Review Article

EFFECTS OF DUAL INHIBITION OF RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM ON CARDIOVASCULAR AND RENAL OUTCOMES: BALANCING THE RISKS AND THE BENEFITS

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INTRODUCTION

Over the last few decades, chronic kidney disease (CKD) has rapidly become a major public health problem at global level [1, 2], including Italy [3]. This is mainly due to the growing incidence of major cardiovascular (CV) risk factors, such as hypertension, dyslipidaemia, obesity and diabetes mellitus, which are the most common underlying causes responsible for the development and progression of CKD [4]. In addition, prevalence of these risk factors progressively increases as glomerular filtration rate (GFR) deteriorates, and it is higher in the presence of albuminuria at any GFR level. Indeed, it has been reported that the lower the renal function, the higher the incidence of CV events; on the other hand, the higher the individual CV risk profile, the higher the risk of having impaired renal function, either as reduced GFR or albuminuria [5, 6]. On the basis of these assumptions, and in view of the progressive ageing of the population, CKD is now considered a major contributor to the burden of CV diseases, without relevant differences for age, gender, and ethnic categories [7, 8].

As a matter of fact, although CKD is usually a progressive disease, most renal patients will prematurely die due to an excess of CV events, including myocardial infarction, stroke, congestive heart failure and CV death, often well before kidney dysfunction has reached its final stage (ESRD). Also, once a patient has reached ESRD or dialysis, while CV risk increases even further, therapeutic interventions seem to lose their effectiveness, probably due to more complex and not fully elucidated pathophysiological interactions between haemodynamic and hormonal mechanisms that may occur at both systemic and renal levels [9-11].

Among different risk factors, hypertension is one of the most frequently associated with CKD [12-15]. Renal disease is commonly complicated by the development of hypertension, and most CKD patients present high blood pressure (BP) levels, despite optimal pharmacological treatment. At the same time, hypertension is a well-known risk factor for the development and progression of CKD. Thus, achieving prompt and effective BP control represents a key issue in the therapeutic strategy to reduce both CV events and disease progression in CKD patients [16].

Current guidelines recommend the use of renin-angiotensin-aldosterone system (RAAS) inhibitors for treating hypertension and achieving the BP targets in CKD patients [17, 18]. Indeed, RAAS inhibiting drugs, such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), antialdosterone agents and direct renin inhibitors (DRI), have demonstrated to provide greater benefits compared to other drug classes on the risk of CV outcomes, even beyond

BP lowering effect [19, 20].

When used in monotherapy (or combined with other BP lowering drug classes), RAAS blocking agents have demonstrated beneficial effects in terms of renal outcomes, specifically including doubling of serum creatinine levels, reduction of GFR and progression toward ESRD especially in the presence of albuminuria [21-23]. Despite evidence of clinical benefits in specific condition as chronic heart failure [24-26] or on intermediate endpoints (i.e. reduction of proteinuria) in patients with CKD [27], the use of combination therapies based on two (or more) drugs active on RAAS has been questioned in patients with hypertension, mostly due to an increased incidence of renal adverse events with no additional benefits on CV outcomes (compared to monotherapy) [28].

On the basis of these considerations, the aim of this narrative review is to assess (the currently) available clinical evidence on the use of combination therapies based on any combination of ACE inhibitors, ARBs, antialdosterone agents or DRI, for the clinical management of hypertension in high risk patients.

DUAL RAAS BLOCKADE ON CARDIOVASCULAR AND RENAL OUTCOMES

Simultaneous pharmacologic blockade of the RAAS at multiple sites has a strong pathophysiological rationale [29, 30] in patients with arterial hypertension. Angiotensin II may also be generated through ACE-independent pathways, and circulating Angiotensin II levels have been shown to gradually return to pre-treatment values under chronic treatment ACE inhibitors, a phenomenon known as ‘‘Angiotensin escape’’. Preliminary results of several small studies and meta-analyses [31-33] suggested a potential for greater renal protection, i.e. greater reduction of proteinuria by combining treatment with an ACE inhibitor and an ARB.

On the basis of these considerations, several trials tested the effectiveness of dual RAAS inhibition on CV and renal outcomes. A detailed description of the clinical characteristics of the populations included in these trials has been reported elsewhere [34]. The effectiveness of these interventions on the incidence of the composite CV endpoint (stroke, myocardial infarction and CV death), unplanned hospitalization for heart failure, composite renal endpoint (doubling of serum creatinine, progression of ESRD, death) outcomes is reported in **Table 1**:

Trials with ACE inhibitors plus ARBs

The Ongoing Telmisartan Alone and in Combination with Ramipril Global End- point Trial (ONTARGET) tested the non-inferiority of a combination therapy based on the ACE inhibitor (ramipril 5-10 mg) plus the ARB (telmisartan 40-80 mg) compared to monotherapy with ACE inhibitor in more than 25,000 high vascular risk patients [35]. The primary CV endpoint of the study was a composite of death from CV causes, myocardial infraction, stroke or hospitalization for heart failure [35]; the primary renal outcome was a composite of doubling of serum creatinine, dialysis, and death [36].

This trial demonstrated that, despite lower BP and greater reduction in albuminuria, combination therapy provided no significantly greater CV benefit and, on the contrary, higher risk of renal outcomes as compared to both monotherapies [35]. In particular, the incidence of the primary endpoint was 16.3% with the combination therapy and 16.5% in the ramipril group (relative risk [RR] 0.99 (odds ratio [OR] with 95% confidence interval [CI] 0.92–1.07). Similarly, the incidence of the secondary outcomes was 14.1% in both ramipril and combination therapy groups [RR (95% CI): 1.00 (0.93-1.09)]. The same results were observed when considering deaths from CV or non-CV causes, as well as in all predefined subgroups of the trial, including those with diabetes. It should be also noted, however, that the majority of patients included in this trial had high-normal BP values and normal renal function at baseline (about one quarter of patients had GFR <60 ml/min/1.73m2 or albuminuria).

A predefined analysis on renal endpoints revealed that patients at low renal risk, such as those without diabetes and hypertension, those without micro or macroalbuminuria and those without overt diabetic nephropathy, when treated with combination therapy, had worse renal outcomes compared to ramipril monotherapy [36]. This has been related to excessive BP reductions starting from high-normal BP values obtained with combination therapy compared to monotherapy. In this regard, acute renal failure requiring dialysis (an endpoint that can be related to a marked reduction in renal blood flow) occurred more frequently in the combination therapy group compared to ramipril group [RR (95% CI): 2.19 (1.13-4.22); P=0.020], whereas chronic dialysis for progression to ESRD was not more commonly observed in the former than in the latter group [RR (95% CI): 1.05 (0.65-1.69); P=0.854] [36]. Similarly, doubling of serum creatinine, a powerful indicator of renal progression, did not occur more often under combination treatment compared to monotherapy with ACE inhibitor [RR (95% CI): 1.20 (0.96-1.50); P=0.110] [36]. Thus, the absence of beneficial effects on CV outcomes and the higher incidence of adverse renal events compared

to that observed in patients with monotherapy should be considered in light of the large and possibly unnecessary BP reduction observed in those patients treated with combination therapy and who had high-normal BP values at baseline.

After the results of the ONTARGET trial, which demonstrated the beneficial effects of combination therapy in decreasing the risk of ESRD only in the relatively small fraction of patients with overt proteinuria, the Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) trial was designed to evaluate the efficacy of combination therapy on renal protection in patients with overt diabetic nephropathy. The trial tested the efficacy of the combination therapy based on an ARB (losartan 50-100 mg) plus either an ACE inhibitor (lisinopril 10-40 mg) or placebo in 1,448 type 2 diabetic patients with urinary albumin-to-creatinine ratio (UACR) of at least 300 mg/g, and an estimated GFR of 30.0-89.9 ml per minute per 1.73 m^2 [37]. Of note, also in this trial baseline BP values fell within the high-normal range for the systolic and in the normal range of diastolic BP. The primary endpoint was the first occurrence of the composite renal outcomes, including change in the estimated GFR, ESRD, or death. The study was early stopped due to safety concerns, namely an increased rate of hyperkalaemia (P<0.001) and acute renal failure (P<0.001) in those patients treated with combination therapy, thus not achieving the statistical power necessary to detect any difference in the incidence of the primary endpoint between two treatment strategies. At the end of the trial, there were 152 primary endpoint events in the monotherapy group and 132 in the combination therapy group [hazard ratio [HR] (95% CI): 0.88 (0.70-1.12); P=0.30)] [37]. There was no benefit from combination therapy compared to monotherapy with respect to ESRD [HR (95% CI): 0.66 (0.41-1.07); P=0.07)] or death [HR (95% CI): 1.04 (0.73-1.49); P=0.75)] [37]. Similarly, no significant difference was observed for the incidence of composite endpoint of stroke, myocardial infarction and heart failure [HR (95% CI): 0.97 (0.76-1.23); P=0.79)], nor the single components of this endpoint between combination and monotherapy [37].

The Long-Term Impact of Renin-Angiotensin System Inhibition on Cardiorenal Outcomes (LIRICO) study was a multicenter, randomized, open label, blinded endpoint trial, which tested the efficacy of the combination therapy of an ACE inhibitor plus an ARB on CV events in patients with moderate or severe albuminuria and diabetes or other CV risk factors [38]. Originally, the primary endpoint included a composite of CV death, non-fatal myocardial infarction, non-fatal stroke, and hospitalization for CV causes. Following the publication of the ONTARGET trial [35], the primary endpoint changed into all-cause mortality, and additional renal endpoints were included, such as ESRD, doubling of serum creatinine, progression from micro to macroalbuminuria, and regression

of albuminuria. At variance with previous studies, in the LIRICO trial study design allowed for comparison between combination therapy and either ACE inhibitor-based or ARB-based monotherapy. Also in this case, however, the trial was early (prematurely) stopped due to slow enrolment, thus resulting underpowered to detect any statistical significance for the incidence of the primary endpoint [38].

At study interruption, after a median follow-up of 2.7 years, no significant differences were observed with regard to the incidence of primary composite outcome between monotherapy with either ACE inhibitor [HR (95% CI): 0.75 (0.47-1.21)] or ARB [HR (95% CI): 0.71 (0.44-1.15)] versus combination therapy [38]. Similarly, no significant differences were found with regard to all-cause mortality between monotherapy with either ACE inhibitor [HR (95% CI): 0.84 (0.42-1.67)] or ARB [HR (95% CI): 1.11 (0.59-2.10)] versus combination therapy, as well as for the single CV components of primary composite CV endpoint [38].

With regard to renal endpoints, no significant differences were observed for the incidence of the predefined renal outcomes, namely doubling of serum creatinine (5.1% with ACE inhibitors, 4.6% with ARBs, and 5.5% with combination therapy), progression to severe albuminuria (14.4% with ACE inhibitors, 15.2% with ARBs, and 13.0% with combination therapy), and regression of albuminuria (20.6% with ACE inhibitors, 21.6% with ARBs, and 22.7% with combination therapy) [38].

Of note, the rate of permanent discontinuation for ARB monotherapy (6.3%) was significantly lower than that for ACE inhibitor monotherapy (15.7%) or combination therapy (18.3%) [38]. It should be also noted, however, that also in this trial baseline BP values were within the high-normal range, and that there were no significant differences in term of BP reductions among treatment strategies during the study.

In summary, two out of three of the aforementioned trials were stopped early due to safety concerns [37] and the third one for slow enrolment [38]. Another one was completed [35], yet it included a very small fraction of patients with overt proteinuria. All these trials enrolled patients with normal or high-normal BP values at baseline. Altogether the results of these trials demonstrated no additional beneficial effects of combination therapy compared to ACE inhibitor or ARB monotherapies on CV outcomes, though a small, not significant reduction of proteinuria and progression to ESRD.

Two recent meta-analyses, including patients with diabetes and albuminuria, concluded that ARB-based therapy reduced risks of ESRD and doubling of serum creatinine level, whilst the combination of ARBs plus ACE inhibitors has no effect on all-cause and CV mortality [39, 40].

Trials with Direct Renin Inhibitor plus ARBs

The DRI aliskiren was first tested as add-on therapy to Losartan in the Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) study [41], which was a randomized, double-blind trial, including approximately 600 patients with diabetes, hypertension and nephropathy, where it delivered greater proteinuria reduction at comparable BP values after 6 months oh therapy. Later on, only one randomized controlled clinical trial tested the combination therapy of aliskiren plus RAAS blocking agents on CV and renal outcomes. The Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (ALTITUDE) study was a double-blind randomized, controlled clinical trial, which included high vascular risk patients with type 2 diabetes and CKD [42]. Included patients were randomized to receive aliskiren (300 mg daily) or placebo on top of optimal antihypertensive therapy, including either ACE inhibitors or ARBs (not the combination of both) [42]. The primary endpoint was a composite of CV (non-fatal myocardial infarction, non-fatal stroke, hospitalization for heart failure, cardiac arrest with resuscitation, and CV death) and renal (doubling of serum creatinine levels, progression of ESRD, dialysis, or CKD death) endpoints. The trial was early stopped after the second interim efficacy analysis, since “the excess risk of adverse events in the aliskiren group could not be offset by a reduction in major CV and renal events” [42].

After a median follow-up of 32.9 months, the primary endpoint had occurred in 783 patients (18.3%) assigned to aliskiren as compared with 732 (17.1%) assigned to placebo (HR: 1.08; 95% CI 0.98 to 1.20; P=0.12) [42]. In particular, with regard to the CV endpoints, there were no significant differences between treatment groups with regard to CV death (P=0.12), myocardial infarction (P=0.72), stroke (P=0.11), and hospitalization for heart failure (P=0.56), with the only exception of an increased occurrence of cardiac arrest in those patients treated with aliskiren than those treated with placebo [HR (95% CI): 2.40 (1.05-5.48); P=0.04] [42]. Effects on secondary cumulative renal endpoint was similar between groups [HR (95% CI): 1.03 (0.87-1.23); P=0.74], though the mean reduction in the UACR was greater in aliskiren compared to placebo group [42]. It should be also noted, however, that the proportion of patients with hyperkalemia was significantly higher in the aliskiren group than in the placebo group (11.2% vs. 7.2%), as was the proportion with reported hypotension (12.1% vs. 8.3%) (P<0.001 for both comparisons) [42].

On the basis of the results of the ALTITUDE trial [42], which reported substantial equivalence in terms of CV endpoints and increased risk of renal endpoints, combination therapy with DRI plus ARB is currently not indicated in patients with diabetes and CKD [43].

Trials with ACE inhibitors or ARBs plus Antialdosterone agents

Pharmacological blockade of aldosterone receptors might provide beneficial effects for both CV and renal outcomes. Small, short-term, interventional trials have shown that the use of spironolactone or eplerenone leads to a reduction in proteinuria in CKD patients. However, evidence from adequately powered studies is lacking. Two meta-analyses indicated that adding aldosterone antagonists reduces proteinuria in patients on long-term ACE inhibitor or ARB-based therapy with persistent proteinuria, but that they have no effect on renal function and long-term renal outcome and mortality [44, 45]. Furthermore, as reported in both meta-analyses, the risk of hyperkalemia is a potentially major side effect with the use of aldosterone antagonists in CKD when GFR is below 30 ml/min per 1.73 m2 [44, 45].

More recently, it has been demonstrated that adding an aldosterone antagonist (spironolactone 25 mg) to the supramaximal dose of an ACE inhibitor (lisinopril 80 mg) in a small sample of patients with type 2 diabetes, hypertension, CKD and persistent macroalbuminuria reduced albuminuria by 34% compared with placebo, an effect that significantly exceeded the 17% reduction observed with the addition of losartan. Changes in albuminuria seemed to reflect a specific effect of aldosterone inhibition, since both clinic and ambulatory BP were similar among groups throughout the study. Despite these positive results on intermediate endpoint proteinuria, long-term data on the efficacy and safety of aldosterone receptor blockade in preventing ESRD and/or CV endpoints in CKD are still needed.

According to both European and US Drug Regulatory Agencies, combination treatment with an aldosterone receptor blocking drug and either ACE inhibitor or ARB can be used in patients with diabetes or CKD, possibly because its use on top of single RAAS inhibiting agent, despite greater risk of hyperkalemia, has been shown to reduce morbidity and mortality in patients with heart failure [46].

CONCLUSIONS

Experimental and clinical evidence clearly indicates that RAAS activation, at both systemic and tissue level, plays a major role in the development and progression of CKD in hypertensive

patients, as well as in the increased incidence of CV events observed in diabetic patients with proteinuria. Monotherapy with a RAAS inhibitor has represented for many years the treatment of choice to control BP and prevent progression or renal damage in these high-risk category of patients, although recent European hypertension guidelines currently recommend the use of combination therapy as first line strategy also in CKD patients [18]. As attractive and logical as it may seem, the hypothesis that more profound inhibition of this hormonal system may provide additional CV and renal protection has not been confirmed by large randomized clinical trials over the last few years [47].

This has probably been due to problems in maintaining renal hemodynamics, when BP is lowered in the context of complete RAAS blockade, especially when total nephron mass is reduced [48]. While association treatment with RAAS blocking agents could provide some protection on renal organ damage, namely a reduction in proteinuria, and could therefore be usefully prescribed to specific subset of patients, caution should be applied when pursuing this treatment in patients with very low GFR (i.e., <30 ml/min/1.73 m2) or in those presenting with little or no albuminuria. In fact, the risk of renal function worsening due to renal ischemia and/or of triggering relevant hyperkalemia should be carefully weighed against the potential benefit in the context of each patient's disease history. Finally, since CKD is an extremely high CV risk condition, clinicians should keep in mind that BP reduction should be viewed in a broader, more integrated clinical context in which it serves the dual scope of providing CV as well as renal protection.

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Table 1.

Effectiveness of dual RAAS blockade on the incidence of predefined CV and renal outcomes. Composite CV endpoint includes stroke, myocardial infarction and CV death. Composite renal endpoint includes doubling of serum creatinine, progression of ESRD, death.

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