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

Nicolas F. Schroten

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

ISBN: 978-90-367-7498-7

Cover design: N.F. Schroten

Layout: perfekt

Printed by perfekt Gaul i Wspólnicy sp.j., ul. Świerzawska 1, Poznań, Poland

rijksuniversiteit groningen

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

Proefschrift

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van de
rector magnificus prof. dr. E. Sterken
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

woensdag 7 januari 2015 om 14.30 uur

door

Nicolas Filip Schroten

geboren op 6 september 1984
te Delft

Promotores
Prof. dr. J.L. Hillege
Prof. dr. R.A. de Boer
Prof. dr. D.J. van Veldhuisen

Copromotor
Dr. K. Damman

Beoordelingscommissie
Prof. dr. M.P. van den Berg
Prof. dr. A.H.J Danser
Prof. dr. J.W.R. Twisk

Paranimfen
Frank P.J. Brouwers
Natalia J. Schroten

Financial support
The research described in this thesis was supported by a grant
of the Dutch Heart Foundation (DHF-2007T046).
Financial support by the Dutch Kidney Foundation for the publication
of this thesis is gratefully acknowledged.

Contents

Introduction

Epidemiology of heart failure and kidney disease

Heart failure and kidney disease have a major impact on life expectancy and on our health care system. The prevalence of heart failure is estimated to be 1-2% in the general population and around 7-8% in subjects > 75 years. This number is, however, increasing due to improved therapeutic options to treat myocardial infarction and increasing age of the population at large. (1,2)

In parallel to heart failure, the prevalence of chronic kidney disease (CKD) is also increasing. In the Netherlands the prevalence of CKD is estimated between 5-7%, although the prevalence strongly increases with age. In subjects aged 75-79 years the prevalence of CKD was more than 25% in subjects without diabetes and even more than 50% in diabetics. (3) With an aging population and increasing prevalence of diabetes the prevalence of CKD will only rise further.

There is a close interaction between heart failure and kidney disease. Heart failure is often complicated by kidney disease and, vice versa, kidney disease is associated with an increased risk for cardiac disease. (4) This strong reciprocal relation has long been recognized and the term the cardio-renal syndrome has been applied to address this interdependency of the kidney and the heart. To better understand and categorize the relation(s) between heart and kidney disease a classification into 5 types of cardio-renal syndrome has been proposed, (5) subdividing cardio-renal syndrome in acute vs chronic and renal disease causing cardiac dysfunction vs cardiac disease causing renal dysfunction. The last group comprises patients with a systemic disease leading to both kidney and cardiac dysfunction. The mechanisms and sequence of events that lead to dysfunction of both organs is often unclear and it may be difficult to classify a patient, because the relation is often bidirectional and may vary within one patient over the course of the disease. Furthermore this classification is not usefull to guide therapy, since it does not take into account the underlying pathophysiological mechanisms. Therefore a better classification based on underlying pathology is much needed.

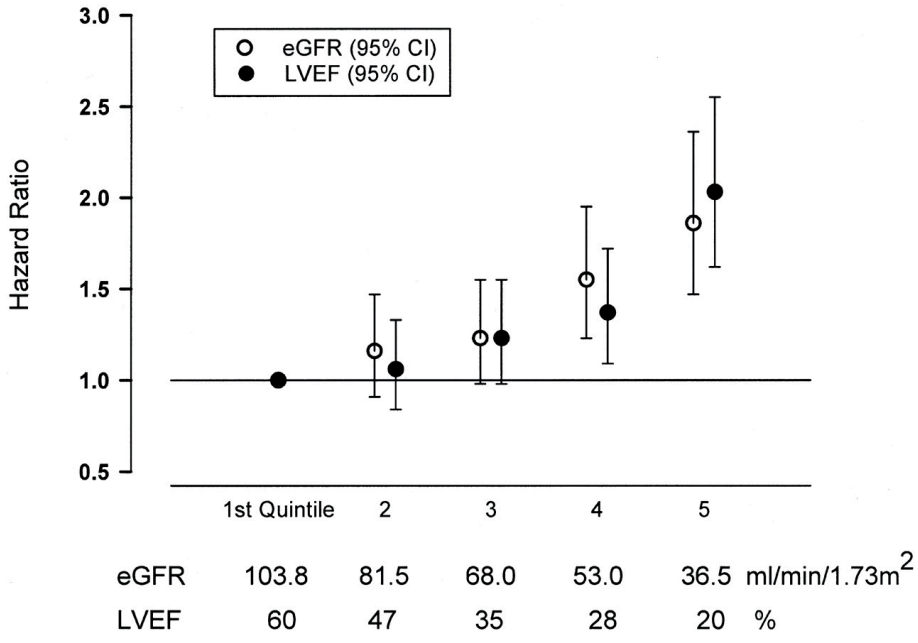
Patients hospitalized for heart failure have a poorer prognosis than most types of cancer, (6) likewise patients on dialysis have an average survival of 9 years for patients between 40-44 years and only 4.5 years for patients between 60-64 years.

(7) But irrespective of the type of cardiorenal syndrome, concomitant presence of both heart failure and kidney disease has a large impact on prognosis; kidney disease accompanying heart failure further worsens prognosis, and heart failure accompanying kidney disease also impairs survival. What is striking is that renal function is a just as strong a predictor for hospitalisation and mortality in heart failure patients as cardiac parameters like left ventricular ejection fraction. (8) (figure 1)

Pathophysiology of the cardiorenal syndrome

The pathophysiology of the cardio-renal syndrome is complex and not fully understood. Several mechanisms have been proposed to explain the correlation between heart failure and renal dysfunction. (9,10) In brief, they can be categorized into hemodynamic factors, neurohormonal factors, inflammation, oxidative stress and therapy.

Figure 1. Multiple adjusted hazard ratios (with their 95% CI) for risk of cardiovascular death or unplanned admission to hospital for the management of worsening CHF across decreasing exact quintiles (median values presented) of both eGFR and LVEF. (Hillege et al. Circulation. 2006; 113: 671-678)



Hemodynamic factors

Heart failure and kidney disease share several common risk factors. The most studied is hypertension, which is a well-known risk factor for ischemic heart disease, (11) heart failure with preserved ejection fraction (12) and kidney disease. (3) Long term hypertension can therefore lead to both heart failure and kidney disease, although which will occur first is variable. Furthermore heart failure is characterized by both decreased cardiac output and congestion. Traditionally, it was thought that decreased cardiac output would be the main determinant of decreased renal function in heart failure patients, but recent studies show that increased central venous pressure and congestion may be even more important. (13, 14) Atherosclerosis is another common pathway for both renal and cardiac disease and there is increasing evidence that decreased renal perfusion, e.g. due to renal artery atherosclerosis, is an often undiagnosed cause of renal dysfunction in heart failure patients. (15) In healthy individuals renal function can be maintained at a stable level despite moderate changes in blood pressure and renal blood flow, due to autoregulation of intraglomerular pressure. In heart failure, however, renal blood flow appears vital for maintaining GFR. (Chapter 5 and 6)

Neurohormonal

Another well studied mechanism for both cardiac and renal disease is activation of the Renin-Angiotensin-Aldosterone-System (RAAS). RAAS blockers have become the cornerstone for treatment for both cardiac and renal disease. However, in the last decade, it has also become clear that the RAAS is more complex than previously thought (Chapter 2) and that RAAS inhibition is not always beneficial. Specifically, trials evaluating dual or triple RAAS blockade have produced troubling data, and nowadays dual or triple blockade is no longer recommended in heart and kidney disease because of little or absent clinical benefit, with increased (serious) side effects. The main side effects reported were hyperkalemia, hypotension and non-fatal stroke, probably relate to excessive reduction of blood pressure and tissue perfusion, furthermore an increased risk for hyperkalemia was observed (17, 18, 35).

It remains unclear if (inappropriate) RAAS activation in healthy individuals is a common risk factor for long-term cardio-renal disease. We demonstrated an association between high renin levels with incident cardiovascular disease, (chapter 3) but not with renal function decline (chapter 4). Other studies have also found conflicting results. (19-21)

Sympathetic nerve activation is yet another important factor in both cardiac and renal disease. This is supported by the observation that beta-blockers are

protective in heart failure and ischemic heart disease, but they also appear to prevent renal function decline. (22) Amongst others sympathetic nerve activity affects renin release, (23) but it has various other effects that are beyond the scope of this thesis. New techniques interfering in sympathetic nerve activation have recently been developed and are currently tested. (24) Hopefully they will shed more light on the exact role of the sympathetic nerve system in the cardio-renal axis.

Inflammation, oxidative stress and metabolic factors

There appears to be an inflammatory status in both heart failure and kidney disease, since many inflammatory markers are elevated in both conditions, (25-27) and their levels are associated with poor prognosis. Furthermore there appears to be a state of oxidative stress in heart failure (28) and kidney disease patients, (29) which may be another explanation why injury or failure of one organ may lead to injury or failure in the other organ. Also metabolic factors may link renal and cardiac disease. For example, patients with end-stage renal disease show accelerated vascular calcification driven by high calcium and phosphorus levels. (30) The main hormones regulating calcium are parathyroid hormone and Vitamin D, but vitamin D may also link cardiac and renal diseas via another pathway. Vitamin D is activated in the kidney and observational studies have shown that low vitamin D levels are associated with increased incidence of cardiovascular disease. (31) One of the potential mechanisms for this association may be the inhibition of renin transcription by active vitamin D. (Chapter 7) Few drug trials, however, have been performed that interfere in the oxidative stress, inflammatory and metabolic pathways, therefore it is unknown if modulation of these pathways will improve prognosis. One exception is diabetes, where it has clearly been demonstrated that early good glucose regulation can prevent both kidney disease and cardiac events. (32)

Therapy

The impact of medical treatment is often underrepresented in the discussion about cardio-renal pathways. Many drugs used to treat cardiac disease affect kidney function. Diuretic treatment is clearly associated with worsening renal function, (33) but also most RAAS blockers can cause a (temporary) decrease in GFR. Interestingly a moderate decrease in GFR when initiating RAAS blocking therapy is not always harmful. (34) Furthermore contrast used during cardiac catheterisations can cause contrast-induced nephropathy.

Aims of this thesis

This thesis aimed to further clarify the role of the RAAS and specifically renin in the pathophysiology of cardio-renal syndrome. Chapter 2 describes what is known so far on the role of renin in heart failure and cardio-renal interaction and provides the rationale for the studies performed in this thesis. Chapter 3 and 4 explore the role of renin in the early development of cardiac and renal disease, by investigating the relation of high renin levels in healthy individuals with cardiac events and renal function decline. Chapter 5 studies the risk factors for renal function decline in chronic heart failure patients and describes renal hemodynamics in these patients. In Chapter 6 and 7 studies investigating new therapies in heart failure targeting the RAAS system are presented. Chapter 6 describes the effect of a direct renin inhibitor on renal blood flow in heart failure patients with moderate renal dysfunction and chapter 7 investigates if vitamin D can suppress RAAS activation in chronic heart failure patients.

References

1. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. Heart 2007;93:1137-1146.
2. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006;355:251--259.
3. Van Blijderveen, J., Straus, S., Zietse, R., Stricker, B., Sturkenboom, M., & Verhamme, K. A population-based study on the prevalence and incidence of chronic kidney disease in the Netherlands. International Urology and Nephrology, 2014:46:583-592.
4. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW, American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Hypertension 2003;42:1050-1065.
5. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. J Am Coll Cardiol 2008;52:1527-1539.
6. Stewart S, MacIntyre K, Hole DJ, Capewell S, McMurray JJ. More 'malignant' than cancer? Five-year survival following a first admission for heart failure. Eur J Heart Fail 2001;3:315--322.
7. Collins AJ, Foley RN, Herzog C, Chavers BM, Gilbertson D, Ishani A, Kasiske BL, Liu J, Mau LW, McBean M, Murray A, St Peter W, Guo H, Li Q, Li S, Li S, Peng Y, Qiu Y, Roberts T, Skeans M, Snyder J, Solid C, Wang C, Weinhandl E, Zaun D, Arko C, Chen SC, Dalleska F, Daniels F, Dunning S, Ebben J, Frazier E, Hanzlik C, Johnson R, Sheets D, Wang X, Forrest B, Constantini E, Everson S, Eggers PW, Agodoa L. Excerpts from the US Renal Data System 2009 Annual Data Report. Am J Kidney Dis 2010;55:S1-420, A6-7.

8. Hillege HL, Girbes AR, de Kam PJ, Boomsma F, de Zeeuw D, Charlesworth A, Hampton JR, van Veldhuisen DJ. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. Circulation 2000;102:203-210.
9. Bongartz LG, Cramer MJ, Doevendans PA, Joles JA, Braam B. The severe cardiorenal syndrome: 'Guyton revisited'. Eur Heart J 2005;26:11-17.
10. Braam B, Cupples WA, Joles JA, Gaillard C. Systemic arterial and venous determinants of renal hemodynamics in congestive heart failure. Heart Fail Rev 2012;17:161-175.
11. Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De Backer G, De Bacquer D, Ducimetiere P, Jousilahti P, Keil U, Njolstad I, Oganov RG, Thomsen T, Tunstall-Pedoe H, Tverdal A, Wedel H, Whincup P, Wilhelmsen L, Graham IM, SCORE project group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 2003;24:987-1003.
12. Lee DS, Gona P, Vasan RS, Larson MG, Benjamin EJ, Wang TJ, Tu JV, Levy D. Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction: insights from the framingham heart study of the national heart, lung, and blood institute. Circulation 2009;119:3070-3077.
13. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, Young JB, Tang WH. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol 2009;53:589-596.
14. Sinkeler SJ, Damman K, van Veldhuisen DJ, Hillege H, Navis G. A re-appraisal of volume status and renal function impairment in chronic heart failure: combined effects of prerenal failure and venous congestion on renal function. Heart Fail Rev 2012;17:263-270.
15. Bourantas CV, Loh HP, Lukaschuk EI, Nicholson A, Mirsadraee S, Alamgir FM, Tweddel AC, Ettles DF, Rigby AS, Nikitin NP, Clark AL, Cleland JG. Renal artery stenosis: an innocent bystander or an independent predictor of worse outcome in patients with chronic heart failure? A magnetic resonance imaging study. Eur J Heart Fail 2012;14:764-772.
16. Damman K, Voors AA, Hillege HL, Navis G, Lechat P, van Veldhuisen DJ, Dargie HJ, CIBIS-2 Investigators and Committees. Congestion in chronic systolic heart failure is related to renal dysfunction and increased mortality. Eur J Heart Fail 2010;12:974-982.
17. Parving HH, Brenner BM, McMurray JJ, de Zeeuw D, Haffner SM, Solomon SD, Chaturvedi N, Persson F, Desai AS, Nicolaides M, Richard A, Xiang Z, Brunel P, Pfeffer MA, ALTITUDE Investigators. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. N Engl J Med 2012;367:2204-2213.
18. Mann JF, Schmieder RE, McQueen M, Dyal L, Schumacher H, Pogue J, Wang X, Maggioni A, Budaj A, Chaithiraphan S, Dickstein K, Keltai M, Metsarinne K, Oto A, Parkhomenko A, Piegas LS, Svendsen TL, Teo KK, Yusuf S, ONTARGET investigators. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. Lancet 2008;372:547-553.
19. Sim JJ, Shi J, Calara F, Rasgon S, Jacobsen S, Kalantar-Zadeh K. Association of plasma renin activity and aldosterone-renin ratio with prevalence of chronic kidney disease: the Kaiser Permanente Southern California cohort. J Hypertens 2011;29:2226-2235.
20. Sever PS, Chang CL, Prescott MF, Gupta A, Poulter NR, Whitehouse A, Scanlon M. Is plasma renin activity a biomarker for the prediction of renal and cardiovascular outcomes in treated hypertensive patients? Observations from the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT). Eur Heart J 2012;33:2970-2979.
21. Terata S, Kikuya M, Satoh M, Ohkubo T, Hashimoto T, Hara A, Hirose T, Obara T, Metoki H, Inoue R, Asayama K, Kanno A, Totsune K, Hoshi H, Satoh H, Sato H, Imai Y. Plasma

renin activity and the aldosterone-to-renin ratio are associated with the development of chronic kidney disease: the Ohasama Study. J Hypertens 2012;30:1632-1638.
22. Bakris GL, Hart P, Ritz E. Beta blockers in the management of chronic kidney disease. Kidney Int 2006;70:1905-1913.
23. Holmer SR, Hengstenberg C, Mayer B, Engel S, Lowel H, Riegger GA et al (2001) Marked suppression of renin levels by beta-receptor blocker in patients treated with standard heart failure therapy: a potential mechanism of benefit from betablockade. J Intern Med 249 (2):167-172.
24. Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, Leon MB, Liu M, Mauri L, Negoita M, Cohen SA, Oparil S, Rocha-Singh K, Townsend RR, Bakris GL, SYMPLICITY HTN-3 Investigators. A controlled trial of renal denervation for resistant hypertension. N Engl J Med 2014;370:1393-1401.
25. Arici M, Walls J. End-stage renal disease, atherosclerosis, and cardiovascular mortality: is C-reactive protein the missing link? Kidney Int 2001;59:407-414.
26. Zebrack JS, Anderson JL, Beddhu S, Horne BD, Bair TL, Cheung A, Muhlestein JB, Intermountain Heart Collaborative Study Group. Do associations with C-reactive protein and extent of coronary artery disease account for the increased cardiovascular risk of renal insufficiency? J Am Coll Cardiol 2003;42:57-63.
27. Zoccali C, Benedetto FA, Mallamaci F, Tripepi G, Fermo I, Foca A, Paroni R, Malatino LS. Inflammation is associated with carotid atherosclerosis in dialysis patients. Creed Investigators. Cardiovascular Risk Extended Evaluation in Dialysis Patients. J Hypertens 2000;18:1207-1213.
28. Heymes C, Bendall JK, Ratajczak P, Cave AC, Samuel JL, Hasenfuss G, Shah AM. Increased myocardial NADPH oxidase activity in human heart failure. J Am Coll Cardiol 2003;41:2164--2171.
29. Vallance P, Leone A, Calver A, Collier J, Moncada S. Accumulation of an endogenous inhibitor of nitric oxide synthesis in chronic renal failure. Lancet 1992;339:572-575.
30. Moe SM, Chen NX. Mechanisms of vascular calcification in chronic kidney disease. J Am Soc Nephrol 2008;19:213-216.
31. Gotsman I, Shauer A, Zwas DR, Hellman Y, Keren A, Lotan C, Admon D. Vitamin D deficiency is a predictor of reduced survival in patients with heart failure; vitamin D supplementation improves outcome. Eur J Heart Fail 2012;14:357-366.
32. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560-2572.
33. Kondo T, Yamada T, Morita T, Furukawa Y, Tamaki S, Iwasaki Y, Kawasaki M, Kikuchi A, Sengoku K, Ozu K, Yamamoto H, Kawai T, Takahashi S, Ishimi M, Hakui H, Fukunami M. Even standard dose of furosemide is associated with the progression of cardiorenal syndrome in patients with chronic heart failure via cardiac sympathetic nerve activation. JACC 2014;63:12_S.
34. Palmer BF. Renal dysfunction complicating the treatment of hypertension. N Engl J Med 2002;347:1256-1261.
35. Makani H, Bangalore S, Desouza KA, et al. Efficacy and safety of dual blockade of the renin-angiotensin system: a meta-analysis of randomized trials. BMJ 2013; 346:f360.