Should all patients at high cardiovascular risk receive renin-angiotensin system blockers?

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Summary

Despite considerable advances in preventative treatment during the last two decades, the increasing burden of cardiovascular (CV) disease constitutes an urgent need for new therapeutic strategies to reduce CV mortality and morbidity in patients at high CV risk. Activation of the renin-angiotensin system (RAS) results in vasoconstrictive, proliferative and pro-inflammatory effects that contribute to the development of atherosclerosis. As a result, the RAS is implicated at all stages of the ‘CV continuum’ that links risk factors such as hypertension and dyslipidaemia with major CV events, congestive heart failure (CHF) and CV death. The RAS therefore represents a rational and ideal therapeutic target in CV risk reduction strategies. Both angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) have been shown to promote beneficial effects on end-organ damage, such as decreases in arterial stiffness and left ventricular hypertrophy (LVH). Several trials have shown that ACE inhibitors and ARBs reduce CV risk in patients with specific risk factors. Furthermore, the HOPE study and, more recently, the ONTARGET study have shown that ramipril and telmisartan reduce CV risk in patients with a high CV risk profile across the ‘CV continuum’. Telmisartan is the first ARB to demonstrate CV prevention in patients at high CV risk, similar to that of the gold-standard ACE inhibitor, ramipril. This extensive clinical trial evidence suggests that ACE inhibitors or ARBs should be part of the standard treatment for patients at risk of CV events. ARBs may represent a preferred option due to their unsurpassed tolerability.

Introduction

Cardiovascular (CV) disease is the most common cause of death worldwide, due to the high prevalence of coronary heart disease and cerebrovascular disease in high- and middle-income countries. It is expected that, by 2030, CV disease will account for 24% of all deaths, retaining its leading position as a result of an increasing prevalence in developing countries and an ageing population. Given this high mortality and morbidity burden, and the associated growing social and economic costs, it is clear that, despite significant advances in preventative medicine in recent years, there remains an urgent need for improved strategies to reduce the burden of CV disease.

The current approach to managing CV risk is based on extensive epidemiological evidence...
linking risk factors such as hypertension, dyslipidemia, obesity and type 2 diabetes mellitus (T2DM) to CV disease. These risk factors are already common in high-income countries, and their incidence is increasing worldwide as developing countries adopt Western lifestyles. For example, it is anticipated that the global prevalence of hypertension will increase by 56%, from 1 billion to 1.56 billion, between 2000 and 2025, while that of T2DM will increase from 171 million in 2000 to between 366 million and 438 million in 2030.

The prevalence of such risk factors is particularly high in patients with existing CV disease. For example, in the European action on secondary and primary prevention through intervention to reduce events (EUROASPIRE III) study, which involved almost 9000 patients with coronary heart disease in 22 European countries, >50% of patients had hypertension or elevated cholesterol, and 35% were diabetic (Figure 1). Furthermore, many patients have multiple concomitant risk factors, which exert additive or synergistic effects on the overall level of risk. Also, in the INTERHEART study, an international case–control study involving almost 30 000 individuals worldwide, hypertension, diabetes, abdominal obesity and smoking each raised the relative risk of myocardial infarction (MI) between 2-fold and 4-fold, but the risk rose by several fold in individuals with a clustering of these risk factors; a smoker with both hypertension and diabetes had a 13-fold greater risk of MI than an individual without these risk factors. Such findings have led to an emphasis in current guidelines on assessing and treating the overall (global) CV risk in an individual patient rather than focusing on a single risk factor. A key step in this strategy is the identification of patients at high risk of CV disease.

Identifying the high-risk patient

CV disease can be regarded as a continuum of stages (Figure 2), which starts from risk factors such as hypertension and dyslipidemia, through the development of organ damage, such as endothelial dysfunction, atherosclerosis and left ventricular hypertrophy (LVH), leading to MI or stroke. MI can be followed by remodelling of the heart and vasculature, which leads to ventricular dysfunction, the development of congestive heart failure (CHF) and ultimately to death. In the early and intermediate stages of this continuum, patients may present a high CV risk (Figure 2). Thus, patients with hypertensive end-organ damage, such as increased arterial stiffness, LVH, microalbuminuria or proteinuria, or carotid atherosclerotic plaques, are at substantially increased risk of CV disease, even when this damage is asymptomatic or subclinical. Furthermore, renal impairment is an independent risk factor for CV disease. This was shown in a large diverse group of adults, in whom reduced estimated glomerular
The renin-angiotensin system and CV risk

The renin-angiotensin system (RAS) plays an important role at all stages of the CV continuum.22,23 The principal effector peptide of this system, angiotensin II, has diverse vasoconstrictor, proliferative and pro-inflammatory actions that contribute to endothelial dysfunction, oxidative stress and vascular inflammation or fibrosis, all of which are central to the development of atherosclerosis (Figure 3).23

For example, angiotensin II enhances the proliferation and migration of vascular smooth muscle cells, and contributes to endothelial dysfunction, stimulating the activity of NAD(P)H and xanthine oxidase, which are the major source of oxygen-free radicals in vascular tissue.24 In addition, angiotensin II increases the expression of pro-inflammatory factors such as interleukins 1 and 6 and tumour necrosis factor (TNF)-α, which have been shown to play an important part in the development of atherosclerosis,21,22 and activates matrix metalloproteases (MMPs), which are implicated in the rupture of atherosclerotic plaques.23,26 These effects are primarily mediated by angiotensin II type 1 (AT1) receptors and opposed by AT2 receptors; the latter receptors are also associated with pro-apoptotic and neuroprotective effects.22,23

Evidence that the RAS plays a central role in the development of CV disease comes from the findings that renin activity is predictive of CV events,27,28 and that (as discussed below) RAS blockade can prevent or reverse end-organ damage and is associated with a reduced risk of CV events in various high-risk patient populations. Of note is that the deleterious effects of RAS activation may promote...
a vicious cycle, with endothelial injury perpetuating further RAS activation.29 The RAS is therefore a rational target for therapeutic strategies aimed at reducing CV risk in high-risk patients. At present, there are two main pharmacological approaches to RAS blockade: angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs). In addition, a direct renin inhibitor, aliskiren, has been approved for the treatment of hypertension in Europe and the USA; the effects of this agent on CV risk are at present being evaluated in clinical trials.30

ACE inhibitors block the production of angiotensin II from angiotensin I, thereby decreasing blood pressure and arteriolar resistance and reducing angiotensin II-mediated effects on inflammation, oxidative stress and tissue remodelling. However, they do not affect angiotensin II production by enzymes such as chymase, especially in CV tissues, and hence angiotensin II concentrations may return to normal levels despite sustained treatment (angiotensin escape).23,31 Furthermore, ACE inhibitors also block the degradation of bradykinin, resulting in accumulation of this peptide. Bradykinin may contribute to the beneficial haemodynamic effects of ACE inhibitors,32 but has also been implicated in adverse events such as cough and angioedema.33

ARBs inhibit the binding of angiotensin II to AT1 receptors, and thus block the deleterious effects of angiotensin II mediated by these receptors. In the presence of AT1 blockade induced by ARBs, residual unbound angiotensin II may bind AT2 receptors, which mediate protective effects in the CV system.34

### Effects of RAS blockade on end-organ damage

As noted above, even subclinical organ damage raises the level of CV risk in hypertensive patients.16 Hence, antihypertensive therapy should aim both to control blood pressure and, where possible, reduce or prevent the development of end-organ damage.35 Both ACE inhibitors and ARBs have been shown to provide effective blood pressure control12,16,36 and to offer beneficial effects on end-organ damage in tissues such as blood vessels, the heart and the kidney.

### Heart

LVH is a recognized risk factor for CV disease,37 and in hypertensive patients there is a significant correlation between elevated angiotensin II concentrations and increased left ventricular mass.38 Both ACE inhibitors and ARBs reduce left ventricular mass to a greater extent than other antihypertensive classes, such as diuretics or β-blockers,39 and several large trials have shown that ARBs reverse established LVH and may delay the development of LVH, in various high-risk populations.40–42

### Blood vessels

It has long been recognized that increased intima-media thickness (IMT) and decreased ventricular compliance resulting from atherosclerosis in large arteries are associated with an increased risk of CV events.12 In addition, recent data have shown that baseline IMT is predictive of CV events, irrespective of blood pressure.16,41 Both ACE inhibitors and ARBs have been shown to reduce IMT or arterial stiffness independent of blood pressure reductions.44–47

### Kidney

Impaired renal function in patients with hypertension or diabetes is associated with a substantial increase in CV risk.16 For example, in a recent study in patients with T2DM, every 50% decrease in estimated glomerular filtration rate was associated with a 2.2-fold increase in CV events and a 3.6-fold increase in CV deaths.48 Both ACE inhibitors49 and ARBs50–52 have been shown to reduce the progression of diabetic nephropathy or prevent the development of nephropathy in patients with microalbuminuria.

### Trials with RAS blockers in high-risk patients

Numerous trials have investigated the impact of RAS blockade with ACE inhibitors or ARBs in patients at high risk of CV events: those with established atherosclerotic disease or overt heart failure. Details of the principal trials are summarized in Table 1.

### Patients with coronary heart disease or acute MI

An overview of four early studies53–56 with ACE inhibitors in patients with acute MI, which involved 100 000 patients who were treated within 24–36 h after the onset of symptoms, showed that 30-day mortality was reduced by 7% (P = 0.004) in patients receiving ACE inhibitors.89 This is consistent with experimental data showing that early RAS blockade reduces infarct size and ventricular enlargement or remodelling, and leads to faster restoration of left ventricular function.90,91 Subsequent studies57–61 showed that ACE inhibitors were also effective in reducing mortality and reinfarction rates in patients...
Table 1  Randomized controlled trials with RAS blockade (ACE inhibitors or ARBs) in patients at high CV risk because of atherosclerotic vascular disease or heart failure

<table>
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<tr>
<th>Study</th>
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<tr>
<td><strong>Coronary heart disease/acute MI</strong></td>
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<tr>
<td>CONSENSUS II$^{53}$</td>
<td>Patients with acute MI</td>
<td>6090</td>
<td>Enalapril or placebo, starting within 24 h of the onset of symptoms</td>
<td>6 months</td>
<td>No difference in 1-month or 6-month survival rates between the groups</td>
</tr>
<tr>
<td>GISSI-3$^{54}$</td>
<td>Patients with acute MI</td>
<td>19394</td>
<td>Lisinopril or open control; nitrates or open control; all treatment started within 24 h of the onset of symptoms</td>
<td>6 weeks</td>
<td>Significant reductions in overall mortality, and mortality plus severe ventricular dysfunction, with lisinopril</td>
</tr>
<tr>
<td>ISIS-4$^{55}$</td>
<td>Patients with acute MI</td>
<td>58050</td>
<td>Captopril or placebo; controlled-release isosorbide 5-mononitrate or placebo; intravenous magnesium or open control</td>
<td>5 weeks</td>
<td>Significant reduction in 5-week mortality with captopril, compared with placebo</td>
</tr>
<tr>
<td><strong>CCS-1$^{56}$</strong></td>
<td>Patients with acute MI</td>
<td>13634</td>
<td>Captopril or placebo</td>
<td>4 weeks</td>
<td>Non-significant reduction in 4-week mortality with captopril</td>
</tr>
<tr>
<td>SAVE$^{57}$</td>
<td>Patients with previous (3–16 days) MI and LVEF ≤40%, but no overt heart failure</td>
<td>2231</td>
<td>Captopril or placebo</td>
<td>Mean 42 months</td>
<td>Significant reductions in all-cause mortality, recurrent MI, fatal recurrent MI and revascularizations with captopril</td>
</tr>
<tr>
<td>AIRE$^{58}$</td>
<td>Patients with previous (3–10 days) MI and clinical evidence of heart failure</td>
<td>2006</td>
<td>Ramipril or placebo</td>
<td>Mean 15 months</td>
<td>Significant reductions in all-cause mortality and sudden death in ramipril-treated patients</td>
</tr>
<tr>
<td>TRACE$^{59}$</td>
<td>Patients with previous (2–6 days) MI and LVEF ≤35%</td>
<td>1749</td>
<td>Trandolapril or placebo</td>
<td>24–50 months</td>
<td>Significant reductions in all-cause and CV mortality and sudden death in trandolapril-treated patients</td>
</tr>
<tr>
<td>SOLVD Treatment$^{60}$</td>
<td>Patients with LVEF ≤35% and overt heart failure</td>
<td>4228</td>
<td>Enalapril or placebo</td>
<td>&gt;3 years</td>
<td>Significant reduction in all-cause mortality with enalapril, mainly due to a decrease in deaths from worsening heart failure</td>
</tr>
<tr>
<td>SOLVD Prevention$^{61}$</td>
<td>Patients with LVEF ≤35% without overt heart failure</td>
<td>2569</td>
<td>Enalapril or placebo</td>
<td>&gt;3 years</td>
<td>Significant decrease in the incidence of death or development of CHF with enalapril</td>
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<table>
<thead>
<tr>
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<tr>
<td>EUROPA62</td>
<td>Patients with stable coronary heart disease but no overt heart failure</td>
<td>13 655</td>
<td>Perindopril or placebo</td>
<td>Mean 4.2 years</td>
<td>Significant reduction in the incidence of CV death, MI or cardiac arrest with perindopril</td>
</tr>
<tr>
<td>QUIET63</td>
<td>Patients with stable coronary heart disease but no systolic dysfunction</td>
<td>1750</td>
<td>Quinapril or placebo</td>
<td>Mean 27 months</td>
<td>No significant difference in the incidence of ischaemic events (cardiac death, resuscitated cardiac arrest, non-fatal MI, revascularization, or hospitalization for angina pectoris) between the groups</td>
</tr>
<tr>
<td>PEACE64</td>
<td>Patients with stable coronary heart disease and normal or slightly reduced ventricular function (mean ejection fraction 58%)</td>
<td>8290</td>
<td>Trandolapril or placebo</td>
<td>Median 4.8 years</td>
<td>No significant difference in the incidence of death from CV causes, MI, or coronary revascularization between the groups</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>Hypertensive or non-hypertensive patients with a history of stroke or TIA</td>
<td>6105</td>
<td>Perindopril (± indapamide) or placebo</td>
<td>4 years</td>
<td>Significant reduction in the risk of stroke with perindopril; also significant reductions in the risk of major CV events or CHF</td>
</tr>
<tr>
<td>PROGRESS65,66</td>
<td>Hypertensive patients with a history of stroke or TIA within the previous 2 years</td>
<td>1405</td>
<td>Eprosartan or nitrendipine</td>
<td>Mean 2.5 years</td>
<td>Significant decrease in total mortality and all CV and cerebrovascular events with eprosartan</td>
</tr>
<tr>
<td>MOSES67</td>
<td>Hypertensive patients with a history of stroke or TIA</td>
<td>1405</td>
<td>Eprosartan or nitrendipine</td>
<td>Mean 2.5 years</td>
<td>Significant decrease in total mortality and all CV and cerebrovascular events with eprosartan</td>
</tr>
<tr>
<td>PRoFESS68</td>
<td>Patients with ischaemic stroke</td>
<td>20 332</td>
<td>Aspirin or extended-release dipyridamole; telmisartan or placebo</td>
<td>Median 2.4 years</td>
<td>No significant differences in the incidence of recurrent stroke, stroke disability, or cognitive function between groups</td>
</tr>
<tr>
<td>Hypertension and high CV risk</td>
<td>Hypertensive patients with LVH</td>
<td>9193</td>
<td>Losartan-based or atenolol-based antihypertensive therapy</td>
<td>≥4 years</td>
<td>Significant reduction in death, MI and stroke with losartan, compared with atenolol</td>
</tr>
<tr>
<td>LIFE40,69</td>
<td>Hypertensive patients at high CV risk because of risk factors such as diabetes or elevated cholesterol, or pre-existing CV disease</td>
<td>15 245</td>
<td>Valsartan or amlodipine</td>
<td>Mean 4.2 years</td>
<td>No significant difference in CV mortality and morbidity between the groups; greater reductions in blood pressure with amlodipine than with valsartan</td>
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<tr>
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<tr>
<td>Jikei Heart Study&lt;sup&gt;71&lt;/sup&gt;</td>
<td>Patients with hypertension, CHD, heart failure or a combination of these disorders</td>
<td>3081</td>
<td>Conventional treatment plus valsartan or other (non-ARB) antihypertensive therapy</td>
<td>Mean 3.1 years</td>
<td>Composite endpoint of cardiovascular morbidity and mortality reached in fewer valsartan-treated patients. No difference in mortality or tolerability</td>
</tr>
<tr>
<td>KYOTO HEART&lt;sup&gt;72&lt;/sup&gt;</td>
<td>Patients with uncontrolled hypertension at high CV risk</td>
<td>3031</td>
<td>Valsartan add-on or non-ARB treatment</td>
<td>Mean 3.27 years</td>
<td>Valsartan treatment improved BP and prevented more CV events than non-ARB treatment</td>
</tr>
<tr>
<td><strong>Heart failure or left ventricular dysfunction</strong></td>
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<tr>
<td>VALIANT&lt;sup&gt;73&lt;/sup&gt;</td>
<td>Patients with MI complicated by left ventricular systolic dysfunction, heart failure, or both</td>
<td>14703</td>
<td>Valsartan, captopril or the two agents in combination</td>
<td>Median 24.7 months</td>
<td>No significant difference in all-cause mortality between the valsartan and captopril groups; also no significant difference in mortality between the combination therapy and captopril groups</td>
</tr>
<tr>
<td>OPTIMAAL&lt;sup&gt;74&lt;/sup&gt;</td>
<td>Patients with acute MI and heart failure</td>
<td>5477</td>
<td>Losartan: 50 mg/day, or captopril: 50 mg t.d.s.</td>
<td>Mean 2.7 years</td>
<td>Non-significant difference in total mortality in favour of captopril</td>
</tr>
<tr>
<td>CONSENSUS&lt;sup&gt;75&lt;/sup&gt;</td>
<td>Patients with severe CHF (NYHA class IV)</td>
<td>253</td>
<td>Enalapril or placebo</td>
<td>Mean 188 days</td>
<td>Significant reduction in overall mortality with enalapril; effect confined to patients with progressive heart failure</td>
</tr>
<tr>
<td>V-HeFT II&lt;sup&gt;76&lt;/sup&gt;</td>
<td>Patients with chronic CHF</td>
<td>804</td>
<td>Enalapril or hydralazine, plus isosorbide dinitrate</td>
<td>Mean 2.5 years</td>
<td>Significant reduction in mortality with enalapril, compared with hydralazine, mainly due to a decrease in sudden death</td>
</tr>
<tr>
<td>ATLAS&lt;sup&gt;77&lt;/sup&gt;</td>
<td>Patients with chronic heart failure (NYHA classes II–IV) and ejection fraction $\leq 30%$</td>
<td>3164</td>
<td>Lisinopril low dose (2.5–5 mg/day) or high dose (32.5–35 mg/day)</td>
<td>39–58 months</td>
<td>Significant reduction in mortality and hospitalizations with high-dose lisinopril, compared with low-dose treatment; also significant reductions in hospitalizations for CV reasons or heart failure</td>
</tr>
<tr>
<td>Val-HEFT&lt;sup&gt;78&lt;/sup&gt;</td>
<td>Patients with heart failure (NYHA classes II–IV)</td>
<td>5010</td>
<td>Valsartan or placebo</td>
<td>Mean 23 months</td>
<td>Significant reduction in CV mortality and morbidity (cardiac arrest with resuscitation, hospitalization for heart failure, or receipt of intravenous inotropic or vasodilator therapy for at least 4 hours) with valsartan</td>
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### Table 1 Continued

<table>
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<tr>
<th>Study</th>
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<tr>
<td><strong>ELITE II</strong></td>
<td>Patients with heart failure (NYHA classes II–IV) and LVEF ≤40%</td>
<td>3152</td>
<td>Losartan, 50 mg/day, or captopril, 50 mg t.d.s.</td>
<td>Median 555 days</td>
<td>No significant differences between the groups in all-cause mortality, sudden death or resuscitated cardiac arrest</td>
</tr>
<tr>
<td><strong>HEAAL</strong></td>
<td>Patients with heart failure (NYHA classes II–IV), LVEF ≤40% and intolerance to ACE inhibitors</td>
<td>3846</td>
<td>Losartan, 50 or 150 mg/day</td>
<td>Median 4.7 years</td>
<td>Decreased rate of death or hospitalization for heart failure with the higher dose</td>
</tr>
<tr>
<td><strong>CHARM</strong></td>
<td>Patients with LVEFs ≤40% already receiving ACE inhibitors (CHARM-Added) or intolerant to ACE inhibitors (CHARM-Alternative); patients with ejection fractions &gt;40% (CHARM-Preserved)</td>
<td>7601</td>
<td>Candesartan or placebo</td>
<td>≥2 years</td>
<td>Significant reductions in CV deaths and hospitalizations for heart failure with candesartan</td>
</tr>
<tr>
<td><strong>I-PRESERVE</strong></td>
<td>Patients with heart failure (NYHA classes II–IV) and LVEF ≤45%</td>
<td>4128</td>
<td>Irbesartan or placebo</td>
<td>Mean 49.5 months</td>
<td>Irbesartan did not improve the outcomes of patients with heart failure and a preserved LVEF.</td>
</tr>
<tr>
<td><strong>Cice et al.</strong></td>
<td>Haemodialysis patients with chronic heart failure (NYHA classes II–III) and LVEF ≤40%</td>
<td>332</td>
<td>Telmisartan 80 mg or placebo added to standard ACE inhibitor therapy</td>
<td>3 years</td>
<td>Significant reductions in all-cause mortality, CV mortality and hospital admissions for CHF with telmisartan.</td>
</tr>
<tr>
<td><strong>General high-risk patients</strong></td>
<td>Patients with vascular disease, or diabetic patients with at least one other risk factor, without left ventricular dysfunction or heart failure</td>
<td>9297</td>
<td>Ramipril or placebo</td>
<td>Mean 5 years</td>
<td>Significant reductions in all-cause and CV mortality, MI, stroke, revascularizations, cardiac arrest, heart failure and diabetic complications with ramipril</td>
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### Table 1 Continued

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<tr>
<td>ONTARGET&lt;sup&gt;788&lt;/sup&gt;</td>
<td>Patients with vascular disease or diabetes with end-organ damage</td>
<td>25620</td>
<td>Telmisartan, ramipril, or both</td>
<td>Median 56 months</td>
<td>Telmisartan was not inferior to ramipril for both the pre-specified primary outcome of death from CV causes, MI, stroke or hospitalization for heart failure, and for the secondary outcome (HOPE primary endpoint; death from CV causes, MI, or stroke); combination therapy had no effect on CV risk, compared with ramipril alone</td>
</tr>
<tr>
<td>TRANSCEND&lt;sup&gt;8,41,42&lt;/sup&gt;</td>
<td>Patients with vascular disease or diabetes with end-organ damage, and intolerance to ACE inhibitors</td>
<td>5926</td>
<td>Telmisartan or placebo</td>
<td>Median 56 months</td>
<td>No significant difference in CV death, MI, stroke or hospitalization for heart failure between the groups; significant reduction in CV death, MI or stroke with telmisartan (HOPE primary endpoint)</td>
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AIRE: Acute Reinfarction Ramipril Efficacy; CCS-1: Chinese Cardiac Study; CONSENSUS: Cooperative North Scandinavian Enalapril Survival Study; CONSENSUS II: Cooperative New Scandinavian Enalapril Survival Study II; GISSI-3: Gruppo Italiano per lo Studio della Sopravvivenza nell’infarto Miocardico-3; HEAAL: effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure; ISIS-4: Fourth International Study of Infarct Survival; ONTARGET<sup>+</sup>: Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial; SAVE: Survival and Ventricular Enlargement; SOLVD: Studies of Left Ventricular Dysfunction; TRACE: Trandolapril Cardiac Evaluation; TRANSCEND<sup>+</sup>: Telmisartan Randomised Assessment Study in aCE iNtolerant subjects with cardiovascular Diseases; V-HeFT II: Second Vasodilator-Heart Failure Trial.
with left ventricular dysfunction or heart failure after MI. A combined analysis of these trials showed that ACE inhibitor therapy reduced mortality from 26.5% to 22.1% (P=0.00001) and the risk of reinfarction from 12.2% to 10.2% (P=0.0004). Studies with ARBs in post-MI patients have shown outcomes not significantly different from those obtained with high doses of the ACE inhibitor, captopril.73,74

Three further trials, EURopean trial on reduction of cardiac events with Perindopril in stable coronary Artery disease (EUROPA),62 QUNiprI Ischemic Event Trial (QUIET)63 and Prevention of Events with Angiotensin-Converting Enzyme inhibition (PEACE),64 investigated the effects of ACE inhibitors in patients with stable coronary heart disease, with or without left ventricular dysfunction. In the EUROPA study, ACE inhibitor therapy was associated with a 20% reduction in the risk of CV death, cardiac arrest or MI, compared with placebo.62 In contrast, neither the QUIET nor the PEACE studies showed significant benefits of ACE inhibitor therapy. Patients in these studies were at lower CV risk than those in the EUROPA study, and thus the potential benefits of RAS blockade were presumably attenuated. Nevertheless, a pooled analysis of the three trials showed that ACE inhibitors were associated with significant reductions in CV mortality and morbidity, compared with placebo; the odds ratio (ORs) for the composite endpoint of CV mortality, non-fatal MI or stroke in patients receiving ACE inhibitors was 0.82 [95% confidence interval (95% CI) 0.76–0.88, P<0.0001].93

**Patients with stroke or TIA**

The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) study examined the impact of the ACE inhibitor perindopril-based antihypertensive therapy in 6105 patients with a history of stroke or TIA.55 The risk of recurrent stroke was reduced by 28% (95% CI 17–38%, P<0.0001) in patients on perindopril-based regimen, compared with placebo-treated patients, with similar reductions in both hypertensive and non-hypertensive patients. The perindopril-based regimen also reduced the incidence of major CV events and CHF, compared with placebo.66

Further evidence for the benefits of RAS blockade in reducing CV risk in stroke patients came from the Morbidity and Mortality after Stroke Eprosartan vs. Nitrendipine for Secondary Prevention (MOSES) study, which compared the ARB eprosartan and the calcium channel blocker nitrendipine in 1405 hypertensive patients who had experienced a stroke or TIA within 2 years previously.57 Blood pressure was reduced to similar extents by both treatments, and there were no significant differences in blood pressure, or in the proportion of patients in whom blood pressure control was achieved, between the groups. However, the incidence of cerebrovascular or CV events was significantly lower in eprosartan-treated patients than in those receiving nitrendipine [incidence density ratio (IDR) 0.79, 95% CI 0.66–0.96, P=0.014]. The reduction in cerebrovascular events was statistically significant [IDR 0.75, 95% CI 0.58–0.97, P=0.03], while the reduction in CV events just failed to attain significance [IDR 0.75, 95% CI 0.55–1.02, P=0.06].

The Prevention Regimen For Effectively avoiding Second Strokes (PRoFESS) study was a randomized, double-blind trial comparing a combination of aspirin plus extended-release dipyridamole with clopidogrel in patients with ischaemic stroke; in addition, patients were randomized to receive the ARB telmisartan or placebo.68 After a median of 2.4 years' follow-up, 9% of the patients in each group had experienced recurrent stroke, and there were no significant differences between the groups in disability (measured by the modified Rankin score and the Barthel Index) or cognitive function (measured by the mini-mental state examination). It should be noted that in this study the duration of follow-up was shorter, and the blood pressure reductions smaller, than in a previous trial in which ARB therapy was associated with a decreased incidence of stroke and preservation of cognitive function in elderly patients.94

**Patients with hypertension and high CV risk**

In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, 9193 hypertensive patients with LVH were randomized to receive losartan-based or atenolol-based treatment for at least 4 years.69 The incidence of the primary endpoint, a composite of CV death, stroke or MI, was significantly lower in the losartan group than in the atenolol group [relative risk (RR) 0.87, 95% CI 0.77–0.98, P=0.02]: this decrease was mainly driven by significant decreases in stroke mortality and morbidity.

The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) study compared the effects of valsartan-based or amldipine-based therapy in approximately 15 000 hypertensive patients who were at high risk of CV events because of additional risk factors such as diabetes or elevated cholesterol, or pre-existing CV disease.70 The blood pressure reductions achieved during the study were greater with amlodipine than with valsartan, particularly during the first 6 months. There was no significant
difference in the primary composite endpoint of CV mortality and morbidity between the two regimens [hazard ratio (HR): 1.04, 95% CI 0.94–1.15, \( P=0.49 \)]. Amlodipine produced significantly greater reductions in non-fatal MI and stroke than valsartan during the first 3 months of the study, which were presumable related to the larger blood pressure reductions achieved. In contrast, valsartan produced greater reductions in heart failure and new-onset diabetes than amlodipine during the later stages of the trial (>36 months).\(^{70}\)

The effects of ARBs in high-risk patients have also been assessed in two open studies in Japan. In the Jikei Heart Study, which involved 3081 patients with hypertension, coronary heart disease or heart failure, the addition of valsartan to standard treatment significantly reduced the number of CV events, compared with standard treatment alone (HR 0.61, 95% CI 0.47–0.79, \( P=0.0002 \)); this reduction was primarily due to decreases in the incidence of stroke or TIA (HR 0.60, 95% CI 0.38–0.95, \( P=0.028 \)), angina pectoris (HR 0.35, 95% CI 0.20–0.58, \( P<0.0001 \)) and heart failure (HR 0.53, 95% CI 0.31–0.94, \( P=0.029 \)).\(^{71}\) Similarly, in the KYOTO HEART Study, the addition of valsartan to standard antihypertensive therapy was associated with a significantly lower incidence of fatal and non-fatal CV events than standard therapy alone (HR 0.55, 95% CI 0.42–0.72).\(^{72}\) The patient population in this study was similar to that in the VALUE study, although the incidence of existing CV disease was lower and the blood pressure reductions achieved were larger.

Patients with coronary disease and left ventricular dysfunction

The Valsartan in Acute Myocardial Infarction (VALIANT) study compared the efficacy of an ACE inhibitor (captopril) and an ARB (valsartan) in patients with heart failure or left ventricular dysfunction after a recent MI.\(^{73}\) There was no significant difference in all-cause mortality between the two groups (HR for valsartan vs. captopril: 1.00, 95% CI 0.90–1.11, \( P=0.98 \)), and valsartan was shown to be non-inferior to captopril for both all-cause mortality and CV mortality and morbidity. Treatment with both drugs concomitantly produced no additional decrease in mortality, compared with either agent alone.

The Optimal Therapy in Myocardial infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) trial, which used the same dose regimens, showed a trend (\( P=0.069 \)) towards higher efficacy for captopril, although the tolerability advantage of losartan was maintained.\(^{74}\)

Patients with left ventricular dysfunction or heart failure

The efficacy of RAS blockade in reducing CV mortality and morbidity was originally demonstrated in a series of landmark trials with ACE inhibitors in patients with left ventricular dysfunction or heart failure.\(^{57,59–61,75,76}\) Subsequently, the Assessment of Treatment with Lisinopril And Survival (ATLAS) study\(^ {77}\) showed that high-dose ACE inhibitor therapy was more effective than lower doses in reducing CV morbidity in heart failure patients; CV mortality was also reduced with high-dose therapy, but this effect did not reach statistical significance in this study. More recently, a number of studies have investigated the effects of ARBs in patients with left ventricular dysfunction and in patients with heart failure.

The Valsartan in Heart Failure Trial (Val-HEFT) trial demonstrated that the addition of valsartan to existing antihypertensive treatment (mainly ACE inhibitor based) reduced hospital admissions for worsening heart failure but had no effect on mortality.\(^ {78}\) This, along with the OPTIMAAL trial, suggests that dual RAS blockade does not confer additional therapeutic efficacy in patients with heart failure, except in the subgroup who are not receiving \( \beta \)-blockers.\(^ {95} \)

The Evaluation of Losartan In The Elderly-II (ELITE II) study compared losartan (50 mg/day) with captopril (100 mg/day) in patients with symptomatic heart failure.\(^ {79}\) All-cause mortality was similar in both groups, but losartan was better tolerated. However, a further study (HEAAL) showed that losartan, 150 mg/day, was significantly more effective than the lower dose of 50 mg/day in reducing the incidence of death or hospitalization for heart failure (HR 0.90, 95% CI 0.82–0.99, \( P=0.027 \)).\(^ {80}\) This suggests that the dose of losartan used in the ELITE II study was probably too low to show a significant benefit. In the Val-HeFT trial with valsartan compared with placebo, a benefit on the composite endpoint of mortality and hospitalization was reported in patients with heart failure [New York Heart Association (NYHA) classes II–IV].\(^ {79}\)

The Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity (CHARM) study programme evaluated the effects of candesartan in a broad patient population including patients with low left ventricular ejection fractions (LVEFs) who were receiving ACE inhibitors (CHARM-Added) or were intolerant to ACE inhibitors (CHARM-Alternative) and patients with preserved left ventricular function (CHARM-Preserved).\(^ {81–84} \) Overall, these studies showed that ARB therapy was significantly more effective than standard antihypertensive treatment in reducing deaths and
hospital admissions for heart failure in patients with decreased left ventricular function. Moreover, in the CHARM-Alternative study, the reductions in these endpoints achieved with ARB therapy were comparable in size to those achieved with ACE inhibitors in the early landmark studies. However, in the CHARM-Preserved trial, candesartan had no significant effect on CV mortality or hospitalizations for heart failure in patients with preserved left ventricular function, although the number of hospitalizations for worsening heart failure was significantly reduced. Similarly, the Irbesartan in HF with preserved EF (I-PRESERVE) trial showed no significant benefit when irbesartan was added to standard antihypertensive treatment in heart failure patients with preserved left ventricular function.

More recently, a study by Cice et al. investigated 332 patients with end-stage renal disease in addition to heart failure and impaired LVEF. Telmisartan 80 mg or placebo was added to standard ACE inhibitor therapy for up to 3 years. A significant improvement was seen in all-cause mortality ($P<0.001$), CV mortality ($P<0.001$) and hospital admission for chronic heart failure ($P<0.0001$) for patients treated with added telmisartan. These beneficial effects of telmisartan were evident after only 6 months' treatment and persisted for the duration of the study.

Studies in a broad spectrum of high-risk patients

Several landmark studies have evaluated the effects of RAS blockade in a broad spectrum of high-risk patients. The Heart Outcomes Prevention Evaluation (HOPE) study compared the effects of ramipril and placebo in 9297 patients who were at high CV risk because of existing vascular disease, or diabetes plus at least one other risk factor, but who did not have left ventricular dysfunction or heart failure. After 5 years, ramipril reduced the incidence of CV death, MI or stroke by $>20\%$, compared with placebo ($RR = 0.78$, $95\% CI 0.70–0.86$, $P<0.001$); ramipril was associated with significant decreases in each component of the composite endpoint, and in all-cause mortality, revascularization procedures, cardiac arrest, heart failure and diabetes-related complications.

Studies with ARBs in hypertensive patients with high CV risk profile generated non-univocal results.

More recently, the effects of the ARB, telmisartan, and the ACE inhibitor, ramipril, on CV risk have been compared in ONTARGET, which involved over 25,000 patients with vascular disease and T2DM with end-organ damage who were randomized to receive ramipril, telmisartan or the two agents in combination. After a median follow-up of 56 months, the incidence of the primary endpoint (a composite of CV death, MI, stroke or hospitalization for heart failure) was 16.5% in the ramipril group and 16.7% in the telmisartan group (RR 1.01, 95% CI 0.94–1.09). However, ramipril was associated with significantly higher incidences of adverse events such as cough (4.2% vs. 1.1%, $P<0.001$) and angioedema (0.3% vs. 0.1%, $P=0.01$), compared with telmisartan. The combination of telmisartan and ramipril did not significantly affect the incidence of the primary endpoint, compared with ramipril alone (RR 0.99, 95% CI 0.92–1.07), but was associated with significantly higher incidences of hypotensive symptoms, syncope and renal dysfunction.

A companion study to ONTARGET*, the TRANSCEND™ study, evaluated the effects of telmisartan in patients who were unable to tolerate ACE inhibitor therapy. Patients were randomized to receive telmisartan or placebo in addition to their existing standard treatment, and followed for a median of 56 months. There was no significant difference between the telmisartan-treated patients and those receiving placebo in the incidence of the primary endpoint (a composite of CV death, MI, stroke or hospitalization for heart failure); HR 0.92, 95% CI 0.81–1.05, $P=0.216$). However, the incidence of the secondary endpoint (the primary composite endpoint but without hospitalization for heart failure) was significantly reduced by telmisartan treatment, compared with placebo (HR 0.87, 95% CI 0.76–1.00, $P=0.048$). This secondary composite endpoint in TRANSCEND™ was similar to the primary endpoint in HOPE. Interestingly, the event rate seen with placebo in the TRANSCEND™ trial (14.8%) is similar to the event rate seen with ramipril in the HOPE trial (14.0%), indicating that patients receiving current standard of care alone are as well protected as those receiving ramipril.

Comparisons between ACE inhibitors and ARBs

The effect of ARBs on the risk of MI was investigated in a meta-analysis of 20 trials, involving almost 109,000 patients, which concluded that ARBs and ACE inhibitors have comparable effects on the risk of MI (OR 1.008, 95% CI 0.926–1.099). This result is consistent with that from the ONTARGET™ study, which directly compared ACE inhibitor and ARB therapy in a large population of high-risk patients. This study clearly showed that telmisartan and ramipril are equivalent in their effects on CV endpoints. Based on such findings, a recent re-appraisal of the
2007 European guidelines for the management of hypertension has concluded that ACE inhibitors and ARBs can be considered to be interchangeable in terms of their effects on CV mortality and morbidity.16

Combination therapy with ACE inhibitors and ARBs

A meta-analysis of 21 randomized controlled trials evaluated the combination of an ACE inhibitor and an ARB in patients with chronic proteinuric renal disease.97 Combination therapy significantly decreased proteinuria, both in patients with and without diabetes (210 mg/day and 582 mg/day, respectively). In one trial, hypertensive patients with type 2 diabetes and microalbuminuria received lisinopril or telmisartan for 6 months, then half of the patients received combination therapy for a further 28 weeks.98 The combination was associated with additional benefit, as shown by a 30% further reduction in albumin excretion rate and superior blood pressure control.

The double-blind valsartan in combination with lisinopril vs. the respective high-dose monotherapies in hypertensive patients with microalbuminuria (VALERIA) trial assessed treatment with valsartan 320 mg, lisinopril 40 mg or the combination (320/20 mg) in 133 patients with hypertension and microalbuminuria (around three-quarters of whom had type 2 diabetes).99 After 30 weeks of treatment, blood pressure reductions were similar in the three treatment groups. However, the mean urinary albumin creatinine ratio, which ranged 9.1–9.6 mg/mmol at baseline, was reduced more with the combination (62%) than with valsartan (51%) or lisinopril (41%) (significant for the combination vs. lisinopril, \( P=0.029 \)).

In both VALIANT73 and ONTARGET88, combination treatment with an ACE inhibitor and an ARB had no additional effect on the risk of CV events, compared with either agent alone, and was associated with an increased risk of adverse events such as syncope or renal dysfunction. Furthermore, a meta-analysis of nine randomized placebo-controlled trials assessed the tolerability of combination treatment with an ACE inhibitor and an ARB vs. an ACE inhibitor alone in patients with heart failure or left ventricular dysfunction.100 Combination therapy was associated with an increased risk of any adverse event, hypotension, worsening renal function and hyperkalemia (but not angioedema or cough). As a result of these studies, the use of such combinations cannot be recommended.16

Conclusions

There is now a substantial body of evidence to support the use of RAS blockers as first-line therapy in all patients at high risk of CV events because of atherosclerotic vascular disease. Although most CV prevention trials have used ACE inhibitors, a number of studies in high-risk patients during the last decade have shown that ARBs are as effective in this setting, and offer a superior tolerability profile to ACE inhibitors. As a result of the clinical trials evidence, the currently available RAS blockers have differing indications, in addition to the common indication for hypertension.101 Several ACE inhibitors (enalapril, lisinopril, quinapril, ramipril and trandolapril) and ARBs [candesartan, valsartan and losartan (in Europe)] are indicated in patients with left ventricular dysfunction or heart failure. Losartan is indicated for stroke prevention in patients with hypertension and LVH. Perindopril is indicated for patients with coronary artery disease, and lisinopril in patients with an acute MI. At present, only telmisartan and ramipril are indicated for the reduction of CV risk. Ramipril is indicated in CV prevention for the reduction of CV morbidity and mortality in patients with manifest atherothrombotic CV disease (history of coronary heart disease or stroke, or peripheral vascular disease) or diabetes with at least one CV risk factor. Telmisartan is indicated in CV prevention for the reduction of CV morbidity in patients with manifest atherothrombotic CV disease (history of coronary heart disease, stroke or peripheral arterial disease) or T2DM with documented target organ damage. RAS blockade with either ACE inhibitors or ARBs should therefore form a central part of strategies to reduce CV risk in such at risk patients. Since the pharmacological characteristics of these agents differ, it should not be assumed that they offer equivalent efficacy or tolerability. The choice between individual agents should therefore be made based on clinical evidence, as reflected in approved indications, and considerations of tolerability.

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