrochlorothiazide, see: [pharmac.govt.nz/medicine-funding-and-supply/medicine-notice/cilazapril/cilazapril-with-hydrochlorothiazide-discontinuation/](https://pharmac.govt.nz/medicine-funding-and-supply/medicine-notice/cilazapril/cilazapril-with-hydrochlorothiazide-discontinuation/)

 For further information on the Accuretic supply issue, see: [pharmac.govt.nz/medicine-funding-and-supply/medicine-notice/accuretic/](https://pharmac.govt.nz/medicine-funding-and-supply/medicine-notice/accuretic/)



**Table 1:** Funded ACE inhibitors and ARBs, available tablet strength and recommended doses.<sup>10</sup> N.B. When switching between ACE inhibitors (and ARBs) it is safest to initiate the new medicine at a lower dose and titrate up to a maintenance dose.

Tablet strength	Diuretic combination tablets	Patients with hypertension		Patients with heart failure	
		Starting dose <sup>†</sup>	Typical maintenance dose <sup>†</sup>	Starting dose <sup>†</sup>	Typical maintenance dose <sup>†</sup>
<b>ACE inhibitors</b>					
<b>Cilazapril*</b>	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
<b>Enalapril<sup>‡</sup></b>	5 mg 10 mg 20 mg	5 mg, once daily	20 mg, once daily	2.5 mg, once daily	10 mg, twice daily**
<b>Lisinopril</b>	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
<b>Perindopril</b>	2 mg 4 mg 8 mg	2–4 mg, once daily	4–8 mg, once daily	2 mg, once daily	4 mg, once daily <sup>§</sup>
<b>Quinapril<sup>¶</sup></b>	5 mg 10 mg 20 mg	quinapril 10 mg + hydrochlorothiazide 12.5 mg <sup>¶</sup> quinapril 20 mg + hydrochlorothiazide 12.5 mg <sup>¶</sup>	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**
<b>Ramipril</b>	1.25 mg 2.5 mg 5 mg 10 mg		1.25–2.5 mg, once daily	5–10 mg, once daily	1.25 mg, once daily <sup>⊘</sup> 10 mg, daily in two divided doses <sup>⊘</sup>
<b>ARBs</b>					
<b>Candesartan</b>	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
<b>Losartan</b>	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. Cilazapril will be delisted at the end of 2023.

† 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](http://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](http://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

¶ In March 2022, Pfizer, the supplier of Accuretic (quinapril + hydrochlorothiazide), advised of a contamination issue and issued a voluntary recall worldwide; PHARMAC withdrew access to Accuretic in New Zealand on 30, June, 2022 and no alternative brand is available. No new patients should be initiated on Accuretic, and those currently taking it should be switched to an alternative regimen, as clinically appropriate, e.g. losartan + hydrochlorothiazide, or any concurrent use of an ACE inhibitor or ARB with a thiazide or thiazide-like diuretic. Accuretic will be delisted by 1 February, 2023

§ N.B. This dose is recommended in the manufacturer's datasheet and on the NZF. However, it may differ from some international recommendations.

⊘ Unapproved indication

## 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.<sup>14–18</sup>

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.<sup>10</sup>

## Titration and dosing are similar


Most of the subsidised ACE inhibitors are available in at least three tablet sizes, allowing for titration and adjustments to dosing (Table 1). All ACE inhibitors require titration to effect over the same timeframe.<sup>10</sup> Table 2 provides dose equivalency for patients switching between ACE inhibitors.

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.<sup>10</sup>

 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](http://www.saferx.co.nz/assets/Documents/c4aeb520bc/ACE_Inhibitor_titration.pdf)

## 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.<sup>19</sup>

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

- The NZF: [www.nzf.org.nz/nzf\\_70421](http://www.nzf.org.nz/nzf_70421)
- Health Navigator: [www.healthnavigator.org.nz/medicines/a/ace-inhibitors/](http://www.healthnavigator.org.nz/medicines/a/ace-inhibitors/) and [www.healthnavigator.org.nz/medicines/a/angiotensin-receptor-blockers-arbs/](http://www.healthnavigator.org.nz/medicines/a/angiotensin-receptor-blockers-arbs/)

**Table 2.** Approximate dose equivalence of funded ACE inhibitors and ARBs

Medicine		Equivalent dose	
<b>ACE inhibitors</b>			
Cilazapril	0.5 – 1 mg	2.5 mg	5 mg
Enalapril	2.5 mg	5 – 10 mg	20 mg
Lisinopril	5 mg	10 mg	20 – 40 mg
Perindopril	2 mg	2 – 4 mg	8 mg
Quinapril	5 mg	10 mg	20 – 40 mg
Ramipril	1.25 mg	2.5 mg	5 – 10 mg
<b>ARBs</b>			
Candesartan	4 mg	8 mg	16 mg
Losartan	25 mg	50 mg	50 – 100 mg

Thames Valley Family Health Team (Ontario). The Dose: An estimation of equivalent doses between ARBs and ACEIs. 2020. Available from: [thamesvalleyfht.ca/wp-content/uploads/2020/05/TheDoseACEIsARBs-drina.pdf](https://www.thamesvalleyfht.ca/wp-content/uploads/2020/05/TheDoseACEIsARBs-drina.pdf) (Accessed Nov, 2022).

Coca A, Kreutz R, Manolis AJ, et al. A practical approach to switch from a multiple pill therapeutic strategy to a polypill-based strategy for cardiovascular prevention in patients with hypertension. *Journal of Hypertension* 2020;38:1890–8. doi:10.1097/HJH.0000000000002464

## 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.<sup>20</sup> 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.<sup>10</sup> 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.<sup>10</sup> 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).<sup>10</sup>

**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.<sup>10</sup>

**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](http://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.<sup>21</sup>

\* 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 3). 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.<sup>6</sup> 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.<sup>7</sup>

**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.<sup>23</sup> Clinical trials have found rates of cough were two and half times higher in people of Asian ethnicity compared to European ethnicity.<sup>23</sup> 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.<sup>24</sup> 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 4). For example, in people with diabetes, increases in

**Table 3:** Recommended monitoring for patients taking ACE inhibitors<sup>19,22</sup>

Monitoring recommended	Prior to initiation	One to two weeks after dose adjustments or changing ACE	After titration to maximum tolerated dose
■ Measure blood pressure	✓	✓	
■ Ask patients about symptoms of hypotension or adverse effects	—	✓	Depending on patient characteristics; at least annually
■ Request tests for: <ul style="list-style-type: none"> <li>– Creatinine</li> <li>– Electrolytes</li> </ul>	✓	✓	

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.<sup>25</sup> 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.<sup>26</sup>

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](http://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.<sup>27, 28</sup> A typical increase is around 0.1–0.2 mmol/L, which does not require intervention.<sup>24</sup> 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.<sup>20</sup>

**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.<sup>23</sup> 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.<sup>23</sup> 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?").<sup>20</sup>

**Table 4:** 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<sup>19, 20</sup>

Decision point	Extent of increase	Action	
<b>Prior to reducing dose or withdrawing treatment</b> 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 <sup>29</sup>			
<b>Mild creatinine or potassium elevation</b>	Creatinine	<ul style="list-style-type: none"> <li>■ &gt; 50% to &lt; 100% higher than baseline (before an ACE inhibitor was initiated)</li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>■ &gt; 266 micromol/L to &lt; 310 micromol/L</li> </ul>	Reduce the dose of ACE inhibitor by half
	Potassium	<ul style="list-style-type: none"> <li>■ Above reference range but &lt;5.9 mmol/L</li> </ul>	
<b>Moderate to severe creatinine or potassium elevation</b>	Creatinine	<ul style="list-style-type: none"> <li>■ &gt;100% above baseline level</li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>■ &gt; 310 micromol/L</li> </ul>	Discontinue ACE inhibitor treatment Consider discussing treatment options with a nephrologist or cardiologist
	Potassium	<ul style="list-style-type: none"> <li>■ &gt; 5.9 mmol/L</li> </ul>	

 A bpac<sup>nz</sup> clinical audit on baseline testing prior to initiating an ACE inhibitor or ARB is available from: [www.bpac.org.nz/Audits/ace-inhibitors-2021.aspx](http://www.bpac.org.nz/Audits/ace-inhibitors-2021.aspx)

## 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.<sup>10</sup> 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 (ARNI), is available fully funded with Special Authority approval for the treatment of patients with chronic heart failure with reduced ejection fraction.

ARBs are now commonly prescribed in New Zealand due to removal of funding restrictions and increasing clinical trial evidence supporting their similar efficacy and improved tolerability compared with ACE inhibitors. The question “*could this patient take an ARB instead of an ACE inhibitor*” is therefore being increasingly asked by primary care clinicians.

Either an ACE inhibitor or an ARB can be used first-line for treating patients with **hypertension** (including those with type 2 diabetes), **chronic kidney disease** and **diabetic nephropathy**\*.<sup>6, 11, 30</sup>

\* Unapproved indication for ARB

In patients with **heart failure**, it is recommended that an ACE inhibitor should be used first-line, and that an ARB can be considered second-line if an ACE inhibitor is not tolerated.<sup>8</sup> However, some recent international guidelines, e.g. the 2022 AHA/ACC/HFSA Heart Failure guidelines from the United States, consider that an ACE inhibitor, ARB or ARNI are all now equal first-line options.<sup>31</sup>

 For further information on the management of patients with heart failure, see: [bpac.org.nz/2022/heart-failure-part-2.aspx](https://www.bpac.org.nz/2022/heart-failure-part-2.aspx).

It is uncertain whether this transition in guidance (i.e. that ACE inhibitors and ARBs can be considered equal first-line options) will be made across other cardiovascular conditions as these medicines still have differing mechanisms of action which may be more/less suitable for different pathologies, and they are associated with different adverse effect profiles.

National Institute for Health and Care Excellence (NICE) 2020 guidelines recommend ACE inhibitors as the first-line option for patients **post-myocardial infarction**.<sup>9</sup> However, this guidance was last updated in 2013, and based on evidence from older studies which yielded mixed results, e.g. the **OPTIMAAL** (2003) and **VALIANT** (2005) clinical trials. A Korean retrospective analysis of patient records between 2005 – 2014 (published in 2020) indicated that those taking an ARB post-myocardial infarction had a reduced risk of major adverse cardiovascular events, subsequent myocardial infarction,

## 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.<sup>36</sup>

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.<sup>37</sup> However, due to the nature of the dataset the authors were unable to adjust for confounding factors such as family history of lung cancer, exposure to environmental pollutants such as radon or asbestos, socioeconomic status and diet.<sup>37</sup> 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.<sup>37</sup> 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.<sup>37, 38</sup> 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.<sup>36</sup> This analysis was reported as “late breaking research” at the ESC Congress 2020 and is expected to be published in *Lancet Oncology* soon.





revascularisation and death compared with those taking an ACE inhibitor.<sup>32</sup> Further investigation is likely required to confirm whether the continued prioritisation of ACE inhibitor use is warranted for this indication.

## 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.<sup>6,9</sup> 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.<sup>20</sup> 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.<sup>23</sup> The incidence of cough in patients taking ARBs is approximately 65–75% lower than in patients taking ACE inhibitors.<sup>33,34</sup> 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.<sup>35</sup>

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.<sup>10</sup> Angioedema is also a rare adverse effect associated with ARB use, but occurs approximately half as often compared to patients taking ACE inhibitors.<sup>36</sup> 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.<sup>37</sup>

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