

ACE

Inhibitors



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ACE POEMs

Patient Oriented Evidence that Matters

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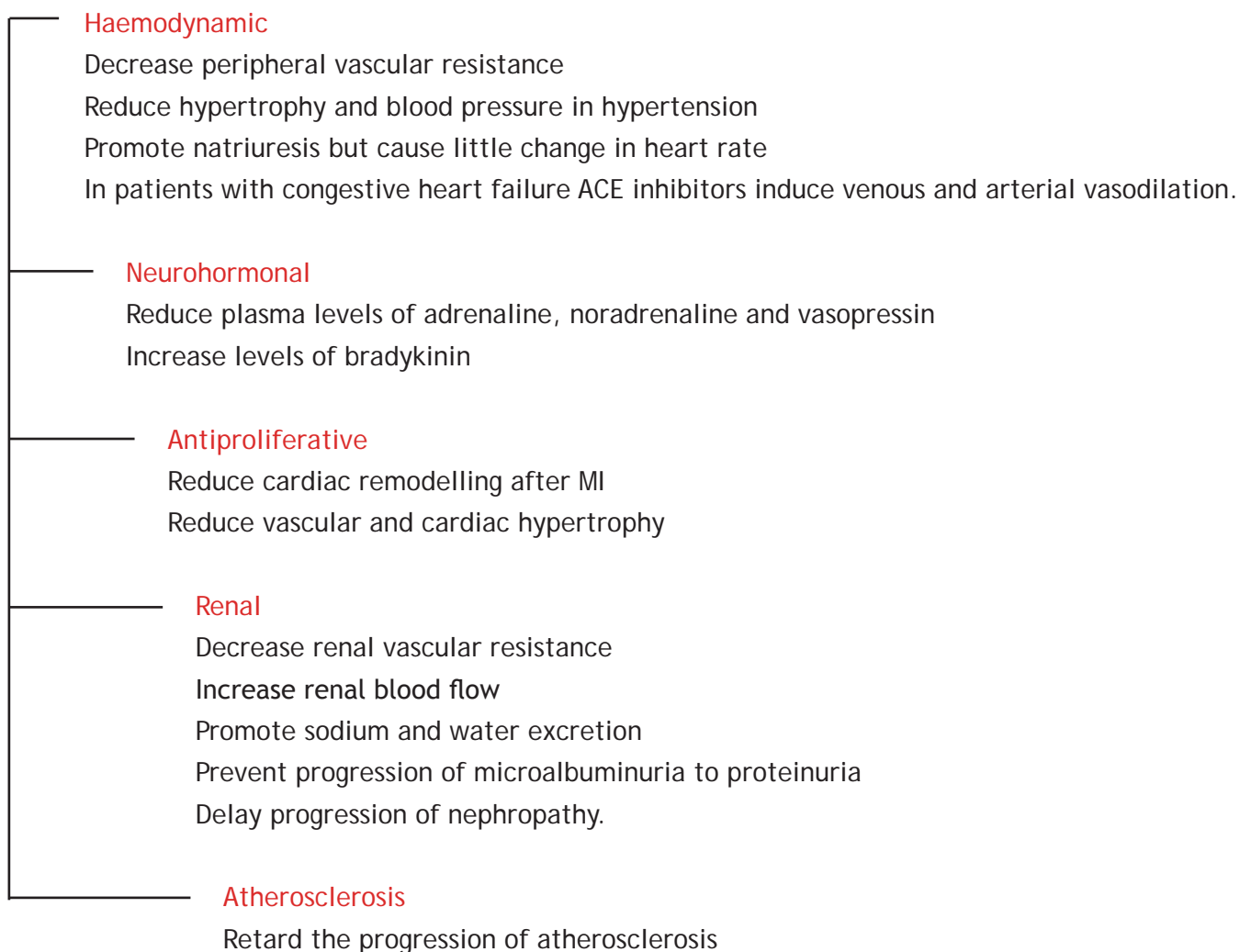
Key Recommendations

1. Unless there are contraindications, use ACE inhibitors for everybody with:
 - Left ventricular dysfunction with or without symptoms of heart failure
 - Diabetic or non-diabetic nephropathy as indicated by microalbuminuria or frank proteinuria
 - Known cardiovascular disease or at high risk of cardiovascular disease.
2. Use an ACE inhibitor or a low-dose thiazide initially for most people with hypertension who have diabetes or are at high risk of diabetes. Ensure BP is maintained below 130/80. Add other agents as indicated.
3. Consider the use of ACE inhibitors for people with diabetes or at high risk of diabetes as they appear to reduce cardiovascular and renal risk and reduce progression to diabetes for those at high risk.
4. When people have indications for ACE inhibitors they are also likely to benefit from statins and low-dose aspirin.
5. Serious adverse effects from ACE inhibitor use can usually be predicted and avoided with careful monitoring.

Background

ACE inhibitors act on the the renin-angiotensin system (RAS). This is a cascade of hormones contributing to the regulation of blood pressure and blood volume. It is triggered by the release of renin from the juxtaglomerular apparatus of the kidney. ACE inhibitors suppress this RAS pathway by inhibiting angiotensin converting enzyme (ACE) which is widely distributed in the circulation and tissues (Veltmar, 1991). This inhibition decreases the formation of a potent vasoconstrictor, angiotensin II, and slows the degradation of the potent vasodilator, bradykinin (Appendix). Other mechanisms of action are still being discovered and the effects of ACE inhibitors involve many body systems.

Figure 1 Effects of ACE inhibitors



(Adapted from The Task force on ACE-inhibitors of the European Society of Cardiology, 2004)

Diabetes

- ACE inhibitors reduce the risk of morbidity and mortality for people with diabetes and microalbuminuria or overt nephropathy.
- ACE inhibitors reduce the risk of morbidity and mortality for people with diabetes and hypertension.
- ACE inhibitors are preferred to beta-blockers for control of blood pressure in people at high risk of diabetes.
- ACE inhibitors may reduce the risk of diabetes in people at high risk of diabetes.
- ACE inhibitors may reduce renal and cardiovascular risks for people with diabetes or at high risk of diabetes.

Diabetic nephropathy is the leading cause of end stage renal disease worldwide and is associated with increased cardiovascular risk. It affects 20 to 30 percent of people with diabetes. Large scale randomised controlled trials have demonstrated the benefits of drugs that act on the RAS system in slowing deterioration in renal function for patients with diabetic nephropathy (Strippoli, 2004). However delaying progression to end stage renal disease and cardiovascular disease requires aggressive management of blood pressure, glucose, and lipids as well as RAS inhibition (Marshall, 2004).

Delaying progression to end stage renal disease and cardiovascular disease for patients with diabetes requires aggressive management of blood pressure, glucose, and lipids as well as RAS inhibition (Marshall, 2004).

The benefits of ACE inhibitor drugs are demonstrated in trials using placebo as control. This has caused some authors to question their validity. The results of a meta-analysis (Casas et al, 2005) show that any protective effect on renal function, other than by controlling blood pressure remains unproven. Until further debate has occurred we still recommend that ACE inhibitors are usually included in the drug regimen of people with diabetes and microalbuminuria or overt nephropathy but stress the importance of obtaining good control of blood pressure i.e. systolic < 130, diastolic < 80 mmHg (NZGG 2003) and other risk factors.

The presence of underlying kidney disease is not a contraindication to ACE inhibitor use. In fact people with underlying renal disease who have a 30% increase in baseline serum creatinine concentrations that stabilise within two months of ACE inhibitor therapy have the most prominent long-term reduction in progression of renal failure (Brewster, 2004).

The New Zealand Guidelines Group (2003) recommend the use of ACE Inhibitors in type 2 diabetes with microalbuminuria (confirmed albumin:creatinine ratio of > 2.5 mg/mmol for men and > 3.5 mg/mmol for women) and for people with overt nephropathy.

People with hypertension and diabetes. Many randomised trials have shown that blood-pressure lowering therapy reduces cardiovascular disease morbidity and mortality in people with diabetes. Many agents (ACE inhibitors, beta-blockers and low-dose thiazides) have proved effective. Choice of agent for a person with diabetes may be influenced by a number of factors including their risk profile (cardiovascular, renal end-organ damage), preferences, and previous experience of therapy, as well as costs. Thiazides may adversely affect glucose and lipid levels, but no RCTs have shown these drugs to increase cardiovascular mortality in type II diabetes.

The International Diabetes Federation recommends initiating medication for lowering blood pressure in diabetes not complicated by raised albumin excretion rate, using any agent except for α -adrenergic blockers, with consideration of costs, and actively titrating the dose according to response. Additionally they recommend that:

- ACE inhibitors and angiotensin II receptor antagonists (AIIIRAs) may offer some advantages over other agents in some situations, (kidney damage, cardiovascular risk protection) but are less effective in people of African extraction.
- You should start with beta-blockers or ACE inhibitors in people with previous MI, ACE-inhibitors or diuretics in those with heart failure.
- Care should be taken with combined thiazides and beta-blockers because of risk of deterioration in metabolic control.

(International Diabetes Federation, 2005).

In practice many people will need more than one agent to achieve adequate control of blood pressure. The achievement of adequate control of blood pressure is more important than the class of antihypertensive used. A combination of both an ACE inhibitor and a low-dose thiazide will suit most people.

People with hypertension who are at high risk of developing diabetes. ACE inhibitors are preferred to beta-blockers for people with hypertension who are at high risk of developing diabetes.

This is because:

- A meta-analysis of the results of randomised clinical studies estimates that ACE inhibitors or AIIIRAs reduce the relative risk of diabetes by 22%. NNT 45 in patients treated for 4 - 5 years (Scheen, 2004).
- Beta-blockers are known to reduce insulin sensitivity (Pollare, 1989).
- Trials suggest that the onset of diabetes is more likely in people receiving a combination of a thiazide diuretic and a beta-blocker compared to people taking other drug combinations for blood pressure control (NICE, 2004).

People at high risk of developing diabetes include those with:

- Impaired glucose tolerance
- Strong family history of type II diabetes
- BMI \geq 30 (NICE, 2004)
- Metabolic syndrome
- People of Maori, Pacific Island or Asian ethnicity.

This does not preclude the use of beta-blockers for people with specific indications such as angina or after myocardial infarction.

ACE inhibitors may reduce the risk of diabetes in people at high risk of diabetes: Scheen (2004) found that 22% fewer people developed diabetes if they were on RAS inhibitors, than a similar group of people at high risk of diabetes, who were not on RAS inhibitors (NNT 45 treated for 4 - 5 years). However this was a post-hoc analysis of trials which were not primarily designed to address the issue of new-onset diabetes. Prospective studies with standardised criteria for the diagnosis of new-onset diabetes as the primary endpoint are needed (Jandeleit-Dahm, 2005). In the meantime clinicians will need to make a clinical judgement considering this possible benefit, the risks of treatment and the views of individual patients.

ACE inhibitors may provide cardiovascular protection for people with diabetes: Several recent trials suggest that both classes of agents that inhibit the RAS system, ACE inhibitors and AIIIRAs, provide cardiovascular protection for people with diabetes (Jandeleit-Dahm, 2005). For example in the HOPE trial population there was a 25% reduction in relative risk of cardiovascular events with ACE inhibitor treatment for people with diabetes. This was independent of their history of hypertension, blood-pressure reduction, microalbuminuria, type of diabetes mellitus, and type of anti-diabetic therapy. As can be expected, people at the highest risk got the greatest benefit.

Cardiovascular Disorders and Nephropathy

ACE inhibitor use in hypertension: There is little doubt that low-dose thiazide diuretics are first-line blood pressure lowering medication for most people (NZGG, 2005) but the choice between ACE inhibitors or beta-blockers as second line therapy may be more difficult.

Unless there are contra-indications, ACE inhibitors are now recommended for use before beta-blockers for people with:

- Diabetes or pre-diabetes,
- Heart failure,
- Nephropathy (microalbuminuria or proteinuria),
- Previous, or at high risk of cardiovascular disease,
- Contra-indications to beta-blockers.

This is because ACE inhibitors appear to have beneficial effects in these conditions which are independent of lowered blood pressure.

For people without the conditions outlined above the decision is more difficult. Current best practice continues to involve tailoring treatments for individuals. Many people will need more than one anti-hypertensive medication and for most people lowering of blood pressure is more important than the class of medication used.

ACE inhibitors are first-line therapy in people with reduced left ventricular systolic function (ejection fraction < 40 - 45%) with or without heart failure symptoms. There is clear evidence that they prolong survival, reduce hospital admissions, slow progression of heart failure and improve quality of life. Over 3.5 years 22 people need to be treated to prevent one death (NNT 22) and 3 people need to be treated to prevent one hospitalisation (NNT 3) (The Task Force, 2004). Benefits are independent of age, sex, baseline use of diuretics, aspirin and beta-blockers, and occur early after start of treatment and persist long term (Flather, 2000).

ACE inhibitors are beneficial in acute myocardial infarction when given within 36 hours. For patients treated for 4 to 6 weeks NNT 200 to prevent one death. Most of these deaths were prevented in the first week post MI (The Task Force, 2004).

ACE inhibitors reduce risk for people with known cardiovascular disease such as coronary heart disease, peripheral arterial disease or stroke or who are at high risk of cardiovascular disease. The number needed to treat (NNT) for five years to prevent one death is 26 (HOPE, 2000).

Nephropathy

ACE inhibitors are beneficial in all forms of non-diabetic renal disease as well as diabetic nephropathy. Trials show a relative risk reduction of approximately 50% in the doubling of serum creatinine or need for dialysis (Brewster, 2004).

Initiation and monitoring

ACE inhibitors are usually safe and well tolerated but serious adverse effects can occur. These can often be predicted and avoided by good baseline monitoring, sensible choices of dosage regimens and attentive ongoing monitoring.

Table 1 Issues to consider when initiating and monitoring ACE inhibitors.

Baseline Monitoring
Contraindications
Medical conditions that increase risks of adverse effects
Physiological parameters
Medications associated with increased risk of adverse effects

Initiation
Choice of ACE inhibitor
Starting and target doses

Ongoing monitoring
Adverse symptoms
Physiological parameters
Response to therapy

Baseline monitoring

Table 2 Baseline monitoring

Contraindications

- Angioedema
- Pregnancy
- Previous allergy to ACE inhibitor

Medical conditions that increase risks of adverse effects

- Severe heart failure
- Sodium or volume depletion
- Peripheral vascular disease or severe generalised atherosclerosis
- Haemodynamically significant valvular heart disease
- Aortic stenosis
- Bilateral renal artery stenosis

Physiological parameters

- Serum creatinine (eGFR)
- Electrolytes
- Blood pressure
- Urinalysis for microalbuminuria

Medications associated with increased risk of adverse effects

- NSAIDs
- Lithium
- Potassium supplements
- Spironolactone
- High dose diuretics
- Hypoglycaemic agents

Specialist advice

Specialist advice should be considered before initiating ACE inhibitors for people with any of the following factors:

- severe or unstable heart failure
 - multiple or high-dose diuretic therapy (e.g. more than 80 mg of furosemide daily or its equivalent)
 - hypovolaemia
 - hyponatraemia (plasma-sodium concentration below 130 mmol/L)
 - pre-existing hypotension (systolic blood pressure below 90 mmHg)
 - renal impairment (eGFR MDRD \leq 50 mL/min or rapidly declining eGFR)
 - high-dose vasodilator therapy, or
 - aged 70 years or over
- (BNF, 2005).

Contraindications

Absolute contraindications to ACE inhibitor therapy are angioedema and previous allergy to an ACE inhibitor. ACE inhibitors and AIIIRAs can cause foetal abnormalities if taken in the 2nd and 3rd trimester of pregnancy. The effects of 1st trimester use are unknown. ACE inhibitors or AIIIRAs should be avoided in pregnancy and stopped as soon as pregnancy is suspected.

Medical conditions that increase risk of adverse effects

Severe heart failure: The initiation of ACE inhibitors for people with severe or unstable heart failure requires a very low starting dose and is usually best done with specialist advice.

People who are sodium or volume depleted are particularly at risk of first dose hypotension when starting ACE inhibitors. Common causes include diarrhoea or urinary loss, CHF, cirrhosis and high dose diuretics.

People with peripheral vascular disease or severe generalised atherosclerosis are at increased risk of renal artery stenosis. Creatinine is monitored carefully after starting therapy, and as a rule of thumb doubling of the creatinine within 3 - 5 days is an indication to stop the ACE inhibitor and seek specialist advice. It may be the first sign of previously undiagnosed bilateral renal stenosis.

Haemodynamically significant valvular heart disease needs full investigation before ACE inhibitors can be started.

Aortic stenosis or bilateral renal artery stenosis: ACE inhibitor therapy may be beneficial for people with aortic or bilateral renal artery stenosis. However caution and increased attention to monitoring are required. People with severe stenosis should be referred for specialist advice.

Checking physiological parameters

Physiological parameters to check before initiating treatment include serum creatinine, serum electrolytes, urinalysis for microalbuminuria and blood pressure.

Mild to moderate degrees of renal impairment, hyperkalaemia, hyponatraemia or hypotension are associated with higher risk of adverse events but are not contraindications to the initiation of an ACE inhibitor. Increased vigilance in monitoring is recommended.

There is no specific level of creatinine beyond which ACE inhibitors cannot be used but an eGFR less than or equal to 50 mL/min is an indication for specialist advice.

Interactions with other medications

An important part of baseline monitoring is to consider interactions with other medications.

NSAIDs are nephrotoxic due to modification of renal perfusion which increases the risk of renal ischaemia.

The combined use of an ACE inhibitor, NSAID and diuretic has been implicated in a significant number of reports of drug induced renal failure to the Australian Adverse Drug Reaction Council (Thomas, 2000). This effect is also seen with COX-2 inhibitors and angiotension II receptor antagonists (Boyd, 2000).

It usually occurs when people on this combination of drugs become volume depleted such as with diarrhoea or vomiting.

Lithium: ACE inhibitors reduce the excretion of lithium and therefore increase the risk of toxicity. If the combination is used, more attentive monitoring of lithium levels is needed.

Potassium supplements increase the risk of hyperkalaemia and are not usually used for patients taking ACE inhibitors.

Spironolactone: The combination of an ACE inhibitor and spironolactone is potentially beneficial in patients with heart failure but should be used in carefully selected patients with close monitoring to reduce the risk of severe hyperkalaemia. In the RALES study (Pitt, 1999) which demonstrated the benefit of spironolactone, 95% of patients were also taking an ACE inhibitor, however patients with elevated serum creatinine or potassium were excluded from the study and regular checks of serum potassium were conducted throughout the duration of the study. Risk factors for hyperkalaemia due to a combination of ACE inhibitor and spironolactone include advanced age, renal impairment, high baseline serum creatinine or potassium, inadequate baseline and treatment monitoring, high dietary potassium intake and possibly, type II diabetes. In these patients the dose of spironolactone is probably best limited to a maximum of 25mg per day and more frequent monitoring instituted (Juurlink, 2004; Wrenger, 2003).

Diuretics: People taking diuretics may be particularly sensitive to the vasodilator effects of ACE inhibitors and are at increased risk of hypotension. This does not preclude the use of low-dose thiazides which can be effectively used with ACE inhibitors. Those on high doses of diuretics (e.g. frusemide 80mg daily) are at particular risk. Consider halving the dose of diuretics especially frusemide when introducing ACE inhibitor therapy.

Hypoglycaemic agents: ACE inhibitors may increase the effect of hypoglycaemic agents. Closer monitoring of blood glucose is often appropriate after initiating ACE inhibitors until blood glucose levels are stable.

Antacids: May reduce the absorption of some ACE inhibitors, however this is of questionable clinical significance. Many sources suggest separating the administration of capotril or enalapril and antacids by two hours.

Aspirin: Despite theoretical possibilities of interactions between aspirin and ACE inhibitors in people with CHF these do not appear to be clinically significant. A retrospective analysis of patients with stable left ventricular systolic dysfunction found no adverse effect on survival in people taking concomitant aspirin and an ACE inhibitor (Aumégeat, 2003). People with CHF should receive low-dose aspirin as well as full-dose ACE inhibition because aspirin significantly improves prognosis for people with atherosclerosis (Brunner-La Rocca, 2003).

Initiating ACE inhibitors

Initiating ACE inhibitors requires consideration of:

- Choice of ACE inhibitor
- Starting and target doses

Choice of ACE inhibitor

The question of which ACE inhibitor in which dose has not yet been fully resolved. The effects of ACE inhibitors are currently attributed to the class as a whole. However there are important differences in their pharmacokinetic properties and the way they bind to tissue ACE. These have not yet been demonstrated to have clinical relevance (The Task Force, 2004) but it is likely that clinical issues will become apparent as a result of ongoing research.

Some authors argue that we should be using the drugs that have been proven in large clinical trials (Bicket, 2002). These tend to be the older drugs which have been around longer such as captopril and enalapril. Others argue that there is a class effect and the choice should be guided by cost and convenience of dosing. The commonest ACE inhibitors dispensed in New Zealand in 2004 were quinapril, cilazapril, enalapril and captopril (bpacnz, 2005).

Combination products

Products combining an ACE inhibitor with a thiazide diuretic are available. The use of combination products precludes independent titration of the doses of the medications involved. Their use is therefore better reserved for people who are on stable doses of both medications and need a simplified regimen to adhere to therapy.

Starting and target doses

‘Start low - go slow’

The reduction of Angiotensin-II mediated vasoconstrictor tone by ACE inhibitors may lead to first-dose hypotension. Reducing the occurrence of first dose hypotension is achieved by starting with a low dose and increasing the dose slowly, for example doubling the dose at no less an interval than two weeks.

People with heart failure or at increased risk of adverse events when starting treatment benefit from starting with a very low dose under close medical supervision. At the same time consideration should be given to halving the dose of any diuretic used.

The target doses of ACE inhibitors are determined by the doses used in the clinical trials which demonstrated their benefits. Trials demonstrating the benefits of ACE inhibitors in heart failure, nephropathy and secondary preventions of MI usually used high target doses.

These are the doses we should aim for in clinical practice unless dose increases are limited by intolerance or adverse effects. For example the following table describes the suggested starting doses and target maintenance doses in heart failure.

ACE inhibitor	Suggested starting dose in heart failure*	Target maintenance dose in heart failure
Quinapril	2.5 mg daily	20 - 40 mg daily**
Cilazapril	0.5 mg daily	1 - 2.5 mg daily
Enalapril	2.5 mg daily	10 - 20 mg b.i.d.
Captopril	6.25 - 12.5 mg daily	50 mg t.i.d.
Lisinopril	2.5 mg daily	20 - 40 mg daily

Adapted from BNF 2005 and NPS 2004.

*The first dose is usually given at night.

**Some authorities suggest the target dose of quinapril should be 20mg b.i.d.

Ongoing monitoring of ACE inhibitor therapy

Routine ongoing monitoring is recommended:

- one to two weeks after starting treatment,
- at each dose change, and
- then at least annually.

High risk patients require more attentive monitoring.

Adverse symptoms	
Angioedema	Discontinue ACE inhibitor consider replacement with AIIRA
Cough	Check other causes (e.g. smoking, CHF, GORD) Most can continue ACE inhibitor May need replacement with AIIRA
Symptomatic hypotension	Consider reducing other antihypertensive or diuretic
Other adverse effects	May include abnormal taste, rash, neutropaenia
Physiological parameters	
Asymptomatic hypotension	Usually no change required
Worsening renal function (Adapted from NICE CHF guidelines, 2003)	
Potassium <6mmol/L or creatinine increase of up to 50% above baseline or >0.2 mmol/L whichever is least	Acceptable during initiation of treatment and should stabilise within the first two months. Review the clinical context. Consider adjustment of other nephrotoxic, potassium sparing or vasodilator medications or high potassium foods.
Creatinine continues to rise after first two months or rises to 50 to 100% above baseline or to between 0.2 to 0.35 mmol/L	Half ACE inhibitor dose but if no response seek specialist advice A rapid rise in creatinine may indicate bilateral renal artery stenosis
Potassium >5.9mmol/L or creatinine over 100% above baseline or above 0.35mmol/L	Stop ACE inhibitor and seek specialist advice
Response to therapy	
ACE inhibitors are mainly used to decrease risk and slow disease progression rather than give symptomatic relief.	Helping the patient understand this is likely to improve adherence to therapy. However significant symptom relief can be achieved in CHF.

Adverse symptoms

Angioedema is a recognised adverse effect of ACE inhibitor therapy and appears to have an incidence of 0.1% to 0.2%. The association between angioedema and ACE inhibitor may be missed because the effect can start years after beginning treatment and recur spontaneously while the drug is continued. Continuation of the ACE inhibitor increases the rate of angioedema recurrence with serious morbidity. Deaths have been reported (Cicardi, 2004).

ACE inhibitor related angioedema is probably related to a build up of bradykinin causing increased vascular permeability and vasodilation (Howes, 2002). It is a class effect and switching to another ACE inhibitor is contraindicated (Vleeming, 1998). Switching to an AIIRA may be considered.

Dry cough occurs in 5% to 10% of patients taking an ACE inhibitor. It is more common in women and Asian people and is not dose related. The cough usually develops after one week to several months of treatment.

ACE inhibitor cough is rarely an indication to stop treatment. Only about 1% to 3% of people on an ACE inhibitor will need to stop treatment because of a cough. If the cough is intolerable stopping treatment will usually resolve the cough within three to five days (The Task Force, 2004). Several treatments for ACE inhibitor cough have been tried and found unsuccessful: these include cromoglycate, indomethacin and sulindac (Morice, 2003).

The cough may be related to increased levels of bradykinin. AIIRAs do not increase these levels, and cough occurs in less than 1% of people on an AIIRA. A change to AIIRA may therefore be considered for people with intolerable ACE inhibitor cough.

If **symptomatic hypotension** does occur, consider lowering the dose of concurrent antihypertensives or diuretics or reducing the dose of the ACE inhibitor. If considering decreasing diuretic dose it is worthwhile checking for signs of pulmonary oedema first.

Other adverse symptoms may include a transient metallic taste (appears to be more common in the elderly and with captopril use), neutropenia and rashes.

Physiological parameters

Asymptomatic hypotension: Does not usually warrant a change in therapy.

Renal function: A rise in serum creatinine and increase in potassium is common with the initiation of an ACE inhibitor. In patients with renal impairment this actually represents an improvement in renal function due to improved renal haemodynamics. Decreasing the dose of the ACE inhibitor in this situation allows the creatinine to return to normal but loses the beneficial effect of long-term preservation of renal function (Palmer, 2003).

Levels of potassium less than 6 mmol/L and creatinine increases that do not go over 50% above baseline or > 0.2 mmol/L are acceptable and should stabilise within two months. It is worth considering the need for any concurrent medications which may have renal toxicity or raise serum potassium, such as NSAIDs or potassium sparing diuretics and review dietary potassium rich foods.

High potassium foods include;

- Tomato juice
- Orange juice
- Bananas
- Apricots
- Spinach
- Avocado
- Milk and milk products

For a comprehensive list of high potassium foods see: http://www.drugs.com/CG/HIGH_POTASSIUM_FOODS_LIST.html

If elevations continue to rise or creatinine is between 50% and 100% above baseline or between 0.2 and 0.35 mmol/L consider halving the dose of ACE inhibitor and seeking specialist advice. A rapid rise in serum creatinine may indicate the presence of renal artery stenosis.

If potassium exceeds 5.9 mmol/L or creatinine is over 100% above baseline or over 0.35 mmol/L stop the ACE inhibitor and seek specialist advice.

Response to therapy

On most occasions ACE inhibitors are used to slow disease progression, reduce deaths and reduce hospitalisations although they may provide symptomatic relief for people with heart failure. Patients who are expecting control of symptoms by ACE inhibitors may be disappointed and discontinue treatment. It is helpful to clarify the role of ACE inhibitors for patients to encourage improved adherence to treatment regimens.

Angiotensin-II receptor antagonists (AIIRAs)

Currently the AIIRAs losartan and candesartan are fully funded on special authority for people who cannot tolerate ACE inhibitors because of cough or who have had angioedema on an ACE inhibitor at any time in the past, or had angioedema (even if not using an ACE inhibitor) in the last 2 years.

ACE inhibitors and AIIRAs both inhibit the RAS system but differences in the way they do this are still being explored and our knowledge is incomplete. Some of these differences are likely to be clinically relevant. People who are considering switching from an ACE inhibitor to an AIIRA will want to consider the comparative adverse effects and benefits of the two drug classes.

Adverse effects of AIIRAs compared to ACE inhibitors

Cough - As AIIRAs do not inhibit the breakdown of bradykinin they rarely produce ACE inhibitor cough.

Angioedema - Recurrence of angioedema associated with ACE inhibitors ceased or was greatly reduced in 85% of people who stopped using the drug. For people who are likely to benefit from continued blockade of the RAS system switching to an AIIRA appears a reasonable alternative. However, although AIIRAs do not increase levels of bradykinin a small percentage of people will continue to get angioedema recurrences (Cicardi, 2004).

Decisions on using an AIIRA in the face of angioedema recurrences will need to be made on a case by case basis including careful consideration of the severity of previous episodes of angioedema and the potential benefits of continued RAS inhibition.

Other adverse effects - Other significant adverse effects are similar to those of ACE inhibitors although they appear to be less likely to lead to discontinuation of treatment. Similar cautions need to be taken in regard to hypotension, hyperkalaemia and renal impairment as for ACE inhibitors.

Benefits of AIIRAs compared to benefits of ACE inhibitors

We found few head to head comparisons of the effectiveness of AIIRAs and ACE inhibitors. These are unlikely to occur because of the costs involved. The following table has been compiled from a variety of sources.

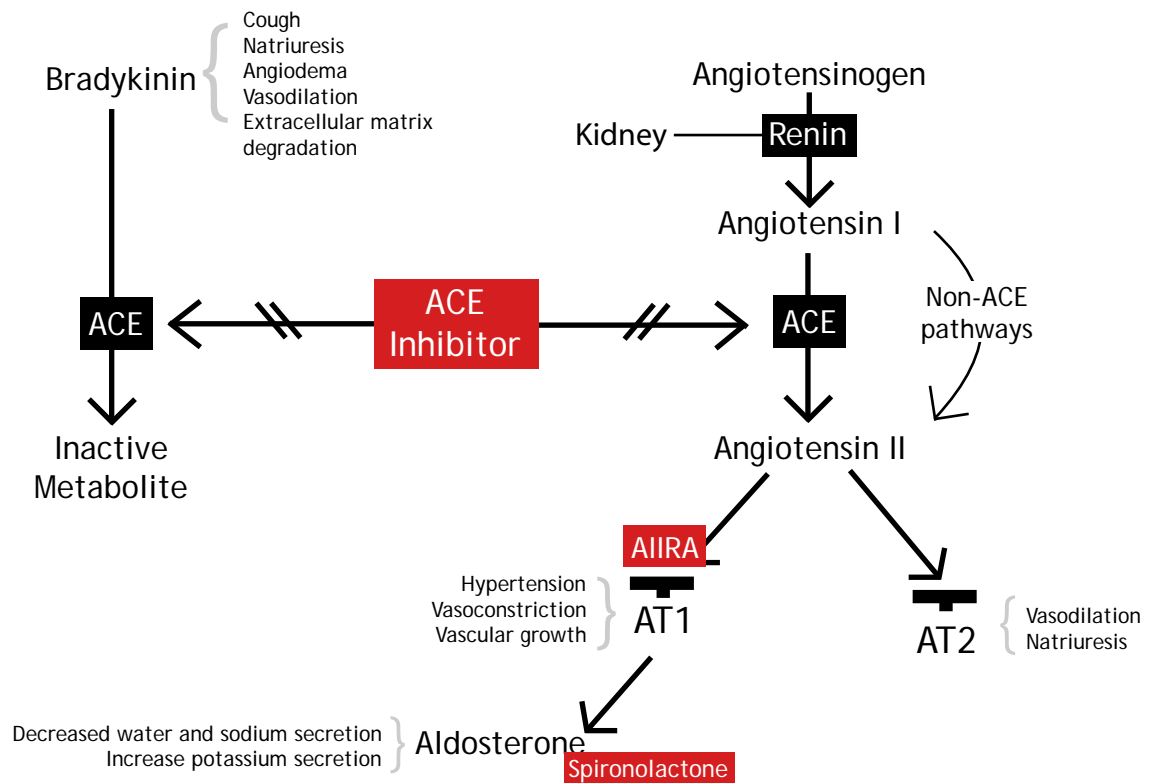
	ACE inhibitors	AIIRAs
Diabetic nephropathy (Strippoli, 2004)	Improve renal outcomes Prevent early deaths	Improve renal outcomes Evidence awaited on early deaths
Heart failure (Yan, 2005)	Improve all cause mortality Improve morbidity	Lower level of evidence for effectiveness but safe and effective alternative for those who cannot tolerate ACE inhibitor
Hypertension	Reduction in blood pressure achieved is more important than class of agent chosen.	Studies are under way.
Secondary prevention of cardiovascular disease (Clinical Evidence, 2005)	Reduces secondary events and deaths	Similar effect but weaker evidence

Combining an AIIRA with an ACE inhibitor

Because AIIRAs and ACE inhibitors interfere with the RAS system in different ways there has been interest in finding beneficial effects from combining these two drugs to produce dual RAS blockade. Some people advocate that this is a rational choice for selected patients (van de Wal, 2005) but there is insufficient evidence to recommend its initiation in primary care. Patients may return from specialist clinics on this combination. Monitoring is the same as for ACE inhibitors.

Appendix

The Renin-Angiotensin System (RAS)



1. A loss of blood or a decrease in blood pressure stimulates renin release from the kidney.
2. Renin cleaves Angiotensinogen to Angiotensin I.
3. Angiotensin converting enzyme (ACE) is present in many tissues (abundant in the lung) inactivates bradykinin, and converts angiotensin I to angiotensin II.
4. Angiotensin II acts at the AT1 and AT2 receptors.
5. AT1 receptor activation leads to vasoconstriction, vascular growth, hypertension and aldosterone synthesis.
6. Aldosterone causes sodium and water retention.
7. ACE inhibitors decrease the formation of angiotensin II (non-ACE pathways are un-inhibited by ACE inhibitors) and decrease the degradation of bradykinin.
8. A build-up of bradykinin occurs, resulting in adverse effects (cough, angioedema) and cardiovascular benefits (vasodilation).
9. AIIRAs block AT1 receptors, without disturbing bradykinin degradation.
10. Spironolactone is an aldosterone antagonist
11. Other poorly characterised receptors include the AT3 receptor and the AT4 receptor.

Angiotensin II levels, sodium concentration and hydrostatic pressure in the small capillaries of the kidney activate renin synthesis.

Renin is a circulating enzyme that cleaves angiotensinogen to produce angiotensin I. Angiotensin-converting enzyme (ACE) converts angiotensin I to angiotensin II, and also degrades bradykinin to its inactive metabolite. Angiotensin II is also produced by enzymes other than ACE, therefore, ACE inhibitors only partially block the RAS system. (Veltmar, 1991).

Angiotensin II acts at two receptors; AT1 (stimulation is associated with negative cardiovascular effects) and AT2 (stimulation is associated with beneficial cardiovascular effects) (Brewster, 2004).

AIIRAs block the action of angiotensin II at the AT1 receptor but not at the AT2 receptor, in theory preventing unwanted cardiovascular effects, and increasing beneficial cardiovascular effects. However, unlike ACE inhibitors, AIIRAs do not enhance bradykinin activity, reducing the incidence of bradykinin mediated adverse effects, but at the expense of a possible reduction in bradykinin mediated cardiovascular benefits (Hilgers, 2002).

The discovery of ACE inhibitors developed from research on the Brazilian pit viper. Toxic effects of the viper's venom was found to produce an increase in bradykinin and a reduction in angiotensin II levels, and a considerable drop in blood pressure. It was revealed that the snake venom was a potent inhibitor of ACE (Cushman, 1991). It was 20 years later, in 1985, that the first ACE inhibitor; captopril, was released onto the market.

During trials of captopril, it was found to have undesirable adverse effects, such as a cough, rash, taste disturbances (metallic or loss of taste) and a short half-life (necessitating 2-3 times daily dosing). The sulfhydryl-moiety of captopril was found to be responsible for such adverse effects. This leads to the development of longer-acting ACE inhibitors lacking the sulfhydryl-moiety, such as enalaprilat (Cushman, 1991).

Enalaprilat was the first dicarboxylate-containing ACE inhibitor to be developed. The sulfhydryl-moiety was replaced by a carboxylate-moiety. However, modifications to achieve a similar potency to captopril lead to unfavourable potency for oral administration. Enalaprilat was only suitable for intravenous administration.

Further development led to the discovery of enalapril, a prodrug of enalaprilat. Studies on the mechanism of action of ACE inhibitors revealed the existence of the angiotensin II receptor and led to medicines that can block it.

Research surrounding the RAS pathway and the pharmacology of blood pressure lowering agents continues today. Future medicines are likely to involve a combination of both ACE inhibiting and angiotensin receptor blocking capabilities.

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