

THE CURRENT INSIGHT ON DUAL RENIN-ANGIOTENSIN SYSTEM BLOCKADE: A DATA REVIEW WITH A FOCUS ON SAFETY

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Manuscript received: November 2014

Abstract

The renin-angiotensin system (RAS) inhibition plays an important role in the therapeutic approach of the hypertensive patient, including the prevention of cardiovascular and renal complications disease. For an enhanced clinical effect, there is a strong biological rationale for dual therapy with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), dual therapy that has been embraced by many clinicians to obtain a more complete RAS blockade, offering cardioprotection and renoprotection. However, clinical trials conducted throughout the last decade have provided conflicting results regarding the benefits and safety of RAS dual blockade in patients with hypertension, heart failure, ischemic heart disease, renal disease or diabetes. In fact, dual therapy did not reduce mortality, but it was associated with an increased harm, thus pleading against the use of this association. The present review aims to be an appraisal of the latest evidence on dual renin-angiotensin system blockade, with a focus on safety.

Rezumat

Inhibarea sistemului renină-angiotensină (SRA) joacă un rol important în abordarea terapeutică a pacientului hipertensiv, în prevenirea bolilor cardiovasculare și renale. Pentru obținerea unui efect terapeutic crescut există o justificare biologică pentru terapia duală cu inhibitorii enzimei de conversie a angiotensinei (IECA) și blocanții receptorilor angiotensinei II (BRA), terapie care a fost utilizată de către mulți medici pentru a obține inhibiția completă a SRA, oferind cardio și nefroprotecție. Cu toate acestea, studiile clinice efectuate în ultimul deceniu au avut rezultate contradictorii cu privire la beneficiile și siguranța inhibiției duale a SRA la pacienții cu hipertensiune arterială, insuficiență cardiacă, boală cardiacă ischemică, boli renale sau diabet. De fapt, terapia duală nu a demonstrat reducerea mortalității, fiind asociată cu un risc crescut de evenimente adverse grave, argumentând împotriva inhibiției duale a SRA. Prezenta lucrare are ca obiectiv sintetizarea celor mai recente date din literatură privind inhibiția duală a sistemului renină-angiotensină, cu accent pe datele de siguranță.

Keywords: dual renin-angiotensin system inhibition, safety, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers

Introduction

The renin-angiotensin system (RAS) role in the regulation of blood pressure has been recognized for many years. The availability of specific inhibitors of the various steps of the renin-angiotensin-aldosterone cascade, like the angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), have offered a valuable therapeutic approach for blood pressure control, reduction of morbidity and mortality in heart failure (HF) patients and delay of the decline of renal function in all hypertensive patients and especially in diabetic ones [3, 5, 6, 9, 12, 25, 30]. However, ACE inhibitors alone are unable to completely block the activation of the RAS because of the alternative pathways for converting angiotensin I to angiotensin II. Thus, the concept of RAS dual blockade was embraced several years ago, having with a strong biological rationale: complete blockade by acting at

two different sites of the pathway with combination therapy. Addition of an ARB to background therapy with an ACE inhibitor was believed to have an enhanced clinical effect on surrogate endpoints such as blood pressure, proteinuria and endothelial dysfunction, offering cardioprotection and renal protection. Therefore, several guidelines of the time mentioned the dual blockade of the RAS, despite a lack of solid evidence on long term efficacy and safety [4, 11, 23, 29]. Combining ACE inhibitors and ARBs may cause important adverse outcomes, such as hyperkalemia, hypotension, renal failure and consequently withdrawal due to drug-related adverse events [19]. But it was not until recently, with the ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) study results, the largest trial on dual RAS inhibition in high-risk patients, that earlier questions on dual therapy safety were clarified. In this trial despite the fact

that the surrogate endpoint proteinuria was reduced with dual therapy compared to monotherapy, a significant doubling of the creatinine levels and of the number of patients on dialysis in the combination arm argued against a nephroprotective effect. Overall the dual therapy had a detrimental effect for the patients' health, with no evidence to support the dual RAS blockade [36]. Moreover VA NEPHRON-D multicentre trial to evaluate the effect of losartan-lisinopril combination compared to losartan alone, on the progression of kidney disease in patients with diabetes, was stopped earlier for the same safety reasons [10].

This paper reviews the most recent data from large randomized controlled trials on safety and tolerability of dual RAS blockade with ACE inhibitors in combination with ARBs, combination therapy that has been lately under much scrutiny and debate.

Materials and Methods

The PubMed database was systematically searched for English language articles, published from January 2001 to January 2014, reporting results from large randomized controlled trials (RCTs) including more than 1000 patients, that were followed for at least 6 months and compared dual RAS blockade (ACE inhibitors in combination with ARBs) with monotherapy (ACE inhibitors or ARBs) and reported safety data. The reference list of articles retrieved was also searched for other potential eligible articles or for articles that fell outside the search criteria (observational studies

and meta-analysis), but that supported any discussions on the topic. We looked for pre-specified deleterious effects, such as hypotension, hyperkalaemia, renal failure, dialysis, withdrawal due to drug related adverse events. Data on mortality was also collected. We extracted data on the following: study design and characteristics, patients' age and sex, underlying renal (baseline serum creatinine) and diabetic disease, type and dosage of the combined intervention and the control (ACE inhibitor or ARB monotherapy), co-medication, co-morbidities, outcome and safety data.

Results and Discussion

Five randomized controlled trials including a total of 49329 patients met our inclusion criteria. Characteristics of included trials are presented in Table I. The follow-up period of individual trials ranged from 23 to 56 months and the number of patients included ranged from 1448 to 25620. Mean age of enrolled patients in these five trials range from 62 ± 11 to 66.5 ± 7.3 years, with the majority of patients being males. In the studies where NYHA class was available, the vast majority of patients were class II and III, with mean ejection fraction between 26.6% and 35.3%. Diabetes and hypertension were present in different percentages in all studies population. Baseline characteristics of included patients are summarized in Table II. Concomitant medication varied between trials as presented in Table III. With the exception of one trial, all patients were taking beta-blockers and diuretics.

Table I

Characteristics of RCTs comparing combination therapy with ACE inhibitors and ARBs *versus* ACE inhibitors or ARBs alone and impact of combined therapy *versus* monotherapy

	Val-HeFT, 2001 ²	CHARM Added, 2003 ²⁴	VALIANT, 2003 ²⁷	ONTARGET, 2008 ³⁶	VA NEPHRON-D, 2013 ¹⁰
Study population	HF, symptomatic	HF (left ventricular)	Acute MI complicated by HF, LVSD or both	Vascular disease or high risk diabetes	Type 2 diabetes
No. of patients	5010	2548	14703	25620	1448
Primary endpoint	Mortality and combined endpoint (mortality and morbidity)	Composite of CV death or hospital admission for HF management	Death from any cause	Composite outcome: death from CV cause, MI, stroke, or hospitalization for HF	First occurrence of a change in estimated GFR, ESRD or death
Combination therapy, dosage*	Any ACE inhibitor + valsartan (160 mg twice daily)	Any ACE inhibitor + candesartan (32 mg daily)	Captopril (50mg thrice daily) + valsartan (80mg twice daily)	Ramipril (10 mg daily) + telmisartan (80 mg daily)	Losartan (100 mg daily) + lisinopril (40 mg daily)
Monotherapy, dosage	Any ACE inhibitor [#]	Any ACE inhibitor ^{##}	Captopril (50mg thrice daily) or valsartan (160 mg twice daily)	Ramipril (10 mg daily) or telmisartan (80 mg daily)	Losartan (100 mg daily)
Follow-up period (months)	23	41	24.7	56	26.4
Impact of combined therapy vs. monotherapy	Overall mortality similar; the incidence for combined endpoint was lower for combination therapy; concerns about safety of the combined therapy.	Further clinically important reduction in relevant CV events with combination therapy.	Combination therapy increased rate of AEs without improving survival.	The combination of the two drugs was associated with more AEs without an increase in benefit.	Combination therapy was associated with an increased risk of AEs with no benefit with respect to mortality. The study was stopped earlier owing to safety concerns.

MI – myocardial infarction; CV – cardiovascular; HF – heart failure; AEs – adverse events; GFR – glomerular filtration rate; ESRD – end stage renal disease; LVSD – left ventricular systolic dysfunction

*Target dose; # No fixed dose; ##No recommended fixed dose, but doses of ACE inhibitor known to reduce morbidity and mortality, judged individually

Table II

Baseline characteristics of patients enrolled in RCTs included in the review

Trial	Val-HeFT, 2001 ²		CHARM Added, 2003 ²⁴		VALIANT, 2003 ²⁷		ONTARGET, 2008 ³⁶		VA NEPHRON-D, 2013 ¹⁰	
	C Ther	M Ther	C Ther	M Ther	C Ther	M Ther (V/C group)	C Ther	M Ther (R/T group)	C Ther	M Ther
Total patients (<i>No</i>)	2511	2499	1276	1272	4885	4909/4909	8502	8476/8542	724	724
Female sex, %	20	20	21.2	21.4	30.5	31.5/31.3	26.5	27.2/26.3	1.2	0.4
Age, years $\pm$ SD	62 $\pm$ 11	63 $\pm$ 11	64.0 $\pm$ 10.7	64.1 $\pm$ 11.3	64.6 $\pm$ 11.9	65.0 $\pm$ 11.8/ 64.9 $\pm$ 11.8	66.5 $\pm$ 7.3	66.4 $\pm$ 7.2/ 66.4 $\pm$ 7.1	64.5 $\pm$ 7.9	64.7 $\pm$ 7.7
Hypertension, %	6.1	7.3	47.7	48.7	55.3	55.7/54.8	68.5	69.0/68.6	-	-
Coronary heart disease, %	57.6	56.8	62.2	62.6	-	-	74.7	74.4/74.5	22	23.1
Myocardial infarction, %	-	-	56.0	55.3	28.2	28.4/27.2	49.3	48.3/49.3	-	-
Diabetes %	25.9	25.1	29.5	30.0	23.5	23.1/22.8	37.9	36.7/38.0	100	100
Proteinuria, %	-	-	-	-	-	-	13.3	13.1/13.2	-	-
Serum creatinine, mg/dL	-	-	-	-	1.1 $\pm$ 0.3	1.1 $\pm$ 0.3/ 1.1 $\pm$ 0.4	1.06 $\pm$ 0.26	1.06 $\pm$ 0.26/ 1.06 $\pm$ 0.26	1.5 $\pm$ 0.4	1.5 $\pm$ 0.4
CHF, %	100	100	100	100	14.4	15.5/14.5	-	-	16	15.2
NYHA class, %										
II	62.1	61.4	24.5	23.7	47.9	49.2/48.0	-	-	-	-
III	36.1	36.3	73.0	72.7	17.3	17.9/16.6	-	-	-	-
IV	1.7	2.2	2.6	3.5	6.4	6.4/6.3	-	-	-	-
EF, %	26.6 $\pm$ 7.3	26.9 $\pm$ 7.0	28.0 $\pm$ 7.5	28.0 $\pm$ 7.5	35.3 $\pm$ 10.3	35.3.0 $\pm$ 10.4/ 35.3.0 $\pm$ 10.4	-	-	-	-

C Ther- Combined therapy; M Ther – Monotherapy; V/ C group– valsartan or captopril monotherapy group; R/ T group– ramipril/ telmisartan group; CHF – chronic heart failure; EF - Ejection Fraction

Table III

Co-medication in RCTs included in the review

Intervention	Val-HeFT, 2001 ²		CHARM Added, 2003 ²⁴		VALIANT, 2003 ²⁷		ONTARGET, 2008 ³⁶		VA NEPHRON-D, 2013 ¹⁰	
	C Ther	M Ther	C Ther	M Ther	C Ther	M Ther (V/C group)	C Ther	M Ther (R/T group)	C Ther	M Ther
Beta-blocker, %	34.5	35.3	55.0	55.9	70.4	70.6/70.1	57.4	56.5/56.9	69.9	68.7
Digoxin, %	67.1	67.6	57.6	59.2	-	-	-	-	-	-
Diuretic, %	85.8	85.2	90.0	90.1	50.3	51.3/49.4	27.7	28.6/27.6	71.3	70.3
Spirinolactone, %	-	-	-	-	9.0	9.1/9.1	-	-	-	-
Aspirin, %	-	-	51.1	51.8	91.1	91.3/91.4	76.0	75.5/75.7	-	-
Anticoagulant(oral), %	-	-	37.9	38.3	-	-	-	-	-	-
Statins, %	-	-	41.4	41.0	34.1	33.8/34.4	61.8	61.0/62.0	-	-
Calcium antagonist, %	-	-	9.6	11.3	-	-	33.7	32.9/32.6	59.3	57.1
Antiplatelet agent, %	-	-	3.1	3.5	24.7	25.1/24.6	81.1	80.5/81.1	-	-

C Ther– Combined therapy; M Ther–Monotherapy; V/ C group–valsartan or captopril monotherapy group; R/ T group–ramipril/ telmisartan group;

In patients with chronic systolic heart failure there is evidence, for a decade already, from Val-HeFT (VALsartan Heart Failure Trial) [2] and CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) [24] trials that the use of combination therapy has some benefits in this population. Val-HeFT was a multi-centre double-blind trial of 5010 subjects with chronic heart failure (CHF) NYHA class II-IV and reduced ejection fraction. Patients were randomized to receive valsartan at a target dose of 160 mg or *placebo* twice daily in addition to an ACE inhibitor. The study demonstrated a benefit in the composite endpoint of mortality and morbidity (defined as hospitalization for HF, cardiac arrest, intravenous therapy) predominantly due to reduction of hospitalizations (relative risk 0.87 [0.77-0.97], $p = 0.009$) and improvement of the clinical signs and symptoms in CHF patients, but no significant benefit on mortality (relative risk 1.02 [0.88-1.18],

$p = 0.80$). Moreover a post-hoc analysis in a subgroup receiving valsartan in combination with ACE inhibitors and beta-blockers revealed a significant adverse effect on mortality [2]. There were a significant number of patients receiving valsartan that discontinued treatment due to adverse events including dizziness, hypotension and renal impairment as presented in Table IV.

Further evidence on the combination therapy was brought by CHARM-Added trial, where addition of candesartan to an ACE inhibitor decreased the risk of cardiovascular death and admission to hospital for CHF, among patients with CHF and low left-ventricular ejection fraction, all these on the expense of adverse events and withdrawals due to renal dysfunction and hyperkalaemia that were higher in the combination therapy group (two and five times higher, respectively). Despite these adverse events and a permanent withdrawal rate of 24% in the combination therapy group *versus* an

18% in the monotherapy group ($p = 0.0003$) the authors considered them infrequent and characteristic,

allaying at that time the concerns about the potential risks of the dual RAS blockade [24].

Table IV

Patients with pre-specified safety events in RCTs included in the review

	Val-HeFT, 2001 ²		CHARM Added, 2003 ²⁴		VALIANT, 2003 ²⁷		ONTARGET, 2008 ³⁶		VA NEPHRON-D, 2013 ¹⁰	
Intervention	C Ther	M Ther	C Ther	M Ther	C Ther	M Ther (V/C group)	C Ther	M Ther (R/T group)	C Ther	M Ther
Follow-up (months)	23		41		24.7		56		26.4	
Death (from any cause) No, (%)	495 (19.7)	484 (19.4)	377 (30)	412 (32)	941 (19.3)	979 (19.9)/ 958 (19.5)	1200** (14.1)	1210 (14.1)/ 1190 (13.9)**	63 (8.7)	60 (8.3)
	$p = 0.80$		$p = 0.086$		$p = 0.98$		Risk ratio (95%CI) = 1 (0.93-1.09)		Hazard ratio (95%CI) = 1.04 (0.73-1.49) $p = 0.75$	
Worsening renal function No, (%) OR Increase in serum creatinine concentration No, (%)	1.1*	0.2*	100(7.8) [□]	52(4.1) [□]	232 (4.8) [#]	213 (4.9) [#] / 148 (3.0)	1148 (13.5)	871 (10.2)/ 906 (10.6)	130 (18)	80 (11)
	$p < 0.001$		$p = 0.0001$		$p < 0.05$		$p < 0.001^{##}$ Relative Risk (95%CI) = 1.33 (1.22-1.44) ^{##}		Hazard ratio (95%CI) = 1.7 (1.3-2.2) $p < 0.001$	
Dialysis No, (%)	NA	NA	NA	NA	NA	NA	65 (0.8)	48 (0.6)/ 52(0.6)	NA	NA
							Relative Risk (95%CI) = 1.37 (0.94-1.98)			
Hypotension No, (%)	1.3%	0.8%	58 (4.5)	40 (3.1)	884 (18.2) [#]	739 (15.1) [#] / 582 (11.9)	406 (4.8)	149 (1.7)/ 229 (2.7)	NA	NA
	$p = 0.124$		$p = 0.079$		NA		$p < 0.001^{##}$ Relative risk = 2.75			
Hyperkalaemia No, (%) OR Mean change in serum potassium concentration (mmol/liter)	0.12 mmol/liter	0.07 mmol/ liter	44(3.4)	9 (0.7)	57 (1.2)	62 (1.3)/ 43 (0.9)	480	283/287	72 (9.9)	32 (4.4)
	$p < 0.001$		$p < 0.0001$		$p < 0.05$		$p < 0.001^{##}$		Hazard ratio (95%CI) = 2.8 (1.8-4.3) $p < 0.001$	
Permanent withdrawal due to AEs No, (%)	249 (9.9)	181(7.2)	309 (24)	233 (18)	1139 (23.4) [#]	1001 (20.5)/ 1055 (21.6)	2495 (29.3)	2099 (24.5)/ 2495 (29.3)	NA	NA
	$p < 0.001$		$p = 0.0003$		$p < 0.05$		$p < 0.001^{##}$ Relative risk = 1.20			

C Ther– Combined therapy; M Ther–Monotherapy; V/ C group – valsartan/ captopril group; R/ T group –ramipril/ telmisartan group; NA – Not Available; AEs – adverse events; * Renal impairment; ** Death from CV cause, MI or stroke; [#] The difference for the captopril group is significant at $p < 0.05$; ^{##} Combination therapy versus ramipril; [□] Increase in serum creatinine concentration

The 2003 VALIANT (VALsartan in Acute myocardial Infarction) double-blind non-inferiority trial showed that in patients with acute myocardial infarction (within 10 days before inclusion) and evidence of heart failure, left ventricular systolic dysfunction or both, there was no difference in death from any cause (primary endpoint) or in death by cardiovascular cause, hospitalization for CHF or recurrent myocardial infarction (secondary endpoints) between the valsartan-captopril combination group and captopril alone group. Furthermore, the valsartan-captopril group had the most drug-related adverse events compared to the captopril group, with a significant difference ($p < 0.05$) for hypotension and renal impairment, resulting either in dose reduction or permanent discontinuation of study treatment (in 23.4% of patients) [27].

The current outlook on dual RAS inhibition is mostly owed to the 2008 ONTARGET study, the largest, longest and most robust randomized trial on 25620 patients with vascular disease without CHF,

among which 9000 with high-risk diabetes [36]. High-risk vascular disease and diabetic patients would be the natural choice to test if a complex intervention like the dual RAS blockade is of benefit, due to high-risk profile of these patients, with several co-morbidities and a well-known clinical course heading to end stage renal disease, in the light that a proven therapeutic effect in a high-risk model can be latter applicable in low-risk populations [28]. Moreover, numerous randomized clinical trials have demonstrated the benefit of ACE inhibitors or ARBs in albuminuria reduction and in slowing the progression of chronic kidney disease (CKD) in diabetic nephropathy, so the concept of RAS dual blockade was already advanced in early 2000s, also supported by publication of CALM (The Candesartan and Lisinopril Microalbuminuria) study [13, 25]. The non-inferiority ONTARGET trial, in high risk CV and diabetic subjects, was designed having a composite primary outcome: death from cardiovascular causes, myocardial

infarction, stroke or hospitalization for heart failure. The study participants were randomized in three arms to receive ramipril, telmisartan or a combination of the two. The reduction of blood pressure was greater in the combination group compared with the single treatment arms, but surprisingly this did not translate into a cardiovascular or mortality benefit as it would have been expected. For the composite primary endpoint the combination therapy did not demonstrate a significant benefit over monotherapy (relative risk 0.99 [0.92-1.07], $p = 0.001$). With a note on safety, the combination therapy was associated with significantly greater number of adverse events like symptomatic hypotension, hyperkalaemia, renal dysfunction (with a greater rate of dialysis), syncope and diarrhoea [36]. In a pre-specified analysis of the ONTARGET trial to determine the effects of combination therapy on a primary renal composite endpoint of dialysis, doubling of serum creatinine, and death, the number of events was increased with combination therapy (14.5%, hazard ratio 1.09[1.01-1.18], $p = 0.037$), despite a reduction in albuminuria. Also, the secondary renal endpoint, dialysis or doubling of serum creatinine was more frequent with combination therapy (2.49%, hazard ratio 1.24[1.01-1.51], $p = 0.038$) [21]. The study authors concluded that the combination therapy was associated with more adverse events without an increase in benefit [35].

The much awaited VA NEPHRON-D (Combination Angiotensin Receptor Blocker and Angiotensin Converting Enzyme Inhibitor for Treatment of Diabetic Nephropathy) trial, powered for CKD progression to validated endpoint, did not come with further expected evidence on the benefits of the combination therapy in diabetic nephropathy, but on the contrary, the study was stopped earlier due to an increased risk of adverse events among these patients [10]. All the trials presented before, except this one, were designed to assess efficacy and not safety. The patients were randomized to receive either losartan alone, or in combination with lisinopril. The primary endpoint was the first occurrence of a decline in estimated GFR, end stage renal disease (defined as initiation of maintenance dialysis or an estimated GFR < 15 mL per minute per 1.73 m^2) or death. Safety outcomes were all cause of mortality, serious adverse events, hyperkalaemia and acute kidney injury. The proportion of serious adverse events attributed to study medication was higher in the combination group than in the monotherapy group. The rate of hyperkalaemia (defined as a potassium concentration $> 6 \text{ mmol/L}$) was more than double in the combination group. Acute kidney injury was the main reason for the higher rate of serious adverse events in the combination group,

accounting for significantly more events when comparing to the monotherapy group (12.2 vs. 6.7 events per 100 person-years, $p < 0.001$). There was no benefit with respect to the primary endpoint, mortality or cardiovascular events in this trial [10].

About Safety from Additional Evidence from Meta-Analysis and Observational Studies

When we are looking for evidence on the effectiveness or safety of different treatments, properly conducted systematic reviews of randomized clinical trials, with or without meta-analysis, will provide the most powerful form of evidence. Most of the reviews and meta-analyses up-to date included the above studies with the exception of VA NEPHRON-D, which was only recently published.

A meta-analysis in patients with HF including 8 trials, among which Val-HeFT, CHARM Added and VALIANT, showed no difference between patients treated with combination therapy and ACE inhibitor therapy alone for overall mortality, hospitalization for any reason, fatal or nonfatal myocardial infarction. However, combination therapy was associated with fewer hospital admissions for heart failure (relative risk 0.81, 95% CI 0.72-0.91), although there was significant heterogeneity across trials. Trials included in the meta-analysis defined worsening of renal function as more than 50% increase of serum creatinine from baseline or as one of the following: death from renal failure, end-stage renal disease requiring chronic dialysis or renal transplantation, or an increase in serum creatinine concentration leading to temporary or permanent discontinuation of study treatment. Hyperkalaemia was usually defined as a serum potassium level more than 5.5 mmol/L or 6 mmol/L or leading to discontinuation of study medication. Symptomatic hypotension was not defined in any of the included trials. Although adverse events were inconsistently reported between these trials, patients treated with combination therapy had a higher risk of worsening renal function and symptomatic hypotension, and their trial medications were more often permanently discontinued [14].

In patients with ischemic heart disease, a 2009 review outlined again the findings of the ONTARGET study, considering these findings moderate-strength evidence that showed similar effects on total mortality and myocardial infarction and an increased risk for discontinuations due to hypotension and syncope with combination therapy compared with ACE inhibitors alone [1].

A meta-analysis quantifying the risk of adverse events of combination therapy (ACE inhibitor plus ARB) *versus* ACE inhibitor alone in left ventricular dysfunction patients suggested that ARBs should not routinely be added to ACE inhibitors therapy

for left ventricular dysfunction due to excess risk, coupled with a lack of consistent mortality benefit. Patients receiving combination therapy had an increased risk of developing any adverse effect by 2.3% (relative risk 1.27, 95% CI 1.15 – 1.40, $p < 0.00001$), hypotension by 1.1% (relative risk 1.91, 95% CI 1.37 – 2.66, $p = 0.0002$), worsening renal function by 1% (relative risk 2.12, 95% CI 1.30 – 3.46, $p = 0.003$), and hyperkalaemia by 0.6% (relative risk 4.17, 95% CI 2.31 – 7.53, $p < 0.00001$) [17].

In patients with micro- and macroalbuminuria, a meta-analysis of studies reported until 2009 on combination therapy, strongly dominated by the results of the ONTARGET trial, also showed lack of evidence to support dual RAS blockade. Complete RAS inhibition resulted in comparable mortality, cardiovascular events and kidney outcomes compared with monotherapy. Adverse event rates were also comparable, except for a higher risk of hypotension compared with ACE inhibitors therapy alone [18]. An earlier meta-analysis of 49 small studies in patients with renal disease concluded that combination of ARBs and ACE inhibitors is more effective in reducing proteinuria than either drug alone, but uncertainty concerning adverse effects and outcomes that are important to patients, limits applicability of these findings to clinical practice. It also outlined that proteinuria is only a surrogate for important progression to renal failure [15]. These results raised significant concerns about the general validity of reduction in proteinuria, as a valid surrogate marker of cardiovascular and kidney protection, since this demonstrated effect of combination therapy did not translate into improved patient-level outcomes in latest studies.

By far, the most comprehensive analysis evaluating the safety and efficacy of dual blockade of the renin-angiotensin system is the Makani 2013 meta-analysis that came to the conclusion that the overall risk of benefit ratio argues against the use of dual therapy [19]. Although it may have seemingly beneficial effects on certain surrogate endpoints, it failed to reduce mortality and is associated with an excessive risk of adverse events. This meta-analysis, aside other evidence, stood for the decision of regulatory authorities in Europe regarding dual blockade of the renin-angiotensin system [7]. The meta-analysis included 33 randomized controlled trials comprising 68405 patients. Dual therapy, compared with monotherapy, was associated with a 66% increase in the risk of hypotension ($p < 0.001$), a 55% increase in the risk of hyperkalaemia ($p < 0.001$), a 41% increase in the risk of renal failure ($p = 0.01$) and a 27% increase in the risk of withdrawal owing to adverse events ($p < 0.001$). Dual RAS blockade was not associated with any significant benefit for

all-cause mortality (relative risk 0.97, 95% CI 0.89 - 1.06) and cardiovascular mortality (relative risk 0.96, 95% CI 0.88 - 1.05) compared with monotherapy; it was associated though with an 18% reduction in admissions to hospital for heart failure (relative risk 0.82, 95% CI 0.74-0.92) [19].

Although the RCTs remain the gold standard of clinical research, observational studies also demonstrated the increased risk of hyperkalaemia and worsening renal function in patients treated with dual therapy. In a retrospective cohort study in 32312 elderly patients in clinical practice, increased risks of adverse renal outcomes and hyperkalaemia were observed in those on combination therapy with an ACE inhibitor and ARB compared with those on monotherapy. In addition, the study pointed out that combination therapy was frequently prescribed for patients without established indications [22]. Another retrospective cohort database study, to assess the incidence of hyperkalaemia and decreased renal function during dual therapy in a community-based setting, demonstrated that hyperkalaemia was 2-fold more common during dual therapy than monotherapy (11.1% and 5.6% of patients, respectively; relative risk 1.96; 95% CI 1.22–3.14, $p < 0.001$). Also renal function worsened as per the mean serum creatinine increase (more than 0.5 mg/dL increase in 7.5% of patients, more commonly in patients with decreased (18.2%) than with preserved (5.2%) baseline renal function, $p < 0.001$). The absolute risks were especially high among patients with reduced baseline renal function [16].

Is there still an indication for combination therapy?

In the light of current evidence, the combination of an ACE inhibitor and an ARB has not been proven to be an effective and safe therapeutic strategy with the exception of some small studies. Initial enthusiasm for the combined treatment has been diminished by the recent ONTARGET and VA NEPHRON-D trials [8, 10, 36]. Given no improvement in outcomes across most patient groups, but an increased risk of adverse events, evidence advocates against the use of dual RAS inhibition [22]. Patients with chronic systolic heart failure, whose symptoms persist in the presence of maximized ACE inhibitors and beta-blockers, but not immediately post myocardial infarction, appear to be the only ones having a recommendation for combined treatment [33]. Because dose is likely to be a factor in experiencing adverse events, a question mark on efficacy and tolerability of patient tailored lower doses of dual therapy still remains for some [23, 34].

Krause *et al* summarized current recommendations of combined therapy in most cardiovascular and chronic kidney diseases, according to U.S. Preventive Services Task Force, with the finding

that there is no clinical or limited clinical evidence to support recommendation for combined therapy (D or I level of evidence) [13].

According to the European Medicine Agency combination of angiotensin-receptor blockers with angiotensin-converting enzyme inhibitors is not recommended anymore and, in particular, patients with diabetes-related kidney problems (diabetic nephropathy) should not be given this combination [7]. The agency advises that where combination of these medicines is considered absolutely necessary, it must be carried out under specialist supervision with close monitoring of kidney function, fluid and salt balance and blood pressure. This would include the licensed use of the ARBs candesartan or valsartan as add-on therapy to ACE-inhibitors in patients with heart failure who require such a combination [7].

The United States Food and Drug Administration has not yet issued any warnings. The American Heart Association guidelines currently do not recommend the use of ACE inhibitors and ARBs together, routine combined use of an ACE inhibitor, ARB, and aldosterone antagonist is considered potentially harmful [35]. In 2012, the National Healthcare Services professionals were advised to initiate combination of an ACE inhibitor and ARB only under specialist supervision in patients with renal disease, taking into account the potential for adverse effects [32]. The Canadian Hypertension Education Program has recommended against use of ARBs and ACE inhibitors together, except in patients with HF refractory to ACE inhibitor [31].

Conclusions

This paper reviews the largest and most comprehensive randomized clinical trials comparing the combination of an ACE inhibitor and an ARB *versus* monotherapy with one of the two. All studies found that dual RAS blockade is associated with a significant increase in the risk of adverse events leading to discontinuation compared with monotherapy. These adverse events (hypotension, hyperkalaemia, worsening renal function), mostly leading to permanent discontinuation of the study treatment, are related directly or indirectly to reduced angiotensin II effect, indicating perhaps that the risk is additive when both types of agents are used.

One might bear in mind that patients in clinical trials are more strictly monitored and adverse events from combination therapy could have been detected earlier, leading to a more appropriate patients' management than under 'real world' conditions. Therefore, it is to be expected that the higher incidence of adverse events associated with combination therapy in randomized controlled trials

to be even higher in clinical practice, with a more significant impact on patients' safety and the whole public health system.

Acknowledgements

This paper was published under the frame of European Social Found, Human Resources Development Operational Programme 2007-2013, project no. POSDRU/159/1.5/136893.

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