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Dual Renin-Angiotensin-Aldosterone System Inhibition for the Treatment of Diabetic Kidney Disease: Adverse Effects and Unfulfilled Promise

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Abstract Diabetic nephropathy (DN) is a major complication of diabetes mellitus (DM) affecting individuals with type 1 or type 2 DM and is the leading cause of chronic kidney disease and end-stage kidney disease (ESKD) in the USA. Estimates of disease burden are projected to increase, with prevalence of nearly one in five adults by 2050. The role of renin-angiotensin-aldosterone system (RAAS) inhibition in delaying the progression of DN utilizing angiotensin-converting enzyme inhibitors or angiotensin receptor blockers has been well established in multiple controlled trials. Given greater reduction of proteinuria with dual RAAS blockade compared to monotherapy alone, the potential benefit of dual therapy on progression of DN has been tested in three large randomized clinical trials. Unfortunately, results from these studies demonstrated lack of benefit of dual blockade on renal or cardiovascular outcomes in patients with diabetes. The overall objectives of this review are to provide both the rationale for dual blockade as potential therapy as well as review the literature of its use in patients with DN.

Keywords Diabetes · Renin · Angiotensin · Aldosterone · Chronic kidney disease · Hypertension

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Introduction

The prevalence of diabetes mellitus (DM) has reached epidemic proportions [1]. Disease estimates are projected to increase, affecting nearly one in five US adults by 2050 [2]. Patients with DM suffer from both micro- and macrovascular complications, such as cardiovascular disease, retinopathy, and nephropathy. Diabetic nephropathy (DN) is a major complication of DM affecting individuals with type 1 or type 2 DM and is the leading cause of chronic kidney disease and end-stage kidney disease (ESKD) in the USA [3]. Those diagnosed with DN are faced with a mean survival of 5–7 years, with excess mortality mainly attributed to cardiovascular complications [4]. Approximately 39 % of patients with chronic kidney disease have DM and 41–44 % of all new cases of ESKD are due to DN. The 5-year survival of diabetic patients on dialysis is only 34 % [5].

Early diagnosis of DM and early intervention are critical in delaying progression to ESKD [2]. Despite increases in the prevalence of DM in the last decade, it is reassuring that the incidence of DN has been declining since 2006 [5]. The recent decline in the incidence of DN has been attributed to better glycemic management, blood pressure control, and widespread use of renin-angiotensin-aldosterone system (RAAS) blockade [4, 6]. Given the underlying pathophysiology, there was hope that dual RAAS blockade could reduce progression even further. In this report, we review the role of RAAS in DN and examine the results of recent trials that evaluated the effect of dual RAAS blockade on hard clinical outcomes in patients with DM.

The Role of RAAS in Diabetic Nephropathy

The pathogenesis of DN is complex and involves several mechanisms. The RAAS has a range of both hemodynamic

and non-hemodynamic effects that contribute to the development of DN (Fig. 1). Renal hemodynamics are altered in DN [7], in large part due to activation of RAAS. Despite the decrease in plasma renin activity in DN, evidence suggests local activation of RAAS that is independent of systemic regulation [8–10]. Sustained hyperglycemia and advanced glycation end products (AGEs) stimulate the generation of tissue angiotensin II (Ang II). Ang II exerts its vasoconstrictive effects on the afferent and the efferent arterioles with an effect greater at the efferent arteriole. This leads to increase in intraglomerular pressure and a concomitant increase in hyperfiltration. In addition to its intraglomerular hemodynamic effects, Ang II enhances proximal sodium reabsorption, increases adrenal aldosterone production, and stimulates production of fibrogenic cytokine transforming growth factor beta (TGF-β) [11, 9, 12]. Ang II is central to the pathogenesis of DN and provides a therapeutic target.

The non-hemodynamic consequences of RAAS activation in DN have been demonstrated in animal [10, 13] and human studies [9]. DM stimulates proximal tubule renin mRNA expression in streptozotocin-induced diabetic rats [10]. Independent of its effect on Ang II production, renin binds to mesenchymal and endothelial cell receptors and stimulates the production of TGF-β [8, 14]. Beyond its hemodynamic effects, increased production of Ang II [10] coupled with upregulation of angiotensin I receptors on the podocytes of diabetic kidneys results in loss of nephrin, podocyte hypertrophy, and at later stage apoptosis [15, 16]. In addition, Ang II alters the anionic charge of the glomerular basement membrane in DN by modulating heparin sulfate proteoglycan synthesis of the podocytes [17]. In the tubule, Ang II induces tubular cell hypertrophy [18] and tubular epithelial-myofibroblast transdifferentiation [19].

Other consequences of RAAS also contribute to the development of DN. Prorenin plasma levels are elevated in diabetic patients [20]. Prorenin is believed to contribute to glomerulosclerosis and renal fibrosis via stimulation of mitogenic and fibrotic factors independent of Ang II [21]. Aldosterone also has a pathogenic role in DN and DM is associated with increased aldosterone production [22]. In addition to its profibrotic properties, which involve stimulation of extracellular matrix production through increased TGF-β

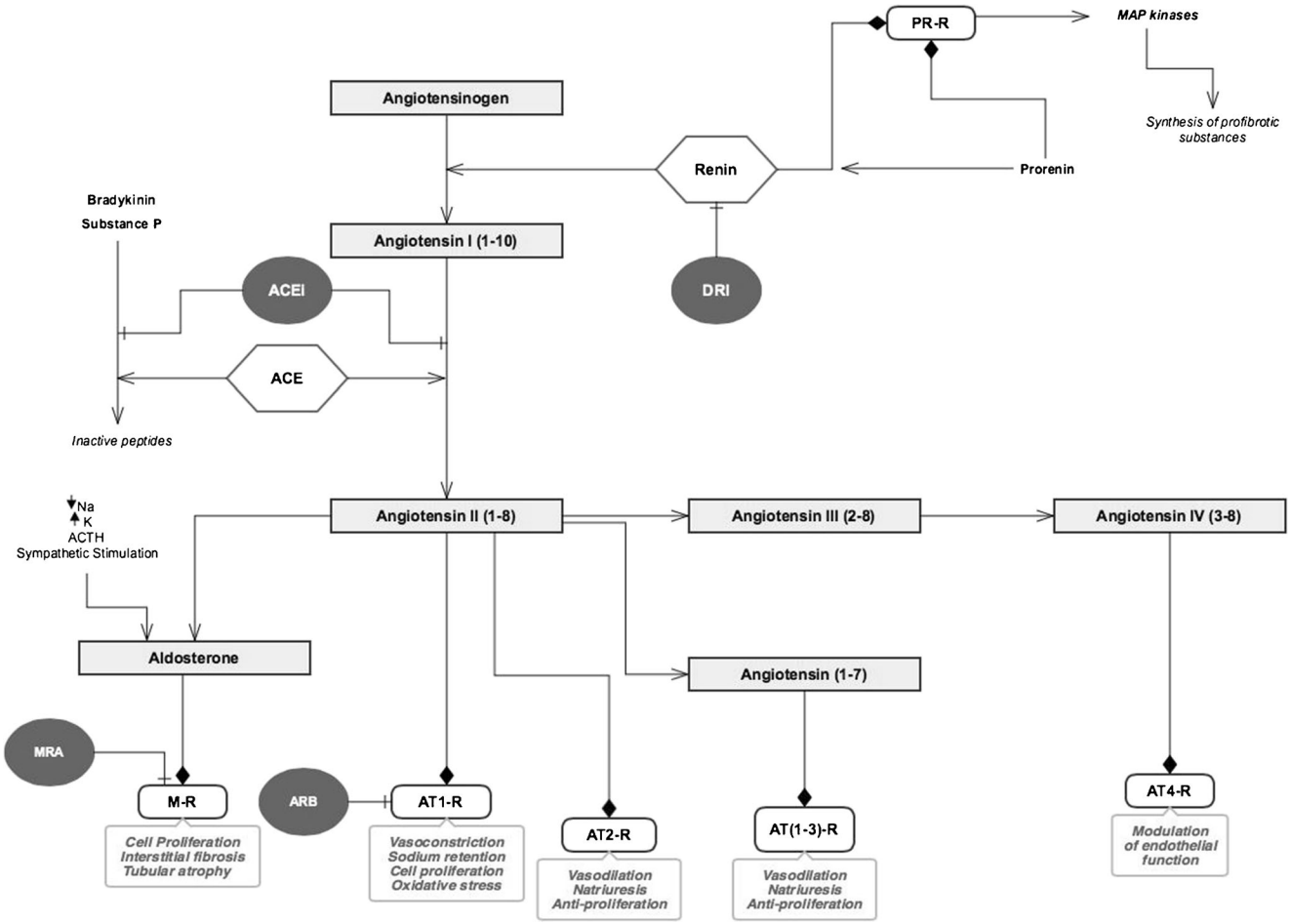

Fig. 1 Hemodynamic and non-hemodynamic effects of the RAAS system contribute to diabetic nephropathy (adapted from Tylicki L, Lizakowski S, Rutkowski B. Renin-angiotensin-aldosterone system blockade for nephroprotection: current evidence and future directions. J Nephrol. 2012 Nov-Dec;25(6):900–10) [42]

production [8] and collagen IV deposition [23], aldosterone is incriminated in the pathogenesis of inflammation in DN. In animal models, aldosterone infusion induces tubulointerstitial and glomerular leukocyte infiltration through upregulation of inflammatory cytokines, including monocyte chemoattractant protein-1 (MCP-1), interleukin-6 (IL-6), and interleukin-1beta (IL-1β) [24], and generation of reactive oxygen species [25]. Treatment with aldosterone receptor blockers attenuates the renal fibrotic and inflammatory processes in animal models [26] and provides evidence of the pathogenic role of aldosterone in DN.

Dual RAAS Inhibition in Animals

Animal and human studies have demonstrated that RAAS blockade with angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) reduces proteinuria, controls hypertension, and slows progression of renal disease. However, ACEi and ARB monotherapy resulted in incomplete inhibition of the RAAS [27]. Experimental studies showed that chronic ACEi or ARB use was associated with an increase in aldosterone level, a concept called "aldosterone escape," and a concomitant rise in Ang II production through ACE- independent pathways [28, 29].

Given the "aldosterone escape" observed with monotherapy, the effect of dual RAAS blockade on disease progression was evaluated in animal models of DN. In hypertensive rats, Ménard et al. first reported a synergistic effect between ACEi (benazepril) and ARB (valsartan) on left ventricular hypertrophy, diastolic dysfunction, and survival [29]. Cao et al. reported that combination therapy with ACEi (captopril) and ARB (irbesartan), in diabetic hypertensive rats, was more effective in reducing albuminuria, glomerulosclerosis, and hypertension, compared to monotherapy with these agents [30]. A recent study by Whaley-Connell et al. described a beneficial effect of combination with a renin inhibitor (aliskiren) and an ARB (irbesartan) on podocyte integrity, tubular injury, and markers of oxidative stress in transgenic rats [31]. In total, dual RAAS blockade decreased blood pressure, reduced albuminuria, and attenuated glomerulosclerosis and podocyte injury. However, the fidelity of these results in humans was unknown.

Dual Blockade—Preliminary Human Studies

Clinical trials in humans have also demonstrated potential benefits to dual RAAS blockade. Early clinical trials of dual RAAS blockade in diabetic patients showed a greater reduction in proteinuria compared to monotherapy with ACEi or ARB [32–34]. More recently, Mehdi et al. randomized 81 patients already receiving lisinopril 80 mg once daily to placebo, losartan 100 mg daily, or spironolactone 25 mg daily [35]. After 48 weeks, clinical and ambulatory blood pressures were similar between groups. Compared with placebo, urine albumin-to-creatinine ratio decreased by 34 % (P=0.007) in the spironolactone group and by 17 % (P=0.20) in the losartan group [35]. In a review of 49 randomized clinical trials of combination therapy with ACEi and ARB, in diabetic and non-diabetic proteinuric patients, combination therapy was more effective in reducing proteinuria compared to

Table 1 Major clinical trials of dual RAAS blockade in diabetic nephropathy

Study	Population	No.	Intervention	Primary outcome	Effect of combination on primary outcome	Comment
ONTARGET	Diabetic and non-diabetic patients with vascular disease	25,584	Telmisartan, ramipril, combination	Composite outcome of CV death, MI, stroke, and hospitalization from heart failure	RR 0.99 (0.92–1.07)	Combination therapy was associated with increased risk of hyperkalemia and renal impairment
ALTITUDE	Type 2 diabetic patients on ACEi or ARB	8606	Aliskiren, placebo	CV mortality, non-fatal MI, stroke, ESRD, need for dialysis, or doubling of serum creatinine	HR 1.08 (0.98–1.20)	Increased risk of hyperkalemia and hypotension with aliskiren
VA NEPHRON–D	Type 2 diabetic patients with eGFR of 30–89.9 ml/min/1.73 m^2 and Ualb/Cr >300 on losartan	1448	Lisinopril, placebo	Decline in eGFR, ESRD, or death	HR 0.88 (0.70–1.12)	Increased incidence of hyperkalemia and acute kidney injury in combination arm

CV cardiovascular, *MI* myocardial infarction, *RR* relative risk, *ACEi* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *ESRD* end-stage renal disease, *HR* hazard ratio, *eGFR* estimated glomerular filtration rate, *Ualb/Cr* urine albumin-to-creatinine ratio

monotherapy alone [11]. Whether reductions in proteinuria utilizing dual blockade would translate into improved patient-level outcomes was yet to be realized.

Dual RAAS Blockade—Recent Large Clinical Trials

Despite the evidence that dual RAAS blockade decreases proteinuria, the question of whether this enhanced antiproteinuric effect would translate into better renal outcomes was unanswered until recently. Data on renal outcomes of dual RAAS blockade comes from three large randomized controlled trials (Table 1). The Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET), a large multicenter randomized placebo-control trial, randomized 25,584 patients with cardiovascular disease or DM to the ARB telmisartan, ACEi ramipril, or dual blockade with a combination of telmisartan and ramipril [36]. After a median follow-up of 56 months, there was no difference between the dual blockade arm and the ramipril arm with regard to the primary cardiovascular composite outcome [36]. However, dual blockade was associated with an increased risk for renal impairment despite greater reduction in proteinuria with dual blockade [36]. Dual blockade was also associated with increased risk for hyperkalemia [36]. Results for the primary renal outcome were similar between those with (N= 6982) and without DM [37]. It is worth noting that only 516 ONTARGET participants had overt DN [37].

The second large study to evaluate dual blockade was the Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (ALTITUDE) study, which randomized 8561 patients already receiving an ACEi or ARB to a renin inhibitor, aliskiren 300 mg daily or placebo [38••]. Over 33 months of follow-up, dual blockade with aliskiren and ACEi or ARB did not reduce the risk for a composite of ESRD, death from renal causes, or a doubling of serum creatinine. Treatment with aliskiren did increase risk for hyperkalemia and hypotension [38••]. As in ONTARGET, dual blockade in ALTITUDE resulted in a significant reduction in albuminuria compared to the control group (14 %, 95 % CI 11 to 17 %) [38••].

The most recent large randomized controlled trial to evaluate dual blockade was the Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) trial [39••]. Patients with diabetes and a urine albumin-to-creatinine ratio of >300 mg/g were initiated on losartan 100 mg daily and then randomized to lisinopril or placebo [40]. The study was stopped after a median follow-up of 2.2 years in 1448 participants due to increased risk for hyperkalemia (hazard ratio [HR] 2.8, 95 % CI 1.8 to 4.3) and acute kidney injury (HR 1.7, 95 % CI 1.3 to 2.2) in the combination arm compared to the placebo arm [39••]. Again, no benefit to dual blockade was observed with regard renal or cardiovascular outcomes. VA NEPHRON-D results confirm the lack of benefit to dual blockade observed in ONTARGET and ALTITUDE but this time in a population with significant proteinuria.

Conclusions

Dual RAAS blockade is an attractive therapeutic strategy for patients with DN: The RAAS is involved in the pathogenesis of DN; there is aldosterone escape with monotherapy and dual therapy with reduced albuminuria and multiple markers of renal damage in animal models and short-term human trials. However, recent large randomized clinical trials have failed to demonstrate a benefit to dual blockade with regard to renal and cardiovascular outcomes. Additionally, dual blockade has increased risk for hyperkalemia and acute kidney injury. New agents to treat hyperkalemia may increase the feasibility of dual blockade, but further research is needed [41]. Finally, additional studies are needed to identify subgroups of patients who may benefit from dual blockade without the increased risk for adverse effects observed in these large trials.

Compliance with Ethics Guidelines

Conflict of Interest Boutros El-Haddad, Scott Reule, and Paul E. Drawz declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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