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Are all angiotensin receptor blockers the same?

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Introduction

This supplement is based on the proceedings of a one-day round-table meeting held on 20th February 2010 to debate whether angiotensin receptor blockers (ARBs) have a class effect or whether they show different efficacy and safety profiles and so should be selected and used on an individual basis. The round-table meeting was initiated and funded by Takeda UK Ltd.

With the patent expiry of the first-in-class ARB, losartan, in March 2010, it is important to decide whether all ARBs are interchangeable since the availability of generic losartan at a price that could be perceived as attractive to primary care trusts (PCTs) and prescribers may result in pressure on physicians to switch patients onto the cheapest generic ARB available. Also, the recent EU Directive 2001/83/EC provides a mechanism for harmonisation of drug labelling for drugs across countries within the EU: this might imply that all ARBs are interchangeable, thus reinforcing the use of a cheaper generic ARB in all clinical situations.

The key conclusion from this meeting was that the evidence base for ARBs varies for the different drugs in this class. Therefore, assuming a class effect may not optimise management decisions for individual patients. Different ARBs have differing pharmacological effects, with potentially different efficacy profiles. Randomised trial evidence differs for the various drugs in this class and so they should not be used interchangeably. The ARB used in a particular setting should be selected based on clinical trial evidence for its use rather than solely on cost considerations. The papers in this supplement provide the evidence for these conclusions and provide guidance for the physician in selecting the most appropriate ARB for various clinical situations

Conflict of interest

MC provides consultancy advice to a number of pharmaceutical and device companies, including Takeda UK Ltd. He holds no stocks or shares in any such company.

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Dr Theresa McDonagh (Presenter)
Dr Peter Meredith (Presenter)
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Comparative ARB pharmacology

Peter Meredith

Differentiation in pharmacokinetics and pharmacodynamics

Angiotensin II receptor blockers (ARBs) are a class of pharmaceutical agents that modulate the renin-angiotensin-aldosterone system (RAAS), which is responsible for blood pressure (BP) regulation and fluid and electrolyte homeostasis.

Losartan was the first ARB to be approved for clinical use. There are currently seven ARBs on the market: losartan, valsartan, candesartan, irbesartan, olmesartan, eprosartan and telmisartan. Despite belonging to the same drug class, these ARBs vary in some aspects of their chemical structure. This leads to important differences in pharmacokinetic and pharmacodynamic characteristics, which may be observed in terms of active metabolite, bioavailability, volume of distribution, terminal half-life, hepatic/renal elimination and protein binding (**table 1**). For example, losartan and candesartan are both pro-drugs, but losartan requires cytochrome P450-mediated biotransformation to yield the active moiety EXP-3174, while candesartan cilexetil is rapidly converted to candesartan by ester hydrolysis during absorption from the gastrointestinal tract.

The mechanisms of antagonism also vary between the ARBs: some show insurmountable antagonism (e.g. candesartan) and others show surmountable antagonism (e.g. losartan). Insurmountable antagonism is characterised by long-lasting inhibition, slow dissociation, irreversible binding, conformational changes and potentially internalisation, whereas surmountable antagonism is characterised by short-lasting inhibition and fast, reversible binding.[1] Losartan only binds at two angiotensin II type 1 receptor (AT_1) sites, compared to candesartan which shows high binding affinity at four sites.[2] It is suggested that the tight binding and slow dissociation of candesartan from the AT_1 receptor may account for the magnitude of the antihypertensive efficacy of candesartan and for its long duration of action, inducing long-lasting suppression of the RAAS[3, 4](**figure 1**).

Differences in ARB efficacy

It has long been established that individuals with elevated BP are at greater risk for cardiovascular or cerebrovascular events, such as stroke, myocardial infarction and heart failure. Epidemiological evidence and findings from outcome trials indicate that the relative risk of cardiovascular events is related to BP levels in a continuous and linear manner.[5] A meta-analysis of 61 cohort studies, together with the results of a meta-analysis of 147 randomised trials,[6,7] suggested that when a single BP-lowering drug at a standard dose reduces diastolic BP by approximately 5 mmHg, there is a resulting reduction of approximately 25% in the relative risk of coronary heart disease events and 35% in the relative risk of stroke. As such, it is logical, when initiating antihypertensive treatment, to use within any given drug class the agents most likely to produce the greatest BP reduction.

There is evidence from clinical trials that the ARBs differ in their duration of action. When the mean change from baseline in systolic BP was evaluated over a 36-hour period for losartan and candesartan, the BP response was seen to be stable over this period in the candesartan-treated patients, whereas a drop in efficacy was seen after 24 hours in the losartan group (**figure 2**).[5] This finding could be of particular importance in patients who are not fully compliant and miss an occasional dose, but would be expected to have less impact on BP with a drug that has a longer and more stable duration of action.

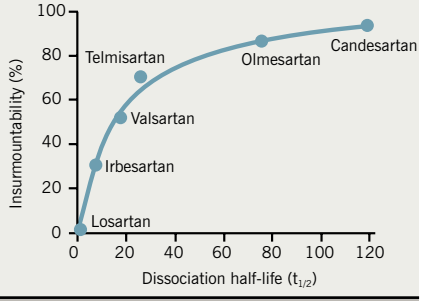
Differences in the magnitude of response between different ARBs have also been evaluated. In 2002, Elmfeldt *et al.* conducted an analysis of the dose-response relationships for the first four available ARBs: losartan, valsartan, irbesartan and candesartan.[8] This investigation demonstrated that differences in efficacy between ARBs do exist, with candesartan showing the greatest dose-related reduction in BP (**figure 3**).

This study was criticised since only data from disparate studies submitted to the Food and Drug Administration (FDA) for regulatory and licensing purposes were analysed. Therefore, to determine whether the pharmacological characteristics of ARBs made a difference to

Table 1. Comparative pharmacokinetics of ARBs

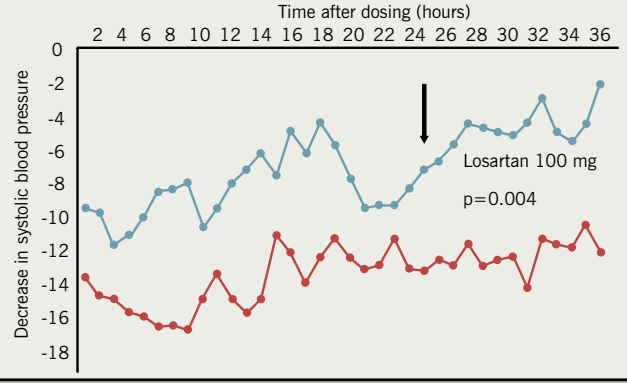
	Telmisartan	Losartan	Irbesartan	Candesartan cilexetil	Valsartan	Olmesartan medoxomil
Active metabolite	No	EXP-3174	No	Candesartan	No	Olmesartan
Bioavailability	40–60%	approx 30%	60–80%	15%	25%	29%
Volume of distribution	500 L	12 L	15–93 L	10 L	17 L	17 L
Terminal $t_{1/2}$	approx 24h	6–9h	11–15h	5–9h	6–9h	12–15h
Hepatic: renal elimination	98:2 no CYP450	65:35 CYP450	80:20 CYP450	60:40 CYP450	69:31 no CYP450	60:40 no CYP450
Protein binding	>99.5%	99.8%	90–92%	>99%	94–97%	99%

Figure 1. Insurmountable and surmountable antagonism



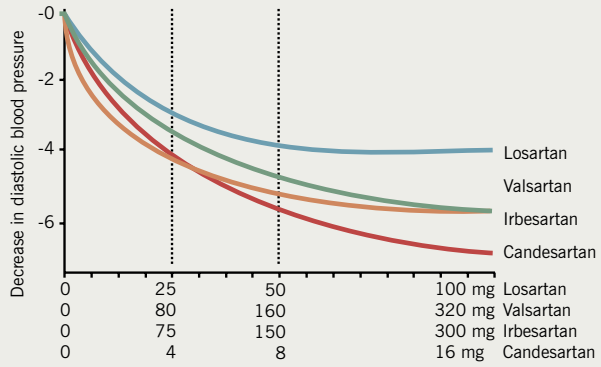
Note: even between the ARBs that have a high degree of insurmountability there is a marked difference in t½, indicating other factors must also be in force.
Redrawn from Van Liefde *et al.* 2009[4]

Figure 2. Mean change from baseline in systolic BP for candesartan *vs.* losartan



Redrawn from Lacourcière and Asmar 1999[5]

Figure 3. Meta-analysis based on US new drug evaluation reports



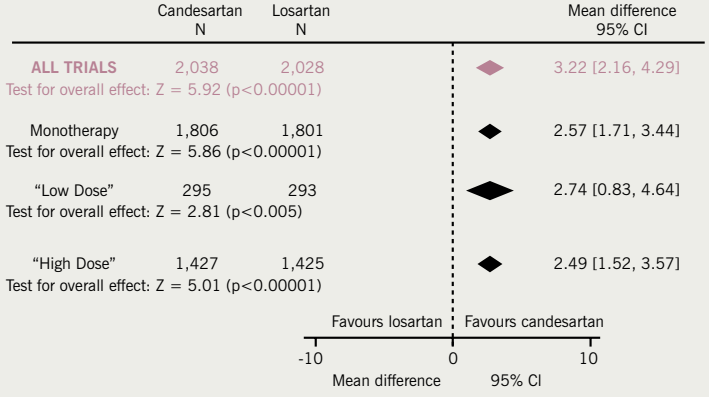
Key: p=0.014 for candesartan versus valsartan.
Redrawn from Elmfeldt *et al.* 2002[8]

antihypertensive efficacy, the author undertook a meta-analysis of all studies in which two ARBs, candesartan and losartan, were compared directly in hypertensive patients.[9] A systematic literature search of databases from January 1980 to October 2008 identified 13 studies in which candesartan and losartan, either as monotherapy or in fixed combination with hydrochlorothiazide (HCTZ), were compared in randomised trials in hypertensive patients. Data from 4,066 patients were included in the statistical analysis, with mean changes in systolic and diastolic BP being compared for each drug alone, and after stratification for dose and for combination with HCTZ. The results showed a consistent benefit for candesartan, averaging a difference of 3.22 mmHg in systolic BP between the two treatments (**figure 4**).

Similar findings were seen for diastolic BP: candesartan monotherapy reduced diastolic BP by an additional 1.8 mmHg compared with losartan, and combination therapy with HCTZ reduced diastolic BP by an additional 4.4 mmHg after candesartan treatment compared to losartan. Although such differences may appear relatively modest, it is known that the overall effect is impressive: using the methodology established by Wald *et al.*,[10] this additional BP response could reduce coronary heart disease events by 32% and reduce stroke by 44%. On the basis of the differential with the combination therapy using HCTZ, similar calculations predict that coronary heart disease events would be reduced by 41% and stroke by 55%.

The results of this meta-analysis are further supported by the Real-Life study, in which the hypothesis that losartan and candesartan have different primary preventive effects on cardiovascular risk in patients without known cardiovascular disease was evaluated at 72 primary care centres in Sweden.[11] Of the 24,943 eligible patients, in all 14,100 were diagnosed with hypertension and prescribed losartan (n=6,771) or candesartan (n=7,329). The median follow-up was two years, with maximal follow-up of nine years (36,339 patient-years). The observational data suggested that there was no difference in overall BP reduction (mean 145/85 mmHg) when comparing the losartan and candesartan groups during follow-up, although 20% more patients in the losartan group required treatment with a thiazide diuretic to achieve BP control compared to those receiving candesartan. However, the candesartan group had a lower adjusted hazard ratio for total cardiovascular disease (0.86, 95% CI 0.77–0.96, p=0.0062), heart failure (0.64, 95% CI 0.50–0.82, p=0.0004), cardiac arrhythmias (0.80, 95% CI 0.65–0.92, p=0.0330) and peripheral arterial disease (0.61, 95% CI 0.41–0.91, p=0.0140). (Baseline factors of age, gender, diabetes and prescription index year were adjusted in the model.) Since there was no evidence of a differential BP reduction between the two groups, this suggests that other mechanisms related to different pharmacological properties of the drugs may be causing different clinical outcomes (**figure 5**).

Figure 4. Meta-analysis of candesartan *vs.* losartan in direct comparator trials (change in systolic BP)



Note: low dose = 4 mg and 8 mg candesartan and 25 mg and 50 mg losartan; high dose = 12 mg, 16 mg and 32 mg candesartan and 100 mg losartan.
Redrawn from Meredith *et al.* 2009[9]

Conclusions

Despite the widespread idea that all ARBs are the same and show a 'class' effect, significant pharmacological differences with respect to efficacy and duration of action are apparent within the ARB class. A recent meta-analysis comparing two members of the ARB class, losartan and candesartan, suggests that such differences may translate into differences in BP reduction, and thus a reduction in cardiovascular risk. Observational data also suggest that patients prescribed the long-acting ARB candesartan have considerably better CV outcomes than those prescribed losartan. Differences do exist between the products within the ARB class, and such differences should be taken into account by the prescribing physician

Conflict of interest

PM has received research grants, honoraria for consultancy, advisory board attendance and speaker fees from a number of pharmaceutical companies, including AstraZeneca, Bayer, Boehringer Ingelheim, GSK, MSD, Pfizer and Takeda.

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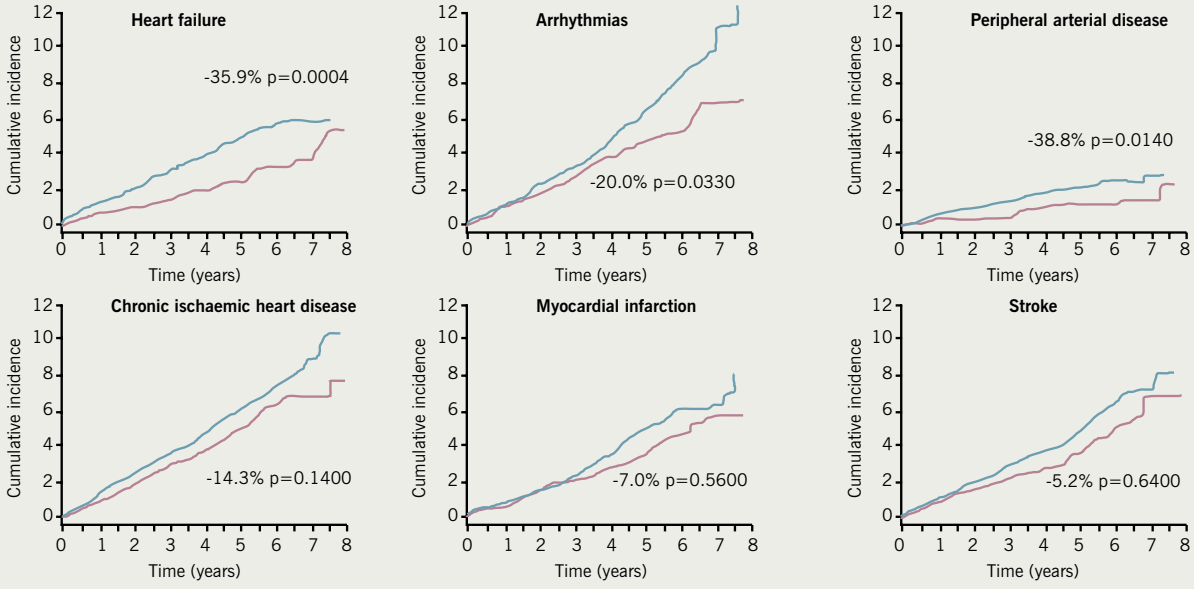
Key messages

- The angiotensin receptor blockers (ARBs) as a class are chemically similar but important pharmacokinetic and pharmacodynamic differences do exist between them
- The ARBs differ in the magnitude and duration of the antihypertensive response: this has important implications in clinical practice

Figure 5. Real-Life study – components of the primary composite outcome with candesartan *vs.* losartan



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ARBs in hypertension

Neil Poulter

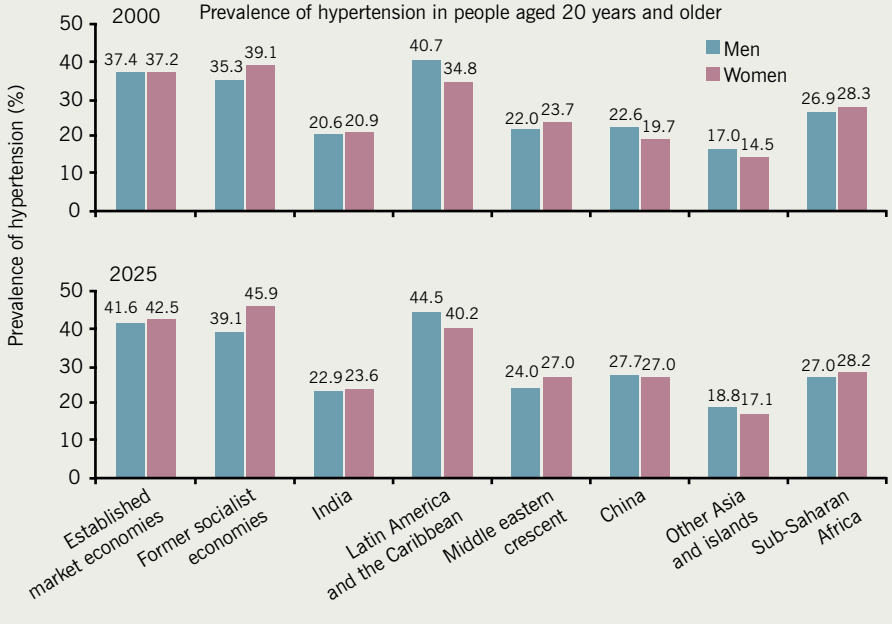
Impact of hypertension

High blood pressure (BP) is one of the leading health risk factors for global mortality, being a higher risk factor than tobacco use, high cholesterol and under-nutrition in both developed and developing regions.[1] The estimated total number of adults around the world with hypertension in the year 2000 was 972 million but this figure is predicted to rise by approximately 60% by 2025 to a total of 1.56 billion, due to an ageing population[2] and the adverse impact of several aspects of development (**figure 1**).

Epidemiological data have established a strong direct relationship between increased BP and raised cardiovascular (CV) disease risk. For individuals aged 40–69 years, each increment in systolic BP of 20 mmHg or diastolic BP of 10 mmHg doubles the risk of CV disease (i.e. stroke, ischaemic heart disease, and other vascular diseases) across the entire BP range.[3]

The World Health Organization has identified high BP as one of the most important preventable causes of premature morbidity and mortality. Antihypertensive drugs have convincingly been shown to be effective treatments for reducing this CV risk. By the mid-1990s an overview of 17 completed randomised trials of antihypertensive treatment by MacMahon *et al.* demonstrated that a 5–6 mmHg reduction in diastolic BP reduced stroke risk by 38% and coronary heart disease (CHD) risk by 16%.[4] There are also other benefits conferred to a variable extent by different antihypertensive therapies, including regression of left ventricular hypertrophy, prevention of dementia, regression of vascular remodelling and atherosclerosis, as well as prevention or delay of the onset of diabetes.

Figure 1. Prevalence of hypertension worldwide



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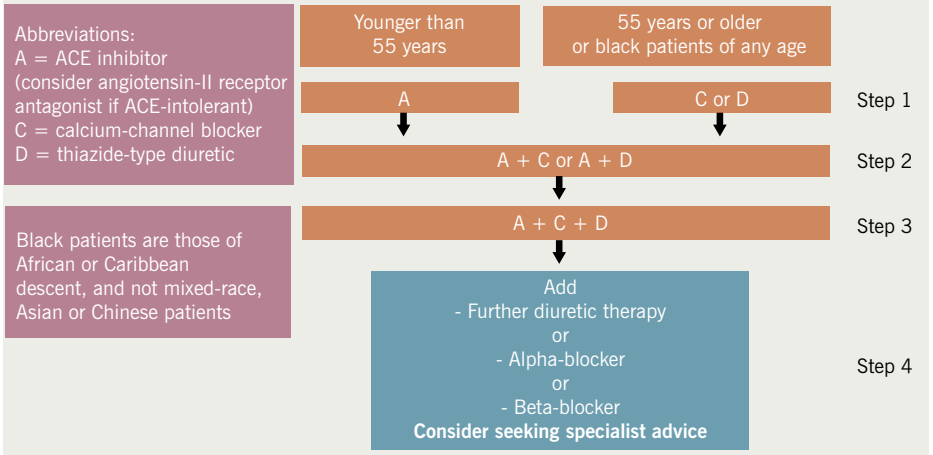
The treatment of hypertension

Management of hypertension in the UK has improved greatly in the last decade due to increased awareness of the significant health risks associated with the condition, improved hypertension management offered by primary care practitioners, and the availability of effective treatment options. Furthermore, the British Hypertension Society (BHS)[5] and National Institute for Health and Clinical Excellence (NICE)/ BHS guidelines[6] have become widely and increasingly adopted by healthcare professionals. These guidelines provide a clear simple treatment algorithm for patients diagnosed with hypertension. For hypertensive patients aged 55 years and over, or black patients of any age, the initial therapy should be either a calcium channel blocker (CCB) or a diuretic (thiazide or thiazide-type diuretic e.g. indapamide or chlorthalidone). In hypertensive patients younger than 55 years, first-choice therapy should be an angiotensin-converting enzyme inhibitor (ACE inhibitor) or an angiotensin receptor blocker (ARB) if an ACE inhibitor is not tolerated (**figure 2**).

However, CV events are most effectively prevented not by simply reducing high BP in isolation but by improving more than one risk factor at once, since CV events often have a multifactorial aetiology. The various classes of antihypertensive drugs exert differential effects on established non-BP risk factors, including high-density lipoprotein (HDL)-cholesterol, triglycerides, pulse rate, potassium levels and glucose levels. In addition, antihypertensive drugs vary in their duration of action, effect on central BP and their effect on BP variability. Therefore, it cannot be assumed that all antihypertensives exert equal CV protection, even with comparable clinic BP-lowering effects, although such BP-lowering effects are important.

Figure 2. NICE/BHS guidelines for drug treatment of hypertension



Key: ACE=angiotensin-converting enzyme; BHS=British Hypertension Society; NICE=National Institute for Health and Clinical Excellence

Reproduced with permission from: National Institute for Health and Clinical Excellence. CG 34 Hypertension: management of hypertension in adults in primary care. London: NICE, 2006. www.nice.org.uk/CG34

ARBs for the treatment of hypertension

While diuretics are often used as first-line therapy in patients with hypertension, their use is associated with the lowest patient compliance, and compliance with beta-blocker therapy is not notably better. Incremental increases in patient compliance are seen for CCBs and ACE inhibitors, but the highest rate of patient compliance with antihypertensive therapy is seen with the ARBs (**figure 3**). However, it is uncertain whether these findings are explained by drug tolerability, financial incentives, newness of the product, selection bias or other factors.[7]

Initially, there were conflicting data regarding use of ARBs for the treatment of hypertension and even a claim that these drugs may increase CV events such as myocardial infarction (MI).[8] However, subsequent systematic reviews and meta-analyses have refuted these findings. McDonald *et al.* evaluated the effect of ARBs on the risk of MI in patients at risk for CV events through a systematic review of controlled trials of ARBs. They identified 19 studies which included 31,569 patients: the use of ARBs was not associated with an increased risk of MI compared with placebo (odds ratio 0.94, 95% confidence interval [CI] 0.75 to 1.16), or with an increased risk of MI when compared with ACE inhibitors (odds ratio 1.01, 95% CI 0.87 to 1.16).[9] Similarly, a meta-analysis by Volpe *et al.* evaluated the effects of treatment using an ARB on the risk of MI, CV and all-cause death, as compared with conventional treatment or placebo. Twenty trials were evaluated comprising 108,909 patients, and this study concluded that the risk of MI was similar in patients treated with an ARB compared with other antihypertensive drugs in a wide range of clinical situations.[10]

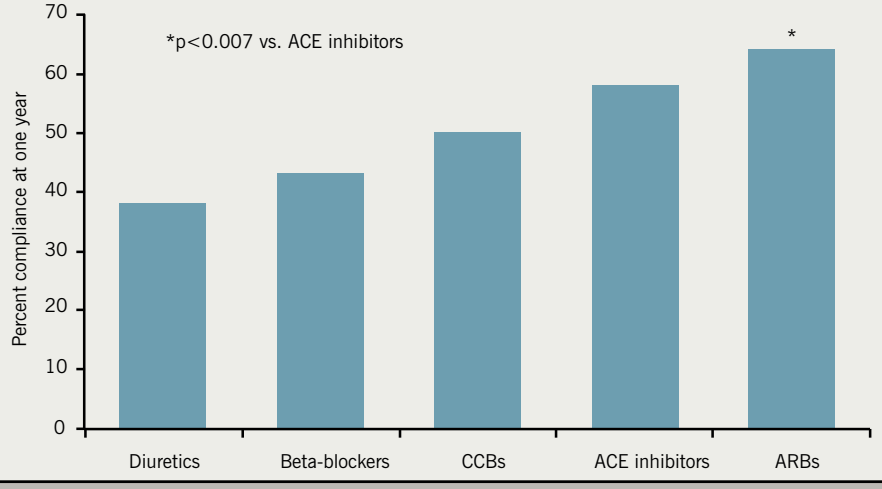
ARBs in hypertension and ventricular hypertrophy

Left ventricular hypertrophy (LVH) is a strong independent indicator of risk of CV morbidity and death in patients with hypertension. Dahlöf *et al.* aimed to establish whether selective blocking of angiotensin II with losartan or atenolol improves LVH beyond the reduction in BP, and whether this consequently reduced CV morbidity and death. Results showed that losartan reduced a composite end point of morbidity and death (driven predominantly by a reduction in stroke) to a greater extent than atenolol for a similar reduction in BP.[11] It would appear that ARBs (in this case, losartan) confer benefits on LVH and CV risk, specifically stroke events, beyond just effectively controlling BP.

ARBs in hypertension and stroke

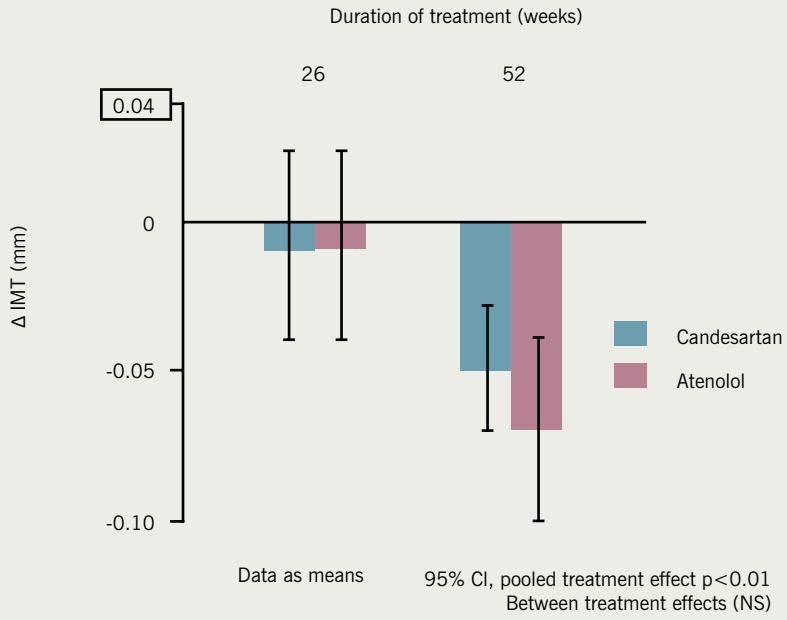
The Candesartan Atenolol Carotid Haemodynamics Endpoint Trial (CACHET) was conducted by Ariff *et al.* to investigate whether ARB treatment compared to beta-blocker treatment caused cardiac and large

Figure 3. Compliance at one year with antihypertensive treatment



Key: ACE inhibitors=angiotensin-converting enzyme inhibitors; ARBs=angiotensin receptor blockers; CCBs=calcium channel blockers.
Redrawn from Bloom BS, 1998[7]

Figure 4. Change in common carotid intima-media thickness (IMT) in the CACHET trial



Redrawn from Ariff B *et al*. 2006[12] with permission from Elsevier

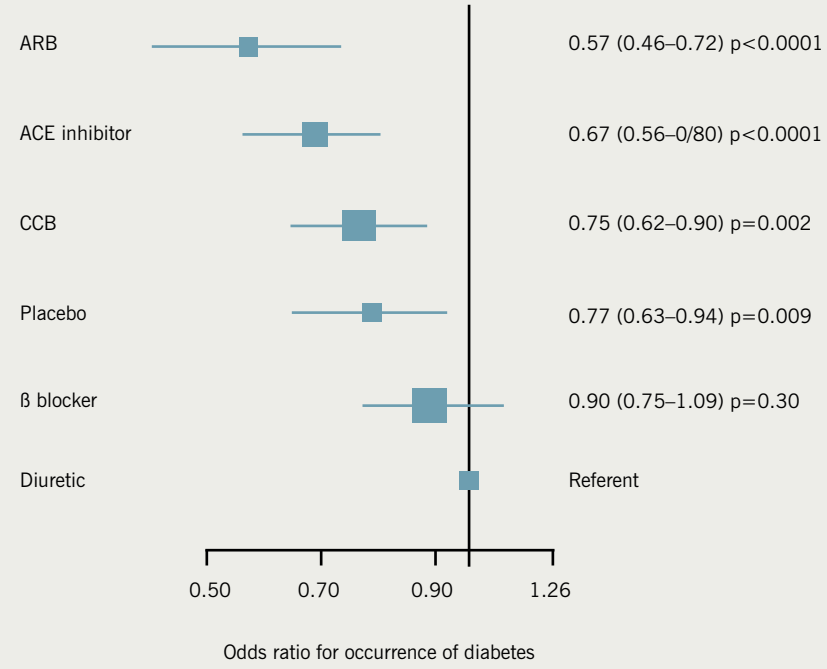
artery remodelling, and the relationship of any arterial remodelling to haemodynamic changes. Results showed that both candesartan (8 to 16 mg per day) and atenolol (50 to 100 mg per day) reduced intima-media thickness (IMT) and intima-media area (IMA) and increased distensibility to similar extents after 52 weeks of treatment. However, despite similar reductions in BP, treatment with atenolol resulted in a lesser reduction in left ventricular mass index, a decrease in lumen diameter and a reduction in carotid blood flow compared with candesartan. Therefore, candesartan demonstrated BP-independent effects on ventricular and carotid arterial structure, which may be a contributory factor to the beneficial effects of antihypertensive treatment with ARBs on some components of CV disease[12] (**figure 4**).

The beneficial effects of ARBs on stroke risk but not CHD risk reduction can also be seen in the results of the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, which demonstrated superior stroke outcome for losartan versus atenolol beyond BP reduction.[11]

The ACCESS study[13] was designed to assess the effects of ARB therapy within 36 hours after a stroke in patients with elevated BP. Cumulative 12-month mortality and the number of vascular events differed significantly in favour of candesartan versus placebo (odds ratio 0.475; 95% CI 0.252 to 0.895). The study concluded that early neurohumoral inhibition using an ARB has beneficial effects in cerebral and myocardial ischaemia and, unless contra-indicated, early antihypertensive therapy using candesartan is a well tolerated therapeutic option.

However, not all ARBs have shown consistent clinical benefits in various randomised clinical trials, perhaps reflecting differential effects on BP lowering. The VALUE trial was designed to test the hypothesis that, for the same BP control, valsartan would reduce cardiac morbidity and mortality more than amlodipine in hypertensive patients with a high CV risk. Results showed that BP was reduced by both valsartan and amlodipine treatments, but the effects of the amlodipine-based regimen were more pronounced, especially in the early period (BP 4.0/2.1 mmHg lower in amlodipine group compared to valsartan group after one month, and lower by 1.5/1.3 mmHg after one year; p<0.001 between groups). These BP differences were associated with a trend

Figure 5. Prevention of type 2 diabetes: impact of antihypertensive agents



Key: ACE=angiotensin-converting enzyme; ARB=angiotensin receptor blocker; CCB=calcium channel blocker.
Redrawn from Elliott W *et al.* 2007[16]

towards fewer fatal and non-fatal strokes in the amlodipine group (322 versus 281 in the valsartan and amlodipine groups, respectively, HR=1.15 [95% CI 0.98, 1.36], p=0.08).[14] Similarly, the PRoFESS trial investigated the effect of lowering BP with the angiotensin receptor blocker, telmisartan within 120 days after a stroke. A total of 20,332 patients were enrolled who recently had an ischaemic stroke and the study evaluated the effects of therapy with telmisartan (80 mg daily) versus placebo. Results showed that therapy with telmisartan initiated after an ischaemic stroke and continued for 2.5 years did not significantly lower the rate of recurrent stroke, major CV events or diabetes compared with placebo.[15]

Diabetogenic potential of antihypertensive drugs

Both diuretics and beta-blockers induce adverse effects on glucose metabolism and may cause new-onset diabetes (NOD). The size of this effect is variable within these two drug classes and is affected by drug dose. Elliott *et al.* undertook a systematic review to assess the effects of antihypertensive agents on the risk of NOD, including 22 clinical trials with 143,153 patients. The study concluded that the risk of NOD with antihypertensive drugs was lowest for ARBs and ACE inhibitors, followed by CCBs and placebo, beta-blockers and diuretics, in rank order[16] (**figure 5**).

It is therefore recommended that the combination of a diuretic and beta-blocker should be avoided for the routine treatment of hypertension, except in cases where compelling reasons apply. Conversely, drugs that block the renin-angiotensin system appear to afford an important degree of protection against the onset of NOD, therefore, drugs such as ACE inhibitors or ARBs (that block the renin-angiotensin system) should usually form part of the cocktail of agents necessary to lower BP in patients with impaired glucose tolerance, and also in patients who already have type 2 diabetes.

Conclusions

Hypertension diagnosis and treatment has improved markedly in the UK in the past decade, with hypertension management being simplified by the publication of the NICE/BHS 'ACD' algorithm. Evidence shows that ARBs are better tolerated compared to the other major drug classes in the treatment of hypertensive patients. ARBs vary in terms of duration of action and BP-lowering efficacy.

Overall, CV protective effects are similar between ACE inhibitors and ARBs, but compared with other agents there is some evidence that ARBs may offer better stroke protection and like ACE inhibitors, may be associated with a reduced risk of developing new-onset diabetes. There is no robust evidence that ARBs are associated with significantly increased CV events, including MI, compared to other antihypertensive drugs

Conflict of interest

NP has served as consultant and received travel expenses, payment for speaking at meetings, or funding for research from several pharmaceutical companies, including Takeda.

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Key messages

- Control of hypertension in the UK is improving, with good guidelines provided by the National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS) 'ACD' algorithm
- Angiotensin receptor blockers (ARBs) demonstrate good efficacy in hypertension and a good safety profile: early fears about increased risk of myocardial infarction (MI) have been discredited by recent meta-analyses and trials

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ARBs in chronic heart failure

Theresa McDonagh

Heart failure epidemiology

The incidence of heart failure (HF) increases with age and its prevalence is increasing due to an ageing population.[1] Although some HF patients can live for many years, absolute survival rates are poor in both sexes, with 50% of men dead at 2.3 years (range: 1.3–2.3 years) and 50% of women dead at 1.7 years (range: 1.32–1.79 years).[2] Recent reports, however, suggest that the prognosis has substantially improved in the UK, thought to be related to better treatment and monitoring.[3,4]

Current treatments

The National Institute for Health and Clinical Excellence (NICE) published guidelines on the diagnosis and management of chronic heart failure in 2003,[5] with more recent guidelines being published by the European Society of Cardiology (ESC)[6] in 2008. The treatment algorithm recommended for patients with heart failure due to left ventricular systolic dysfunction in the ESC guideline is shown in **figure 1**.

Based on these guidelines, current first-line pharmacological therapy comprises a combination of oral loop diuretics, angiotensin-converting enzyme inhibitors (ACE inhibitors) and beta-blockers. If an ACE inhibitor is not tolerated then an angiotensin receptor blocker (ARB) can be used instead. If patients fail to respond symptomatically then specialist advice needs to be obtained, but options at this point include spironolactone at 25 mg per day (based on the RALES study[7]) or candesartan up to a dose of 32 mg per day (based on the CHARM-Added study[8]).

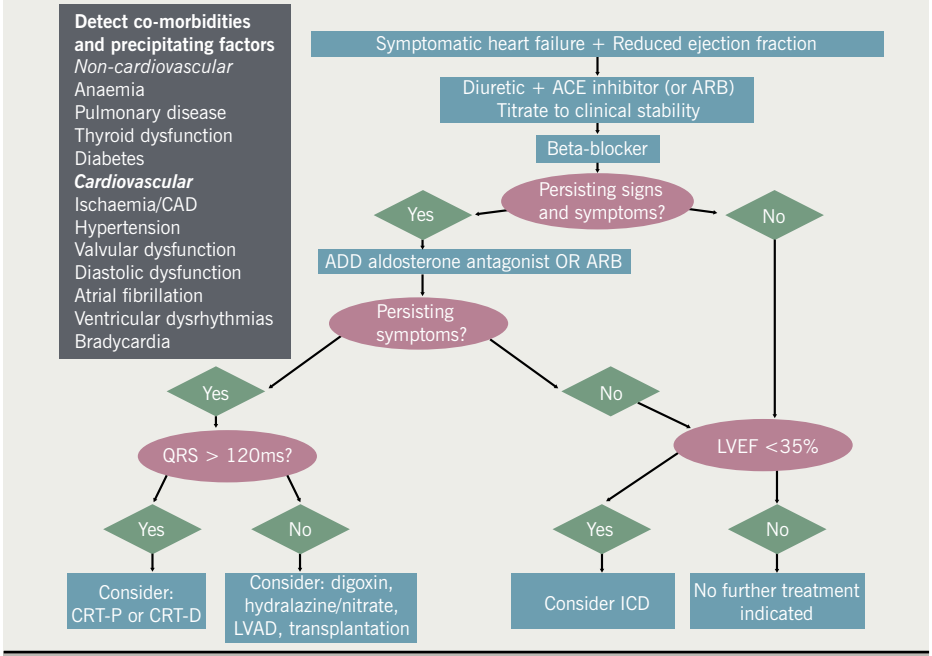
Clinical trial evidence for ARB treatment of heart failure

The evidence for the use of ARBs in HF is based on a large number of randomised studies, starting with the first-in-class ARB, losartan.

ELITE study

The ELITE study[9] compared losartan with captopril in 722 elderly ACE inhibitor-naïve patients with HF. Patients treated with losartan were found to have fewer hospital admissions for HF compared to those in the captopril group (risk reduction 32% [95% confidence interval [CI] -4% to + 55%], p=0.075). The unexpected finding was an impressive reduction in all-cause mortality (4.8% *vs.* 8.7%; risk reduction 46% [95% CI 5%, 69%], p=0.035), although this was not the primary study end point. These surprise findings led to the design of the much larger ELITE II trial.

Figure 1. Treatment strategy for use of drugs and devices in patients with symptomatic heart failure and systolic dysfunction

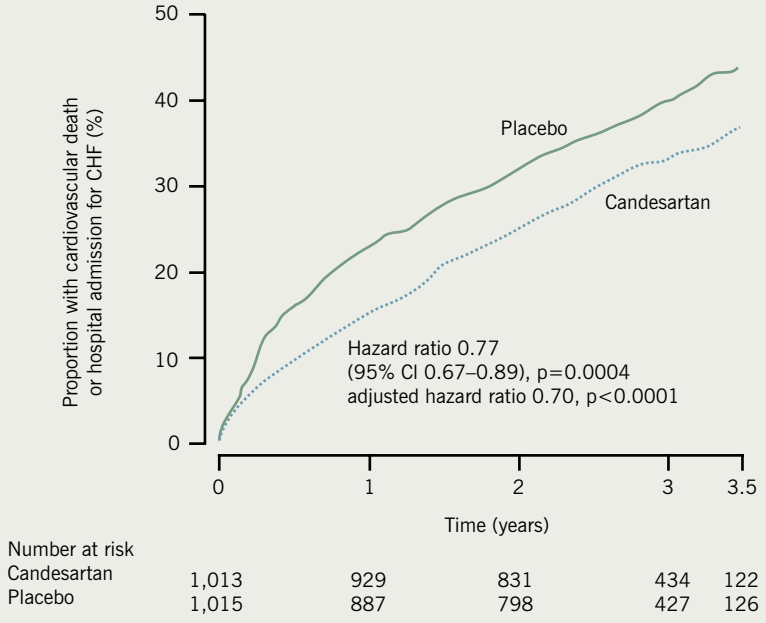


Key: ACE=angiotensin-converting enzyme; ARB= angiotensin receptor blocker; CAD=coronary artery disease; LVEF=left ventricular ejection fraction; ICD= implantable cardioverter defibrillator; CRT= cardiac resynchronisation therapy; LVAD=left ventricular assist device

ELITE II study

The ELITE II study[10] was performed to confirm whether losartan 50 mg once daily was superior to captopril 50 mg three times daily in improving patient survival and if it was better tolerated. A total of 3,152 patients aged ≥60 years with New York Heart Association (NYHA) class II-IV HF and ejection fraction of ≤40% were enrolled. During the two-year trial, 7.3% of the captopril group and 9% of the losartan group experienced sudden cardiac death and/or resuscitated cardiac arrest. Although the difference in outcome was not statistically significant between losartan and captopril in terms of reducing all-cause mortality (11.7 *vs.* 10.4% average annual mortality rate) or sudden death or resuscitated arrests (9.0 *vs.* 7.3%), (hazard ratios 1.13 [95% CI 0.95, 1.35], p=0.16; and 1.25 [95% CI 0.98, 1.60], p=0.08, respectively), there was a trend to worse outcome in the losartan group. The outcomes were also worse in the subgroup of patients on beta-blockers plus losartan, so this combination is not recommended with losartan. Losartan was better tolerated, with significantly fewer patients discontinuing losartan treatment compared to captopril due to adverse effects (9.7 *vs.* 14.7%, p<0.001), including cough (0.3 *vs.* 2.7%). The study concluded that although ACE inhibitors remained the treatment of choice

Figure 2. Proportion of cardiovascular death or hospitalisation in the CHARM-Alternative study[13]



for patients with HF, the ARB could be used in those who could not tolerate an ACE inhibitor.

Val-HeFT study

The Val-HeFT study[11] recruited 5,010 patients and demonstrated a combined end point of death or hospitalisation due to HF that was 13.2% lower when valsartan rather than placebo was added to 'standard treatment' (relative risk 0.87; [97.5% CI 0.77, 0.97], p=0.009). This was predominantly due to a lower number of patients hospitalised for HF (18.2% in the placebo group and 13.8% in the valsartan group, p<0.001). However, in a post-hoc analysis of subgroups according to baseline treatment with ACE inhibitors or beta-blockers, valsartan showed an adverse effect in patients receiving both ACE inhibitors and beta-blockers in combination, raising concerns about the potential safety of this triple combination.

CHARM programme

The CHARM programme was designed to assess candesartan therapy in relatively low-risk HF patients, with eligibility defined simply as patients aged ≥18 years with a NYHA class II-IV of at least four weeks' duration. The entire CHARM programme included 7,601 patients from 26 countries worldwide. It comprised three randomised, double-blind, placebo-controlled clinical trials, each in a distinct patient population with symptomatic HF:[12] CHARM-Alternative in patients with left ventricular ejection fraction (LVEF) ≤40% and intolerant of ACE inhibitors; CHARM-Added in patients with LVEF ≤40% who tolerated and were treated with whichever ACE inhibitor the patient's physician chose; and CHARM-Preserved in patients with LVEF >40%, who may or may not have received an ACE inhibitor.

In the CHARM-Alternative[13] study 2,028 patients were randomised and evaluated for a median of 33.7 months. All patients included in this study were ACE inhibitor-intolerant. During follow-up, 33% of patients receiving candesartan had a primary outcome of cardiovascular (CV) death or hospitalisation for HF, compared with 40% of those on placebo. This represented a 23% relative risk reduction (RRR) for CV death or hospitalisation (p=0.0004) (**figure 2**).

The CHARM-Added study randomised 2,548 patients and showed that candesartan was associated with a statistically significant 15% reduction in the relative risk of CV death or hospital admission.[8] Importantly, the adverse effect on clinical outcomes of combining an ACE inhibitor with a beta-blocker and an ARB that was found with valsartan in Val-HeFT was not found in the CHARM-Added study.[8]

CHARM-Preserved[14] did not show conclusive evidence of benefit for candesartan, with no significant difference between candesartan and placebo for the composite end point of CV death or HF hospital admission, although fewer patients in the candesartan group were admitted to hospital for HF (230 *vs.* 279, p=0.017). As a result, candesartan is not licensed for this patient population.

HEAAL study

The HEAAL study[15] was a double-blind study investigating losartan use ('low' dose 50 mg versus 'high' dose 150 mg) in ACE inhibitor-intolerant patients. Recently reported results from 3,846 patients showed that, with 4.7-year median follow-up in each group, 828 (43%) patients in the 150 mg group versus 889 (46%) in the 50 mg group died or were hospitalised for HF (hazard ratio [HR] 0.90, [95% CI 0.82, 0.99], p=0.027). Therefore it was concluded that losartan 150 mg daily reduced the rate of death or admission for HF compared with losartan 50 mg daily and suggested that the appropriate dose of an ARB for patients with heart failure may be higher than the doses most commonly used to treat hypertension (although it should be noted that the 150 mg dose is currently unlicensed).

However, there is some conflicting evidence from clinical trials regarding the benefits conferred by ARBs in the treatment of HF occurring in the context of acute myocardial infarction, including the effect of combining ARBs with standard therapies, as shown from the two studies below.

OPTIMAAL study

The OPTIMAAL study[16] was conducted in 5,477 patients to test the hypothesis that losartan 50 mg once daily would be superior or non-inferior to captopril 50 mg three times daily. Results showed a non-significant difference in total mortality in favour of captopril, with 499 deaths in the losartan group (18%) compared to 447 (16%) in the captopril group (relative risk 1.13 [95% CI 0.99, 1.28], p=0.07). However, losartan was significantly better tolerated than captopril, with fewer patients discontinuing study medication. On the basis of these results, it was concluded that ACE inhibitors should remain first-choice treatment in patients after complicated acute myocardial infarction but that ARBs were a suitable alternative in patients unable to tolerate an ACE inhibitor. The dose of 50 mg losartan used may have been the reason for the result, but the results of a higher dose (such as 150 mg used in one arm of the HEAAL study) are unknown.

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VALIANT study

The VALIANT study[17] enrolled a total of 14,703 patients with HF, left ventricular systolic dysfunction, or both, after acute MI, who were treated with captopril, valsartan or a combination of both drugs. The primary end point was death from any cause. During a median follow-up of 24.7 months, 979 patients in the valsartan group, 941 patients in the valsartan/captopril group and 958 patients in the captopril group died (hazard ratio in the valsartan group compared with the captopril group, 1.00; [97.5% CI 0.90, 1.11]; p=0.98; hazard ratio in the valsartan/captopril group compared with the captopril group, 0.98; [97.5% CI 0.89, 1.09]; p=0.73). The study concluded that valsartan was as effective as captopril in patients who were at high risk for CV events after myocardial infarction. However, the combined valsartan and captopril group had the most drug-related adverse events without improving survival. Most guidelines continue to suggest that in post-MI heart failure an ACE inhibitor remains first-line, but an ARB should be considered if the ACE inhibitor is not tolerated.

Conclusions

There is good evidence supporting the use of ARBs in HF. According to the ESC guidelines, ARBs are recommended first-line in combination with a diuretic in patients who are ACE inhibitor-intolerant, or second-line in patients who fail to respond to the combination of diuretic plus ACE inhibitor. If patients fail to respond symptomatically to therapy with a diuretic, ACE inhibitor and beta-blocker, then candesartan or spironolactone can be added. Usually this would be decided by a specialist. The results of randomised trials though are not uniform, and it would be unwise to disregard the differences in outcome related to agent, dose and clinical context. The strongest evidence base for ARBs in chronic heart failure remains with the CHARM programme. Indeed, in patients with symptomatic CHF and LVEF ≤40%, candesartan is the only ARB found to reduce all-cause mortality, CV death and HF hospitalisations significantly when added to standard therapies, including ACE inhibitors, beta-blockers and an aldosterone antagonist ●

Conflict of interest

TMcD has received honoraria from unrestricted educational grants, provided by Takeda, for speaking at several heart failure-related meetings.

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Key messages

- Despite advances in care of patients with chronic heart failure (CHF), absolute survival remains poor in both men and women
- Patients need to be monitored closely and the dose of neurohormonal antagonists titrated to achieve maximum benefit
- Guidelines from the National Institute for Health and Clinical Excellence (NICE) and the European Society of Cardiology (ESC) exist to guide pharmacological options
- Candesartan is the angiotensin receptor blocker (ARB) with the strongest evidence for use in CHF, based on the results of the CHARM study

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ARBs in renal disease

Mark Kearney

Renal disease and diabetes

Diabetic nephropathy is estimated to affect up to 40% of patients with type 2 diabetes. Diabetic nephropathy is characterised by proteinuria, hypertension, progressive decline in renal function and increased mortality (up to 12% per year in patients with increased creatinine levels).

Microalbuminuria is known to be a marker of increased cardiovascular (CV) risk. It is not clear whether reducing microalbuminuria on its own is associated with an improved cardiovascular prognosis, but in secondary analyses from studies of angiotensin receptor blockers (ARBs) in people with type 2 diabetes, reduction in albuminuria was associated with a decreased risk of a CV event. Observational analyses from the RENAAL trial found that the magnitude of albuminuria reduction predicted the reduced risk of CV events **(figure 1).**[1]

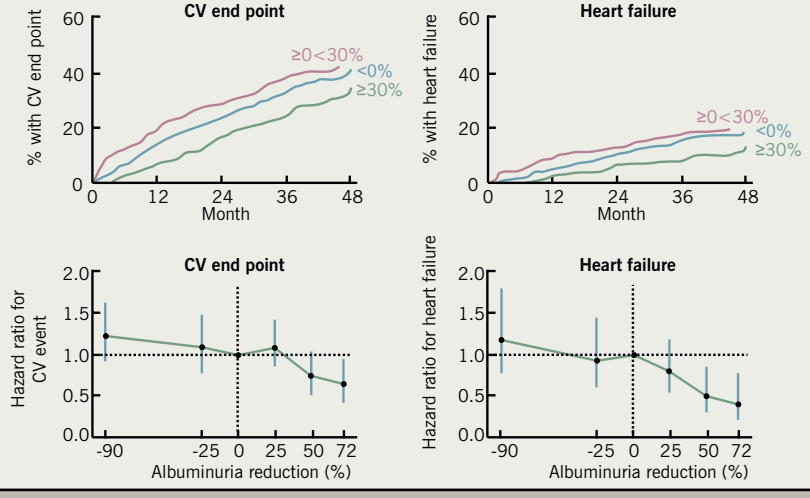
Generally, treatment of risk factors such as hypertension will also reduce albuminuria.[2] A strategy of targeting treatment specifically to albuminuria has not been tested prospectively in patients with diabetes, but interventions that reduce albuminuria or delay its increase (such as use of ARBs, even in conventionally normotensive patients) may prove to be a useful therapy for diabetic kidney disease.

RAAS inhibition and diabetic nephropathy

Many studies have documented the beneficial effects of both angiotensin-converting enzyme inhibitors (ACE inhibitors)[3,4] and ARBs[5–7] on renal function, showing benefits beyond those of simply blood pressure control. Most studies of ARBs have used either irbesartan or losartan. In a comparison of the calcium channel blocker (CCB) amlodipine versus irbesartan, results from Lewis *et al.* showed that irbesartan was associated with a risk of the primary composite end point (defined as a doubling of the baseline serum creatinine concentration, the onset of end-stage renal disease, or death from any cause) 20% lower than that in the placebo group (p=0.02) and 23% lower than that in the amlodipine group (p=0.006), with this effect considered to be independent of effect on blood pressure lowering.[7] Mogensen *et al.* also compared the effects of an ACE inhibitor and an ARB, by assessing the efficacy of lisinopril, candesartan or both on blood pressure and urinary albumin excretion in 199 patients with hypertension, microalbuminuria and type 2 diabetes. The study found that candesartan 16 mg once daily was as effective as lisinopril 20 mg once daily in reducing blood pressure and microalbuminuria in hypertensive patients with type 2 diabetes. Combination treatment was well tolerated and more effective in reducing blood pressure than either drug alone and it also reduced the urinary albumin:creatinine ratio to a greater extent than either drug alone.[8] In a direct comparison of the ARBs telmisartan and losartan in the AMADEO study,[9] telmisartan was shown to be superior to losartan in reducing proteinuria in hypertensive patients with diabetic nephropathy, despite a similar reduction in blood pressure.

In an attempt to consolidate the individual study results, a meta-analysis by Kunz *et al.* analysed 49 studies involving 6,181 participants, which reported the results of 72 comparisons comprising ARBs versus placebo, ACE inhibitors, CCBs, or the combination of ARBs and ACE inhibitors in patients with microalbuminuria or proteinuria (from whatever cause) with or without diabetes. The ARBs and ACE inhibitors were found to reduce proteinuria to a similar degree, with the combination of ARBs and ACE inhibitors reducing proteinuria more than either agent alone. However, the limitations to this research were that most studies were small, varied in quality, and did not provide reliable data on adverse drug reactions so the effect of combination therapy on the adverse event profile could not be evaluated.[10]

Figure 1. Kaplan-Meier curves for cardiovascular (CV) and heart failure end points, stratified by month-6 change in albuminuria: data from the RENAAL study



De Zeeuw D, Remuzzi G, Parving HH *et al.*[1] Reprinted with permission from Wolters Kluwer/Lippincott, Williams & Wilkins

Conclusions

In conclusion, there are numerous agents available to block the RAAS and improve the outcome for patients with diabetic nephropathy. Multiple studies have examined the effect of different ACE inhibitors and ARBs, either as monotherapy or in combination, and have demonstrated the effectiveness of both classes of agents in lowering blood pressure and reducing both cardiovascular mortality and morbidity in various at-risk patient populations, including patients with type 2 diabetes. Current UK guidelines recommend treatment with an ACE inhibitor, or with an ARB if the ACE inhibitor is not tolerated.[11] In general, the randomised clinical trials in patients with diabetic nephropathy have used losartan or irbesartan: both are licensed for use in patients with hypertension and type 2 diabetic nephropathy. However, the recent

AMADEO study has also shown telmisartan to have efficacy in this area

Conflict of interest

MTK received an honorarium from Takeda for his contribution to this supplement.

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Key messages:

- Increased proteinuria is associated with increased cardiovascular mortality and morbidity, and therefore identifies patients at high risk who should be targeted for effective reduction of cardiovascular risk factors
- Treatment of cardiovascular risk factors such as hypertension and hypercholesterolaemia has a positive effect on the development and progression of renal dysfunction
- Losartan and irbesartan have been shown to slow the progression of renal disease

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Costs and benefits of ARBs in practice

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National Health Service (NHS) costs in England grew from about £40 billion in the year 2000 to £100 billion today. That is, they have approximately doubled in real terms within a decade. However, the current economic climate in the UK has led to increasing cost awareness in the NHS. NHS managers have been charged with making £15–20 billion efficiency savings by 2015.[1] Although the health service will not lose funding, GPs are under pressure to prescribe low-cost generic medicines wherever possible.[2]

This brief paper considers how such cost pressures may affect the use of angiotensin receptor blockers (ARBs) in the NHS, given that although losartan is the first drug in this class to become generic in March 2010, others will quickly follow suit. Valsartan loses patent protection in 2011, with candesartan and irbesartan following in 2012.

Indications for ARB use

Recent data indicate that candesartan is presently the most widely used ARB in England, accounting for almost a third of all ARB prescriptions. This is in part because it has been competitively priced compared with other ARBs. In average prescription cost terms, candesartan has in recent years enjoyed an approximate 25% price advantage over its main high-volume competitor (**table 1**).

At present, there are variations with respect to the licensed indications for ARBs in the UK. All drugs in the class are licensed for the treatment of hypertension whereas only three (candesartan, losartan and valsartan) are indicated for chronic heart failure. Valsartan alone is licensed for use post-myocardial infarction (MI) in patients with left ventricular systolic dysfunction (LVSD). Irbesartan and losartan are the only ARBs presently approved for the treatment of nephropathy in patients with type 2 diabetes mellitus.

However, it is often assumed that all ARBs are equivalent. If this is believed uncritically, then NHS pharmaceutical advisers and economists may be influenced exclusively by price considerations. The advent of generic level price competition 'class effect' prescribing, such that all drugs within a class are assumed to have identical safety and efficacy profiles,[3] in some instances could undermine public interests in both continuity of care and the optimisation of individual and/or population level health outcomes.

Broader implications of changing ARB presciptions

Usher-Smith has highlighted the challenges involved in switching patients' medicines for purely cost-saving purposes.[2, 4] He reported his experience within a PCT that encouraged switching established patients from losartan to candesartan in 2005–2006 on cost grounds. Such a policy had originally been estimated to generate a national three-year saving of £128 million. However, in August 2007, the price of losartan was decreased, resulting in reduced actual annual savings. This illustrates the point that the outcomes of cost-reducing measures may be dependent upon unpredictable market adjustments

Table 1. Costs and percentage share of prescriptions associated with ARBs (England, 2008)

	Packs sold (1,000s)	Cost of drug (1,000s)	Average cost of prescription	% pack volume share
Candesartan (Amias)	4,381.54	64,081.32	£14.63	31.8%
Eprosartan (Teveten)	252.065	4,253.96	£16.88	1.8%
Irbesartan (Aprovel)	2,456.42	47,682.99	£19.41	17.8%
Losartan (Cozaar)	3,229.94	66,971.60	£20.73	23.4%
Olmesartan (Olmetec)	892.742	13,673.59	£15.32	6.5%
Telmisartan (Micardis)	750.432	11,952.23	£15.93	5.4%
Valsartan (Diovan)	1,835.56	46,551.36	£25.36	13.3%

Source: Department of Health [Data exclude combined preparations. See also the NHS Regional Drug and Therapeutics Centre, Newcastle, January 2010 cost comparison charts.]

that can undermine their cost-effectiveness even though in this particular instance a significant drop in blood pressure was seen after patients switched to candesartan. This could have been a drug-related effect, or alternatively the effect of enhanced case management associated with the effort of supporting switching. In general, it is the case that moving patients who are well established on one medicine to another demands not only increased clinician time, but also risks undermining their confidence in their clinician and reducing adherence rates. Further, if the drugs are not fully interchangeable this may have additional consequences on outcomes and (in time) overall care/service costs.

In this context, the 'Real-Life' study[5] discussed by Meredith in this supplement looked retrospectively at candesartan and losartan use in primary care centres in Sweden. It found there was no difference in blood pressure (BP) reduction when comparing the losartan and candesartan groups (although more patients in the losartan arm required a thiazide to achieve the same BP reduction), but that candesartan use was associated with a significantly lower risk of cardiovascular events compared with losartan. The results published to date do not make it possible to quantify the reduced economic burden associated with candesartan use in this context. However, they do raise the possibility that short-term financial gains associated with a general switch to losartan therapy before other ARBs lose patent protection might be offset by factors linked, say, to reduced 24-hour BP control.

Conclusions

Making the best possible use of health resources is an important end. Yet factors other than price advantage alone should be considered before accepting policy decisions to switch patients automatically from one therapeutic agent to another. Care should be taken not to ignore clinically significant utility variations within the ARBs; since these drugs are both effective and relatively free from side effects, they may become more widely used in future as prices fall across the board.

Research such as that by Usher-Smith[2] and Kjeldsen *et al.* [5] indicates that the routine 'switching' of patients from one drug to another, based on short-term unit price differences alone, might prove counter-productive. Such policies are only defensible when there is robust evidence both that the switch is beneficial and that it justifies the time and effort needed to support patients adequately during the transition from a familiar medicine to a new one. Switching should be backed by evidence regarding relevant population health outcomes relative to the overall costs incurred and the financial resources released for alternative use

Conflict of interest

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Key messages

- The NHS is under pressure to contain costs through the prescribing and supply of low-cost generic medicines whenever appropriate
- Losartan is the first angiotensin receptor blocker (ARB) to come off-patent (in March 2010). This may prompt some primary care trusts (PCTs) and practices to switch patients who are currently taking other ARBs to generic losartan
- There is evidence that different ARBs have pharmacologically distinct actions, which may differentially affect patient outcomes. Switching patients may not reduce financial costs as much as initially anticipated due to additional clinician time and effort needed to manage patients and because, from an economic perspective, long-term health outcomes may be impaired
- A patient-centred, evidence-based approach is needed, rather than one uncritically focused on unit drug costs.

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