

The role of renin-angiotensin-aldosterone system in the progression of chronic kidney disease

GIUSEPPE REMUZZI, NORBERTO PERICO, MANUEL MACIA, and PIERO RUGGENENTI

Unit of Nephrology, Azienda Ospedaliera Ospedali Riuniti di Bergamo, Italy; Clinical Research Center for Rare Diseases “Aldo & Cele Daccò,” Mario Negri Institute for Pharmacological Research, Bergamo, Italy; and Servicio de Nefrología y Unidad de Investigación, Hospital Universitario Ntra. Sra de Candelaria, Santa Cruz de Tenerife, Spain

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The renin-angiotensin-aldosterone system (RAAS) is a well known regulator of blood pressure (BP) and determinant of target-organ damage. It controls fluid and electrolyte balance through coordinated effects on the heart, blood vessels, and Kidneys. Angiotensin II (AII) is the main effector of the RAAS and exerts its vasoconstrictor effect predominantly on the postglomerular arterioles, thereby increasing the glomerular hydraulic pressure and the ultrafiltration of plasma proteins, effects that may contribute to the onset and progression of chronic renal damage. AII may also directly contribute to accelerate renal damage by sustaining cell growth, inflammation, and fibrosis. Interventions that inhibit the activity of the RAAS are renoprotective and may slow or even halt the progression of chronic nephropathies. ACE inhibitors and angiotensin II receptor antagonists can be used in combination to maximize RAAS inhibition and more effectively reduce proteinuria and GFR decline in diabetic and nondiabetic renal disease. Recent evidence suggests that add-on therapy with an aldosterone antagonist may further increase renoprotection, but may also enhance the risk hyperkalemia.

Maximized RAAS inhibition, combined with intensified blood pressure control (and metabolic control in diabetics) and amelioration of dyslipidemia in a multimodal approach including lifestyle modifications (Remission Clinic), may achieve remission of proteinuria and renal function stabilization in a substantial proportion of patients with proteinuric renal disease. Ongoing studies will tell whether novel drugs inhibiting the RAAS, such as the renin inhibitors or the vasopeptidase inhibitors, may offer additional benefits to those who do not respond, or only partially respond, to this multimodal regimen.

Chronic kidney disease (CKD) is a major public health problem, and preventing CKD and/or delaying progression of CKD patients to end-stage renal disease (ESRD) is a major task for the nephrology community [1]. This looks like an achievable target, in particular because of the availability of renoprotective drugs that may interfere with disease progression such as the inhibitors of

the renin-angiotensin-aldosterone system (RAAS). After the first inhibitor of angiotensin II (AII) system, the angiotensin-converting enzyme (ACE) inhibitor captopril, became available for clinical use in the early 1980s [2], other drugs have become progressively available that interfere with RAAS activity, such as AII-type 1 receptor blockers (ARBs) and the aldosterone (Aldos) antagonists that inhibit AII and Aldos activity by competitively antagonizing their binding to specific receptors [3]. In a short future, novel agents that interfere with renin activity (such as aliskiren) will also become available for clinical use [4], which will further increase the armamentarium of drugs that may interfere with the sequence of events, eventually resulting in AII and Aldos production at different levels and that, used in combination, may achieve an almost complete inhibition of the RAAS. In addition, to identify the optimal regimens to maximize renoprotection, major efforts should be made in identifying and treating all patients at risk, with the final aim to delay or even prevent the onset and progression of chronic renal disease and related complications [5].

ROLE OF THE RAAS IN THE DEVELOPMENT AND PROGRESSION OF RENAL DISEASE

The RAAS is the best known regulator of blood pressure (BP) and determinant of target-organ damage from hypertension. It also controls fluid and electrolyte balance through coordinated effects on the heart, blood vessels, and kidneys. AII is the main effector of the RAAS [6]. In the classic pathway of the RAAS, renin is secreted from the juxtaglomerular apparatus of the kidney and acts on the circulating precursor angiotensinogen to generate angiotensin I. Angiotensin I has little effect on BP and is converted in the lungs by ACE to AII. AII acts on the heart and the kidneys by binding to the G protein-coupled receptors type 1 (AT₁) and type 2 (AT₂). The AT₁ receptor mediates the more deleterious effects of AII—that is, vasoconstriction and cardiac and vessel hypertrophy. In addition

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to the conversion of angiotensin I to AII, ACE inactivates the vasodilator peptide bradykinin [3]. Recently, it has been discovered that the ACE type-2 (ACE2) cleaves angiotensin I into the inactive angiotensin 1–9, which is converted by ACE in the vasodilator and antiproliferative angiotensin 1–7, respectively [7, 8]. Although ACE2 is known to be present in the human kidney, there were no data on tissue distribution in renal disease [7]. In a recent study, renal biopsies from patients with diverse renal diseases including transplant patients were studied. In control kidneys, ACE2 was present in tubular and glomerular epithelium and in vascular smooth muscle cells and the endothelium of interlobular arteries [9]. In all renal diseases, neo-expression of ACE2 was found in glomerular and peritubular capillary endothelium. ACE inhibitor treatment did not alter ACE2 expression [9]. In vivo, AII enhances the vascular tone of both afferent and efferent glomerular arterioles and modulates intraglomerular capillary pressure and glomerular filtration rate (GFR). AII exerts its vasoconstrictor effect predominantly on the postglomerular arterioles, thereby increasing the glomerular hydraulic pressure and the filtration fraction, and impairs the size-selective function of the glomerular barrier to macromolecules, such as plasma proteins [10]. Intracapillary hypertension and increased ultrafiltration of plasma proteins may contribute to the onset and progression of chronic renal damage [11]. Nonhemodynamic effect of angiotensin may also be important in renal disease progression [6]. These include increased production of reactive oxygen species; upregulation of cytokines, cell adhesion molecules, and profibrotic growth factors; induction of transforming growth factor- β expression, increased synthesis of extracellular matrix proteins; stimulation of plasminogen activator inhibitor-1 production by endothelial and vascular smooth muscle cells; and macrophage activations and infiltrations [12]. Finally, AII augments adrenal production of Aldos, a recently recognized contributor to renal and cardiac injury [13]. Aldos is the principal mineralocorticoid produced in the zona glomerulosa layer of the adrenal cortex. It is also produced in endothelial and vascular smooth muscle cells in the heart, blood vessels, and brain. Acting through epithelial mineralocorticoid receptors in the kidney, cardiovascular system, and other organs, Aldos plays a major role in salt and water homeostasis and potassium excretion, and mediates renal and vascular remodeling [13]. In addition, to amplify some of the effects of AII, Aldos may also directly contribute to endothelial dysfunction, as suggested by evidence that mineralocorticoid receptor blockade with spironolactone may increase nitric oxide (NO) bioactivity and improve endothelial dysfunction [14]. In recent experimental studies, nanotechniques showed that Aldos may also remodel human endothelium in vitro by increasing the size and stiff-

ness of endothelial cells, which favors protein leakage through intercellular gaps [15]. In addition to AII, other angiotensin peptides may exert clinically relevant vasoactive actions. Angiotensin 1-7 (A1-7), a heptapeptide derived from angiotensin I and/or from AII, may antagonize AII, especially in situations of an overactive RAAS, such as during sodium restriction [16], an effect that results in renal vasodilation and increased natriuresis [17]. Also, digestion of the angiotensin I and AII by angiotensinases-peptidases, aminopeptidases, carboxypeptidases, or endopeptidases result in different peptide fragments with distinct functions from those of AII. Angiotensin IV (the 3–8 peptide) binds selectively the AT₄ receptor and stimulates plasminogen activator inhibitor-1 release [18]. The biologic significance of these novel peptides is under investigation.

THE RELATIONSHIP BETWEEN RAAS ACTIVITY, PROTEIN TRAFFIC, AND RENAL DISEASE PROGRESSION

Experimental data from animal models have shown that there are a wide variety of glomerular insults that result in a common pathway of increased glomerular hypertension, systemic hypertension, glomerular permeability, and proteinuria. These diverse pathologies appear to incite a vicious cycle of injury and inflammation, resulting in a common pathophysiologic mechanism, in which glomerular injury leads to proteinuria, interstitial inflammation, and, ultimately, scarring [11]. The importance of glomerular hypertension and hyperfiltration in response to nephron loss was established by Brenner et al [19]. After nephron loss, the remaining nephrons develop glomerular capillary hypertension, and the single-nephron GFR increases (hyperfiltration). These changes are thought to be adaptive in that they help to initially maintain the overall GFR. However, they have negative long-term effects and ultimately lead to renal insufficiency and ESRD. Proteinuria has been considered an indicator of glomerular disease severity [20]. The proposed effects of proteinuria on the kidney include increased severity of glomerulosclerosis, tubulointerstitial inflammation, and subsequent fibrosis, thereby contributing to progressive renal function loss. These facts have permitted the establishment of a “proteinuria hypothesis” that consists of three postulates: higher levels of proteinuria predict adverse clinical outcomes; reduction of proteinuria correlates with slowing of renal progression; and proteinuria is a surrogate end point and target of clinical interventions [21]. Glomerular hypertension in both diabetic and nondiabetic chronic nephropathies leads to increased glomerular permeability and excessive protein filtration. The protein ultrafiltrates are toxic to the proximal tubules, resulting in tubular damage and finally scarring [11]. The degree of proteinuria correlates with

the magnitude of renal damage in experimental models, and proteinuria reduction helps to preserve renal function [11]. Proteins in the urine are normally absorbed by endocytosis in the proximal tubules. During periods of heavy proteinuria, the filtered proteins accumulate in lysosomes in the proximal tubular cells, causing cell disruption and injury [22, 23]. Proteins may also incite a toxic response through stimulation of the expression of proinflammatory cytokines. Cultured proximal tubule cells that are exposed to albumin, transferrin, or immunoglobulin G produce increased amount of endothelin-1 (ET-1), a powerful vasoconstrictor that also contributes to inflammation and fibrosis [24]. Exposure to albumin or transferrin also increases the production of monocyte chemotactic protein-1, which, in proximal tubule cell cultures that maintain polarity, is preferentially excreted into the basolateral compartment, suggesting a possible mechanism for interstitial inflammatory infiltrates in vivo [25]. These findings have been echoed in both immune (Heyman nephritis) and non-immune (5/6 nephrectomy) models of nephropathy, in which albumin, immunoglobulins, and complement localize to proximal tubules that later develop inflammatory infiltrates [26]. ET-1 expression is also increased, and the degree of expression correlates with the rate of progression [27]. Treatment with angiotensin-converting enzyme inhibitor (ACEI), which decreases filtered proteins, also decreases the production of these inflammatory cytokines and preserves renal function [28]. Lastly, the increased glomerular permeability may result in excess ultrafiltration of some complement proteins fractions that may be directly toxic to the proximal tubules and incite injury. In a subtotal nephrectomy model of renal insufficiency, C3 staining was associated with the appearance of interstitial infiltrates. Treatment with ACEI, which lowered proteinuria, also decreased C3 staining [29].

Interventions that reduce glomerular capillary hypertension, such as blockade of the RAAS [30, 31] or a low-protein diet [19], slow the progression of chronic nephropathy in experimental forms of nephropathy. Inhibition of the RAAS, either through reducing the production of AII with ACEI or by blocking the action of AII at the AT-R1 receptor level with ARBs, is particularly effective at preventing renal injury. The benefit seen with these drugs is beyond that which would be expected from their antihypertensive effects. Compared with a non-ACEI regimen that achieved equivalent systemic BP control, captopril better reduced glomerular hypertension and renal injury [30]. In humans, proteinuria was the strongest predictor of renal disease progression: the higher baseline proteinuria, the faster GFR decline [32]. It is now widely accepted that proteinuria reduction is an appropriate therapeutic goal in CKD with proteinuria [33]. In patients from the Ramipril Efficacy In Nephropathy (REIN) long-term follow-up study,

who were at high risk of rapid progression to ESRD, 36 months of treatment with the ACEI ramipril reversed the tendency of GFR to decline with time and prevented progression to dialysis [34]. Recently, the Reduction of Endpoints in Type 2 Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) study showed that 6-month protein/creatinine ratio reduction predicts renal and cardiovascular events in diabetic patients [35]. In summary, there is robust experimental evidence and a number of hints from clinical observations that increased protein ultrafiltration and excretion may contribute to the pathogenesis of structural lesions and disease progression in nephropathy [1].

THE CONTRIBUTION OF THE RAAS ACTIVATION TO CHRONIC INFLAMMATION AND TISSUE DAMAGE

CKD is characterized by a state of chronic inflammation that is associated with oxidative stress, endothelial dysfunction, and vascular calcification and wasting [36]. The mechanism for this inflammatory status seems to be related to a combination of diverse factors that cause an altered immune balance [36]. Also, emerging evidence suggests that AII is not only a vasoactive peptide, but also a true cytokine that regulates cell growth, inflammation, and fibrosis [12, 37]. Thus, some of AII-induced effects are mediated by the production of a large array of growth factors. AII in vivo increases tumor necrosis factor- α production in the kidney and also upregulates other proinflammatory mediators, including interleukin 6, monocyte chemotactic protein-1, and nuclear factor- κ B, which is associated with the presence of glomerular and interstitial inflammatory cells in the kidney [37]. This scenario opens the possibility that AII contributes to the pathogenesis of renal diseases also by favoring the infiltration and activation of immunocompetent cells [38]. A recent study has also revealed that angiotensin IV, via AT4 receptors, activates nuclear factor- κ B pathway and increases proinflammatory genes [39]. There are some data showing that some of the beneficial effects of the RAAS blockade may be related to anti-inflammatory properties of ACEI and ARBs [36]. In an experimental study, Anderson et al reported an impaired cytokine-induced nuclear factor- κ B translocation from the cytoplasm to the nucleus in captopril preincubated monocytes [40]. In a clinical study, Stevinkel et al found low plasma levels of tumor necrosis factor- α and C-reactive protein (CRP) in ESRD patients treated with ACEI [41]. Also, in the SOLVD trial, those patients treated with an ACEI reduced the risk of weight loss, which supports the hypothesis of relationships among wasting, the RAAS, and inflammation [42]. Although future clinical studies are necessary to confirm the relevance of this hypothesis for human disease conditions, this line of research could

indicate new directions concerning RAAS blockade and immunosuppression in renal diseases.

GENETIC DETERMINANTS OF THE RAAS

Several polymorphisms of genes coding for components of the RAAS have been identified [43]. The most important polymorphisms that have deserved numerous studies were I/D polymorphism, a variant of the angiotensinogen gene, the M235T polymorphism, and the variant A¹¹⁶⁶C polymorphism of the AII type-1 receptor gene [44]. The exact mechanism by which the polymorphisms of the RAAS could influence the progression of kidney disease is not clear. Several studies have suggested a potential role for I/D polymorphism of the ACE gene in the progression of renal diseases and in cardiovascular complications of patients with CKD [45]. In the REIN study, the DD genotype was associated with faster progression and better response to ACE inhibition therapy, in particular in women [46]. Also, when angiotensinogen and AII-type-1 receptor polymorphisms were analyzed, most of the studies did not disclose any definitive relation to renal disease progression [44]. However, in hypertensive patients it has been suggested that the combination of DD polymorphism type for ACE, TT for angiotensinogen, and AC/CC for AII-type-1 receptor gene, could contribute in a synergistic way to organ damage [47]. The relation between the degree of response to renoprotective therapies and polymorphism types has brought inconclusive results. A subanalysis of the REIN study showed that only men with the DD type had a favorable response to the treatment with ramipril [48]. In summary, to date, results on the RAAS polymorphisms as determinants of progression of CKD and of response to renoprotective therapies are conflicting.

RENOPROTECTION THROUGH TREATMENTS THAT INHIBIT THE RAAS

Drugs acting on the RAAS include agents that directly inhibit the synthesis and release of renin or AII (renin and ACE inhibitors), drugs that antagonize the receptor effects of AII (ARBs), the aldosterone-receptor antagonists, and a new class of combined ACEI and neutral endopeptidase inhibitors, called the vasopeptidase inhibitors (VPIs).

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Early studies of the mechanisms of conversion of angiotensin I to II, and of bradykinin hydrolysis, led to the isolation (from snake venom) and synthesis of small peptide inhibitors of ACE (kininase II) [2, 3]. ACEI proved to be highly successful in the treatment of hypertension

and related target-organ damage, including left ventricular hypertrophy, heart failure, and postmyocardial infarction left-ventricular remodeling, renal insufficiency, and diabetes with proteinuria. After the introduction of captopril for clinical use [2, 3], several ACEIs have been developed, and many have been approved for the treatment of hypertension, heart failure, diabetic nephropathy, and/or left ventricular dysfunction. ACEIs differ in their ability to penetrate and bind tissue sites for prolonged periods [3].

Diabetic nephropathy

Type 1 diabetes. The seminal study from Lewis et al [49] found that in patients with overt nephropathy of type 1 diabetes, ACE inhibition with captopril induced a clear reduction in proteinuria, as compared with treatment not directly interfering in the RAAS. This effect was associated with a slower decline in GFR and a reduction of the primary end point “doubling of serum-creatinine” of approximately 50%. The European Microalbuminuria Captopril Study showed that in microalbuminuric patients with type 1 diabetes, ACE inhibition decreases the risk to develop overt nephropathy by approximately 75% [50], which proves that ACE inhibition also has beneficial renal effects at the earlier stage of incipient nephropathy.

Type 2 diabetes. Six small studies that included 352 patients uniformly found that ACE inhibition also reduces proteinuria more effectively than conventional therapy in overt nephropathy of type 2 diabetes [51]. The sub-study in 3577 patients with diabetes (primarily type 2) of the Heart Outcomes Prevention Evaluation trial showed that, compared with placebo, treatment with the ACEI ramipril resulted in a 24% reduction of the risk to develop overt nephropathy in patients who were either normo- or microalbuminuric [52]. More recently, The Bergamo Nephrology Diabetic Complications Trial demonstrated that the ACEI trandolapril, as compared with non-RAAS inhibition antihypertensive therapies, halved the risk to develop microalbuminuria in hypertensive patients with type 2 diabetes and normoalbuminuria [53]. This effect exceeded what could be expected on the basis of BP reduction and was non-enhanced by combined therapy with the non-dihydropyridine calcium-channel blocker.

Nondiabetic nephropathy

In nondiabetic renal disease, there is a clear renoprotective advantage of ACEI as compared with BP-lowering therapies not interfering with the RAAS. The REIN study included 352 patients with chronic nephropathies of nondiabetic origin who were randomized to treatment with ramipril or placebo on top of other antihypertensive agents. The main finding was that ramipril treatment resulted in a slower decline in GFR compared with placebo, despite equivalent BP control [32]. A later

analysis indicated that in a subset of patients on prolonged treatment with ramipril, the GFR stabilized and then progressively increased [54]. Recently, the African American Study of Kidney Disease and Hypertension trial demonstrated that the renoprotective effect of ACE inhibition is superior to that of conventional antihypertensive regimens (including beta blockers and calcium-channel blockers) in black patients [55], a population so far considered to be poorly responsive to RAAS blockade.

ANGIOTENSIN RECEPTOR BLOCKERS

The ARBs are highly effective and well-tolerated antihypertensive medications, and recent clinical trials have shown that these agents have renoprotective effects beyond lowering BP. At present, there are several orally active ARBs available. The ARBs are nonpeptide compounds that specifically block the binding of AII to the AT₁ receptor [3]. They do not interact with AT₂ receptors. The block of feedback inhibition of renin release activates the RAAS cascade and AII production. The AII generated may interact with AT₂ receptors, an effect that may result in vasodilatation and further BP reduction and, according to some recent experimental evidence, may result in inhibition of angiotensin and revascularization. There are some structural differences among ARBs that result in differences in pharmacokinetics and pharmacodynamics [3]. However, differences in antihypertensive potency and duration of action of the ARBs have been inconsistently reported [56]. Recently, a possible beneficial effect of telmisartan on metabolic syndrome has been described. In fact, this ARB can function as a partial agonist of peroxisome proliferator-activated receptor- γ [57]. The clinical significance of these differences among members of the class remains to be determined in outcome trials.

Nephropathy associated with type 2 diabetes

Two important studies that included more than 1500 patients with type 2 diabetes and overt nephropathy, the Irbesartan in Diabetic Nephropathy Trial [49] and the RENAAL trial [35], found that ARB treatment, as compared with conventional therapy, reduced the relative risk of reaching the primary composite end point (doubling of serum creatinine, ESRD, or death) by 20% and 16%, respectively. In addition, the Irbesartan in Diabetic Nephropathy Trial showed a reduction of the risk to reach the primary end point by 23% as compared with calcium-channel blockade by amlodipine, the third treatment arm in this study. Two other studies also showed the beneficial effect of ARB at the stage of incipient nephropathy, the Microalbuminuria Reduction with Valsartan study [58] and the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria study [59]. More recently, the DE-

TAIL study, a non-inferiority study that compared telmisartan and enalapril in 250 patients with type 2 diabetes and microalbuminuria and macroalbuminuria [60], found that telmisartan was not inferior to enalapril according to predefined criteria. Data showed that at 5-year follow-up, GFR had decreased by 17.5 mL/m/1.73 m² with telmisartan and by 15 mL/m/1.73m² with enalapril.

SELECTIVE ALDOSTERONE-RECEPTOR ANTAGONISTS

Several experimental studies have raised the possibility that Aldos in addition to AII may have a role in progression of chronic renal disease [61, 62]. Chrysotomou and Becker, in eight patients with various renal diseases and persistent proteinuria (>1 g/d) and despite treatment with enalapril for more than 12 months and add-on therapy with spironolactone 25 mg per day, decreased proteinuria by 54% as compared with pretreatment values [63]. This effect, however, was almost entirely driven by the reduction in proteinuria observed in the five patients with type 2 diabetes. Recently, a new aldosterone-receptor blocker, eplerenone, has been described, which differs from spironolactone by virtue of higher selectivity for the Aldos receptor [64]. A double-blind, prospective study evaluated eplerenone, enalapril, and a combination of both agents in patients with type 2 diabetes mellitus, mild-to-moderate hypertension, and proteinuria during a 24-week period [64]. Eplerenone decreased microalbuminuria independent of its antihypertensive activity. Compared with enalapril, the renoprotective properties of eplerenone were significantly better, however, and the reduction in albumin excretion with combination therapy was significantly more effective than monotherapy with either drug. Elevated potassium levels were observed, and more patients were withdrawn for hyperkalemia in the combination group. A subsequent follow-up study is being conducted to determine if lower doses of eplerenone will maintain reductions in albumin excretion without substantially increasing potassium levels [64]. Combinations of low-dose eplerenone with a low-dose thiazide-type diuretic appear to be options worth investigating, because the overall cardiovascular benefit brought about by reducing BP would be increased by the blockade of extrarenal aldosterone receptors provoked by eplerenone.

RENIN INHIBITORS

Blockade of the renin-angiotensinogen reaction is an attractive therapeutic tool to synergize the renoprotection of RAAS inhibition, not only because this action is the rate-limiting step in the RAAS, but also because the active site of renin is highly selective for angiotensinogen [65]. In a recent study, the new molecule aliskiren

(SPP100) showed that 150-mg daily doses were as effective as irbesartan 150 mg in lowering BP with a safety and tolerability profile comparable with placebo [4]. The co-administration of aliskiren with valsartan, in mildly sodium-depleted normotensive individuals, had a synergistic effect on RAAS hormone levels [66]. Other renin inhibitors are in earlier phases of investigation (i.e., enalkiren, zalkiren) [65].

VASOPEPTIDASE INHIBITORS

VPIs are novel antihypertensive medications that simultaneously inhibit ACE and neutral endopeptidase (NEP) [67]. NEP catalyzes the hydrolysis of atrial natriuretic peptide (ANP), brain natriuretic peptide, and C-type natriuretic peptide. Simultaneous inhibition of the RAAS and NEP system by VPIs results in vasodilation, natriuresis, and diuresis, and decreases peripheral vascular resistance and BP to a greater extent than ACE inhibition alone. Thus, VPIs represent a new and attractive therapeutic strategy for the treatment of cardiovascular disease. In a recent experimental study in the remnant kidney model, the administration of a VPI, AVE7688, at the stage of overt nephropathy reduced proteinuria and lessened renal damage better than enalapril at doses that afforded a comparable BP control. Finding that AVE7688 corrected the imbalanced ratio between the vasoconstrictor ET-1 and the vasodilators NO and ANP, may explain the superior renoprotection of vasopeptidase over ACE inhibitors [68]. The risk/benefit profile of VPI therapy on top of the best renoprotective therapy, however, is still a matter of investigation [69]. At present, several VPIs are in various stages of development. Omapatrilat is one that has undergone the most extensive clinical development, in particular in heart failure. However, the high incidence of angioedema compared with enalapril—as reported in the Omapatrilat Cardiovascular Treatment Assessment Versus Enalapril trial—might limit its use [70].

MULTIPLE DRUG TREATMENT: PRACTICAL GUIDELINES TO ACHIEVE REMISSION AND REGRESSION

Intensified BP and metabolic control in diabetics, reduction of proteinuria, block of the RAAS, and lifestyle changes (smoking cessation, weight reduction) may achieve chronic renal disease remission, with GFR stabilization and proteinuria reduction to subclinical ranges in a consistent proportion of patients with diabetic or nondiabetic chronic nephropathies [5]. Targets of treatment are BP less than 120/80 mm Hg, proteinuria less than 0.3 g/24 h, low-density lipoprotein (LDL) less than 100 mg/dL, LDL plus very LDL less than 130 mg/dL, and hemoglobin-A1c less than 7.5% (in diabetes) [5]. Maximized inhibition of the RAAS by combined treat-

ment with ACEI and ARB is the key component of this multidrug regimen. In this sense, the Combination Treatment of Angiotensin Receptor Blocker and Angiotensin Converting Enzyme Inhibitor in Non-diabetic Renal Disease study showed that in patients with non-diabetic nephropathies, dual RAAS blockade withtrandolapril and losartan provided better renoprotection than either drug alone [71]. In the same way, the Candesartan and Lisinopril Microalbuminuria study found that in type 2 diabetic patients with incipient nephropathy, lisinopril and candesartan achieved more reduction in albuminuria than each treatment alone; however, this was an effect that was also associated with more effective BP reduction [72]. Further blockade of the system by add-on therapy with an Aldos antagonist could possibly offer additional renoprotection but may have the drawback of severe hyperkalemia [13]. In experimental animals, add-on statin therapy, in addition to ameliorate lipid profile, may achieve further proteinuria reduction [73]. Whether 3-hydroxy-3-methylglutaryl coenzyme A inhibition added to maximized RAAS inhibition may achieve further renoprotection is a matter of investigation.

THE RAAS BLOCKADE IN CHRONIC ALLOGRAFT REJECTION

In Western countries, allograft rejection is becoming the third cause of ESRD. The functional and structural changes of chronic renal allograft nephropathy (CAN) show similarities with those observed in other forms of chronic progressive renal disease, in which inadequate functioning nephron mass has been considered the key event [74]. In a meta-analysis of 100 controlled and uncontrolled studies involving 2494 patients, Kasiske et al found that ACEIs were renoprotective in patients with CAN [75]. Data from retrospective studies show that early ACEI or ARB are well tolerated in renal transplant patients, and may even shorten the time of graft function recovery [76]. The risk/benefit profile of RAAS inhibition early posttransplant, however, remains to be established, along with the possibility that this approach may achieve effect in CAN prevention.

THE ECONOMIC COST OF THE RAAS BLOCKADE

Direct and indirect costs of ERDS are increasing exponentially worldwide. The economic impact of delayed progression to ESRD would be enormous, as documented by findings that a 30% reduction in the rate of GFR decline would translate into savings of more than \$60 billion in the United States by the year 2010 [77]. Clearly, there is a pressing need for effective identification and early treatment of patients at risk, including

type 2 diabetics with nephropathy, who currently represent the largest part of patients at risk of ESRD [78, 79]. Despite the cost of screening and early treatment, studies show that early intervention, in particular with RAAS inhibitors, is cost-effective. Thus, the economic evaluation of the RENAAL study showed that losartan and conventional therapy compared with placebo and conventional therapy significantly reduced the number of days with ESRD by 33.6 per patient over 3.5 years. This reduction in ESRD days resulted in a decrease in cost associated with ESRD of US \$5144 per patient. After accounting for the cost of losartan, the reduction in ESRD days resulted in a net savings of US \$3522 per patient over 3.5 years [80]. In a cost-effectiveness analysis from the data of REIN Study, patient-year of chronic (long-term) dialysis avoided quantification, and statutory health insurance expenses were analyzed. Results from this evaluation show that ramipril offers enormous savings from the perspective of the statutory health insurance provider (third-party payer) and per patient-year of chronic (long-term) dialysis after 1, 2, and 3 years of treatment [81]. Also, an analysis performed from the REIN study estimated the direct medical costs of conservative and renal replacement therapy from a payer's perspective [82]. The time to ESRD was predicted by two different models based on the rate of GFR decline (DeltaGFR) and incidence of ESRD (events) measured in 117 and 166 patients, respectively. Both in the DeltaGFR-based or events-based models, ramipril delayed progression to ESRD and prolonged patient survival by 1.5 to 2.2 and 1.2 to 1.4 years, respectively, and saved US \$16,605 to \$23,894 during the patient's lifetime and US \$2422 to \$4203 yearly direct costs per patient. Thus, early intervention is feasible and cost-effective. Now, the key problem is allowing access to essential medicine for all patients in need, in particular those in the poorest or developing countries [83].

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Reprint requests to Giuseppe Remuzzi, MD, FRCP "Mario Negri" Institute for Pharmacological Research Via Gavazzeni, 11, 24125 Bergamo, Italy.
E-mail: gremuzzi@marionegri.it

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