ORIGINAL ARTICLE

A meta-analysis of randomized trials of telmisartan versus losartan for reduction of ambulatory blood pressure

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A previous meta-analysis of a few randomized controlled trials (RCTs) suggests a significant reduction in ambulatory blood pressure (BP) with telmisartan as compared with losartan monotherapy. We performed an updated meta-analysis of RCTs of telmisartan versus losartan therapy for reduction of ambulatory BP in patients with hypertension. MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials were searched through July 2012 using PubMed and OVID. Eligible studies were RCTs of telmisartan versus valsartan therapy enrolling individuals with hypertension and reporting ambulatory BP as an outcome. For each study, data regarding changes from baseline in ambulatory (24 h, last 6 h, morning, daytime and nighttime) BP in both the telmisartan and losartan groups were used to generate mean differences (MDs) and 95% confidence intervals (CIs). Of 34 potentially relevant articles screened initially, 9 reports of RCTs enrolling a total of 2409 patients with hypertension were identified and included. Pooled analysis suggested significant reductions in all of 24-h (MD of systolic/diastolic BP, $-2.09/-1.57$ mm Hg; 95% CI, $-3.39/-2.32$ to $-0.79/-0.82$ mm Hg), last 6-h ($-2.96/-2.15$ mm Hg; $-3.80/-2.72$ to $-2.13/-1.59$ mm Hg), morning ($-2.71/-2.37$ mm Hg; $-3.73/-3.33$ to $-1.69/-1.41$ mm Hg), daytime ($-1.74/-1.73$ mm Hg; $-3.27/-2.84$ to $-0.20/-0.62$ mm Hg) and nighttime BP ($-2.70/-2.08$ mm Hg; $-4.07/-3.24$ to $-1.33/-0.92$ mm Hg) among patients randomized to telmisartan versus losartan therapy. In conclusion, telmisartan therapy appears to reduce ambulatory BP more than losartan therapy in patients with hypertension.

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Keywords: ambulatory blood pressure; hypertension; losartan; meta-analysis; telmisartan

INTRODUCTION

In the most recent (2011) recommendations (updating the 2004 and 2006 clinical guidelines) from the NICE (National Institute for Health and Clinical Excellence) on the management of hypertension,¹ ambulatory blood pressure (BP) monitoring should be used to confirm the diagnosis of hypertension if the clinic BP is 140/90 mm Hg or higher. Further, for people identified as having a 'white coat effect' (that is, a discrepancy of more than 20/10 mm Hg between clinic and average daytime ambulatory BP (or average home BP) measurements at the time of diagnosis), ambulatory (or home) BP monitoring as an adjunct to clinic BP measurements should be considered to monitor the response to antihypertensive treatment with lifestyle modification or drugs.¹ Telmisartan is the longest acting angiotensin II type 1 receptor blocker currently available, and its mean elimination half-life is approximately 24 h in patients with mild-to-moderate hypertension who receive 20 to 160 mg per day telmisartan for 4 weeks.² Thus, telmisartan would be expected to reduce ambulatory BP more than the other angiotensin II type 1 receptor blockers. Indeed, a previous meta-analysis³ suggests a

significant reduction in ambulatory BP with telmisartan as compared with losartan (classified as shorter-acting) monotherapy. The results were, however, based on data pooled from a few randomized controlled trials (RCTs). Therefore, the appropriate role of telmisartan by comparison with losartan therapy on ambulatory BP in the hypertensive population remains unclear. We performed an updated meta-analysis of RCTs of telmisartan versus losartan therapy for reduction of ambulatory BP in patients with hypertension.

METHODS

Search strategy

All RCTs of telmisartan versus losartan therapy enrolling patients with hypertension and reporting ambulatory BP were identified using a two-level search strategy. First, public domain databases including MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials were searched using Web-based search engines (PubMed, OVID). Second, relevant studies were identified through a manual search of secondary sources including references of initially identified articles and a search of reviews and commentaries. All references were downloaded for consolidation, elimination of duplicates and

Table 1 Trial design and patient characteristics

Trial	Randomization		Patient (n)		Age (year)		Men (%)		Baseline clinic BP (mm Hg)				Definition in ambulatory BP monitoring			
	Telmisartan	Losartan	Telmisartan	Losartan	Telmisartan	Losartan	Telmisartan	Losartan	Systolic	Diastolic	Telmisartan	Losartan	Morning	Daytime	Nighttime	
Ding <i>et al.</i> ⁵	40 mg	50 mg	31	25	50.5±11.9	52.7±10.9	54.8	66.7	153.6±11.5	101.1±5.5	154.5±12.2	99.1±4.8	2000–2400	NA	1200–2400	
Fogari <i>et al.</i> ⁶	40 mg	50 mg	30		52±5		60		161.75±13.4	97.8±6.2			NA	0700–2300	2300–0700	
(Crossover design)																
Lacourcière <i>et al.</i> ⁷	40 mg	50 mg	195	196	54.0±8.9	54.2±9.7	61	60	153.8±12.9	98.8±5.5	155.4±12.0	99.5±5.1	NA	NA	NA	
+ 12.5 mg HCTZ																
	80 mg	12.5 mg	200		53.4±10.8		57		156.1±12.1	99.7±5.6						
HCTZ																
Mallion <i>et al.</i> ⁸	40 mg	50 mg	52	50	58	56	67	58	161.9±14.7	100.8±4.2	162.4±16.3	100.7±4.5	0600–1159	0600–2200	2201–0559	
HCTZ																
Masuda <i>et al.</i> ⁹	80 mg	50 mg	52		57		65		164.2±15.3	101.8±4.9			NA			
40 mg																
(Crossover design)																
	40 mg	50 mg	30		61.2±2.5 (s.e.)		60		≥130 (Inclusion criteria)	≥80 (Inclusion criteria)				Average period during which subjects were awake/upright	Average period during which subjects were asleep/supine	
Minami <i>et al.</i> ¹⁰	40 mg	50 mg	21		63.1±11.6		38.1		≥130 (Inclusion criteria)	≥85 (Inclusion criteria)			0600–0800	0600–2130	2200–0530	
+ 12.5 mg HCTZ																
Neutel <i>et al.</i> ¹¹	40 mg	50 mg	318	320	52.1±10.2	52.6±9.6	66.4	66.3	153.9±11.5	99.8±4.1	153.8±11.1	99.5±4.2	0600–1159	0600–2159	2200–0559	
+ 12.5 mg HCTZ																
	80 mg	50 mg	167		53.2±10.2		59.9		154.8±12.7	100.0±4.1						
+ 12.5 mg HCTZ																
Smith <i>et al.</i> ¹²	40/80 mg	50/100 mg	344	338	53.2±9.9	54.4±10.0	65.0	61.4	NA	95–109			0600–1159	0600–2159	2200–0559	
Vitale <i>et al.</i> ¹³	80 mg	50 mg	20	20	55.3±12.4	56.2±11.0	60	55	151.3±7.1	91.2±7.4	89.8±8.7	149.7±9.0	NA	0600–2259	2300–0559	

Abbreviations: BP, blood pressure; HCTZ, hydrochlorothiazide; NA, not available; s.e., standard error.

further analysis. The databases were searched through July 2012. Keywords included *ambulatory*, *24 hour*, or *24 h*; *telmisartan*; *losartan*; *randomized*, *randomised*, *randomly*, or *randomization*.

Study selection and data abstraction

Studies considered for inclusion met the following criteria: the design was a RCT (including a quasi-randomized crossover design study); the study population was patients with hypertension; patients were randomly assigned to telmisartan versus losartan therapy (not only monotherapy but also combination therapy); main outcomes included ambulatory BP; and the results were published in English-language peer-reviewed journals. Data regarding detailed inclusion criteria, duration of treatment, changes from baseline to final ambulatory BP were abstracted (as available) from each individual study.

Statistical analysis

We conducted a meta-analysis of summary statistics from the individual trials because detailed, patient-level data were not available for all trials. For each study, data regarding changes from baseline in ambulatory (24 h, last 6 h, morning, daytime and nighttime as defined by the authors of each individual study) BP in both the telmisartan and losartan groups were used to generate mean differences (MDs) and 95% confidence intervals (CIs). When a MD itself of BP changes in the two groups was reported, we directly extracted it with its 95% CI. Missing standard deviations were imputed according to the Cochrane Handbook.⁴ Study-specific estimates were combined in the random-effects model for its conservative summary estimate and incorporating both between and within study variance. All analyses were conducted using Review Manager version 5.1 (Nordic Cochrane Centre, Copenhagen, Denmark).

RESULTS

Of 34 potentially relevant papers screened initially, we excluded 9 non-original articles, 13 irrelevant-design studies and 3 duplicate publications. Nine reports of eligible RCTs^{5–13} of telmisartan versus losartan therapy enrolling a total of 2409 patients with hypertension and reporting ambulatory BP were identified and included (Table 1). Of these studies, six studies provided data on effectiveness for the comparison between telmisartan and losartan in monotherapy,^{5,6,8,9,12,13} and three studies compared these two agents in fixed-dose combination with 12.5 mg hydrochlorothiazide.^{7,10,11} Methodological quality of the trials by using the scoring system developed by Jadad *et al.*¹⁴ and adverse events are summarized in Tables 2 and 3, respectively.

Pooled analysis demonstrated a statistically significant reduction in changes (from baseline to final) of all of 24-h (MD of systolic BP, -2.09 mm Hg; 95% CI, -3.39 to -0.79 mm Hg; P for effect = 0.002; P for heterogeneity < 0.0001; Figure 1a; MD of diastolic BP, -1.57 mm Hg; 95% CI, -2.32 to -0.82 mm Hg; P for effect < 0.0001; P for heterogeneity = 0.004; Figure 1b), last 6-h (MD of systolic BP, -2.96 mm Hg; 95% CI, -3.80 to -2.13 mm Hg; P for effect < 0.00001; P for heterogeneity = 0.69; Figure 2a; MD of diastolic BP, -2.15 mm Hg; 95% CI, -2.72 to -1.59 mm Hg; P for effect < 0.00001; P for heterogeneity = 0.61; Figure 2b), morning (MD of systolic BP, -2.71 mm Hg; 95% CI, -3.73 to -1.69 mm Hg; P for effect < 0.00001; P for heterogeneity = 0.39; Figure 3a; MD of diastolic BP, -2.37 mm Hg; 95% CI, -3.33 to -1.41 mm Hg; P for effect < 0.00001; P for heterogeneity = 0.15; Figure 3b), daytime (MD of systolic BP, -1.74 mm Hg; 95% CI, -3.27 to -0.20 mm Hg; P for effect = 0.03; P for heterogeneity < 0.00001; Figure 4a; MD of diastolic BP, -1.73 mm Hg; 95% CI, -2.84 to -0.62 mm Hg; P for effect = 0.002; P for heterogeneity < 0.00001; Figure 4b) and nighttime BP (MD of systolic BP, -2.70 mm Hg; 95% CI, -4.07 to -1.33 mm Hg; P for effect = 0.0001; P for heterogeneity = 0.0003; Figure 5a; MD of diastolic BP, -2.08 mm Hg; 95% CI, -3.24 to

Table 2 Methodological quality of trials

Trial	Blinding						Quality score
	Allocation concealment	Participants	Investigators	Outcomes assessors	Lost to follow-up (%)	ITT	
Ding <i>et al.</i> ⁵	Unclear	Yes	Yes	Yes	Yes	8	4
Fogari <i>et al.</i> ⁶	Unclear	Yes	Yes	Yes	UA	0	3
Lacourcière <i>et al.</i> ⁷	Unclear	No	No	Yes	Yes	1	2
Mallion <i>et al.</i> ⁸	Unclear	Yes	Yes	Yes	Yes	8	4
Masuda <i>et al.</i> ⁹	Unclear	UA	UA	UA	UA	UA	0
Minami <i>et al.</i> ¹⁰	Unclear	UA	UA	UA	UA	0	1
Neutel <i>et al.</i> ¹¹	Unclear	No	No	Yes	UA	UA	1
Smith <i>et al.</i> ¹²	Unclear	Yes	Yes	Yes	Yes	NA	3
Vitale <i>et al.</i> ¹³	Adequate	Yes	Yes	Yes	UA	UA	3

Abbreviations: ITT, intention to treat analysis; NA, not available; UA, unable to assess.

Table 3 Adverse events and withdrawals

Trial	Telmisartan/losartan		
	Adverse events		
	Overall (%)	Drug related (n)	Withdrawals (n)
Ding <i>et al.</i> ⁵	12.9/13.3	3/3	0/1 ^a
Fogari <i>et al.</i> ⁶	NA	2/3	0/0
Lacourcière <i>et al.</i> ⁷	22 (18) ^b /14	10% (7%) ^b /5%	3 (2) ^b /1
Mallion <i>et al.</i> ⁸	NA	NA	1/5
Masuda <i>et al.</i> ⁹	NA	NA	NA
Minami <i>et al.</i> ¹⁰	0/0	0/0	1 ^c
Neutel <i>et al.</i> ¹¹	NA	4.4% (6.0%) ^b /2.8%	2.5% (0.6%) ^b /0.9%
Smith <i>et al.</i> ¹²	22.8 (20.2) ^b / 22.2 (23.3) ^d	NA	NA
Vitale <i>et al.</i> ¹³	0/0	0/0	NA

Abbreviation: NA, not available.

^aNot deemed to be treatment related.

^b40 mg (80 mg) telmisartan.

^cBecause of hospitalization for the treatment of chronic hepatitis C (unknown group).

^d50 mg (100 mg) losartan.

-0.92 mm Hg; P for effect = 0.0004; P for heterogeneity < 0.00001; Figure 5b) with telmisartan relative to losartan.

To assess the impact of qualitative heterogeneity in trial design and patient selection on the pooled effect estimate, we performed several sensitivity analyses for 24-h BP. First, we excluded three quasi-randomized crossover design studies;^{6,9,10} combining the remaining trials generated an amplified and still statistically significant result favoring telmisartan over losartan therapy for 24-h BP (MD of systolic BP, -2.49 mm Hg; 95% CI, -3.39 to -1.58 mm Hg; P < 0.00001; MD of diastolic BP, -1.96 mm Hg; 95% CI, -2.64 to -1.28 mm Hg; P < 0.00001) with no statistically significant heterogeneity (P = 0.23 for systolic BP; P = 0.09 for diastolic BP). Second, we excluded three low quality-score (0 or 1) studies.^{9–11} Without them, there was still a statistically significant benefit for telmisartan therapy over losartan therapy for 24 h BP in pooled analysis of the remaining trials (MD of systolic BP, -2.14 mm Hg;

Figure 1 Forest plot of 24-h systolic (a) and diastolic (b) blood pressure among patients with hypertension randomized to telmisartan versus losartan therapy. CI, confidence interval; IV, inverse variance. A full color version of this figure is available at the *Hypertension Research* journal online.

Figure 2 Forest plot of last 6-h systolic (a) and diastolic (b) blood pressure among patients with hypertension randomized to telmisartan versus losartan therapy. CI, confidence interval; IV, inverse variance. A full color version of this figure is available at the *Hypertension Research* journal online.

Figure 3 Forest plot of morning systolic (a) and diastolic (b) blood pressure among patients with hypertension randomized to telmisartan versus losartan therapy. CI, confidence interval; IV, inverse variance. A full color version of this figure is available at the *Hypertension Research* journal online.

Figure 4 Forest plot of daytime systolic (a) and diastolic (b) blood pressure among patients with hypertension randomized to telmisartan versus losartan therapy. CI, confidence interval; IV, inverse variance. A full color version of this figure is available at the *Hypertension Research* journal online.

95% CI, -3.84 to -0.45 mmHg; $P = 0.01$; MD of diastolic BP, -1.66 mmHg; 95% CI, -2.56 to -0.75 mmHg; $P = 0.0003$) with still statistically significant heterogeneity ($P = 0.0001$ for systolic BP; $P = 0.009$ for diastolic BP). Our additional search identified four RCTs¹⁵⁻¹⁸ of telmisartan versus valsartan therapy for the

reduction of ambulatory BP. Including these valsartan-control trials in the primary meta-analysis generated an attenuated and still statistically significant result favoring telmisartan over losartan or valsartan therapy for 24-h BP (MD of systolic BP, -1.73 mmHg; 95% CI, -2.94 to -0.52 mmHg; P for effect = 0.005, P for heterogeneity

Figure 5 Forest plot of nighttime systolic (a) and diastolic (b) blood pressure among patients with hypertension randomized to telmisartan versus losartan therapy. CI, confidence interval; IV, inverse variance. A full color version of this figure is available at the *Hypertension Research* journal online.

<0.00001 ; Figure 6a; MD of diastolic BP, -1.13 mm Hg; 95% CI, -2.09 to -0.17 mm Hg; P for effect = 0.02 , P for heterogeneity <0.00001 ; Figure 6b).

DISCUSSION

The results of our analysis suggest that telmisartan therapy may reduce ambulatory BP (by $2.09/1.57$ mm Hg for 24-h, $2.96/2.15$ mm Hg for last 6-h, $2.71/2.37$ mm Hg for morning, $1.74/1.73$ mm Hg for daytime and $2.70/2.08$ mm Hg for nighttime BP) relative to losartan therapy in patients with hypertension. A previous meta-analysis (indirect comparisons) including data from 1556 patients has demonstrated that 80 mg telmisartan exhibits the greatest efficacy, producing significantly ($P < 0.0125$) greater reductions in 24-h systolic BP (-12.4 mm Hg) than 50 mg losartan (-8.2 mm Hg), 80 mg valsartan (-8.9 mm Hg) or 40 mg telmisartan (-9.9 mm Hg), and in 24-h diastolic BP (-7.9 mm Hg) than 50 mg losartan (-5.1 mm Hg) or 80 mg valsartan (-5.5 mm Hg).¹⁹ A recent meta-analysis³ combining results of only three or four RCTs revealed a significant reduction in BP for the last 6-h (MD for systolic BP, -2.56 mm Hg; 95% CI, -4.02 to -1.10 mm Hg; $P = 0.0006$; MD for diastolic BP, -2.39 mm Hg; 95% CI, -4.13 to -0.66 mm Hg; $P = 0.007$), 24-h (MD for systolic BP, -2.47 mm Hg; 95% CI, -4.55 to -0.40 mm Hg; $P = 0.02$; MD for diastolic BP, -2.49 mm Hg; 95% CI, -4.42 to -0.56 mm Hg; $P = 0.01$), daytime (MD for systolic BP, -3.22 mm Hg; 95% CI, -5.11 to -1.34 mm Hg; $P = 0.0008$; MD for diastolic BP, -2.18 mm Hg; 95% CI, -3.78 to -0.57 mm Hg; $P = 0.008$) and nighttime periods (MD for systolic BP, -2.16 mm Hg; 95% CI, -4.27 to -0.06 mm Hg; $P = 0.04$; MD for diastolic BP, -2.24 mm Hg; 95% CI, -4.34 to -0.14 mm Hg; $P = 0.04$) with telmisartan in direct comparison with losartan. The present meta-analysis is more

comprehensive, including data on 2409 patients with hypertension randomized to therapy with telmisartan or losartan from nine trials. We recently performed the most exhaustive meta-analysis²⁰ of 50 RCTs (enrolling a total of 10 494 patients) of telmisartan versus other angiotensin II type 1 receptor blocker therapy for the reduction of 'clinic' (not 'ambulatory') BP. In its sub-analysis of 22 RCTs including 3983 patients, telmisartan therapy significantly reduced both systolic and diastolic 'clinic' BP over losartan therapy (MD for systolic BP, -3.17 mm Hg; 95% CI, -3.98 to -2.35 mm Hg; $P < 0.00001$; MD for diastolic BP, -1.83 mm Hg; 95% CI, -2.63 to -1.04 mm Hg; $P < 0.00001$). These results of our previous meta-analysis²⁰ for 'clinic' BP may strengthen the findings of the present meta-analysis for 'ambulatory' BP.

The circadian variation in BP, which occurs in most individuals, is well known, with a steep rise in BP during the early morning hours.²¹ This coincides with the time of day when there is an increase in the risk of cardiovascular events. The incidence of cardiovascular complications is directly related to the systolic BP on arising.²² Extrapolation of these observations would suggest that anti-hypertensive therapy should provide BP control throughout the dosing interval.¹² With a drug that is taken once daily in the morning, as telmisartan and losartan usually are, the end of the dosing interval is thus a critical period because it coincides with the period of increased cardiovascular vulnerability.²³ A drug that is more able to sustain its anti-hypertensive effect during the early morning period should, therefore, be advantageous and may confer protection against cardiovascular events.¹² Because the present meta-analysis did not evaluate the incidence of cardiovascular or cerebrovascular events and of mortality from such events, some caution should be needed in interpretation of the results.

Figure 6 Forest plot of 24-h systolic (a) and diastolic (b) blood pressure among patients with hypertension randomized to telmisartan versus losartan or valsartan therapy. CI, confidence interval; IV, inverse variance. A full color version of this figure is available at the *Hypertension Research* journal online.

The findings of our sensitivity analysis suggest that between-study heterogeneity may be due to quasi-randomized crossover design studies. In addition to the parallel group studies, the use of double-blind two-period or multiple period crossover designs can provide valid data for the dose finding of new antihypertensive drugs and their comparative evaluation.²⁴ One or more control times are supplied by each of the cases themselves, to control for confounding by constant characteristics and self-confounding between the trigger's acute and chronic effects.²⁵ Reports of crossover trials, however, frequently omit important methodological issues in design, analysis and presentation.²⁶ The CONSORT (Consolidated Standards of Reporting Trials) reporting guidelines²⁷ have not been extended specifically for crossover trials as yet. Guidelines for the conduct and reporting of crossover trials might improve the conduct and reporting of studies using this important trial design.²⁶ Exclusion of the three quasi-randomized crossover design studies^{6,9,10} from the primary analysis for 24-h BP resulted in no between-study heterogeneity and did not substantively alter the results. The notable difference between the trials was the methodological quality score¹⁴ of the included studies: 0–1, three trials;^{9–11} 2–3, four trials;^{6,7,12,13} 4, two trials.^{5,8} Although eliminating the three low quality-score (0 or 1) studies^{9–11} from the primary analysis for 24-h BP did not substantially change the pooled point estimates, there was still statistically significant between-study heterogeneity. Thus, methodological quality of the trials may not contribute to between-study heterogeneity of results.

Our analysis must be viewed in the context of its limitations. First, we used only data from RCTs. Patients enrolled in RCTs may not be representative of patients typically seen in clinical practice. However, because RCTs balance both known and unknown confounders across treatment groups, this is the study design least vulnerable to bias. Second, our results may be influenced by a publication bias favoring telmisartan that was marketed later than losartan. This risk was minimized through an exhaustive search of the available literature. Third, we used the random-effects rather than fixed-effects estimate as the summary measure. In order to calculate a CI for a fixed-effects meta-analysis, the assumption is made that the true effect of intervention (in both magnitude and direction) is the same value in every study (that is, fixed across studies), which implies that the observed differences among study results are due solely to the play of chance, that is, that there is no statistical heterogeneity.²⁸ When there is heterogeneity that cannot readily be explained, one analytical approach is to incorporate it into a random-effects model. For any particular set of studies in which heterogeneity is present, a CI around the random-effects pooled estimate is wider than a CI around a fixed-effect pooled estimate.²⁸ To make a more conservative evaluation, we used the random-effects rather than fixed-effects model despite the presence or absence of between-study heterogeneity of results by means of standard χ^2 -tests.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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