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## New roles for renin in heart failure and cardio-renal interaction

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## SUMMARY AND FUTURE PERSPECTIVES

Heart failure and kidney disease often co-exist and are strongly related. In addition the combination of heart failure and renal dysfunction yields a very poor prognosis. The interaction between heart and kidney function is complex and incompletely understood. Furthermore, patients with renal dysfunction are often excluded from cardiology trials. One of the main pathophysiological pathways that link heart failure and kidney disease is the renin-angiotensin-aldosterone system (RAAS). Although renin, as the most important protein in this system, has been discovered over 100 years ago, there is still much unknown about the RAAS. The studies in this thesis are aimed to gain more insight into the role of renin in the development and progression of cardiovascular and renal disease, as well as new therapies to block renin and its effects on renal hemodynamics in heart failure patients.

In **chapter 2** recent discoveries and current knowledge on the role of renin and prorenin in heart failure and cardio-renal interaction are summarized. RAAS blockers are the cornerstones in treatment of heart failure, diabetic and hypertensive kidney disease. Angiotensin and aldosterone escape, however, appear to limit the effectiveness of current RAAS blockers. This increase of angiotensin and aldosterone after prolonged treatment with RAAS inhibitors appears to occur via alternate pathways including chymase and tissue RAAS activation. Furthermore, several parallel pathways have been discovered including various angiotensin subtypes other than angiotensin I and II. The recent development of an orally active direct renin inhibitor, Aliskiren, has provided us with a new way to target the RAAS system at its origin and thus provide a more effective RAAS blockade. But the theory that renin merely activates the RAAS and blocking the enzymatic activity of renin will suffice has recently been challenged by the discovery of the (pro-) renin receptor. Binding to this receptor of renin or pro-renin, previously thought to be an inactive precursor activates several intracellular cascades. The clinical significance of these pathways is still unclear. In conclusion, the importance of the RAAS in the pathophysiology of advanced cardiovascular and renal disease is undisputed, but there are several questions remaining. This thesis zooms in on the role of renin in the early development of cardiac and renal disease.

## RENIN IN THE EARLY DEVELOPMENT OF CARDIAC AND RENAL DISEASE

In **chapter 3** the role of renin in the early development of cardio-vascular disease is examined. Indeed in a large community based cohort, high renin levels were associated with an increased risk for cardiovascular events, independent of traditional risk factors like hypertension. It describes an intriguing relationship for renin levels in the normal range. Furthermore we show that anti-hypertensive medication has a great impact on RAAS activation and needs to be taken into account when measuring components of the RAAS system. This questions whether chronic classical RAAS activation may be the common pathway that leads to cardiac and renal disease, or that perhaps renin induces cardiac and renal disease via other non-classical RAAS pathways, e.g. the (pro-) renin receptor.

From **chapter 4** it becomes clear that the concept of elevated renin causing both cardiac and renal disease is not straightforward. In the same population, elevated renin levels were associated with decreased kidney function at baseline, but elevated renin levels did not result in a more rapid decline of kidney function in the following years. Unexpectedly, kidney function appeared to recover partially in patients with high baseline renin levels. This may be explained by the hypothesis that elevated renin levels do not cause kidney damage per se, but rather act as a kidney damage marker, perhaps reflecting (temporary) renal hypo-perfusion.

## RENAL HEMODYNAMICS AND NEURO-HORMONAL ACTIVATION IN CHRONIC HEART FAILURE PATIENTS

In **chapter 5** we describe long-term changes in renal hemodynamics in a cohort of chronic heart failure patients with reduced ejection fraction. These patients were followed up for 3 years. At the start and end of the follow up time renal blood flow and filtration were measured using radioactive labeled tracers. Herein we found that the main determinant for GFR change over time is the change in renal blood flow. This demonstrates that in contrast to healthy individuals, in heart failure patients GFR is largely dependent on renal blood flow. Traditional risk factors for chronic kidney disease were not predictive for renal function decline in heart failure patients.

In **chapter 6** we describe a trial in which we aimed to improve renal blood flow in patients with heart failure and decreased GFR using the direct renin inhibitor aliskiren. Unfortunately, the ARIANA-CHF-RD trial had to be discontinued prematurely, because an interim safety analysis showed no improvement in renal blood flow and a decrease in GFR. In addition, aliskiren became under scrutiny because of safety issues observed in other studies, although this was not the primary reason to discontinue the trial. Considering the changes in renal hemodynam-

ics observed in our trial, it was evident that aliskiren provided additional RAAS inhibition on top of ACE inhibitors or angiotensin blockers and in some patients, mineralocorticoid receptor antagonists, but it is questionable if this is beneficial or harmful in patients with both heart failure and decreased GFR.

Another trial targeting the RAAS system in heart failure patients is described in **chapter 7**. The VIT-D-CHF trial showed that 6 weeks of vitamin D administration may lower plasma renin concentration in heart failure, and that it is safe. This makes it a very interesting treatment, since renin levels are very high in heart failure patients and even in patients on RAAS blockers high renin levels are associated with increased morbidity and mortality. Therefore vitamin D may prove to be one of the cheapest and safest drugs to improve outcome in heart failure patients.

## FUTURE PERSPECTIVES

Prevention of cardiovascular disease is the best treatment; However, this requires early detection of subjects at risk and available therapeutic options to target risk factors involved in the pathophysiology. Current cardiovascular and kidney disease risk calculators include several important treatable risk factors, like hypertension and hyperlipidaemia and have greatly improved preventive treatment. Despite this, cardiovascular disease remains one of the main causes of death. (1, 2)

In chapter 3 we show that high plasma renin levels are associated with increased cardiovascular risk, but it remains to be elucidated if renin is the causal factor for this increased risk. The development of direct renin inhibitors makes it possible to study if direct renin inhibition is able to reduce cardiovascular risk, but will require large cohorts with long follow-up. Furthermore current direct renin inhibitors block renin activity but increase renin concentration. (3) The discovery of the pro-renin receptor (4) makes it plausible that high renin concentrations may be harmful independently of renin activity, angiotensin and aldosterone. New drugs aimed to decrease renin concentration rather than activity are therefore warranted.

Besides the classical renin-angiotensin-aldosterone cascade many alternate pathways have been discovered that generate different variants of angiotensin including angiotensin 1-7, III and IV. (Chapter 3) The effect of these variants on cardiovascular risk has yet to be established. Some variants may have beneficial and other harmful effects. Current RAAS blocking therapy is limited by its side effects. A better understanding of the various alternate pathways and the development of drugs to target these pathways may open the possibility to provide RAAS guided therapy in order to block the harmful effects but stimulate the positive one. For example, measurement of (changes in) plasma renin activity could

adequately identify patients that did not respond to direct renin inhibition. (5) In addition, new drugs are currently tested that try to amplify the beneficial components of the RAAS system. Neutral endopeptidase (NEP) inhibitors like omapatrilat and LCZ696 inhibit the degradation of vasodilative substances. They have shown additive blood pressure lowering effect of NEP inhibitors in combination with ACE inhibitors and ARBs. (6) and LCZ696 has even shown to reduce mortality and hospitalization in heart failure patients. (7) What is interesting is the observation that ACE inhibitors and ARBs show anti-inflammatory and metabolic properties. It appears that ACE inhibitors and ARBs may slow the development of new onset diabetes via its peroxisome proliferator-activated receptor-gamma properties. (8) These developments will shift therapy from RAAS blockade to RAAS modulation.

Another factor limiting adequate therapy is the lack of easily obtainable parameters for kidney (dys-) function. Currently the main parameters for kidney function are estimated GFR using serum creatinine and urinary albumin excretion as a marker of glomerular damage. RAAS blockers often lower GFR and thus increase serum creatinine, but this does not imply kidney damage, but rather a decreased glomerular pressure. (9) Likewise a decrease in glomerular pressure decreases albuminuria, but this doesn't mean that the permeability of the glomerulus has changed. (10) Currently new markers for kidney damage and function are being studied including Cystatin C, Neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1) and N-acetyl- $\beta$ -D-glucosaminidase (NAG). (11,12) Some appear to have incremental value over creatinine and albumin for early detection of kidney disease and function, but studies are needed to investigate if treatment guided by these markers can improve outcome.

## CONCLUSION

RAAS activation plays an important role in the pathophysiology of patients with established cardiovascular and renal disease, but it is less clear if high RAAS activity is harmful in healthy subjects. High plasma renin levels are associated with an increased risk for cardiovascular disease but not with renal function decline in subjects not using anti-hypertensive medication. It remains speculative if renin blockade in healthy subjects with high renin levels is beneficial, but from our data we conclude this is unlikely to have major impact in the general population.

In heart failure patients, renal blood flow is the main determinant of GFR. High plasma renin activity is associated with poor outcome, but we could not demonstrate a beneficial effect of direct renin blockade in heart failure patients with reduced GFR on renal blood flow. Although the direct renin inhibitor aliskiren lowers plasma renin activity, its use was associated with increased plasma renin concentration and a neutral effect on renal blood flow. Administration of

vitamin D lowers both renin concentration and activity in heart failure patients, albeit moderately and it remains to be elucidated if this translates in improved outcome.

## 5-YEARS OUTLOOK

In the past decades several RAAS blockers have been developed that are now the cornerstone for the treatment of heart failure and kidney disease. Increasing RAAS blockade, however, only increases side effects and does not improve outcome. The focus is now shifting from RAAS blockade to RAAS modulation. Side effects of the treatment remain a major issue and limit treatment options. Current heart failure guidelines have the same treatment algorithm for all patients. (13) Medication is uptitrated until side effects occur. With a better understanding of the RAAS system and cardio-renal interaction we may prevent the occurrence of side effects rather than act after they happen. Through measurement of various RAAS components and new markers for kidney function we may select the appropriate RAAS modulation before initiation of treatment in the near future instead of using a process of trial and error. This will hopefully lead to both fewer side effects, but also more effective treatment.

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