

VIEWPOINT

The Sudden Demise of Dual Renin-Angiotensin System Blockade or the Soft Science of the Surrogate End Point

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Physicians have embraced the concept of dual renin-angiotensin system (RAS) blockade hoping that it would translate into better blood pressure control as well as incremental nephroprotective and cardioprotective effects. With regard to blood pressure, a small additional fall with dual RAS blockade was observed when compared with that seen in monotherapy. Numerous studies have shown a reduction of albuminuria with dual RAS blockade. However, the recent findings in the ONTARGET (Renal Outcomes With Telmisartan, Ramipril, or Both, in People at High Vascular Risk) study of significantly more doubling of the creatinine and dialysis in the combination arm despite lesser albuminuria emphasized the fallacy of surrogate end points and argue against nephroprotective effects of dual RAS blockade. In heart failure, dual RAS blockade was associated with more hypotension, worsening of renal function, and hyperkalemia than was angiotensin-converting enzyme inhibitor therapy alone. In conclusion, recent outcome and safety data have shattered the halo of dual RAS blockade for hypertension, nephroprotection, and heart failure. Unless data emerge to the contrary, dual RAS blockade should no longer be used in clinical practice. (J Am Coll Cardiol 2009;53:468–70) © 2009 by the American College of Cardiology Foundation

Ever since experimental data by Menard et al. (1) showed what was somewhat euphemistically called a “synergistic” effect of angiotensin-converting enzyme (ACE) inhibition and angiotensin receptor blockade (ARB), practicing and academic physicians have embraced the concept of dual renin-angiotensin system (RAS) blockade. The rationale behind dual RAS blockade derived from data showing an escape phenomenon with ACE inhibitor monotherapy resulting in angiotensin I accumulation and thereby generating angiotensin II (2,3). It was hoped that the addition of an ARB would provide a more complete blockade of the RAS and that, indeed, a complete blockade would translate into better blood pressure control as well as incremental nephroprotective and cardioprotective effects (3,4). So enticing was the concept of dual RAS blockade that despite a lack of solid evidence on safety and efficacy it found entrance into recent guidelines (5).

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Blood Pressure

Most blood pressure studies showed a small additional drop in systolic and diastolic pressure when an ARB was added to an ACE inhibitor and vice versa, regardless of the dose level of the first drug. A thorough systematic review and meta-analysis (6) collected 14 blood pressure studies in hypertensive patients in which patients were evaluated by 24-h ambulatory blood pressure monitoring. The authors found that the combination of an ACE inhibitor and an ARB reduced blood pressure by an average of 4/3 mm Hg when compared with monotherapy. However, it was not clear whether this modest subadditive effect was attributable to an interaction between the 2 classes of drugs because of their pharmacokinetic properties or whether there was indeed a synergistic effect. The authors stated that in their opinion an appropriately designed study would show that combined RAS blockade confers little advantage over monotherapy with regard to blood pressure (6). Thus, for lowering of millimeters of mercury there seems to be little if any reason to use dual RAS blockade. The incremental fall in blood pressure with dual RAS blockade compared with that seen with monotherapy is certainly a fraction only of what is commonly observed with the addition of either a thiazide or calcium antagonist.

Albuminuria

Numerous studies have suggested benefits of dual RAS blockade in patients with albuminuria or albuminuria when com-

pared with either monotherapy with an ARB or an ACE inhibitor (7). In a thorough meta-analysis of 49 studies involving over 6,000 patients, Kunz et al. (8) found “encouraging” evidence that dual RAS blockade reduced proteinuria by 20% to 25% more than either drug alone (8). The most recent landmark study, the ONTARGET (Renal Outcomes With Telmisartan, Ramipril, or Both, in People at High Vascular Risk) study, is no exception in this regard (9). The increase in albuminuria was reduced with a combination of telmisartan and ramipril when compared with monotherapy. However, the finding of significantly more doubling of the creatinine and dialysis in the combination arm despite the lesser albuminuria strongly argues against a nephroprotective effect of dual RAS inhibition. Even in the large diabetic subgroup of more than 700 patients with overt (≥ 300 mg/g creatinine) proteinuria, in whom the loss of GFR was several times faster than in patients without diabetes, dual RAS blockade had no significant effect on renal outcome when compared with ramipril alone or telmisartan alone (R. Schmieder, personal communication, November 2008).

These findings in the ONTARGET study clearly emphasize the fallacy of the surrogate end point (i.e., the surrogate, albuminuria moves in the “right” direction whereas the real end point, doubling of creatinine and dialysis, moves in the opposite direction). This divergence between real end point and surrogate end point should not be surprising in view of the experimental studies in sodium-depleted animals (10). In this model, combined blockade of the RAS led to loss of weight, increase in creatinine, and death—a sequence of events that was preventable with a high sodium diet. Although most of our hypertensive patients are not sodium depleted, we should remember that diuretic therapy is an exceedingly common therapeutic approach in essential hypertension, and diuretic-induced volume depletion may be sufficient to cause harm in some patients on dual RAS blockade.

Conversely, dietary sodium intake has been shown to affect albuminuria. Verhave et al. (11) found a correlation between dietary sodium intake and albumin excretion independent of other risk factors such as blood pressure. Thus, sodium intake seems to be a double-edged sword in patients on dual RAS blockade. A high-sodium diet may abolish the antiproteinuric effects whereas a low-sodium diet may lead to hypotension and a fall in glomerular filtration rate.

Heart Failure

The CHARM-Added (Effects of Candesartan in Patients With Chronic Heart Failure and Reduced Left-Ventricular Systolic Function Taking Angiotensin-Converting-Enzyme Inhibitors) trial reported some benefits when candesartan was added to an ACE inhibitor in patients with New York Heart Association functional class III to IV heart failure and a left ventricular ejection fraction of 40% or lower (12). The addition of candesartan reduced all components of the

primary outcome, the total number of hospital admissions for CHF, but not all-cause mortality. A meta-analysis looking at all the studies in aggregate including the CHARM-Added trial found no reduction in all-cause mortality but a 23% reduction of heart failure hospitalizations (13). Of note, in the CHARM-Added trial, significantly more patients discontinued study medication in the combination arm because of an adverse event or abnormal laboratory values (increase in creatinine, hyperkalemia) in the combination therapy arm than in the placebo/ACE inhibitor arm. Indeed, a recent thorough meta-analysis looking at safety and tolerability of dual RAS blockade in over 18,000 patients with left ventricular dysfunction showed a significantly increased risk of adverse events leading to discontinuation of dual RAS blockade compared with monotherapy (14). Hypotension, worsening of renal function, and hyperkalemia (odds ratios of 1.91, 2.12, and 4.17, respectively) were more common with combination therapy than with the ACE inhibitor alone. The authors concluded that this excess risk coupled with the lack of a consistent mortality benefit suggested that ARBs should not routinely be added to ACE inhibitors for left ventricular dysfunction (14).

Direct Renin Inhibitors and Aldosterone Antagonists

In a thorough prospective, randomized study of 599 patients, mean urinary albumin to creatinine ratio was reduced by 20% more with dual RAS blockade of aliskiren and losartan than with losartan alone despite a very small difference in blood pressure between the treatment groups (15). The authors, apparently impressed by these results, enthusiastically concluded that “aliskiren appears to have a renoprotective effect that is independent of its blood pressure-lowering effect” (15). However, given the surrogate end point failure in the ONTARGET study, the extrapolation from albuminuria to renal function is no longer acceptable. Clearly to establish benefits, if any, of dual RAS blockade with direct renin inhibitors, ironclad outcome data on renal function will have to be provided.

In contrast, for dual RAS blockade with aldosterone antagonists such as spironolactone and eplerinone, both the surrogate end point and real end point move in parallel. Thus, at least in heart failure, the benefits of adding spironolactone or eplerinone to either an ACE inhibitor or an ARB have been well documented.

Conclusions

The recent ONTARGET study data (9) have shattered the halo of dual RAS blockade not only for hypertension but also for nephroprotection. The meta-analysis of Lakhdar

Abbreviations and Acronyms

ACE = angiotensin-converting enzyme

ARB = angiotensin receptor blockade

RAS = renin-angiotensin system

et al. (14) has cast doubts on the safety of dual RAS blockade in patients with left ventricular dysfunction. In retrospect, many enticing features of dual RAS blockade were based on surrogate end point findings and, therefore, may have represented more wishful thinking rather than solid science. This would indicate that the Food and Drug Administration's reluctance to accept albuminuria/proteinuria as a valid surrogate is well founded (16). Leapfrogging of surrogate data can no longer substitute for patient exposure in clinical outcome studies (17). Unless data emerge to the contrary, dual RAS blockade is dead until further notice.

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