

# Telmisartan and cardioprotection

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**Abstract:** Cardiovascular risk reduction has been the target of several large clinical trials in the last decade. As the activation of the renin-angiotensin-aldosterone system (RAAS) plays a central role in the pathogenesis of atherosclerosis and cardiovascular disease, RAAS blockade has been suggested to be among the most efficient cardioprotective interventions, as revealed with the angiotensin converting enzyme (ACE) inhibitors trials. The angiotensin receptor blockers' (ARBs) efficacy in lowering blood pressure has been very well established. Telmisartan is however the first ARB to show a promising role in reducing cardiovascular risk in high-risk patients. This article will highlight the role of telmisartan in cardioprotection, underlying specifically the results of two major randomized controlled trials: ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and TRANSCEND (Telmisartan Randomized Assessment Study in aCE-iNtolerant subjects with cardiovascular Disease).

**Keywords:** telmisartan, cardioprotection, ONTARGET, TRANSCEND

## Introduction

Although death rates from cardiovascular disease have significantly declined over the last 10 years, the burden of the disease remains very high. In 2006, cardiovascular disease was responsible for 34.3% (831,272) of all deaths in the US. The estimated direct and indirect cost of cardiovascular disease for 2010 is US\$503.2 billion.<sup>1</sup> A great deal of effort has been directed toward treating cardiovascular and controlling its traditional risk factors.

The chronic activation of the renin-angiotensin-aldosterone system (RAAS) plays a central role in the pathogenesis of atherosclerosis, hypertension, left ventricular hypertrophy (LVH), myocardial infarction, and heart failure.<sup>2</sup> The inhibition of the RAAS can be achieved by inhibiting the angiotensin-converting enzyme (ACE) or by directly blocking the angiotensin receptors. The use of ACE inhibitors is known to reduce mortality and cardiovascular risk in high-risk patients.<sup>3</sup> On the other hand, the use of angiotensin receptor blockers (ARBs) is well established for the treatment of hypertension and in patients with heart failure or following myocardial infarction. Until recently, their role in cardioprotection remained unclear.

This review article highlights the results of the clinical trials examining the efficacy of the ARB telmisartan across the cardiovascular spectrum (Table 1). The cardioprotective role of telmisartan is further discussed in the review of the ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and TRANSCEND (Telmisartan Randomized Assessment Study in aCE-iNtolerant subjects with cardiovascular Disease) studies.

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Table 1 Summary of telmisartan clinical trials

Study	Number of patients	Patient population	Duration	Primary end points	Intervention	Main outcomes	Reference
PRISMA I, II	1613	Hypertension	14 weeks	Change from baseline in mean ambulatory systolic BP and diastolic BP during the final 6 hours of the 24-hour dosing cycle	Telmisartan 80 mg/day vs ramipril 5 or 10 mg/day	Telmisartan is more effective than ramipril throughout the 24-hour period and during the early morning	6
DETAIL	250	Type 2 diabetes + hypertension + early diabetic nephropathy	5.0 years	Change in glomerular filtration rate	Telmisartan 80 mg/day vs enalapril 20 mg/day	Telmisartan is not inferior to enalapril in providing long-term renoprotection in persons with type 2 diabetes (change in glomerular filtration rate for telmisartan $-17.9$ mL per minute per $1.73$ m <sup>2</sup> , $-14.9$ mL per minute per $1.73$ m <sup>2</sup> for enalapril; treatment difference $-3.0$ mL per minute per $1.73$ m <sup>2</sup> 95% CI: $-7.6$ to $1.6$ mL per minute per $1.73$ m <sup>2</sup> )	8
INNOVATION	527	Type 2 diabetes + microalbuminuria (Japanese)	1.3 years	Transition rate from incipient to overt nephropathy	Telmisartan 80 mg/day vs telmisartan 40 mg/day vs placebo	Telmisartan reduced transition from incipient to overt nephropathy (16.7% telmisartan 80 mg, 22.6% telmisartan 40 mg, 49.9% placebo; both telmisartan doses vs placebo, $P < 0.0001$ )	9
VIVALDI	885	Type 2 diabetes + hypertension + overt nephropathy	1 year	Change from baseline in the 24-hour proteinuria	Telmisartan 80 mg/day vs valsartan 160 mg/day	Similar reduction 33% with both telmisartan and valsartan	10
AMADEO	860	Type 2 diabetes + hypertension + overt nephropathy	1 year	Difference in the urinary albumin to creatinine ratio	Telmisartan 80 mg/day vs losartan 100 mg/day	Reduction significantly better with telmisartan 29.8% vs losartan 21.4% ( $P < 0.031$ )	11
ONTARGET	25,620	Coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage	4.7 years	Composite endpoint of cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure	Telmisartan 80 mg/day vs ramipril 10 mg/day vs combination	Telmisartan was equivalent to ramipril in patients with vascular disease or high risk diabetes (RR: 1.01; 95% CI: 0.94–1.09)	15
TRANSCEND	5926	Intolerance to ACE inhibitors + coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage	4.7 years	Composite endpoint of cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure	Telmisartan 80 mg/day vs placebo	Telmisartan did not reduce composite of four cardiovascular outcomes in high risk patients with intolerance to ACE inhibitors (HR: 0.92; 95% CI: 0.81–1.05; $P = 0.216$ )	16

PROFESS	20,332	Age > 50 years + recent ischemic stroke (120 days)	2.5 years	Recurrent stroke, new-onset diabetes, and composite endpoint of major cardiovascular events (stroke, myocardial infarction, worsening or new heart failure, or death from cardiovascular causes)	Telmisartan 80 mg/day vs placebo	In patients with ischemic stroke, telmisartan did not prevent recurrent stroke (HR: 0.95; 95% CI: 0.86–1.04; $P = 0.23$ ), major cardiovascular events (HR: 0.94; 95% CI: 0.87–1.01; $P = 0.11$ ), or new-onset diabetes (HR: 0.82; 95% CI: 0.65–1.04; $P = 0.10$ )	17
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**Abbreviations:** ACE, Angiotensin-converting enzyme; AMADEO, A comparison of telmisartan versus losartan in hypertensive type 2 Diabetic patients with Overt nephropathy; DETAIL, Diabetics Exposed to Telmisartan and Enalapril; INNOVATION, Incipient to Overt: Angiotensin II Blocker; Telmisartan, Investigation on Type 2 Diabetic Nephropathy; ONTARGET, Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial; PRISMA, Prospective Randomized Investigation of the Safety and efficacy of Micardis vs ramipril using Ambulatory blood pressure monitoring; PROFESS, PRoventOn regimen For Effectively avoiding Second Strokes; TRANSCEND, Telmisartan Randomized Assessment Study in aCE-INtolerant subjects with cardiovascular Disease; VIVALDI, investigate the efficacy of telmisartan versus VALsartan in hypertensive type 2 Diabetic.

## Telmisartan and blood pressure (BP) control

Hypertension is a major risk factor for cardiovascular disease. The ARBs are broadly effective in lowering BP with relatively few side effects, notably the absence of cough and angioedema, which represents their major advantage over ACE inhibitors. Telmisartan is an ARB that was approved by the Food and Drug Administration (FDA) for the treatment of hypertension in November 1998, and is proven to provide efficient and lasting BP control when compared to other agents. In one meta-analysis of 28 randomized controlled trials involving 5157 patients, telmisartan had a superior BP control over different ACE inhibitors (enalapril, ramipril, and perindopril), fewer drug-related adverse events, and better tolerability in hypertensive patients.<sup>4</sup> In another meta-analysis of eleven studies involving 1832 patients, telmisartan resulted in a significant reduction in diastolic BP (weighted mean difference 1.52 mmHg; 95% confidence interval [CI]: 0.85–2.19) and systolic BP (2.77 mmHg; 95% CI: 1.90–3.63) when compared with losartan, as well as a significant reduction in 24-hour mean ambulatory BP.<sup>5</sup>

Furthermore, evidence suggests that cardiovascular risk may be subject to circadian variation, with peak morning incidence of myocardial infarction and stroke correlating with the early morning BP surge. Antihypertensive agents differ in their ability to control 24-hour BP. Ideally antihypertensive therapy should maintain control of BP throughout the 24-hour dosing cycle and especially in the last 6 hours of the cycle. In two prospective trials, PRISMA I and II (Prospective, Randomized Investigation of the Safety and efficacy of Micardis vs ramipril using Ambulatory BP monitoring) patients with essential hypertension were randomized to receive telmisartan 80 mg/day ( $n = 802$ ) or ramipril 5 mg/day or 10 mg/day ( $n = 811$ ) for 14 weeks.<sup>6</sup> The primary endpoint was the change from baseline in mean ambulatory systolic BP and diastolic BP during the final 6 hours of the 24-hour dosing cycle. After 14 weeks, telmisartan was more effective than ramipril in controlling BP throughout the 24-hour period and during the early morning (mean systolic/diastolic  $-4.1/-3.0$  mmHg,  $P < 0.0001$ ). These results may be attributable to the long effect duration of telmisartan, which is sustained throughout the 24-hour dosing period.<sup>6</sup>

## Telmisartan, urinary protein excretion, and cardiovascular risk

The importance of urinary protein excretion as a cardiovascular risk factor has been established by a number of large studies. The HOPE (Heart Outcomes Prevention

Evaluation) study, which included 9043 high-risk patients, showed a correlation between the degree of albuminuria and cardiovascular risk, both in individuals with and without diabetes. After adjustment for other risk factors, the relative risk (RR) of major cardiovascular events (cardiovascular death, myocardial infarction, or stroke) associated with microalbuminuria was 1.83 (95% CI: 1.64–2.05).<sup>7</sup> ACE inhibitors are well known to reduce microalbuminuria and improve renal function. In the DETAIL (Diabetics Exposed to Telmisartan and Enalapril) trial, telmisartan was not inferior to the ACE inhibitor enalapril in preventing the progression of renal dysfunction, measured as the decline in the glomerular filtration rate in patients with diabetes.<sup>8</sup> Furthermore, in the INNOVATION (Incipient to Overt: Angiotensin II Blocker, Telmisartan, Investigation on Type 2 Diabetic Nephropathy) study, 527 diabetic hypertensive and normotensive Japanese patients with microalbuminuria were randomized to telmisartan 40 mg, telmisartan 80 mg, or placebo.<sup>9</sup> The transition to overt diabetic nephropathy was dose dependent and significantly lower in the telmisartan 80 mg and telmisartan 40 mg groups compared with placebo (16.7% and 22.6% vs 49.9%, respectively;  $P < 0.0001$ ) over a 30-month follow up period. Telmisartan also reduced transition to overt nephropathy in normotensive patients, suggesting a BP independent effect.<sup>9</sup> In the VIVALDI (inVestIgate the efficacy of telmisartan versus VALsartan in hypertensive type 2 DIabetic) trial, telmisartan 80 mg/day and valsartan 160 mg/day produced similar reductions in 24-hour urinary protein excretion rates by 33% after 12 months of treatment in diabetic patients with hypertension and overt nephropathy.<sup>10</sup> It is thought that their renoprotective benefit in VIVALDI, was solely due to the antihypertensive effect. However, in the AMADEO (A comparison of telMisartan versus losArtan in hypertensive type 2 DiabEtic patients with Overt nephropathy) trial, telmisartan 80 mg/day was superior to losartan 100 mg/day in terms of renoprotective properties. Telmisartan showed a greater reduction in the urinary albumin to creatinine ratio than the losartan (29.8% and 21.4%, respectively;  $P < 0.031$ ), despite similar BP reduction.<sup>11</sup>

## Telmisartan and prevention of cardiovascular disease in high-risk patients

Multiple randomized controlled trials demonstrated reduction of mortality and hospital admissions in patients with heart failure when treated with an ARB.<sup>12</sup> When compared to atenolol, ARBs decreased vascular events in patients with

hypertension and LVH.<sup>13</sup> In addition, ARBs were comparable to ACE inhibitors in patients with acute myocardial infarction and heart failure in terms of all-cause mortality.<sup>14</sup>

The ONTARGET trial is a landmark large trial that established the role of ARBs in reducing cardiovascular events in high-risk patients.<sup>15</sup> ONTARGET studied patients with coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage. Patients with congestive heart failure were excluded. Participants who could not tolerate ACE inhibitors were studied in a parallel trial with telmisartan vs placebo. In ONTARGET, 25,620 patients were randomized to receive telmisartan 80 mg/day, ramipril 10 mg/day, or the combination of both drugs, and were followed for 56 months. The primary outcome was a composite of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure. Telmisartan was equivalent to ramipril for the primary outcome (telmisartan 16.7%, ramipril 16.5%, RR: 1.01; 95% CI: 0.94–1.09). Telmisartan caused lower rates of cough (1.1% vs 4.2%;  $P < 0.001$ ) and angioedema (0.1% vs 0.3%;  $P = 0.01$ ) and a higher rate of hypotensive symptoms (2.6% vs 1.7%;  $P < 0.001$ ) when compared with ramipril. The combination of the two drugs did not improve outcomes and was associated with more adverse events including a significantly higher rate of discontinuation (29.3% vs 24.5% with ramipril and 23.0% with telmisartan;  $P < 0.001$ ). These findings suggest that RAAS blockade with either telmisartan or ramipril is optimal for cardiovascular risk reduction, and that telmisartan is comparable to ramipril in patients with vascular disease or high risk diabetes, with fewer cough and angioedema events.

In the TRANSCEND trial, 5926 high-risk patients intolerant to ACE inhibitors, but otherwise similar to ONTARGET population, were randomized to receive telmisartan 80 mg/day or placebo.<sup>16</sup> After 56 months, telmisartan did not reduce a composite endpoint of cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure in patients with cardiovascular disease or diabetes with end-organ damage (telmisartan 15.7%, placebo 17%, hazard ratio [HR]: 0.92; 95% CI: 0.81–1.05,  $P = 0.216$ ). However, telmisartan reduced the secondary composite outcome of cardiovascular death, myocardial infarction, and stroke (telmisartan 13%, placebo 14.8%; odds ratio [OR]: 0.86; 95% CI: 0.74–1.00;  $P = 0.045$ ), which was the HOPE composite outcome. In contrast with the HOPE study, a neutral effect of telmisartan on hospitalizations for heart failure was observed, and may be due to a higher use of diuretics (32.8%) and  $\beta$ -blockers (57.2%) in the placebo arm of TRANSCEND, in contrast with 15.2% and 39.8%,

respectively in the placebo arm of the HOPE trial a decade ago. Therefore TRANSCEND validates the role of ARBs in reducing cardiovascular risk in high-risk patients and does not contradict ONTARGET.

PRoFESS (PREventiOn regimen For Effectively avoiding Second Strokes) is another large randomized controlled trial that enrolled 20,322 patients older than 50 years of age who had an ischemic stroke in the previous 120 days and were clinically and neurologically stable.<sup>17</sup> Patients were randomized to receive telmisartan 80 mg/day vs placebo, and were followed for 2.5 years. The primary outcome was recurrent stroke, and secondary outcomes were major cardiovascular events (death from cardiovascular causes, recurrent stroke, myocardial infarction, or new or worsening heart failure) and new-onset diabetes. Therapy with telmisartan initiated soon after an ischemic stroke and continued for 2.5 years did not significantly lower the rate of recurrent stroke, major cardiovascular events, or diabetes. Post hoc analyses showed that from 6 months on, recurrent stroke rate was lower in the telmisartan group (5.3% vs 6.0%; HR: 0.88; 95% CI: 0.78–0.99). This finding suggests a time-dependent benefit of telmisartan and that the trial duration may have been too short to detect a difference.

In the NAVIGATOR (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research) trial, valsartan, as compared with placebo, did not significantly reduce the incidence of cardiovascular outcomes among patients with impaired glucose tolerance and cardiovascular disease or risk factors (8.1% vs 8.1%; HR: 0.99; 95% CI: 0.86–1.14;  $P = 0.85$ ).<sup>18</sup>

## Telmisartan and effects on left ventricular mass

ACE inhibitors are known to reduce LVH. The effects of telmisartan and ramipril on LVH were studied in a subsequent analysis of the ONTARGET and TRANSCEND trials.<sup>19</sup> In TRANSCEND, the prevalence of LVH at entry was 12.7%. After 5 years of therapy, it was reduced to 9.9% in the telmisartan group, when compared to 12.8% in the placebo group (OR: 0.79; 95% CI: 0.68–0.91;  $P = 0.0017$ ). Furthermore, telmisartan reduced new-onset LVH by 37% when compared with placebo. However in patients with LVH at entry, regression of LVH was similar in both groups. In ONTARGET, telmisartan showed a trend to be slightly, but not significantly, more effective than ramipril in reducing LVH (OR: 0.92; 95% CI: 0.83–1.01;  $P = 0.07$ ). The combination of the telmisartan and ramipril did not provide any additional benefit compared to ramipril (OR: 0.93; 95% CI: 0.84–1.02;  $P = 0.12$ ).

New-onset LVH was associated with a higher risk of primary outcome during follow-up (HR: 1.77; 95% CI: 1.50–2.07). Greater LVH regression with an ARB compared with an ACE inhibitor was observed, and might be explained by the overactivation of angiotensin II type 2 receptor after blocking the effects of angiotensin II at the angiotensin II type 1 receptor by ARBs.

## Telmisartan and atrial fibrillation

Evidence is emerging for a role of RAAS in the pathophysiology of atrial fibrillation and a possible role for ACE inhibitors and ARBs in primary and secondary prevention of atrial fibrillation. A meta-analysis of 23 randomized controlled trials involving 87,048 patients showed that RAAS inhibition reduced the OR for atrial fibrillation by 33% ( $P < 0.00001$ ). In primary prevention, RAAS inhibition was effective in patients with heart failure, hypertension, and LVH but not in post-myocardial infarction patients. In secondary prevention, the addition of RAAS inhibition to antiarrhythmic drugs and medical therapy was also effective.<sup>20</sup> In the secondary outcomes of the ONTARGET trial, new-onset atrial fibrillation was similar in the telmisartan group (6.9%) and the ramipril group (6.5%) (RR: 0.97; 95% CI: 0.86–1.09), as well as with the combination of both drugs.<sup>15</sup> These data suggest a certain role for RAAS inhibition in the prevention of atrial fibrillation, but further large trials are needed to address this specific role.

## Telmisartan and prevention of diabetes mellitus

RAAS blockade may play a role in the prevention of diabetes. In a post hoc analysis of the HOPE trial, ramipril was associated with a 34% reduction in the risk of new-onset diabetes (RR: 0.66; 95% CI: 0.51–0.85;  $P < 0.001$ ) when compared with placebo.<sup>21</sup> However in the DREAM (Diabetes REDuction Assessment with ramipril and rosiglitazone Medication) trial, ramipril did not reduce the primary outcome of diabetes or death in patients with impaired fasting glucose or impaired glucose tolerance at low risk for cardiovascular events, however follow-up was for 3 years only.<sup>22</sup> On the other hand, in a meta-analysis of 13 studies involving approximately 67,000 patients, ACE inhibitors and ARBs reduced significantly new-onset diabetes mellitus in patients with hypertension or other cardiovascular risk factors with a RR of 0.79 (95% CI: 0.74–0.85) for ACE inhibitors and 0.78 (95% CI: 0.73–0.84) for ARBs.<sup>23</sup>

In the ONTARGET trial, incidence of new-onset diabetes was similar in the telmisartan and ramipril groups.<sup>15</sup>

In PROFESS trial, telmisartan did not prevent new-onset diabetes in patients with ischemic stroke.<sup>17</sup> In contrast, in the TRANSCEND trial, telmisartan reduced significantly the secondary outcome of new-onset diabetes compared to placebo (HR: 0.85; 95% CI: 0.71–1.02;  $P = 0.081$ ).<sup>16</sup> Most recently in the NAVIGATOR trial, valsartan reduced by 14% the incidence of diabetes among patients with impaired glucose tolerance and cardiovascular disease or risk factors.<sup>18</sup>

Finally, accumulating evidence suggests that telmisartan is a partial agonist of the peroxisome proliferator activated receptor-gamma (PPAR- $\gamma$ ).<sup>24</sup> Multiple in vitro and animal studies showed that the activation of this pathway is important in dyslipidemia, metabolic syndrome, and vascular disease.<sup>25–27</sup> Although clinical data is limited, the pleiotropic effect of telmisartan as a selective PPAR- $\gamma$  modulator may play an important role in the prevention and treatment of diabetes and cardiovascular disease.<sup>28,29</sup>

## Conclusion

Telmisartan is an ARB approved by the FDA for the treatment of hypertension since November 1998. In October 2009, based on the results from the ONTARGET trial, telmisartan was the first ARB to be granted FDA approval for reduction of cardiovascular risk in high-risk patients unable to take ACE inhibitors. Within the RAAS inhibition agents, telmisartan is characterized by a long duration of effect providing 24-hour BP control. Although providing similar renoprotective effects, telmisartan was associated with a better reduction of protein excretion than valsartan. In addition, evidence is emerging for a potential role of telmisartan and other ARBs in the prevention of new-onset diabetes and the prevention of atrial fibrillation. Finally, based on the ONTARGET and TRANSCEND studies, RAAS blockade with telmisartan is shown to provide optimal cardioprotection in high-risk patients, along with a good tolerance profile.

## Disclosure

The authors report no conflicts of interest in this work.

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