Dual Blockade of the Renin-Angiotensin System in Diabetic Nephropathy

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The accelerated progression of atherosclerosis in diabetes is most probably the end result of the cumulative impact of the major risk factors that are more prevalent in diabetic subjects, namely obesity and dyslipidemia, the derangement in carbohydrate metabolism (hyperglycemic environment, hyperinsulinism, and insulin resistance), a prothrombotic tendency, and, perhaps most important, microalbuminuria and hypertension (1–5). At least two additional cardiovascular risk factors are probably more pronounced in diabetes; they are endothelial dysfunction (6) and an inflammatory reaction in the affected blood vessels mediated by the proinflammatory interleukins and expressed by elevated levels of C-reactive protein (7).

Microalbuminuria is often the first clinical manifestation of early microvascular derangement. In type 2 diabetes, it is the hallmark of subsequent diabetic nephropathy and a surrogate marker of cardiovascular disease and increased cardiovascular mortality (8). Furthermore, the presence of microalbuminuria predicts a worse outcome after percutaneous coronary intervention. The 2-year mortality after percutaneous coronary intervention in diabetic patients with microalbuminuria was increased by 85% compared with individuals with normal urinary albumin excretion (9). Microalbuminuria is associated with echocardiographic evidence of left ventricular hypertrophy and identifies overall cardiovascular risk also in hypertensive nondiabetic patients (10,11). It is therefore mandatory to screen all diabetic as well as nondiabetic hypertensive patients for the presence of microalbuminuria. Indeed, all the relevant professional associations have included annual screening for microalbuminuria in their recommendations (12,13). Treatment strategies aimed at reducing urinary albumin excretion were found to be effective in retarding the progression of renal disease, as manifested by prolongation of the time to doubling of serum creatinine and postponement of end-stage renal disease and the need to renal replacement therapy (14–17).

Furthermore, the magnitude of early decline in albuminuria in response to a given therapeutic intervention is a reliable predictor of subsequent renoprotective effect of this therapy (18).

In type 1 diabetes, many patients who initially develop microalbuminuria subsequently revert to normoalbuminuria (18,19); therefore, the association between spontaneous or therapy-induced changes in albumin excretion rate and the subsequent progression of nephropathy is less clear (20).

The elucidation of the infrastructure of the renin-angiotensin-aldosterone system and the development of specific inhibitors of various steps in its biochemical cascade have emerged as the most significant means to control blood pressure, reduce cardiovascular sequelae, and retard the decline in renal function in all hypertensive patients and especially in diabetic patients (21,22). The four drug classes target angiotensin II and aldosterone through either direct or complimentary mechanisms. The renin inhibitors reduce the conversion of angiotensinogen to angiotensin I, and ACE inhibitors block the conversion of angiotensin I to the active peptide angiotensin II and increase the availability of bradykinin. Angiotensin-receptor blockers (ARBs) selectively antagonize angiotensin II at the AT1 receptors and increase the activation of the AT2 receptors. Finally, the aldosterone-receptor blockers reduce the metabolic and the proliferative effects of aldosterone (Fig. 1).

When appropriate dosage was used, long-term studies in hypertensive and in diabetic patients could demonstrate little if any difference in blood pressure lowering and in the cardiovascular as well as the renoprotective efficacy between the various renin-angiotensin-aldosterone system inhibiting or blocking agents (23,24); there may, in fact, be a small advantage of ACE inhibitors over ARBs, at least as far as cardiovascular protection is considered (25). There is little doubt that the major predictive factor of subsequent cardiovascular as well as kidney protection is the degree of blood pressure lowering (26–30). Control of hypertension is, therefore, paramount to postpone or possibly prevent end-stage renal disease and cardiovascular complications.

The complexity of the renin-angiotensin-aldosterone system and the proven efficacy of the various blocking and inhibiting agents stimulated the design of clinical trials to test the hypothesis that, in such a complex system, combining the effect of two or more drugs may offer better results than a single intervention. Diabetic nephropathy was the natural choice as the research platform because of the high-risk profile of these patients, the well-known downhill clinical course all the way to end-stage kidney, and, therefore, the ability to clearly define and demonstrate the efficacy of therapeutic interventions. In a high-risk model, any therapeutic effect is augmented and may be later applicable in other lower-risk constellations. Abe et al. (31) in Japan examined the renoprotective effect of the addition of an ARB (losartan) or an ACE inhibitor to conventional antihypertensive regimens or to ACE inhibitor–based regimens in patients with diabetic nephropathy. The drug doses were titrated to obtain predetermined blood pressure reduction goals. They found no advantage of dual renin-angiotensin system (RAS) blockade over the combination of a single RAS blocker with conventional antihypertensive regimens. These results corroborate the con-
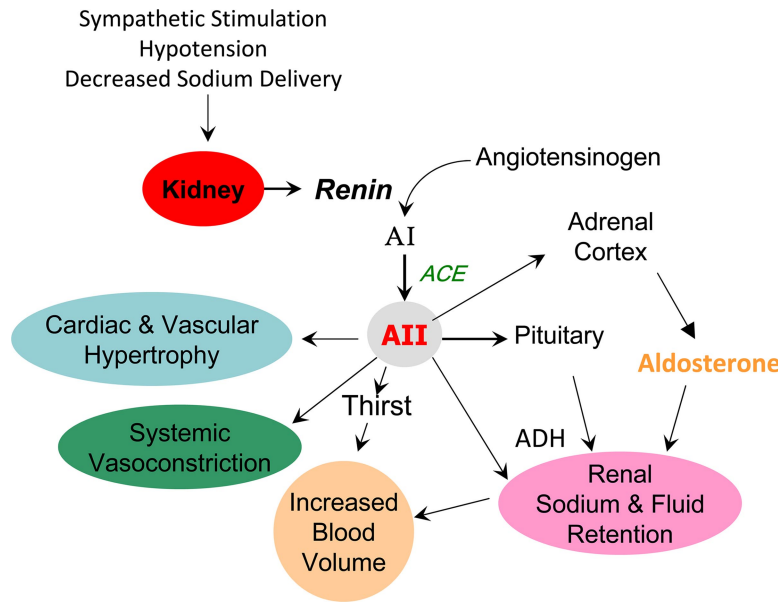
Figure 1—*The renin-angiotensin-aldosterone cascade and the various options to block the system. AI, angiotensin I; AII, angiotensin II.*

	Risk ratio (95% CI)
ARBs vs. placebo	0.66 (0.63–0.69)
ARBs vs. ACE inhibitors	1.08 (0.96–1.22)
ARBs vs. calcium-channel blockers	0.62 (0.55–0.70)
ARBs + ACE inhibitors vs. ARBs	0.75 (0.61–0.92)
ARBs + ACE inhibitors vs. ACE inhibitors	0.82 (0.67–1.01)

clusions of a large study in high-risk hypertensive patients (32) where, after 3.2 years' follow-up, candesartan-based regimens rendered equipotent cardiovascular and renal protection to amlodipine-based regimens. In a rather short-term 20-week study, the IMPROVE investigators found no advantage of dual RAS blockade with irbesartan and ramipril over ramipril alone in reducing albuminuria in high-risk hypertensive subjects (33).

So far, the largest and best controlled study that compared the antihypertensive effect and cardiovascular and renal protection in high-risk hypertensive and diabetic patients was the ONTARGET trial (24). In this prospective study, >25,000 patients were randomized to antihypertensive treatment protocols based on an ARB (telmisartan), an ACE inhibitor (ramipril), or the combination of both. After a mean follow-up period of 56 months, telmisartan was equivalent to ramipril in all aspects (albeit with a better side-effect profile). The combination of the two drugs was associated with more adverse events without an increase in benefit.

The results of five parallel-group studies and 16 crossover studies comprising together 654 patients and comparing dual RAS blockade with ARBs and ACE inhibitors to either agent alone were pulled together by MacKinnon et al. (34). They concluded that the dual therapy was safe in patients with proteinuric renal dis-ease. The dual blockade was associated with a minor increase in serum potassium and a small decline in glomerular filtration rate, as compared with each of the single agents. Also, the combination therapy was associated with a significant further decrease in proteinuria in diabetic as well as nondiabetic patients. Definite end points of renoprotection could not be assessed in this analysis because of the small number of patients and the short follow-up period. Kunz et al. (35) extracted, in hitherto the largest meta-analysis, the results of 110 studies in which the effect of either an ACE inhibitor or an ARB on proteinuria in renal disease was compared with the combination of the two agents. All the studies were short-lived and comprised together 6,181 patients. In 72 studies, the follow-up periods were only 1–4 months, whereas in the remaining 38 studies, the follow-up lasted 5–12 months. As expected, both ARBs and ACE inhibitors reduced proteinuria compared with placebo or calcium-channel blockers and were equipotent when compared with each other. The combination of ARBs and ACE inhibitors further reduced proteinuria more than either agent alone. The ratio of means for combination therapy versus ARBs was 0.76 (CI 0.68–0.85) over 1–4 months and 0.75 (CI 0.61–0.92) over 5–12 months. For combination therapy versus ACE inhibitors, the ratio of means was 0.78 (CI 0.72–0.84) over 1–4 months and 0.82 (CI 0.67–1.01) over 5–12 months (Table 1). The studies included in the meta-analysis were small, of short duration, and of variable quality. Therefore, the uncertainty regarding the important end points, mainly preservation of kidney function and cardiovascular protection, could not be resolved. Also, the issues of possible preponderance of adverse effects of the dual therapy and the stability of the therapeutic effect over time remained undecided, thus limiting the applicability of the results to clinical practice.

The theoretical added benefit of double renin-angiotensin-aldosterone system blockade was further explored using the remaining drug classes, namely aldosterone receptor antagonists and the new renin inhibitor aliskiren. Based on the well-known observation of the aldosterone-escape phenomenon under single RAS blockade with either an ACE inhibitor or an ARB (36), Schjoedt et al. (37) examined the effect of spironolactone as an add-on agent to other RAS blockers on nephritic-range albuminuria in patients with diabetic nephropathy. The addition of low-dose (25 mg) spironolactone resulted in a further decline of 32% in albumin excretion rate. The short 2-month duration of this study precludes any conclusions as to renoprotection. A recent systematic review (38) suggested that adding aldosterone blockers to ACE inhibitors or to ARBs significantly reduced albuminuria. The long-term safety of this regimen cannot be determined however.

The novel renin inhibitor aliskiren was tested, both alone or in combination with ACE inhibitors, in animal models of diabetic nephropathy and in short-term clinical studies on hypertensive subjects (39,40). This agent is probably equipotent to the other major drugs in lowering blood pressure and in reducing protein-

uria. There are, as yet, no long-term studies that would permit a discussion on clinically relevant effects.

Management of hypertension is, no doubt, the most significant intervention in preventing diabetic renal as well as cardiovascular disease. Tight control of blood pressure to recommended target levels affords long-term complication-free periods for diabetic patients. There seems to be a wide consensus that RAS blocking agents offer better renal protection than other drugs with equivalent antihypertensive potency. However, despite numerous studies, there is no real evidence that using double blockade offers an advantage in clinically relevant end points over the already time-honored single RAS blockade in combination with thiazide diuretics and calcium channel blockers.

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