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Comparison of the effects of losartan versus ramipril on several adipocytokines and vascular remodeling biomarkers

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Angiotensin II receptor antagonists, also known as angiotensin receptor blockers (ARBs), AT1-receptor antagonists or sartans, block the activation of angiotensin II AT1 receptors. ARBs directly cause vasodilatation, reduce secretion of vasopressin, and reduce the production and secretion of aldosterone. Angiotensin-converting enzyme (ACE) inhibitors block the conversion of angiotensin I to angiotensin II and inhibit the breakdown of bradykinin, resulting in physiological benefits that confer cardioprotective and renoprotective properties.

Both ARBs and ACE inhibitors are classes of drugs frequently used for the treatment of hypertension in daily clinical practice. They have protective effects on the heart and kidney and also lower blood pressure as well as improve insulin sensitivity.
There are a number of studies on the effects of either ARBs or ACE inhibitors on metabolic parameters, cytokines or cardiovascular biomarkers[1]. However, there are very few, if any, studies directly comparing the effects of ARBs with those of ACE inhibitors on metabolic parameters.

In the current issue of *Hypertension Research*, Derosa and coworkers describe a study in which they recruited 228 Caucasian hypertensive subjects (115 males and 113 females) in a double-blind clinical trial. The authors found that 14 months of treatment with losartan improved a wide range of metabolic parameters (M value and levels of adiponectin, retinol-binding protein-4 (RBP-4), resistin, visfatin, vaspin) and vascular remodeling biomarkers (metalloproteinase-2 (MMP-2), MMP-9), whereas ramipril had no effect on any

of these parameters[2] [figure 1], although those two drugs reduced blood pressure to comparable levels.

Several investigators have reported that losartan treatment increased total serum adiponectin and high-molecular-weight adiponectin in IFG/IGT[3] or hypertensive subjects[4]. Telmisartan was also demonstrated to increase serum adiponectin levels[1]. In contrast, another study showed that 8 weeks of telmisartan treatment had a neutral effect on insulin resistance, as assessed by HOMA-IR in hypertensive subjects with metabolic syndrome.

So what is the potential mechanism by which these ARBs increased adiponectin levels? Is this directly related to AT1 receptor block? The most conceivable explanation for this is peroxisome proliferator-activated receptor (PPAR) activation by these ARBs. A subset of ARBs, including losartan, induce the activity of PPAR by partial agonism[5]. Of note, this activation was independent of AT1R expression and therefore not related to AT1R-blocking properties[5]. PPAR functions as a transcriptional regulator in adipose tissue, where it regulates multiple genes involved in lipid and glucose metabolism. In the case of telmisartan, our groups and others[6] have shown that telmisartan treatment produced significant reductions in visceral fat areas but not subcutaneous areas evaluated by computed tomography in Japanese subjects with metabolic syndrome. Since plasma adiponectin level is inversely associated with visceral fat accumulation, we presumed that adiponectin increased after telmisartan treatment mainly through visceral fat mass reduction. In rats, visceral fat accumulation is suppressed by telmisartan treatment[7]. Telmisartan also

modulates adipocyte size and fat accumulation, resulting in protection against diet-induced visceral obesity. It is also likely that the increased expression of mitochondrial energy expenditure genes in skeletal muscle is the mechanism by which telmisartan decreases visceral fat accumulation, as previously shown in rat models. For the association between ramipril treatment and plasma adiponectin, on the other hand, previous findings are conflicting. One study performed in a randomized, double-blind, placebo-controlled cross-over manner showed 10 mg of ramipril, 16 mg of candesartan, or combination therapy increased plasma adiponectin levels when compared with baseline values[8]. Another study has shown that 9-week treatment with 10 mg of ramipril did not cause significant changes in adiponectin levels in patients with type 2 diabetes.

Derosa et al. also investigated the effects of losartan versus ramipril treatment on several other metabolic parameters and vascular remodeling biomarkers[2]. To the best of our knowledge, there appears to be no previous report on the association of losartan and/or ramipril treatment with changes in RBP-4, visfatin or vaspin. Also, there are very few reports, if any, on the effect of treatment with these compounds on serum resistin levels. A small crossover study by a Norwegian group composed of 23 hypertensive patients showed that there was no significant difference in blood levels of resistin (11.7 +/- 1.0 vs. 11.3 +/- 0.7 ng/mL) between treatment with amlodipine 10 mg or losartan 100 mg + amlodipine 5 mg, respectively. Since RBP-4, visfatin, vaspin and resistin are closely related to insulin resistance, the altered levels of these molecules along with adiponectin in the losartan group compared to the ramipril group in the current study suggest that losartan may have

considerable advantages over ramipril in the prevention of atherosclerotic disease or diabetes. The present finding that losartan but not ramipril caused a reduction in both matrix metalloproteinase (MMP)-2, and MMP-9 after 14 months ($P<0.05$) also suggests that losartan more effectively prevents the destabilization of plaques, as expected, since MMPs are key enzymes involved in degrading extracellular matrix. However, a previous report[9] showed that 10 mg once daily during 24 weeks of ramipril treatment reduced gene and protein expression of both MMP-2 and MMP-9.

To what degree does losartan or ramipril prevent the incidence of cardiovascular disease or the onset of diabetes? The Losartan Intervention for Endpoint Reduction (LIFE), the Heart Outcomes Prevention Evaluation (HOPE) and the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) studies are large-scale randomized control trials (RCT) demonstrating the clinical outcome of using either losartan or ramipril.
LIFE is a trial comparing the effect of losartan vs. atenolol, a selective β1 receptor antagonist, with regard to the incidence of cardiovascular mortality, fatal or nonfatal stroke, myocardial infarction or new-onset diabetes. The trial involved the recruitment of 9193 hypertensive subjects with LVH. Main outcomes are a 25% further reduction in stroke and 25% reduction of new-onset diabetes for losartan compared to atenolol, without a significant difference in MI incidence between groups. It should be noted, however, that LIFE did not necessarily demonstrate that long-term losartan therapy prevents the onset of diabetes because the study was performed with a β1 receptor antagonist rather than a placebo as control.

HOPE and DREAM are placebo-controlled RCT for investigating the long-term outcomes of ramipril use, with the former utilizing cardiovascular events as endpoints and with the latter utilizing new-onset diabetes or death as endpoints. The use of ramipril vs. placebo is associated with a 22% reduction in cardiovascular events without significant reductions in new-onset diabetes.

So what about head-to-head RCT comparing ARBs versus ACE inhibitors?

There are several RCT comparing ARBs versus ACE inhibitors in terms of mortality, morbidity or cardiovascular events as endpoints, but not the use of losartan vs. ramipril specifically. In the ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), 25,620 subjects from 730 centers in 40 countries were high-risk patients with coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage. Patients were randomized to groups treated with 80 mg of telmisartan, 10 mg of ramipril or both drugs and followed for 3.5 to 5.5 years. The authors concluded that telmisartan was an equally effective alternative to ramipril and that there is no additional advantage from the combination of full doses of telmisartan and ramipril compared with ramipril alone. The Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL) is a trial involving 5477 patients with confirmed acute myocardial infarction and heart failure recruited from 329 centers in seven European countries. Patients were randomly assigned and titrated to a target dose of losartan (50 mg once daily) or captopril (50 mg three times daily), with all-cause mortality as the primary endpoint. They concluded that ACE inhibitors should remain the first-choice treatment in

patients after complicated acute myocardial infarction. The VALsartan In Acute myocardial iNfarcTion (VALIANT) study compared the effect of valsartan (4909 patients), valsartan plus captopril (4885 patients), or captopril (4909 patients) on death from any cause in subjects with acute myocardial infarction who had already undergone conventional therapy. The authors concluded that valsartan is as effective as captopril in patients who are at high risk for cardiovascular events after myocardial infarction. Thus none of these three large-scale RCT concluded that ARBs are superior to ACE inhibitors with respect to long-term mortality, incidence of cardiovascular disease or new onset of diabetes.

Are the observed favorable effects in the current study pharmacologic class effects or specific to the drugs studied? As mentioned earlier, certain ARBs may utilize mechanisms involved in PPAR activation that are independent of AT1 R-blocking properties. Indeed, Derosa and coworkers[10] reported very recently a study comparing the effects of 1-year treatment with 8 mg/d candesartan or 10 mg/d olmesartan on various metabolic parameters related to insulin resistance. They report that candesartan but not olmesartan caused favorable changes in M-value, adiponectin, visfatin, RBP-4 and C-reactive protein, although comparable reductions were observed in blood pressure. These results suggest that the observed changes in metabolic parameters may be due to compound-specific effects rather than class effects. In the future, to compare head-to-head long-term outcomes, studies should consider specific ARBs or ACE inhibitors rather than broadly compare ARBs vs. ACE inhibitors.

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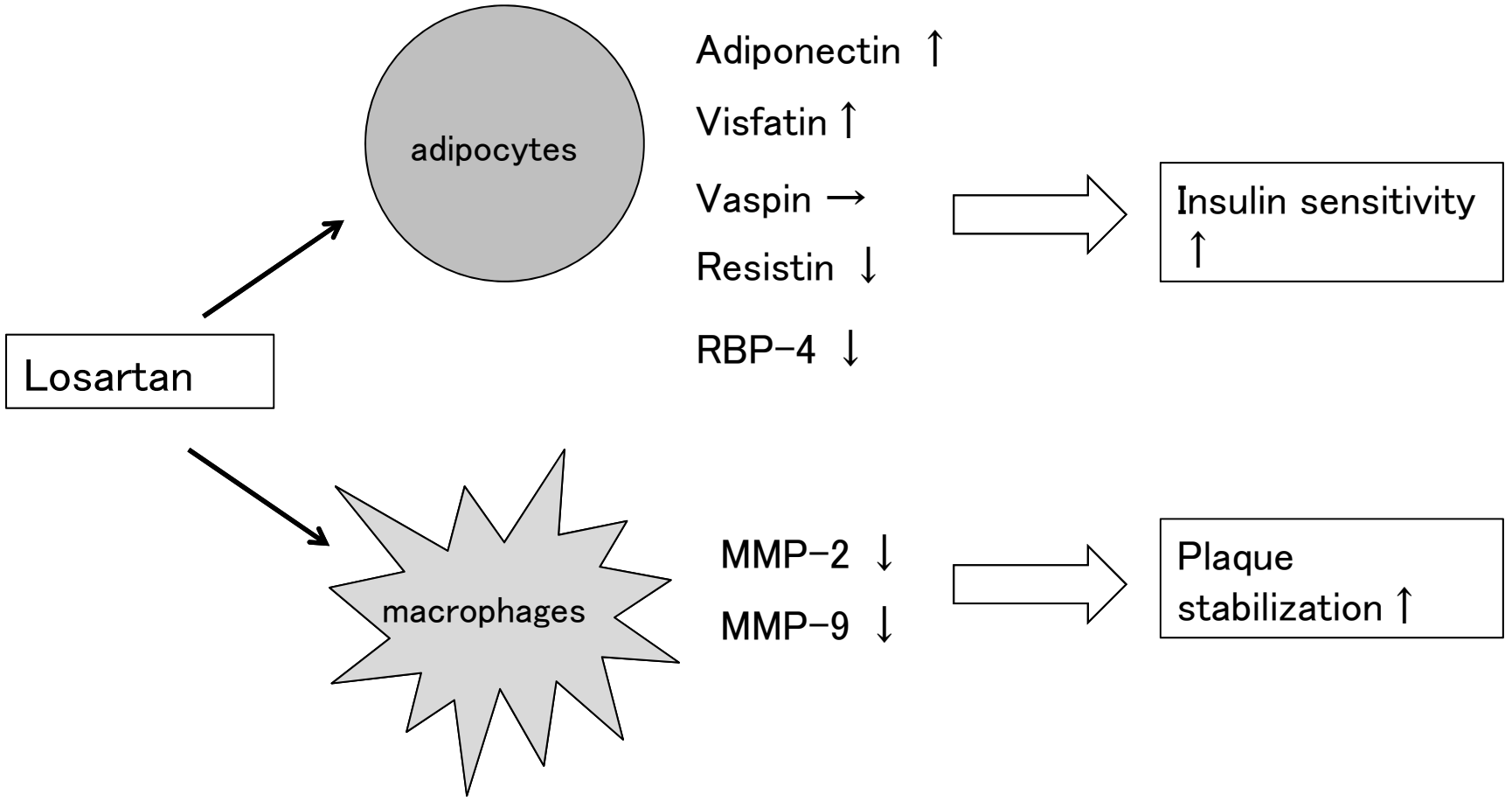
Figure legend

Figure 1

Proposed effects of losartan therapy on adipocytokine and metalloproteinase production, as clarified in the study by Derosa and coworkers[2].

Figure 1


adipocytes
Adiponectin ↑
Visfatin ↑
Vaspin →
Resistin ↓
RBP-4 ↓
Insulin sensitivity ↑
Losartan
macrophages
MMP-2 ↓
MMP-9 ↓
Plaque stabilization ↑