New standards in hypertension and cardiovascular risk management: focus on telmisartan

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REVIEW

New standards in hypertension and cardiovascular risk management: focus on telmisartan

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Abstract: Blockade of the renin–angiotensin system is an important approach in managing high blood pressure, and has increasingly been shown to affect cardiovascular disease processes mediated by angiotensin II throughout the cardiovascular and renal continua. Telmisartan is an angiotensin II receptor blocker (ARB) displaying unique pharmacologic properties, including a longer half life than any other ARB, that result in large and sustained reductions of blood pressure. In patients with mild-to-moderate hypertension, telmisartan has proved superior to other antihypertensive agents (valsartan, losartan, ramipril, perindopril, and atenolol) in controlling blood pressure particularly towards the end of the dosing interval. There is also clinical evidence that telmisartan reduces left ventricular hypertrophy, reduces arterial stiffness and the recurrence of atrial fibrillation, and confers renoprotection. The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET®) study has demonstrated that telmisartan has similar cardiovascular protective effects to ramipril in a large, high-risk patient population but was better tolerated. The powerful and sustained blood pressure control apparent in clinical trials, together with cardiovascular protection and tolerability demonstrated in ONTARGET® means that telmisartan may be a preferred option for patients with hypertension.

Keywords: angiotensin II receptor blocker, cardiovascular disease, hypertension, renin–angiotensin system, telmisartan

Introduction

Angiotensin II, which is generated by the renin–angiotensin system (RAS), plays a pivotal role in hypertension and cardiovascular disease. Thus, pharmacologic regulation of angiotensin II is central to the control of blood pressure and prevention of its pathophysiologic effects on the cardiovascular system, including the kidney and the brain.

The angiotensin-converting enzyme (ACE) inhibitors target one of the enzymes that generate angiotensin II from angiotensin I (Figure 1). However, angiotensin II is not produced exclusively by this mechanism; other enzymes, such as chymase, are also able to generate angiotensin II.[1] The angiotensin II receptor blockers (ARBs) overcome the detrimental effects of angiotensin II by preventing it binding to the type 1 receptors (AT_1). This review examines evidence for the efficacy of telmisartan in the treatment of high blood pressure, and explores the body of the evidence that telmisartan prevents disease mediated by angiotensin II throughout the cardiovascular and renal continua.

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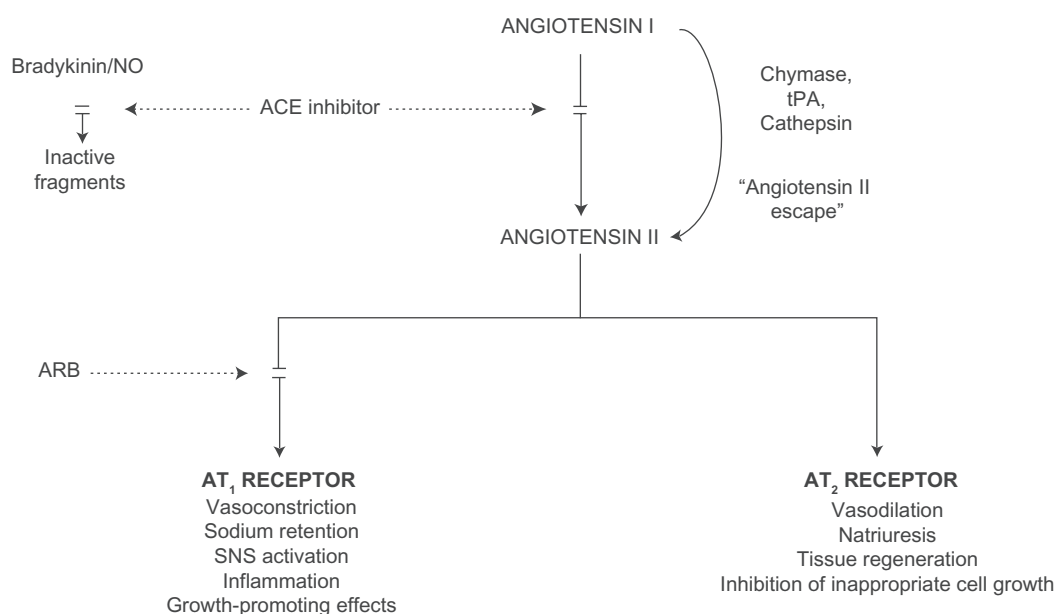Fax +39 0812545179
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Figure 1 Mechanism of blockade of the renin–angiotensin system.
Abbreviations: SNS, somatic nervous system; tPA, tissue plasminogen activator.

Pharmacology of telmisartan

There are currently seven commercially available ARBs, with telmisartan offering unique pharmacologic features compared with the other agents of its class. Telmisartan displays insurmountable, but reversible binding to the AT_1 receptor, and it has the highest binding affinity for this receptor among commercially available ARBs.[2] As well as providing long-term blockade of the AT_1 receptor, telmisartan has minimal affinity for the AT_2 receptor (K > 10,000 nM) or for acetylcholine, catecholamine, dopamine, histamine, serotonin, or imipramine receptors.[3] Telmisartan is also highly lipophilic, which facilitates oral absorption and benefits tissue and cell penetration, as demonstrated by its large volume of distribution of approximately 500 L,[4,5] thereby blocking both systemic and local RAS. Unlike other ARBs, which are excreted to varying extents via the kidneys,[6,7] more than 90% of telmisartan is eliminated in the feces.[8] An important distinguishing feature of telmisartan is its long terminal elimination half-life of about 24 hours, suggesting a long duration of action.[5] It has been shown in healthy volunteers that, at peak plasma concentrations, telmisartan 80 mg reduces the response to exogenous angiotensin II by about 90%, and approximately 40% inhibition persists for 24 hours.[9]

Telmisartan modulates peroxisome proliferator-activated receptor γ (PPARγ), an established therapeutic target in the treatment of insulin resistance, diabetes, and metabolic syndrome.[10] It has effects that are characteristic of PPARγ ligands on metabolism.[11–14] In addition, there is a growing body of evidence that PPARγ activation raises adiponectin production and exerts anti-inflammatory, anti-oxidative and anti-proliferative effects on vascular walls, thus decreasing the risks for atherosclerosis.[15,16] Although PPARγ activation has been reported for other commercially available ARBs,[17–19] the effects on PPARγ activity have been shown to be considerably weaker than achieved with telmisartan and occur at much higher concentrations.[19,20] Thus, the unique PPARγ-inducing properties of telmisartan, which are achievable at therapeutic doses, may have the capacity for targeting both diabetes and cardiovascular disease.

The importance of sustained blood pressure control

Hypertension is well recognized as a major risk factor for cardiovascular and renal morbidity and mortality. The importance of blood pressure lowering has been established through epidemiologic and clinical studies, and has led to a broad consensus from guideline bodies on the targets for blood pressure control. Improved control of blood pressure is vital to obtain maximum benefit.

Patients typically prefer to take their medication in the morning. To optimize patient compliance, once-daily dosing is important. However, for a once-daily drug taken in the morning, early morning is the time of trough efficacy and may pose a problem in the management of hypertension. In one study, approximately 60% of patients with apparently controlled hypertension when

measured in the office during the day had, in reality, uncontrolled blood pressure (systolic blood pressure [SBP]/ diastolic blood pressure [DBP] > 130/85 mmHg) determined by ambulatory blood pressure monitoring (ABPM) in the early morning.[21] An antihypertensive agent's duration of action must be sufficient to control blood throughout the dosing interval and, ideally, if the next dose is delayed or missed.[22]

A further consideration is that, during the morning, incidences of cardiovascular events increase dramatically and are more frequent than at any other time of the day.[23–25] Blood pressure follows a circadian rhythm, being lowest at night and increasing suddenly in the morning upon awakening.[26] This early morning blood pressure surge (EMBPS) is caused primarily by orthostatic changes but is also linked to circadian changes in the RAS.[27–29]

Antihypertensive efficacy of telmisartan

The efficacy of telmisartan in the primary care setting has recently been demonstrated in the MICARDIS® Community Access Trial (MICCAT-2) involving 1619 patients.[30] The patients had uncontrolled hypertension, 675 having blood pressure that was not controlled despite prior receipt of conventional therapy. The patients in the trial were treated with telmisartan 40 mg, titrated to 80 mg or a combination of telmisartan 80 mg plus hydrochlorothiazide (HCTZ) 12.5 mg. Office SBP/DBP fell by 22.7/12.6 mmHg in the previously untreated patients and by 16.8/10.3 mmHg in the previously treated patients. After telmisartan treatment, blood pressure was controlled in 79% of the patients.

An accurate reflection of the extent of blood pressure control at different stages of the dosing interval is provided by self-measurement of blood pressure in the home or by 24-hour ABPM using an automated device.[31] In MICCAT-2, ABPM showed that telmisartan alone or in combination with HCTZ produced significant reductions in blood pressure as shown in both day-time and night-time mean SBP/DBP. Furthermore, telmisartan reduced SBP/DBP by 17.2/10.1 mmHg in the 4 hours post-awakening in the 95 patients who had an EMBPS of SBP > 30 mmHg.[32]

A large number of clinical studies have demonstrated the antihypertensive efficacy of telmisartan versus other antihypertensive agents. Key studies, as described below, are summarized in Table 1. It should be noted that relative efficacy in fixed-dose studies depends upon the doses employed, which typically related to the doses approved or intended for clinical practice when the study was conducted.

Results should be interpreted with caution in cases where the doses employed are less than the current, clinically-available maximal dose.

Telmisartan versus other ARBs

In Japanese hypertensive patients, home blood pressure measurement confirmed that telmisartan reduces blood pressure more than other ARBs.[33] At the lower doses typically used in Japan, once-daily telmisartan 10 to 40 mg taken in the morning achieved greater blood pressure reductions in the early morning than once-daily valsartan 40 to 80 mg, candesartan 2 to 12 mg, or losartan 25 to 100 mg. Comparison of the morning effect on blood pressure versus the evening effect on blood pressure showed that, in particular, the effect of losartan did not persist for 24 hours.

Ambulatory blood pressure monitoring has shown that telmisartan 80 mg confers significantly greater blood pressure lowering than several other ARBs. When compared with valsartan 160 mg, telmisartan provided sustained antihypertensive efficacy and superior control of blood pressure during the early morning period.[34,35] Differences between the treatments were also apparent for seated SBP. This measure was significantly reduced by telmisartan compared with valsartan (12.1 vs 8.2 mmHg, respectively; $P = 0.0281$), while the reduction in DBP was also numerically greater with telmisartan.[35] Pooled data from two studies showed that, after active therapy, last 6-hour mean DBP was reduced by 7.6 mmHg with telmisartan compared with 5.8 mmHg with valsartan ($P = 0.0044$) and last 6-hour mean SBP was reduced by 11.1 mmHg with telmisartan as opposed to 9.1 mmHg with valsartan ($P = 0.0066$).[35] After a dose was deliberately missed, 24-hour mean DBP was reduced by 7.2 mmHg with telmisartan compared with 5.5 mmHg with valsartan ($P = 0.0004$), and the reduction in 24-hour mean SBP after a missed dose was 10.7 mmHg with telmisartan and 8.7 mmHg with valsartan ($P = 0.0024$).

Similarly, 3 ABPM studies comparing telmisartan 40 or 80 mg with losartan 50 or 100 mg demonstrated that telmisartan provided greater reductions than losartan in both the 24-hour mean SBP and DBP and in the in last 6 hours of the dosing interval.[36–38]

There are fewer data comparing the antihypertensive efficacy of telmisartan with ARBs other than valsartan and losartan. A 1-year comparative study in patients with mild hypertension and type 2 diabetes showed that telmisartan produced a superior reduction in blood pressure compared with eprosartan.[39] Two small-scale clinical studies have compared the blood pressure lowering effects of telmisartan

Table 1 Summary of studies comparing the antihypertensive efficacy of telmisartan

References	Duration	No of pts	Active comparators	Baseline in-clinic seated SBP/DBP (mmHg)	SBP/DBP reduction at study endpoint (mmHg)	Response rate (% pts)
Versus other ARBs						
Nishimura et al[33]	4 weeks	72	Telmisartan (T) 10–40 mg od Losartan (L) 25–100 mg od Candesartan (C) 2–12 mg od Valsartan (V) 40–80 mg od	Baseline values not stated in paper. Patients had home morning and evening SBP and/or DBP of <180 and ≥135 mmHg and <120 and ≥85 mmHg, respectively	Home evening SBP/DBP: T:−24.7/−15.1* L:−15.7/−11.4 C:−15.9/−11.6 V:−21.8/−11.4 Home morning SBP/DBP: T:−21.9/−12.5* L:−7.9/−3.0 C:−11.4/−11.0 V:−17.0/−9.5	
White et al[34]	8 weeks	490	Telmisartan 80 mg od Valsartan 160 mg od	T: 154.0/99.0 V: 153.0/99.0	Last 6 h: T:−11.0/−7.6* V:−8.7/−5.8 After missed dose: T:−10.3/−6.9 (24 h) V:−8.7/−5.9 (24 h)	
Lacourcière et al[35]	8 weeks	930	Telmisartan 40–80 mg od Valsartan 80–160 mg od	T: 157.3/100.1 V: 156.0/100.0	Last 6 h: T:−11.1/−7.6* V:−9.1/−5.8 After missed dose: T:−10.7/−7.2 (24 h)* V:−8.7/−5.5 (24 h)	
Mallion et al[36]	6 weeks	223	Telmisartan 40–80 mg od Losartan 50 mg od	T 40 mg: 161.9/100.8 T 80 mg: 164.2/101.8 L: 162.4/100.7	Daytime: T 40 mg:−11.5/−7.3* T 80 mg:−13.3/−8.3* L:−8.7/−5.3 Night-time: T 40 mg:−11.5/−7.6* T 80 mg:−13.1/−8.2* L:−7.0/−4.5 Morning: T 40 mg:−10.6/−6.8* T 80 mg:−12.8/−7.7* L:−7.8/−4.3	SBP response (≥10 mmHg change from baseline): T 40 mg: 56.1 T 80 mg: 69.8* L: 45.6 DBP response (<90 mmHg and/or ≥10 mmHg change from baseline): T 40 mg: 40.4 T 80 mg: 52.8* L: 29.8
Smith et al[37]	8 weeks	720	Telmisartan 40–80 mg od Losartan 50–100 mg od	Baseline BP not given in paper. Patients included in study had mild-moderate hypertension (seated DBP 95–109 mmHg)	Last 6 h: T:−9.9/−6.6* L:−7.8/−5.1	SBP response (<140 mmHg and/or ≥10 mmHg change from baseline): T: 62.3 L: 56.6

Reference	Duration	N	Treatment	Baseline	Results
Ding et al[38]	6 weeks	61	Telmisartan 40 mg od Losartan 50 mg od	T:153.6/101.1 L: 154.5/99.1	18–24 h: T:−16.0/−12.1* L:−11.8/−7.0 DBP response (<90 mmHg and/or ≥10 mmHg change from baseline): T:45.0 L:41.1 SBP response (<140 mmHg or ≥10 mmHg reduction from baseline): T:90.3 L:92.0 DBP response (<90 mmHg or ≥10 mmHg reduction from baseline): T:77.4 L:72.0
Derosa et al[39]	52 weeks	119	Telmisartan 40 mg od Eprosartan (E) 600 mg od	T: 143.0/92.0 E: 144.0/91.0	After 12 months: T:−8.0/−8.0 E:−7.0/−4.0
Nakayama et al[40]	2 × 8 weeks (treatment switch)	20	Telmisartan 40 mg od Olmesartan (O) 20 mg od	Patients at baseline treated with valsartan then switched to telmisartan or olmesartan. Baseline SBP/DBP: 133.6/75.5	Mean 24 h: T:−0.9/+1.8 O:−4.2/−0.9* Daytime: T:−3.4/+1.3 O:−5.6/−1.9* Night-time: T:+3.5/+4.0 O:−1.9/+0.7*
Sasaki et al[41]	2 × 3 months (treatment switch)	20	Telmisartan 40 mg od Olmesartan 20 mg od	Pre-treatment: 129.9/73.2	In-clinic: T:−0.4/−0.5 O:−1.1/−0.6 Home morning: T:−0.0/+0.3* O:+1.9/+1.6 Home evening: T:−0.3/−0.5 O:−0.3/−1.1
Versus ACE inhibitors					
Williams et al[42]	14 weeks	801	Telmisartan 80 mg od Ramipril (R) 5–10 mg od	T: 158.5/100.1 R: 158.3/100.1	Last 6 h: T:−12.1/−8.5* R 10 mg:−8.4/−5.8 Mean 24 h: T:−14.5/−9.8* R 10 mg:−11.6/−7.7 SBP/DBP response (<130/80 mmHg or ≥10 mmHg reduction from baseline): T:76.2/61.9* R:66.9/54.8

(Continued)

Table 1 (*Continued*)

References	Duration	No of pts	Active comparators	Baseline in-clinic seated SBP/DBP (mmHg)	SBP/DBP reduction at study endpoint (mmHg)	Response rate (% pts)
Lacourcière et al[43]	14 weeks	812	Telmisartan 40–80 mg od Ramipril 2.5–10 mg od	T: 153.9/99.7 R: 152.5/99.8	Last 6 h: T: −12.7/−8.8* R 10 mg: −7.9/−5.4 Mean 24 h: T: −14.8/−9.9* R 10 mg: −10.7/6.7	SBP/DBP response (<130/80 mmHg and/or ≥10 mmHg reduction from baseline): T: 70.7/60.5* R: 62.7/46.8
Gosse et al[44]	14 week	1613	Telmisartan 40–80 mg od Ramipril 2.5–10 mg od	T: 156.1/99.9 R: 155.1/100.0	Mean 24 h: T: −14.0/−9.6* R 10 mg: −11.1/−7.2 Early morning: T: −12.7/−8.5* R 10 mg: −7.9/−5.2 Night-time: T: −11.0/−8.5* R 10 mg: −8.4/−5.9	
Nalbantgil et al[46]	6 weeks	60	Telmisartan 80 mg od Perindopril (P) 4 mg od	T: 167.4/102.2 P: 167.6/101.4	In-clinic: T: −27.7/−12.4 P: −25.9/−10.1 Mean 24 h	DBP response (≤85 mmHg): T: 66.6* P: 46.6
Ragot et al[47]	12 weeks	441	Telmisartan 40 mg od Perindopril 4 mg od	T: 158.0/98.0 P: 159.0/98.0	Mean between-treatment difference in in-clinic SBP/DBP: −3.4/−2.5* (in favor of telmisartan)	SBP/DBP normalization rate (<135/<85 mmHg): T: 46/58* P: 32/46
Stergiou et al[48]	5 weeks	36	Telmisartan 80 mg od Lis (L) 20 mg od	T: 134.2/88.2 L: 134.3/87.5	Mean 24 h: T: −7.7/−7.1 L: −9.0/−7.1	
Neutel et al[49]	52 weeks	578	Telmisartan 40–160 mg od Lis 10–40 mg od	T: 153.4/100.8 L: 152.5/100.5	In-clinic: T: −21.1/−16.3 L: −19.3/−15.4	
Versus β-blockers						
Freytag et al[51]	26 week	533	Telmisartan 40–120 mg od Atenolol (A) 50–100 mg od	T: 166.5/102.0 A: 164.5/101.4	In-clinic: T: −20.9/−14.4* A: −16.7/−13.3	DBP response (≤90 mmHg and/or ≥10 mmHg change from baseline): T: 84 A: 78
Alcocer et al[52]	8 weeks	58	Telmisartan 80 mg od Atenolol 50 mg od	T: 158.4/99.2 A: 153.8/97.9	In-clinic: T: −20.4/−13.0* A: −9.1/−8.6	

Reference	Duration	N	Treatment	Baseline BP	BP change	Response
Galzerano et al[53]	44 weeks	82	Telmisartan 80 mg od Carvedilol (C) 25 mg od	T: 159.6/97.8 C: 157.8/95.7	Mean 24 h: T: −31.0/−19.6 C: −29.6/−17.0	
Versus CCBs						
Lacourcière et al[54]	12 weeks	232	Telmisartan 40–120 mg od Amlodipine 5–10 mg od	Baseline BP not stated in paper. Patients included in study had mild-moderate hypertension (seated DBP 95–114 mmHg)	In-clinic: T: −16.5/−11.6 A: −17.4/−11.6 Night-time and last 4 h: Significantly greater DBP reductions with telmisartan vs amlodipine (values not provided)	DBP response (24-h DBP <85 mmHg or ≥10 mmHg change from baseline): T: 81 A: 66
Derosa et al[55]	12 month	116	Telmisartan 40 mg od Nifedipine (N) GITS 20 mg	T: 139.0/95.0 N: 140.0/94.0	In-clinic: T: −7.0/−9.0 N: −10/−10	
Versus HCTZ						
McGill, Reilly[56]	8 weeks	818	Telmisartan 20–160 mg od HCTZ (H) 6.25–25 mg od	T: 153.2/100.7 H: 153.3/100.7	In-clinic: T 40 mg: −12.2/−10.7 T 80 mg: −15.4/−11.5 H 12.5 mg: −6.9/−7.3	SBP response (≥10 mmHg change from baseline): T 40 mg: 60 T 80 mg: 66 H 12.5 mg: 36 DBP response (≤90 mmHg and/or ≥10 mmHg change from baseline): T 40 mg: 67 T 80 mg: 69 H 12.5 mg: 47
Galzerano et al[57]	12 months	69	Telmisartan 80 mg od HCTZ 25 mg od	T: 157.0/96.0 H: 154.0/95.0	Mean 24 h: T: −24.0/−13.0* H: −10.0/−8.0	DBP < 90 mmHg or reduction in both SBP and DBP of ≥10 mmHg: T: 74 H: 56
Manolis et al[58]	2–4 weeks	1039	Telmisartan 20–80 mg od HCTZ 12.5 mg od	T 20 mg: 163.5/83.7 T 40 mg: 162.7/83.4 T 80 mg: 162.4/83.2 H: 162.5/83.5	In-clinic: T 20 mg: −4.2/−2.4 T 40 mg: −6.5/−3.3 T 80 mg: −5.6/−3.0 H: −15.7/−1.9	
Combination treatment						
McGill, Reilly[56]	8 weeks	818	Telmisartan 20–160 mg od plus HCTZ 6.25–25 mg od	T + H: 154.5/100.7	In-clinic: T 40 mg + H: −18.8/−12.6** T 80 mg + H: −23.9/−14.9**	SBP response (≥10 mmHg change from baseline): T 40 mg + H: 81 T 80 mg + H: 85**

(Continued)

Table 1 (*Continued*)

References	Duration	No of pts	Active comparators	Baseline in-clinic seated SBP/DBP (mmHg)	SBP/DBP reduction at study endpoint (mmHg)	Response rate (% pts)
						DBP response (≤90 mmHg and/or ≥10 mmHg change from baseline): T 40 mg + H: 63 T 80 mg + H: 79**
Lacourcière et al[59]	6 weeks	1402	Telmisartan 40–80 mg plus HCTZ 12.5 mg od Losartan 50 mg plus HCTZ 12.5 mg od	T 40 mg + H: 155.0/100.0 T 80 mg + H: 156.5/100.2 L 50 mg + H: 155.2/99.8	Last 6 h: T 40 mg + H:−17.2/−11.3* T 80 mg + H:−18.0/−12.0* L 50 mg + H:−14.6/−9.4 In-clinic: T 40 mg + H:−16.8/−11.3* T 80 mg + H:−18.5/−12.3* L 50 mg + H:−14.0/−8.7	SBP response (<130 mmHg and/or ≥10 mmHg reduction from baseline): T 40 mg + H: 79.1* T 80 mg + H: 82.3* L 50 mg + H: 76.7 DBP response (24-h mean DBP <85 mmHg or ≥10 mmHg reduction from baseline): T 40 mg + H: 60.3* T 80 mg + H: 69.4* L 50 mg + H: 55.0
White et al[60]	8 weeks	1109	Telmisartan 80 mg plus HCTZ 25 mg od Valsartan 160 mg plus HCTZ 25 mg od	T + H: 154.6/101.8 V + H: 154.3/101.9	In-clinic: T + H:−23.6/−17.5* V + H:−20.9/−16.1	
White et al[61]	8 weeks	1185	Telmisartan 80 mg plus HCTZ 25 mg od Valsartan 160 mg plus HCTZ od	T + H: 154.1/101.8 V + H: 154.9/101.6	In-clinic: T + H:−24.6/−18.2* V + H:−22.5/−17.0*	
Fogari et al[62]	16 weeks	145	Telmisartan 80 mg plus HCTZ 12.5 mg od Olmesartan 20 mg plus HCTZ 12.5 mg od	T + H: 169.7/103.7 O + H: 169.1/104.1	Mean 24 h: T + H:−20.8/−14.3* O + H:−17.7/−11.3 Daytime: T + H:−21.0/−12.9* O + H:−18.7/−11.7 Night-time: T + H:−21.1/−14.3* O + H:−16.7/−10.0	
Lacourcière et al[63]	8 weeks	491	Telmisartan 80 mg plus HCTZ 12.5 mg od Telmisartan 80 mg od	T + H: 148.9/96.4 T: 148.7/96.6	In-clinic: T + H:−12.6/−8.0* T:−7.0/−4.9	Normalized SBP/DBP response (<140/90 mmHg): T + H: 41.5* T: 26.1

Study	Duration	N	Treatment	Baseline BP	BP reduction	Response rates (%)
Sharma et al[64]	10 weeks	840	Telmisartan 80 mg plus HCTZ 12.5 mg od Valsartan 160 mg plus HCTZ 12.5 mg od	T + H: 156.8/92.1 V + H: 157.1/91.7	Last 6 h: T + H: −18.4/−9.7* V + H: −14.5/−77	DBP response (DBP < 90 mmHg): T + H: 52.4* T: 35.5 SBP response (24-h mean SBP < 130 mmHg and/or ≥10 mmHg reduction): T + H: 79.9 V + H: 75.6 DBP response (24-h mean DBP < 90 mmHg and/or ≥10 mmHg reduction): T + H: 79.9 V + H: 77.3
Neldam, Edwards[65]	14 weeks	1000	Telmisartan 80 mg plus HCTZ 12.5 mg od Amlodipine (Am) 10 mg plus HCTZ 12.5 mg od	T + H: 161.0/87.3 Am + H: 161.7/86.8	SBP during last 6 h: T + H: −18.3 Am + H: −17.4	SBP response (24-h mean SBP < 130 mmHg and/or ≥10 mmHg reduction from baseline): T + H: 86.4 Am + H: 85.1
Schumacher, Mancia[66]	7 days to 2 years	8023	Telmisartan 10–160 mg plus HCTZ 6.25–25 mg od Telmisartan 10–160 mg od	T + H: 157.6/101.4 T: 158.3/98.7	In-clinic: T + H: −21.1/−14.2 T: −13.8/−8.7	
Littlejohn et al[67]	8 weeks	1461	Telmisartan 20–80 mg plus amlodipine 2.5–10 mg od Telmisartan 20–80 mg od Amlodipine 2.5–10 mg od	Overall: 153.2/101.7	In-clinic: T 80 mg + Am 10 mg: −26.4/−20.1** T 80 mg: −14.3/−14.0 Am 10 mg: −20.7/−17.1	DPB response (<90 mmHg or ≥10 mmHg reduction from baseline): T 80 mg + Am 10 mg: 91.2 T 80 mg: 78.0 Am 10 mg: 85.5 SBP response (<140 mmHg or ≥15 mmHg reduction from baseline): T 80 mg + Am 10 mg: 90.4 T 80 mg: 65.2 Am 10 mg: 82.3

*$P < 0.05$ vs active comparator; **$P < 0.05$ vs respective monotherapies.
Abbreviations: ACE, angiotension-converting enzyme; ARB, angiotensin II receptor blocker; CCBs, calcium channel blockers; HCTZ, hydrochlorothiazide, once daily.

40 mg versus olmesartan 20 mg in Japanese patients. In one open-label study of 20 patients with early-stage type 2 diabetes and hypertension, olmesartan was shown to provide greater blood pressure reductions than telmisartan.[40] Conversely, in a separate study, telmisartan was shown to be more effective than olmesartan for controlling early morning blood pressure, in addition to improving glucose and cholesterol levels in patients with hypertension, chronic heart failure and metabolic syndrome.[41] A PubMed search identified no clinical trials directly comparing the antihypertensive effects of telmisartan versus irbesartan.

Telmisartan versus ACE inhibitors

Other evidence for telmisartan providing effective blood pressure control comes from two 14-week studies of identical design – Prospective, Randomized Investigation of the Safety and efficacy of MICARDIS® versus ramipril using ABPM (PRISMA™) – conducted in 1613 hypertensive patients in Europe and South Africa (PRISMA™ I) and in the USA and Canada (PRISMA™ II). In PRISMA™ I, telmisartan titrated from 40 to 80 mg and given in the morning provided superior blood pressure control than ramipril titrated from 2.5 to 5 to 10 mg.[42] Notably, this difference was observed throughout all periods of the 24-hour dosing interval and resulted in significantly greater reduction in SBP/DBP than ramipril during the last 6 hours ($P < 0.001$).[42] Similar results were recorded in PRISMA™ II.[43] The pooled analysis of the PRISMA™ I and II trials documented that 24-h mean SBP/DBP reductions were significantly greater with telmisartan than ramipril (−14.1/−9.6 vs −11.1/−7.2, respectively) and superiority of telmisartan over ramipril was also apparent during the last 6 hours (difference: 4.8/3.3 mmHg ($P < 0.0001$)).[44] Furthermore, the findings of a meta-analysis of individual data from 1 million patients in 61 prospective studies suggest that the statistically significant greater reduction in last 6-hour mean SBP in patients treated with telmisartan in the PRISMA™ studies is of clinical relevance in improving long-term prognosis.[45]

The antihypertensive effect of telmisartan was examined in a double-blind comparison of telmisartan 80 mg and perindopril 4 mg. Both agents produced similar reductions in 24-hour mean SBP/DBP at the end of the 8-week study.[46] However, telmisartan provided significantly greater reductions in hourly mean DBP in each of the last 8 hours of the dosing period. Telmisartan 40 mg was also compared with perindopril 4 mg in a 12-week, open-label study, with the dose being doubled in patients who failed to respond (DBP ≥ 90 mmHg) at week 6.[47] Reductions in trough SBP/DBP from baseline were significantly greater with telmisartan at both 6 and 12 weeks.

Using both 24-hour ABPM and clinic blood pressure measurements, telmisartan 80 mg was found to be as effective as lisinopril 20 mg in reducing SBP and DBP, with telmisartan provide sustained blood pressure control throughout the 24-hour dosing interval.[48] Higher doses of telmisartan (40, 80, and 160 mg) and lisinopril (10, 20, and 40 mg) were compared in another, larger titration-to-response study measuring trough clinic blood pressure and comprising 578 patients who could also receive HCTZ up to a dose of 25 mg.[49] Control of DBP was similar in patients receiving either telmisartan or lisinopril.

As well as telmisartan generally producing greater reductions in SBP and DBP that were particularly evident towards the end of the dosing period, telmisartan is better tolerated than ACE inhibitors. Comparative studies have consistently shown that incidences of cough were lower with telmisartan than with perindopril,[46,47] lisinopril,[49] or ramipril.[42,43] The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET®) study, which was an outcome study in a broad cross-section of patients who were at high risk for cardiovascular diseases and who could tolerate ACE inhibitors, the rates of cough and angioedema were significantly lower with telmisartan than with ramipril.[50] Moreover, telmisartan was associated with better tolerability and greater treatment adherence. The differences in tolerability and adherence between telmisartan and ramipril may well have implications for patients who need long-term treatment to reduce their cardiovascular risk.

Telmisartan versus beta (β)-blockers

Beta-blockers have been compared with telmisartan in several studies of short or longer duration. In a titration-to-response study of 533 patients (with HCTZ added as needed to achieve blood pressure control; mean baseline seated BP 165.8/101.8 mmHg), full SBP response (≤89 mmHg and/or ≥10% reduction from baseline) was achieved by 84% of telmisartan-treated patients and 78% of atenolol-treated patients (nonsignificant).[51] In addition, 80% achieved a ≥10 mmHg reduction in trough SBP with telmisartan 40 to 80 to 120 mg compared with only 68% of patients receiving atenolol 50 to 100 mg ($P = 0.003$).[51] In addition, telmisartan had the advantage of being better tolerated: over the 26-week study, side effects were experienced by 53% of patients receiving telmisartan but by 61% of those treated with the β-blocker. Most notably, there were fewer incidences of fatigue and male impotence. The superiority of telmisartan

was also demonstrated in an 8-week open-label comparison of telmisartan 80 mg and atenolol 50 mg in 58 patients.[52]

Telmisartan was compared with carvedilol in a multicenter study on their effects on left ventricular mass (LVM) in patients with mild-to-moderate hypertension.[53] As part of the study, ABPM was performed at baseline and after 44 weeks' treatment with telmisartan 80 mg or carvedilol 25 mg in 82 patients. The 24-hour mean SBP/DBP reductions were similar in both treatment groups. However, night-time and last 6-hour mean reductions were numerically greater with telmisartan, although statistical significance was not achieved.

Telmisartan versus calcium channel blockers

When telmisartan 40 mg (titrated to 80 mg at 4 weeks and to 120 mg at 8 weeks for patients whose DBP remained >90 mmHg) and amlodipine 5 mg (5 mg at 4 weeks to 10 mg at 8 weeks for patients whose DBP remained >90 mmHg)[54] were compared, ABPM demonstrated that both agents produced similar, significant decreases in 24-hour mean SBP/DBP ($P < 0.0001$). Telmisartan, however, was superior to amlodipine with respect to the reductions in DBP at night and during the early morning hours: reduction in DBP in the last 4 hours of the dosing interval was 3.4 mmHg greater with telmisartan than with amlodipine ($P < 0.05$). In addition, a 24-hour mean DBP < 85 mmHg were observed in 71% of telmisartan-treated patients but only in 55% of those receiving amlodipine. Telmisartan was also better tolerated: the incidence of adverse events, particularly edema, was lower with telmisartan (5%) than with amlodipine (22%; $P = 0.05$).

Another 12-month study, primarily designed to evaluate left ventricular hypertrophy (LVH), compared the antihypertensive efficacy of telmisartan 40 mg with that of nifedipine gastrointestinal therapeutic system (GITS) 20 mg.[55] Similar and significant reductions from baseline in SBP/DBP were observed in the two treatment arms.

Telmisartan versus HCTZ

Telmisartan has been shown to provide more effective control of high blood pressure than HCTZ. In an 8-week factorial study comparing telmisartan (20, 40, 80, or 160 mg), 3 doses of HCTZ (6.25, 12.5, or 25 mg) and combinations of these doses, telmisartan 40 and 80 mg resulted in greater reductions in SBP and DBP than HCTZ 12.5 mg.[56]

In a 12-month study to determine the effect of telmisartan and HCTZ on LVH in hypertensive patients, 24-hour ABPM was performed at baseline and after 12 months'

double-blind treatment with telmisartan 80 mg or HCTZ 25 mg.[57] At the end of the study, significant reductions from baseline in 24-hour mean SBP/DBP were detected in both treatment groups, but the blood pressure-lowering effect of 24/13 mmHg with telmisartan versus 10/8 mmHg with HCTZ was significantly superior ($P < 0.01$).

Another study was performed in 1039 patients with isolated systolic hypertension.[58] Trough office SBP was reduced by 15.6 mmHg and 17.9 mmHg in the telmisartan 40 and 80 mg arms after 6 weeks, respectively. This lowering was similar to that of 15.7 mmHg recorded with HCTZ 12.5 mg. However, significantly more patients achieved the target reduction in SBP (<140 mmHg or >20 mmHg reduction) with telmisartan 80 mg than with HCTZ 12.5 mg ($P = 0.03$).

Combination treatment in difficult-to-treat patients and high-risk populations

Blood pressure in some patients is ineffectively controlled with monotherapy, and they require a combination of antihypertensive agents to achieve target blood pressure. The combination of telmisartan and HCTZ has been shown to provide greater reductions in blood pressure than either component alone. After a 4-week, placebo run-in period, patients were randomized to receive placebo, telmisartan 20, 40, 80 or 160 mg/day, HCTZ 6.25, 12.5 or 25 mg/day, or one of 12 combinations of the two agents in a trial involving 818 patients with mild-to-moderate hypertension.[56] The analysis focused on two combinations: telmisartan 40 mg/HCTZ 12.5 mg and telmisartan 80 mg/HCTZ 12.5 mg. After 8 weeks, telmisartan 80 mg/HCTZ 12.5 mg significantly reduced mean supine trough blood pressures by 23.9/14.9 mmHg compared with placebo, which represented a 8.5/3.4 mm Hg greater decrease than that achieved with telmisartan 80 mg alone and a 17.0/7.7 mmHg greater decrease than HCTZ 12.5 mg alone (both $P < 0.01$). There was a significant reduction in SBP of 18.8 mmHg with telmisartan 40 mg/HCTZ 12.5 mg compared with placebo, and this decrease was significantly greater than that achieved with either monotherapy.

Data from two studies evaluating the combination of telmisartan and HCTZ showed that it produced significantly greater SBP and DBP reductions in the last 6 hours of the dosing interval compared with losartan/HCTZ.[59] Two studies of identical design have also shown that the fixed-dose combination of telmisartan 80 mg/HCTZ 25 mg lowered trough blood pressure to a greater extent than valsartan 160 mg/HCTZ 25 mg in patients with stages 1 and 2 hypertension.[60,61] In a comparison of telmisartan 80 mg/HCTZ 12.5 mg with olmesartan 20 mg/HCTZ 12.5 mg, the telmisartan/HCTZ

combination gave a greater reduction in 24-h blood pressure, and this difference was also seen in daytime and night-time blood pressure values.[62]

There have been several studies that have investigated the combination of telmisartan and HCTZ in patients whose blood pressure is not adequately controlled by telmisartan alone. In one such study, patients whose DBP remained above 90 mmHg after 8 weeks of treatment with telmisartan 80 mg were randomized to telmisartan 80 mg or telmisartan 80 mg/HCTZ 12.5 mg for a further 8 weeks.[63] Greater reductions in blood pressure were achieved with the combination, such that blood pressure had been normalized (defined as SBP < 140 mmHg and DBP < 90 mmHg) in 41.5% of patients receiving the combination versus 26.1% of patients receiving monotherapy.

Patients who are at a particular risk of cardiovascular disease include those who are obese or have type 2 diabetes. It often proves especially difficult to achieve the rigorous control of blood pressure required in these patients. Superior blood pressure lowering of telmisartan 80 mg plus HCTZ 12.5 mg, compared with valsartan 160 mg/HCTZ 12.5 mg over 24 hours and during the early morning hours was demonstrated in the Study of MICARDIS® on Obese/Overweight Type 2 diabetics with Hypertension (SMOOTH®).[64]

The elderly, another group in which it can be difficult to achieve satisfactory blood pressure control, were recruited into ATHOS® (A comparison of Telmisartan plus HCTZ with amlodipine plus HCTZ in Older patients with predominantly Systolic hypertension). In 1000 patients (≥60 years) with isolated systolic hypertension, telmisartan 40 to 80 mg plus HCTZ 12.5 mg was compared with amlodipine 5 to 10 mg plus HCTZ 12.5 mg.[65] Although there was no significant difference between the two groups in the change from baseline in SBP during the last 6 hours of the dosing interval (which was the primary end point), telmisartan/HCTZ resulted in significantly greater reductions in 24-hours, morning and daytime SBP than amlodipine/HCTZ. The ATHOS study indicates that the combination of telmisartan plus HCTZ provides effective blood pressure control in elderly patients.

A common finding of these studies was that the placebo-like tolerability profile of telmisartan was maintained when it was given in combination with HCTZ. In an analysis of 50 trials involving 16,416 patients, the overall incidence of adverse events was low and similar between telmisartan monotherapy and the telmisartan/HCTZ combination.[66]

The combination of telmisartan and amlodipine has also been demonstrated to provide more powerful reductions in blood pressure than monotherapy with either telmisartan or amlodipine.[67] In a factorial design study, patients with stage 1 or 2 hypertension received placebo, telmisartan (20 to 80 mg), amlodipine (2.5 to 10 mg) or a combination of the two agents. The reductions in the in-clinic DBP and SBP observed with the combinations of most clinical interest (40 or 80 mg plus amlodipine 5 or 10 mg) were all significant. The greatest overall reductions (−26.4/−20.1 mmHg) were achieved with the telmisartan 80 mg/amlodipine 10 mg combination. This was also associated with the greatest response rates and blood pressure control. In the study, the treatments were well tolerated and, notably, the high incidence of edema with amlodipine 10 mg monotherapy (17.8%) was reduced by 37% to 65% when telmisartan was used in combination.[68] Therefore, the combination of telmisartan and amlodipine represents a treatment option that delivers large reductions in blood pressure and thereby likely reducing the risk of cardiovascular events.

Cardiovascular protective effects of telmisartan

The concept of the cardiovascular and renal continua was introduced to explain the pathologic processes connecting risk factors to clinical events of increasing severity and ultimately resulting in end-organ damage and death (Figure 2). Hypertension is one such risk factor. There is a large body of evidence, from ex vivo and in vivo studies to demonstrate that modulation of the RAS with ARBs and ACE inhibitors interferes with several of the pathophysiological mechanisms that lead to target organ damage (TOD), which, if uncontrolled, can be life-threatening.

The cardioprotective properties of ARBs have yet to be determined for all agents in this class and direct comparisons on the effects of ARBs on target organ protection are sparse. Furthermore, within-class comparisons are made difficult given that cardiovascular outcome studies of ARBs have been conducted in very different patient populations, ranging from low risk patients with hypertension (eg, the Losartan Intervention For Endpoint reduction in hypertension [LIFE][69] and Valsartan Antihypertensive Long-term Use Evaluation [VALUE][70] trials) through to patients with severe underlying cardiovascular disease (eg, the Valsartan Heart Failure Trial [ValHeFT],[71] Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity [CHARM] trial,[72] and Valsartan in Acute Myocardial Infarction Trial [VALIANT]).[73]

Current evidence focusing on telmisartan suggest that pleiotropic effects manifest as improvements in endothelial
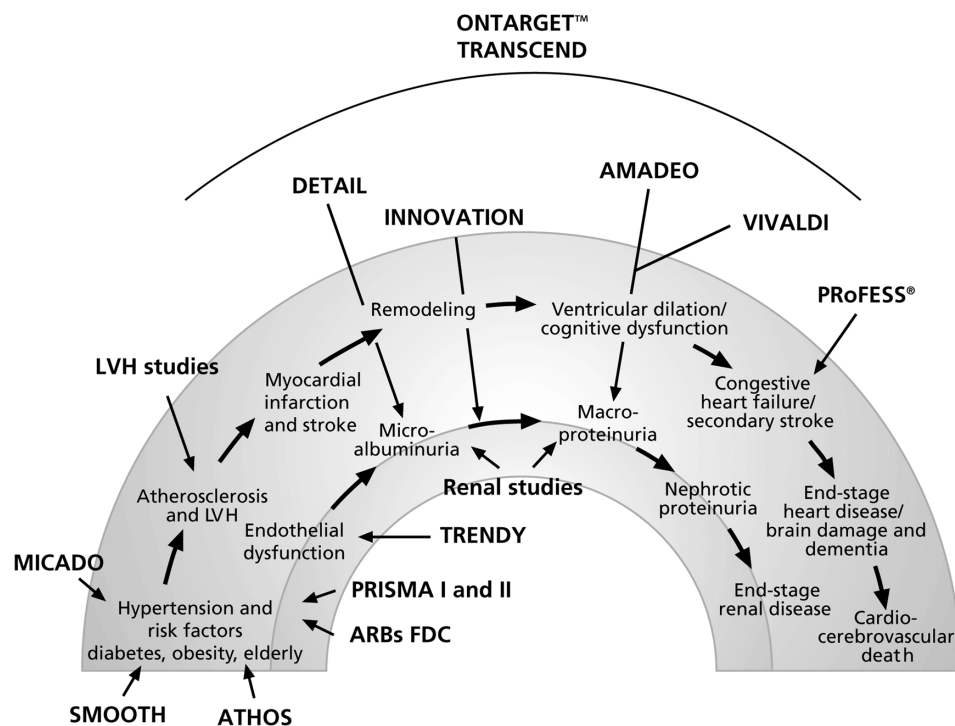
Figure 2 The cardiovascular and renal continua of disease and studies evaluating the efficacy of telmisartan.
Abbreviations: ARB, angiotension II receptor blocker; FDC, fixed-dose combination; LVH, left ventricular hypertrophy.

dysfunction, reductions in LVH, renoprotection in normotensive and hypertensive subjects, improvements in metabolic parameters, and potential benefits in cerebrovascular disease, as discussed below.

Telmisartan and endothelial function

One mechanism by which telmisartan may prevent TOD is by reducing or reversing endothelial dysfunction, which is one of the first signs of vascular damage and is partly driven by oxidative stress.[74] Telmisartan reduced superoxide production, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity, and markers of oxidative stress in apolipoprotein E-deficient mice.[75] In addition, telmisartan decreased the size of atherosclerotic lesions.[75] In spontaneously hypertensive rats, telmisartan expression of NADPH oxidase is reduced and there was increased expression of endothelial nitric oxide synthase, which is likely to contribute to reduced oxidative stress.[76]

Oxidative stress also promotes the accumulation of advanced glycation end (AGE) products.[77] Together with their cell-surface receptor (RAGE), AGEs are a major cause of the microvascular damage that accompanies the hyperglycemia of diabetes. In cultured endothelial cells, telmisartan prevents angiotensin II-induced upregulation of RAGE expression.[78] Corroboration for this effect is provided by studies in telmisartan-treated spontaneously hypertensive rats in which the RAGE expression that would normally accompany intraocular age expression did not occur.[79]

Platelet-derived growth factor (PDGF) is a mitogen that is upregulated by oxidative stress and inflammatory stimuli.[80] It is known to be produced by smooth muscle cells and is one of the most potent growth factors that is involved in the progression of macroangiopathy as seen in diabetes. Telmisartan has been shown to reduce angiotensin II-induced oxidative stress and thereby suppressed the expression of PDGF-B in cultured bovine retinal pericytes.[81,82]

Clinical evidence for improvements in endothelial function with telmisartan is provided by the Telmisartan versus Ramipril in renal ENdothelial DYsfunction (TRENDY®) study.[83] Both telmisartan 40 mg and ramipril 5 mg improved endothelial function, assessed by measuring renal plasma flow in response to the infusion of N^G-monomethyl-l-arginine acetate (l-NMMA), in patients with mild-to-moderate hypertension and normo- or microalbuminuria. Another measure of endothelial function, brachial artery flow-mediated dilation, was improved by 36% by ramipril 2.5 mg, 96% by telmisartan 40 mg, and by 111% with the combination in nonhypertensive patients with well-controlled type 2 diabetes mellitus, but without coronary artery disease, left ventricular dysfunction, or microalbuminuria.[84]

Telmisartan and arterial stiffness

Arterial stiffness is an important risk factor for cardiovascular mortality[85] and is increased on acute infusion of angiotensin II.[86] Prior administration of telmisartan significantly attenuated this acute response, as indicated by changes in systemic vascular resistance and the pulse wave stiffness index.[87] Furthermore, in patients with type 2 diabetes and mild-to-moderate hypertension, telmisartan 40 mg for 3 weeks reduced arterial stiffness measured by pulse wave velocity along the carotid–femoral route.[88] Another study in patients with hypertension suggests that the improvement in pulse wave velocity is greater than predicted on the basis of blood pressure changes.[89]

Metabolic effects of telmisartan

Vascular risk factors of hypertension, hyperglycemia, and atherogenic dyslipidemia are prevalent abnormalities in subjects with type 2 diabetes. Diabetes increases cardiovascular risk to the same extent as a prior myocardial infarction (MI) in a nondiabetic subject.[90]

Studies in hypertensive patients have shown consistently that telmisartan improves insulin sensitivity and lipid profiles. For example, in patients with type 2 diabetes (managed with diet and exercise) and mild hypertension, telmisartan 40 mg was significantly more effective than eprosartan 600 mg in reducing low-density lipoprotein (LDL)-cholesterol, total cholesterol, and triglycerides.[39] In another study conducted in patients with type 2 diabetes treated with oral hypoglycemics, telmisartan 40 mg produced significantly greater reductions than nifedipine GITS 20 mg in LDL-cholesterol and total cholesterol.[55] The effects of telmisartan on lipid parameters have been also been observed in smaller study[91] and in a post-marketing surveillance study in which people with and without diabetes were treated with telmisartan 40 to 80 mg for at least 1 year.[92] In the latter study, triglycerides were reduced by 17.4 mg/dL and cholesterol by 16.4 mg/dL in the population as a whole and were 22.7 mg/dL and 23.8 mg/dL, respectively, in patients with hypercholesterolemia. Among patients with diabetes, the reductions were 22.7 mg/dL and 17.4 mg/dL, respectively.

Telmisartan has been demonstrated to improve markers of glycemic control, such as glycosylated hemoglobin[93,94] and insulin[91] in patients with type 2 diabetes. Reductions in insulin resistance with telmisartan have also been demonstrated in nondiabetic subjects.[95,96] Moreover, telmisartan 80 mg lowered insulin resistance, as measured by the homeostasis model assessment method, to a significantly greater extent than losartan 50 mg in hypertensive patients with metabolic syndrome.[97] Free plasma glucose, glycosylated hemoglobin and response to the oral glucose tolerance test were also significantly improved by telmisartan.

Telmisartan in renal impairment

The progression of renal disease can be halted by RAS blockade mediated through reductions in glomerular pressure and through decreased inflammation and oxidative stress. Evidence for the renoprotective effect of telmisartan comes from studies that together have demonstrated positive benefits on renal function in the renal continuum from endothelial dysfunction through to reductions in macroalbuminuria.

In the TRENDY® study, telmisartan not only improved renal endothelial function in patients with type 2 diabetes but also preserved renal function.[83] In comparison with ramipril, telmisartan significantly improved resting renal plasma flow, renal vascular resistance, and lowered albuminuria.

The Diabetics Exposed to Telmisartan And enalaprIL (DETAIL®) study showed the long-term benefit of telmisartan in patients with type 2 diabetes and either micro- or macro-albuminuria.[98] Glomerular filtration rate (GFR) declined in the first year with both treatments, but this effect has also been observed with ACE inhibitors and other ARBs, and has been attributed to a hemodynamic effect.[99,100] Thereafter, the rate of decline was markedly reduced, such that by year 3, the annual decline in GFR had stabilized to approximately 2 mL/min/1.73 m^2, which is substantially lower than the 10 to 12 mL/min/1.73 m^2 that is typical in untreated diabetics with macroalbuminuria.[101]

Telmisartan has also been shown to reduce albuminuria compared with HCTZ in nondiabetic patients with isolated systolic hypertension[102] and to reduce microalbuminuria by 69% over the course of a 12-month, noncomparative study in hypertensive patients.[103] Other studies confirmed that telmisartan reduced macroalbuminuria in patients with mild and moderate renal failure.[104,105] The effects of telmisartan on proteinuria may well be additive to those of ACE inhibitors.[106]

Several large-scale clinical studies have been completed that demonstrate the beneficial effects of telmisartan on renal function. The Incipient to Overt: Angiotensin II Blocker, Telmisartan, Investigation on Type 2 Diabetic Nephropathy (INNOVATION®) study was performed in normotensive, as well as in hypertensive, Japanese patients.[107] Over a mean of 1.3 years' treatment, both telmisartan 40 and 80 mg significantly reduced transition rates to overt nephropathy in comparison with placebo. Reduced transition rates to overt nephropathy remained after adjustment for changes in SBP

and in normotensive patients, suggesting telmisartan had a blood pressure-independent effect.

The sister studies, 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 (AMADEO™), and inVestigate the efficacy of MICARDIS® versus VALsartan in hypertensive type 2 DIabetic patients with overt nephropathy (VIVALDI®) evaluated the effect of telmisartan on macroalbuminuria. In AMADEO™, telmisartan reduced urinary protein:creatinine significantly more than losartan after 52 weeks (29% versus 20% from baseline, respectively; $P = 0.03$), despite similar blood pressure control.[108] This suggests that there are intra-class difference in the renal effects of ARBs, which is consistent with additional properties beyond the blood pressure-lowering effect. In VIVALDI®, telmisartan 80 mg provided identical reductions in urinary protein excretion (33% from baseline) to valsartan 160 mg and there were no significant differences between the two agents in serum creatinine, creatinine clearance, or estimated GFR changes.[109] These studies suggest that telmisartan may slow the progression of diabetic nephropathy in this group of patients.

Cardiac disease

The presence of LVH in patients with established hypertension nearly triples the incidence of coronary heart disease and stroke, and increases the incidence of heart failure about seven-fold.[110] Reducing LVM significantly reduces cardiovascular risk.[111] Angiotensin II plays a central role in cardiac hypertrophy, causing a trophic response to increased blood pressure and having direct proliferative effects.[112] The clinical evidence that telmisartan reduces LVM comes from several studies. For example, telmisartan reduced LVM from 151.6 to 135.1 g/m^2, largely due to decreased thickness of the left ventricular wall, in hypertensive patients.[113] Telmisartan has been compared with other antihypertensives, including diuretics, β-blockers, ACE inhibitors, and other ARBs. Telmisartan 80 mg proved superior to HCTZ 25 mg, with the reduction in LVM being significantly greater with telmisartan for a given percentage change in blood pressure.[57] Telmisartan 80 mg was more effective in reducing LVM than carvedilol 25 mg, despite there being no significant difference in 24-hour mean SBP/DBP reductions between the two treatments.[53] Addition of telmisartan 80 mg to ramipril 5 mg provided further beneficial effects on LVM, although there were similar reductions in blood pressure with either monotherapy or combination.[114]

A 12-week study showed that replacing twice-daily enalapril 10 mg with once-daily telmisartan 10 to 80 mg does not produce any acute deterioration of exercise capacity or clinical status in patients with mild-to-moderate congestive heart failure (CHF) (New York Heart Association [NYHA] Class II or III and left ventricular ejection fraction ≤40%).[115] The study also found no differences in changes of other parameters, such as ejection fraction, NYHA classification, and mean SBP between the treatment groups.

Atrial fibrillation

ARBs and ACE inhibitors have been shown to be effective in preventing atrial fibrillation in patients with heart failure or left ventricular dysfunction, as seen in the meta-analysis by Healey and colleagues.[116] The RAS plays an important role facilitating new onset or recurrence of atrial fibrillation. It mediates atrial remodeling by increasing blood pressure, intracavitary atrial pressure, and arrhythmogenic atrial remodeling, by facilitating coronary atherosclerosis and by increasing reactive oxygen substances and favoring atrial fibrosis. Blocking the RAS may prevent left atrial dilatation, atrial fibrosis, dysfunction, and conduction velocity slowing.

There are different clinical scenarios involving prevention of atrial fibrillation in the hypertensive patient (ie, those who have not had any previous episodes of atrial fibrillation, and those with parossistic or persistent atrial fibrillation who either do not need any anti-arrhythmic therapy, or those with persistent atrial fibrillation who do require anti-arrhythmic therapy to maintain sinus rhythm following cardioversion). Previous studies suggest that inhibition of RAS with ARBs or ACE inhibitors may prevent new onset atrial fibrillation in patients without any previous episodes of atrial fibrillation,[117] and recurrence after cardioversion in hypertensive patients requiring antiarrhythmic therapy.[118] Previously, we investigated whether telmisartan prevented the recurrence of atrial fibrillation in hypertensive patients who did not require antiarrhythmic therapy. We compared the efficacy of telmisartan and carvedilol in preventing the recurrence of atrial fibrillation in 154 hypertensive patients with a recent history of atrial fibrillation.[119] There was an atrial fibrillation episode in 14.2% (10/70) of patients who received telmisartan compared with 37% (23/62) of those receiving carvedilol ($P < 0.005$). In addition to preventing recurrence of atrial fibrillation, the time to a recurrence of atrial fibrillation was longer with telmisartan than with carvedilol. This difference in the rates of new episodes of atrial fibrillation between the agents was not related to changes in blood pressure, left atrial

size, although a greater left ventricular mass reduction in the telmisartan group was observed. This suggests preventive properties of telmisartan were a pharmacologic effect. It is possible that telmisartan favorably interferes with electrical and structural atrial remodeling in hypertensive patients.

Cerebrovascular disease

For each 2 mmHg increase in SBP, the risk of stroke is increased by 10%.[45] Angiotensin II pathways appear not only to be implicated in blood pressure control and body fluid homeostasis, but may also contribute to the pathogenesis of stroke via the stimulation of AT_1 receptors.[120] The use of ARBs may not only prevent the ischemic effect of angiotensin II mediated via AT_1 receptors, but also stimulate the unoccupied AT_2 receptors with a consequent improvement of brain ischemia. Intra-cerebroventricular infusion of an ARB for 5 days has been shown to induce neuronal regrowth after cerebral ischemia and to reduce expression of transcription factors c-Fos and c-Jun that are associated with programmed cell death and neurodegeneration.[121] To date, evidence of possible beneficial effects of telmisartan on cerebrovascular disease are provided by studies in animals.

In rats, telmisartan is able to cross the blood–brain barrier and block the effects of centrally administered angiotensin II.[122] Furthermore, at doses that had no effect on blood pressure, telmisartan delayed the onset of stroke in spontaneously hypertensive, stroke-prone animals.[123] In cerebral arterioles, telmisartan reversed the vasoconstrictor effect of angiotensin II, changing the response to a vasodilatory one[124] and overcame the cerebral arterial remodeling occurring in spontaneously hypertensive rats.[125]

Although the effect of telmisartan on stroke has yet to be demonstrated in clinical studies, the effects of telmisartan on cognitive function have been examined in elderly subjects with hypertension.[126] In addition to providing superior blood pressure control compared with lisinopril 20 mg plus HCTZ, telmisartan 80 mg given with HCTZ 12.5 mg improved performance on cognitive tests significantly more than lisinopril/HCTZ.

Telmisartan outcome trials

The ONTARGET® program consists of two long-term, large-scale, double-blind, multinational outcome studies – the ONTARGET® study[50] and the parallel Telmisartan Randomized AssessmeNt Study in aCE iNtolerant subjects with cardiovascular Disease (TRANSCEND®) study.[127]

The ONTARGET® study compared telmisartan 80 mg monotherapy to ramipril 10 mg monotherapy and the combination to ramipril alone. The primary endpoint was a composite of cardiovascular mortality, nonfatal MI, nonfatal stroke, and hospitalization for CHF. Secondary endpoints included newly diagnosed CHF, cardiovascular revascularization, newly diagnosed diabetes, cognitive decline/dementia, new onset of atrial fibrillation, and nephropathy. ONTARGET® was conducted in patients who could tolerate ACE inhibitor therapy, whereas TRANSCEND® compared telmisartan with placebo in addition to best standard of care in patients intolerant of this class using the same endpoints as ONTARGET®.

In the ONTARGET® study, the primary outcome occurred in 1423 patients (16.7%) in the telmisartan group, 1412 patients (16.5%) in the ramipril group, and in 1386 (16.3%) in the combination-therapy group.[50] Telmisartan was non-inferior to ramipril, and the combination offered no additional protective effect. The results for the secondary outcome of death from cardiovascular causes, myocardial infarction or stroke were consistent with those of the primary outcome.

Even though individuals who were intolerant to ACE inhibitors had been excluded from the trial, 360 patients in the ramipril group stopped their medication because of cough compared with only 93 patients in the telmisartan group. Angioedema resulted in 25 patients discontinuing ramipril compared with 10 patients in the telmisartan group. Rates of cough and angioedema were also higher in the combination group than in the telmisartan group. In the combination group, significantly more patients stopped because of hypotensive symptoms, diarrhea, or renal impairment than in the ramipril group. The incidence of these events was also numerically higher than in the telmisartan group, although no statistics were reported for this comparison.

On the basis of the ONTARGET® results, telmisartan is the only ARB proven to have cardiovascular protective effects in a broad cross section of high-risk patients. It is as effective as ramipril but is associated with less angioedema and cough. The combination offers no additional efficacy advantage compared with the monotherapies. As the authors of the ONTARGET® publication state, the choice between telmisartan and ramipril 'will depend on the preferences of the patients and physicians and the individual's susceptibility to specific adverse events'.

In the TRANSCEND® study, telmisartan was well tolerated among patients who were unable to tolerate ACE inhibitors. Although the reduction in the primary outcome (which included hospitalizations for heart failure) with telmisartan did not achieve statistical significance, it did

significantly reduce the risk of the composite outcome of cardiovascular death, myocardial infarction, or stroke by 13%.[127] Moreover, adherence to telmisartan was high and better in the comparison arm, in which patients received the best standard of care. It is reasonable to assume that the greater tolerability and treatment adherence observed with telmisartan in both ONTARGET® and TRANSCEND® will be of benefit for many patients who are likely to require life-long treatment.

The potential cerebroprotective efficacy of telmisartan was evaluated in the Prevention Regimen For Effectively avoiding Second Strokes (PRoFESS®) study.[128] The 4-year study compared telmisartan and placebo on top of usual care, including antihypertensives to control blood pressure, in 20,000 patients with known prior ischemic stroke. The study had a 2×2 factorial design, with patients also receiving either aspirin plus dipyridamole extended release or clopidogrel alone. The primary outcome was time to recurrent stroke, while secondary outcomes included the onset of vascular events including bleeding events or CHF. There was non significant trend favoring telmisartan over usual care for the primary endpoint.[129] Exploratory analyses indicate that after excluding the first 6 months of treatment, the incidence of recurrent stroke or major vascular events was significantly lower with telmisartan. The mean treatment period was 2.5 years and a longer treatment period may have allowed the trends that were observed to become significant.

Conclusions

The pharmacologic features of telmisartan enable it to provide greater and more sustained antihypertensive efficacy than many other antihypertensive agents, and compared with other antihypertensive in other classes, telmisartan is well tolerated. Telmisartan in combination with HCTZ or amlodipine provides greater reductions in blood pressure than the respective monotherapies, and these combinations are well tolerated. The antihypertensive efficacy of telmisartan monotherapy and combinations should translate into increased protection against cardiovascular events. There is also growing evidence that telmisartan and ARBs have beneficial effects on various stages of the cardiovascular and renal continua that may not be solely explained by the lowering of blood pressure. ONTARGET® has shown that telmisartan provides similar cardiovascular protection to ramipril in high-risk patients, while being better tolerated and associated with greater treatment adherence; the latter property is likely to be important in the long-term management of cardiovascular risk.

The attributes of telmisartan and the clinical evidence of its efficacy suggest that it should be one of the preferred options for the treatment of hypertension in mild to moderate hypertensive patients and make it an attractive foundation for use in combination therapy. The findings of both ONTARGET® and TRANSCEND® demonstrate that telmisartan provides a protective benefit when added to other therapies. Its effect on cardiovascular endpoints combined with its proven tolerability suggest that telmisartan could be considered as a potential treatment for patients with vascular disease or high-risk diabetes, irrespective of whether or not they can tolerate ACE inhibitors.

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Disclosures

The authors disclose no conflicts of interest.

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