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Mechanisms and Treatment of CKD

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ABSTRACT

As CKD continues to increase worldwide, along with the demand for related life-saving therapies, the financial burden of CKD will place an increasing drain on health care systems. Experimental studies showed that glomerular capillary hypertension and impaired sieving function with consequent protein overload play a pathogenic role in the progression of CKD. Consistently, human studies show that proteinuria is an independent predictor of progression and that its reduction is renoprotective. At comparable BP control, inhibitors of the renin-angiotensin system (RAS), including angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), more effectively than non-RAS inhibitor therapy reduce proteinuria, slow progression to ESRD, and even improve the kidney function achieving disease regression in some cases. In participants with diabetes, RAS inhibitors delay the onset of microalbuminuria and its progression to macroalbuminuria, and ACE inhibitors may reduce the excess cardiovascular mortality associated with diabetic renal disease. In addition to RAS inhibitors, however, multimodal approaches including lifestyle modifications and multidrug therapy will be required in most cases to optimize control of the several risk factors for CKD and related cardiovascular morbidity. Whether novel medications may help further improve the cost-effectiveness of renoprotective interventions is a matter of investigation.

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STRUCTURAL AND FUNCTIONAL ADAPTATION IN RENAL FAILURE

A Concept Coming from Far Away

In 1936, in a lecture on the renal function in disease,[1] Robert Platt, argued that "when we turn to the uremic syndrome there is no difficulty whatever in accepting a high glomerular pressure, together with loss of nephrons (destroyed by disease) as an explanation of the peculiarities of renal function in this stage of kidney disease. . . The raised glomerular pressure will increase the amount of filtrate produced by each nephron, and thus compensate for a time for the destruction of part of the kidney. But eventually there are too few nephrons remaining to produce an adequate filtrate, even though they work under the highest possible pressure, supplemented by a high systemic BP. Nitrogen retention then ensues, followed by the symptoms of uremia." A few years later, he came to the precursory observation that "most if not all the functional disturbances are known to occur in animal experiments as a result of reduction in the amount of functioning renal substance—that is, loss of nephrons. In such experiments the remaining nephrons enlarge and take on a volume of work they are never called upon to perform. The same occurs in human disease, and our concept of renal failure should not be one of disordered function, but rather one of extremely efficient function by a renal remnant now too small for its task."[2]

In the mid-1960s, investigators from the Harvard Medical School of Boston, Massachusetts, led by Barry M. Brenner, took advantage from the availability of a sensitive, servo-null microtransductor system suitable for continuous measurement of microcirculatory pressures[3] that allowed to make measurements of the critical determinants of glomerular filtration in a unique strain of Wistar rats with some glomeruli situated on the renal surface to demonstrate that there is a reciprocal relationship between nephron number and glomerular BP.[4]

The following years were devoted to investigating the pathogenic role of glomerular hypertension in the progression of renal disease and to assessing whether correction of this disordered adaptation —or maladaptation[5]—to nephron mass reduction is renoprotective.[6]

FROM GLOMERULAR HYPERTENSION TO PROTEINURIA AND PROGRESSION

Identifying the Final Common Pathway

In 1932, a few years before the lecture by Robert Platt, Alfred Chanutin and Eugene Ferris[7] observed that removal of

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three-quarters of the total renal mass in the rat, in addition to increase intraglomerular pressures,[1] led to abnormal glomerular permeability and proteinuria. At that time, proteinuria was considered a marker of the extent of glomerular damage, despite the fact that Franz Volhard and Theodor Fahr in 1914[8] and Wilhelm von Mollendorf and Philipp Stohr in 1924[9] had already found that exuberant protein excretion in the urine could *per se* promote renal injury. In 1954, Jean Oliver[10] suggested that protein droplets he first recognized in the cytoplasm of tubular cells were possibly due to impairment in the process of reabsorption of plasma proteins normally carried out by the renal tubule and proposed that proteinuria could lead to structural and functional nephron damage.

Later on, dextran clearance studies showed that enhanced intraglomerular capillary pressure stretches glomerular walls that, in addition to leading to direct glomerular cell injury,[11] may also impair the selective function of the glomerular capillary, an effect explained by the appearance of very large pores that exceed the sizes observed in normal conditions and allow increased filtration of plasma proteins.[12] Mechanical strain may also increase angiotensin II (AngII) production and the expression of angiotensin type 1 receptors in podocytes,[13] and AngII may directly impair the glomerular barrier sieving function—possibly through inhibited nephrin expression—independent of its hemodynamic effects.[14] Moreover, disruption of glomerular permselectivity with eventual proteinuria and progressive glomerulosclerosis is observed in experimental models that are characterized by normal capillary glomerular pressure, such as adriamycin or puromycin nephrosis[15] and aging-associated glomerulosclerosis in male Munich-Wistar rats.[16] Thus, impaired glomerular sieving appears to initiate and perpetuate parenchymal damage, and ultimately renal scarring and insufficiency, through a common pathway that, independent of capillary pressure, results in increased protein content of the glomerular filtrate with protein overload to glomerular and tubular epithelial cells (Figure 1).[17,18] Indeed, podocytes exposed to excessive protein load release TGF-β, ultimately inducing differentiation of mesangial cells into myofibroblasts.[19–21] Protein overload in the tubules induces tubular cells to release cytokines, chemokines, growth factors, and vasoactive molecules, which leads to abnormal interstitial accumulation of inflammatory cells, extracellular matrix collagen, fibronectin, and other components that are responsible for interstitial fibrosis.[22,23] Notably, glomerular permeability dysfunction results in the passage of complement factors into Bowman's space and the tubular lumen.

Moreover, tubular cells themselves synthesize complement factors under stress conditions, leading to cytotoxic, proinflammatory, and fibrogenic effects.[20] In turn, tissue injury induced by protein traffic promotes the generation of reactive oxygen species and an endoplasmic reticulum stress response by renal cells.[24] This leads to the oxidative modification of membrane lipids, proteins, and DNA, thereby initiating cell-death responses that result in tissue inflammation and local recruitment of macrophages and lymphocytes, further fueling the inflammatory process.[22]

The altered interstitial milieu promotes epithelial-mesenchymal transition, a process by which differentiated epithelial cells undergo a phenotypic conversion into matrix-producing fibroblasts and myofibroblasts. This phenomenon is considered to reflect an adaptive response of

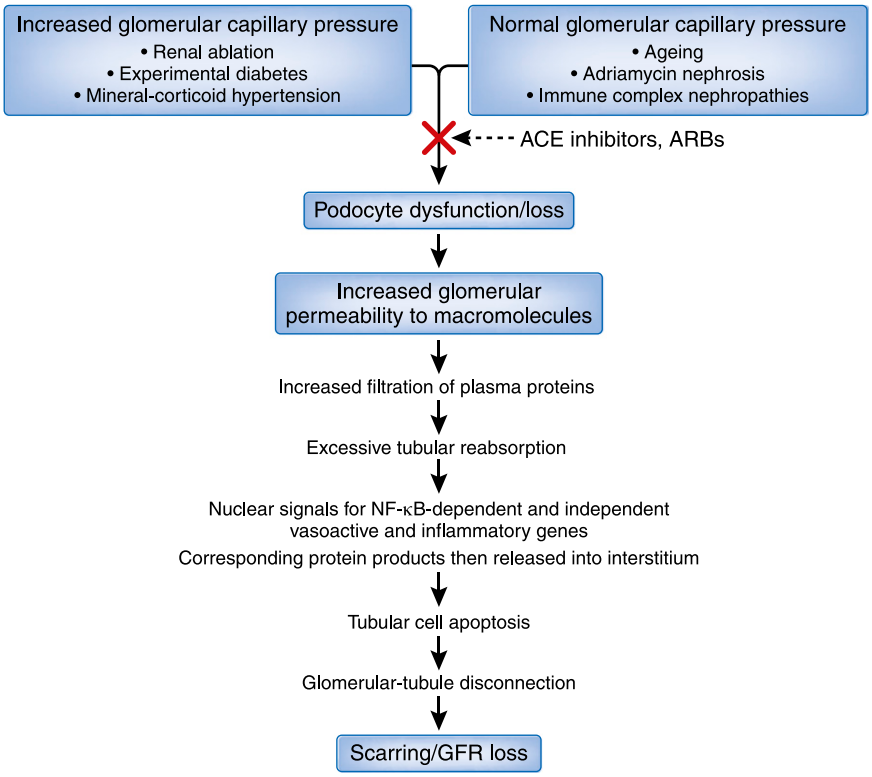

Figure 1. Enhanced protein traffic with or without glomerular capillary hypertension: a common pathway in the progression of chronic proteinuric nephropathies. In different experimental models of proteinuric CKD associated with normal or increased glomerular capillary pressure, podocyte dysfunction and loss results in increased glomerular permeability to macromolecules with consequent increase in protein ultrafiltration. Protein tubular overload may sustain a sequence of events eventually resulting in tissue scarring and GFR loss. By restoring glomerular sieving function RAS inhibitors such as ACE inhibitors and ARBs may limit protein overload and delay or prevent progression of kidney damage and dysfunction.

epithelial cells to an unfavorable microenvironment,[25] possibly also involving endothelial cells and glomerular podocytes that may undergo mesenchymal transition after injury and promote further exacerbation of proteinuria and glomerulosclerosis.

AMELIORATING GLOMERULAR SIEVING DYSFUNCTION AND PROTEINURIA

Therapeutic Advantages of RAS Inhibitors

More than 60 years ago, Addis speculated that the severity of renal disease could be ameliorated by reducing the excretory burden for nitrogen through dietary protein restriction.[26] Micropuncture studies in the 1980s actually showed that dietary protein restriction abrogates the adaptative rise in glomerular pressure and thereby slows the tendency to renal disease progression in the hyperfiltering kidneys of rats with reduced nephron mass[27] as well as in experimental diabetes[28] and mineral-corticoid–induced hypertension.[29] In the above studies, protection against progression of glomerulosclerosis was associated with a reduction in proteinuria mediated by restored permselective properties of glomerular capillaries.[17] Whether and to which extent these findings could be translated into human disease remained elusive until 1996 when a meta-analysis of 1413 patients included in five randomized, controlled trials of the effect of protein restriction on the progression of nondiabetic renal disease showed that the overall risk of kidney failure or death was reduced by protein restriction compared with unrestricted protein intake.[30] A subsequent meta-analysis, however, failed to demonstrate any significant effect of a low protein diet on GFR decline in 585 type 1 and type 2 diabetic patients included in 12 controlled studies.[31]

On the other hand, evidence that glomerular capillary hypertension is often maintained by angiotensin-dependent mechanisms fueled a series of experimental studies aimed to test the long-term renoprotective effects of inhibitors of the RAS such as ACE inhibitors and ARBs.[32] At comparable systemic BP control, ACE inhibitors more effectively than combined therapy with hydralazine, reserpine, and a diuretic reduced glomerular capillary pressure and slowed disease progression in experimental models of CKD characterized by glomerular capillary hypertension such as reduced nephron mass[33] and streptozotocin-induced diabetes,[34] an effect that, again, was invariably associated with a consistent reduction in proteinuria. Analysis of the fractional clearances of polydisperse neutral macromolecules of graded molecular size (Ficoll) showed that the antiproteinuric effect of the ARB, losartan, in rats with streptozotocin-induced diabetes was explained by a restored sieving function of the glomerular barrier with a shifting of the pore-size population toward sizes even smaller than those calculated for normal controls.[35] To note, the ACE inhibitor, enalapril, had a significant renoprotective effect also in male MWF/Ztm rats that develop massive proteinuria and glomerulosclerosis in the absence of glomerular capillary hypertension.[16] The above findings provided additional evidence that, independent of capillary hypertension, impaired glomerular sieving function with consequent protein overload plays a pathogenic role in the progression of experimental renal disease and that its amelioration may protect the kidney from the toxic effects of enhanced protein traffic (Figure 1).[17]

RENOPROTECTION

From Bench to Clinic

In two clinical lectures on albuminuria delivered at Guy's Hospital in 1890, James F. Goodhart concluded that the outcome of chronic parenchymatous nephritis could not be improved because at that time there was no drug "that can be depended upon to lessen the output of albumen."[36] Pivotal studies in patients with diabetic[37] and nondiabetic[38] CKD found that short-term proteinuria reduction achieved by intensified BP control was associated with slower GFR decline on subsequent follow-up. Consistently, results of the Modified Diet in Renal Disease (MDRD) study showed that reduction of proteinuria achieved by intensified BP control was associated with slower GFR decline, in particular in patients with more severe proteinuria to start with.[39] The first randomized clinical trial to demonstrate a specific renoprotective effect of ACE inhibitor therapy run by Bjork *et al.*[40] in 40 patients with type 1 diabetes and overt nephropathy showed that enalapril more effectively than the β-blocker, metoprolol, slowed GFR decline in this population, an effect that was associated with a remarkably larger reduction in albuminuria, but also with more BP reduction in the enalapril arm. These findings were confirmed and extended by evidence from the Captopril Collaborative Study that captopril reduced proteinuria and the risk of doubling of serum creatinine or progression to ESRD compared with non-ACE inhibitor therapy in 409 type 1 diabetic patients with overt nephropathy, an effect that, again, was associated with more BP reduction in the ACE inhibitor treatment arm.[41] Even larger BP differences between treatments did not allow to assess whether slower progression observed with benazepril compared with non-ACE inhibitor therapy in 583 patients with nondiabetic CKD was indeed mediated by an intrinsic renoprotective effect or simply by better BP control.[42]

The Ramipril Efficacy in Nephrology (REIN) study was the first trial to formally test the role of proteinuria in the progression of kidney disease and of proteinuria reduction in renoprotection.[43–45] The trial showed that in 352 patients with proteinuric nephropathies from different etiologies, higher proteinuria at inclusion was associated with faster GFR decline and progression to ESRD on follow-up.[46,47] At comparable BP control, ramipril therapy slowed GFR decline and progression to ESRD more effectively than non-ACE inhibitor therapy, an effect that was largely explained by the antiproteinuric effect of ramipril.[43–45] These findings were confirmed and extended by results of the African American Study of Kidney Disease and Hypertension (AASK) trial showing

that ramipril retarded progression more effectively than metoprolol or amlodipine in patients with urinary protein/creatinine ≥0.2[48] and of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL)[49] study and Irbesartan Diabetic Nephropathy Trial (IDNT)[41] showing that the ARBs, losartan and irbesartan, compared with non-RAS inhibitor therapy reduced doubling of serum creatinine and ESRD in type 2 diabetes patients with overt nephropathy.

To note, in the REIN trial, larger proteinuria reduction and less residual proteinuria on follow-up were both associated with slower GFR decline and more effective protection against progression to ESRD, independent of treatment allocation.[50] Larger proteinuria reduction predicted slower progression, and even fewer cardiovascular events,[51] also in type 2 diabetes patients with overt nephropathy included in the RENAAL[52] and IDNT[53] trials. The predictive/pathogenic role of proteinuria was confirmed by a pooled analysis of 2387 CKD patients included in 11 trials showing that irrespective of the treatment adopted, short-term changes in proteinuria were strongly consistent with long-term renal outcome. Reduction of proteinuria was invariably associated with improved outcome, whereas no effect on proteinuria predicted any long-term benefit. A worsening of proteinuria was never associated with improvement.[54]

Notably, in the REIN and RENAAL studies, ACE inhibitor and ARB therapy preserved residual renal function also in patients with stage 4–5 CKD.[55,56] These findings were prospectively confirmed by a randomized controlled study of 224 patients with a serum creatinine >3.0 mg/dl that showed that, over 3.4 years, 40% less patients on benazepril progressed to ESRD compared with placebo, despite similar BP control.[57] ACE inhibitors may even preserve diuresis, reduce proteinuria,[58] and prevent cardiovascular events[59] in dialysis patients with residual kidney function, and prolong graft survival in kidney transplant recipients.[60] Ongoing trials are addressing whether RAS inhibitor therapy effectively reduces cardiovascular events in hemodialysis patients (ClinicalTrials.gov identifier: NCT00985322; CRG010600030).

ACE INHIBITORS, ARBS, OR BOTH?

Among 360 nondiabetic CKD patients included in the Renoprotection of Optimal Antiproteinuric Doses (ROAD) study, those randomized to 3.7-year treatment with benazepril or losartan in a dose that was uptitrated until the maximum antiproteinuric effect had a reduced incidence of the combined endpoint of doubling of serum creatinine, ESRD, or death compared with those on conventional antihypertensive doses of both medications.[61] Independent of treatment dose, however, the effect of benazepril and losartan on considered outcomes was similar. In apparent harmony with the above findings, the authors of the Diabetics Exposed to Telmisartan and Enalapril (DETAIL) trial concluded that, on the basis of predefined criteria, telmisartan did not appear to be less effective than enalapril in 250 type 2 patients with diabetes with hypertension and micro- or macroalbuminuria.[62] In actual fact, however, GFR reduction at 5 years was 20% larger in the telmisartan group and 27 of the 120 patents on telmisartan (22.5%) had fatal or nonfatal cardiovascular events compared with 21 of the 130 taking enalapril (16.1%). Unfortunately, no statistics were provided to know whether the above differences were significant.

In the Irbesartan Microalbuminuria Type 2 Diabetes in Hypertensive Patients (IRMA) 2 trial, full-dose (300 mg/d) irbesartan therapy reduced the 2-year incidence of progression to macroalbuminuria from 14.9% to 5.2% compared with placebo and increased the rate of regression to normoalbuminuria from 21% to 34%.[63] The Bergamo Nephrologic Diabetes Complications Trial (BENEDICT)-B showed that ACE inhibitor therapy with trandolapril was associated with rates of progression to macroalbuminuria or regression to normoalbuminuria similar to those observed with full-dose irbesartan in the IRMA 2 trial. The novel finding here was that, in patients with regression of microalbuminuria, the rate of fatal and nonfatal cardiovascular events was reduced by almost 50% (from 18.9% to 9.8%) compared with those without regression.[64]

The BENEDICT trial found that 3.6 year treatment with the ACE inhibitor, trandolapril, compared with non-ACE inhibitor therapy reduced the risk of progression to microalbuminuria from 10.9% to 5.8% in 1204 type 2 diabetes patients with normal urinary albumin excretion at inclusion, an effect that was observed at comparable BP control between treatment arms.[65] A virtually identical study, the ROADMAP study, repeated 7 years later with an ARB instead of an ACE inhibitor in a similar typology of patients showed that 3.2 years of olmesartan therapy reduced the incidence of microalbuminuria compared with placebo from 9.8% to 8.2%, an effect that was observed in parallel with better BP control on olmesartan and that was not significant any longer when analyses were adjusted for BP levels in the two treatment arms.[66] Overall, in the above two trials, trandolapril and olmesartan reduced the hazard for microalbuminuria by 56% and 23% versus placebo, respectively. Because cumulative incidence of microalbuminuria was virtually identical in placebo arms of both studies (Figure 2, left panel), the larger renoprotective effect of trandolapril (Figure 2, right panel) was unlikely explained by different patient risk, and actually was observed despite larger BP reduction in the olmesartan treatment group. Even more important, there was an almost five-fold increase in fatal cardiovascular events on olmesartan versus placebo compared with a 70% reduction in trandolapril (hazard ratios versus placebo were 4.94 for olmesartan and 0.31 for trandolapril, respectively). The excess cardiovascular mortality on olmesartan was significant, which confirms previous evidence of superior cardioprotective effect of ACE inhibitor compared with ARB therapy[67] and, combined with similar data from the Olmesartan Reducing Incidence of

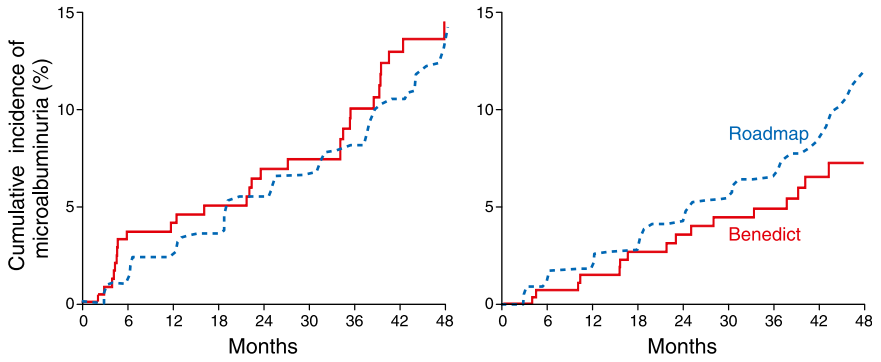

Figure 2. Effects of trandolapril and olmesartan on microalbuminuria prevention in normoalbuminuric type 2 diabetes patients. Left and right panels show the cumulative incidence of microalbuminuria in the placebo and in the treatment arms in the BENEDICT (continued line) and ROADMAP (dashed line) trials, respectively. The incidence of events was similar in the placebo arms of the two studies, but was reduced in the trandolapril arm of BENEDICT compared with the olmesartan arm of ROADMAP.

End Stage Renal Disease in Diabetic Nephropathy Trial (ORIENT),[68] led the US Food and Drug Administration to alert that olmesartan "is not recommended as a treatment to delay or prevent protein in the urine (microalbuminuria) in diabetic patients."[69]

All of the above data, together with several cost-effectiveness analyses—including the one recently performed with the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET)[70] showing that the use of ARB telmisartan instead of ACE inhibitor ramipril increases costs by 6.3%—suggest that independent of the underlying renal disease and severity of proteinuria/albuminuria, ACE inhibitors should be considered first-line therapy for their superior renocardioprotective effect, whereas ARBs should be left as rescue therapy in patients with intolerance to ACE inhibitors or, possibly, as add-on therapy in those with residual proteinuria/albuminuria.

Several animal models of proteinuric disease documented that combined ACE inhibitor and ARB therapy reduces proteinuria and prevents and even regresses glomerulosclerotic, tubulointerstitial, and vascular lesions more effectively than single drugs.[71,72] Studies in humans comparing the antiproteinuric effect of combined versus single drug therapy with ACE inhibitors and ARBs were flawed by higher BP reduction in the dual treatment arm.[73] To address this issue, in a randomized, crossover study, 24 patients with nondiabetic CKD received full doses of benazepril or valsartan, or half doses of the two drugs used in combination.[74] BP similarly declined in all three treatment arms, whereas proteinuria declined significantly more with dual RAS blockade. Patients were all then maintained on dual RAS inhibitor therapy and prospectively followed-up. Their GFR decline over the following 6 years was significantly slower than in matched reference patients receiving single drug RAS blockade with full dose of an ACE inhibitor[75]

More recently, the ESPLANADE trial[76] showed that, in 186 patients with chronic proteinuric nephropathies, the larger reduction in proteinuria achieved by combined therapy with benazepril and valsartan compared with benazepril alone, was associated with concomitant reduction in total, LDL, and HDL cholesterol, and apoB and apoA levels, an effect that in the long term might translate into reduced cardiovascular risk.

In apparent contrast with the above findings, *post hoc* analyses of outcome data of 25,620 patients with established atherosclerotic vascular disease or diabetes included in ONTARGET,[77] showed that the prespecified composite endpoint of any dialysis, renal transplantation, doubling of serum creatinine, or death occurred more frequently in those receiving combination treatment with telmisartan and ramipril than in those receiving each drug alone. The finding that the excess of composite outcomes was associated with decreased albuminuria and less progression to micro or macro- albuminuria led some authors to reconsider the use of proteinuria as surrogate for progressive renal disease.[78] However, 87% of study patients had normal urinary albumin excretion at inclusion and only 4% had overt proteinuria. Thus, such patients were not exposed to the nephrotoxic effects of protein overload, which may explain why their rate of renal function loss was similar to that observed in the general population,[79] and was not appreciably affected by either single or dual RAS inhibitor therapy.[80–82]

These data are consistent with previous evidence that RAS inhibitor therapy does not appreciably affect renal progression in patients with 24-hour proteinuria >0.5–2 g.[80–82] They should not, however, be extrapolated to patients with proteinuric nephropathies. Ongoing randomized trials are prospectively addressing whether dual RAS blockade prevents progression to ESRD more effectively than single RAS blockade in patients with type 2 diabetes and overt proteinuria (VALID and VA NEPHRON-D; ClinicalTrials.gov registry numbers: NCT00494715 and NCT0555217, respectively).

As for the excess of adverse renal outcomes on combination treatment, it must be emphasized that this trend was largely driven by the more frequent need for acute hemodialysis to treat transient kidney dysfunction in patients with excessive BP reduction or hypovolemia that improved with treatment withdrawal.[77] Thus, need of dialysis was a treatment-related adverse effect facilitated by dual RAS inhibition in participants at risk because of established atherosclerotic vascular disease and could not be considered as a renal outcome related to proteinuria or renal disease progression.[83] Of particular interest, in ONTARGET patients, independently of treatment allocation, early changes in albuminuria predicted long-term progression to doubling of serum creatinine

or ESRD (2-year halving or doubling of albuminuria versus baseline predicted 30% less or 40% more events, respectively, throughout the whole study period). Thus, that proteinuria is a suitable surrogate endpoint for renal function does not need to be re-examined, at least on the basis of the ONTARGET findings.[83]

FROM NEPHROPROTECTION TO KIDNEY REGENERATION: CAN THE KIDNEY SELF-REPAIR?

In a broad range of animal models of proteinuric kidney disease, ACE inhibitors, ARBs, or both not only prevented progressive renal damage, but also induced regression of glomerulosclerotic, tubulointerstitial, and vascular lesions.[84–86] A long-term follow-up of the REIN study showed that the rate of measured GFR decline progressively improved to a level of about 1 ml/min per 1.73 m^2 per year after at least 5 years of continued ramipril use, which approximates the average age-related loss in GFR over time in healthy participants.[87] Moreover, a breakpoint was identified in the slope of GFR changes over time that started to increase after 36 months of treatment a finding that led to hypothesize that renal disease can regress.[88]

Using a technique for three-dimensional reconstruction of the glomerular capillary tuft, Andrea Remuzzi *et al.*[84] showed in rats with advanced proteinuric nephropathy that administration of high-dose lisinopril reduced the volume of sclerosis in most glomeruli, unless they were almost totally sclerosed, and increased the volume of normal capillary tissue by up to 40%. Kidney repair has been definitely documented in seven proteinuric patients with idiopathic membranous nephropathy treated with the anti-CD20 mAb, rituximab; these patients, in parallel with complete remission of the nephrotic syndrome, showed reabsorption of characteristic subepithelial electron-dense immune deposits and reversion of foot process effacement and loss of intact slit diaphragms at repeat biopsy evaluation.[89] Consistently, the possibility of morphologic regression of chronic structural changes was confirmed by a morpho-functional study showing that in eight patients with type 1 diabetes and mild to advanced nephropathy, renal histology lesions regressed after 10 years of euglycemia made possible by pancreas transplantation.[90]

ACE inhibitors can boost renal repair by promoting survival and repair of podocytes, preventing mesangial cell hyperplasia, and inducing glomerular endothelial cell remodeling. Other mechanisms include reduction of the expression of plasminogen activator inhibitor 1, an inhibitor of matrix degradation, decreased expression of collagen I and IV and TGF-β, and increased metalloproteinase activity.[86] Regression of glomerulosclerosis and neoformation of glomerular tissue has been linked also to progenitor or stem cells of renal or extrarenal origin and ACE inhibitors or ARBs may promote their mobilization and/or activation at the site of renal injury.[91]

AN INTEGRATED THERAPEUTIC APPROACH TO CKD

The Remission Clinic Example

The integrated use of different treatments against the same target, such as uncontrolled cell or viral replication, has dramatically improved the outcome of severe diseases such as cancer and AIDS. By analogy, a multimodal intervention strategy using all available tools to target a major pathogenic factor in the progression of CKD such as proteinuria seems a rational approach to maximizing renoprotection in CKD patients.[54] Solid experimental data[71] and evidence that such multimodal intervention normalized proteinuria and stabilized the GFR in a young girl with heavy proteinuria and rapidly worsening renal function while on standard therapy with antihypertensive dosages of an ACE inhibitor[92] provided the background for a standardized intervention protocol, the Remission Clinic program. This program was implemented through an informatic support (http://clinicalweb.marionegri.it/remission/) and applied to all CKD patients with heavy proteinuria despite therapy.[75] This multimodal intervention strategy included lifestyle modifications such as sodium[93] and protein[30] intake restriction, smoking cessation, body weight loss,[94] optimal BP (target systolic/diastolic $<$130/80 mmHg) and metabolic control (target hemoglobin A1C $<$7.5%) in patients with diabetes, correction of metabolic acidosis[95] and hyperphosphatemia,[96] use of statins,[76,97,98] and dual RAS blockade with maximum tolerated doses of ACE inhibitors and ARBs, probably the mainstay of proteinuria management in this setting.[99] In a matched-cohort study, we compared the outcome of 56 CKD patients receiving the Remission Clinic approach because of persistent 24-hour proteinuria $>$3 g despite standard antihypertensive doses of an ACE inhibitor with that of 56 matched historical reference patients who had received ACE inhibitor therapy titrated to target BP.[99] Over a median follow-up of 4 years, GFR decline was almost fourfold slower with the Remission Clinic approach and only two patients compared with 17 reference patients progressed to ESRD, a difference that was highly significant. The finding that proteinuria reduction independently predicted slower GFR decline and less progression to ESRD further confirmed the importance of targeting proteinuria to slow renal disease progression. Therapy was well tolerated and no patient was withdrawn because of hyperkalemia.[99] Based on the above findings, a multicenter network has been established to assess whether the Remission Clinic approach can be safely and effectively applied in everyday practice.[75]

WHAT IS NEW IN THE PIPELINE?

Perspectives, Uncertainties, and Disappointments

RAS Inhibition

One of the most promising novel drugs on the table was the renin inhibitor, aliskiren, which had been found to significantly reduce albuminuria versus placebo in 599 type 2 diabetes patients with nephropathy who received background

losartan therapy (Table 1).[100] Enthusiasm for this novel drug, however, was recently tempered when the Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints, testing aliskiren on top of RAS inhibitor therapy in patients with type 2 diabetes and renal impairment compared with a placebo add-on, was prematurely interrupted due to an increase in adverse events, including a concerning excess of strokes, and no apparent benefits among patients randomized to aliskiren.[101]

Renin inhibition is one of the mechanisms that have been suggested to support the antiproteinuric effect of the vitamin D receptor agonist, paricalcitol. In a short-term trial in albuminuric patients with diabetes on background ARB therapy, this drug significantly reduced albuminuria, but the results were confounded by the lower BP on active treatment compared with placebo.[102] The finding that the antiproteinuric effect of paricalcitol was particularly prominent in participants with sodium intake >200 mEq/d provided the background for a controlled trial to assess whether paricalcitol therapy may have a room for those patients who respond poorly to RAS inhibitor therapy because of high salt intake in the Salt Intake and Antiproteinuric Effect of Paricalcitol inType 2 Diabetes (PROCEED; Clinical Trials.gov identifier: NCT01393808).

Since the 2001 report that aldosterone antagonist therapy with spironolactone added-on ACE inhibitor therapy reduced proteinuria in eight patients with diabetic and nondiabetic CKD,[103] at least 10 randomized controlled trials consistently report a reduction in proteinuria ranging from 30% to 58% with spironolactone or eplerenone in patients with diabetic or nondiabetic CKD receiving background ACE inhibitor and/or ARB therapy.[104] Of interest, the antiproteinuric effect was not confined to participants with aldosterone breakthrough.[105] However, these encouraging findings are tempered by the excess risk of hyperkalemia particularly in patients with decreased GFR. Thus, long-term efficacy and safety data are needed before aldosterone antagonism therapy can be recommended in the wider nephrology context.

Whether targeting BP levels <130/80 mmHg recommended target may add to the renoprotective effect of RAS inhibition in patients with proteinuric CKD has also been challenged by the REIN-2 study[106] and by a recent systematic review including patients from the AASK and MDRD trials,[107] and may also raise safety concerns, in particular in participants with diabetes.[66]

Other Pathways

Drugs are also being developed that may reduce renal disease progression targeting mechanisms downstream of proteinuria. In this line, pirfenidone, a TGF-β inhibitor, reduced renal function loss in small studies with FSGS[108] or diabetes[109] patients, but the high rate of dropouts raised serious concerns about the safety of this compound in particular in patients with diabetes. Bardoxolone methyl is an antioxidant and anti-inflammatory molecule that in a large trial of 227 diabetic patients with GFR <45 ml/min per 1.73 m^2 increased estimated GFR over placebo in a dose-dependent fashion. This effect, however, was associated with increased BP and albuminuria, which raised concerns whether the renal effect of increasing GFR was actually due to hyperfiltration, a major determinant of accelerated glomerular damage.[110] An ongoing long-term randomized trial with hard endpoints is assessing whether this drug is actually able to safely improve renal survival in stage IV–V CKD patients with diabetes (ClinicalTrials.gov identifier: NCT01351675).

Another compound with anti-inflammatory properties is bindarit, an inhibitor of monocyte chemoattractant protein-1 (MCP-1) able to retard renal disease and prolong survival in murine lupus.[111] It reduced albuminuria in two small studies in macroalbuminuric patients with lupus nephritis[112] or type 2 diabetes,[113] but adequately powered trials are needed to assess whether this beneficial effect may actually translate into slower progression in the long term.

Endothelin (ET)-1 is a potent vasoconstrictor peptide with proinflammatory, mitogenic, and profibrotic effects that may contribute to CKD progression.[114] Combined blockade of ET_A and ET_B receptor by avosentan therapy on top of RAS blockade reduced BP and albuminuria in type 2 diabetes patients with overt nephropathy but was associated with serious safety concerns related to fluid retention.[115] Interest in ET antagonists was recently revived by encouraging results observed with selective ET_A receptor blockade with atrasentan. Again, however, albuminuria reduction was associated with signs of fluid retention.[116] Whether combined endothelin-converting enzyme/neutral endopeptidase inhibitor therapy by daglutril may achieve the same antiproteinuric effect of ET inhibition, avoiding treatment-related sodium retention because of the natriuretic effect of enhanced atrial natriuretic peptide bioavailability, is currently under investigation in type 2 diabetes patients with overt nephropathy (ClinicalTrials.gov identifier: NCT00160225).

Sulodexide, a heterogeneous mixture of sulfated glycosaminoglycans thought to improve glomerular selectivity, was suggested to decrease albuminuria in small studies in diabetes patients.[117] However, results of a randomized, controlled trial in 1056 diabetic patients with overt nephropathy that has been recently stopped because of futility, definitely signaled the end of this line of research.

Data on the renoprotective effect of uric acid reduction by allopurinol therapy are encouraging (see Turner *et al.*[118] for review), but need confirmation in adequately powered trials, whereas the renoprotective effect of anemia correction by erythropoietin congeners has been definitely challenged, at least in overt nephropathy of type 2 diabetes, by results of the Trial to Reduce Cardiovascular Events with Aranesp Therapy.[119]

TAKE-HOME MESSAGES

CKD is an important multiplier of risk for many chronic noncommunicable diseases, including cardiovascular

Table 1. Novel medications under investigation for the treatment/prevention of CKD

Drug	Mechanism of Action	Main Findings	Pitfalls
Aliskiren	Blockade of renin	The AVOID study showed that, in 281 type 2 diabetic patients with hypertension and overt nephropathy who were receiving ARB therapy, aliskiren reduced the urinary albumin/creatinine ratio by 20% compared with placebo during 24 wk of follow-up	Advantages of aliskiren versus ACE inhibitors and ARBs still unproven. Results of ALTITUDE raised concern on the safety of the compound
VDR agonist	Inhibition of renin synthesis (?)	In the randomized, controlled VITAL study, VDR agonist paricalcitol reduced albuminuria in a dose-dependent fashion in 281 type 2 patients with diabetes on background ARB therapy. Albuminuria reduction was associated with a decline in BP and eGFR	Long-term studies are needed to assess the efficacy of paricalcitol and other vitamin D analogs on top of maximal RAS inhibition on hard endpoints
Pirfenidone	Inhibition of TGF-β–mediated fibrosis	Pirfenidone reduced the rate of GFR decline over 12 months in 18 patients with FSGS, with no effect on BP or proteinuria. A RCT in 77 patients with diabetic nephropathy, a 1400-mg daily dosage was associated with a significantly lower decline in eGFR compared with placebo. Conversely, the 2400-mg dose led to a high rate of discontinuation and no difference in eGFR decline compared with placebo	Results on the efficacy are limited to small studies with short follow-up. Safety is an additional matter of concern
Bardoxolone methyl	Activation of over 250 cytoprotective genes, with protective activity on immune-mediated inflammation	A RCT showed that, in 227 patients with type 2 diabetes, bardoxolone increased eGFR, BP, and albuminuria	Bardoxolone-induced increased eGFR, BP and albuminuria may promote accelerated progression of diabetic nephropathy. Further long-term studies with measured GFR and hard endpoints are needed to test the safety/efficacy profile of this drug
Bindarit	Inhibition of CCL2 (also known MCP-1)	In 22 participants with lupus nephritis, bindarit reduced albuminuria by 90%	Still preliminary findings
ET-1 antagonist	Inhibition of ET-1–mediated arterial vasoconstriction, glomerular hypertension, increased proteinuria, and interstitial fibrosis	A RCT testing the antiproteinuric effect of endothelin type A antagonist avosentan was prematurely terminated due to an excess of cardiovascular events in the avosentan-treated group. Another RCT testing a more selective ET_A antagonist, atrasentan, showed an antiproteinuric effect with fewer side effects	Lack of strong data in support of ET-1 antagonists and poor safety profile represent major hurdles to use of these drugs
Sulodexide	Restoration of heparane sulfate component of basement membrane	Initial studies in diabetic nephropathy showed an antiproteinuric effect of sulodexide and other glycosaminoglycans. However, in a recent RCT, including the largest number of diabetic patients, sulodexide failed to decrease albuminuria when used on top of ACE inhibitor or ARB therapy	No clear evidence of any additional antiproteinuric or renoprotective effect of sulodexide over ACE inhibitors or ARBs

AVOID, Aliskiren in the Evaluation of Proteinuria in Diabetes trial; ALTITUDE, Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints; VITAL, Vitamin D and Omega-3 Trial; VDR, vitamin D receptor; eGFR, estimated GFR; RCT, randomized controlled trial; MCP-1, monocyte chemoattractant protein-1; ET-1, endothelin-1.

disease[120] and cancer.[121] In the United States alone, the health care costs for people with CKD requiring treatment for heart disease and other health problems made worse by their kidney disease exceeded $60 billion in 2007. The per-patient costs for dialysis in those participants who progress to ESRD are between $150,000 and $200,000 per year. The <1% of the population in need of renal replacement therapy consumes up to 5% of health care budgets.[122] As kidney

disease continues to increase worldwide, along with the demand for related life-saving therapies, the financial burden of CKD care will place an increasing drain on health care systems. According to the World Health Organization, CKD and other noncommunicable diseases decrease the potential annual growth rate in gross domestic product by 1%–5% in developing countries experiencing rapid economic growth.[123]

Thus, intervention strategies to prevent renal disease onset and progression are of paramount importance to reduce the clinical and economic burden of CKD. Multimodal approaches including lifestyle modifications and multidrug therapy will be required in most cases to optimize control of the several risk factors for CKD and related cardiovascular morbidity. RAS inhibition with ACE inhibitors and/or ARBs is probably the mainstay of renocardioprotective therapy in patients with proteinuric nephropathies. In analogy with what was initially proposed for secondary prevention of cardiovascular events, a fixed-dose combination therapy (a polypill),[124] including a RAS inhibitor, a diuretic, and a statin, might help in improving patient compliance, which often represents any hurdle to the applicability of any multidrug therapy.

Availability of out-of-patent drugs might dramatically reduce costs of CKD prevention and treatment programs. Cost-effectiveness analyses[70,125] consistently show that this renocardioprotective approach could allow remarkable savings for health care providers facing an epidemic of noncommunicable renal diseases. Intriguingly, recent experimental and clinical observations that regression of glomerular structural changes and remodeling of the glomerular architecture is achievable are offering entirely novel perspectives for renal disease treatments.

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DISCLOSURES

None.

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