Telmisartan in High Cardiovascular Risk Patients

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Abstract

The worldwide morbidity and mortality burden of cardiovascular disease (CVD) is overwhelming and caused by increasing life expectancy and an epidemic of risk factors, including hypertension. Therapeutic options targeting different areas of the renin–angiotensin–aldosterone system (RAAS) to disrupt pathophysiological processes along the cardiovascular continuum are available. Angiotensin-converting enzyme (ACE) inhibitors are first-line treatments for CVD and angiotensin receptor blockers (ARBs) are suitable alternatives. Both ACE inhibitors and ARBs prevent CVD by lowering blood pressure (BP). Additionally, several studies have demonstrated that RAAS blockade can reduce cardiovascular risk beyond what might be expected from BP lowering alone. However, the ARBs are not all equally effective. Telmisartan is a long-lasting ARB that effectively controls BP over the full 24-hour period. Recently, the Ongoing telmisartan alone and in combination with ramipril global endpoint trial (ONTARGET) study showed that telmisartan reduces cardiovascular events in high cardiovascular risk patients similarly to the gold standard ACE inhibitor ramipril beyond BP lowering alone, but with a better tolerability. Based on the results of the ONTARGET and Telmisartan randomized assessment study in ACE intolerant subjects with cardiovascular disease (TRANSCEND) studies, telmisartan is indicated for the reduction of cardiovascular morbidity. This article aims to review current guidelines for the management of CVD and consider key data from clinical trials and clinical practice evaluating the role of telmisartan in CVD.

Keywords

Angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, cardiovascular continuum, cardiovascular risk, hypertension, telmisartan

Disclosure: The author has no conflicts of interest to declare.

Acknowledgements: Writing and editorial assistance was provided by Touch Briefings, which was contracted by Boehringer Ingelheim International GmbH for these services. The author meets criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE), was fully responsible for all content and editorial decisions, and was involved at all stages of manuscript development. The author received no compensation related to the development of the manuscript.

Received: 10 December 2011 **Accepted:** 4 January 2012 **Citation:** *European Cardiology*, 2012;8(1):10–6

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Support: The publication of this article was funded by Boehringer Ingelheim. The views and opinions expressed are those of the author and not necessarily those of Boehringer Ingelheim.

The greatest burden of cardiovascular disease (CVD) is due to non-fatal morbidity and its consequences; whereas CVD accounts for approximately 17 million deaths each year worldwide, current estimates indicate that CVD associated with asymptomatic disease and target organ damage as a result of undetected cardiovascular risk factors affects 128 million people worldwide.[1,2] Moreover, the worldwide incidence of CVD is increasing, not only in line with increasing life expectancy, but also because of an escalating epidemic of risk factors (including hypertension, obesity, diabetes, high cholesterol levels and smoking) that is not restricted to the developed world.[2,3] Indeed, hypertension, acknowledged in a World Health Organization report as being among the most significant avoidable reasons for early mortality, affected 972 million people worldwide in 2000, and it is estimated that it will affect 1.56 billion people by 2025.[4] Only 2–7 % of individuals are free from CVD risk factors, and >70 % of at-risk individuals have multiple risk factors that act synergistically to potentiate the total risk.[1,5,6]

The progression of CVD can be thought of as a continuum, from the presence of risk factors to the development of organ damage and diseases – such as atherosclerosis, left ventricular hypertrophy (LVH), coronary artery disease, myocardial infarction (MI), stroke, cardiovascular remodelling and heart failure – and ultimately to death (see *Figure 1*).[7,8] This has led to the idea that intervention at any stage along the CVD continuum can disrupt the pathophysiological process and prevent disease progression.[7] A key player in CVD is the renin–angiotensin–aldosterone system (RAAS).[9–11] Activation of the RAAS results in the accumulation of the primary effector peptide angiotensin II, which, via angiotensin type I (AT1) receptors, causes inflammation, vasoconstriction, thrombosis, fibrosis and superoxide formation.[12] Thus the RAAS has been implicated in the pathophysiological processes underlying CVD[10,12] and is a logical target for disruption of the CVD continuum.[13,14]

Two different classes of agents target the production of angiotensin: angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs).[15,16] The principal indication of both drug classes is to alleviate hypertension. Multiple clinical trials have also evaluated different ACE inhibitors and ARBs for preventing cardiovascular-related events – with varying degrees of success. Among these clinical trials, some of the most important ones are (see also *Table 1*):

Table 1: Latest Evidence on the Role of Angiotensin-converting Enzyme Inhibitors and Angiotensin Receptor Blockers in Cardiovascular Risk Prevention

	Ramipril 10 mg	Perindopril 8 mg	Trandolapril 4 mg	Valsartan 160 mg	Losartan 50 mg	Olmesartan 40 mg	Irbesartan 300 mg	Telmisartan 80 mg	Telmisartan 80 mg	Telmisartan 80 mg
Trial	HOPE[17]	EUROPA[18]	PEACE[19]	NAVIGATOR[20]	LIFE[21]	ROADMAP[22]	ACTIVE I[23]	ONTARGET[24]	TRANSCEND[25]	Telmisartan in haemodialysis patients with chronic heart failure[26]
Patients	9,297 with diabetes or vascular disease	13,655 with stable coronary artery disease	8,290 with coronary artery disease	9,306 with impaired glucose tolerance and CV disease or risk factors for CVD	9,193 with essential hypertension and LVH	4,447 with type 2 diabetes and at least one CV risk factor	9,016 with AF and one or more extra risk factors for stroke	25,620 at high risk of CV events	5,926 intolerant to ACEIs	332 haemodialysis patients with CHF
Comparator	Placebo	Placebo	Placebo	Placebo	Atenolol	Placebo	Placebo	Ramipril	Placebo	Placebo
CV endpoint	Reduced rates of a composite of MI, stroke and CV death	Reduced rates of MI, cardiac arrest and CV death	Equivalence for MI, coronary revascularisation and CV death	Equivalence for the extended and core CV outcomes	Reduced morbidity and CV death with losartan	Equivalence for morbidity plus mortality; higher CV mortality with olmesartan	Equivalence for a composite outcome of stroke, MI and vascular death	Equivalence for reducing risk of a composite of MI, stroke, CV death or hospitalisation for HF	Equivalence for a composite outcome of CV death, MI, stroke or hospitalisation for HF	All-cause and CV mortality, and hospitalisation for CHF
Significance	p<0.001	p=0.0003	p=0.43	p=0.43 and 0.85, respectively	p=0.021	p=0.0115 for CV mortality	p=0.846	p<0.01	p=0.216	p<0.0001 and 0.0001, respectively
Marketing authorisation	FDA and EMA approved	FDA and EMA approved	None	None	FDA and EMA approved	None	None	FDA and EMA approved	FDA and EMA approved	None

Key to Table 1

ACEIs = angiotensin-converting enzyme inhibitors; AF = atrial fibrillation; CHF = chronic heart failure; CV = cardiovascular; CVD = cardiovascular disease; EMA = European Medicines Agency; FDA = Food and Drug Administration; HF = heart failure; LVH = left ventricular hypertrophy; MI = myocardial infarction.

- the Heart outcomes prevention evaluation (HOPE) study;[17]
- the European trial on reduction of cardiac events with perindopril in stable coronary artery disease (EUROPA) study;[18]
- the Prevention of events with angiotensin-converting enzyme inhibitor therapy (PEACE) study;[19]
- the Nateglinide and valsartan in impaired glucose tolerance outcomes research (NAVIGATOR) study;[20]
- the Losartan intervention for endpoint reduction in hypertension (LIFE) study;[21]
- the Randomized olmesartan and diabetes microalbuminuria prevention study (ROADMAP);[22]
- the Atrial fibrillation clopidogrel trial with irbesartan for prevention of vascular events (ACTIVE I) study;[23]
- the Ongoing telmisartan alone and in combination with ramipril global endpoint trial (ONTARGET);[24]
- the Telmisartan randomized assessment study in ACE intolerant subjects with cardiovascular disease (TRANSCEND);[25] and
- the Telmisartan in haemodialysis patients with chronic heart failure study.[26]

Furthermore, several of these studies demonstrated that RAAS blockade can reduce cardiovascular risk beyond what might be expected from blood pressure (BP) lowering alone.[24,25]

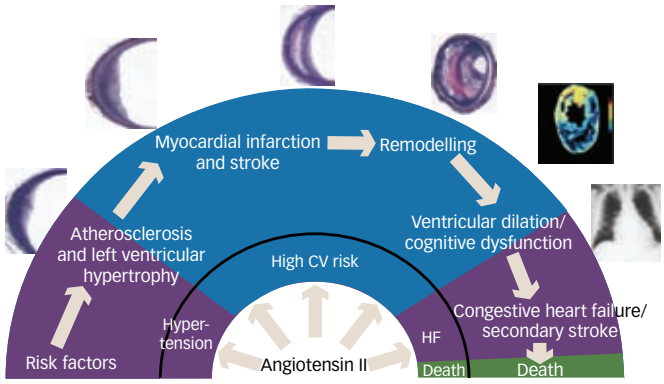
The ARB telmisartan is indicated in Europe as monotherapy for both the treatment of hypertension in adults and the reduction of cardiovascular morbidity in patients with manifest atherothrombotic CVD (including history of coronary heart disease, stroke or peripheral arterial disease) as well as in patients with type 2 diabetes mellitus and documented target organ damage.[27] This article aims to review current guidelines for the management of CVD and consider key data from clinical trials and clinical practice evaluating the role of telmisartan in CVD.

International Guidelines Recommendations

Hypertension is a primary risk factor for CVD[28] and antihypertensive therapy is usually required in addition to lifestyle modifications. Guidelines from the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) favour the use of ACE inhibitors post-MI and in patients with hypertension, heart failure, left ventricular dysfunction, diabetic and non-diabetic nephropathy, LVH, carotid atherosclerosis, proteinuria or microalbuminuria, atrial fibrillation (AF) and metabolic syndrome.[29]

Moreover, the joint ESH/ESC guidelines favour the direct use of ARBs, not only for hypertension but also post-MI and for heart failure, diabetic nephropathy, proteinuria or microalbuminuria, LVH, AF and metabolic syndrome.[29] In a more recent version of the guidelines, these preferences have not changed.[30] The ESH/ESC guidelines also favour ARBs in those patients in whom there is an indication for, but who are intolerant to, ACE inhibitors.[29] Intolerance to ACE inhibitors is usually due to cough (which may affect up to 35 % of patients) or angiooedema (which could potentially be life-threatening).[31–34]

Figure 1: Angiotensin II is Central to Cardiovascular Disease Progression



CV = cardiovascular; HF = heart failure. Image reproduced with the kind permission of Professor Böhm. Adapted from Dzau, et al., 1991,[7] Dzau, et al., 2006[8] and Yusuf, et al., 2004.[91]

Pharmacodynamic and Pharmacokinetic Profile of Telmisartan

Detailed reviews on the properties of telmisartan have been published elsewhere.[35–38] Briefly, telmisartan is a potent and selective AT1 antagonist with no apparent affinity for angiotensin type II (AT2) receptors or ACE. After oral administration, maximum plasma levels occur within 0.5–2 hours and peak bioavailability is 57 %. It is almost exclusively eliminated in the faeces (>98 %) and has an elimination half-life of 20–24 hours. This is the longest of all the currently available ARBs and makes a once-daily dosing regimen with telmisartan sufficient for effective lowering of BP over the full 24-hour period. Typical doses are 40 mg or 80 mg once daily, either as monotherapy or in combination with additional antihypertensives if BP is inadequately controlled.

Clinical Uses of Telmisartan in Cardiovascular Disease

Hypertension and beyond Blood Pressure Lowering

The circadian pattern of BP is well known, with a steady increase in BP occurring in the early hours.[39,40] Cardiovascular events also exhibit a circadian rhythm with peak occurrence in the first few hours after wakening that may be caused by the early morning surge in BP.[39,40] The antihypertensive effectiveness of telmisartan, due to its ability to reduce BP over the full 24-hour period, was evaluated in a meta-analysis of five trials involving a total of 1,566 patients.[41] Compared with the first generation ARBs losartan and valsartan, telmisartan offered greater and more consistent systolic and diastolic BP lowering during the morning period (see *Figure 2*) and over the 24-hour period as a whole.[41] Additional, separate trials have demonstrated that telmisartan is more effective in controlling BP than either valsartan or losartan over the full 24-hour period.[42–46] Moreover, telmisartan is better able to control BP than valsartan in the event of a missed dose.[47] Indirect comparisons indicate that telmisartan is at least as effective as the newer generation ARBs, including candesartan, irbesartan and olmesartan, in reducing BP.[48] The effectiveness of telmisartan in reducing BP has also been compared with that of ACE inhibitors. Telmisartan controlled BP more effectively than ramipril during the morning period and over the 24-hour period as a whole,[49] and was also more effective than enalapril[50] and perindopril,[51] and at least as effective as lisinopril.[52]

Metabolism

Metabolic syndrome is not clearly defined but refers to a cluster of interrelated metabolic risk factors for CVD, including insulin resistance or glucose intolerance, visceral obesity, dyslipidaemia and hypertension.[53,54] The involvement of hypertension suggests that drugs that target the RAAS may be of therapeutic benefit, particularly ARBs. Telmisartan improved insulin sensitivity in patients with metabolic syndrome compared with valsartan[55] or losartan.[56] Furthermore, telmisartan was more effective than irbesartan at improving metabolic parameters in diabetic patients with or without hypertension.[57,58] Recently, a meta-analysis of two randomised, double-blind, placebo-controlled trials with telmisartan, in which the incidence of new onset diabetes was measured as a pre-specified secondary endpoint, has been performed. This meta-analysis of the TRANSCEND and Prevention regimen for effectively avoiding second strokes (PROFESS) trials indicates that telmisartan can reduce the risk of new onset diabetes by approximately 16 % compared with placebo in high cardiovascular risk patients without heart failure. This antidiabetic effect of telmisartan is similar in its overall magnitude to that observed with ACE inhibitors in placebo-controlled clinical trials in patients without heart failure.[59]

Left Ventricular Hypertrophy

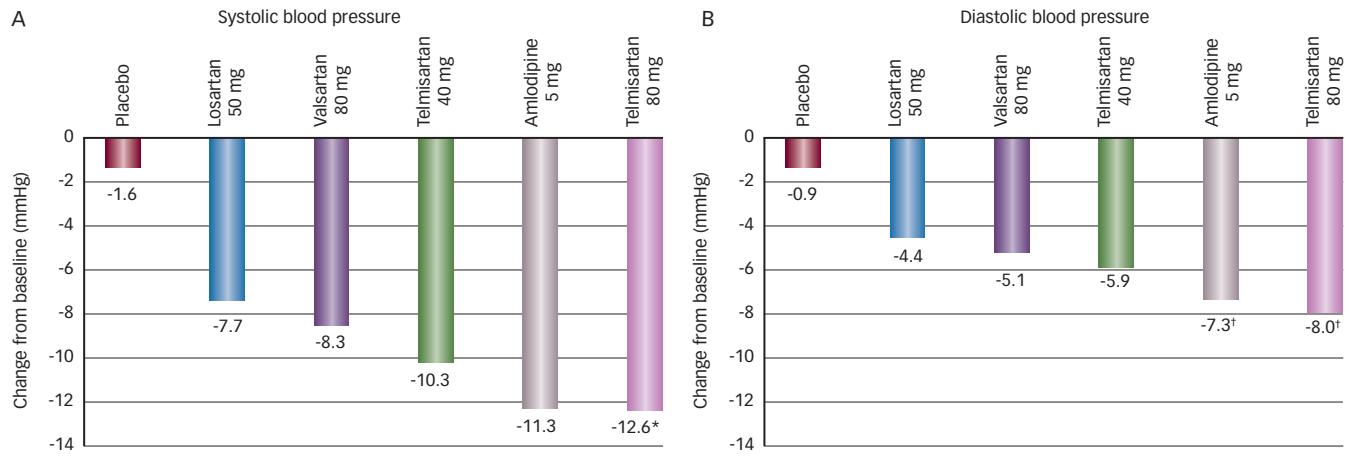
A sub-analysis of data from the ONTARGET and TRANSCEND studies examined the effects of telmisartan on LVH. The prevalence of LVH at entry into the TRANSCEND study was 12.7 % and treatment with telmisartan reduced prevalence to 9.9 % after five years, whereas prevalence remained at 12.8 % with placebo.[60] The rate of new onset of LVH was lower in the telmisartan group than in the placebo group (5.0 % versus 7.9 %, respectively [p<0.001]).[25] In the TRANSCEND study, telmisartan statistically significantly reduced LVH overall by 21 % (p=0.0017) versus placebo. The rate of new onset of LVH was statistically reduced by 37 % (p=0.0001) in the telmisartan group versus placebo. LVH regression was similar in both groups. At the end of the ONTARGET study, the prevalence of LVH was lower for telmisartan (9.7 %) than for both ramipril (10.5 %) and combined therapy (10.2 %), but not significantly so.[60] It is important to note that new onset of LVH was associated with a higher risk of the primary outcome. The therapeutic equivalence of telmisartan and ramipril was also demonstrated by a decrease in left ventricular mass (LVM) as measured by cardiac magnetic resonance imaging (MRI) in a subgroup of the ONTARGET study.[61] The ability of telmisartan to decrease LVM has also been demonstrated in separate studies.[62,63]

Renal Function

In the ONTARGET study, rates of renal impairment were similar in the telmisartan (10.2 %) and ramipril (10.6 %) groups, but significantly greater in the combination group (13.5 %).[24] More specific analysis of renal outcomes demonstrated an equivalence between telmisartan and ramipril for the composite primary outcome of dialysis, doubling of serum creatinine and death (13.4 % versus 13.5 %, respectively) and an increased rate for dual therapy (14.5 %).[64] Telmisartan was also associated with lower rates of albuminuria than ramipril.[64] A subgroup analysis of patients from the ONTARGET and TRANSCEND studies with low glomerular filtration rates and elevated albuminuria demonstrated no benefits of telmisartan over ramipril or placebo for the primary renal composite outcome of dialysis or doubling of creatinine levels.[65]

The Incipient to overt: angiotensin II receptor blocker, telmisartan, investigation on type 2 diabetic nephropathy (INNOVATION) study

Figure 2: Mean Reduction in Blood Pressure during the Morning Period with Angiotensin Receptor Blockers



** = p<0.0125 versus losartan 50 mg or valsartan 80 mg and p<0.05 versus telmisartan 40 mg; † = p<0.0125 versus losartan 50 mg or valsartan 80 mg.*
A: mean reduction in systolic blood pressure; B: mean reduction in diastolic blood pressure. Values were obtained during the morning period (06.00 am–11.59 am). All individuals received concomitant amlodipine (5 mg). Reproduced from Neutel and Smith, 2003.[41]

demonstrated the benefit of telmisartan compared with placebo for preventing the transition from incipient to overt nephropathy in Japanese patients with type 2 diabetes[66] and for preventing the progression to microalbuminuria.[67] Moreover, the non-inferiority of telmisartan compared to a different ACE inhibitor, enalapril, for renoprotection in patients with type 2 diabetes and nephropathy has been demonstrated in the Diabetes exposed to telmisartan and enalapril (DETAIL) study.[68]

The AMADEO (A trial to compare telmisartan 40 mg titrated to 80 mg versus losartan 50 mg titrated to 100 mg in hypertensive type 2 diabetic patients with overt nephropathy) and VIVALDI (Investigate the efficacy of telmisartan versus valsartan in hypertensive type 2 diabetic patients with overt nephropathy) studies evaluated the effect of telmisartan on macroalbuminuria. In the AMADEO study, telmisartan reduced the urinary protein:creatinine ratio significantly more than losartan after 52 weeks (29.8 % versus 21.4 % from baseline, respectively [p=0.027]), despite similar BP control.[69] In the VIVALDI study, telmisartan 80 mg provided identical reductions in urinary protein excretion (33 % from baseline) to valsartan 160 mg,[70] but urinary 8-iso-prostaglandin F2α levels decreased by 14 % with telmisartan and by 7 % with valsartan (p=0.040).

Atrial Fibrillation

Data from the ONTARGET study demonstrated equivalence for the onset of new AF between telmisartan (6.7 %), ramipril (6.9 %, relative risk 0.97, 95 % confidence interval [CI] 0.86–1.09) and dual therapy (6.5 %, relative risk 0.96, 95 % CI 0.85–1.07).[24] Similarly, the TRANSCEND study demonstrated equivalence between telmisartan (6.4 %) and placebo (6.3 %) (hazard ratio 1.02, 95 % CI 0.83–1.26, p=0.829) for the onset of AF.[25] However, telmisartan is effective in preventing AF recurrence in hypertensive patients with a history of AF[71] and more effective than ramipril in reducing the recurrence (telmisartan 12.9 %, p<0.01 versus amlodipine and p<0.05 versus ramipril; ramipril 25.5 %, p<0.01 versus amlodipine) and severity of AF in hypertensive patients with metabolic syndrome.[72]

Endothelial Function and Arterial Stiffness

The endothelium is a principal regulator of vascular homoeostasis and endothelial dysfunction is thought to play a role in hypertension-associated vascular change.[73] Telmisartan had more favourable effects on functional parameters associated with endothelial function than valsartan in hypertensive patients, despite similar BP-lowering effects.[74] Telmisartan and ramipril had similar effects on renal endothelial function in patients with hypertension and type 2 diabetes, but, in the Telmisartan versus ramipril on renal endothelium function in type 2 diabetes (TRENDY) study, telmisartan also improved resting renal plasma flow whereas ramipril did not.[75] In addition, telmisartan reduced arterial stiffness to a greater extent than placebo in hypertensive patients with type 2 diabetes.[76]

Inflammation

Angiotensin promotes atherosclerosis through pro-inflammatory mechanisms,[77] therefore RAAS blockers may be therapeutically beneficial in CVD. Telmisartan has been shown to reduce markers of inflammation, such as C-reactive protein and interleukin-6, at least as effectively as ACE inhibitors, including ramipril, or other ARBs, such as valsartan and olmesartan, in hypertensive or diabetic patients.[78–81]

Cardiovascular Risk Reduction in High-risk Patients

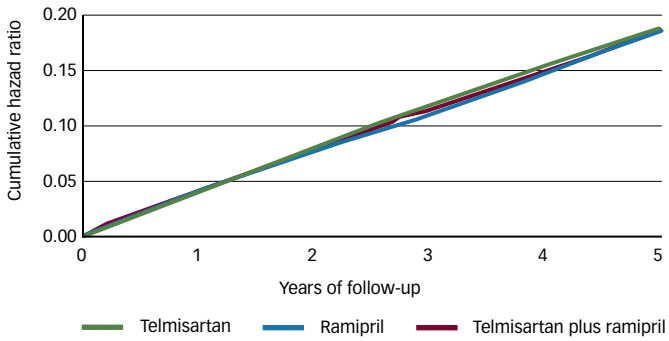
In addition to the ability of ARBs to reduce BP, the Candesartan in heart failure assessment of reduction in mortality and morbidity (CHARM Alternative) study demonstrated their ability to reduce cardiovascular death and hospitalisation for congestive heart failure in patients with previous heart failure.[82] The ability of telmisartan to reduce cardiovascular morbidity and mortality in high-risk patients with CVD or diabetes mellitus and end-organ damage – but not heart failure – was examined in the ONTARGET study in a population similar to that studied in the HOPE trial (see *Table 1*).[83] The primary outcome was a composite of death from cardiovascular causes, MI, stroke or hospitalisation due to heart failure. A total of 25,577 patients were followed until a primary event occurred or until the end of the study (median 56 months).[24] At study onset, 85 % of patients had CVD, 69 % had hypertension and 38 % had diabetes. Comparison of the three treatment groups (telmisartan alone, telmisartan with ramipril and ramipril alone) showed that the rate of primary events was similar for patients receiving telmisartan (16.7 %) or ramipril (16.5 %), with no additional benefit from combined therapy (16.3 %) (see *Figure 3*).

Table 2: Clinical Evidence of Angiotensin Receptor Blockers Use in Patient Populations with Cardiovascular Risk Factors or Cardiovascular Disease

	Losartan	Eprosartan	Irbesartan	Olmesartan	Valsartan	Candesartan	Telmisartan
Hypertension	x	x	x	x	x	x	x
Treatment of renal disease	x		x				
Prevention of stroke in LVH	x						
High cardiovascular risk							x
Type 2 diabetes with target organ damage							x
Atherothrombotic CVD, e.g., coronary heart disease							x
Peripheral vascular disease							x
Stroke							x
HF (or left ventricular dysfunction)	x				x*	x	

** = including recent myocardial infarction; CVD = cardiovascular disease; HF = heart failure; LVH = left ventricular hypertrophy. Source: Ruilope, 2011.[92]*

Figure 3: Kaplan–Meier Curves for the Primary Outcome in Patients Receiving Telmisartan, Ramipril, or Telmisartan plus Ramipril



Numbers at Risk						
Telmisartan	8,542	8,177	7,778	7,420	7,051	1,687
Ramipril	8,576	8,214	7,832	7,420	7,093	1,703
Telmisartan plus ramipril	8,502	8,133	7,738	7,375	7,022	1,718

The primary outcome was a composite of death from cardiovascular causes, myocardial infarction or stroke, or hospitalisation for heart failure. Reproduced from Yusuf, et al., 2008.[24]

Moreover, the telmisartan group had significantly lower rates of cough (1.1 % [p<0.001]) and angiooedema (0.1 % [p=0.01]) than the ramipril group (4.2 % and 0.3 %, respectively) and than the combination group (4.6 % and 0.2 %, respectively). It was associated with significantly fewer discontinuations of therapy than in the ramipril and combination groups (23 % versus 24.5 % [p=0.02] and 29.3 %, respectively).[24] Despite offering similar cardiovascular prevention to ramipril, telmisartan therefore has a better overall efficacy:tolerability ratio.[84]

In the companion TRANSCEND trial, a total of 5,926 patients were randomised to telmisartan or placebo and the primary outcome was a composite of cardiovascular death, MI, stroke or hospitalisation for heart failure.[83] The rate of primary events favoured telmisartan (15.7 %) over placebo (17.0 %), but not significantly so.[25] However, telmisartan did significantly reduce the rate of the secondary outcome, a composite of cardiovascular death, MI and stroke (which was the primary endpoint in the HOPE study) compared with placebo (13.0 % versus 14.8 %, respectively [p=0.048]). The rate of permanent discontinuations again was in favour of telmisartan (21.6 %) over placebo (23.7 %), but not significantly so. Telmisartan therefore offers cardiovascular prevention compared with placebo, particularly from cardiovascular death, MI or stroke.

Safety and Tolerability of, and Adherence to, Telmisartan

In a retrospective analysis of 50 double-blind studies with a total of 8,023 hypertensive patients, telmisartan monotherapy was associated with a lower incidence of adverse events (AEs) (2.03 per patient-year) compared with placebo (2.73 per patient-year).[85] When double-blind and open-label studies were evaluated (total 16,416 patients), discontinuation of treatment due to AEs was similar between the telmisartan monotherapy (4.5 %) and placebo (4.6 %) groups.[85] Moreover, in a post-marketing survey of 19,870 patients with a substantial proportion at higher risk of AEs receiving telmisartan, only 1.9 % of patients reported an AE and global tolerability was rated as good or very good by 96.8 % of patients.[86] In terms of adherence to treatment, in a cohort of hypertensive patients, the highest levels of treatment persistence were observed in those patients receiving ARBs (18.8 %), including telmisartan as monotherapy. Treatment adherence to ACE inhibitors was 11.4 %. Telmisartan was well tolerated and showed favourable safety.[87]

Discussion

In selecting a treatment to prevent CVD, consideration should be given to agents whose actions extend beyond BP lowering. In addition to treating hypertension, telmisartan is indicated for cardiovascular prevention. However, target BP levels have yet to be clearly defined and aggressive antihypertensive treatment may be associated with increased adverse outcomes; for instance, the incidences of all the individual components of the primary composite endpoint from the ONTARGET study, except stroke, were associated with a J-shaped curve in relation to BP.[88] Nonetheless, the ONTARGET study results show that treatment with telmisartan confers significant benefits to a wide range of high-risk CVD patients, including those with manifest atherothrombotic disease and diabetes with end-organ damage, who represent the majority of patients seen in primary and secondary care practices worldwide. Moreover, the findings from the TRANSCEND study demonstrate that telmisartan is a suitable therapeutic alternative to ramipril in those individuals who are intolerant to ACE inhibitors. However, the cardiac and renal preventive effects of telmisartan may not be solely explained by its antihypertensive action, but by additional benefits arising from its effects on markers of inflammation, metabolic factors and endothelial dysfunction.

The prolonged action of telmisartan relative to other ARBs, its favourable safety, tolerability and good patient adherence make it an attractive option for the long-term treatment of hypertension and reduction of cardiovascular morbidity compared with agents showing

equivalent cardiovascular preventive effects. Telmisartan is the only ARB shown to offer cardiovascular morbidity prevention in patients with complicated diabetes or evidence of coronary artery disease without heart failure. Based on the outcomes of the ONTARGET and TRANSCEND trials, telmisartan can be considered as an effective treatment strategy for CVD prevention in patients at high vascular risk.

Prescribers have to consider not only efficacy but also tolerability, and therefore think in terms of the efficacy:tolerability ratio. In large-scale trials, ARBs, and mainly telmisartan, have been shown to be as efficient as ACE inhibitors and their gold standard, ramipril. Elsewhere, these same trials have shown advantages of telmisartan over ramipril in terms of tolerability and drug discontinuation. Therefore consideration of the efficacy:tolerability ratio favours ARBs, including telmisartan.

It has been suggested that results observed with telmisartan may be considered as a "class effect" and therefore could be extrapolated to the other ARBs. Such extrapolation is contradictory to the available data. Telmisartan has unique pharmacological properties, which differ from those of other ARBs and are likely to have clinical implications. Furthermore, results from large clinical trials using different ARBs may support the available data, and have led to different indications (see *Table 2*). Finally, results from the ONTARGET study suggested no additional benefit from the combination of telmisartan and ramipril, in comparison to ramipril monotherapy. It should be noted that extrapolation of these negative results to other combinations and to other populations would be arbitrary and hazardous. Further studies using other combinations of two inhibitors of the RAAS, such as a direct renin inhibitor with an ARB or anti-aldosterone in different populations are needed.

Future Developments

The worldwide burden of CVD will further increase, principally due to the inadequate implementation of prevention approaches, the rising obesity epidemic, the ageing population and the existence of cardiovascular risk factors. The ONTARGET study showed that telmisartan offers similar cardiovascular prevention to ramipril in high-risk patients, while being better tolerated and associated with greater treatment adherence, which is likely to be significant in the future long-term management of cardiovascular risk. Further analysis of the ONTARGET study findings may establish the role of therapy in the long-term decrease of overall cardiovascular burden, in particular absolute risk reduction, and may also help in the development of risk estimation scores populated with real-life data. Further studies of ACE inhibitors and ARBs in the development of new-onset diabetes and in patients with metabolic syndrome are still necessary. With respect to telmisartan, trials are currently in progress or recruiting to assess its efficacy in AF and stroke.[89,90] Outcomes from these studies will allow improved distinction between ARBs in terms of their efficacy in decreasing cardiovascular risk in hypertensive patients and in those without hypertension. In the future, clinicians will most likely be learning much more about the many functions of ARBs beside their antagonism of the angiotensin II receptor. ■

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