Towards an integrated approach on RAAS-blockade

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SUMMARY AND GENERAL DISCUSSION

Chapter 10
Summary

The studies described in this thesis address the therapeutic effects of pharmacological blockade of the renin-angiotensin aldosterone system (RAAS) from a pathophysiological perspective, analyzing the role of environmental as well as genetic determinants of the efficacy of RAAS-blockade, with the eventual aim to improve their application in renal and cardiovascular disease. Our set of studies summarized here, together with other studies from our group, sheds new light on several ongoing discourses on the mechanisms underlying the efficacy of RAAS-blockade, and the possibilities to improve therapeutic benefit.
Setting the stage

Chapter 2 analyses the association between pre-intervention rate of renal function decline and outcome of renoprotective intervention, in relation to angiotensin converting enzyme (ACE) I/D genotype, and the specific mode of intervention, namely angiotensin converting enzyme inhibition (ACEi) versus beta-blockade. In a prior analysis it has been found that patients with the DD genotype had a significantly steeper slope of renal function decline compared to ID and II patients during specific renoprotective intervention [1]. This has been interpreted as patients with the DD genotype were resistant to the beneficial effects of the intervention regimens. Our current analysis shows, that before intervention, the rate of renal function decline was even steeper in the DD subjects, and that the improvement in rate of renal function loss during intervention was larger than in the other genotypes. Thus, the interpretation of the interaction between ACE I/D genotype and response to ACEi clearly requires a more balanced perspective, taking into account both the impact of ACE I/D genotype on natural course of the disease, and the impact on the benefits of intervention, respectively. For better understanding of the underlying mechanisms, it would be useful to be able to dissect the effects on susceptibility to renal damage, and those on response to pharmacological intervention. These lines of investigation were further pursued in the subsequent chapters. For future intervention studies in progressive renal function loss, our analysis emphasizes the importance of documenting the pre-intervention rate of renal function decline as a possible randomization parameter, to avoid heterogeneity in renal prognosis between different study arms.

Environmental and genetic factors in relation to the response to ACEi

It has been known for a long time that dietary sodium restriction enhances the effects of ACEi, whereas these effects are blunted by a high sodium intake. However, the mechanisms underlying this interaction are incompletely understood. In chapter 3 we provide a possible explanation for the potentiation of the response to ACEi by low sodium. In healthy volunteers we found that low sodium diet potentiated the rise in angiotensin (ang) I that occurs during ACEi. This rise in ang I occurs because the renin response to volume depletion is preserved during ACEi, and even enhanced by lack of negative feedback by ang II. Whereas ang I itself is not biologically active, it is a substrate for ang 1-7 which has vasodilator and anti-proliferative properties. The rise in ang I during ACEi was paralleled by an increase in ang 1-7, both ang I and ang 1-7 were likewise potentiated by low sodium. The levels of ang II during ACEi were similarly low on low and high sodium diet. As a result the ratio of ang II/ang I was reduced more effectively during ACEi plus low sodium as compared to ACEi plus high sodium. This suggests that ACE is more effectively blocked during the low sodium condition. This indirect evidence is supported by previous experimental studies from our group, showing that the conversion of ang I in tissue is more effectively blocked during low sodium, possibly by induction of tissue ACE by
high sodium. In addition, the pronounced rise in ang 1-7 during ACEi plus low sodium, relative to the suppressed ang II levels that are not modulated by sodium status during ACEi might be relevant. Our data show that, during ACEi, low sodium shifts the balance in the RAAS towards predominance of the ACE2 - ang 1-7 - mas-receptor axis, which might well, be relevant to the enhanced therapeutic effect.

Chapter 4 sheds additional light on the interaction between sodium status and therapeutic effect of ACEi. It describes the effects of pharmacological (ACEi, ang II infusion) and physiological (low versus high sodium diet) modulation of the RAAS on adiponectin. Adiponectin is a novel adipokine, with anti-proliferative and anti-inflammatory effects. We found that adiponectin was suppressed by ang II infusion, and increased by physiological and pharmacological suppression of RAAS activity. Thus, high sodium, ACEi, and their combination lead to increased circulating adiponectin levels. This provides novel insights in the regulation of this adipokine and suggests that adiponectin may provide a link between RAAS activation and metabolic status, in addition to other interactions that are outlined below. Moreover, it shows that RAAS-blockade is not to be considered as a single-pathway intervention, but rather as an intervention with pleiotropic effects. The relative importance of the various effects of RAAS-blockade can apparently be modulated by sodium status. This insight provides interesting perspectives for future application of RAAS-blockade, as modulation of sodium status could potentially be used to modulate the desired effect as well.

As these and previous studies consistently showed an effect of sodium status on the response to ACEi, we hypothesized that neglect of the environmental factor sodium might account for discrepancies between studies on the impact of ACE I/D genotype on the response to ACEi. In fact previous studies from our department already demonstrated gene-environment interaction between sodium intake and the ACE I/D genotype as regards the response to exogenous ang I, with unmasking of the phenotypic differences by high sodium intake, and annihilation of the phenotypic differences during low sodium [2-4].

In the study described in chapter 5 we investigated whether such a gene-environment interaction might also be true for the response to ACEi. To preclude bias by possible effects of the ACE I/D genotype on susceptibility and course of disease, this study was conducted in healthy volunteers. In support of our hypothesis the blood pressure response to ACEi was selectively blunted by high sodium in subjects with the DD genotype only. This was accompanied by a blunted sensitivity to ang II infusion. Low sodium intake corrected both abnormalities in the DD genotype. These results are in line with previous data on induction of tissue ACE by high sodium without and during ACEi in experimental animals [5;6], and suggest that this might in particular occur in the DD genotype, as a possible mechanism underlying a blunted response to ACEi during high sodium. These results support our assumption that sodium status should be accounted for when evaluating the impact of genetic factors on the response to RAAS-blockade.
Impact of ACE on susceptibility to renal damage

Chapter 6 provides an overview of the abnormalities in the RAAS in diabetes mellitus, focused on a possible pathogenetic role of ACE activity, and accordingly, the possible effects of its genetic regulation and the ACE I/D genotype. We found gene-environment interaction between ACE I/D genotype and diabetes on the level of plasma ACE. In uncomplicated diabetes ACE level was lowest in II, intermediate in ID and highest in DD genotype. However, for each genotype ACE level was higher than for the corresponding genotype in healthy subjects. Significant interaction was present between diabetes and genotype with the largest diabetes-induced increase in ACE level in DD homozygotes. Interestingly, the higher ACE levels in diabetes were also associated with a more pronounced response to ang I, supporting its pathophysiological impact. The elevated ACE level in diabetes has long been regarded as an epiphenomenon, reflecting endothelial damage and shedding of ACE. However, our data strongly suggest that the elevated plasma ACE in diabetes is not just an epiphenomenon but could have pathophysiological relevance, or is a marker of elevated ACE at other, pathophysiologically relevant sites. Moreover, epidemiological studies reported an association between genetically elevated ACE levels and diabetic nephropathy. This is in line with experimental evidence supporting a role of higher renal ACE as a factor that predisposes to renal damage [7]. Our data suggest that this may be particularly relevant in the diabetic patient.

The alleged role of renal ACE in the susceptibility to renal damage, and its development towards progressive renal function loss prompts for in-depth exploration of its role in renal damage. To investigate whether renal tissue ACE can potentially have a causal role in the susceptibility for renal damage, we measured renal ACE activity in healthy rats, and analysed whether the level of renal ACE was a predictor of the extent of renal damage induced by a well-established experimental trigger for renal damage, namely adriamycin, as described in chapter 7. In support of our hypothesis, in these outbred Wistar rats individual differences in renal ACE activity predicted the severity of adriamycin induced proteinuria and renal damage, both in terms of proteinuria and renal damage development. A higher renal ACE activity predisposes to a less favorable course of renal damage. These experimental data are in accordance with the results from chapter 2 that show faster progression of renal damage in the DD subjects with higher ACE activity.

A homologue of ACE, ACE2 was identified in the year 2000. As ACE2 might be a counter player of ACE we subsequently investigated the renal expression of ACE2 in human renal disease, as described in chapter 8. The ACE - ang II - AT1-receptor axis has consistently been found to be activated in renal disease. Its counterpart has gained interest over the last years. In human kidney disease and in transplanted kidneys we found neo-expression of ACE2 in glomerular and peritubular capillary endothelium. This might reflect a possible protective mechanism involved in renal disease, as it has been hypothesized that a disrupted balance between intrarenal ACE and ACE2 with consequent high
levels of ang II might contribute to progressive renal damage [8]. However, other studies found down-regulation or no alteration of ACE2 during early diabetic nephropathy [9;10]. It would be very interesting to have data on ACE expression in our biopsies and evaluate the balance between ACE and ACE2. Recently, in hypertensive renal disease it was shown that the balance between ACE2 and ACE is shifted towards ACE2 which might reflect a protective mechanism [11]. Future studies should focus on the balance between the two axes, and study tissue ACE and ACE2 together.

In chapter 9 we described a new animal model for the human ACE I/D genotype. In human populations ACE I/D genotype has been studied extensively in relation to cardiovascular and renal disease and therapy response to ACEi, but many controversies remain as regards its pathophysiological impact. Our studies described in the previous chapters clearly demonstrate the presence of gene-environment interactions with sodium status and diabetes, respectively. Gene-gene interactions have been described as well [12;13]. Unraveling of the various genetic and environmental interactions might be greatly facilitated by availability of a good animal model. Identification of a micro satellite marker in the rat ACE gene, in intron 13, has allowed differentiation of ACE alleles between the Brown Norway (B) and Lewis (L) strains and has shown phenotypic differences between the B and L alleles. When comparing two different inbred rat strains for pathophysiological differences related to their different ACE levels, phenotype differences might also be due to differences in other genes. Therefore, we developed a rat model for genetically determined high and low ACE activity, respectively, on an outbred background, in the Wistar rat, as a model for the human ACE I/D genotype. Both serum and tissue ACE activity in heart and kidney were related to the variation in the B/L allele, with higher values in the BB homozygote. Functional conversion of ang I in aortic rings was also higher in Wistar BB homozygotes, supporting functional impact of the difference between the two alleles. Finally, with immunohistochemistry, a clear difference between tubular ACE expression with more staining in Wistar BB was found in the kidney. In the heart and aorta such differences could not be detected, supporting tissue- or organ-specific impact of the genetic regulation. The Wistar B/L genotype provides a new model to study the interaction between genetic and environmental determinants of ACE expression to further gain insight in its involvement in experimental cardiovascular and renal injury and the response to intervention.

**General discussion**

**ACE genotype and ACE activity**

Since the discovery of the ACE I/D genotype in 1990 by Rigat et al. [14] and the first major study that reported an association between the D-allele and myocardial infarction [15], an impressive volume of data on the ACE I/D genotype has been published. After a start with great expectations, Pinto et al. stated already in 1999 that the ACE genotype seems to be the victim of its own success [16]. An
enormous amount of association studies have been published, decreasing the insights on possible clinical applicability with each novel association published, and making it more unlikely that a simple, one-dimensional explanation would become available to explain the wide variety of associations.

The disappointment and conflicting results concerning the ACE I/D genotype can be explained in several ways. First, it has been pointed out that many association studies were subject to methodological flaws [17] and poor characterization of the phenotype, selection bias by competing risks of the DD genotype on cardiovascular mortality, lack of adjustment for disease duration and complications [17]. Even more important, renal and cardiovascular diseases as well as therapy response are complex phenotypes. The expectation that a single, common, genotype might provide a simple explanation for a variety of disorders would therefore be overly naïve. In association studies, little attention has been paid to complex gene-environment interactions and the pathogenetic mechanism that may link the ACE I/D genotype to cardiovascular and renal disease and therapy response to RAAS-blockade. Furthermore, the ACE I/D genotype is just 1 of >160 polymorphisms of the ACE gene [18;19]. Our studies show that studying a clear phenotype, like very healthy subjects, and selecting one important environment factor give proof of an important gene-environment interaction. Therefore, we believe that for future genetic studies both phenotypic and environmental characteristics should be standardized a much as possible.

Originally the ACE I/D genotype was proposed to account for 47% of the total phenotypic variance of circulating ACE activity [14]. More recent studies suggest that this percentage is around 20% [20-22]. The ACE I/D genotype is located in a non-coding region (intron 16) of the ACE gene, it is unclear how ACE I/D genotype contributes causally to the well-established association with serum and tissue ACE activity. A number of possibilities have been forwarded. First, it is known that intronic variations can influence various regulatory mechanisms of transcription, including splicing efficiency [23]. Thus, the ACE I/D genotype could exert effects on transcription via alteration of undocumented regulatory pathways. Second, it has been hypothesized that ACE I/D genotype is linked to another, functional polymorphism that is responsible for the differences in ACE activity. Detailed haplotype and linkage disequilibrium studies have been performed resulting in several candidate haplotypes [24], yet no conclusive evidence has been provided to date. Nevertheless, the ACE I/D genotype is still the most consistently associated with tissue and circulating ACE mRNA levels and activity, warranting future research to elucidate the mechanism behind this association.

Recently, Danser et al. proposed that ACE phenotyping may be a better way to improve individual ACEi treatment titration than ACE genotyping [25]. Our data in healthy subjects and outbred Wistar rats (chapter 3 and 7) support the importance of ACE phenotyping, as we demonstrated a clear correlation of serum ACE activity during high sodium with the blood pressure response to ACEi, as well as the response to exogenous ang II. Moreover, in outbred Wistar rats we show that phenotypic
variations in renal tissue ACE activity predict the development of renal damage. Suitable animal models, like the Wistar B/L model (chapter 9) or congenic ACE rats [26] will be helpful to unravel the complex role of the ACE genotype in renal and cardiovascular damage and the response to therapy. Analysis of gene-environment interaction is of clinical interest. First, clinical conditions such as the presence of diabetes (chapter 4) can act as environmental factors that unmask, or elicit relevant pathophysiological effects of the genetic predisposition to higher ACE levels. Second, environmental factors, such as glycaemia or sodium status could be target for intervention to ameliorate the risk associated with the gene-environment interaction.

Another issue which might explain conflicting results from studies on the ACE I/D genotype is inappropriate characterization of the phenotype. In chapter 2, for instance, we show clearly that there is good therapy response in DD subjects in term of slope improvement. These new insights do not oppose the previous results published by van Essen et al., [1] but allow a more balanced interpretation, showing that actually, there was significant benefit of treatment in DD subjects. This shows the importance of careful characterisation and interpretation of the phenotype. Future studies should clearly define the phenotype studied, and prospectively modify alleged interacting factors to assess their effects. In chapter 3 we studied young healthy male volunteers to avoid interaction with severity of disease. By studying subjects as their own control we could dissect the effect of a change in sodium status as an environmental factor, demonstrating interaction between the ACE I/D genotype, sodium intake and the response to ACEi.

The predictive effect of renal ACE activity for the susceptibility to proteinuric renal damage (chapter 7) supports a causal role of ACE in renal damage [27]. It may be relevant in this respect that renal ACE activity is increased in response to injury as well [28;29], which may well result in a vicious circle of progressive renal damage. In diabetes, ACE has consistently been found to be upregulated in renal biopsies in particular in the DD genotype [30-32]. The latter is in accordance with our finding (chapter 4) that the diabetes-associated increase in ACE activity is associated with the ACE I/D genotype. Together, these data are consistent with a role for renal ACE in the pathogenesis of non-diabetic and diabetic renal damage, but they do not allow proper dissection of cause and consequence. Moreover, effects of elevated renal ACE activity may be counterbalanced by effects of ACE2. We found endothelial neo expression of ACE2 in the kidney in various renal disorders, including diabetic nephropathy (chapter 8) [33]. The endothelial neo expression of ACE2 corresponds to findings by others showing endothelial neo expression of ACE in diseased human kidneys. This suggests colocalization, which would allow for a counterbalancing effect of ACE2 when ACE activity is increased. However, this issue clearly needs further study. Functional studies should be performed to elucidate its precise role in counterbalancing ACE. Studies with ACE2 inhibitors, once available, would be of particular interest.
Response to ACE inhibition and sodium: shifting the balance in the RAAS

Despite almost thirty years of extensive research, the mechanisms of action of ACEi are still not completely understood [25]. Our results allow some interesting new insights. The data from chapter 5 support a role for ang 1-7, especially during low sodium. Moreover, we show a clear decrease in the ratio between circulating levels of ang II on one hand and ang I and ang 1-7 on the other hand during ACEi combined with low sodium. These data indicate that alterations in angiotensin levels and balance between them explain the enhanced efficacy of RAAS-blockade during low sodium. On a general sense, our results show that the RAAS should preferably be studied in its entirety, i.e. considering both “axes” simultaneously as the net effect may be related to the balance between these two. Interestingly, alterations in ACE2 during RAAS-blockade have also been reported. Renal ACE2 activity is increased in response to ACEi and ang II type 1 (AT-1) receptor blockade [9;34]. Several studies in the heart show corresponding results during ACEi, AT-1 receptor blockade and aldosterone antagonist treatment [35-38]. It would be very interesting to study the role of ACE2 in relation to sodium status and the balance with ACE during this condition.

So sodium depletion by either dietary sodium restriction or diuretic treatment enhances the therapy response to RAAS-blockade for blood pressure and proteinuria [39-42], increasing the top of the dose-response. In addition to the short-term studies in human, animal studies have shown that sodium status also modifies long term renal outcome. Our current studies suggest that the altered balance between angiotensins contributes to the better outcome during low sodium. It should be noted that sodium status may also have direct effects on renal and cardiovascular target organ damage. Experimental studies show specific effects of sodium status on tissue injury independent of changes in blood pressure. Increased salt intake results in increased renal levels of TGF-β [43;44], whereas dietary sodium restriction led to a blood pressure independent improvement in endothelial function [45]. So, excessive salt intake might play a direct role in cardiovascular and renal disease. Moreover, high sodium intake can increase renal and vascular ACE activity [5;46]. Furthermore, increased salt intake has been linked to higher local synthesis of aldosterone in the heart and the vessels and increased production of reactive oxygen species in both renal cortex and vascular beds [47-49]. So, multiple mechanisms and pathways may be involved in the eventual outcome. In follow-up of our studies, further exploration of the observed interactions between sodium status, the response to RAAS-blockade, and ACE I/D genotype should preferably focus on the impact on mechanisms of target organ damage at tissue level, to better elucidate the gene-environment interaction between the ACE I/D genotype, sodium status and therapy response to ACEi in cardiovascular and renal disease.
Environmental factors: interaction with adiponectin and weight excess

Our current studies, together with other recent results from our group and others, allow interesting interferences on the interaction between environmental factors and RAAS-activity. We found a clear link between adiponectin levels and RAAS activity (chapter 6). Ang II appears to have a role in the regulation of this novel adipokine which is produced in adipocytes only. The anti-inflammatory and cardioprotective properties of adiponectin are increasingly recognized. Over the last years the role of the RAAS in obesity and its function in fat tissue has gained considerable interest. Adipose tissue has been shown to produce and release numerous bioactive molecules including leptin, pro-inflammatory cytokines, and all components of the RAAS [50;51] Our results on adiponectin provide convincing evidence for another link between the RAAS and fat tissue.

Both circulating and tissue levels of all components of the RAAS have been shown to be elevated in obese individuals [52-54]. Moreover, in humans weight loss is associated with amelioration of the increased RAAS activation both in plasma and adipose tissue, which may contribute to the decrease in blood pressure induced by weight loss [50], and to the decrease in sodium-sensitivity of blood pressure that accompanies weight loss. Furthermore, an association between the angiotensinogen polymorphism (AGT 235T genotype) and obesity was shown by the group of Hollenberg [55]. Interestingly, the same polymorphism has been linked to sodium sensitivity [56]. These studies support another gene-environment interaction, namely between the RAAS, sodium intake and weight excess.

Also in the kidney, weight excess may lead to an increase in components of the RAAS. In rats Barton et al. found an increased intrarenal ACE associated with obesity, mediated by endothelin [57]. In human, elevated serum ACE activity has been found during obesity [54]. Very few studies reported on the ACE genotype and obesity. In the Olivetti Prospective Heart Study weight gain was more prominent in DD subjects [58]. However, it would be very interesting to study the possible gene-environmental interaction between the ACE genotype, obesity, and sodium intake, as obesity and overweight are associated with an increased propensity to extracellular fluid volume expansion.

Several lines of evidence suggest a link between obesity, insulin resistance and RAAS activity. We recently reported that a higher body mass index (BMI) is associated with glomerular hyperfiltration, with higher GFR and filtration fraction in response to higher sodium intake in otherwise healthy subjects. This renal hemodynamic pattern suggests inappropriately high intrarenal activity of the RAAS in overweight subjects. This assumption is supported by studies demonstrating that overweight is associated with a more pronounced renal hemodynamic response to RAAS-blockade [59]. Furthermore, a higher BMI is associated with increasing insulin resistance [60;61]. Hepatic production of angiotensinogen is enhanced by higher insulin levels [62]. In addition, increased insulin resistance was reported during high sodium in rats and in healthy volunteers [63;64]. These findings may seem at
variance with the higher adiponectin levels that we observed during high sodium intake (chapter 6) and that could be expected to result in better insulin sensitivity. Nevertheless, the effects of ang II infusion clearly demonstrate that higher ang II levels could lead to lower levels of adiponectin, and the other way round, ACEi and high sodium, both associated with lower levels of ang II, resulted in higher adiponectin, so these data are highly robust. It should be mentioned here, that we only investigated the link between the RAAS and adiponectin levels in healthy subjects. It would be very interesting to study in more detail the link between several adipokines and the RAAS in obese subjects.

The (possible) interaction between the various determinants of RAAS-activity and the downstream effects on target organ damage are summarized in figure 1. These links between the RAAS, obesity, sodium intake and their interrelated consequences for the progression of cardiovascular and renal disease need more attention, especially since the prevalence of obesity is increasing alarming. It is to be noted in this respect that overweight and obesity are associated with an increased cardiovascular and renal risk. RAAS-blockade might be a logical intervention to ameliorate the consequences of excessive RAAS activation in subjects with weight excess, but this option remain to be explored. Future studies should define the obese/overweight phenotype clearly and further explore the role of the RAAS and it's genetic regulation in obesity, and especially relate this to environmental factors like sodium status as this factor is potentially modifiable for preventive and therapeutic purposes.

One important issue when studying the RAAS and adipokines in relation to obesity is renal function. As discussed in the appendix adiponectin levels might be influenced by renal clearance [65-69]. Whereas data in dialysis strongly support the impact of impaired renal excretion on adiponectin levels, data in patients with variable degrees of renal function impairment are less clear. These studies estimate renal function from renal function formulas and relate this to adiponectin levels. Interestingly, Becker et al. didn’t find a relation between adiponectin and renal function when the latter was measured by the golden standard with $^{125}$I-iothalamate clearance [70]. Our results of chapter 6 are
in accordance with this. In renal function formulas, age, sex and body surface area are used to normalize creatinine values between patients. Moreover, $^{125}$I-iothalamate measurements are corrected for body surface area as well. Adiponectin relates to bodyweight and age [71;72]. As stated in the appendix, in general, correction of renal function for body weight or surface is a problem when analyzing for obesity-associated issues, as the “correction” factors can annihilate (or elicit) precisely the relationships that are being sought for. The most appropriate way to normalize renal function for differences between individuals is still unresolved, especially when it comes to obesity [73;74]. Therefore, to be on the safe side, in studies on the relationship of BMI and renal function [75;76] it would be cautious to support the robustness of renal function data expressed per body surface area, by analyzing the renal function data also without normalization, or after normalization for height. This important issue should be taken into account for future studies looking at the relationships between the RAAS, obesity and renal function as presented in figure 1.

**Conclusion and future perspectives**

The role of the RAAS in cardiovascular and renal disease is much more complicated than initially assumed. Whereas blockade of the system by ACEi or AT-1 blockade has turned out to be one of the most effective therapies in prevention and treatment of cardiovascular and renal disease, still in many patients the response to therapy is insufficient to prevent ongoing cardiovascular and renal damage. This warrants further exploration of the mechanisms underlying progressive target organ damage and the response to RAAS-blockade. The increasing knowledge on both genetic and environmental factors influencing the RAAS and the response to intervention will hopefully improve the individual therapeutic efficacy in the future. This thesis demonstrates the pleiotropic diversity of the system and provides clues to strategies to improve and target individual therapy response. Further exploration of the role of ACE2 and ang 1-7 may allow making better use of the protective properties of the RAAS by the ACE2-ang 1-7-mas-receptor axis. Manipulation of sodium status can be used as a tool to orchestrate the pleiotropic effects of RAAS-blockade, as during high sodium intake effects on adiponectin become apparent. The other way round, sodium restriction can be used as a tool to circumvent resistance to ACEi in the DD genotype. It is fascinating that after more than a century of research on the RAAS we are still getting better insights in the (patho-) physiology of the system, thus further increasing the window of opportunity for improving the therapeutic efficacy of RAAS-blockade.
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