

## Review Article

# Preclinical and Clinical Effects of RAS Inhibition with a Focus on Telmisartan

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Blockade of the renin-angiotensin system with angiotensin II receptor blockers (ARBs) provides blood pressure (BP)-independent effects throughout the cardiovascular (CV) continuum. In the landmark ongoing telmisartan alone and in combination with ramipril global endpoint trial (ONTARGET), telmisartan reduced CV events in patients at high CV risk, similar to the angiotensin-converting enzyme inhibitor, ramipril. This reduction in CV events is a consequence of non-BP effects on disease pathophysiology which have been demonstrated in preclinical and clinical studies. For example, telmisartan significantly reduces markers of inflammation, such as interleukin-6 and C-reactive protein, and improves markers of vascular function, such as pulse wave velocity. Both these are associated with target organ damage. Telmisartan also has numerous potentially beneficial metabolic effects in preclinical studies. Telmisartan reduces markers of renal disease and its progression, left ventricular hypertrophy, and the risk of primary or secondary atrial fibrillation. Many of these effects are shared with other RAS inhibitors. However, several studies indicate differential effects between telmisartan and other ARBs. These differences probably reflect telmisartan's distinct pharmacologic profile, including the longest plasma half-life, high receptor-binding affinity, and highest lipophilicity of the class. These differences suggest that the results of ONTARGET do not necessarily extrapolate to other ARBs.

## 1. Introduction

The renin-angiotensin system (RAS), and most importantly angiotensin II, is central to the pathogenesis of a variety of clinical conditions along the cardiovascular (CV) continuum, from risk factors such as hypertension and diabetes, to atherosclerosis and left ventricular hypertrophy (LVH), and ultimately to myocardial infarction (MI), stroke, and heart failure (Figure 1) [1–3]. Blockade of the RAS can be achieved at different levels of the system with renin inhibitors, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin II receptor blockers (ARBs). ARBs differ from other RAS blockers in that they block the action of angiotensin II at the angiotensin AT<sub>1</sub> receptor but allow continued activation of other receptors—most notably, the angiotensin AT<sub>2</sub> receptor. There is little evidence as yet for event-reducing CV effects of renin inhibitors, beyond blood pressure (BP) reduction, but some ACE inhibitors and ARBs are now proven to reduce the risk of CV disease in a variety of at-risk patient types, including hypertensive patients,

patients with atherosclerosis, LVH, coronary heart disease, heart failure, or diabetic patients with target organ damage, for example, diabetic nephropathy [4–9].

In the ongoing telmisartan alone and in combination with Ramipril global endpoint trial (ONTARGET), telmisartan was the first ARB demonstrated to prevent CV events in patients at high CV risk, similar to the risk reduction with ramipril; importantly, telmisartan was better tolerated than ramipril [6, 10]. Telmisartan is the only ARB indicated for the reduction of CV morbidity in patients with manifest atherothrombotic CV disease (history of coronary heart disease, stroke, or peripheral arterial disease) or type 2 diabetes mellitus with documented target organ damage [11]. Agents within the ARB drug class exhibit different pharmacologic profiles [12, 13]. Telmisartan has a relatively long dissociation half-life from the AT<sub>1</sub> receptor and a long plasma half-life (24 h) compared with other ARBs, thus providing sustained BP control over the whole dosing interval [14]. Telmisartan has a high binding affinity for the AT<sub>1</sub> receptor compared with other ARBs, and is highly lipophilic with the

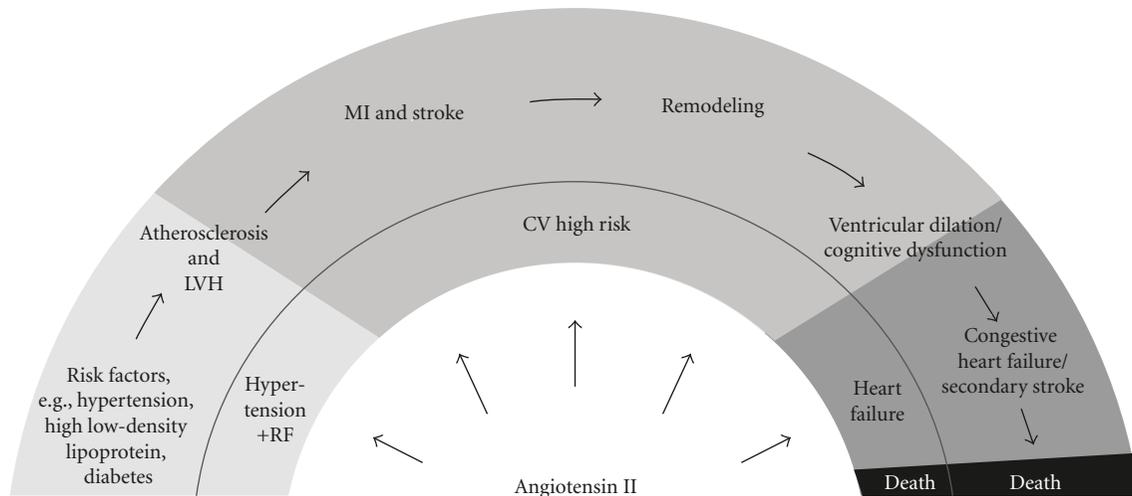


FIGURE 1: The cardiovascular continuum.

greatest volume of distribution [14]. These pharmacologic properties of telmisartan versus other ARBs may translate into differences in clinical outcomes. Although there have been limited comparative clinical studies of CV outcomes with ARBs, there have been a number of studies examining pathophysiologic and intermediate end points. These could shed light on the effects of telmisartan seen in ONTARGET, and in particular whether these effects can be translated into other ARBs.

This review aims to assess the effects of ARBs on CV disease pathophysiologies along the CV continuum. The particular focus will be on telmisartan, to investigate the evidence for a direct effect of this agent on CV disease processes that may have contributed to the effects on CV outcomes seen in ONTARGET. The bulk of research on telmisartan has investigated aspects of CV disease related to inflammation, vascular function, metabolic status, and target organ damage, such as renal disease and CV and cerebrovascular changes. Within each section, this review will briefly consider the evidence for ARBs in general, before examining the preclinical and clinical evidence on telmisartan, including comparative studies versus other ARBs where they exist. Suitable papers were identified by searching MEDLINE for studies on ARBs that included keywords related to the topics under consideration.

## 2. Inflammation

Inflammation is involved in the pathogenesis and continuation of atherosclerosis and contributes to the development of hypertension and its complications [15]. Angiotensin II acts as a proinflammatory cytokine, inducing inflammation through the upregulation of reactive oxygen species, adhesion molecules, and inflammatory cytokines [16]. Therefore, RAS inhibition has the potential to reduce inflammation in patients at risk of CV disease, and this is supported by several *in vitro* studies. For example, losartan (as well as captopril or amlodipine, but not atenolol or hydrochlorothiazide (HCTZ)) produced marked anti-inflammatory effects

at clinically relevant serum concentrations, as shown by interleukin-1 beta (IL-1 $\beta$ ) secretion by polymorphonuclear leukocytes from patients with essential hypertension [17].

Studies in humans have confirmed these effects. In two studies of hypertensive patients with or without diabetes, valsartan or candesartan for 6 months decreased serum high-sensitivity C-reactive protein (hs-CRP) and IL-6 [18, 19]. In another study of high-risk hypertensive diabetic patients with high baseline IL-6 (>2.0 ng/L;  $n = 54$ ), valsartan 320 mg for 16 weeks significantly reduced IL-6 (a decrease from 3.5 to 2.4 with valsartan 320 mg versus an increase from 3.2 to 3.5 with placebo,  $P = 0.035$ ) [20]. In a small study of hypertensive patients with coronary artery disease, for 3 months both irbesartan and enalapril significantly reduced serum metalloproteinase 9 protein ( $P < 0.001$  and  $P < 0.05$ , resp.), but only irbesartan reduced hs-CRP and IL-6 (both  $P < 0.01$  versus baseline) [21]. Another study has shown that olmesartan on a background of HCTZ significantly reduced vascular microinflammation, as shown by serum hs-CRP ( $-15.1\%$ ;  $P < 0.05$ ), hs-tumor necrosis factor (TNF) $\alpha$  ( $-8.9\%$ ;  $P < 0.02$ ), IL-6 ( $-14.0\%$ ;  $P < 0.05$ ), and monocyte chemoattractant protein-1 (MCP-1) ( $-6.5\%$ ;  $P < 0.01$ ) versus placebo [22].

Telmisartan has also been shown in animal models to reduce the levels of several markers of inflammation, such as interleukins and TNF $\alpha$ . In a rat model, telmisartan protected against experimental autoimmune myocarditis, partly by suppressing inflammatory cytokines and oxidative stress [23]. In this model, compared with vehicle-treated rats, telmisartan decreased myocardial expression of inflammatory cytokines (such as IL-6 and TNF $\alpha$ ), nicotinamide adenine dinucleotide phosphate (NADPH) oxidase subunits, and decreased endoplasmic reticulum stress markers. In an obese mouse model, telmisartan or captopril reduced chemically induced colon carcinogenesis by attenuating chronic inflammation and reducing oxidative stress in obese mice [24]. This was shown by decreased expression of TNF $\alpha$  messenger ribonucleic acid (mRNA) in the colonic mucosa and significantly reduced levels of a marker of oxidative

damage to deoxyribonucleic acid compared with a control group.

There is some evidence that telmisartan provides greater anti-inflammatory effects than other RAS blockers. In a mouse model, telmisartan reduced atherosclerotic lesion progression and reduced the expression of inflammatory factors to a greater extent than ramipril [25]. In vitro, telmisartan (unlike losartan or its active metabolites EXP-3174 and EXP-3179) reduced endothelial inflammation and oxidative cell damage in human umbilical vein endothelial cells [26].

Consistent with these preclinical studies, telmisartan has shown differential effects in human subjects compared with other ARBs. In hypertensive patients with significant coronary artery stenosis, 8-month treatment with telmisartan (but not valsartan) significantly decreased IL-6 and TNF $\alpha$  as well as late lumen loss ( $0.1 \pm 0.4$  versus  $0.3 \pm 0.5$  mm;  $P = 0.001$ ) [27]. In metabolic syndrome patients, switching from valsartan to telmisartan for 12 weeks significantly reduced hs-CRP ( $0.77$  versus  $0.60$  mg/L;  $P = 0.022$ ) as well as microalbuminuria ( $28.1$  versus  $18.9$  mg/g·Cr;  $P = 0.001$ ) [28]. In a small study, telmisartan had a more potent antioxidative effect than losartan through its ability to enhance superoxide dismutase activity in type 2 diabetic patients with microalbuminuria. Of note is that oxidative stress induced by excessive superoxide plays a central role in the pathogenesis of diabetic nephropathy.

### 3. Arterial Stiffness and Vascular Changes

Inflammation in the blood vessels triggers a series of pathologic changes, such as endothelial dysfunction, calcification, vascular growth, and remodeling [29]. These changes, many of which are moderated by angiotensin II, can lead to arterial wall stiffness, which is an independent predictor of CV events in patients with hypertension [30].

The major evidence for the effects of telmisartan on vascular stiffness comes from studies of pulse wave velocity (PWV), also an independent marker of target organ damage [31]. In the Framingham Heart study, each standard deviation increase in carotid-femoral PWV was associated with a 48% increase in the adjusted risk of a first major CV event (hazard ratio (HR), 1.48; 95% confidence interval (CI), 1.16–1.91;  $P = 0.002$ ) [30]. Clinical studies show that telmisartan reduces PWV in hypertension [32–35], hypertension plus type 2 diabetes [36, 37], and in hypertension plus chronic kidney disease [38]. Another measure of arterial stiffness is the cardioankle vascular index. In hypertensive patients, 12-month treatment with telmisartan had beneficial effects on the cardioankle vascular index, as well as on albuminuria, 24-hour BP, and metabolism compared with calcium channel blockers (CCBs) [39].

Angiotensin II is also involved in the formation of aneurysms [40], and telmisartan has been found to prevent their formation in two animal models. In mice deficient in regulator of G-protein signaling 2 (RGS2; a negative regulator of AT $_1$  receptors), telmisartan reduced the incidence of aneurysms [41]. In rat aortic tissue, telmisartan prevented abdominal aortic aneurysm progression independently of

reducing BP, by inhibition of proteolysis, apoptosis, and inflammation [42].

Comparative studies on the vascular effects of ARBs have mainly been conducted in animal models. For example, in a model of stroke-prone hypertensive rats, telmisartan reduced vascular remodeling to a greater degree than losartan, an effect attributed to reduced NADPH oxidase activity [43]. In an in vitro study, telmisartan (but not candesartan, irbesartan, or eprosartan) significantly inhibited the proliferation of vascular smooth muscle cells and cardiac fibroblasts in culture when tested at clinically relevant concentrations [44]. At least one comparative human study has been conducted. In Japanese hypertensive patients, telmisartan provided greater vascular protection than losartan over 1 year, as shown by progression of intima-media thickness of common carotid artery, despite similar BP reductions [45].

### 4. Insulin Resistance and New-Onset Diabetes

Inflammation and vasoconstriction, and the resulting fibrosis, apoptosis, and pancreatic  $\beta$ -cell death are thought to be the mechanisms that link angiotensin II to metabolic disturbances, such as the development of insulin resistance and new-onset diabetes [46]. RAS blockade improves blood flow and microcirculation in skeletal muscles, which enhances insulin and glucose delivery to the insulin-sensitive tissues, facilitating insulin signaling at the cellular level, and improving insulin secretion by the  $\beta$  cells [47]. RAS blockade would also be expected to reverse the deleterious effects of angiotensin II in the pancreas such as fibrosis, inflammation, apoptosis, and  $\beta$ -cell death [46].

Numerous clinical trials and meta-analyses have found that while diuretics and  $\beta$ -blockers may worsen insulin resistance and impair glucose tolerance, RAS blockers have the potential for positive metabolic effects [47]. A systematic review of 22 clinical trials involving 143,153 individuals without diabetes showed that the risk of new-onset diabetes was lowest for ARB treatment (8.4%; odds ratio (OR), 0.57; 95% CI, 0.46–0.72;  $P < 0.0001$ ), followed by ACE inhibitors (7.1%; OR, 0.67; 95% CI, 0.56–0.80;  $P < 0.0001$ ), CCBs (7.2%; OR, 0.75; 95% CI, 0.62–0.90;  $P = 0.002$ ), placebo (6.8%; OR, 0.77; 95% CI, 0.63–0.94;  $P = 0.009$ ), and  $\beta$  blockers (7.6%; OR, 0.90; 95% CI, 0.75–1.09;  $P = 0.30$ ) [48].

This reflects the fact that major ARB trials generally reduce new-onset diabetes. The relative risk reduction for new-onset diabetes (as a secondary end point) was 25% with losartan versus atenolol in hypertensive patients with LVH in the losartan intervention for endpoint reduction in hypertension (LIFE) study ( $P = 0.001$ ) [4], 23% with valsartan versus amlodipine in high-risk hypertensive patients in the valsartan antihypertensive long-term use evaluation (VALUE) study ( $P < 0.0001$ ) [49], and 25% with candesartan versus placebo in hypertensive patients in the study on cognition and prognosis in the elderly (SCOPE) trial ( $P = 0.09$ ) [47]. In the nateglinide and valsartan in impaired glucose tolerance outcomes research (NAVIGATOR) trial, valsartan significantly reduced the development of diabetes compared with placebo in patients with impaired glucose tolerance and one or more CV risk factors (if  $\geq 55$  years old) or established

CV disease (if  $\geq 50$  years old) (33.1% versus 36.8%; HR, 0.86; 95% CI, 0.80–0.92;  $P < 0.001$ ) [50].

ONTARGET found telmisartan to have a similar effect on new-onset diabetes to ramipril (telmisartan 7.5%, ramipril 6.7%, and dual RAS blockade 6.1%) [6]. However, in the telmisartan randomised assessment study in ACE intolerant subjects with cardiovascular Disease (TRANSCEND), which was a parallel study to ONTARGET in 5926 ACE inhibitor-intolerant patients [51], telmisartan did not reduce the incidence of new-onset diabetes versus placebo (21.8% versus 22.4%; relative risk, 0.95; 95% CI, 0.83–1.10;  $P = 0.51$ ) [52]. On the other hand, a combined analysis of TRANSCEND and the prevention regimen for effectively avoiding second strokes (PROFESS) trial did find a significantly reduction in the incidence of new-onset diabetes by 16% compared with placebo [53].

In addition to the standard effects of ARBs on angiotensin II-mediated processes, telmisartan acts as a selective peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) modulator [54, 55]. Although several ARBs exhibit this property, there is a clear order of potency, with telmisartan being the most potent, followed by irbesartan, then losartan [54–56]. Importantly, telmisartan is the only ARB that may modulate PPAR $\gamma$  activation at physiologic plasma concentrations, an effect that is likely to be related to telmisartan high lipophilicity. Several studies have found that telmisartan can influence PPAR $\gamma$  gene expression. In treatment-naïve hypertensive patients, 3-month telmisartan (but not amlodipine) treatment significantly increased PPAR $\gamma$  mRNA levels ( $P = 0.006$ ) in peripheral monocytes [57], and, in treatment-naïve patients with the metabolic syndrome, high-dose (160 mg once daily) telmisartan for 14 weeks induced monocytic PPAR $\gamma$  genes [58]. An in vitro study found that telmisartan, but not candesartan or losartan, upregulated PPAR $\gamma$  expression [59]. However, other ARBs may also have some clinically meaningful PPAR $\gamma$  activity in one study in humans, treatment with losartan for 2 months increased PPAR $\gamma$  genes versus no treatment in monocytes, probably through the action of the transient losartan aldehyde metabolite, EXP3179 [60].

Numerous in vitro and animal studies have compared the effects of telmisartan with other RAS blockers on metabolic outcomes. Telmisartan or perindopril similarly protected pancreatic islet function in rats fed a high-fat diet; mechanisms included downregulation of islet inflammation, oxidative stress, endoplasmic reticulum stress, and apoptosis [61]. In rats, telmisartan or irbesartan (not eprosartan) induced adiponectin in adipocytes, and this was associated with improved insulin sensitivity [62]. In an in vitro study, telmisartan, but not candesartan, increased glucose transporter 4 levels at the plasma membrane [63]. In one study, both telmisartan and the PPAR $\gamma$  agonist, rosiglitazone, reduced adipose tissue inflammation (measured by markers such as MCP-1) and improved insulin resistance and glucose intolerance in a diet-induced obesity mouse model [64]. Similarly, both telmisartan or rosiglitazone, but not valsartan, ameliorated hyperglycemia and the metabolic profile in diabetic hypertensive rats via PPAR $\gamma$  modulation [65].

Comparative studies in humans are also common but are generally characterized by small patient numbers [66]. Broadly speaking, however, these studies show that telmisartan provides greater efficacy than other ARBs [66]. In a randomized, open-label, 24-week study, telmisartan/rosuvastatin provided favorable effects compared with irbesartan/rosuvastatin or olmesartan/rosuvastatin on glucose metabolism in patients with hypertension, impaired fasting glucose, and dyslipidemia [67]. Telmisartan, but not olmesartan, improved adiponectin levels in hypertensive patients with glucose intolerance [68]. In patients with the metabolic syndrome, telmisartan improved glucose sensitivity versus losartan [69], valsartan [70], and irbesartan [71]. Telmisartan also improved glucose sensitivity versus irbesartan in nondiabetic, obese, and insulin-resistant hypertensive patients [71, 72]. Another study found a benefit with telmisartan but not olmesartan in overweight/obese hypertensive patients [73]. Several studies have found that replacement of valsartan or candesartan with telmisartan improved fasting plasma insulin or glucose [74–76].

Overall, these studies confirm the beneficial metabolic profile of ARBs and point towards potential differences in the metabolic effects of telmisartan compared with other ARBs. Such differences may be linked to the PPAR $\gamma$ -modulating effects of telmisartan, or could be a consequence of other pharmacologic differences. However, in the absence of clear evidence of differences in larger trials, the clinical implications of these difference remain uncertain.

## 5. Albuminuria and Renal Disease

As with other effects on target organ damage, the predominant beyond-BP effect of ARBs on the kidney is related to the reduction of inflammation and oxidative stress [77, 78] although stimulation of the angiotensin II type 2 receptor may also be important to the effects of ARBs on the kidney [79].

There is substantial evidence for the efficacy of ARBs in reducing microalbuminuria or slowing the progression to proteinuria and overt nephropathy. Notably, ARBs have been shown to be superior to CCBs in the irbesartan diabetic nephropathy trial (IDNT) [9], the microalbuminuria reduction with valsartan (MARVAL) study [80], and the recent Japanese valsartan amlodipine randomized trial (VART) study, in which valsartan significantly improved the secondary end point of urinary albumin to creatinine ratio (UACR) versus amlodipine (–61.3% versus +34.9%;  $P < 0.0001$ ) [81]. The randomized olmesartan and diabetes microalbuminuria prevention (ROADMAP) study sought to assess whether olmesartan could delay or prevent the occurrence of microalbuminuria in patients with type 2 diabetes and normoalbuminuria [82]. After a median 3.2 years, there was a nonsignificant increase (17%) in the time to onset of microalbuminuria with olmesartan after adjustment for differences in BP reduction. However, this was accompanied by increased CV mortality versus placebo (0.7% versus 0.1%;  $P = 0.01$ ).

Preclinical models have found that telmisartan also has direct protective effects on the kidney. In a rat model

of glomerulonephritis, high-dose telmisartan ameliorated glomerular and tubulointerstitial damage [83]. Possible pathways included growth factor signaling, the mammalian target of rapamycin signaling, protein ubiquitination, the Wnt/ $\beta$  catenin pathway, and hypoxia signaling. Telmisartan also reduced the urinary albumin excretion rate (UAER) and proteinuria to a greater degree than amlodipine in a rat model of aldosterone-induced glomerular injury [84]. In spontaneously hypertensive rats fed with a high-fat diet, telmisartan was more effective than valsartan in reducing body weight, renal inflammation (MCP-1), and renal injury (UAER and glomerular damage) [85].

In humans, telmisartan improved renal endothelial function similar to ramipril in a randomized, double-blind study of 96 patients with hypertension and type 2 diabetes treated for 9 weeks [86]. This was accompanied by significant increases in nitric oxide activity of the renal endothelium (indicating reduced oxidative stress) with telmisartan ( $P < 0.001$ ) and ramipril ( $P = 0.018$ ). Telmisartan significantly reduced the transition from incipient to overt nephropathy compared with placebo in the incipient to overt: Angiotensin II blocker, telmisartan, investigation on type 2 diabetic nephropathy (INNOVATION) study. This trial enrolled 527 hypertensive Japanese patients with type 2 diabetes who were treated with telmisartan or placebo for 52 weeks [87]. For the primary end point, the rates of transition from incipient to overt nephropathy were significantly lower for telmisartan 80 mg (16.7%) and telmisartan 40 mg (22.6%) compared with placebo (49.9%) (both  $P < 0.0001$ ). BP reductions were similar across groups. Telmisartan and enalapril were found to be similarly effective in slowing the loss of glomerular filtration rate (GFR) in the diabetics exposed to telmisartan and enalapril (DETAIL) study, in which 250 patients with early nephropathy (normal GFR but UAER between 11 and 999  $\mu\text{g}$  per minute) were randomized to telmisartan 80 mg or enalapril 20 mg daily for 5 years [88]. The mean change in the GFR with telmisartan compared with enalapril was  $-17.9$  versus  $-14.9$  mL/minute/1.73  $\text{m}^2$  (difference  $-3.0$ ; 95% CI,  $-7.6$ – $1.6$ ). A subgroup analysis of ONTARGET showed that the rate of the primary renal outcome (a composite of dialysis, doubling of serum creatinine, and death) was similar for telmisartan and ramipril (13.4% versus 13.5%; HR, 1.00; 95% CI, 0.92–1.09) [89]. In the TRANSCEND study, progression of albuminuria was significantly lower with telmisartan than with placebo (32% versus 63%;  $P < 0.001$ ) [89].

Telmisartan has been found to exert a greater antiproteinuric effect than losartan. In A telmisartan 80 mg versus losartan 100 mg in hypertensive type-2 diabetic patients with overt nephropathy (AMADEO) study, 860 patients with diabetic nephropathy were treated with telmisartan or losartan for 1 year. Despite matched BP reductions, telmisartan provided a significantly greater reduction in UACR compared with losartan (29.8% versus 21.4%;  $P = 0.03$ ) [90]. In a related study, the trial to investigate the efficacy of telmisartan versus valsartan in hypertensive type 2 diabetic patients with overt nephropathy (VIVALDI) found similar reductions in 24-hour UAER with telmisartan 80 mg versus valsartan 160 mg in 885 patients with hypertension

and diabetic nephropathy (33% reduction in both groups, although patients in the valsartan group required additional antihypertensive comedication) [91]. However, the inflammatory parameter, urinary excretion of 8-iso-prostaglandin  $\text{F}_{2\alpha}$  (8-iso-PGF $_{2\alpha}$ ), decreased significantly more with telmisartan versus valsartan (14% versus 7%,  $P = 0.040$ ).

## 6. LVH and Cardiac Remodeling

LVH is a common form of target organ damage associated with hypertension that increases the risk for CV morbidity and mortality [92], and, as with other forms of target organ damage, angiotensin II plays a central role in promoting LVH [93]. ARBs as a class are among the most effective antihypertensives in reducing LVH [94], an effect that is probably due to their interruption of the fibrotic and trophic effects of angiotensin II [95].

In rat/mouse models of LVH, telmisartan has shown beneficial effects on reducing endoplasmic reticulum stress, apoptosis, and indexes of cardiac hypertrophy [96, 97]. In one study, the development of LVH in rats was accompanied by changes in the expression of 17 proteins, primarily involved in cell structure, metabolism, stress, and signal transduction. Importantly, these changes were prevented or attenuated by telmisartan treatment [98]. Telmisartan has also been found to improve left ventricular function significantly and ameliorate the progression of cardiac remodeling in rats with chronic heart failure [99]. Activation of PPAR $\gamma$ -dependent pathways are thought to be involved in development of cardiac hypertrophy, and several studies have investigated whether PPAR $\gamma$  modulation with telmisartan contributes to its effects on LVH. In a rat model of MI, telmisartan prevented cardiac remodeling by reducing cardiac hypertrophy and fibrosis; this study suggested that the mechanisms involved an anti-inflammatory effect and PPAR $\gamma$  activation in addition to suppression of angiotensin II activity [100]. In diabetic rats, telmisartan improved ischemia/reperfusion injury, whereas a PPAR $\gamma$  antagonist worsened ischemia/reperfusion injury, suggestive of a role for PPAR $\gamma$  activation [101]. In a hypertensive rat model, both telmisartan and olmesartan had beneficial effects on cardiac structure and function [102]. As olmesartan has little PPAR $\gamma$  activity, this indicates that the mechanism may be pressor related or AT $_1$  receptor dependent, and other recent research suggests that pioglitazone may not attenuate the development of LVH [103].

Telmisartan is more effective than HCTZ and carvedilol in regressing LVH, which supports other evidence that RAS blockers have particular efficacy on this outcome [104, 105]. Similarly in TRANSCEND, telmisartan significantly reduced the risk of developing LVH compared with placebo (most patients received non-ARB/ACE inhibitor antihypertensive therapy) by 21% overall (OR, 0.79; 95% CI, 0.68–0.91;  $P = 0.0017$ ) and by 37% for new-onset LVH (OR, 0.63; 95% CI, 0.51–0.79;  $P = 0.0001$ ) [106]. Overall, the effects of telmisartan on LVH appear to be similar to those of other RAS blockers. In patients with acute MI, telmisartan was equivalent to enalapril in suppressing vascular inflammation and reducing LVH [107]. In a subgroup analysis of 287

patients who underwent magnetic resonance imaging in ONTARGET, telmisartan was equivalent to ramipril in improving left ventricular mass (LVM) and volume at 2 years [108]. In hypertensive patients, reductions in LVM were similar with telmisartan (11.4%) and ramipril (9.9%), despite similar BP reductions in the groups [109]. One small double-blind study of hypertensive patients (nine with LVH) showed that telmisartan or losartan for 6 months provided similar reductions in LVM index and BP [110].

## 7. Atrial Fibrillation

One functional consequence of the effects of RAS blockade on cardiac remodeling may be a reduction in the incidence of atrial fibrillation (AF). For example, in the LIFE study, 8851 hypertensive patients at risk of AF were followed up for 5 years. New-onset AF was significantly reduced by losartan compared with the  $\beta$ -blocker atenolol (6.8 versus 10.1 per 1000 person-years; relative risk 0.67; 95% CI, 0.55–0.83;  $P < 0.001$ ), despite similar BP reductions [111]. This hypothesis was supported by two meta-analyses: firstly, 23 randomized, controlled trials ( $n = 87,048$ ) found that ARBs and ACE inhibitors reduced the OR for primary or secondary AF by 33% ( $P < 0.00001$ ) [112]. In a second meta-analysis of 11 randomized controlled trials ( $n = 56,308$ ), the relative risk of primary or secondary AF was reduced by both ARBs (29%,  $P = 0.00002$ ) and ACE inhibitors (28%,  $P = 0.01$ ) [113].

However, more recent randomized, placebo-controlled studies of valsartan, olmesartan, and irbesartan have been disappointing [114–116]. Valsartan and placebo were associated with similar rates of recurrent AF over 1 year in patients with previous AF as well as CV disease, diabetes, or left atrial enlargement (51.4% versus 52.1%; adjusted HR, 0.97; 96% CI, 0.83–1.14;  $P = 0.73$ ) [114]. Olmesartan and placebo groups had similar rates of AF burden (percentage of days with paroxysmal AF) over 12 months in a study of patients with documented paroxysmal AF without structural heart disease [115]. In high-risk patients with AF, for 4 years irbesartan and placebo were associated with similar rates of composite CV outcome (risk of stroke, MI, or death from vascular causes) (5.4% versus 5.4% per 100 person-years; HR, 0.99; 95% CI, 0.91–1.08;  $P = 0.85$ ) or this composite outcome plus hospitalization for heart failure (7.3% versus 7.7% per 100 person-years; HR, 0.94; 95% CI, 0.87–1.02;  $P = 0.12$ ) [116].

In contrast to recent studies with other ARBs, clinical trials with telmisartan have shown reductions in the incidence of AF. In the high-CV-risk patients in ONTARGET, telmisartan was as effective as ramipril on the end point of new-onset AF (with an incidence of 6.7% versus 6.9%, resp.) [6]. In hypertensive patients with the metabolic syndrome and a history of AF, telmisartan was more effective than ramipril in reducing the recurrence of AF over 1 year (12.9% versus 25.5%;  $P < 0.05$ ) as well as the severity of AF, despite a similar BP reduction [117]. In patients with hypertension and a history of AF, telmisartan was associated with a significantly lower rate of new episodes of AF compared with

the  $\beta$  blocker, carvedilol (14.3% versus 37.1%;  $P < 0.003$ ), again despite a similar BP reduction [118].

## 8. Cerebrovascular Disease

Angiotensin II may contribute to the pathogenesis of stroke [119]. Recently, in stroke-prone spontaneously hypertensive rats, telmisartan, ramipril, and the combination had similar beneficial effects on stroke incidence. However, telmisartan and telmisartan/ramipril provided superior neuroprotection compared with ramipril alone in normotensive rats with induced cerebral ischemia, as shown by improved nitric oxide, reduced infarct volume, and inflammation (TNF $\alpha$ ), and induced neurotrophin receptor and neuronal survival [120]. In the PRoFESS trial in 20,332 patients, telmisartan initiated soon after an ischemic stroke did not significantly reduce the rate of recurrent stroke, major CV events, or new-onset diabetes compared with standard care over a 2.5-year period [121]. However, in a post-hoc exploratory analysis, the rate of recurrent stroke was lower with telmisartan compared with standard care after 6 months (5.3% versus 6.0%; HR, 0.88; 95% CI, 0.78–0.99) [121].

Antihypertensive medications may reduce the incidence of Alzheimer's disease. In a randomized study of elderly hypertensive patients with probable Alzheimer's disease, 6-month treatment with telmisartan reduced cognitive decline compared with amlodipine [122]. Cognitive function test scores were unchanged in the telmisartan group and significantly higher in the amlodipine group. In addition, telmisartan increased cerebral blood flow in the right supra-marginal gyrus, superior parietal lobule, cuneus, and lingual gyrus compared with amlodipine, while amlodipine increased cerebral blood flow only in the right cingulate gyrus compared with telmisartan.

## 9. Conclusions

The ONTARGET trial was a landmark for clinical practice, proving for the first time that an ARB, telmisartan, could prevent CV events in high-CV-risk patients to a degree similar to ramipril. Since CV disease occurs as a progressive continuum, such effects on CV outcomes imply an effect on the underlying disease pathology as well as intermediate end points, such as target organ damage. This review has sought to investigate the evidence for telmisartan's effects on these CV disease processes, with a view to assisting in interpretation of the ONTARGET trial results.

There is substantial evidence, reviewed here, that blockade of the angiotensin II receptor by telmisartan has a direct and beneficial effect of key aspects of CV disease. In common with other blockers of the RAS, telmisartan has been shown to reduce inflammation and oxidative stress, which is the most important process linking the direct effect of angiotensin II to CV disease progression. This likely explains the effects observed on vascular wall stiffness and downstream effects on target organ damage, such as reduced albuminuria and renal dysfunction, reduced LVH, and reduced risk of AF. Telmisartan also improves metabolic parameters, an effect that may be due to RAS blockade but

which may also be related to telmisartan's ability to modulate PPAR $\gamma$ .

The extent to which pharmacologic differences between ARBs translate into clinically meaningful effects is difficult to confirm, but, on the evidence reviewed here, telmisartan may have superior effects over certain other ARBs—with the strongest evidence being the superiority of telmisartan over losartan on the reduction in proteinuria in the AMADEO study. Since proteinuria is a strong indicator of CV risk, it seems reasonable to expect that differential effects between these two drugs on CV outcomes are likely.

In summary, the prevention of CV events with telmisartan observed in ONTARGET is likely to be a consequence of the direct effects of telmisartan on CV disease pathology, notably effects on inflammation and target organ damage. Differences exist between ARBs on these intermediate end points, which reflect differences in their pharmacology. Whether other ARBs have effects similar to telmisartan on CV outcomes remains to be tested.

## Conflict of Interests

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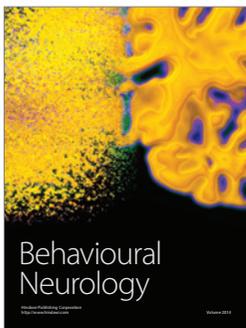
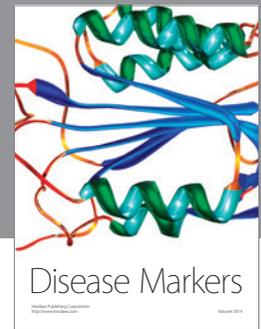
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