Dual Blocking of the Renin Angiotensin System: A Settled Issue?

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Abstract

The renin-angiotensin system (RAS) exerts wide-ranging effects on cardiovascular and kidney function. Oddly, this system that was designed to preserve normal hemodynamics may become harmful in certain clinical situations. For this reason, RAS inhibition is a highly effective therapeutic approach, not only to lower blood pressure but also to reduce kidney and cardiovascular disease morbidity and mortality. In some patients however, these beneficial effects of RAS inhibition are incomplete or absent. For these less than ideal results, several reasons have been proposed; e.g.: angiotensin escape, over production of angiotensin from negative feedback, local tissue RAS, etc. To secure better RAS blocking, some clinicians have proposed increasing the dose of angiotensin converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB's) beyond the recommended doses or combining two RAS inhibitors. In high-risk patients though, this more intensive RAS inhibition should be undertaken with great precaution, as tissue perfusion may be highly renin-dependent and serious adverse side effects could take place. This issue is yet to be settled as patients with significant proteinuria can be benefitted by intensive RAS inhibition. The purpose of this article is to review the evidences accrued on the use of intensive or dual blocking of RAS. We analyze potential purposes and hazards in the light of actual population data as published in recent trials.

Keywords: Renin angiotensin system; Chronic kidney disease; Dual RAS blocking

Introduction

The renin angiotensin system (RAS) plays an all-encompassing role in cardiovascular regulation. Indeed, the early notion defining its function as vasoconstrictive was expanded to a much broader physiological spectrum, including sodium regulation and structural cardiovascular changes. Moreover, many studies have shown the synthesis and release of various components of the RAS in a number of organs. Further research revealed disparate RAS effects on vascular tone and sodium excretion. That is, RAS can induce vasoconstriction or vasodilatation, natriuresis or sodium retention, hypertrophy or decreased proliferation, all depending on a diversity of angiotensin peptides that can bind to different receptors. The complexity of this system explains the multiplicity of its effects.

Predictably, inhibition of RAS at various levels potentially could yield multiple benefits. Indeed, treatments with either angiotensin converting enzyme inhibitors (ACEi), or angiotensin II receptor blockers (ARB's) have shown important beneficial effects, many of which are independent from hypertension control. Actually, RAS inhibition is effective not only in treating essential hypertension, but also in renovascular hypertension, heart failure, diabetic nephropathy, various kidney diseases, (particularly when associated to heavy proteinuria), atherosclerosis, acute coronary syndrome, vasculitis, ventricular hypertrophy, atrial fibrillation, insulin resistance, multiple sclerosis and others. Progression in most of these conditions is linked to RAS pathobiological effects. The validity of this notion has been shown in a number of clinical trials. Unfortunately, it remains to discriminate between the putative roles of circulating vs local RAS effects in most clinical situations. The available data suggest that both play important functions and thus, measuring plasma renin activity may fail to predict the response to RAS inhibition. Be that as it may, the pathogenic relevance of plasma renin activity levels is undeniable [1,2].

The renin-associated risks take place through Ang II effects. Therefore, preventing the conversion of Ang I to Ang II, or blocking the AT1 receptor should avoid the risk. However, ACE inhibitors block the synthesis of Ang II only partially and conversion of Ang I to Ang II can be achieved by mean of other enzymes [3]. Moreover, parallel activation of non-ACE pathways may generate angiotensin peptides capable of stimulating the AT1 receptors. These phenomena have been proposed as an explanation for the alleged ACE "escape" [3]. Likewise, ARBs efficacy can be hampered in the presence of very high Ang II levels (resulting from negative feedback) that could compete for the receptor AT1 (first order kinetics). In brief, Ang II escape has been reported with both ACE inhibitors and ARBs [4].

Because of these observations suggesting that RAS inhibition may be less than complete, some investigators have attempted to improve the blocking of the system by using doses higher than those usually recommended [4]. Conceivable, this could afford a more complete inhibition of RAS and hence, better hypertension control and organ protection. This approach should cause little or no harm as experimental and clinical evidences have shown remarkable clinical tolerance. Indeed, RAS inhibitors are well tolerated even in clinical and experimental conditions of reduced renal function [5].

In brief, the notion implies getting greater protective effects on organ tissues by intensive RAS blocking [6,7]. In particular, reducing proteinuria is a mayor goal in chronic kidney diseases, both in diabetic and non-diabetic nephropathies.

Intensive RAS Blockade

Intensive RAS Blockade has been approached by 2 means: supramaximal doses of RAS inhibitors, and dual blockade [8].

Supramaximal doses of RAS inhibitors

Weinberg M et al. studied elderly normotensive patients suffering from diabetic nephropathy, focal sclerosis, membranous nephropathy

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and post-infectious glomerular disease. Proteinurias in nephrotic range were treated with increasing doses of Candesartan. Protein excretion rate decreased progressively as the Candesartan doses were increased. These effects were independent from blood pressure levels. The authors observed no changes in serum creatinine or serum potassium despite large doses of Candesartan.

Dual RAS blockade

In early studies, dual blockade seemed to show beneficial effects on some therapeutic targets. For instance the CALM trial evaluated combination therapy (candesartan/lisinopril) in hypertensive patients with microalbuminuria [8]. They found a significant reduction in diastolic blood pressure and in protein excretion rate with combined candesartan-lisinopril therapy compared to single treatment with either drug. In this study the incidence of side effects were low and similar in both groups. Parving HH et al had also shown the anti-proteinuric effect of combination therapy with losartan-enalapril in Diabetes Type 1 [9].

Regrettably, studies evaluating dual RAS blockade have been largely inconsistent. For instance, while in the ALLAY, dual blocking was associated with strong advantages over monotherapy, the results where negative in the ONTARGET and disappointing in the ALTITUDE. A possible explanation for these contradictions could lie in differences in inclusion and exclusion criteria. Actually, when inclusion criteria are too broad, the risk/benefit relationship could be displaced toward higher rate of complications, simply by including patients with excessive risk.

For instance, in the ONTARGET, comparing telmisartan plus ramipril against single therapy, no added benefit could be shown for the dual blocking and it even suggested that the combination could be detrimental. However, patients in this trial were diabetic with features of high cardiovascular risk, and normal or near normal baseline blood pressure. Indeed, in the combined therapy group mean baseline blood pressure was 141.9 ± 17.6 / 82 ± 10,4 mmHg. Thus, patients with basal blood pressure below the mean could have suffered periods of critically low coronary, brain or kidney perfusion. Upon reviewing the reported adverse effects, it can be concluded that falls, syncope, increased serum creatinine, hyperkalemia and stroke may all have resulted from diminished tissue perfusion.

From the ONTARGET results it could be concluded that dual blocking yields no benefit in terms of kidney function. However, this seems unjustified for several reasons: a) only a few patients had significant proteinuria (damage prevention could hardly be shown where no active damage seemed evident, in a short term study and with near-normal blood pressure levels); b) kidney function was normal on average (mean value: 73.6 mL/min) and c) only 36.7% of the patients were diabetics and almost 1/3 had normal blood pressure.

In addition, in the ONTARGET, statistical power for renal outcomes was reached by adding mortality rate and acute hemodialysis (HD) that not always relate to kidney disease progression. Nevertheless, the rates of HD and increased serum creatinine were similar between groups. A fall in glomerular filtration rate (GFR) is expected and even desired, since it indicates reduction in glomerular pressure. Indeed, RAS inhibitors have shown to decrease GFR through a hemodynamic mechanism that is not overtly detrimental. Actually, patients with higher serum creatinine levels post RAS inhibition get the highest cardiovascular benefits [10,11]. This was confirmed in a post hoc analysis of the RENAAL Study.

Unfortunately, in the ONTARGET, urinary albumin excretion rate was not assessed on a yearly basis, the serum creatinine was not measured with a standardized or centralized method and the doubling of serum creatinine was not confirmed. Moreover, the indication for HD was arbitrary and non-protocol specified. In many patients the reason for chronic HD was undefined.

Similar drawbacks showed the ALTITUDE. In this study, mean baseline systolic pressure was 137 ± 16.2 mmHg while baseline diastolic pressure was 74.1 ± 9.8 mmHg in the losartan+ lisinopril group. Most of the serious adverse effects could have been the result of poor perfusion pressure, a predictable complication in high-risk patients, many of which had blood pressure in the lower range of normal. Again, falls, fainting, non-fatal cerebrovascular accidents, hyperkalemia and increased serum creatinine are well known complications of inadequate perfusion and therefore avoidable. In the ALTITUDE, patients with serum potassium concentrations greater than 5 mMol/L were randomized to dual drug treatment. This is important, because trial definitions may not reflect the clinical significance of a side effect. For instance, combination therapy compared to monotherapy was associated with an increased risk for moderate hyperkalemia (serum potassium >5.5 mMol/L) but not of clinically significant hyperkalemia (serum K > 6 mMol/L).

A third multicentric trial showing negative results from dual blocking was recently published by Friend LF et al. [12]. This study evaluated losartan against losartan plus lisinopril in Diabetic patients with a mean age of 64.7 ± 7.7 and 64.5 ± 7.9 years of age respectively. The design of this study eluded some of the reservations that had emerged with the ONTARGET and the ALTITUDE. However, the baseline blood pressure for the losartan+placebo group was 136.9 ± 16.5 mmHg for the losartan+lisinopril group. Again these statistics indicate that some patients were at the limit of perfusion in this largely elder population. Moreover, close to ¼ of the patients suffered coronary artery disease. The authors correctly acknowledge these features. The fall in perfusion pressure is supported by the two most important reasons for discontinuation in this trial: hyperkalemia and acute kidney injury. The latter, an abrupt loss of kidney function can result from a transient hemodynamic change, not necessarily a permanent injury to the kidney. Lastly, the authors report lack of benefit, but a mean 2.2 years follow up may be insufficient to see renal protection.

In summary, combination therapy of RAS inhibitors may offer potential cardio-renal benefits. Its utilization has shown tolerability compared to placebo, particularly in patients at high risk for congestive heart failure, diabetes mellitus or CKD. It should be kept in mind that in Chronic Kidney Disease (CKD), the goal is not only blood pressure control, but also reduction of proteinuria. Indeed, high protein excretion rate is a risk factor for kidney disease progression, and its reversion delays progression [13,14].

Nevertheless, patients at high cardiovascular risks should be carefully monitored. Double or intensive blocking may be a needed therapeutic approach to prevent cardiac or renal disease progression and careful monitoring clinical and laboratory parameters could offer a desirable alternative over hemodialysis or transplantation.

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