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## Effects of telmisartan on arterial stiffness in Type 2 diabetes patients with essential hypertension

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### Abstract

Arterial wall stiffness, an important independent risk factor for cardiovascular disease in patients with hypertension, is worsened by the coexistence of diabetes mellitus. This randomised, prospective, double-blind, crossover trial assessed the effects of telmisartan on arterial stiffness in patients with Type 2 diabetes with essential hypertension. After a two-week placebo wash out period, 28 ambulatory patients received telmisartan (40 mg) or placebo for three weeks. Following a second two-week placebo wash out period, patients received the alternate treatment for a further three weeks. Augmentation index and central blood pressure (BP) were determined using the SphygmoCor™ device and pulse wave velocity (PWV) was measured using an automatic device, the Complior™, at the beginning and the end of each period. Telmisartan significantly reduced the carotid–femoral PWV compared with placebo (mean adjusted treatment difference  $-0.95$  m/s; 95% CI:  $-1.67$ ,  $-0.23$  m/s;  $p=0.013$ ). Peripheral and central diastolic, systolic and pulse pressures were also significantly reduced with telmisartan compared with placebo. In conclusion, telmisartan reduces arterial stiffness and peripheral and central BPs as assessed by PWV and pulse contour analysis in hypertensive patients with Type 2 diabetes. These properties of telmisartan suggest that it may improve cardiovascular outcome in this patient population.

### Introduction

Cardiovascular disease is two to three times more common among patients with Type 2 diabetes mellitus than in the general population and it is a major contributor to their increased morbidity and mortality.<sup>1</sup> Hypertension is one of the modifiable risk factors for cardiovascular disease and effective control of blood pressure (BP) in diabetic patients with hypertension can markedly reduce the incidence of cardiovascular events and mortality in this population.<sup>1–3</sup>

Arterial stiffness is an independent risk factor for cardiovascular mortality in hypertensive patients;<sup>3</sup> it is associated with atherosclerosis and is exacerbated in Type 2 diabetes.<sup>4</sup> With vascular stiffening, pulse wave velocity (PWV) increases and the pressure wave characteristics change. This causes the reflected wave to arrive earlier during systole, thus augmenting central systolic BP (SBP) with a consequential increase in pulse pressure

(PP). Such changes are difficult to detect using only conventional sphygmomanometry at the level of the peripheral arteries.<sup>5</sup> In this regard, PWV measurement is widely used as an index of arterial stiffness<sup>4</sup> and pulse wave contour analysis (PWA) is used to calculate central pressures, augmentation and the augmentation index.<sup>6</sup>

Peripheral BP can be reduced by a variety of antihypertensives, but these drugs vary in their effects on the arterial wall. Some  $\beta$ -blockers, for example, do not improve central pressures acutely and are less effective in reducing stiffness than other antihypertensive drugs.<sup>7,8</sup> Angiotensin-converting enzyme inhibitors (ACE-I) can reduce arterial stiffness (as assessed by augmentation index) beyond that expected for BP-lowering alone.<sup>9</sup> The improvements in arterial stiffness observed with ACE-Is may in part be due to direct effects on the arterial wall mediated by angiotensin II (Ang II) acting at its AT<sub>1</sub>-receptor.<sup>10</sup>

Angiotensin receptor blockers (ARB) prevent the binding of Ang II to the AT<sub>1</sub>-receptor, providing a more profound blockade of the renin–angiotensin system than ACE-Is. Therefore, this class may be particularly effective in reducing arterial stiffness and central BP. Telmisartan is an ARB that provides effective 24-hour BP control with once-daily dosing and is well tolerated.<sup>11–18</sup> The aim of this study was to assess the effect of telmisartan on arterial stiffness and central BP in patients with Type 2 diabetes mellitus and hypertension.

### Materials and methods

#### Study design

This was a prospective, double-blind, randomised, placebo-controlled, three-week crossover study with an intermediate placebo period. Following a two-week placebo run-in period, eligible patients underwent baseline assessments and were randomised in a 1:1 ratio to take either telmisartan (40 mg) or placebo once-daily for three weeks. At the end of a second two-week placebo wash out period, patients returned to the clinic for repeat baseline assessments and commencement of the second three-week treatment period taking the alternate study drug. Assessments were repeated at the end of each treatment period. All patients gave written informed consent and the study protocol was approved by the appropriate ethics committee.

### Study population

Patients were aged  $\geq 30$  years and fulfilled the following inclusion criteria: mild-to-moderate essential hypertension (diastolic BP [DBP]  $\geq 85$  mmHg,  $\leq 110$  mmHg); Type 2 diabetes mellitus according to the World Health Organization (WHO) classification; HbA<sub>1C</sub>  $< 9.0\%$ ; any anti-diabetic therapy should have been stable for at least three months. The major exclusion criteria included the following: severe or secondary hypertension, body mass index  $< 22$  kg/m<sup>2</sup> or  $> 35$  kg/m<sup>2</sup>, severe renal or hepatic impairment, recent cardiovascular disorders, or concomitant use of insulin or medications known to affect BP.

### Study endpoints

The primary efficacy endpoint was the change from baseline in PWV over the carotid-femoral route. Secondary efficacy endpoints included the change from baseline of the following: PWV over the carotid-radial route; central or peripheral SBP, DBP and PP; augmentation index; first and second peak delay and subendocardial viability index.

### Clinical measurements

PWV was determined using an automatic device, the Complior™ (Artech Medical, Paris, France), which allows online pulse wave recording and automatic calculation of PWV.<sup>19</sup> Briefly, the pressure waveforms were recorded simultaneously using specific pressure-sensitive transducers. When the operator observed a pulse waveform of sufficient quality on the computer screen, digitisation was suspended, and calculation of the time delay (t) between the two pressure upstrokes initiated. Measurement was repeated over 12 seconds. The distance travelled by the pulse wave was measured over the body surface as the distance between the two recording sites (D); pulse transit time (t) was determined by the Complior™. PWV was automatically calculated as  $PWV = D/t$ . Validation of this method and its reproducibility have been reported previously.<sup>19</sup>

Pulse contour analysis and central BP measurements were performed using the SphygmoCor™ device (PWV, Sydney, Australia). The pressure wave was recorded at the radial artery using a handheld pencil probe based on applanation tonometry. For BP determinations, brachial and radial BPs were considered equivalent. The device allows calculation of central BP and analysis of the pulse contour with determination of the augmentation index, first and second peak delay and subendocardial viability index. Details of the procedure have been described elsewhere.<sup>20</sup>

### Statistical analysis

Analyses of efficacy were performed on the intention-to-treat (ITT) population, defined as all randomised subjects who had taken at least one dose of study medication. In order for a subject to be included in a particular efficacy analysis, it was necessary for them to have complete data from both treatment periods. The changes from baseline for the PWV and PWA measures and central and periph-

**Table 1** Patient baseline characteristics (intention-to-treat population).

	Telmisartan 40 mg/ placebo (n=13)	Placebo/ telmisartan 40 mg (n=14)	Total (n=27)
Age (years)	62.7 $\pm$ 6.8	62.3 $\pm$ 12.0	62.5 $\pm$ 9.7
Male, n (%)	11 (85)	8 (57)	19 (70)
BMI (kg/m <sup>2</sup> )	27.9 $\pm$ 3.6	28.7 $\pm$ 4.4	28.3 $\pm$ 4.0
Smoker or ex-smoker, n (%)	8 (62)	3 (21)	11 (41)
Alcohol usage, n (%)	8 (62)	2 (14)	10 (37)

Mean $\pm$ standard deviation; BMI: body mass index.

eral pressures were compared between treatments using an analysis of variance, taking into account variation due to subject, treatment period, appropriate baseline value and treatment. An estimate for the treatment difference, with a 95% confidence interval, was produced together with a corresponding p-value. With 24 evaluable subjects, the study was powered at 90% to detect at least a 0.75 m/s difference in the primary variable (PWV carotid-femoral route) between telmisartan and placebo. A test was conducted to assess the presence of carryover effects. Residual checks were performed to verify that the assumptions of the model had been satisfied.

## Results

### Patients

A total of 28 patients were randomised into the study, of which 27 were eligible to be included in the ITT population (13 patients received telmisartan followed by placebo and 14 received placebo followed by telmisartan). Baseline characteristics of the patients are summarised in Table 1. Baseline peripheral SBP/DBP was similar for both treatments (147.6/89.8 mmHg and 149.9/89.7 mmHg for telmisartan and placebo, respectively) as were the baseline central SBP/DBP (140.6/90.7 mmHg and 141.7/90.5 mmHg for telmisartan and placebo respectively). Baseline values for PWV and augmentation index are presented in Table 2.

### Arterial stiffness and pulse wave analysis

Following treatment for three weeks, telmisartan significantly reduced the PWV over the carotid-femoral route compared with placebo (Figure 1, Table 2). The mean adjusted treatment difference was  $-0.95$  m/s favouring telmisartan (95% CI:  $-1.67$ ,  $-0.23$  m/s;  $p=0.013$ ). Telmisartan also reduced the PWV over the carotid-radial route compared with placebo (Table 2), although the effect was less pronounced. The treatment difference approached statistical significance, with a mean adjusted value of  $-0.64$  m/s in favour of telmisartan (95% CI:  $-1.29$ ,  $0.01$  m/s;  $p=0.052$ ).

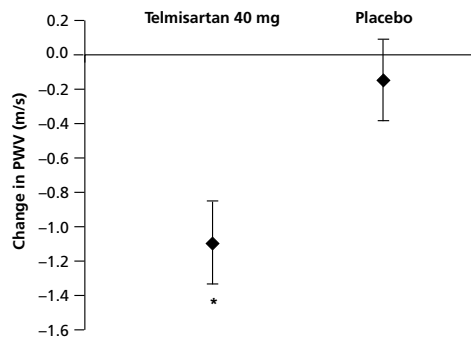
With regard to the augmentation index, although telmisartan provided a greater decrease from baseline when compared with placebo

**Table 2** Treatment effect on pulse wave velocity (PWV) and augmentation index (intention-to-treat population).

	Telmisartan 40 mg	Placebo
<b>Carotid–femoral PWV (m/s)</b>		
n	20	20
Baseline, mean±SD	12.53±2.50	13.07±1.84
Adjusted mean change from baseline (95% CI)	-1.096* (-1.596, -0.595)	-0.146 (-0.647, 0.355)
<b>Carotid–radial route PWV (m/s)</b>		
n	22	22
Baseline, mean±SD	10.35±1.77	10.83±1.38
Adjusted mean change from baseline (95% CI)	-0.804 (-1.254, -0.354)	-0.164 (-0.614, 0.287)
<b>Augmentation index (%)</b>		
n	23	23
Baseline, mean±SD	32.2±8.9	28.4±11.9
Adjusted mean change from baseline (95% CI)	-2.9 (-5.3, -0.4)	0.2 (-2.2, 2.7)

Telmisartan versus placebo \*p≤0.05.

**Figure 1** Adjusted mean changes from baseline (±SEM) in pulse wave velocity (PWV; carotid–femoral route) after three weeks of treatment with telmisartan 40 mg or placebo. \*p=0.013 (intention-to-treat population).



(Table 2), the mean adjusted treatment difference of -3.1% (95% CI: -6.6, 0.5%), did not achieve statistical significance (p=0.09). Results of the effect of telmisartan on other secondary pulse wave analyses (Table 3) were not significantly different from placebo.

**Blood pressure**

Compared with placebo, telmisartan produced significant decreases in central and peripheral DBP, SBP and PP (Figure 2, Table 4). Interestingly, the effect of telmisartan on BP in peripheral arteries was very similar to that seen in central arteries.

**Discussion**

Arterial stiffness increases with age<sup>21</sup> and is exacerbated by hypertension.<sup>22</sup> In patients with diabetes mellitus, arterial stiffness is accelerated and present even in the early stages of the disease.<sup>23-25</sup> Patients with diabetes also often have atherosclerosis and hypertension and are predisposed to cardiovascular disease.

An increase in arterial stiffness leads to an increase in PWV and to a decrease in the ability of the arteries to buffer the pressure wave. One consequence of this arterial alteration is an increase in the amplitude and early return of the reflected

**Table 3** Secondary variables from pulse wave analysis. Results are expressed as the mean change from baseline after three weeks on treatment (intention-to-treat population).

	Telmisartan 40 mg	Placebo
Ejection duration (%)	-8.3±13.4	-0.3±22
First peak delay (ms)	2.9±12.2	2.3±9.0
Second peak delay (ms)	-10.2±19.2	3.4±15.7
Subendocardial viability (%)	1.4±17.1	4.4±16.8

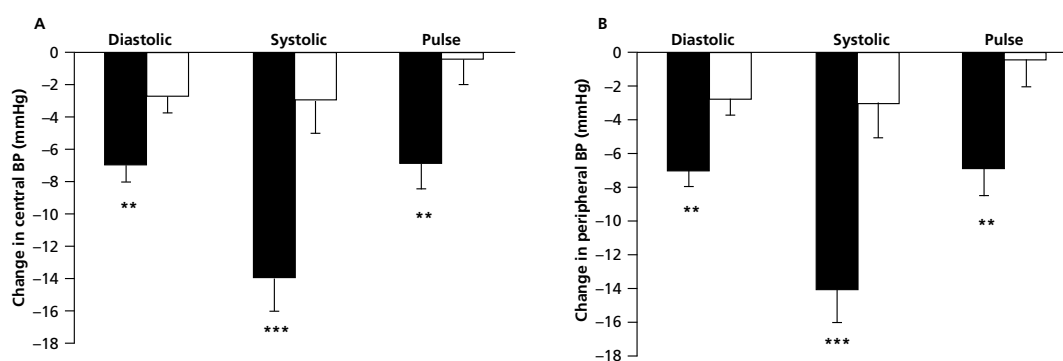
Mean change from baseline±SD.

pressure wave with augmentation of central SBP and PP. Increased SBP leads to left ventricular hypertrophy and is an important predictor of cardiovascular risk.<sup>26-28</sup> However, there is also increasing evidence that elevation of PP, rather than SBP or DBP alone, is an important independent predictor of cardiovascular risk.<sup>29-32</sup> Recently, Franklin<sup>33</sup> studied normotensive and untreated hypertensive patients over a 20-year period in a population-based cohort from the Framingham Heart Study. PP was found to be superior to DBP and SBP as a marker of both arterial stiffness and also the risk of coronary heart disease. These findings highlight the importance of arterial stiffness as a marker of cardiovascular disease.<sup>29,30</sup>

Direct evidence of the role of arterial stiffness in cardiovascular morbidity has been demonstrated by Blacher *et al.*,<sup>34</sup> and more recently by Laurent *et al.*,<sup>3</sup> who have shown that arterial stiffness, as evaluated by PWV, is an independent predictor of cardiovascular and all-cause mortality in hypertensive patients.

The results of the present study showed that PWV (carotid–femoral route) was significantly reduced after three weeks of treatment with telmisartan compared with placebo. Additionally, PWV measured via the carotid–radial route was also reduced by telmisartan and approached statistical significance over placebo. These findings may reflect the different physical characteristics of the two vessels: the aorta is relatively more

**Figure 2** Adjusted mean effects of telmisartan 40 mg (filled bars) compared with adjusted mean effects placebo (unfilled bars) on central (A) and peripheral (B) diastolic, systolic and pulse pressures (intention-to-treat population). Error bars show standard errors. Telmisartan 40 mg significantly reduced central and peripheral blood pressures (BPs) compared with placebo. \*\* $p \leq 0.01$ , \*\*\* $p \leq 0.001$ .



**Table 4** Treatment effect of telmisartan 40 mg compared with placebo on central and peripheral systolic (SBP), diastolic (DBP) and pulse pressures (PP) after three weeks (intention-to-treat population).

	SBP	DBP	PP
<b>Central blood pressure, (mmHg)</b>			
Adjusted mean difference	-11.0	-4.5	-6.4
95% CI	-16.8, -5.3	-7.6, -1.3	-10.8, -2.0
p-value	$p=0.001$	$p=0.008$	$p=0.006$
<b>Peripheral blood pressure, (mmHg)</b>			
Adjusted mean difference	-11.1	-4.3	-6.5
95% CI	-17.0, -5.1	-7.4, -1.3	-11.2, -1.8
p-value	$p=0.001$	$p=0.008$	$p=0.009$

$n=23$  for both telmisartan 40 mg and placebo groups.

elastic than the radial artery, which is more muscular, so treatment effects on arterial wall distensibility may be less obvious. The associated augmentation index, which indicates the effect of early wave reflection on central SBP, was also reduced by telmisartan, although this reduction did not reach statistical significance.

As expected, compared with placebo, telmisartan significantly reduced peripheral DBP and SBP. However, it is of interest to note that telmisartan also provided similar significant decreases in central BPs. The beneficial effect of peripheral DBP and SBP control in the prevention of cardiovascular events has been widely studied.<sup>35</sup> With regard to patients with diabetes mellitus, the Hypertension Optimal Treatment (HOT) study<sup>36</sup> demonstrated that intensive BP control was particularly beneficial in the diabetic subgroup. Similarly, the UK Prospective Diabetes Study (UKPDS)<sup>1</sup> showed that tight control of peripheral BP halved the incidence of stroke and heart failure.

Telmisartan also significantly reduced PP to a similar degree in both peripheral and central arteries. This is a notable finding, owing to the importance of PP as a cardiovascular risk factor. The pathophysiological consequences of widening PP result from effects in central rather than peripheral arteries. However, the importance of central pressures in this regard is not widely recognised

and treatment is targeted against peripheral BP.<sup>37</sup> Certainly, peripheral BP changes induced by some antihypertensive agents may be smaller than those achieved centrally,<sup>38</sup> and alone may not be fully representative of the beneficial effects of treatment on larger arteries. In this regard, the significant decreases in central as well as peripheral DBP, SBP and PP found with telmisartan are interesting and are not inconsistent with findings for some ACE-Is.<sup>39-41</sup> The possibilities represented by combining an ACE-I with an ARB are even more intriguing.<sup>42</sup>

In conclusion, assessment of PWV in conjunction with central PP can provide additional useful information on the efficacy of antihypertensive therapies, particularly since increased arterial stiffness and widening PP are associated with end-organ damage and are independent predictors of cardiovascular risk. An antihypertensive agent that can significantly reduce arterial stiffness and improve both central and peripheral PP may potentially provide greater beneficial effects on cardiovascular outcomes, beyond that seen with BP-lowering alone. Telmisartan reduced arterial stiffness, as indicated by carotid-femoral PWV, and significantly improved central and peripheral DBP, SBP and PP in hypertensive patients with Type 2 diabetes. Whether telmisartan can influence cardiovascular outcomes beyond BP control warrants further investigation in clinical studies.

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