WeMeReC
Welsh Medicines Resource Centre
Canolfan Adnoddau Moddion Cymru

Bulletin

"Independent prescribing information for NHS Wales"

ACE inhibitors and ARBs

The renin-angiotensin-aldosterone system (RAAS) helps maintain haemodynamic stability by regulating blood pressure (BP), water, and electrolyte balance. Inappropriate or abnormal activation of the system can lead to excessive vasoconstriction, abnormal muscular hypertrophy, and fibrosis. This is associated with many cardiovascular disorders including hypertension, chronic heart failure (CHF), myocardial infarction (MI), and stroke, and with renal disorders such as diabetic nephropathy.[1] The RAAS and pharmacological targets for current therapies are shown in figure 1 (page 4).

This bulletin outlines the appropriate prescribing and monitoring of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), specifically in hypertension and CHF. ACE inhibitors have the more robust evidence base for these conditions and are more widely used, but ARB use is increasing. Current recommendations support the selection of the class of agent but not of any specific agent within a class, except on the basis of differences in marketing authorisations (see the Summaries of Product Characteristics) or cost.

Monitoring treatment

When initiating an ACE inhibitor or ARB it is important to measure baseline renal function and serum electrolytes.[2,3,4] Tests should be repeated one to two weeks after initiation, and when increasing the dose.[5] In **hypertension**, when a patient is established on treatment, renal function and electrolytes should be measured at least annually. In **CHF**, monitoring should preferably be carried out within days if the patient's condition or medication changes. Once stable, further monitoring should be carried out at least every six months.[3]

Further monitoring is required for both classes of agent in certain patients; for example those with co-morbidities, those taking certain other medications, and anyone taking an ACE inhibitor together with an ARB (see page 5).[5,6]

Summary

- Biochemical monitoring of patients taking ACE inhibitors or ARBs is often neglected, but should be undertaken at base-line and then repeated following initiation, dose changes, and regularly thereafter.
- An ACE inhibitor or low-cost ARB is considered first line for hypertension in non-black patients under the age of 55.
- An ACE inhibitor in combination with a beta-blocker is first-line therapy for CHF.
- Combining an ACE inhibitor with an ARB is not recommended in hypertension but may have a place in specialist care of CHF. Such therapy frequently leads to an increase in adverse effects.
- Beneficial renal effects of therapy are important in managing chronic kidney disease (CKD) and diabetic nephropathy. However, these medicines can also impair renal function in some patients. The risks are greater in salt- or volume-depleted patients.
- Hyperkalaemia is an adverse effect of therapy. The risk is increased in patients with renal impairment; those taking certain medicines, such as potassium-sparing diuretics, aldosterone antagonists, or ciclosporin; and in those taking an ACE inhibitor and ARB in combination.
- ACE inhibitors and ARBs are contraindicated in pregnancy. A medicine from a different class is preferred in women who may want to have children.

Several studies have shown that recommendations for biochemical monitoring are frequently not adhered to, sometimes resulting in serious adverse events. One recent study of monitoring in patients beginning treatment for hypertension in primary care found that only 59% of patients taking ACE inhibitors received baseline monitoring.[7] Many were not monitored again: the proportion receiving any form of further monitoring was 38%. Perhaps encouragingly, follow up was more likely in older patients and those with pre-existing diabetes.[7]

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Hypertension

Hypertension is a major preventable cause of morbidity and mortality in the UK.[2] It is a significant risk factor for ischaemic and haemorrhagic stroke, MI, heart failure, CKD, cognitive decline, and premature death. Hypertension in patients with diabetes mellitus is associated with additional adverse outcomes, including a more rapid decline in renal function and, therefore, the treatment of elevated BP is likely to be more beneficial.

Who to treat

Hypertension should be established by at least two separate measurements. Confirmatory ambulatory blood pressure monitoring (ABPM) may be required, but if this is unsuitable, home blood pressure monitoring (HBPM) may be used (see Box 1).[2]

Box 1 Stages of Hypertension

- **Stage 1:** clinic BP ≥140/90 mmHg; confirmed by ABPM or HBPM at ≥135/85 mmHg.
- **Stage 2:** clinic BP ≥ 160/100 mmHg; confirmed by ABPM or HBPM at ≥ 150/95 mmHg.
- **Severe:** clinic systolic ≥ 180 mmHg or diastolic ≥ 110 mmHg.

In addition to lifestyle interventions, which should be offered to all patients, pharmacological treatment is recommended if a patient has: [2]

- Stage 1 hypertension and is < 80 years with at least one of: formally assessed target organ damage, renal disease, diabetes, established cardiovascular disease, or a formally established 10-year risk equivalent to ≥ 20%.
- Stage 2 hypertension at any age.
- Severe hypertension at any age (same-day referral for specialist care if accelerated hypertension or suspected phaeochromocytoma).

The place of ACE inhibitors and ARBs

The National Institute for Health and Clinical Excellence (NICE) recommends that an **ACE inhibitor** or a **'low-cost' ARB** is offered first line to patients under the age of 55.[2] In patients older than this and for all black patients of African or Caribbean family origin, a calcium channel blocker (CCB) should be offered first line. If a CCB is not suitable, or if there is evidence or high risk of CHF, a thiazide-like diuretic should be offered. An ACE inhibitor or ARB is recommended second line for most patients who receive a CCB (or diuretic) first. In all cases, where possible, the first choice should be a medicine that is taken once daily.[2]

Clinic BP measurements should be used to assess the effect of therapy. This should be undertaken frequently at the initiation of therapy and if the dose is changed, until BP is at or below target, and at least annually thereafter.[2]

The evidence

When used to lower BP, ACE inhibitors have been shown to reduce cardio- and cerebrovascular events, and all-cause mortality. In comparative clinical trials, their effects have been similar to those of CCBs and diuretics.[1,5,8] ACE inhibitors have been shown, as have ARBs, to be more effective than CCBs in the prevention of CHF in patients with hypertension, although somewhat less effective than diuretics.[9]

ACE inhibitors and ARBs are relatively more efficacious in hypertensive patients with higher plasma renin activity.[10] As benefits derived in terms of outcomes correlate with BP reduction, these agents are advocated in patients in whom plasma renin is a significant factor, typically younger, non-black patients.[2,5,10] (Plasma renin declines with increasing age and is lower in black patients of African and Caribbean origin.) A laboratory measure of renin activity is available and measuring the renin concentration in order to target therapy may be an option in the future; studies are ongoing into the feasibility of this approach.[10]

In the hierarchy of treatments, the NICE hypertension guideline now positions low-cost ARBs alongside ACE inhibitors, rather than as an option to consider only if ACE inhibitors are contraindicated or not tolerated. This is based on the results of three studies which, when pooled together showed no significant difference between the two groups of medicines for clinical outcomes.[2,11,12,13] A recent publication has refuted a previous finding that patients treated with ARBs may suffer an increased risk of MI.[14] However, it should be noted that the evidence base for ARBs is still significantly smaller than for ACE inhibitors.

If an ARB is to be prescribed, it is useful to bear in mind that the choice of agent will have significant cost implications. Not all ARBs can be considered to be 'low cost' as some are still protected by patent. Historically, when patents expire, costs do not drop quickly but reduce gradually over an extended period. Several ARBs are available as generics, but only losartan is currently priced comparably to generic ACE inhibitors. Changes in basic NHS list prices are reflected in the Drug Tariff, which can be found at www.ppa.org.uk/ppa/edt_intro.htm.

Chronic heart failure

CHF is a complex clinical syndrome that results from the inability of the heart to maintain cardiac output. It is caused by myocardial dysfunction and is generally categorised as either heart failure due to **left ventricular systolic dysfunction (LVSD)**, which is associated with a reduced left ventricular ejection fraction, or **heart failure with a preserved ejection fraction (HFPEF)**.[3] In the community, there are roughly equal numbers of patients with each. There is evidence of a trend towards prognoses improving, but 30-40% of patients still die within a year of diagnosis.[3]

Who to treat

CHF is difficult to diagnose as the presenting signs and symptoms are often non-specific, especially in elderly patients, and may be attributed to co-morbidities. The diagnosis is made by combining a careful detailed history – hypertension, previous MI, atrial fibrillation (AF), and coronary artery disease are significant – with clinical examination and tests.

Patients who have had a previous MI should be referred for echocardiography and specialist assessment within two weeks.[3] Serum natriuretic peptides, either B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NTproBNP), should be measured in patients without previous MI (taking into account local arrangements). High levels carry a poor prognosis and such patients should also be referred for echocardiography.[3] Clinicians should be aware that levels may be reduced by obesity and treatments such as ACE inhibitors, ARBs, diuretics, beta-blockers, and aldosterone antagonists and that high levels can have several causes other than CHF. For reference levels see NICE Guideline.[3] The level of serum natriuretic peptide does not differentiate LVSD from HFPEF.

All patients with CHF require monitoring, which should include, as a minimum:[3]

- clinical assessment of functional capacity, fluid status, cardiac rhythm (including pulse), cognitive status and nutritional status.
- medication review – assessing efficacy and any adverse effects of treatment.
- serum urea, electrolytes, creatinine, and estimated glomerular filtration rate (eGFR).

The place of ACE inhibitors and ARBs

Patients with HFPEF should be treated in line with NICE guidance for co-morbidities such as hypertension, ischaemic heart disease, AF, and diabetes. Those with LVSD should be offered both an ACE inhibitor and a beta-blocker licensed for CHF if these are not contraindicated.[3] Both should be titrated up to the optimum dose without unnecessary delay. Clinical judgement should be exercised when deciding which agent to start first; there appears to be no significant difference in outcomes either way.[3]

An ARB licensed for heart failure may be considered if an ACE inhibitor is not tolerated. Regarding cough, it is worth noting that the incidence associated with ACE inhibitors is difficult to establish and, in studies of CHF, reported incidences are higher than drug-induced withdrawal rates.[15] Second-line treatment that combines an ARB with an ACE inhibitor is an option if a patient remains symptomatic despite optimal therapy (see below). Specialist advice should be sought.[3]

The evidence

Most evidence for treatment is in **LVSD** where ACE inhibitors improve symptoms, reduce hospitalisation rates, and improve survival rates across all age groups.[1,3] The target or the highest tolerated dose of ACE inhibitor should be achieved as soon as possible; the dose may be doubled at short intervals – for example, every two weeks.[3,16] As discussed in the WeMeReC Bulletin, November 2008,[16] doses used in clinical practice are sometimes suboptimal.

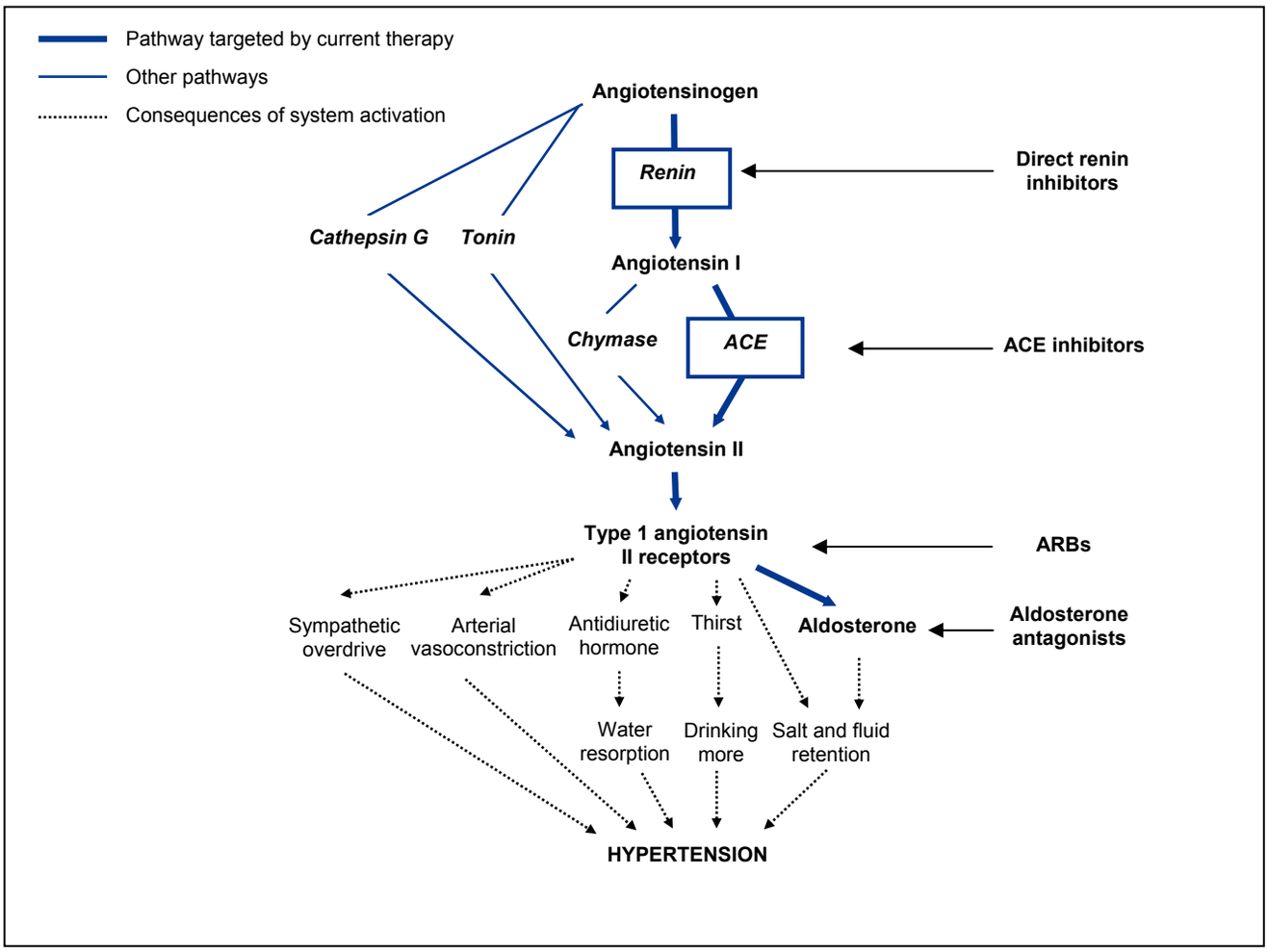
Again, the evidence base for ARBs is smaller than that for ACE inhibitors. As a first-line alternative, where ACE inhibitors are not tolerated, ARBs appear to perform similarly in terms of patient outcomes.[1] For use second-line, see '*Combined ACE inhibitor and ARB therapy*' (page 5).

In **HFPEF**, patients have similar symptoms and many of the same outcomes as in LVSD. Hypertension is frequently present and patients may have diabetes or ischaemic heart disease. It is likely that an ACE inhibitor would be prescribed and be effective for one of these co-morbid conditions. Placebo-controlled trials in HFPEF have shown that an ACE inhibitor can significantly reduce CHF hospitalisation at one year, but may not affect other outcomes such as all-cause mortality, cardiovascular mortality, quality of life, or CHF hospitalisation beyond one year.[3,17,18] Serious adverse effects do not appear to significantly differ between active treatment and placebo.[17,18]

Placebo-controlled studies of ARBs in HFPEF have shown no significant effect on CHF hospitalisation, all-cause mortality, or cardiovascular mortality.[3,19,20] There is, however a significant increase in the rate of hyperkalaemia and/or raised serum creatinine with active treatment.

Figure 1. A simplified schematic of the renin-angiotensin-aldosterone system (RAAS)

(Adapted from: Renin-angiotensin-aldosterone system blockade for cardiovascular diseases: current status[1])



The RAAS cascade is initiated when renin, produced by the kidneys in response to reduced renal perfusion pressure, cleaves hepatically produced angiotensinogen into the biologically inactive angiotensin I. In turn, this is hydrolysed by ACE, produced mainly in the lungs, into the active angiotensin II (A-II), which is an agonist of the various A-II receptors. The effects of activating the type 1 A-II receptor are wide-ranging and include arterial vasoconstriction, sympathetic overdrive, thirst, direct fluid and salt retention, aldosterone production leading to further fluid and salt retention, and anti-diuretic hormone production that promotes water resorption.[1,5,21]

In addition to ACE inhibitors and ARBs, medicines targeting other parts of the system are available. An example of a commonly used agent is the aldosterone antagonist spironolactone, which has an established role in the treatment of CHF.[3] Beta-blockers also have an effect on the RAAS, reducing renin secretion. The direct renin inhibitor aliskiren▼ is available for use in essential hypertension, although this is not recommended by the All Wales Medicines Strategy Group[22] due to insufficient clinical and cost-effectiveness data in comparison to other antihypertensive agents. More recently, due to reported adverse outcomes, the European Medicines Agency has recommended that aliskiren-containing medicines should not be used concomitantly with ACE inhibitors or ARBs in any patients, but particularly in those with diabetes mellitus or moderate to severe renal failure. (See www.wales.nhs.uk/awmsg, *Things to know about…aliskiren* at www.wemerec.org, and www.ema.europa.eu.)

Additionally there are some novel therapies in development, including two anti-RAAS vaccines and a type 2 A-II receptor agonist. (Activation of the type 2 A-II receptor also has wide-ranging effects, partially opposing those of the type 1 receptor; these include vasodilation, antifibrosis, apoptosis, natriuresis, and reduced inflammation.)[21]

Combined ACE inhibitor and ARB therapy

It has been proposed that combining an ACE inhibitor and an ARB might confer benefit over the use of either agent alone due to their different mechanisms of action. Standard doses of ACE inhibitors only partially inhibit the ACE. Other enzymes such as chymase, cathepsin G and tonin circumvent this, producing A-II by other mechanisms (see figure 1, page 4). This leads to the phenomenon known as 'A-II escape'.[1] Adding an ARB to also antagonise the type 1 A-II receptor should, in theory, more completely antagonise the RAAS cascade than using an ACE inhibitor alone.

Combination therapy is not recommended for the treatment of hypertension.[2] Large randomised controlled trials comparing an ACE inhibitor, an ARB, and a combination of the two for the prevention of various cardiovascular outcomes have found no significant differences in efficacy between the three regimens.[13] Combination therapy is, however an option in heart failure, where an ARB may be added as a second-line agent.[3] Several clinical trials have shown that the addition of an ARB to an ACE inhibitor alone or an ACE inhibitor/beta-blocker combination may confer some benefit on CHF hospitalisation rates.[3,23]

Combining ACE inhibitor and ARB therapy is associated with significantly more adverse effects than monotherapy, including hypotension and related symptoms, hyperkalaemia, renal dysfunction, and an increase in the need for dialysis.[3,13,23] One longitudinal study of combination therapy in the elderly (the majority of patients did not have an established indication for receiving treatment) reported an excess of renal dysfunction and hyperkalaemia in those receiving the combination.[24]

It is, therefore, imperative that scrupulous monitoring of serum urea, electrolytes, creatinine, and eGFR is carried out where combination therapy is used. It is likely that there will have been specialist involvement before a patient is treated with such a combination and advice on monitoring should be available. The patient should be aware of the signs of hypotension and BP should be monitored regularly.

Use for renal disorders

ACE inhibitors (or ARBs if ACE inhibitors are not tolerated)[4] delay disease progression in patients with **CKD**. CKD often exists together with other conditions, such as hypertension, cardiovascular disease, and diabetes. To avoid late diagnosis, patients with such conditions should have eGFR assessed. Where appropriate, they should also undergo testing for proteinuria by determining the urinary albumin:creatinine ratio (ACR). Different ACR thresholds for ACE inhibitor/ARB treatment exist in patients with CKD, with lowered thresholds in those with hypertension and/or diabetes. Unless contraindicated, **all patients with diabetic nephropathy** causing proteinuria or with established microalbuminuria should receive ACE inhibitor or ARB therapy.[6]

Adverse effects

First-dose **hypotension** is not uncommon with short-acting ACE inhibitors such as captopril. This is not often a problem with the longer-acting agents or when ACE inhibitors are used as monotherapy for hypertension. The risk of symptomatic hypotension may, however, be minimised if patients take the initial dose at bed-time.

With ACE inhibitors, **dry cough** may become troublesome on continued use. The reported incidence of cough in clinical studies has varied very widely, but appears to be in the region of 10% across the class. Around a quarter of those affected withdraw from medication due to cough.[18] It is thought that twice as many women are affected as men.[5] The mechanism is not fully understood but is thought to be due to the accumulation of kinins. The incidence of dry cough with ARBs is lower and so a change of therapy might prove beneficial if an ACE inhibitor is not tolerated.

Renal impairment and diabetes, especially with nephropathy, in patients taking ACE inhibitors and ARBs are risk factors for **hyperkalaemia**. There is also an increased risk of hyperkalaemia when ACE inhibitors or ARBs are used in combination with potassium-sparing diuretics and such combinations should be avoided where possible. If the concurrent use of aldosterone antagonists is required in CHF or for resistant hypertension (at 'Step 4'), caution should be exercised and serum potassium should be closely monitored.[2,6] Care should be taken when using other medicines with the potential to raise potassium concentrations, for example, potassium salts and ciclosporin.[6]

In certain circumstances, ACE inhibitors and ARBs have the **potential to impair renal function**. The elderly are particularly at risk, as are patients who are taking other medicines that affect renal function, such as nonsteroidal anti-inflammatory drugs.[6] ACE inhibitors and ARBs are contraindicated in patients with bilateral renal artery stenosis or with stenosis in a renal artery supplying a single functional kidney due to the risk of acute renal impairment.

Interacting medicines are best avoided in patients with known or suspected renovascular disease and should be used with particular caution in those who may have undiagnosed or clinically silent disease, for example patients with peripheral vascular disease. The risk of renal failure also increases in salt- and volume-depleted patients, for example, those taking concurrent diuretics or the acutely ill and dehydrated.[5,6] If serum creatinine rises markedly during treatment, treatment should be stopped, and the patient promptly referred to a specialist.

Urticaria and **angioedema** are uncommon but potentially severe adverse effects, again thought to be mediated by the accumulation of kinins with ACE inhibitor therapy – treatment should be withdrawn if this occurs. The incidence is lower with ARBs and, if the therapeutic response to an ACE inhibitor had been good, an ARB may be substituted. Re-challenge with an ACE inhibitor should not be undertaken.[5,6]

ACE inhibitors and ARBs are contraindicated in **pregnancy** as they are associated with teratogenicity in the early stages. In later pregnancy they may cause foetal renal impairment and oligohydramnios. A drug from a different class is preferred in women who may want to have children.[5,6]

A modestly increased cancer risk in certain patients taking ARBs was suggested by one recent meta-analysis. However, the regulatory authorities in Europe and North America have reviewed subsequent data from three meta-analyses and two large observational studies and conclude that there is no significant association between these medicines and overall cancer risk.[25]

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