Blood pressure-independent effects of telmisartan on regression of left ventricular mass: A meta-analysis and meta-regression of randomized controlled trials

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In a recent meta-analysis [1] of randomized controlled trials, angiotensin receptor blockers (ARBs) may induce regression of left ventricular (LV) mass (LVM). Although the meta-analysis included 20 ARB-trials (6 losartan-, 4 telmisartan-, 4 valsartan-, 3 irbesartan-, and 2 candesartan-trials; and 1 eprosartan-trial), not class- but drug-specific effects on LVM remain unclear. Telmisartan is a unique ARB with selective peroxisome proliferation-activated receptor-gamma (PPAR-γ)-modulating activity [2]. Because the PPAR-γ-dependent pathway is critically involved in the inhibition of cardiac hypertrophy [3], telmisartan would be especially expected to reduce LVM. Indeed, in a non-comparative study [4], the 1-year use of telmisartan improved LV hypertrophy (LVH) in patients with hypertension. We perform a meta-analysis and meta-regression of randomized controlled trials of telmisartan therapy for reduction of LVM in hypertensive patients.

To identify all prospective randomized controlled trials of telmisartan therapy enrolling patients with hypertension, public domain databases including MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials were searched through May 2012 using Web-based search engines (PubMed, OVID). Keywords included *telmisartan*; *ventricular/cardiac*; *hypertrophy/mass/remodeling*; and *randomized*, *randomised*, *randomly*, or *randomization*. Studies considered for inclusion met the following criteria: the design was a prospective randomized controlled clinical trial; the study population was patients with hypertension; patients were randomly assigned to telmisartan versus other anti-hypertensive drug therapies (including other ARBs); and main outcomes included LVM or LVM index (LVMI). For each study, data regarding final LVM/LVMI in both the telmisartan and control groups were used to generate standardized mean differences (SMDs) and 95% confidence intervals (CIs), on the assumption that baseline LVM/LVMI would be equal between the groups because of appropriate randomization. When standard deviations (SDs) were unavailable, missing SDs were imputed according to the Cochrane Handbook [5]. Study-specific estimates were combined in both fixed- and random-effects models. Sensitivity analyses were performed to assess the contribution of each study to the pooled estimate by excluding individual trials one at a time and recalculating the pooled SMD estimates for the remaining studies. Publication bias was assessed graphically using a funnel plot and mathematically using an adjusted rank-correlation test and a linear regression test. The blood pressure (BP) difference was assigned a negative value when the final BP level was lower in the telmisartan compared with control. The association between the difference in final systolic BP (Δ final SBP) (mm Hg) and the SMD in final LVM/LVMI was investigated using unrestricted maximum likelihood meta-regression analysis with inverse variance weighting. The intercept of the regression line estimated the value of the SMD when the Δ final SBP is zero. The slope of the regression line estimated the SMD for a unit change in Δ final SBP. All analyses were conducted using Comprehensive Meta-Analysis version 2 (Biostat, Englewood, NJ).

Our comprehensive search identified 9 prospective randomized controlled clinical trials of telmisartan versus other anti-hypertensive drug therapies enrolling patients with hypertension [6–14] (Table 1). In total, our meta-analysis included data on 698 patients with hypertension randomized to therapy with telmisartan or other anti-hypertensive drugs. Pooled analysis demonstrated a statistically significant reduction in final LVMI with telmisartan relative to other anti-hypertensive drug therapies in the fixed-effects model (SMD, −0.29; 95% CI, −0.44 to −0.14; $p=0.0002$; Fig. 1). There was minimal trial heterogeneity ($p=0.44$) and accordingly no difference in the pooled result from random-effects modeling. In general, exclusion of any single trial from the analysis did not substantively alter the overall result of our analysis (Fig. 2). To assess publication bias we generated a funnel plot of the effect size versus the reciprocal of standard error for each trial (Fig. 3). There was no evidence of significant publication bias ($p=0.17531$ and 0.17623 by the adjusted rank-correlation test and the linear regression test, respectively). The magnitude of the achieved reduction in final LVMI was not associated with the size of Δ final SBP (slope of the regression line, 0.01461; 95% CI, −0.02151 to 0.05072; $p=0.42791$; Fig. 4). At zero Δ final SBP, the estimated reduction in final LVMI was significantly less than zero (intercept of the regression line, −0.26236; 95% CI, −0.42721 to −0.09752; $p=0.00181$).

The results of our analysis suggest that telmisartan therapy may reduce LVMI over other anti-hypertensive drug therapies in patients with hypertension, which were robust in sensitivity analyses. The meta-regression analysis confirms that the size of the reduction in BP achieved with telmisartan is not a major determinant of the size of the reduction in LVM. In addition, a potentially important BP-independent effect of telmisartan on the reduction in LVM has been identified. In particular, there was clear evidence of reduction in LVM with telmisartan even in the absence of any reduction in BP. Telmisartan prevents unfavorable cardiac remodeling through a reduction of cardiac hypertrophy and fibrosis, and an anti-inflammatory effect and PPAR-γ activation are suggested to be important in addition to suppression of angiotensin II activity [15]. In rats with chronic heart failure, telmisartan significantly reduced levels of cardiac fibrosis, hypertrophy and its marker molecules, and PPAR-γ protein expression compared with those of vehicle-treated rats [16]. There was a significant reduction of the plasma brain natriuretic peptide level, cardiac fibrosis area, infiltration of macrophages, and size of cardiomyocytes, while expression of PPAR-γ was enhanced, in the noninfarcted myocardium of rats from the telmisartan-treated group compared with the other 3 groups (vehicle control group, non-PPAR-γ agonistic ARB [losartan]-treated group, and telmisartan plus specific PPAR-γ antagonist-treated group) [15]. Further, results of a substudy [17] of the ONTARGET [Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial] [18] and the TRANSCEND

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Table 1
Trial design, systolic blood pressure, and left ventricular mass index.

	Fountoulaki (2005) [6]	Galzerano (2004) [7]	Galzerano (2005) [8]	Galzerano (2012) [9]	Lim (2011) [10]	Martina (2003) [11]	ONTARGET (2009) [12]	Petrovic (2005) [13]	TALENT (2011) [14]
Inclusion criteria	Mild-to-moderate hypertension	Mild-to-moderate hypertension	Mild-to-moderate hypertension	Mild hypertension in sinus rhythm experienced ≥1 ECG-documented AF episode within 6 months	Uncomplicated essential hypertension	Mild-to-moderate essential hypertension	Cardiovascular disease or high-risk diabetes	Moderate-to-severe hypertension	Mild-to-moderate essential hypertension
Follow-up	3 months	12 months	44 weeks	12 months	12 weeks	6 months	2 years	6 months	1 year
Intervention									
Telmisartan	40–80 mg	80 mg	80 mg	80 mg	80 mg	80 mg ± 12.5-mg HCT	80 mg	40 mg (1 month) → 80 mg (5 month)	40/80 mg
Control	2.5–5.0-mg nebivolol	25-mg HCT	25-mg carvedilol	25-mg carvedilol	160-mg valsartan	50-mg losartan ± 12.5-mg HCT	10-mg ramipril	2.5-mg (1 month) → 5-mg (5 month) ramipril	50/100-mg losartan
Patient number									
Telmisartan	20	41	36	70	30	15	100	25	29
Control	20	28	34	62	30	15	90	25	28
SBP (mm Hg)[a]									
Baseline									
Telmisartan	153.0 ± 4.8	157 ± 11	159.6 ± 10.2	154.7 ± 7.7	153.2 ± 18.9	170 ± 14	141 ± 17	170.4 ± 35.5	152.1 ± 16.5
Control	155.7 ± 6.8	154 ± 10	157.8 ± 11.1	153.0 ± 1.5	151.7 ± 16.2	160 ± 18	142 ± 17	170.0 ± 31.5	150.6 ± 10.6
Final									
Telmisartan	120.1 ± 8.2	133 ± 7	128.6 ± 6.5	123 ± 6.1	133.3 ± 15.5	146 ± 23	135 ± 22	135.3	131 ± 12
Control	123.6 ± 8.3	144 ± 11	128.2 ± 5.6	125 ± 5.6	129.2 ± 15.1	137 ± 15	138 ± 17	137.5	132 ± 13
LVMI (g/m^2)[a]									
Measurement	2D-UCG	3D-UCG	3D-UCG/MRI	3D-UCG	3D-UCG	2D-UCG	MRI	2D-UCG	2D-UCG
Baseline									
Telmisartan	97.4 ± 12.9	141 ± 16	140.67 ± 12.96	137.8 ± 10.6	126.3 ± 26.8	115 ± 23	35 ± 7 ($g/m^{2.7}$)	129.01 ± 60.15	102.1 ± 15.8
Control	98.1 ± 15.7	139 ± 20	135.87 ± 16.65	134.7 ± 15.2	124.2 ± 24.3	117 ± 22	38 ± 8 ($g/m^{2.7}$)	128.43 ± 63.70	98.3 ± 20.0
Final									
Telmisartan	83.4 ± 8.2	125 ± 19	118.67 ± 12.36	117.8 ± 10.7	116.7 ± 25.3	101 ± 14	34 ± 7 ($g/m^{2.7}$)	114.30 ± 32.17	95.1 ± 24.6
Control	84.2 ± 12.9	135 ± 22	123.11 ± 12.22	124.7 ± 14.5	130.6 ± 41.6	101 ± 25	36 ± 7 ($g/m^{2.7}$)	115.72 ± 33.93	90.9 ± 21.6

2D, two dimensional; 3D, three-dimensional; AF, atrial fibrillation; ECG, electrocardiogram; HCT, hydrochlorothiazide; LVMI, left ventricular mass index; MRI, magnetic resonance imaging; SBP, systolic blood pressure; SD, standard deviation; UCG, ultrasound cardiography.

[a] Mean ± standard deviation.