New Approaches to Blockade of the Renin–Angiotensin–Aldosterone System:

Evidence From Randomized Controlled Trials (RCTs) of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II–Receptor Blockers — Questions Remain Unsolved

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Abstract. Recent randomized controlled trials showed that blockade of the renin–angiotensin system (RAS) by angiotensin-converting enzyme (ACE) inhibitors and angiotensin II–receptor blockers (ARBs) reduced cardiovascular and renal events. These drugs are widely used in the management of cardiovascular and renal diseases. Results from Randomized Controlled Trials (RCTs) so far, however, also raise several questions to be addressed. It should be noted that the residual event rate in the treatment arm in outcome studies that have employed ACE inhibitors or ARBs remains high. Such insufficient efficacy of RAS inhibition may result from the fact that neither ACE inhibitors nor ARBs completely suppress activity of RAS. Since then effort has been made to determine whether the dual blockade of RAS could provide further improvement in cardiovascular and renal outcome. This review extracts unsolved questions in the treatment with RAS inhibitors from outcome studies and discusses them from the clinical pharmacological point of view.

Keywords: Randomised Clinical Trial (RCT), angiotensin II–receptor blocker (ARB), angiotensin-converting enzyme (ACE) inhibitor, chronic kidney disease (CKD), heart failure

1. Randomized Controlled Trials (RCTs) of renin–angiotensin system (RAS) inhibitors in hypertensive patients: Is there any “beyond blood pressure” effect?

Effectiveness of angiotensin-converting enzyme (ACE) inhibitor for prevention of stroke, myocardial infarction, and heart failure in elderly hypertensive patients was firstly tested in the STOP2 (the Swedish Trial in Old Patients with Hypertension 2) trial (1). Results were not so dramatic, that is, there was no apparent advantage from treatment with either ACE inhibitor or Ca²⁺-channel blocker over conventional diuretics and β -blocker. Then

the ACE inhibitor captopril challenged conventional therapy again in hypertensive patients in the CAPPP (the Captopril Prevention Project the Captopril Prevention Project) trial (2), which disappointingly showed higher risk of stroke in captopril-treated patients largely because of inappropriate randomization and resultant differences in baseline and achieved blood pressure. The most tragic and ironically the largest RCT for ACE inhibitor was the ALLHAT (the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) trial (3), which could not show any benefit of either “newer” antihypertensive amlodipine or lisinopril over diuretics as for prevention of myocardial infarction. Moreover, risk of stroke was significantly higher in the lisinopril arm than the diuretics arm presumably because of differences in achieved blood pressure in the ALLHAT trials. Unlike the ALLHAT trial, the ANBP2 (The Australian National

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Blood Pressure Study 2) trial showed significant reduction of myocardial infarction in elderly hypertensive patients receiving ACE inhibitor compared to those who receiving diuretics (4). However, it is of note that only 60% patients received allocated treatment in the ANBP2 trial. In addition, the fact that diuretics could be given to patients belonging to ACE inhibitor group may have confounded results. In terms of ARB, there was no study that showed apparent beneficial effect of ARB as for prevention of myocardial infarction in hypertensive patients. The LIFE (the Losartan Intervention For Endpoint reduction in hypertension study) trial showed significant reduction of risk of stroke but not myocardial infarction in hypertensive patients with left ventricular hypertrophy treated by losartan compared to those who were treated with atenolol (5). Although difference in achieved blood pressure seemed not large enough to explain reduction of stroke risk in the LIFE trial, this result is more likely to be explained by inferiority of atenolol in terms of prevention of stroke rather than a pleiotropic effect of ARB. Results from the SCOPE (The Study on Cognition and Prognosis in the Elderly) trial also showed significant reduction of risk of stroke but not myocardial infarction in hypertensive patients treated by candesartan compared to those who were treated by other antihypertensive drugs (6). However, unlike the LIFE trial, difference in blood pressure may explain the results. Comparison of the Ca^{2+} -channel blocker amlodipine and ARB valsartan was made in the VALUE trial where valsartan was expected to reduce cardiac morbidity and mortality beyond its blood pressure-lowering effect (7). However, amlodipine showed a more pronounced blood pressure lowering effect, which was associated with fewer incidences of myocardial infarction and stroke in the amlodipine group. A series of Japanese studies showed that addition of valsartan to conventional antihypertensive treatment reduced cardiovascular events (8, 9). However, results of these studies should be interpreted with caution because of very few serious cardiovascular events such as myocardial infarction and PROBE (Prospective Randomised Open Blinded Endpoint) design. After all, although several RCTs were intended to show the advantage of RAS inhibitors over conventional treatment including Ca^{2+} -channel blocker in hypertensive patients, obtained conclusion was that reduction of cardiovascular risk was almost dependent on how far blood pressure was lowered. In fact, a recent meta-analysis of 147 RCTs showed all the classes of antihypertensive drugs have a similar effect in reducing myocardial infarction and stroke for a given reduction in blood pressure (10). Does it mean that RAS blockade does not have any pathophysiological advantage over other means of blood pressure lowering despite much experimental evidence? Or Is RAS blockade with

currently available drugs insufficient? There is no clear answer to these questions but some assumptions. One would claim that the HOPE (Heart Outcomes Prevention Evaluation) trial successfully showed the blood pressure-independent effect of ACE inhibitor because 20% reduction of risk for myocardial infarction with ACE inhibitor is greater than would be expected from blood pressure reduction (3 mmHg in systolic blood pressure) (11). This result was reproduced by the EUROPA (Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease) trial (12). However, these results should be carefully interpreted for several reasons. First, most patients in the HOPE or EUROPA trial had coronary artery disease with history of myocardial infarction in half of them and presumably had advanced atherosclerosis. In such patients, stabilization of atherosclerotic plaque by ACE inhibitor, if any, could lead to reduction in cardiac mortality and morbidity. However, such favorable effect of ACE inhibitor does not necessarily benefit every hypertensive patient for a short period. In fact, there was no significant effect of ACE inhibitor on cardiovascular events in patients with less advanced coronary heart disease (13, 14). Second, in the HOPE trial, ramipril was dosed in the evening. Consequently, blood pressure during nighttime (17 mmHg in systolic blood pressure) but not office blood pressure was remarkably reduced in the ramipril group of the HOPE trial (15). Therefore reduction of cardiovascular event seen in the HOPE trial may be more related to blood pressure reduction than originally ascribed. Third, a meta-regression analysis by Staessen et al showed that the actual odds ratio (0.79) for MI in the HOPE trial was within the 95% confidence interval of the predicted odds ratio (0.77 to 0.93) based on change in systolic blood pressure (16). After all, results from the HOPE and EUROPA trials are more plausibly extrapolated to patients with moderate to severe coronary artery disease and even in such patients, discriminating between blood pressure dependent and independent effects on cardiovascular outcome is almost impossible.

2. RAS inhibitor in heart failure: Which is the best third neuroendocrine blocker in heart-failure patients?

It is well established that ACE inhibitor and β -blocker prolonged time to death for any reasons in all grades of chronic heart failure. However, it has been shown that the activity of RAS is not fully suppressed by ACE inhibitors and the mortality rate of patients remains high even with ACE inhibitor and β -blocker. A clinical question to be addressed is, therefore, whether further inhibition of RAS by adding ARB or spironolactone to ACE

inhibitor treatment improves mortality. The Val-Heft (Valsartan Heart Failure Trial) trial was firstly undertaken to see if ARB could be the best third drug (17). Although addition of valsartan reduced combined end-point, that is, mortality and hospitalization for heart failure, total mortality itself was not altered (19.7% in the valsartan group and 19.4% in the placebo group). The VALIANT (Valsartan in Acute Myocardial Infarction Trial) trial also showed no apparent benefit when valsartan was added to ACE inhibitor in patients with left ventricular dysfunction after myocardial infarction (18). Unlike the Val-Heft trial, the CHARM (the Candesartan in Heart failure–Assessment of Reduction in Mortality and morbidity programme) added trial reduced total mortality by 11%, although this study was not sufficiently powered for total mortality (19). This discrepancy between two studies cannot be clearly explained and possible differences in performance among ARBs are unsolved questions. On the other hand, there seems to be no discrepancy between two trials of aldosterone blockers. The RALES trial showed that spironolactone significantly reduced total mortality by 30% in patients with severe heart failure (20). The EPHASUS (Eplerenone Post-acute Myocardial Infarction Heart Failure Efficacy and Survival Study) trial showed that eplerenone reduced total mortality by 15% in patients with left ventricular dysfunction after myocardial infarction (21). These results from RCTs could not clearly answer which to use as the third neuroendocrine blocker in heart failure patients because of the discrepancy between RCTs of ARBs and lack of evidence for aldosterone blocker in patients with mild to moderate heart failure. Moreover, risk of lethal adverse reaction such as hyperkalemia associated with combination of ARB or aldosterone blocker and ACE inhibitor in “real world” heart failure patients may be considerably higher than expected from RCTs in selected patients (22). The direct renin-inhibitor aliskiren may be another candidate for the third neuroendocrine blocker. In fact, the ALOFT (the ALiskiren Observation of heart Failure Treatment study) trial showed that addition of aliskiren to ACE inhibitor / β -blocker in heart-failure patients improved neurohumoral profile including N-terminal pro-BNP and was well tolerated (23). Although early trials such as ALOFT suggest promise, this combination is the subject of ongoing large-scale outcome studies at the moment.

3. RAS in chronic kidney disease (CKD): Can efficacy of dual blockade be properly assessed by albuminuria?

Inhibition of RAS undoubtedly confers protection against progression of diabetic and non-diabetic renal

diseases. However, again in outcome studies in patients with kidney disease, there have been high residual event rates even in patients allocated to RAS inhibition. Moreover, the RENAAL (the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) trial clearly showed renal protection by losartan but no effect on total mortality in type 2 diabetes (24). The IDNT (the Irbesartan Diabetic Nephropathy Trial) trial showed that irbesartan certainly reduced renal events compared to amlodipine, but amlodipine was superior to irbesartan in terms of protection against stroke and myocardial infarction (25). These trials suggest that ARB monotherapy may be insufficient as RAS blockade or RAS blockade itself is insufficient as drug intervention for renal as well as cardiovascular protection. Therefore aggressive RAS blockade by combination of ARB and ACE inhibitors and, very recently, of ARB and renin inhibitor was evaluated mainly by albuminuria or proteinuria but not true renal end-point in CKD patients. Results so far have suggested benefit of dual RAS blockade compared to monotherapy either with ACE inhibitors or ARBs (26, 27). Meta-analysis by Kunz et al. showed that dual blockade of RAS reduced proteinuria by 20% – 25% compared to monotherapy (26). However, it should be emphasized that clinical validity of albuminuria as a surrogate marker has not been established in a broad range of patients. FDA stated that proteinuria is accepted in a very restricted sense (28). Indeed the ONTARGET (The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) trial that compared monotherapy with ramipril or telmisartan with the combination raised doubts against surrogacy of albuminuria for renal events (29). In this study albuminuria increased to a lesser extent, but there were significantly higher renal event rates in the combination therapy arm compared to either monotherapy arm. Although results from the ONTARGET trial cannot be directly extrapolated to CKD patients because of different clinical background, efficacy and safety of dual blockade should be assessed in CKD patients by true end-point with great caution. Careful dose-finding studies may also help identify appropriate dose and combination.

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References

- 1 Hansson L, Lindholm LH, Ekblom T, Dahlöf B, Lanke J, Scherstén B, et al. Randomised trial of old and new antihyperten-

- sive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension 2 study. *Lancet*. 1999;354:1751–1756.
- 2 Hansson L, Lindholm LH, Niskanen L, Lanke J, Hedner T, Niklason A, et al. Effect of angiotensin converting enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet*. 1999;353:611–616.
- 3 ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. *JAMA*. 2002;288:2981–2997.
- 4 Second Australian National Blood Pressure Study Group. A comparison of outcomes with angiotensin-converting-enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med*. 2003;348:583–592.
- 5 LIFE Study Group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet*. 2002;359:995–1003.
- 6 SCOPE Study Group. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. *J Hypertens*. 2003;21:875–886.
- 7 VALUE Trial Group. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet*. 2004;363:2022–2031.
- 8 Jikei Heart Study Group. Valsartan in a Japanese population with hypertension and other cardiovascular disease (Jikei Heart Study): a randomised, open-label, blinded endpoint morbidity-mortality study. *Lancet*. 2007;369:1431–1439.
- 9 KYOTO HEART Study Group. Effects of valsartan on morbidity and mortality in uncontrolled hypertensive patients with high cardiovascular risks: KYOTO HEART Study. *Eur Heart J*. 2009;30:2461–1269.
- 10 Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ*. 2009;338:b1665.
- 11 HOPE (Heart Outcomes Prevention Evaluation) Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med*. 2000;342:145–153.
- 12 European trial on reduction of cardiac events with perindopril in stable coronary artery disease investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet*. 2003;362:782–788.
- 13 The PEACE Trial Investigators. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med*. 2004;351:2058–2068.
- 14 CAMELOT Investigators. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. *JAMA*. 2004;292:2217–2225.
- 15 Svensson P, de Faire U, Sleight P, Yusuf S, Ostergren J. Comparative effects of ramipril on ambulatory and office blood pressures. A HOPE substudy. *Hypertension*. 2001;38:e28–e32.
- 16 Staessen JA, Wang JG, Thijs L. Cardiovascular protection and blood pressure reduction: a meta-analysis. *Lancet*. 2001;358:1305–1315.
- 17 Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med*. 2001;345:1667–1675.
- 18 Valsartan in Acute Myocardial Infarction Trial (VALIANT) Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med*. 2003;349:1893–1906.
- 19 CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet*. 2003;362:767–771.
- 20 Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med*. 1999;341:709–717.
- 21 Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003;348:1309–1321.
- 22 Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med*. 2004;351:543–551.
- 23 Aliskiren Observation of Heart Failure Treatment (ALOFT) Investigators. Effects of the oral direct renin inhibitor aliskiren in patients with symptomatic heart failure. *Circ Heart Fail*. 2008;1:17–24.
- 24 RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345:861–869.
- 25 Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*. 2001;345:851–860.
- 26 Kunz R, Friedrich C, Wolbers M, Mann JF. Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin angiotensin system on proteinuria in renal disease. *Ann Intern Med*. 2008;148:30–48.
- 27 MacKinnon M, Shurraw S, Akbari A, Knoll GA, Jaffey J, Clark HD. Combination therapy with an angiotensin receptor blocker and an ACE inhibitor in proteinuric renal disease: a systematic review of the efficacy and safety data. *Am J Kidney Dis*. 2006;48:8–22.
- 28 National Kidney Foundation Home Page 2008
<http://www.kidney.org/professionals/physicians/proteinuria.cfm>
- 29 ONTARGET Investigators. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet*. 2008;372:547–553.