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Benefits and risks of dual inhibition of the renin–angiotensin aldosterone system for kidney disease

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ABSTRACT

A In most cases, neither angiotensin converting enzyme (ACE) inhibitor therapy nor angiotensin II receptor blockers (ARBs) therapy alone inhibits completely the renin-angiotensin aldosterone system (RAAS). The drawbacks of ACE inhibitors are the ACE escape and aldosterone escape phenomenon, which are related to the tissue construction of angiotensin II and aldosterone by enzymes besides ACE. Combination of RAAS inhibition may avoid the ACE and aldosterone escape events that increases the efficiency of ACE inhibitors and ARBs and obstruct all angiotensin II and aldosterone actions accordingly. ONTARGET, largest trial of combination against alone RAAS blockade therapy in patients with vascular diseases or diabetes along with disease of such organs displayed that combination therapy advised no extra-benefit in reducing advance to end-stage renal disease in diabetic patients and decreasing the risk of cardiovascular. Certainly, in this trial, the administration of dual RAAS blockade therapy of an ACE inhibitor plus ARB was correlated with a higher degree of side effects in comparison to monotherapy. In addition to the study of ONTARGET, the ORIENT, VALIANT, VA NEPHRON-D and HALT-PKD trials also proved this finding. Adverse events associated with combination therapy of ACE inhibitor plus ARB is including hyperkalemia, low blood pressure, acute kidney injury (AKI) and withdrawal because of side effects.

Implication for health policy/practice/research/medical education:
There are currently no proven benefits of the combined angiotensin converting enzyme inhibitor plus angiotensin II receptor blockers over single drug renin-angiotensin aldosterone system blockade. Therefore, it is assumed that dual RAAS blockade of angiotensin converting enzyme inhibitor and angiotensin II receptor blocker should remain for exceptional conditions.
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Mini-Review

Introduction

The renin-angiotensin aldosterone system (RAAS) except for the adjustment of blood pressure, plays a vital role in advance of renal injuries via hemodynamic and non-hemodynamic effects. The participation of the RAAS in renal injury processes is through angiotensin II and aldosterone actions (1). In most cases, neither angiotensin converting enzyme (ACE) inhibitor therapy nor angiotensin II receptor blockers (ARBs) therapy alone inhibits completely the RAAS. The drawbacks of ACE inhibitors are the angiotensin II and aldosterone escapes phenomenon, which are correlated with the construction of angiotensin II and aldosterone by agents besides ACE. Combination of RAAS inhibition may avoid the angiotensin II and aldosterone escapes events that reduces the efficiency of ACE inhibitors and ARBs and obstruct all angiotensin II and aldosterone actions (2). Really, more reductions in blood pressure and albuminuria are detected with diverse ACE inhibitors plus ARBs combinations. Such outcomes have induced many therapists to administrate dual RAAS inhibition (3). There are numerous fields which dual RAAS inhibition is regarded as an appropriate therapy choice including control of hypertension, in individuals at risk for vascular disease (4), post-myocardial infarction (5), decreased ejection fraction types of heart failure, reduction in morbidity and cardiac remodeling (9,10) and reduce proteinuria types in patients suffering from diabetic

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nephropathy (6,7), and pediatric IgA nephropathy (8). In patients with diabetic nephropathy, combination therapy with ACE inhibitors plus ARBs is predicted to have stronger anti-inflammatory and anti-oxidant results from renal perspective and stronger inhibition from the advance of atherosclerosis and diabetic nephropathy against single therapy. The reduction rate of serum and urinary interleukin 18 concentrations, albumin-to-creatinine ratio (ACR) and 8-hydroxy-2'-deoxyguanosine in the combination therapy were significantly larger than in the monotherapy (11). In 2001, Valsartan Heart Failure Trial (Val-HeFT) study that was focused on cardiovascular and not renal pathology. The positive effect of combination of the ACE inhibitors plus ARB treatment in patients with heart failure in Val-HeFT study was displayed on the mortality and morbidity outcomes. Furthermore, it was reported that the treatment with the combination of ACE inhibitors plus ARB significantly decreased all-cause mortality, cardiovascular death, and heart failure-related hospitalizations in hemodialysis patients, as compared to the treatment with ACE only (12). The combination treatment of ARB and ACE inhibitor in non-diabetic renal disease (COOPERATE) was the first medical trial to show the benefits and long-term efficacy of combination therapy with an ACE inhibitor plus ARB on hard renal outcomes in 2003 (13). However, the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), the biggest trial of combination against single therapy in individuals with vascular diseases (cardiac or cerebral) or diabetic patients (14,15), displayed that combination therapy advised no extra-benefit in reducing advance to end-stage renal disease in diabetic patients and decreasing the risk of cardiovascular (16). Certainly, in that trial, the administration of ramipril (ACE inhibitor) plus telmisartan (ARB) is correlated with a greater degree of fainting (syncope), amplifying of serum creatinine up to two times or dialysis and significant 33% increase in risk of renal damage than monotherapy, without benefit on the lethal and non-lethal cardiovascular results (17). In ONTARGET trial, the frequent reported incidence of renal damage, promotes this theory that the long-term renal benefit would dominate the risks related to combination therapy, when there is minimum proteinuria (18).

Up to now several recommendations on combination RAAS blockade therapy have been observed in studies (19). In 2009, despondency climaxed with the withdrawal of COOPERATE trial from the Lancet and COOPERATE trial detected a number of conflicts and inaccuracy in data, after an organized examination.

Although dual RAAS blockade with ACE inhibitors plus an ARB of the "Olmesartan Reducing Incidence of End stage renal disease in diabetic Nephropathy Trial" (ORIENT) study, reduced proteinuria; however renal or cardiovascular outcomes did not improve (20). Furthermore, the combination therapy of ACE inhibitor (captopril) plus ARB (valsartan) against monotherapy in the Valsartan in Acute Myocardial Infarction (VALIANT) cohort trial was investigated in patients with acute myocardial infarction for 10 days, which no extra-profits were observed with dual RAAS blockade therapy while several number of adverse effects was observed as well (10,21). The outcomes of the Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) follow up are obtained in diabetic patients with macro-albuminuria and stage III chronic kidney disease (CKD) who received an ACE inhibitor (lisinopril) plus an ARB (losartan); without any significant effect on renal outcome. These trials of combination therapy, in total did not show the decrease in cardiovascular or renal diseases. In contrast, it seems that combination therapy conveys more side effects. The outcomes of the VA-NEPHRON-D trial clarify that combination therapy of ACE inhibitor plus ARB could not presently be suggested for the treatment of diabetic patients. The other trial that would evaluate the effect of dual RAAS blockade on kidney disease development is the Halt Progression of Polycystic Kidney Disease (HALT-PKD) study. ACE inhibitor alone controlled blood pressure in most patients with autosomal dominant polycystic kidney disease (ADPKD) and an estimated glomerular filtration rate (eGFR) of 30-90 ml/min/1.73 m^2. The HALT-PKD trials were planned to control the effect of severe blockade of the RAAS and blood-pressure control on the development of kidney disease in patients with stage III of ADPKD. The dual RAAS blockade against ACE inhibitor alone did not show an extra-benefit (22).

A previous meta-analysis suggested that dual RAAS blockade can be applied for diabetic nephropathy with proteinuria, but must be applied carefully in patients with advanced CKD, because of the higher incidence of hyperkalemia and acute kidney injury (AKI) (16).

Studies regarding the efficiency and renoprotection properties among ACE inhibitors, ARB or combination RAAS therapy in pre-dialysis patients showed various results. In contrast to ARB, or ACE inhibitors monotherapy, combination therapy displays a greater risk of mortality in diabetic group and a greater proportion of hyperkalemia too. Thus, ARB alone particularly is further protective and better than combination therapy in pre-dialysis patients (23).

Search strategy

For this mini-review, we searched PubMed/Medline, Web of Science, Scopus, DOAJ (Directory of Open Access Journals), Embase and Google Scholar, using keywords including; angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, renin-angiotensin aldosterone system, acute kidney injury and hyperkalemia.

Adverse events associated with combination therapy of ACE inhibitor plus ARB

Hyperkalemia

Potassium plays important role in keeping electrolyte

equilibrium, control of blood pressure, additional sodium levels decrease, and decreasing osteoporosis, and the risk of urolithiasis. Potassium secretion is controlled mainly by serum aldosterone concentrations and the sodium reabsorption. ACE inhibitor plus ARB especially dual RAAS blockade is effective treatment agents that can potentially produce or aggravate hyperkalemia, especially among patients with basic CKD. Dual RAAS blockade may damage extra-renal/transcellular potassium nature as well as decrease potassium excretion in patients with renal damage. Therefore, patients with CKD who are at specific risk for hyperkalemia should take a drug that more inhibits potassium excretion by interfering with the RAAS. To minimalize risk of hyperkalemia in patients which combination therapy started, the stage of CKD and serum potassium level must be assessed carefully, then complementary medications and diet that decrease risk of hyperkalemia must be achieved (24).

Hypotension

Hypotension is not a particular adverse event with combination therapy; however, it is induced by comorbidity that causes volume depletion or a decrease in sodium reabsorption.

Acute kidney injury

In ONTARGET study, risk of acute renal failure like requirement for dialysis due to dual RAAS blockade treatment by ACE inhibitor plus ARB is almost doubling of single administration of ACE inhibitor or ARB (25,26). Reasons for renal dysfunction on RAAS blockade therapy can be included poor renal perfusion (like low-cardiac output and dehydration), renovascular disease (like renal artery stenosis), drugs (like radiocontrast and nonsteroidal anti-inflammatory drugs) and infections (like bacterial infection) (27). Glomerular filtration pressure is mainly decreased with ACE inhibitor and ARB particularly in patients with long-term treatment. Pre-renal afferent arteriolar blockade because of other drugs for example non-steroidal anti-inflammatory drugs and hypertension can cause AKI in patients on ACE inhibitor plus ARB. ACE inhibitor and ARB can also increase radiocontrast induced AKI.

Withdrawal because of side effects

Withdrawal of ACE inhibitor or ARB during treatment in hospital for heart failure was connected to higher rates of mortality. Yearly mortality was 28.2% in patients who continued on ACE inhibitor/ARB versus 41.6% in patients who discontinued ACE inhibitor/ARB therapy (28).

Conclusion

It is concluded that in human diseases, there are currently no proven benefits of the combined ACE inhibitor plus ARB over single drug RAAS blockade. Therefore, it is assumed that dual RAAS blockade of ACE inhibitor and ARB should continue as standard treatment in the models in which beneficial effects have been satisfactorily confirmed. In the models where such dual therapy was not finally better, monotherapy of RAAS blockade (either ACE inhibitor or ARB) should be administered. It is suggested that dual RAAS blockade can be applied for diabetic nephropathy with proteinuria, but must be applied carefully in patients with advanced CKD, because of the higher incidence of hyperkalemia and AKI.

Author's contribution

AS, NN and SM contributed equally to preparation of the study and paper. AS and NN were included in preparing the concept and design. NN and SM revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing and revising the final draft of the manuscript. All authors have read and approved the content of the manuscript and confirmed the accuracy of any part of the paper.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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