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. Guidelines that recommend use of an ACE inhibitor support the use of any medicine in this class as they are regarded as having similar benefits and risks. High rates of cilazapril use could lead to problems if supply issues were to develop.

**KEY PRACTICE POINTS:**

- In New Zealand, approximately 60% of people taking angiotensin-converting enzyme (ACE) inhibitors are prescribed cilazapril. The high use of cilazapril in New Zealand, and low use internationally, leaves New Zealand vulnerable to supply issues.
- Consider the range of subsidised ACE inhibitors and whether an ACE inhibitor other than cilazapril could be prescribed when initiating treatment:
  - The benefits and risks associated with ACE inhibitors are similar across the class
  - Most ACE inhibitors can be taken as once-daily tablets
  - Contraindications, cautions and medicines interactions are similar for all ACE inhibitors

**Use of cilazapril in New Zealand is very high compared to other countries**

Approximately half a million people in New Zealand are prescribed an angiotensin-converting enzyme (ACE) inhibitor, and of these, approximately 60% are prescribed cilazapril, making it the ninth highest prescribed medicine by number of prescriptions in New Zealand. Even though a range of ACE inhibitors are now subsidised, familiarity means cilazapril remains a favoured choice for many clinicians when prescribing an ACE inhibitor. However, the high rates of use in New Zealand increases exposure to supply issues, particularly as cilazapril is used infrequently or not at all in other countries such as Australia and the United Kingdom.

If supply issues were to develop, large numbers of patients would need to be switched to an alternative ACE inhibitor. ACE inhibitors widely used overseas that are subsidised in New Zealand include perindopril and lisinopril.
ACE inhibitors are prescribed for a variety of indications

ACE inhibitors are generally prescribed in primary care for:

- Hypertension; either an ACE inhibitor, angiotensin receptor blocker (ARB), calcium channel blocker (CCB) or thiazide diuretic are recommended as first-line options*. An ACE inhibitor is preferred for patients with, or at high risk of, diabetes or with chronic kidney disease.1
- Heart failure with reduced ejection fraction; an ACE inhibitor is typically initiated alongside a diuretic and beta blocker.5–7 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 quinapril are approved for this indication.6, 7
- Diabetic nephropathy10; this is an unapproved indication.

* In people of African or Caribbean ethnicity, a thiazide diuretic or CCB are recommended as first-line options as evidence suggests ACE inhibitors are less effective in these population groups.5

There are a range of subsidised ACE inhibitors

ACE inhibitors subsidised 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. Subsidised combination formulations of cilazapril or quinapril with a diuretic are also available.

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, 8, 11 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.5, 12

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.13–17

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Table 1: Subsidised ACE inhibitors, available tablet strength and recommended doses

<table>
<thead>
<tr>
<th>Tablet strength</th>
<th>Cilazapril (mg)</th>
<th>Enalapril (mg)</th>
<th>Lisinopril (mg)</th>
<th>Perindopril (mg)</th>
<th>Quinapril (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor + diuretic combination tablets</td>
<td>cilazapril 5 mg + hydrochlorothiazide 12.5 mg</td>
<td></td>
<td></td>
<td></td>
<td>quinapril 10 mg + hydrochlorothiazide 12.5 mg</td>
</tr>
<tr>
<td>Typical maintenance dose*</td>
<td>In patients with hypertension</td>
<td>2.5–5 mg, once daily</td>
<td>20 mg, once daily</td>
<td>20 mg, once daily</td>
<td>4–8 mg, once daily</td>
</tr>
<tr>
<td>In patients with heart failure</td>
<td>5 mg, once daily</td>
<td>10 mg, twice daily*</td>
<td>20 mg, once daily</td>
<td>4 mg, once daily</td>
<td>10 mg, twice daily**</td>
</tr>
</tbody>
</table>

* 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

** Can be once daily if tolerated
Other factors which 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.9

**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.9

Once-daily medicines are recommended where possible to make dosing and adherence simpler for patients. Once-daily dosing is possible with any of the subsidised 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.9

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, compared to one fixed dose available for cilazapril combination tablets.

**Prescribing ACE inhibitors**

In order to reduce reliance on cilazapril, clinicians are encouraged to initiate patients on an ACE inhibitor other than cilazapril.

**All ACE inhibitors require a low starting dose with titration to effect** over a number of weeks, with the same rate of titration regardless of which ACE inhibitor is prescribed.9 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.9 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.9 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).9

**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.9

**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.18

* 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?”)

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**Table 2: Recommended monitoring for patients taking ACE inhibitors**19, 20

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

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Monitoring for adverse effects

Monitoring patients for the development of adverse effects is recommended during initiation of treatment and after adjusting doses of ACE inhibitors (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. 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.

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. Clinical trials have found rates of cough were two and half times higher in people of Asian ethnicity compared to European ethnicity. 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 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 dilatation of the efferent (post-glomerular) blood vessels. 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. 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.

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: www.bpac.org.nz/2018/triple-whammy.aspx

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

<table>
<thead>
<tr>
<th>Decisor point</th>
<th>Extent of increase</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior to reducing dose or withdrawing treatment</td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>Mild creatinine or potassium elevation</td>
<td>Creatinine: ▪ &gt; 50% to &lt; 100% higher than baseline (before an ACE inhibitor was initiated) OR ▪ &gt; 266 micromol/L to &lt; 310 micromol/L</td>
<td>Reduce the dose of ACE inhibitor by half</td>
</tr>
<tr>
<td>Potassium: ▪ Above reference range but &lt; 5.9 mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate to severe creatinine or potassium elevation</td>
<td>Creatinine: ▪ &gt; 100% above baseline level OR ▪ &gt; 310 micromol/L</td>
<td>Discontinue ACE inhibitor treatment</td>
</tr>
<tr>
<td>Potassium: ▪ &gt; 5.9 mmol/L</td>
<td>Consider discussing treatment options with a nephrologist or cardiologist</td>
<td></td>
</tr>
</tbody>
</table>
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. A typical increase is around 0.1–0.2 mmol/L, which does not require intervention.

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.

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. 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. 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 receptor blocker (ARB) instead of an ACE inhibitor?”).

Changing ACE inhibitors

Where appropriate, clinicians are encouraged to consider switching patients from cilazapril to another ACE inhibitor to reduce risks associated with supply. However, changing from cilazapril may not always be appropriate, e.g. in a patient with heart failure who is stabilised on treatment. Switching is also unadvisable in patients who are unable to be monitored following the change, patients at greater risk of adverse effects, e.g. frail people at risk of falls, and patients who are highly distressed about the change.

When changing treatment, patients can discontinue one ACE inhibitor and initiate a different ACE inhibitor at a comparable dose (Table 1) the following day. Although ACE inhibitors are regarded as clinically equivalent, individual patients may respond differently. Patients should 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.

Patient information sheets for subsidised ACE inhibitor and ARB medicines are available from the NZF: www.nzf.org.nz/nzf_70421
Angiotensin receptor blockers block the binding of angiotensin II to angiotensin type 1 (AT1) receptors. In New Zealand, losartan and candesartan are fully subsidised ARBs and both can be prescribed without restriction in primary care (Table 4); Special Authority criteria were removed from candesartan on 1 July, 2018.

A simple rule of thumb is ACE inhibitor first, switch to an ARB if intolerable adverse effects develop

Despite both ARBs and ACE inhibitors being designed to affect angiotensin signalling, guidelines recommend that patients with heart failure, hypertension or who have had a myocardial infarction should use an ACE inhibitor in preference to an ARB. This is because clinical trial evidence shows that ACE inhibitors provide better outcomes than ARBs and because more clinical trials have been conducted using ACE inhibitors. For patients with chronic kidney disease or diabetic nephropathy, ARBs are an equally effective alternative to ACE inhibitor treatment.

An ARB and ACE inhibitor should not be used in combination for patients with hypertension, following a myocardial infarction or with diabetic nephropathy. For some patients with chronic heart failure an ACE inhibitor and ARB are used in combination, however, this regimen would typically be initiated in secondary care.

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. The incidence of cough in patients taking ARBs is approximately 65–75% lower than in patients taking ACE inhibitors. 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.

Monitoring is the same as for patients taking ACE inhibitors

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. Angioedema is also a rare adverse effect associated with ARB use, but occurs approximately half as often compared to patients taking ACE inhibitors. 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.

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

Choosing an ACE inhibitor or ARB

- **ACE inhibitor first-line**
  - Conditions where an ACE inhibitor should be used first-line, with an ARB as a second-line option for patients who develop adverse effects
  - Heart failure
  - Following a myocardial infarction
  - Hypertension, including people with type 2 diabetes

- **Either ACE inhibitor or ARB first-line**
  - Conditions where evidence and guidelines suggest either medicine class can be used first-line
  - Chronic kidney disease
  - Diabetic nephropathy

Table 4: Subsidised ARBs, available tablet sizes and recommended doses

<table>
<thead>
<tr>
<th></th>
<th>Losartan</th>
<th>Candesartan</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tablet strength</strong></td>
<td>12.5 mg, 25 mg, 50 mg, 100 mg</td>
<td>4 mg, 8 mg, 16 mg, 32 mg</td>
</tr>
<tr>
<td></td>
<td>Also losartan 50 mg + hydrochlorothiazide 12.5 mg</td>
<td></td>
</tr>
<tr>
<td><strong>Starting dose</strong></td>
<td>In patients with hypertension</td>
<td>25–50 mg, once daily</td>
</tr>
<tr>
<td></td>
<td>In patients with heart failure</td>
<td>12.5 mg, once daily</td>
</tr>
<tr>
<td></td>
<td>4 mg, once daily</td>
<td></td>
</tr>
<tr>
<td><strong>Typical maintenance dose</strong></td>
<td>In patients with hypertension</td>
<td>50 mg, once daily</td>
</tr>
<tr>
<td></td>
<td>In patients with heart failure</td>
<td>150 mg, once daily</td>
</tr>
<tr>
<td></td>
<td>32 mg, once daily</td>
<td></td>
</tr>
</tbody>
</table>

* Starting and maintenance doses depend on the condition being treated and the patient’s response to treatment; lower 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
References:


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