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The future of renoprotection: Frustration and promises

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The global burden of end-stage renal disease is growing [1]. During the last decade, the dialysis population has been growing at an average of 7% per year. There are now approximately 1.1 million people worldwide on renal replacement therapy, and, according to reliable estimates, the number of maintenance dialysis patients will double in 10 years. The total cumulative cost for renal replacement therapy in the next decade will exceed $1 trillion [2], a really shocking figure from any point of view.

Renal replacement therapy is widely available for anyone in need in high-income countries, while in middle-income countries treatment is restricted to a selected population of patients. No treatment at all is available in low-income countries, where people with chronic kidney disease are dying of uremia [3].

The impossibility to have access to a life-saving treatment such as dialysis in many parts of the world underlines dramatically the existing inequalities that do not have any prospect of solution. In fact, during the next decade, the possibility that low-income countries could afford dialysis programs is unlikely, while even high-income countries have to face the prospect of some form of rationed care.

How could the global burden of chronic kidney disease be diminished in the future? At the present, there are no definitive cures for most acquired kidney diseases, and there is not reasonable expectation that gene therapy will be available soon enough to treat genetic forms of kidney diseases, such as polycystic kidney disease. Renal transplantation is limited by organ shortage [4], a worldwide problem that is not likely to be soon resolved by xenotransplantation. The best we can do at the present time is to concentrate our efforts in the prevention of progression of renal diseases.

During the last 20 years we have learned a great deal concerning the mechanisms involved in the progression of kidney disease, and we have devised strategies, based on a combination of drug interventions and lifestyle changes, to prevent it. The challenge for the future is to improve our knowledge on these mechanisms and discover other tools for protecting renal function from progressive deterioration. Also, a major task will be to reach all those who could benefit of the currently available treatment strategies, in the rich as well in the poor countries.

MECHANISMS OF PROGRESSION

Glomerular hypertension and hyperfiltration

In 1982, the somewhat somnolent world of nephrology was abruptly awakened by Brenner, Meyers, and Hostetter [5] who exposed their hypothesis on the mechanisms of progression of chronic kidney disease in a seminal paper. Central to their hypothesis was the concept, later confirmed by an abundance of experimental data from their Boston laboratory and from many others in the world, that progressive deterioration of renal function was the result of compensatory glomerular hemodynamic changes in response to nephron loss. In a widely used experimental model of renal mass reduction, the remaining nephrons undergo hypertrophy, reduced arteriolar resistance, and increased glomerular blood flow [6]. Since afferent arteriolar tone decreases more than the efferent one, intraglomerular pressure and the amount of filtrate formed by single nephron rise.

The role of angiotensin II

The role of angiotensin II in progression of renal disease has been object of extensive investigation (for a review, see [7]). In vivo, angiotensin II enhances the vascular tone of both afferent and efferent glomerular arterioles and modulates intraglomerular capillary pressure and glomerular filtration rate (GFR). Angiotensin II exerts its vasoconstrictor effect predominantly on the postglomerular arterioles, thereby increasing the glomerular hydraulic pressure and the filtration fraction. High glomerular capillary pressure increases the radius of the pores in the glomerular membrane, thus impairing the size-selective function of the membrane

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to the macromolecules [8]. Besides these glomerular hemodynamic effects of angiotensin II, other studies have revealed several nonhemodynamic effects of angiotensin II that may also be important. In isolated perfused kidneys, infusion of angiotensin II results in a loss of glomerular size permselectivity and proteinuria, an effect that has been attributed to both hemodynamic activity of angiotensin II and its direct effect on glomerular permselectivity [9]. Podocytes have a complex cytoskeleton with contractile properties, and there are angiotensin II receptors on their surface [10]. These findings have suggested that angiotensin II may alter permselective properties of the glomerular barrier by mediating contraction of the foot processes ultimately changing slit diaphragm architecture and allowing proteins to escape more easily into the urinary space [11]. Evidence that angiotensin II depolarizes podocytes by opening a chloride conductance related to cytoskeleton via an angiotensin II type 1 receptor is in line with such a possibility [12]. Angiotensin II concentration in the Bowman's space is up to 1000-fold higher than in the vasculature space, suggesting that angiotensin II is produced by local renin-angiotensin system.

Angiotensin II also modulates renal cell growth, which, in turn, may contribute to tubulointerstitial injury [13]. Increased expression of *c-fos* and *Egr-1*, the immediate early genes whose activation precedes cell proliferation, has been shown in proximal tubular cells exposed to angiotensin II [14].

The peptide, acting through angiotensin II type 1 receptors, also induces hypertrophy in tubular cells by up-regulating the gene for transforming growth factor β1 (TGF-β1), which, in turn, leads to increased synthesis of collagen type IV [15]. Remodeling of the interstitial architecture may also occur as a result of transformation of tubular cells, an additional event promoted by the enhanced synthesis of TGF-β1 stimulated by angiotensin [16].

Angiotensin II also stimulates the production of plasminogen activator inhibitor-1 (PAI-1) and may therefore further increase the accumulation of the extracellular matrix through inhibition of its breakdown by matrix metalloproteinases, which require the conversion to an active form by plasmin [17]. By stimulating macrophage activation and phagocytosis, angiotensin II may enhance the inflammatory component associated with chronic renal injury [18]. Angiotensin II up-regulates genes and stimulate secretion of peptides with chemotactic and vasoactive properties [19].

In experimental animals, repeated infusions of angiotensin II cause interstitial fibrosis and lead to the deposit of type IV collagen, a process that suggests the morphogenic effect of angiotensin II on tubulointerstitial structure [20].

Proteinuria

Proteinuria is not merely a consequence of glomerular hyperfiltration, a marker of altered glomerular barrier integrity. Soon after the formulation of the Brenner's hypothesis, it was proposed that abnormal protein trafficking through the glomerular capillary might also contribute to progression of renal disease.

In rats with age-related proteinuria [21], or with adriamycin-induced nephrosis [22], protein reabsorption droplets accumulated in the proximal tubular cells. Also, focal breaks of tubular basement membranes, and extravasation of the tubular content in the renal interstitium were demonstrated in rat renal biopsies.

Both in vitro and in vivo, protein overload causes increased production of inflammatory mediators such as endothelin-1, monocyte chemoattractant protein-1 (MCP-1), regulated upon activation, normal T cell expressed and secreted (RANTES), a chemotactic cytokine for monocytes and memory T cells and osteopontin [23]. The molecular mechanisms that lead to chemokine overexpression are mediated by nuclear factor-kappaB (NF-kB), a transcription factor that promotes nuclear translocation of the DNA [24, 25]. There is in vitro evidence that albumin and IgG caused a dose-dependent increase in NF-kB activation in proximal tubular cells, an event that is followed by up-regulation of RANTES and MCP-1 [26, 27].

In specimen of renal biopsies of patients with severe proteinuria, NF-kB activation has been shown in tubular cells, concomitant to up-regulation of proinflammatory chemokines [28].

Complement components also may play a major role in proteinuria-induced interstitial damage. Complement proteins are filtered through the glomerulus, and deposits of C3 and C5b-9 are found in proximal tubular cells in a number of experimental models of proteinuric nephropathies [23]. Intracellular C3 staining was present in proximal tubular cells prior to the development of inflammation [29]. Activation of complement system in tubular cells is associated with alterations of the cytoskeleton, production of reactive oxygen species, and synthesis of proinflammatory mediators [30].

Podocyte dysfunction

Recent data are in support of the possibility that the excessive protein load of the cells can be a factor underlying progressive podocyte injury (Fig. 1) [31]. Signs of enhanced uptake of plasma proteins by podocytes, as assessed by immunofluorescence analysis of albumin, IgG and complement C3, were found in remnant kidneys of rats with 5/6 renal mass reduction at 7 days after surgery, in a very early stage of disease. The granular intracellular pattern was entirely consistent with accumulation of proteins by endocytosis. By dual staining of sections of

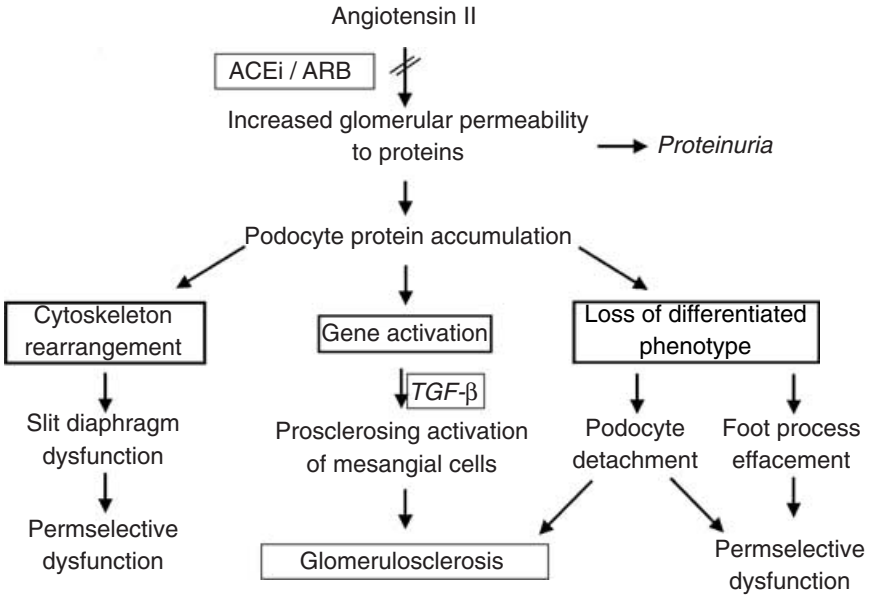

Fig. 1. Schematic representation of podocyte disfunction caused by protein overload in chronic nephropathies. Abbreviations are: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; TGF-β, transforming growth factor-β.

kidneys taken at 14 days after surgery, the abnormal expression of desmin, a marker of podocyte injury, was confined to the podocytes showing intracellular staining for plasma proteins. In addition, protein-laden podocytes showed loss of expression of synaptopodin, an actin-associated molecule first detectable during foot process formation and thus an indicator of differentiated phenotype of the cell. These data were taken to suggest that the enhanced endocytosis of protein may concur to the perturbation of podocyte function that is currently recognized to play major role in generating adhesive lesion and sclerosis. A causal link between protein load and podocyte dysfunction indeed was established by findings that the exposure of cultured podocytes to albumin (10 mg/mL) induced both loss of synaptopodin staining and expression and release of TGF-β1, a major stimulus for extracellular matrix production in the glomerulus. Moreover, the conditioned medium of albumin-laden podocytes induced the expression of the myofibroblast-associated molecule α-smooth muscle actin in cultured mesangial cells. Such response was inhibited by the addition of neutralizing anti-TGF-β1 antibody.

To dissect the relative contribution of angiotensin II and proteinuria on chronic renal damage, we used a protein overload model of nephropathy in animals with targeted gene deletion of the angiotensin II type 1A receptor (AT1 −/−) as compared to wild-type mice (AT1 +/+). A group of normal animals not exposed to overload proteinuria acted as control.

AT1 −/− animals developed proteinuria, renal failure, and glomerular sclerosis, although to a lesser degree than AT1 +/+ animals. In both models renal endothelin-1 expression and synthesis was increased as compared to normal contros. These data confirm that protein trafficking through the glomerular barrier has an intrinsic toxicity that is independent from the mediation of angiotensin II [32].

The activation of a variety of molecules, such as cytokines, growth factors, and vasoactive substances, may result in abnormal accumulation of extracellular matrix collagen, fibronectin, and other components that are responsible for interstitial fibrosis. The proinflammatory mediators promote local recruitment of macrophages and lymphoctes [33], which, in turn, can stimulate the transformation of interstitial cells into myofibroblasts. Proximal tubular epithelial cells can interact with interstitial fibroblasts to promote fibrogenesis via release of profibrogenic molecules [34].

In summary, there is robust experimental evidence and a number of hints from clinical observations that proteinuria is responsible for interstitial inflammation and subsequent fibrosis, thereby contributing to progressive renal function loss.

THE CONCEPT OF RENOPROTECTION

The experimental demonstration that the blockade of angiotensin II with an angiotensin-converting enzyme (ACE) inhibitor slowed the progressive loss of renal function in a number of animal models or renal diseases, including diabetic nephropathy [35, 36], offered the opportunity, for the first time, to devise a treatment strategy that was not limited to passively accompany patients to their destiny of dialysis, but was aimed to preserve renal function as long as possible. The concept of renoprotection has then emerged.

In rats with renal mass reduction or diabetic nephropathy, ACE inhibitors reduced glomerular capillary

hypertension and slowed renal disease progression, while other antihypertensive drugs did not reduce glomerular hypertension and did not prevent progression, even if systemic blood pressure was controlled [35]. In these early experiments, ACE inhibitors have shown that these compounds reduced proteinuria in animals.

The antiproteinuric effect has been initially attributed to the reduction of glomerular hypertension, but a direct effect of ACE inhibitors on glomerular membrane permeselectivity to macromolecules has been also demonstrated [37].

In in vitro and in vivo experiments, ACE inhibitors are able to prevent the expression of inflammatory mediators such as NF-kB, RANTES, MCP-1, and insulin-like growth factor [38]. This may result both from inhibition of angiotensin II, whose proinflammatory properties have been described, and from decreased exposure of tubular cells to toxic effect of proteins.

In the remnant kidney model, the ACE-inhibitor treatment limited the up-regulation of TGF-β1 in podocytes, as well as the abnormal expression of α-smooth muscle actin in mesangial cells [38].

The development of a new class of the drugs, the angiotensin receptor blockers (ARBs) has offered another opportunity to further improve the renoprotection. The combination of two drugs, an ACE inhibitor and an ARB, in an experimental model of chronic nephropathies was associated with greater reduction of proteinuria and a trend toward less renal injury than with each drug alone [39]. The near complete abolition of angiotensin II activity is instrumental to achieve full renal protection.

Until now, we have considered as the main goal of our treatments the arrest of renal disease progression. However, the kidney has a great potential of regeneration after injury. Experimental evidence is accumulating that there is potential for regression of renal scarring, as shown in a recent paper by Fogo [40], in which the mechanisms of regeneration are reviewed. Of note, the potential antifibrotic role of drugs that block the renin-angiotensin II system is underlined [41].

TRANSLATION OF EXPERIMENTAL RESULTS IN CLINICAL TRIALS

The 1980s have been the decade of the experimental studies and the 1990s the decade of the translation of the experimental evidence into clinical trials. A number of small studies were performed to assess the protective effects of ACE inhibitors in chronic nephropathies, but the first statistically robust demonstration of the validity of such approach was provided by an American collaborative study in type 1 diabetes who had proteinuria greater than 500 mg/day and serum creatinine concentration was $<$ or $=$ 2.5 mg/dL [42].

Two hundred seven patients received captopril and 202 received a placebo. The primary end point of doubling the base-line serum creatinine concentration was reached in 25 patients in the captopril group, as compared with 43 patients in the placebo group ($P = 0.007$). Captopril treatment was associated with a 50% reduction in the risk of the combined end points of death, dialysis, and transplantation that was independent of the small disparity in blood pressure between the groups.

The role of proteinuria as a promoter of progression and its impact on renal outcome was explored by the Ramipril Efficacy in Nephropathy (REIN) study [43]. This study was designed to assess the hypothesis that ACE inhibition could be superior to other antihypertensive drugs in reducing proteinuria, limiting the decline in GFR, and preventing end-stage renal disease in patients with chronic nephropathies. In this study, patients were randomly assigned to receive ramipril or conventional antihypertensive therapy to maintain diastolic blood pressure at 90 mm Hg or less. A prestratification strategy recognized two levels of proteinuria (stratum 1 $>$1 and $<$3 g/24 hours; stratum 2 $\geq$ 3 g/24 hours).

The study showed that while blood pressure control was similar in the two treatment groups, ACE inhibitor therapy decreased the progression to end-stage renal disease by 50% [43, 44]. Among patients with proteinuria of 3 g/24 hours or more, those who received the ACE inhibitor had a significantly slower rate of decline in GFR than did patients receiving conventional antihypertensive therapy. It was also found that the ramipril-induced reduction in rate of urinary protein excretion was the only time-dependent covariate that predicted a lower decline in GFR and lower incidence of progression to end-stage renal disease; this finding clearly indicated that renoprotection is linked to reduction of protein traffic.

The study was continued for 2 years (the REIN follow-up study), during which period all patients previously on placebo were switched to ACE inhibitor [44]. In patients continuing to receive ramipril, GFR further decreased to approximately 1 mL/min per year during follow-up, a figure similar to that associated with normal aging. Patients who switched from conventional therapy to ramipril also benefited from the treatment.

One of the most impressive findings of this prolonged follow-up, was that after about 36 months of treatment with ramipril, no additional patients progressed to the point of requiring dialysis, whereas patients switched from conventional therapy to ramipril continued to develop end-stage renal disease. To further investigate the nature of the time-dependent improvement in GFR change, it was looked for a break point in the individual GFR slopes of patients receiving continued ramipril therapy. It could be predicted that after the break point, ten patients receiving continued ramipril therapy would never progress to end-stage renal disease and that

another ten had such improved GFR slopes that progression to end-stage renal disease would be delayed by about 5 years.

This analysis provides evidence that the tendency of GFR to decline with time can be halted and remission is achievable in some patients with chronic renal disease.

The decade of large clinical trials in nephrology was closed when the results of three important studies were published in the *New England Journal of Medicine* [45–47]. All three studies examined the role of ARBs in type 2 diabetic nephropathy. The role of ARBs in overt diabetic nephropathy was explored in two trials published in 2001. In one study, 1715 patients with type 2 diabetic nephropathy were randomized to receive ARB irbesartan [45], calcium channel blocker amlodipine, or placebo. The primary composite end point was doubling of serum creatinine, end-stage renal disease, or death. Treatment with irbesartan resulted in a risk reduction for primary composite end point of 20% lower than placebo and 23% than amlodipine.

The Reduction of End Points in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study evaluated the renal protective effect of losartan versus placebo (on top of conventional antihypertensive therapy, with the exclusion of ACE inhibitors) in 1513 patients with overt type 2 diabetic nephropathy [46]. The primary composite end point was doubling of serum creatinine, end-stage renal disease, or death. The ARB losartan reduced the incidence of doubling serum creatinine by 25% and the risk of end-stage renal disease by 28%. The death rate was similar in the two groups, which both attained the same blood pressure level. Proteinuria declined by 35% in losartan group.

A statistical review and evaluation by the Food and Drug Administration, available to the public on the internet [47], showed that there may be a difference in the effect of losartan in terms of hazard reduction between Asia and other regions of the world. Patients recruited in Asia appeared to benefit from losartan to a greater extent than patients from other regions. As a matter of fact, most of the benefit of losartan in this study seems to be due to the results in Asian patients.

One other study evaluated the renoprotective effect of the ARB irbesartan in hypertensive patients with incipient nephropathy [48]. The end point of the study was the time of onset of overt albuminuria. In 2 years follow-up, only 5.2% of patients receiving 300 mg of irbesartan reached the end point, as compared with 14.9% of patients on placebo. The groups had similar blood pressure control, a finding that suggests that ARBs are renoprotective independently of their antihypertensive effect.

Although we have limited our review to only a few clinical studies, several other trials have been published, some of them small in size, with little statistical power, and with short follow up. However, they all point in one direction: blockade of renin-angiotensin system is beneficial in most chronic nephropathies. There is also the support of meta-analysis, which concluded that ACE inhibition is superior to other antihypertensive treatment in preventing progression of nondiabetic renal disease [49].

This may be not true in overt nephropathy of type 2 diabetes. The results of several clinical trials have shown, with one exception, that no significant difference was found in terms of renoprotection, as measured as prevention of GFR decline over time, between ACE inhibitors and other antihypertensive agents [50]. Indeed, in patients with type 2 diabetic nephropathy, overt proteinuria, and renal insufficiency, an ACE inhibitor was not able to modify renal hemodynamics and glomerular sieving properties, despite effective blood pressure control [51]. In summary, currently available treatments have uniformly shown that reduction of blood pressure *per se* is beneficial in patients with type 2 diabetic nephropathy, while the effect of renin-angiotensin system blockade is probably less relevant than in type 1 diabetic nephropathy or nondiabetic nephropathies. However, as Thomas Starzl once said in another context, "Whenever that happens, if door opens a little bit, then there is a crush of effort to try to jam it open." The results of the last decade of experiments and trials are an important platform of knowledge to devise the best strategy in preventing diabetic nephropathy in the next 10 years.

THE FUTURE OF RENOPROTECTION

The evidences from both experimental studies and clinical trials suggest that the current practice can at the best postpone end-stage renal disease for few years, and not avoid dialysis for most patients during their lifetime. The dream of no more dialysis is still largely a dream, but nephrologists are doing their best to reduce the number of patients reaching end-stage renal disease. It is somewhat paradoxical that renal doctors, probably the only ones among their peers, are working hardly to reduce their own business.

Not all goals are likely to be met in the short term. We have already described the apparent resistance to current therapies of type 2 diabetic nephropathy.

Two other important cause of uremia are polycystic kidney disease and chronic allograft rejection. Polycystic kidney disease is object of intensive investigation concerning the molecular genetic and cellular pathophysiologic mechanisms responsible for the development of the disease, and a great many potential therapeutic agents or treatment strategies are under scrutiny [52]. The next two decades will probably witness the development of the clinical phase of these studies.

Allograft rejection is becoming the third cause of end-stage renal disease in several countries. Studies aimed to improve current antirejection therapy, or induce

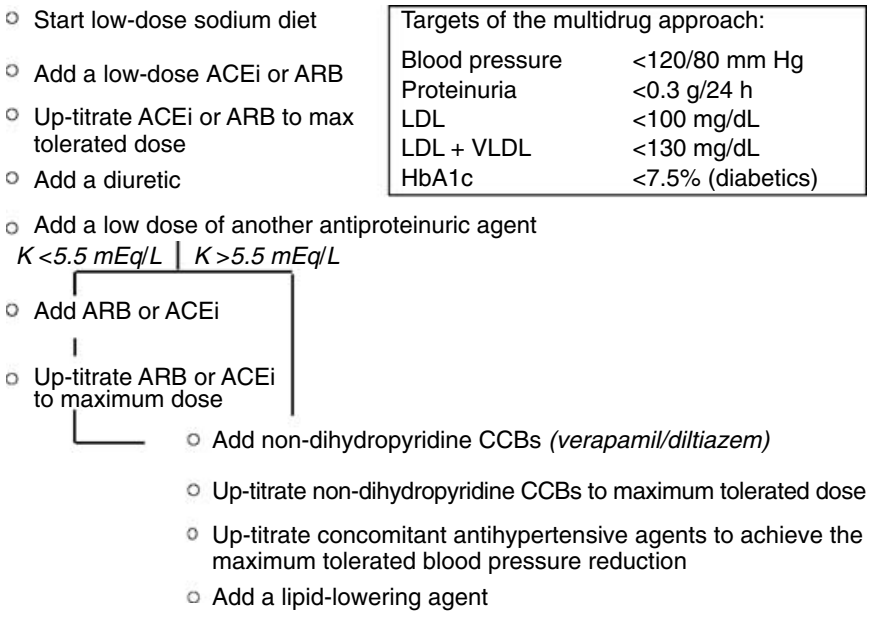

Fig. 2. Algorithm of the remission clinic for chronic nephropathies. In the box the targets for remission clinic are reported. Abbreviations are: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers. CCB, calcium channel blockers; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; HbA_{1c}, hemoglobin A_{1c}.

longlasting tollerance, are under way and hold promise for the future [53].

A significant reduction of the incidence of end-stage renal disease is likely to be achieved in the next future for nondiabetic chronic nephropathies, provided that we can improve the degree of renoprotection. This goal may be attainable with a more complex strategy than with a single pharmacologic intervention.

In analogy with other major medical diseases, for example cancer, HIV infection, organ transplantation, a multidrug intervention may be the strategy needed to significantly retard dialysis [54]. Experimental and clinical data support this notion. In an animal model of nephrotic syndrome, the accelerated passive Heyman nephritis, the addition of an ARB to an ACE inhibitor lessened the damage, and the further addition of lipid-lowering drug further amelioreted the outcome [39]. On the clinical ground, there are few trials that show that the combination of an ACE inhibitor with an ARB afford a greater renoprotection than each drug used alone. The COOPERATE study [55] compared a combined treatment of ACE inhibitor and angiotensin II receptor blocker, with monotherapy of each drug at its maximum dose, in patients with nondiabetic renal disease. Eleven percent of patients on combination treatment reached the combined primary end point of time to doubling of serum creatinine concentration or end-stage renal disease compared with 23% of patients on trandolapril alone (hazard ratio 0.38, 95% CI 0.18–0.63, $P = 0.018$) and 23% of those on losartan alone (hazard ratio 0.40, 95% CI 0.17–0.69, $P = 0.016$). Although good, these results show that further strategies for complete management of progressive nondiabetic renal disease is still elusive, since some patients reached the primary end point on combined treatment.

Interest has been growing lately on the potential role of an aldosterone blocking agent, eplerenone, in cardiovascular diseases [56]. Data presented at the 62nd Scientific Session of the American Diabetes Association suggested that the association of eplerenone and enalapril reduced microalbuminuria in type 2 diabetic patients to a greater extent than each drug alone, although hyperkalemia was a cause of withdrawal from the study for a significant number of patients [57].

Looking for a more effective treatment, the role of lifestyle changes should not be overlooked. Smoking cessation per se may reduce disease progression by 30%, which qualifies as the single most important renoprotective measure [58]. Physical activity has always been considered instrumental to the loss of excess weight, but it may have an intrinsic favorable effect, as documented by a small study in 20 patients with chronic kidney disease who were assigned to 12-week regular aquatic exercise or the armchair [59]. During this short period of time, the body mass index did not change in either group. However, proteinuria decresed by 50% in those who performed aquatic exercise, while it did not change in the sedentary group.

The multidrug approach to chronic nephropathies has been formalized in an interventional protocol that has been named remission clinic (Fig. 2) [60]. Patients with chronic kidney disease and proteinuria greater than 1 g/24 hours are initially treated with a low starting dose of an ACE inhibitor, which is then increased up to the maximum dose. Then, if the goals of blood pressure <120/80 mm Hg and proteinuria <0.3 g/24 hours are not achieved,

an ARB is added at half-maximum dose. Again, dose is increased stepwise. Throughout this uptitration of ACE inhibitor, or ARB, for optimal blood pressure control or prevention of hypokalemia, the addition of diuretics is usually needed. If, after this step target blood pressure and proteinuria are not achieved, the next antiproteinuric drug to be added is usually a nondihydropiridinic calcium channel blocker.

In those with serum low-density lipoprotein (LDL) cholesterol >100 mg/dL, a statin is added, and in those with diabetes glycemic control is reinforced to achieve hemoglobin A_{1c} (HbA_{1c}) <7.5%. Both interventions (lipid reduction and tight glycemic control) are supposed to contribute to renoprotection [50, 61].

This multiple drug approach has been tested in more than 40 patients in our unit, and we could prove that is feasible and effective. However, it is difficult to test in a formal study since any further addition of new or old drug to ACE inhibitors or ARBs in a multiple intervention trial would require a very large number of subjects and would be too costly for any company to support [54]. We probably should make better use of small but well-designed and rigorously condcted study with carefully selected marker of renal progression.

The concept of multidrug approach for renal disease is extraordinarily remiscent of the recent proposal of Law et al [62] in the *British Medical Journal* to develop a single pill containing aspirin, a statin, three antihypertensive agents at half dose, and folic acid for the prevention of cardiovascular disease. The "super" pill, as the media had immediately dubbed the provocative proposal, could be indeed valuable, perhaps with some adjustments, for patients with chronic nephropathies.

One of the potential advantages of this "super" pill is that such intervention could be made available also to patients of poor countries. There are little and sparse data on incidence and prevalence of chronic kidney diseases in developing countries [63]. What is certain is that in all low-income countries there are no dialysis facilities, or not enough for all in need, and people still die of uremia.

Simple and unexpensive screening programs are feasible at low cost in poor countries, and also simple and unexpensive treatments are plausible and possibly effective. As an example, the Kidney Help Trust Rural Project in India [64] was able to screen for high blood pressure, diabetes, and chronic kidney disease in a rural population of 25,000 people with the help of six health social workers, at a cost of less than $ 6000 per year, a mere 25 cents per capita. An excellent blood pressure control was achieved among hypertensive patients, while blood glucose control in diabetics was considered good. This could be the perfect condition to test the validity of the idea of a "super" pill.

The cost is the key factor to be considered here. A number of strategies have been devised to increase the access to essential medicine where they are most needed, from discounted prices for medicine, softening of patent protection, drug donation [65]. Among several possible funding stategies, a global fund for kidney disease, modeled on the example of the Global Fund for AIDS, Tuberculosis and Malaria, may be proposed. Drug companies, whose products such as ACE inhibitors and other antihypertensive drugs have proved to be very profitable, and also of dialysis machine manufacturers, whose earnings are colossal, could support such a fund with a minimal percentage, 1% to 3%, of the revenues from antihypertensive drugs or dialysis product. The contribution by the industry to the fund for the advancement of the global health, even with small part of the profit, is a moral obligation.

Of course the government, the intergovernamental institutions like the World Health Organization (WHO), the World Bank, and UNO, and nongovernamental organizations are called to play their role and it is a fundamental one. Also the International Society of Nephrology, by establishing the Commission for the Global Advancement of Nephrology (COMGAN), whose chairmen were Barry Brenner and John Dirks from 1993 to 1999, and who have committed themselves to the cause of combating kidney disease worldwide, especially in developing countries.

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