

Renin-angiotensin system drugs: dual therapy

Key therapeutic topic

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[nice.org.uk/guidance/ktt2](https://www.nice.org.uk/guidance/ktt2)

Options for local implementation

- Dual therapy with an angiotensin-converting enzyme (ACE) inhibitor plus an angiotensin receptor blocker (ARB) has only a limited place in treatment, specifically in a small minority of people with heart failure.
- Review and, if appropriate, revise prescribing of dual therapy to ensure it is in line with NICE guidance on [hypertension](#), [chronic heart failure](#), [chronic kidney disease](#), [myocardial infarction – secondary prevention](#), [type 1 diabetes](#) and [type 2 diabetes](#).

Evidence context

The [June 2014 edition of Drug Safety Update](#) highlighted a European safety review into dual therapy with an ACE inhibitor plus an ARB. This review concluded that no significant benefits of dual therapy were seen in people who did not have heart failure and there was an increased risk of hyperkalaemia, hypotension, and impaired renal function. See the NICE medicines evidence commentary [Efficacy and safety of dual blockade of the renin-angiotensin system](#) for more information. UK Medicines Information (UKMi) has also published a medicines question and answers resource on [the rationale and evidence for combining ACE inhibitors with ARBs for treating hypertension and for preventing vascular events](#).

Dual therapy has only a limited place in treatment, specifically in a small minority of people with heart failure. The NICE guideline on [chronic heart failure](#) recommends that, after seeking specialist advice, the addition of an ARB licensed for heart failure is an option that could be considered for people who remain symptomatic despite optimal therapy with an ACE inhibitor and a beta-blocker (see table 1 for details). Candesartan and valsartan are the only ARBs licensed as add-on therapy to

ACE inhibitors in this situation. The MHRA states that the triple combination of an ACE inhibitor, an ARB, and a mineralocorticoid receptor antagonist or other potassium-sparing diuretic in people with heart failure is not recommended. UKMi has published a medicines question and answers resource on the [use of a combination of ACE inhibitors with ARBs in patients with heart failure](#).

In the [June 2014 edition of Drug Safety Update](#), the MHRA advised that people with diabetic nephropathy should not be given an ARB with an ACE inhibitor because they are already prone to developing hyperkalaemia. Combining the direct renin inhibitor, aliskiren, with an ACE inhibitor or an ARB is also strictly contraindicated in people with kidney impairment (estimated glomerular filtration rate <60 ml/minute/1.73 m²) or diabetes.

For further information on renin-angiotensin system drugs see the NICE pathways on [hypertension](#), [chronic heart failure](#), [chronic kidney disease](#), [myocardial infarction – secondary prevention](#) and [diabetes](#). A separate key therapeutic topic on [acute kidney injury \(AKI\): use of medicines in people with or at increased risk of AKI](#) is also available.

Table 1 Summary of NICE recommendations on the use of renin-angiotensin system drugs in various indications

Indication	Relevant NICE guideline	Recommendation in relation to renin-angiotensin system drugs	Recommendation in relation to dual blockade with renin-angiotensin system drugs
Hypertension	Hypertension in adults: diagnosis and management . NICE guideline CG127 (August 2011)	Offer people aged under 55 years step 1 antihypertensive treatment with an ACE inhibitor or a low-cost ARB. If an ACE inhibitor is prescribed and is not tolerated (for example, because of cough), offer a low-cost ARB.	Do not combine an ACE inhibitor with an ARB to treat hypertension.

<p>Heart failure</p>	<p><u>Chronic heart failure in adults: management.</u> NICE guideline CG108 (August 2010)</p>	<p>Offer both ACE inhibitors and beta-blockers licensed for heart failure to all patients with heart failure due to left ventricular systolic dysfunction. Consider an ARB licensed for heart failure as an alternative to an ACE inhibitor for patients with heart failure due to left ventricular systolic dysfunction who have intolerable side effects with ACE inhibitors.</p>	<p>Seek specialist advice and consider adding an ARB licensed for heart failure (especially if the patient has mild to moderate heart failure) if a patient remains symptomatic despite optimal therapy with an ACE inhibitor and a beta-blocker. Other options are adding an aldosterone antagonist licensed for heart failure or hydralazine in combination with nitrate.</p>
<p>Myocardial infarction (MI) – secondary prevention</p>	<p><u>Myocardial infarction: cardiac rehabilitation and prevention of further MI.</u> NICE guideline CG172 (November 2013)</p>	<p>Offer people who present acutely with an MI an ACE inhibitor as soon as they are haemodynamically stable. Continue the ACE inhibitor indefinitely. Offer people after an MI who are intolerant to ACE inhibitors an ARB instead of an ACE inhibitor.</p>	<p>Do not offer combined treatment with an ACE inhibitor and an ARB to people after an MI, unless there are other reasons to use this combination.</p>

<p>Chronic kidney disease (CKD)</p>	<p><u>Chronic kidney disease in adults: assessment and management.</u> NICE guideline CG182 (July 2014)</p>	<p>Offer a low-cost renin-angiotensin system antagonist^a to people with CKD and:</p> <ul style="list-style-type: none"> • diabetes and an albumin:creatinine ratio of 3 mg/mmol or more • hypertension and an albumin:creatinine ratio of 30 mg/mmol or more • an albumin:creatinine ratio of 70 mg/mmol or more (irrespective of hypertension or cardiovascular disease). 	<p>Do not offer a combination of renin-angiotensin system antagonists^a to people with CKD.</p>
<p>Type 1 diabetes</p>	<p><u>Type 1 diabetes in adults: diagnosis and management.</u> NICE guideline NG17 (August 2015)</p>	<p>Start a trial of a renin-angiotensin system blocking drug as first-line therapy for hypertension in adults with type 1 diabetes. ACE inhibitors should be started and, with the usual precautions, titrated to full dose in all adults with confirmed nephropathy (including those with microalbuminuria alone) and type 1 diabetes. If ACE inhibitors are not tolerated, ARBs should be substituted.</p>	<p>Combination therapy with an ACE inhibitor and an ARB is not recommended.</p>

Type 2 diabetes	<u>Type 2 diabetes in adults: management.</u> NICE guideline NG28 (December 2015)	First-line antihypertensive drug treatment should be a once-daily, generic ACE inhibitor. Exceptions to this are people of African-Caribbean descent or women for whom there is a possibility of becoming pregnant. If continuing intolerance to ACE inhibitor (other than renal deterioration or hyperkalaemia), change to an ARB.	Do not combine an ACE inhibitor with an ARB to treat hypertension.
<p>^a A renin-angiotensin system antagonist is defined in the NICE guideline on chronic kidney disease as a drug that blocks or inhibits the renin-angiotensin system including ACE inhibitors, ARBs and direct renin inhibitors.</p>			

Prescribing data

A [prescribing comparator](#) was previously available to support this key therapeutic topic – ACE inhibitor % items. This comparator has been retired from Q1 2015/16 data onwards and therefore data are not presented^[1].

^[1] For details of any update to the comparators refer to the [Health and Social Care Information Centre website](#) and the [Information Services Portal](#), Business Services Authority.

Update information

February 2016 This topic was retained for the 2016 update of Medicines optimisation: key therapeutic topics. The evidence context has been updated in the light of new guidance and important new evidence as appropriate.

About this key therapeutic topic

This document summarises the evidence base on this key therapeutic topic which has been identified to support Medicines Optimisation. **It is not formal NICE guidance.**

For information about the process used to develop the Key therapeutic topics, see the [integrated process statement](#).

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