Sodium intake and therapy resistance to ACE inhibition
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Introduction

High blood pressure and proteinuria are main risk factors for end-stage renal disease (1). Blood pressure control is therefore a cornerstone in prevention of progressive renal function loss, together with reduction of proteinuria. Moreover, renal patients are also at particularly high cardiovascular risk (2). Recent studies provided evidence that even mild renal function impairment is associated with an elevated cardiovascular risk (3-5). This unfavorable risk profile in the renal patient prompts us to invest great effort to improve overall prognosis by optimal blood pressure control as well as additional measures.

Recent studies provided new insights into the optimal blood pressure target in renal patients and into the specific renoprotective effects of different classes of antihypertensive drugs. We will expand on these optimal targets by addressing the impact of individual differences in therapy response. These individual differences - that we will denote as “response variability” - reflect an important, but underrated phenomenon: for any intervention - even of proven efficacy - individual differences in therapeutic benefit are large. Exploration of the mechanisms underlying these differences in responsiveness to therapy may allow important progress in improving prognosis in renal patients.

Target blood pressure in renal patients

Whereas the unfavorable cardiovascular risk profile in renal function impairment is well-established, the optimal target blood pressure for overall risk reduction in renal patients has not prospectively been investigated so far. The HOT study, designed to establish the benefits of a lower target diastolic blood pressure (<90 vs <85 vs <80 mmHg) for cardiovascular events in a total of 18,790 hypertensive patients, also included 470 subjects with serum creatinine between 1.5 – 3.0 mg/dl at entry (4). The adjusted relative risk for major cardiovascular events was 2.05 (95% CI 1.47-2.88) in subjects with renal function impairment, in spite of similar blood pressure. There was a tendency towards benefit of the lower blood pressure target in patients with renal function impairment, but this did not reach statistical significance. However, the study was not powered for the purpose of analyzing the data in the renal patients specifically.

As to the target blood pressure for renoprotection, the Modification of Diet in Renal Disease trial remains a landmark study (6). This trial is still the only prospective study evaluating the value of low target blood pressure in renal patient, in addition to the effect of low protein diet. The secondary analysis (7) from the trial convincingly demonstrated that the severity of proteinuria before treatment is the main determinant of the benefit of obtaining lower target blood pressure. When proteinuria was 1-3 g/day, a mean arterial pressure of 98 mmHg (corresponding to 135/80 mmHg) provided additional renoprotection, whereas this benefit
was absent if proteinuria was less than 1 g/day. Moreover, in patients with proteinuria > 3g/day an additional benefit was found for an even lower blood pressure: a mean arterial pressure of 92 mmHg (125/75 mmHg). Thus, higher proteinuria before treatment is a prompt for a lower target blood pressure.

The importance of blood pressure control for renoprotection was confirmed by a recent meta-analysis, demonstrating a linear association between obtained blood pressure and rate of renal function loss across nine intervention studies (8), with no apparent J-curve. Thus, rigorous blood pressure control should be pursued in renal patients. It is to be noted, that the reduction of proteinuria at onset of antihypertensive therapy - and residual proteinuria during therapy - consistently predicts the subsequent rate of renal function loss (9-11). In addition to blood pressure control, reduction of proteinuria is an excellent surrogate parameter for long term renoprotection. Therefore, it was recommended that, in addition to blood pressure, treatment should be titrated on reduction of proteinuria (12).

As proteinuria is a major cardiovascular risk factor as well, it would be logical to expect that benefit of a lower blood pressure on cardiovascular end-points would also be more readily apparent in proteinuric patients, in particular as reduction of proteinuria is associated with an improvement of lipid profile (13). So far, no data on hard end-points are available to support this assumption, but new guidelines already anticipate and suggest treatment goals less than 130/80 for patients with renal disease (JNC7) (14).

**Choice of antihypertensive regimen**

All currently available classes of antihypertensives can be used in renal patients. As to antihypertensive efficacy, there is no specific benefit of one class over another (15), although one would intuitively favor diuretics. Usually combination treatment is required to obtain blood pressure control. As reduction of proteinuria predicts renoprotective benefit, regimens that specifically reduce proteinuria have advantages for renoprotection. Effective antihypertensive regimens generally also lower proteinuria, with the exception of dihydropyridine calcium channel blockers (16). Blockade of the renin-angiotensin-aldosterone system (RAAS), by ACE inhibition or AT1-blockade, has specific antiproteinuric properties in addition to the antihypertensive effect, which is likely to account for their additional efficacy in renoprotection (10;17-19). Whilst this is particularly apparent in populations with overt proteinuria (19), proteinuria reduction is also renoprotective in populations with only low-grade proteinuria (10;11;18-20).
Optimization of treatment

As treatment should be guided by optimal reduction of blood pressure and proteinuria, therapy should be titrated towards these goals. Several considerations are important.

Sodium status

In spite of the proven renoprotective potential of RAAS-blockade, its efficacy is consistently blunted by sodium overload. The blunted efficacy during conditions of sodium excess was noted already early after introduction of ACE inhibitors in clinical practice (21), and has been documented in essential hypertensives as well as proteinuric patients. Dietary sodium restriction, or co-treatment with a diuretic should therefore be applied if therapy response is insufficient (22;23).

Considering that the unfavorable effect of high sodium intake on the response to ACE inhibition has been known for almost two decades, and considering the important place of ACE inhibitors in the therapeutic arsenal, it may be somewhat surprising that the mechanism of this blunting is still largely unknown.

Optimal dosing

Dose is also important to consider. Animal experiments suggest that doses of ACE inhibitors higher than needed for optimal blood pressure control, induce additional renoprotection (24). Data in humans seem to be consistent with this finding, as the optimal dose of ACE inhibitors and AT1 blockade for specific renal effects (as estimated from proteinuria reduction) appears to be higher than the optimal antihypertensive dose in many patients. Conversely, an antiproteinuric dose response can be present without effects on blood pressure, particularly in normotensive patients (25). Recent data from Laverman et al show that the dose response for blood pressure reduction with Angiotensin-II-receptor-antagonist may be different for the antiproteinuric response (in press Kidney Int Suppl 2004). Taken together, these data suggest that dose response for blood pressure and for specific renal effects may not be the same, notwithstanding the antiproteinuric effect of reduction of blood pressure.

Combination regimens

Considering the therapeutic benefits of both ACE inhibition and AT1 blockade, several studies addressed their combination, assuming that RAAS blockade at different levels simultaneously might result in more effective blockade, and thus afford greater therapeutic benefit. In non-insulin-dependent diabetes mellitus the combination of lisinopril and candesartan was more effective than either drug as a monotherapy after 12 weeks of treatment (26). However, as relatively low doses were used, similar effects might well have been obtained by increasing the dose of the single agents. In renal patients small studies suggest an added effect of dual
blockade, but these studies did not test the single drugs at the top of their dose-response either (27-29). A large recent study in Japan, the COOPERATE trial, however, found a reduced risk in patients treated with a combination of both fixed high dose trandolapril and losartan compared to high dose of trandolapril or losartan alone (30). Blood pressure level was maintained below 130/80 during the study using all non RAAS blocking agents and was similar in all groups during the complete study. However, in the group treated with dual RAAS blockade proteinuria was significantly more reduced compared to a similar reduction in either mono-therapy group. The differences in renoprotection are probably due to this much larger antiproteinuric effect of dual blockade. Laverman et al have shown individual dose-dependent differences in maximum reduction of proteinuria (31). A combination of both maximally effective ACE inhibition and AT1-blokade reduced both proteinuria as well as blood pressure further than one agent alone. Thus, a more individualized approach could further increase renoprotection. This individual approach is discussed in more detail below.

**Individual response variability**

**Individual determinants of therapy response.**

Even for regimens of well-established benefit at group level, interindividual differences in therapeutic benefit are often considerable. The usual aim in hypertension and renal disease trials is to obtain a statistically significant effect at group level. From this perspective, response variability between patients is a confounding factor prompting for larger studies, in order to obtain statistical significance in spite of the individual differences. Older as well as recent studies, however, suggest that it might be fruitful not to focus exclusively on what groups of patients have in common, but also to explore the mechanisms underlying the differences between patients, as this might define better targets for intervention. (32;33)

Evidence for individual determinants of therapy response in hypertension was elegantly provided by Dickerson et al (34) who applied a rotation schedule testing four classes of antihypertensive drugs in each patient. Patients with a good response to ACE inhibition also responded well to beta-blockade, whereas no correlation with the response to diuretic or calcium channel blocker was found. So far, no similar studies were performed in renal patients. However, we performed together with Parving’s group a 2-class rotation protocol with ACE inhibition and AT1-blockade in non-diabetic and diabetic proteinuric patients (33). In this study, both ACE inhibition and AT1- blockade effectively reduced blood pressure and proteinuria at group level in non-diabetic and diabetic patients. Analysis of individual data revealed, first, a large variability in responsiveness between individuals, ranging from an excellent response to absence of response for both drugs. Remarkably, the individual response to both classes was strongly correlated (Figure 1a). This was true for both blood
pressure and proteinuria. Additive information was obtained studying different doses of both drugs. Whereas increasing the dose of the ACE inhibitor from 10 to 20 mg enhanced the blood pressure response at group level, patients with an absent or poor response remained relatively poor responders (figure 1b).

Thus, in terms of therapy response, differences between patients by far exceeded the differences between the drugs, and between the different doses. This implicates that exploration of the mechanisms underlying these individual differences has great potential to improve responsiveness to therapy, and consequently long-term prognosis.

It is important to realize that, from an individual perspective, many basic issues remain to be explored. There is hardly any knowledge, for instance, on individual differences in dose response to renoprotective drugs. We do not know, for instance, whether there are individuals that would benefit from higher doses than normally used and how to recognize them. In our opinion, the impressive difference between individuals prompts us to address these questions.

**Will genetic factors provide the answer?**

As illustrated above, patient factors are important in response variability. Which factors could be involved? It was proposed long ago that differences in response to specific intervention reflect the patients’ individual pathophysiological characteristics (32). Both genetic and environmental factors (e.g.: severity of pretreatment renal damage (35), duration of disease, dietary habits, and co-morbidity) and their interaction may be involved. Clearly, therapy
response is a complex phenomenon. The exploration of individual determinants of therapy response got new momentum from the developments in genetics (36). Differences in genetic make-up have long been known to modify drug metabolism (namely, slow versus rapid acetylators of hydralazine) but recently the number of studies demonstrating an association between pharmacodynamics and genetic factors increased dramatically (37).

The basic concept of genetic determinants of therapy response is simple: a drug interacts with its biological target, for instance a drug receptor. When a genetic alteration leads to a modified target, the response is modified as well. Thus, it would be possible to predict therapy response from single genetic variants. Whereas this may apply to certain animal models (38) and to selected conditions (39), it is becoming increasingly clear that therapy response should be considered a complex phenotype, rather than a simple phenotype. This makes sense, as therapy response is not only determined by one-way drug-target interaction, but also by many other biological factors, such as activity of multiple counter regulatory and backup pathways. The concept is illustrated by recent studies on the genetic determinants of the blood pressure response to thiazides. Elegant studies from Bianchi’s group not only demonstrated an association between the alpha-adducin polymorphism and the response to diuretics, but also provided possible cellular mechanisms involved (40;41). These investigators also demonstrated interaction between alpha-adducin genotype and ACE (I/D) genotype in volume regulation (42). Finally, they recently showed that ACE genotype also affects the response to thiazide (43) This line of evidence seems to refute the single-gene model for the response to thiazides, and points to the characteristics of volume regulation as a main intermediate factor between genetic factors and therapy response.

Considering the importance of RAAS blocking therapy, not surprisingly many studies examined the effects of genetic polymorphisms in the RAAS as possible determinants of therapy response. ACE insertion/deletion polymorphism has so far was the most extensively investigated, and this has been reviewed elsewhere (44). As the deletion polymorphism is associated with the level of circulating and tissue ACE (45;46), it would seem logical to expect that ACE genotype modifies the response to ACE inhibition. The available association studies, however, display large discrepancies as reviewed by Boonstra et al (44) and by Danser and Schunkert (47). We attempted to clarify these discrepancies by not only analyzing for interaction between ACE genotype and therapy response, but by also taking into account sodium intake, as a well known modifier of the response to ACE inhibition. The study of Van der Kleij et al (48) provided the first evidence (albeit post-hoc) for gene-environment interaction between the ACE genotype and sodium intake, as shown in figure 2 for blood pressure response (the response of proteinuria was concordant). These data suggest that sodium dependency of the response to ACE inhibition depends on genotype.
Moreover, they suggest that sodium restriction blunts the impact of ACE genotype on therapy response, as with low sodium intake therapy response was similar in ACE insertion/insertion and ACE deletion/deletion homozygotes. This interaction between sodium intake and ACE genotype was supported by prospective data in healthy volunteers (49) and in patients with uncomplicated type I diabetes (50). Whereas this interaction cannot explain all discrepancies, it illustrates the advantage of analyzing pharmacogenetic issues from a pathophysiological angle rather than by mere association. Considering the relationship between RAAS and volume status, focusing on the interaction between sodium status and the pathophysiological consequences of genetic polymorphisms of the RAAS may prove fruitful (51).

**Conclusions**

Rigorous blood pressure control is important in renal patients to protect against the high risk for renal and cardiovascular damage. So far, there are no indications of a J-curve. Particular attention should be given to reduction of proteinuria. Proteinuria warrants lower target blood pressures for renoprotection: whether lower targets will also provide additional protection against cardiovascular damage remains to be investigated, although there is some evidence emerging (52). The individual differences in responsiveness to antihypertensive therapy are considerable, even for interventions of proven benefit at group level. Exploration of the mechanisms underlying individual determinants of therapy response, and the design of individual strategies for optimization of therapy response should in the coming years guide our efforts to improve prognosis in renal patients.
REFERENCE LIST


