Prescribing ACEI and ARBs (Sartans)
For Cardiac Patients - Key Messages

This guidance represents the consensus view of the South East London Cardiac Network Cardiac Prescribing Forum. The guidance does not, however, override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

1. When choosing between prescribing an angiotensin converting enzyme inhibitor (ACEI) or prescribing an angiotensin receptor blocker (ARB) – an ACEI should always be used first-line. There are no compelling indications for using an ARB first-line.

2. On the basis of clinical evidence, cost effectiveness and patient tolerability, the ACEIs of choice within the sector are ramipril capsules or lisinopril tablets for:
   - heart failure
   - hypertension
   - reduction of CV risk in patients at high risk of CV events (ramipril only)
   - secondary prevention post-myocardial infarction (MI)

3. ACEI should be initiated at a low dose and titrated to the maximal tolerated dose in order to maximise the cardioprotective effects of the agent.
   - Target daily dose of ramipril is 10mg
   - Target daily dose of lisinopril varies depending on the indication
   For further information on doses, see frequently asked questions (FAQ) document, the BNF and individual drugs summary of product characteristics (SPC).
   It is recommended that the words ‘increase dose as tolerated’ are added to discharge letters to encourage dose titration.

4. A persistent dry cough is a commonly reported adverse effect of ACEI therapy. Cough is not necessarily an indication for drug withdrawal and patients should be strongly encouraged to persevere with therapy, as this symptom usually resolves within 1 – 4 weeks but may persist for up to 3 months. If medication withdrawal proves necessary, re-challenge at a later date once symptoms have resolved. If ACEI therapy cannot be withdrawn temporarily in this way, consider switching to an alternative ACEI in the first instance.

5. In comparison to ACEI, ARBs have limited outcome data to support their use. For this reason the primary indication for an ARB is failure to tolerate an ACEI. This is usually due to persistent dry cough that is interfering with the patients’ quality of life and has failed to resolve over time or following withdrawal and rechallenge or switch of ACEI therapy.

6. When used second line to an ACEI, the ARB chosen should reflect the evidence base, current licensed indications and cost-effectiveness:
   - Heart failure: candesartan
   - Hypertension: losartan (patent expires 2009), candesartan (patent expires 2012) or irbesartan (patent expires 2012)
   - Secondary prevention post-MI: valsartan

## Contents

<table>
<thead>
<tr>
<th>Question</th>
<th>Page No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Why are ACEI recommended first-line?</td>
<td>3</td>
</tr>
<tr>
<td>2. Are there any circumstances where ARBs should be used first-line?</td>
<td>3</td>
</tr>
<tr>
<td>3. What indications are the individual ACEI and ARBs licensed for and what are their target doses?</td>
<td>3</td>
</tr>
<tr>
<td>4. Why should ACEI be titrated to the target dose (or maximum tolerated dose within the dose range)?</td>
<td>3</td>
</tr>
<tr>
<td>5. What does head to head data between ACEI and ARBs show?</td>
<td>5</td>
</tr>
<tr>
<td>6. What is the evidence to support ACEI versus ARB to reduce CV outcomes in patients with diabetes, with or without renal disease?</td>
<td>5</td>
</tr>
<tr>
<td>7. What is the evidence to support ACEI versus ARBs in Black patients?</td>
<td>6</td>
</tr>
<tr>
<td>8. Are there dose equivalents between ACEI and ARBs?</td>
<td>7</td>
</tr>
<tr>
<td>9. How should ACEI doses be titrated safely</td>
<td>7</td>
</tr>
<tr>
<td>10. What should I do if creatinine increases after I have initiated an ACEI?</td>
<td>7</td>
</tr>
<tr>
<td>11. What level of renal impairment is too high for ACEI/ARB initiation? When should patients be referred to secondary care before initiation?</td>
<td>8</td>
</tr>
<tr>
<td>12. What potassium level is too high for ACEI initiation or dose titration? Do ARBs have less effect on potassium?</td>
<td>8</td>
</tr>
<tr>
<td>13. What blood pressure is too low for ACEI initiation or dose titration?</td>
<td>9</td>
</tr>
<tr>
<td>14. How can first dose hypotension with ACEI’s be avoided? What do I do if my patient is on a loop diuretic?</td>
<td>9</td>
</tr>
<tr>
<td>15. How do I deal with ACEI induced cough?</td>
<td>9</td>
</tr>
<tr>
<td>16. In what circumstances is dual therapy (ACEI plus ARB) warranted</td>
<td>10</td>
</tr>
<tr>
<td>17. When both an ACEI and ARB are required, do you optimise the ACEI before adding ARB?</td>
<td>11</td>
</tr>
<tr>
<td>18. How can I tell if my patient has RAS? What do I do about it? What implications does RAS have for ACEI / ARB?</td>
<td>11</td>
</tr>
<tr>
<td>19. Is aortic stenosis a contraindication for ACEI / ARB?</td>
<td>12</td>
</tr>
<tr>
<td>20. If my patient has had angioedema with an ACEI, can they have an ARB?</td>
<td>12</td>
</tr>
<tr>
<td>21. Are there any medications that interact with ACEI or ARBs?</td>
<td>12</td>
</tr>
</tbody>
</table>
1. Why are ACEI recommended first-line?
ACE inhibitors are supported by a robust outcomes-driven evidence base over a wide range of indications including heart failure, hypertension, post-MI secondary prevention and CV risk reduction. In contrast, ARBs have a more limited evidence base, and have not shown superiority over ACEI in any large-scale clinical trials (see also Q5). A recent large head-to-head study, ONTARGET, a recent randomised clinical trial comparing telmisartan alone to ramipril alone or the combination of the two drugs in over 28,000 patients, concluded that telmisartan was non-inferior to ramipril in terms of efficacy, but was associated with fewer adverse effects. The combination use of ACEI and ARB conferred no improvement in clinical effect but increased the risk of adverse events. A recent evidence-based review concluded that ACEI and ARB should be treated as equal in terms of efficacy. As generic ACEI are significantly less expensive than ARBs, ACEI should always be considered first-line.

- ACE Inhibitors and Angiotensin II Receptor Blockers: London New Drugs Group Oct 2007

2. Are there any circumstances where ARBs should be used first-line?
There are currently no compelling indications for the use of ARBs routinely first line.

3. What indications are the individual ACEI and ARBs licensed for and what are their target doses?
Not all ACEI and ARBs are licensed for use in all different cardiovascular indications. It is recommended that a licensed agent, with trial evidence to support its use is chosen for the indication being managed.

- For essential hypertension, the dose should be titrated according to response until blood pressure control is achieved, bearing in mind that higher ACEI doses confer better CV protection
- For other indications, particularly heart failure and for cardioprotection in those with or at risk of cardiovascular disease, the ACEI (or ARB if ACEI not tolerated) MUST be titrated to the target dose or the maximal tolerated dose if the target dose cannot be achieved (ie due to hypotension, renal dysfunction etc.)

Licensed indications with the usual recommended starting and target doses are outlined in Table 1 (over page)

NB: The patent for losartan expires in 2009, and a large reduction in price is anticipated. Therefore, where an ARB is to be used second-line to an ACEI for the treatment of hypertension, losartan is preferred.

4. Why should ACEI be titrated to the target dose (or maximum tolerated dose within the dose range)?
Most outcome studies of ACE inhibitors aimed to titrate patients to achieve specific target doses, usually the maximum dose within the dose range. In order to realise the prognostic benefits that these drugs have demonstrated in trials, it is necessary to ensure that patients achieve the same target doses in clinical practice (or the maximum tolerated dose if this cannot be achieved). Audit has shown clearly that ACE Inhibitors are often inappropriately prescribed at doses lower than those used in the key clinical trials.
There have been very few prospective studies comparing the effects of low dose and high dose ACEI in terms of long-term outcomes. The ATLAS study looked at lisinopril 2.5mg or 5mg daily and compared it to lisinopril 32.5mg or 35mg daily in patients with heart failure. There were fewer hospital admissions and a trend towards lower mortality in the group treated with high-dose ACEI. Post-hoc analysis of many cardiovascular studies has concluded that the patients that gained the most health-benefit during the course of the study were those that were treated with higher doses of ACEI.


### Table 1: Licensed Indications and Doses for Selected ACEI and ARB

<table>
<thead>
<tr>
<th>Licensed Indication</th>
<th>Agent</th>
<th>Starting Dose *</th>
<th>Target Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart Failure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td>Ramipril</td>
<td>1.25mg once daily</td>
<td>5mg twice daily</td>
</tr>
<tr>
<td></td>
<td>Lisinopril</td>
<td>2.5mg once daily</td>
<td>35mg once daily</td>
</tr>
<tr>
<td>ARBs (2nd line)</td>
<td>Candesartan</td>
<td>4mg once daily</td>
<td>32mg once daily</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td>Ramipril</td>
<td>1.25mg daily</td>
<td>Max 10mg once daily</td>
</tr>
<tr>
<td></td>
<td>Lisinopril</td>
<td>10mg daily</td>
<td>Max 80mg once daily</td>
</tr>
<tr>
<td>ARBs (2nd line)</td>
<td>Losartan</td>
<td>50mg once daily Elderly &gt; 75yrs, 25mg daily</td>
<td>Max 100mg once daily</td>
</tr>
<tr>
<td></td>
<td>Candesartan</td>
<td>8mg once daily Hepatic impairment: 2mg once daily Renal impairment: 4mg once daily</td>
<td>Max 32mg once daily</td>
</tr>
<tr>
<td></td>
<td>Irbesartan</td>
<td>150mg once daily Elderly &gt; 75yrs, 75mg once daily</td>
<td>Max 300mg once daily</td>
</tr>
</tbody>
</table>

| **Reduction of Cardiovascular risk** |       |                 |             |
| ACE Inhibitor                   | Ramipril | 2.5mg once daily | 10mg once daily |

| **Secondary Prevention post MI** |       |                 |             |
| ACE Inhibitors                  | Ramipril | 2.5mg twice daily | 5mg twice daily or 10mg daily (for compliance) |
|                               | Lisinopril | SBP > 120mmHg: 5mg day 1&2, then 10mg once daily SBP 100-120mmHg: 2.5mg once daily | 10mg daily |
| ARB (2nd line)                  |Valsartan | 20mg twice daily | 160mg twice daily |

*See BNF or Summary of Product Characteristics for full information on recommended dose reductions in renal or hepatic impairment

---

**5. What does head to head data between ACEI and ARBs show?**

In terms of outcome studies, there is very little head to head data between ACEI and ARBs across all of the cardiac indications.

- **Hypertension**: There are no outcome studies that directly compare ARBs to ACEI or other ARBs.
Heart Failure: The only direct head-to-head study, ELITE-2 failed to show its primary end-point of reduced CV events in patients treated with losartan compared to captopril. This study was designed to show superiority of losartan over captopril and failed to do this. It was not powered to demonstrate equivalence and this therefore cannot be assumed based on the results of this study.

Post-MI: There have been two post-MI studies comparing ACEI and ARBs, OPTIMAAL and VALIANT. OPTIMAAL failed to demonstrate that losartan was superior or non-inferior to captopril in terms reducing mortality in patients with post-MI heart failure. The VALIANT study demonstrated that valsartan and captopril were equally effective in reducing rates of death and cardiovascular events in patients with heart failure post-MI.

CV risk reduction in high-risk patients: ON-TARGET, a non-inferiority study comparing telmisartan alone to ramipril alone or to a combination of the two agents, demonstrated that telmisartan was non-inferior to ramipril in terms of the primary end-point of death from cardiovascular causes, myocardial infarction, stroke or hospitalisation for heart failure. Primary events rates occurred in 16.5% of patients in the ramipril arm, 16.7% of patients in the telmisartan arm and 16.3% of patients in the combination therapy arm. In comparison with the ramipril group, the telmisartan group had lower rates of cough (1.1% versus 4.2% (P<0.001), and angioedema (0.1% versus 0.3%, P=0.01), but higher rates of hypotensive symptoms (2.6% versus 1.7%, P=0.001). Patients receiving the combination treatment showed increased hypotension, syncope and renal dysfunction.

In terms of CV outcomes therefore, there is no evidence that ARBs are superior to ACEI. Since publication of the ON-TARGET study the evidence to demonstrate non-inferiority is more robust. Taking this into account, on the basis of cost-effectiveness, it is therefore appropriate to utilize ACEI first line, substituting ARBs only where ACEI are not tolerated.

Table 2: Comparative Costs of ACEi and ARBs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Common Doses</th>
<th>Basic NHS cost per month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramipril</td>
<td>2.5 - 10mg daily</td>
<td>£0.90 - £1.48</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>10 - 40mg daily</td>
<td>£0.76 - £2.62</td>
</tr>
<tr>
<td>Losartan</td>
<td>50 - 100mg daily</td>
<td>£12.80 - £16.18</td>
</tr>
<tr>
<td>Candesartan</td>
<td>8 - 32mg daily</td>
<td>£9.89 - £16.13</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>150 - 300mg daily</td>
<td>£12.57 - £16.91</td>
</tr>
<tr>
<td>Valsartan</td>
<td>80 – 160mg daily</td>
<td>£16.44 - £23.80</td>
</tr>
</tbody>
</table>

From Drug Tariff @ www.ppa.nhs.net accessed 26.06.08

6. **What is the evidence to support ACEI versus ARB to reduce CV outcomes in patients with diabetes, with or without renal disease?**

Most diabetic patients die of CV events, therefore protection against such events is of paramount importance in this patient group. However, proteinuria is itself a risk factor for CV events, and patients with diabetic kidney disease are at incrementally higher CV risk. Treatment strategies should therefore aim to protect against CV events and preserve renal function in this group of patients.

- Evidence to demonstrate superiority of ACEI over ARB (or vice versa) in diabetic patients is lacking as there have been no head to head studies. Subgroup analysis of the recently published On-TARGET study, which included over 9,000 diabetic patients (37% of the study population), showed no difference between telmisartan and ramipril in terms of the primary endpoint (death from CV causes, myocardial infarction, stroke or hospitalisation for heart failure).
- ACEI and ARBs have been shown to reduce proteinuria in patients with diabetic kidney disease. There is also evidence that ACEI and ARBs delay progression to end-stage renal disease, demonstrated in different populations with diabetes. A recent Cochrane review (Strippoli 2004) investigated the use of ACEI or ARB in patients with diabetic kidney disease and concluded that ACEI used at maximal doses (compared to lower doses) reduced mortality in this group of patients. The group were unable to determine which drug class provides better protection, due to the lack of head to head studies.

Recent NICE guidance on the management of type 2 diabetes issued in May 2008 clearly emphasises the role of ACEI first-line in this patient group, and advised that ARBs should only be used in those patients unable to tolerate ACEI first-line. This is in line with the results of the Cochrane review and the current NHS PRODIGY guidance. Where ARBs are utilised second line in this group of patients, only losartan (for renal protection in type 2 diabetic patients with nephropathy (macroalbuminuria)) and irbesartan (for the treatment of renal disease in patients with hypertension and type 2 diabetes as part of an anti-hypertensive regimen) are currently licensed.

- NICE Clinical Guideline 66: Type 2 Diabetes. Issued May 2008

7. **What is the evidence to support ACEI versus ARBs in Black patients?**

Of eighteen studies identified in the literature that discuss this issue, only two compared ACEI and ARB prospectively in head to head studies.

- The first study of 40 black patients compared enalapril and eprosartan (supported by Smith Kline Beecham Pharmaceuticals) and looked at blood pressure lowering efficacy as a secondary endpoint, however the study numbers were insufficient to show any significance difference in either diastolic or systolic blood pressure between the two study arms.
- The second study of 51 African-American patients (supported by AstraZeneca) showed no difference between candesartan and enalapril monotherapy in terms of systolic blood pressure lowering, but a greater reduction in diastolic blood pressure with candesartan. This difference amounted to an absolute additional dBP reduction of 1.2mmHg in the candesartan treated arm, so the clinical relevance is questionable.
There is therefore no evidence-base to support the use of ARBs in preference to ACEI's in black patients. From a cost-effectiveness perspective, in line with for non-black patients, ACEI should always be used first-line.

Key messages from the literature regarding blood pressure management in black patients are that:

- ACE inhibitors and ARBs (as well as beta-blockers) are generally less effective as monotherapy in black hypertensives
- The addition of a diuretic to ACEI or ARB therapy improves the BP response in black patients

This supports the approach to BP management in black patients which is advocated by NICE / BHS guidance. First line therapy in this group of patients should be thiazide diuretic or calcium channel blocker – however, use of a thiazide initially will enhance the BP lowering effect of an ACEI when added at Step 2 of the guideline. As discussed above, there is currently no evidence that ARBs should be used in preference to ACEI in this group of patients.

- NICE Hypertension Guideline CG34. 2006 at [www.nice.org.uk](http://www.nice.org.uk); accessed 7th Oct 2007

8. Are there dose equivalents between ACEI and ARBs?
There are no evidence-based dose for dose equivalents between ACE inhibitors and angiotensin receptor blockers at this time.

- ACE Inhibitors and Angiotensin II Receptor Blockers: London New Drugs Group Oct 2007

9. How should ACEI doses be titrated safely?
Baseline blood pressure (BP) and U&Es (serum creatinine, estimated glomerular filtration rate, serum potassium) should be obtained before initiation of an ACEI.

BP and U&Es should be checked within two weeks of initiation or change of dose, and then annually thereafter.

ACEI dose should only be increased if:

- Systolic blood pressure (SBP) > 90mmHg
- Serum creatinine increases by less than 30% on each dose titration
- Potassium <5.5 mmol/L.

If serum creatinine increases by more than 50% after initiation then stop the ACEI and seek specialist advice.

- Guideline for Prescribing Angiotensin Converting Enzyme Inhibitors (ACEI) in Coronary Heart Disease Lambeth and Southwark PCT 2007
- NICE CG5 guidance for chronic heart failure, July 2003.

10. What should I do if creatinine increases after I have initiated an ACEI?
If the serum creatinine remains unchanged from the baseline then continue to up-titrare the ACEI with monitoring of creatinine, potassium and blood pressure.
If the serum creatinine increases by >30% from baseline:
- Stop potentially nephrotoxic drugs (e.g. NSAIDs)
- Stop non-essential vasodilators (e.g. Alpha-blockers)
- Stop potassium-retaining drugs (e.g. amiloride)
- Reduce doses of diuretics if no signs of heart failure

Repeat U&Es after 1 week and if the creatinine is still raised by >30% then halve the ACEI dose. If the raised creatinine persists then seek specialist advice.

If the serum creatinine increases by >50% or the value is > 350 micromol/L then stop the ACEI and seek specialist advice.

- Guideline for Prescribing Angiotensin Converting Enzyme Inhibitors (ACEI) in Coronary Heart Disease Lambeth and Southwark PCT 2007
- NICE CG5 guidance for chronic heart failure, July 2003.

11. What level of renal impairment is too high for ACEI/ARB initiation? When should patients be referred to secondary care before initiation?
The main contra-indication to ACEI use is severe bilateral renal artery stenosis. Renal dysfunction is not a contra-indication to prescribing an ACEI. ACEI initiation should be cautious in patients with a baseline creatinine of >150µmol/L or eGFR <60ml/min (moderate to severe renal impairment). These patients should be referred to a specialist centre for advice.

- Guideline for Prescribing Angiotensin Converting Enzyme Inhibitors (ACEI) in Coronary Heart Disease Lambeth and Southwark PCT 2007
- NICE CG5 guidance for chronic heart failure, July 2003.

12. What potassium level is too high for ACEI initiation or dose titration? Do ARBs have less effect on potassium?
In all cases, the rate of rise in serum potassium and the actual potassium level should be considered:
- An increase in serum potassium to <5.5 mmol/L is acceptable.
- If the potassium level is 5.6 - 5.9 mmol/L then concomitant medications/dietary factors should be reviewed. Concomitant drugs that may increase potassium levels include potassium-sparing diuretics (eg. Amiloride and spironolactone), heparins and potassium supplements. The potassium level should be repeated in 1-2 weeks after review.
- If the potassium level is > 6 mmol/L then the ACEI should be stopped and specialist advice obtained.

Potassium levels should be monitored at least annually for patients taking ACEI and ARBs.

Recent NICE guidance on the management of diabetics with renal dysfunction does not consider declining renal function or hyperkalaemia to be valid reasons for switching from ACEI to ARB. Where these issues are of concern, specialist advice should be sought.

- Guideline for Prescribing Angiotensin Converting Enzyme Inhibitors (ACEI) in Coronary Heart Disease Lambeth and Southwark PCT 2007
- NICE CG5 guidance for chronic heart failure, July 2003.
13. What blood pressure is too low for ACEI initiation or dose titration?
Systolic blood pressures of less than 90mmHg are considered too low for ACEI initiation or dose titration, except under expert supervision.
Following initiation or dose titration:
- If the blood pressure falls but the patient remains asymptomatic with hypotension, then a reduction in dose is not usually required.
- If the blood pressure falls and the patient becomes symptomatic (dizziness, lightheadedness, confusion) then stop non-essential anihypertensives (eg. Alpha-blockers, or diuretics if there are no signs of congestion), if symptomatic hypotension remains then consider reducing ACEI dose to see if symptoms improve.
If symptomatic hypotension persists – seek specialist advice.
- NICE CG5 guidance for chronic heart failure, July 2003.
- Guideline for Prescribing Angiotensin Converting Enzyme Inhibitors (ACEI) in Coronary Heart Disease Lambeth and Southwark PCT 2007

14. How can first dose hypotension with ACEI’s be avoided? What do I do if my patient is on a loop diuretic?
The first dose of an ACEI may cause hypotension although this is rare with the longer acting agents. Patients who are on a low sodium diet, on dialysis, dehydrated, taking high doses of diuretics or have heart failure may be more sensitive. ACEI therapy should be initiated at a low dose and is often administered at night, just before bed, to reduce the impact of any rapid haemodynamic changes. Once the dose has been established, the ACEI can be taken any time of the day (preferable the same time of day every day) for compliance. When initiating ACEI therapy, patients should be counseled to raise themselves slowly from a sitting or lying position in order to minimise any feelings of dizziness.

The BNF advises that:
“If the dose of diuretic is greater than 80mg furosemide or equivalent, the ACEI should be initiated under close supervision and in some patients the diuretic may need to be reduced or discontinued at least 24 hours beforehand (or longer depending on the duration of action). If high dose diuretic therapy cannot be stopped, close observation for at least 2 hours after administration of the first dose of ACEI or until the BP has stabilised is recommended. The lowest possible ACEI dose should be prescribed in these cases. Close monitoring of sodium and potassium is required”
- BNF 53 (March 2007) Ramipril SPC (Sept 2007)

15. How do I deal with ACEI induced cough?
Chronic cough is a well-described class effect of ACEI. It is typically dry and is associated with a tickling or scratching sensation in the throat. It is persistent, non productive and usually worse at night. Incidence of reports vary and have been reported in the range of 0.7 - 48% although this can also be agent dependent. It is of note that in some cases of cough the ACEI is not the causative agent. Certain patient groups appear more susceptible, namely the elderly, females, Chinese, Japanese, Indians, Blacks and those with CHF. Onset can occur any time from day one through to ten months, though it usually starts soon
after the ACEI is initiated. Spontaneous resolution over a few weeks may occasionally occur during continued treatment or with substitution of another ACEI.

**ACCP guidelines** recommend encouraging the patient to persevere (see also Key Messages document) but if that is not acceptable then recommend the following approaches:

1) **Withdraw and rechallenge (cough may not reoccur)**
   - If the cough is interfering with the patient’s quality of life a trial without the ACEI can be undertaken to confirm the causation. Following discontinuation the cough can take from four days up to as long as four weeks to resolve. (NB, the resolution of cough may be delayed in a subgroup of patients for up to 3 months). If the cough resolves after the cessation of therapy, a repeat trial may be attempted. In a minority of patients, cough will not recur though re-challenge with the offending agent usually results in recurrence of the cough within days to weeks. Re-challenging with another ACEI may not result in recurrence in all patients.

2) **Switch ACEI and reassess in four weeks**
   - Substitution with an alternative ACEI can be tried, if there is a compelling reason why therapy cannot be temporarily withdrawn

3) **Stop ACEI and switch to ARB**
   - In patients in whom persistent or intolerable ACEI cough occurs despite the strategies above, therapy should be switched, when indicated, to an ARB.

The cough is generally not dose-related although dose reduction in some patients may sometimes lead to improvement.

- **BNF 53 (March 2007),**
- **Micromedex ‘ACE Inhibitor-Induced Cough’**
- **London New Drugs Group APC/DTC Briefing Document, Oct 2007 ‘ACE Inhibitors and Angiotensin II Receptor Antagonists’**

16. **In what circumstances is dual therapy (ACEI plus ARB) warranted?**

   **Chronic kidney disease:** There are no long term trials to support the combination of an ACEI and ARB in diabetic/non diabetic kidney disease. In small short-term trials a benefit has been shown however it is unclear if this benefit may be due to effective blood pressure control. Therefore combination therapy should not be common practice and should only be used under specialist supervision. NICE guidance on the treatment of chronic kidney disease is due in September 2008.

   **Hypertension:** There are no long-term trials to support the routine use of these agents together in hypertension. Synergistic blood pressure lowering effects have been seen in the combination therapy in heart failure trials, however in these studies it is unclear if the benefits seen were due to a reduction in blood pressure alone. In the recently published ONTARGET study combination therapy was associated with no additional clinical benefit but significantly more adverse events. Therefore combination therapy should not be common practice and should only be used under specialist supervision.

   **Congestive Heart Failure**
NICE guidance 2003 states that the triple combination of ACEI/Beta-blocker/ARB should be avoided, pending the results of further trials. However more recent guidelines; SIGN 2007 and ESC 2005 include the use of triple therapy for symptomatic patients on dual therapy with an ACEI and Beta blocker following the publication of key trials:

- The CHARM-Added trial showed a statistically significant reduction in CV death among heart failure patients taking candesartan and ACEI therapy compared to ACEI therapy alone.
- The ValHeFt trial reported no significant difference in mortality between patients treated with standard therapy (including an ACEI) or standard therapy plus valsartan. The addition of valsartan to standard therapy was associated with a significant reduction in hospitalizations due to heart failure.
- The VALIANT trial looked at the combination in patients with recent MI with LVSD and clinical evidence of CHF. This showed no significant differences in CV mortality or morbidity with combination therapy of valsartan and captopril versus captopril or valsartan alone.

In all three trials, side effects were more marked with combination therapy. Note: only candesartan is licensed for use in chronic HF and only valsartan is licensed for post-MI heart failure.

Overall, the routine use of ACE inhibitor / ARB combination therapy is **not recommended** and should be reserved for patients with resistant congestive heart failure or renal disease, or severe unresponsive hypertension following specialist advice.

17. When both an ACEI and ARB are required, do you optimise the ACEI before adding ARB?
   As discussed in Q16, there is little data to support the use of combination therapy. The addition of an ARB should therefore only be considered when the ACEI dose has been fully optimised, and under specialist supervision.

18. How can I tell if my patient has RAS? What do I do about it? What implications does RAS have for ACEI / ARB?
   Renal artery stenosis (RAS) refers to narrowing of the afferent renal artery lumen, mostly commonly due to atherosclerosis. This stenosis limits renal blood flow and hence the glomerular filtration pressure. Auto-regulation, dependant on the action of Angiotensin II, leads to constriction of the efferent artery to maintain filtration pressure within the kidney. Risk factors for RAS include hypertension, increasing age, evidence of renal insufficiency (although this may not be present), atherosclerosis in other vascular beds (coronary, cerebrovascular, peripheral), diabetes mellitus and smoking.
Administration of ACEI or ARBs will block the regulatory response aimed at maintaining renal perfusion pressure and therefore may lead to a rapid decline in renal function. The main concern is patients with known bilateral renal artery stenosis, where inappropriate prescribing of ACEI or ARB can cause renal failure. Patients with unilateral RAS, will maintain renal function in the unaffected kidney and can still be considered for ACEI therapy. In patients with established bilateral RAS, ACEI or ARB should only be initiated under specialist supervision.

However, RAS may be asymptomatic and undiagnosed and it is therefore essential to ensure appropriate monitoring is undertaken post-initiation of ACEI or ARB to ensure that these cases can be identified early. RAS is characterised by a sudden deterioration in renal function following initiation of ACEI or ARB. As discussed in Q 9&10, if serum creatinine increases by more than 50% after initiation, the ACEI/ARB should be stopped and specialist advise sought.

19. **Is aortic stenosis a contraindication for ACEI / ARB?**
ACEI and ARB have traditionally been considered contraindicated in aortic stenosis, although this is no longer listed specifically in the summary of product characteristics for most agents in this class. There is also emerging evidence that, under specialists supervision, ACEI (or ARB) may have a role in the management of this indication. However, ACEI or ARB should only be initiated cautiously in patients with aortic stenosis, under the supervision of a specialist, with close monitoring.

- Cozaar ® Summary of Characeristics Merck, Sharp and Dohme. Jan 2007

20. **If my patient has had angioedema with an ACEI, can they have an ARB?**
The SPCs state that ARBs are not recommended in patients who have had angioedema with an ACEI.

> “Anaphylactic reactions, angioedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx and/or tongue have been reported rarely in patients treated with losartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors.”

However, in the CHARM-Alternative trial, 38 out of 39 patients who had angioedema / anaphylaxis previously with ACE inhibitors were treated successfully with candesartan to reduce cardiovascular death and hospital admission in patients with chronic heart failure and left-ventricular systolic dysfunction. Only one of 39 patients in the candesartan group with a history of angioedema on ACE inhibitors had recurrence leading to permanent drug discontinuation. It was reported that the patient who experienced angioedema with candesartan did not warrant hospital admission. The investigators concluded that ARBs may be considered in patients with a history of angioedema / anaphylaxis with ACE inhibitors. However, in these circumstances, ARBs should be initiated by a specialist with caution, at low doses and with careful monitoring.


21. **Are there any medications that interact with ACEI or ARBs?**
Due to the hypotensive effect of these groups of drugs, there is potential for an enhanced
effect by any drug that also lowers blood pressure. *(see question 16)*

Other interactions relate to the increase in serum potassium levels caused by ACE inhibitors
and ARBs, particularly in the presence of other risk factors such as increased age or renal
insufficiency. Hyperkalaemia may occur with ciclosporin, potassium salts, K-sparing diuretics
e.g. amiloride and aldosterone antagonists e.g. spironolactone. Patients should also be
advised to avoid potassium-containing salt substitutes.

Both ACE inhibitors and ARBs reduce the excretion of lithium, leading to an increased risk of
toxicity. The development of this interaction may be delayed.

NSAIDs present an increased risk of deterioration in renal function or acute renal failure
when prescribed with ACE inhibitors or ARBs, particularly if poor renal perfusion is present

Telmisartan can increase the plasma concentration of digoxin when used concomitantly.

- *BNF 53, Stockley’s Drug Interactions (via Medicines Complete online March 2008)*

---

This document has been developed through a partnership of Pharmacists, Consultants, GPs and nurses in South East London. The
aim is to provide support to clinicians making decisions regarding the use of ACEI and ARB in clinical practice. The FAQ will be
reviewed every two years, or earlier if necessary. If you have any comments on the questions here, or have suggestions of other
questions to be included, please email helen.williams11@nhs.net

Representatives from the following organisations contributed to the development of this document:

- Guys and St Thomas’ Foundation Trust
- King’s College Hospital Foundation Trust
- Princess Royal University Hospital, Farnborough
- Queen Elizabeth Hospital, Woolwich
- Queen Mary’s Hospital, Sidcup
- University Hospital Lewisham
- Bexley PCT
- Bromley PCT
- Greenwich PCT
- Lambeth PCT
- Lewisham PCT
- Southwark PCT