Letter to the Editor

Telmisartan and Carotid Intima-Media Thickness Regression: A Class Effect of Angiotensin-Receptor Blockers?

To the Editor:

We read with great interest the article by Dr. Nakamura *et al*. that was recently published in *Hypertension Research* (*1*). In this paper, the authors compared the renovascular effects of telmisartan and amlodipine in hypertensive patients with chronic kidney disease and mild renal insufficiency. Among other results, a significant increase in carotid intima-media thickness (IMT) was demonstrated in the amlodipine group after 12 months of treatment as compared to baseline values. In the telmisartan group, however, the investigators found a significant IMT regression; as they commented, it remains to be determined whether this regression is specific to telmisartan or constitutes a class effect of angiotensin-II receptor blockers (ARBs).

Previous studies on the effect of ARBs on IMT have yielded conflicting results. In 2002, the LAARS study enrolled 280 hypertensive patients that were randomized to receive losartan (50 mg) or atenolol (50 mg) for 24 months and demonstrated a significant annual IMT decrease of 0.038±0.004 mm in the losartan group (*2*). Similarly, Tedesco *et al*. demonstrated a significant IMT regression after 24 months of losartan treatment (*3*). Moreover, Olsen *et al*. (*4*) and Sonoda *et al*. (*5*) showed that losartan resulted in a significant IMT decrease (0.83±0.11 to 0.79±0.16 mm and 0.87±0.14 to 0.79±0.16 mm, respectively) in hypertensive patients within 3 and 1 years of treatment, respectively. In contrast, losartan failed to induce a significant IMT regression within 12 months of treatment in a study by Uchiyama-Tanaka *et al*. (*6*).

As in the losartan trials, studies on the effect of candesartan on IMT have yielded conflicting results. Ariff *et al*. (*7*) and Ono *et al*. (*8*) demonstrated that candesartan leads to a significant IMT reduction of 0.05 mm and 0.13 mm within 12 and 24 months respectively. However, these findings were not confirmed by Ichihara *et al*., who showed that IMT remained unchanged when candesartan was added in patients already receiving calcium channel blockers (*9*). Similarly, candesartan did not induce a significant IMT regression in a study by Tomás *et al*. (*10*). However, this study was underpowered to identify a beneficial effect of candesartan on IMT since it involved a small sample size (n=34) and lasted only 3 months.

Valsartan has been shown not to induce IMT regression. In a recent article by Okura *et al*., valsartan (80–160 mg) did not influence IMT after 24 months of treatment (*11*). Similar results were demonstrated in a study by Kosch *et al*., but that study followed patients for only 3 months (*12*). On the other hand, treatment with irbesartan in the SILVHIA study resulted in a significant IMT reduction compared with atenolol, which was used as control (*13*).

The conflicting results of the aforementioned studies raise serious concerns as to whether the beneficial effect of telmisartan on IMT shown by Nakamura *et al*. (*1*) can be considered a class effect of ARBs. We believe that further studies are necessary to clarify this issue.

George NTAIOS
Christos SAVOPOULOS
Apostolos HATZITOLIOS
First Propedeutic Department of Internal Medicine
AHEPA Hospital
Aristotle University
Thessaloniki, Greece

1. Nakamura T, Inoue T, Suzuki T, *et al*: Comparison of renal and vascular protective effects between telmisartan and amlodipine in hypertensive patients with chronic kidney disease with mild renal insufficiency. *Hypertens Res* 2008; **31**: 841–850.
2. Ludwig M, Stapff M, Ribeiro A, *et al*: Comparison of the effects of losartan and atenolol on common carotid artery intima-media thickness in patients with hypertension: results of a 2-year, double-blind, randomized, controlled study. *Clin Ther* 2002; **24**: 1175–1193.
3. Tedesco MA, Natale F, Calabrò R: Effects of monotherapy and combination therapy on blood pressure control and target organ damage: a randomized prospective intervention study in a large population of hypertensive patients. *J Clin Hypertens* (*Greenwich*) 2006; **8**: 634–641.
4. Olsen MH, Wachtell K, Neland K, *et al*: Losartan but not atenolol reduce carotid artery hypertrophy in essential hypertension. A LIFE substudy. *Blood Press* 2005; **14**: 177–183.
5. Sonoda M, Aoyagi T, Takenaka K, Uno K, Nagai R: A one-year study of the antiatherosclerotic effect of the angiotensin-II receptor blocker losartan in hypertensive patients. A comparison with angiotension-converting enzyme inhibitors. *Int Heart J* 2008; **49**: 95–103.
6. Uchiyama-Tanaka Y, Mori Y, Kishimoto N, *et al*: Comparison of the effects of quinapril and losartan on carotid artery intima-media thickness in patients with mild-to-moderate arterial hypertension. *Kidney Blood Press Res* 2005; **28**: 111–116.
7. Ariff B, Zambanini A, Vamadeva S, *et al*: Candesartan- and atenolol-based treatments induce different patterns of carotid artery and left ventricular remodeling in hypertension. *Stroke* 2006; **37**: 2381–2384.
8. Ono H, Minatoguchi S, Watanabe K, *et al*: Candesartan decreases carotid intima-media thickness by enhancing nitric oxide and decreasing oxidative stress in patients with hypertension. *Hypertens Res* 2008; **31**: 271–279.
9. Ichihara A, Kaneshiro Y, Takemitsu T, Sakoda M, Itoh H:

Benefits of candesartan on arterial and renal damage of non-diabetic hypertensive patients treated with calcium channel blockers. *Am J Nephrol* 2006; **26**: 462–468.
10. Tomás JP, Moya JL, Barrios V, *et al*: Effect of candesartan on coronary flow reserve in patients with systemic hypertension. *J Hypertens* 2006; **24**: 2109–2114.
11. Okura T, Watanabe S, Kurata M, *et al*: Long-term effects of angiotensin II receptor blockade with valsartan on carotid arterial stiffness and hemodynamic alterations in patients with essential hypertension. *Clin Exp Hypertens* 2008; **30**: 415–422.
12. Kosch M, Levers A, Lang D, *et al*: A randomized, double-blind study of valsartan *versus* metoprolol on arterial distensibility and endothelial function in essential hypertension. *Nephrol Dial Transplant* 2008; **23**: 2280–2285.
13. Mörtsell D, Malmqvist K, Held C, Kahan T: Irbesartan reduces common carotid artery intima-media thickness in hypertensive patients when compared with atenolol: the Swedish Irbesartan Left Ventricular Hypertrophy Investigation *versus* Atenolol (SILVHIA) study. *J Intern Med* 2007; **261**: 472–479.

Response to: Telmisartan and Carotid Intima-Media Thickness Regression: A Class Effect of Angiotensin-Receptor Blockers?

To the Editor:

As Dr. Ntaios *et al*. have suggested, it is important to consider whether the beneficial effect of telmisartan on intima-media thickness (IMT) is a class effect of angiotensin receptor blockers (ARBs). Telmisartan has the unique property of being a peroxisome proliferator–activated receptor (PPAR)-γ activator. We have recently proposed classifying telmisartan as a "metabolic sartan" (*1*). To reduce cardiovascular mortality or morbidity, more intense effort should be focused on aggressively modifying risk factors atnd the early stage of vascular failure (*1*). We believe that telmisartan has different properties for targeting vascular failure. Recently, Grassi *et al*. (*2*) reported that telmisartan 1) is effective in favoring the regression of cardiac and vascular organ damage, 2) reduces arterial stiffness and improves vascular distensibility and 3) reverses the endothelial dysfunction typical of the hypertensive state, particularly when complicated by chronic kidney disease (CKD) or metabolic syndrome. Telmisartan Randomized Assessment Study in ACE-I Intolerant Patients with Cardiovascular Disease (TRANSCEND) Investigators (*3*) have reported that telmisartan was well tolerated in patients unable to tolerate angiotensin-converting enzyme (ACE) inhibitors, and that it modestly reduced the risk of the composite outcome of cardiovascular death, myocardial infarction, or stroke. Few studies have compared various ARBs in renovascular protection, including IMT in CKD patients. Recently, Ohtake *et al*. (*4*) reported that ARB monotherapy can significantly reverse pathological changes in chronic glomerulonephritis. Bakris *et al*. (*5*) reported that telmisartan is superior to losartan in reducing proteinuria in hypertensive diabetic nephropathy patients. We are now studying the effects of various ARBs on renovascular protection, including IMT, to determine whether ARBs show a class effect in hypertensive CKD patients. In any event, establishing the effect of telmisartan on IMT will require a large-scale clinical trial designed to compare it with other ARBs.

Tsukasa NAKAMURA
Department of Medicine
Shinmatsudo Central General Hospital
Matsudo, Japan

Teruo INOUE
Koichi NODE
Department of Cardiovascular and Renal Medicine
Saga University Faculty of Medicine
Saga, Japan

1. Inoue T, Node K: Telmisartan as a metabolic sartan for targeting vascular failure. *Expert Opin Pharmacother* 2008; **9**: 1397–1406.
2. Grassi G, Quarti-Trevano F, Mancia G: Cardioprotective effects of telmisartan in uncomplicated and complicated hypertension. *J Renin Angiotensin Aldosterone Syst* 2008; **9**: 66–74.
3. TRANSCEND Investigators: Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomized controlled trial. *Lancet* (in press).
4. Ohtake T, Oka M, Maesato K, *et al*: Pathological regression by angiotensin II type 1 receptor blockade in patients with mesangial proliferative glomerulonephritis. *Hypertens Res* 2008; **31**: 387–394.
5. Bakris G, Burgess E, Weir M, *et al*: Telmisartan is more effective than losartan in reducing proteinuria in patients with diabetic nephropathy. *Kidney Int* 2008; **74**: 364–369.