Hypertension Research (2011) 34, 441–442

www.nature.com/hr

COMMENTARY

Synergistic protection against vascular inflammation with a calcium channel blocker and a statin

Yoichiro Hirata and Masataka Sata

Hypertension Research (2011) **34,** 441–442; doi:10.1038/hr.2010.275; published online 27 January 2011

Cardiovascular disease (CVD) is a leading cause of death worldwide. As CVD drives high healthcare costs in surviving events such as stroke and heart failure, better strategies to facilitate to prevent CVD have become priorities for most healthcare systems. Modification of cardiovascular risk factors is essential to reduce incidence of CVD. Cardiovascular risk factors are highly interactive and thereby contribute synergistically to the pathogenesis of atherosclerotic diseases.[1] Epidemiologic studies revealed that hypertension usually occurs in conjunction with other metabolically linked risk factors; such as glucose intolerance, obesity, left ventricular hypertrophy and dislipidemia.[2] Cowie estimated that over half of the hypertensive population also has dyslipidemia.[3] It has also become clear that CVD risk factors tend to increase the total or absolute CVD risk in a multiplicative rather than additive manner.[4] Thus, individual treatment strategies should be based on absolute cardiovascular risk, which could be determined by the synergistic effect of all cardiovascular risk factors rather than on individual risk factors.[5] To effectively reduce CVD risk in hypertensive patients at high cardiovascular risk, concomitant lipid-lowering therapy with HMG-CoA reductase inhibitors, stains, would be necessary as well as rigorous blood pressure control with two or more antihypertensive agents. These recommendations concur with the results of large clinical trials that demonstrated clinical benefit of statin therapy in hypertensive patients with normal lipid levels.[6]

The antihypertensive efficacy of amlodipine and the lipid-lowering efficacy of atorvastatin are well established. The efficacy of the combined administration of amlodipine and atorvastatin in reducing coronary risk factors and cardiovascular morbidity has been evaluated in adult patients in several trials. Two randomized, double-blind, double-dummy, multicenter trials (AVALON, RESPOND) compared the efficacy of the co-administration of amlodipine and atorvastatin with that of single-agent therapy or placebo over 8 weeks. Five non-comparative, titration-to-goal, multicenter studies (GEMINI, GEMINI-ALAA, JEWEL I, JEWEL II, CAPABLE) evaluated the efficacy of the fixed-dose combination amlodipine/atorvastatin in a clinical-practice setting over 14, 16 and 20 weeks.

A 2×2 factorial analysis of the data from the randomized, double-blind, multicenter trial evaluated the efficacy of amlodipine plus atorvastatin over 3.3 years (ASCOT-LLA). The randomized ASCOTT-LLA included patients with a total cholesterol concentration $\leqslant 250\,mg\,dl^{-1}$ who were already enrolled in ASCOT-BPLA.[6] ASCOT-BPLA was a large, multicenter trial that used a PROBE (prospective, randomized, open-label and blinded endpoint) evaluation design to compare amlodipine-based with atenolol-based therapy in hypertensive patients.[7] Patients eligible for ASCOT-LLA were further randomized to receive atorvastatin or placebo in addition to the blood pressure lowering medication in a double-blind manner. A predefined 2×2 factorial analysis of ASCOT-LLA data was carried out to assess whether additive/synergistic effects existed between the antihypertensive and lipid-lowering medications used in the trial. ASCOT-LLA was terminated early after a median follow-up of 3.3 years instead of the planned 5 years because of a greater reduction in non-fatal myocardial infarction and fatal coronary heart disease in patients randomized to atorvastatin compared with those randomized to placebo.

In this study, the relative risk of non-fatal myocardial infarction and coronary heart disease was reduced by 36% in the group receiving atorvastatin plus either antihypertensive regimen compared with the group receiving placebo plus either antihypertensive regimen. Furthermore, the 2×2 factorial analysis demonstrated a reduction of 53% in the relative risk of the primary endpoint of non-fatal myocardial infarction or fatal coronary heart disease in the atorvastatin plus amlodipine-based treatment group compared with a reduction of 16% in the atorvastatin plus atenolol-based treatment group. This difference in risk reduction between the treatment groups was statistically significant. The relative risk of total cardiovascular events and procedures (secondary endpoint) was also reduced significantly more with atorvastatin plus amlodipine-based treatment than with atorvastatin plus atenolol-based treatment. The extent to which total and low-density lipoprotein cholesterol were lowered by atorvastatin was not different between amlodipine-based or atenolol-based treatment groups. Furthermore, no additional reduction in blood pressure was achieved by adding atorvastatin or placebo to either antihypertensive agent. These findings support the notion that amlodipine and atorvastatin could exert synergistic effects to reduce coronary heart disease events independently of lipid level and blood pressure.

Although a number of large clinical trials demonstrated synergistic benefits of amlodipine/atorvastatin in patients with multiple

Y Hirata and Dr M Sata are at the Department of Cardiovascular Medicine, Institute of Health Bioscience, the University of Tokushima Graduate School, 3-18-15 Kuramoto-cho, Tokushima-city, Tokushima 770-8503, Japan. Y Hirata is also at the Department of Pediatrics, University of Tokyo Graduate School of Medicine, Tokyo 113-8655, Japan.
E-mail: sata@clin.med.tokushima-u.ac.jp

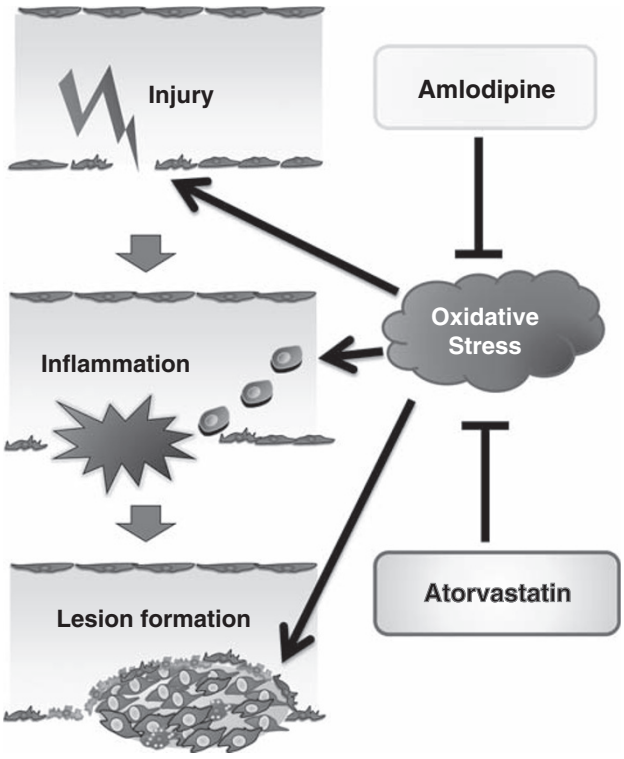

Figure 1 Synergistic vascular protection with amlodipine and atorvastatin. Amlodipine and atorvastatin synergistically reduce oxidative stress, which promotes leukocytes adhesion and consequent vascular inflammation after mechanical injury.

cardiovascular risk factors, there are only a few basic studies evaluating the mechanism of the effects on the vascular inflammation. In this issue of *Hypertension Research*, Hagita *et al*. elegantly demonstrated a potential synergistic effect of the combination of a calcium channel blocker and a statin on the vascular inflammation after mechanical vascular injury *in vivo*.[8] In this study, the authors evaluated the effects of a combination of a calcium channel blocker (amlodipine) and a statin (atorvastatin) by focusing on their effects on leukocyte recruitment to the vasculature. The authors recently developed a novel intravital microscopic system to directly monitor leukocyte recruitment in atheroprone arteries *in vivo* by taking advantage of the mouse model of endovascular injury developed by Sata *et al*.[9] This injury resembles balloon angioplasty, which is characterized by complete endothelial denudation and acute onset of medial smooth muscle cell apoptosis followed by reproducible neointima formation. Using this technique, the authors evaluated the effects of atorvastatin and amlodipine on the recruitment of leukocytes to the site of vascular injury. Low doses of atorvastatin or amlodipine failed to inhibit leukocyte adhesion. However, co-administration of both drugs at low doses significantly reduced leukocyte adhesion to the injured artery by reducing oxidative stress (Figure 1). The authors convincingly demonstrated synergistic protective effects of combination of amlodipine and atorvastatin in reducing vascular inflammation.

Recent joint guidelines from the European Society of Hypertension and the European Society of Cardiology recommend that all hypertensive patients at high cardiovascular risk should be considered for statin treatment even if their baseline serum total cholesterol and low-density lipoprotein cholesterol levels are not elevated.[10] Concomitant antihypertensive therapy and a statin will be indicated in a high proportion of hypertensive individuals as well as those with concomitant hypertension and dyslipidemia. The combination of amlodipine/atorvastatin offers a convenient and effective approach to managing two important risk factors simultaneously for hypertensive patients at risk of CVD or for those with concomitant hypertension and dyslipidemia. Large clinical trials demonstrated synergistic benefits of amlodipine/atorvastatin in patients with multiple cardiovascular risk factors. In this regard, Hagita *et al*.'s findings in the present study provide valuable information about the mechanism of synergistic protective effects of amlodipine and atorvastatin on the cardiovascular system.

1 Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: a marker of atherosclerotic risk. *Arterioscler Thromb Vasc Biol* 2003; **23**: 168–175.
2 Kannel WB. Risk stratification in hypertension: new insights from the Framingham Study. *Am J Hypertens* 2000; **13**: 3S–10S.
3 Cowie MR. Simultaneous treatment of hypertension and dyslipidaemia may help to reduce overall cardiovascular risk: focus on amlodipine/atorvastatin single-pill therapy. *Int J Clin Pract* 2005; **59**: 839–846.
4 Rosendorff C, Black HR, Cannon CP, Gersh BJ, Gore J, Izzo Jr JL, Kaplan NM, O'Connor CM, O'Gara PT, Oparil S. Treatment of hypertension in the prevention and management of ischemic heart disease: a scientific statement from the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention. *Circulation* 2007; **115**: 2761–2788.
5 Jackson R, Lawes CM, Bennett DA, Milne RJ, Rodgers A. Treatment with drugs to lower blood pressure and blood cholesterol based on an individual's absolute cardiovascular risk. *Lancet* 2005; **365**: 434–441.
6 Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003; **361**: 1149–1158.
7 Dahlof B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005; **366**: 895–906.
8 Hagita S, Osaka M, Shimokado K, Yoshida M. Combination of amlodipine and atorvastatin synergistically reduces leukocyte recruitment to the mechanically injured mouse femoral artery. *Hypertens Res* 2011; **34**: 450–455.
9 Sata M, Maejima Y, Adachi F, Fukino K, Saiura A, Sugiura S, Aoyagi T, Imai Y, Kurihara H, Kimura K, Omata M, Makuuchi M, Hirata Y, Nagai R. A mouse model of vascular injury that induces rapid onset of medial cell apoptosis followed by reproducible neointimal hyperplasia. *J Mol Cell Cardiol* 2000; **32**: 2097–2104.
10 Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Struijker Boudier HA, Zanchetti A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Erdine S, Kiowski W, Agabiti-Rosei E, Ambrosioni E, Lindholm LH, Manolis A, Nilsson PM, Redon J, Struijker-Boudier HA, Viigimaa M, Adamopoulos S, Bertomeu V, Clement D, Farsang C, Gaita D, Lip G, Mallion JM, Manolis AJ, O'Brien E, Ponikowski P, Ruschitzka F, Tamargo J, van Zwieten P, Waeber B, Williams B. 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). 2007; **28**: 1462–1536.