Strategies to optimize renoprotective therapy in proteinuric renal patients

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Chapter 1

Introduction and scope of this thesis
‘Dreaming of no more dialysis’ entitled the interview with G. Remuzzi in The Lancet of 1998 when the results of the REIN follow-up trial were published in the same journal (1,2). The study showed that in patients with progressive renal failure assigned to treatment with the angiotensin-converting enzyme (ACE) inhibitor ramipril, the need for dialysis could be prevented within the study follow-up of almost 4 years. Patients that initially were assigned to placebo but shifted to ramipril during the study displayed a considerable reduction of the rate of renal function decline when ramipril was started. These results elicited the hope that the dream of ‘no more dialysis’ could be fulfilled.

Yet, since the publication of the REIN study, the number of patients that suffer from progressive renal failure has still increased and, notably, also the number of patients depending on renal replacement therapy. The Dutch End Stage Renal Disease Registry reported in their annual report of 2006 that nowadays about 11,000 patients depend on renal replacement therapy in The Netherlands, of whom 5,500 patients are receiving dialysis treatment (3). The last decade the number of patients that depend on dialysis showed an 1.3% yearly increase. Albeit life-saving, dialysis has a tremendous negative impact on the lives of renal patients, as it impairs the quality of life and the risk of premature cardiovascular death is enormous. For example, in The Netherlands the annual mortality rate in dialysis patients amounts to 20%.

Obviously to enable further improvements in prevention of renal function loss, or even remission of renal function loss, new strategies are urgently needed. To this purpose, different approaches could be followed. On the one hand, many innovative approaches are extensively studied. Unfortunately, promising new strategies, as gene therapy and stem cell therapy, have shown limited or no success in experimental conditions, whilst clinical application will not be foreseen in the near future. An
illustrative experimental study indicates, for instance, that stem cell therapy, representing a so-called regenerative strategy directed to *in situ* repair of the kidney, seems to act as a two-edged sword, as stem cells may contribute to repair processes as well as the persistence of triggers for renal scarring (4). On the other hand, from clinical studies, as the REIN, several common risk factors for progressive renal failure have emerged that could be subject to therapy. Such *symptomatic* approach comprising the identification and treatment of new determinants of progressive renal failure is challenging and is the focus of this thesis.

**CURRENT INSIGHTS OF PROGRESSIVE RENAL FUNCTION DECLINE**

Throughout the last decades substantial progress has been made in understanding progressive renal failure. In respect of renoprotective treatment strategies, three important early hypotheses are still relevant. Firstly, the notion that high blood pressure is not merely a symptom of renal failure but also an important risk factor in the progression of renal function decline was a crucial step forward in renoprotective treatment (5,6). Since then, antihypertensive treatment is regarded as the cornerstone of therapy directed to attenuation of progressive renal function decline. Secondly, Brenner and co-workers postulated that loss of nephrons as result of renal injury can elicit a vicious circle of progressive renal function decline (7). They hypothesized that after loss of functioning nephrons, the remaining (remnant) nephrons exhibit a compensatory response aimed at preservation of glomerular filtration rate, at the expense of glomerular hypertension that eventually leads to glomerular capillary damage, glomerular protein leakage, and finally glomerulosclerosis, and further nephron loss. The fact that antihypertensive treatment exerts a beneficial effect on renal function is, according to this hypothesis, due to the reduction of glomerular pressure that results from the systemic blood pressure lowering, and/or specific reduction of glomerular pressure by post-glomerular vasodilation, as occurs during blockade of the renin-angiotensin-aldosterone system (RAAS). Thirdly, more than a decade ago, Remuzzi and co-workers came up with the concept that proteinuria is not only a symptom of renal damage but plays a key role itself in progressive renal function loss (8,9). They demonstrated that albumin that leaks into the tubular lumen exerts tubulotoxic effects leading to renal scarring, and that antiproteinuric treatment can prevent these sequelae (8). Accordingly, they postulated that proteinuria reduction is pivotal for renoprotection, as subsequently supported by the results of the previously mentioned REIN trial and several subsequent studies. Figure 1 summarizes the current understanding of progressive renal failure. In this figure, several factors are included that were identified previously to play a role in the sequelae of progressive renal failure and might be accessible for therapeutic intervention.
Aims and Scope of the Thesis

Starting from the generally held concept that antihypertensive treatment is a prerequisite for renoprotective treatment, and that the degree of proteinuria reduction predicts long-term renal outcome, a series of intervention studies are carried out aimed to optimize the antiproteinuric response. Feasibility of improving the response to therapy by better use of currently available classes of drugs as well as new modes of intervention was studied. Finally, the impact of better proteinuria reduction on cardiovascular risk was assessed, as outlined in the following paragraphs.

Part I. Renoprotective strategies: blood pressure or more?

The benefit of antihypertensive therapy in chronic renal failure is reviewed in chapter 2. The evidence from the large clinical trials showing that antihypertensive treatment with agents that interfere in the RAAS exert a specific renoprotective effect as compared to other classes of antihypertensive drugs is discussed. In addition, available evidence that specific renoprotective action of an agent seems related to its proteinuria lowering effect is reviewed. In chapter 3, it is hypothesized that the angiotensin type 1 receptor (AT1) antagonist telmisartan may have renoprotective characteristics by a specific antiproteinuric action beyond its blood pressure lowering effect. In this study, a direct comparison of telmisartan with an agent of another antihypertensive class, hydrochlorothiazide, in a double-blind, randomized, placebo-controlled large scale
clinical trial in patients with isolated systolic hypertension blood pressure was performed.

**Part II. Optimizing renoprotection: reducing residual proteinuria**

RAAS blockade is effective in attenuating the progression of renal function decline but can not prevent the development of end-stage renal disease in many patients. In order to fully confer the benefit of the renoprotective effects of RAAS blockers, different therapeutic approaches to optimize the response to RAAS blockade may be useful. Such optimization strategies could then be used to maximize the antiproteinuric response to RAAS blockers, as also discussed in the introduction to Part II. In chapter 4, 5 and 6, different strategies to improve the antiproteinuric effectiveness of RAAS blockade are tested. Firstly, changing the dosing time of the ACE inhibitor trandolapril on proteinuria in non-diabetic proteinuric patients was tested in chapter 4. Previously a relative therapy resistance to this long-acting ACE inhibitor was observed during the night when dosed in the morning (10). It was hypothesized that better antiproteinuric efficacy during the night by changing the dosing time may contribute to lower residual 24-h proteinuria. The effect of dosing in the evening and twice daily on the nocturnal therapy resistance and residual proteinuria was studied as compared to dosing in the morning. Secondly, in chapter 5 the modulation of sodium status during RAAS blockade-based proteinuria reduction was studied in non-diabetic proteinuric patients in a double blind randomized placebo-controlled cross-over design. Early on, it has been demonstrated that low sodium intake improved the response to an ACE inhibitor, and that co-treatment with hydrochlorothiazide restored the response to ACE inhibitor therapy that had been blunted by high sodium intake (11,12). The studies on effects of intensified measures on sodium status have not so far been undertaken. The combination of two sodium-depleting measures was assumed to further improve the response to the AT1 antagonist losartan. In chapter 6, feasibility of titration with different measures to recommended levels of residual proteinuria (< 1 g/d) was tested. It has been postulated earlier that lowest residual proteinuria will allow to stop further progression of renal function decline, or to enable remission of renal function (13). In this study, low sodium in combination with hydrochlorothiazide, dual RAAS blockade and dose-titration with an ACE-inhibitor were stepwise applied to pursue lowest levels of proteinuria.

**Part III. Optimizing renoprotection: intervention in new pathophysiological pathways**

In the following chapters, several strategies to reduce proteinuria by targeting pathways other than the RAAS were explored. In Chapter 7, it was hypothesized that cyclooxygenase-2 (COX-2) inhibitors may have antiproteinuric efficacy. COX-2 inhibitors may represent an old concept in a new fashion. Non-steroidal anti-
inflammatory drugs (NSAID), acting by interfering in prostaglandin synthesis, were the first effective antiproteinuric agents for symptomatic proteinuria reduction, even before ACE inhibitors were introduced (14). Their full development as renoprotective agents was hampered, among others due to high incidence of intolerance to these drugs. For instance, these agents are associated with adverse effects on the gastrointestinal and central nervous systems. The new selective COX-2 inhibitors also interfere in the prostaglandin system, albeit in a different way. In the study described in chapter 7, the antiproteinuric potency of two doses of the selective COX-2 inhibitor rofecoxib were tested and compared with the traditional NSAID indomethacin. In addition, the antiproteinuric efficacy of rofecoxib was compared with the ACE inhibitor lisinopril. In chapter 8, antiproteinuric efficacy of the newly developed drug palosuran was tested in a phase II double blind, randomized, placebo-controlled cross-over study in diabetic patients characterized by having microalbuminuria and hypertension. This drug represents a new concept of interfering in the sequelae of hyperfiltration, development of albuminuria and progression of chronic renal failure as observed in renal patients. Palosuran has shown to be an effective blocker of the urotensin system. The peptide urotensin II has been described as one of the most potent vasoconstrictive peptides in mammals, possibly even more potent than angiotensin and endothelin, and is involved in the pathophysiology of diverse nephropathies as well as in hypertension (15). Accordingly, blockade of this system was hypothesized to exert renoprotection, as measured by proteinuria reduction.

Part IV. Optimizing renoprotection: reduction of cardiovascular risk?

Hitherto, one could conclude that residual proteinuria predicts subsequent renal risk, but it is not completely clear whether this is also true for the residual cardiovascular risk. Considering that proteinuria is a potent cardiovascular risk factor, residual proteinuria might also be a predictor of cardiovascular risk, as for instance by data from a recent large clinical trial conducted in patients with diabetic nephropathy (RENAAL study) (16). Chapters 9 and 10 address effects of antiproteinuric intervention on proteinuria-associated cardiovascular risk factors. Firstly, the prevalence of the elevated cardiovascular risk in proteinuric patients in relation to the classical risk factors, as well as the possible benefits of the current antiproteinuric treatments in cardiovascular risk management, are discussed in chapter 9. Proteinuric patients have distinct abnormalities in their cholesterol metabolism and these abnormalities may contribute to their elevated cardiovascular risk. Secondly, chapter 10 shows the results of dose-titration with single and dual RAAS blockade on proteinuria and lipid profiles, especially HDL metabolism and HDL function, in non-diabetic proteinuric patients. Finally, in chapter 11 the predictive value of proteinuria reduction on long-term major cardiovascular
complications was investigated.

**General discussion**

In conclusion, the results of the studies described in this thesis are discussed in chapter 12 and put into the perspective of the available literature, thereby identifying specific patient factors that may contribute to the residual renal risk. It is questioned whether these specific factors can be seized in order to resolve the remaining risk for progression to end-stage renal disease and the remaining cardiovascular risk in each individual patient.

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