Published in final edited form as:

Int J Cardiol. 2009 March 6; 132(3): 297–299. doi:10.1016/j.ijcard.2008.11.150.

Targeting converging therapeutic pathways to overcome hypertension

Kwang Kon Koh^{a,*} and Michael J. Quon^b

^a Division of Cardiology, Gachon University, Gil Medical Center, Incheon, South Korea

^b Diabetes Unit, Laboratory of Clinical Investigation, NCCAM, NIH, Bethesda, Maryland, USA

Keywords

Hypertension; Combination treatment; Atherosclerosis; Blood pressure

To practicing clinicians and physician-scientists, it is evident that reliable, reproducible, convenient, and precise methods for measurement of blood pressure are essential to guide clinical therapy and research. Even assuming adequate measurements are available, controversy exists regarding whether blood pressure control per se or additional effects of anti-hypertensive therapies determine maximal health benefits. Failure of short-acting calcium channel blockers to reduce cardiovascular disease despite adequate control of blood pressure is an important evidence that contributes to this controversy [1,2].

That is, distinct outcomes between different treatment regimens suggest that control of blood pressure per se is not the only important consideration. Indeed, some believe that prevention of atherosclerosis progression is more crucial than control of blood pressure per se. However, it is more likely that blood pressure control combined with amelioration of atherosclerosis is essential for preventing and treating cardiovascular diseases. Only 14% of coronary events in hypertensive men and 5% in hypertensive women occur in the absence of additional cardiovascular risk factors. Therefore, appropriate targeted therapy for hypertensive patients involves risk stratification. Overall improvement in multivariate risk profiles contributes to achieving optimal therapeutic goals (Fig. 1) [3]. Indeed, multivariate adjustment demonstrates that better control of blood pressure accounts for about half of the differences in coronary events (and ~40% of differences in stroke events) between treatment regimens tested [4]. Accordingly, an optimal treatment plan for patients with hypertension involves simultaneously targeting both blood pressure and atherosclerosis. Consistent with this view, thiazide diuretics and old generation beta blockers are losing favor while newer generations of calcium channel blockers, renin–angiotensin–aldosterone system blockers, and statins are emerging as superior therapies.

Solid evidence from robust clinical trials should be the principal basis for developing rational hypertension management guidelines. It is imperative that clinicians are well informed and educated regarding the development of treatment plans according to evidenced-based guidelines. Therapeutic life style changes including increased physical activity, lower calorie intake, and diets high in potassium and low in sodium intake are clearly beneficial. However,

compliance with these interventions is problematic and their effects are not large in terms of secondary prevention.

Hypercholesterolemia and hypertension have synergistic deleterious effects on endothelial dysfunction and increased incidence of cardiac events [5]. Recent experimental studies have shown the reciprocal relationships between insulin resistance and endothelial dysfunction (Fig. 2) [6]. Experimental studies have shown a cross-talk between hyperlipidemia and renin–angiotensin–aldosterone system at multiple steps [7]. Thus, combination therapy with statins or peroxisome proliferator-activated receptor agonists and renin–angiotensin–aldosterone system blockers may be more beneficial than monotherapy. Indeed, we demonstrate that ramipril or losartan combined with simvastatin or candesartan combined with fenofibrate significantly reduces blood pressure, improves the lipoprotein profile and endothelial function and reduces inflammatory markers and insulin resistance to a greater extent than monotherapy in patients with type 2 diabetes [8] or hypercholesterolemic, hypertension [9], or hypertriglyceridemic, hypertension [10]. These superior benefits of combination therapy are likely mediated by both distinct and interrelated mechanisms that simultaneously target blood pressure, atherosclerosis, and coronary heart disease (Fig. 3) [6,7,11]. In summary, based on solid evidence from both translational basic science and clinical intervention trials, there is an emerging support for simultaneously targeting multiple therapeutic pathways in the optimal treatment of hypertension.

Acknowledgment

This study was supported in part by grants from established investigator award (2007–1), Gil Medical Center, Gachon University (KKK) and by the intramural research program, NCCAM, NIH (MJQ).

References

1. Yusuf S. Calcium antagonists in coronary artery disease and hypertension. Time for reevaluation? *Circulation* 1995;92:1079–82. [PubMed: 7648648]
2. Tijssen JG, Hugenholtz PG. Critical appraisal of recent studies on nifedipine and other calcium channel blockers in coronary artery disease and hypertension. *Eur Heart J* 1996;17:1152–7. [PubMed: 8869855]
3. Kannel WB. Risk stratification in hypertension: new insights from the Framingham Study. *Am J Hypertens* 2000;13:3S–10S. [PubMed: 10678282]
4. Dahlof B, Sever PS, Poulter NR, et al. 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. [PubMed: 16154016]
5. Rodriguez-Porcel M, Lerman LO, Herrmann J, Sawamura T, Napoli C, Lerman A. Hypercholesterolemia and hypertension have synergistic deleterious effects on coronary endothelial function. *Arterioscler Thromb Vasc Biol* 2003;23:885–91. [PubMed: 12663373]
6. Kim J, Montagnani M, Koh KK, Quon MJ. Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms. *Circulation* 2006;113:1888–904. [PubMed: 16618833]
7. Koh KK, Han SH, Quon MJ. Inflammatory markers and the metabolic syndrome: insights from therapeutic interventions. *J Am Coll Cardiol* 2005;46:1978–85. [PubMed: 16325028]
8. Koh KK, Quon MJ, Han SH, et al. Vascular and metabolic effects of combined therapy with ramipril and simvastatin in patients with type 2 diabetes. *Hypertension* 2005;45:1088–93. [PubMed: 15883229]
9. Koh KK, Quon MJ, Han SH, et al. Additive beneficial effects of losartan combined with simvastatin in the treatment of hypercholesterolemic, hypertensive patients. *Circulation* 2004;110:3687–92. [PubMed: 15569835]

10. Koh KK, Quon MJ, Han SH, et al. Additive beneficial effects of fenofibrate combined with candesartan in the treatment of hypertriglyceridemic, hypertensive patients. *Diabetes Care* 2006;29:195–201. [PubMed: 16443859]
11. Han SH, Quon MJ, Kim J, Koh KK. Adiponectin and cardiovascular disease: response to therapeutic interventions. *J Am Coll Cardiol* 2007;49:531–8. [PubMed: 17276175]

Fig. 1.

Risk of coronary heart disease increases stepwise with the extent of risk factor clustering. Hypertensive patients are more appropriately targeted for therapy by such risk stratification and the goal of the therapy should be to improve the multivariate risk profile. Modified from Kannel [3].

Fig. 2.

A. Parallel phosphatidylinositol 3-kinase-dependent insulin signaling pathways in metabolic and vascular tissues synergistically couples metabolic and vascular physiology under healthy conditions. B. Parallel impairment in insulin signaling pathways under pathological conditions contributes to synergistic coupling of insulin resistance and endothelial dysfunction.

Reproduced from Kim et al. [6].

Fig. 3.

Many stimuli initiate transcription of genes in endothelium that encode protein mediators of inflammation and hemostasis. Renin–angiotensin–aldosterone system (RAAS) is the most important in the pathogenesis of atherosclerosis. Angiotensin II (Ang II) binds to angiotensin II type I receptor (AT1R) and produce oxygen free radicals by using enzymes. Oxygen free radicals dissociate inhibitory factor, IκB and thus activate NF-κB. Activated NF-κB stimulates the expression of proinflammatory genes in the nucleus and the production of proinflammatory proteins such as chemokines and cytokines. Recent experimental studies have shown the reciprocal relationships between insulin resistance and endothelial dysfunction. Experimental studies have shown a cross-talk between hyperlipidemia and RAAS at multiple steps. Combined therapy with statins, peroxisome proliferators-activated receptors (PPARs), and RAAS blockades show additive beneficial effects on endothelial dysfunction and insulin resistance when compared with monotherapies in patients with cardiovascular risk factors by both distinct and interrelated mechanisms. Modified from Dr. Koh [6,7,11].