

The renin-angiotensin system in the hypertensive kidney

Citation for published version (APA):

van Twist, D. (2016). *The renin-angiotensin system in the hypertensive kidney: clinical studies in patients with essential hypertension, fibromuscular dysplasia, and the atherosclerotic renal artery stenosis*.

Document status and date:

Published: 01/01/2016

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

Valorization addendum

Valorization addendum

Research should not only be focused on gaining knowledge per se, but should in some way create value for the society. In this valorization addendum we describe how the findings presented in this thesis could provide relevant benefit for the general public.

Cardiovascular disease is a socio-economic issue

The focus in this thesis is on patients with high blood pressure (hypertension). As already discussed in Chapter 1, hypertension is a major threat for human society as it is the most important individual risk factor for death and affects more than 1 billion people worldwide.¹⁻³ At least 7% of the disability-adjusted life years (the cumulative number of life years lost due to illness, disability, or early death) can be attributed to hypertension in the global population, thereby even beating tobacco smoking (6.3%) and air pollution (4.3%) in the top three of most important individual risk factors for disease burden.⁴ This disease burden consists predominately of cardiovascular diseases such as myocardial infarction and stroke. In Europe, the costs related to cardiovascular diseases were estimated on € 169 billion annually in 2003.³ A recent report from Canada revealed that the average individual with hypertension had annual health care costs of \$ 5768, of which \$ 2341 were directly attributable to hypertension.⁵ Although health care costs (in- and outpatient care, costs of medications) account for most of the costs involved (62%), a substantial part of these costs is not directly health care related: loss of productivity due to the inability to work represents 21% of these costs (i.e. more than € 35 billion annually) and costs for informal care (e.g. by family members that care for the patient and therefore cannot contribute to society otherwise) represent 17% of these costs.³ As the global incidence of hypertension is still rising,⁶ one can expect that more and more people will suffer from hypertension related diseases in the upcoming decades.^{7,8} This will increase the already gigantic social and economic burden for the society even further. Fortunately, blood pressure reduction is able to decrease the incidence of cardiovascular disease (and subsequently reductions in death and disease burden).^{9,10} However, blood pressure remains above target despite treatment in more than 50% of patients with hypertension.^{11,12} These difficult-to-control patients therefore continue to be at risk for death and cardiovascular diseases.

Understanding pathophysiological mechanisms

The ultimate goal of cardiovascular research is the development of new, better therapeutic strategies and finding ways to select or diagnose those people who will

benefit (in terms of prevention of death or morbidity) from these new strategies. To develop new diagnostic and therapeutic strategies, the first and most important step is to understand the pathophysiological mechanisms involved in a disease. From this knowledge, hypotheses can be formulated on how a disease could be cured or controlled. As the kidney and the renin-angiotensin system both play an important role in the regulation of blood pressure and thus in the development and maintenance of high blood pressure that is what we focused on in this thesis. Several findings in this thesis (for example the influence of sodium intake on the effects of angiotensin-(1-7) and on the effects AT₁-receptor blocker eprosartan, the renin-angiotensin system in fibromuscular dysplasia, and the differences in pathophysiological mechanisms between fibromuscular dysplasia and atherosclerotic renal artery stenosis) provided us with more insight into the pathophysiological mechanisms involved in high blood pressure. Although the research in this thesis did not lead to a change in the treatment of difficult-to-treat hypertension yet, the increased understanding of pathophysiological mechanisms brings us a step closer to this ultimate goal. The implications of our findings are summarized in the paragraphs below.

New pharmacotherapeutic strategies

In the present thesis we demonstrated that angiotensin-(1-7), a peptide within the renin-angiotensin system, is able to increase renal blood flow (Chapter 2). Even in patients with difficult-to-control hypertension, angiotensin-(1-7) can induce vasodilation in the organ that plays a key role in blood pressure regulation: the kidney. This finding opens up opportunities for using the angiotensin-(1-7)-pathway as a therapeutic target in the treatment of difficult-to-control hypertension. As described in Chapter 4, promising progress has been made regarding the development of such drugs. One way to use angiotensin-(1-7) as a target could be to increase the levels of angiotensin-(1-7) in the circulation, for example by enhancing the activity of the enzyme ACE2 [which produces angiotensin-(1-7)] or by supplementation of angiotensin-(1-7) via an oral formula that releases angiotensin-(1-7) slowly to the circulation. Furthermore, drugs with similar actions as angiotensin-(1-7), i.e. so-called agonists which stimulate the same processes in the human body as angiotensin-(1-7), are currently under development. In animal models the abovementioned experimental drugs have already been evaluated. Interestingly, they did not only reduce blood pressure,¹³⁻¹⁵ but also had beneficial effects on atherosclerosis, kidney disease, and cardiac function,¹⁵⁻²⁰ indicating that such drugs could also become a new treatment option for patients with other cardiovascular and/or kidney diseases besides high blood pressure. Our finding that angiotensin-(1-7) is able to exert these effects in patients with difficult-to-control hypertension as well (in spite of several changes that occur in the kidneys of such patients due to long term exposure to high blood pressure) indicates that these experimental drugs could be beneficial in humans.

However, we also found that the effects of angiotensin-(1-7) (and not the effects of AT₁-receptor blocker eprosartan; Chapter 5) are attenuated by low sodium intake, presence of high levels of angiotensin II (Chapter 2), and/or the presence of an atherosclerotic renal artery stenosis (Chapter 3). This suggests that the effectiveness of new drugs targeting the angiotensin-(1-7) pathway might be reduced under those conditions, which should be taken account during the further development of such drugs.

The right treatment to the right patient at the right time

Although renal artery fibromuscular dysplasia is quite prevalent among patients with high blood pressure (studies estimate a prevalence between 1.7 and 5.8%),^{21,22} research on this disease is very scarce. Up till now, most knowledge on this disease is based on case-series and theoretical assumptions derived from other renovascular diseases. In this thesis we aimed to improve our understanding of the pathophysiological mechanisms in this relatively frequently occurring disease. Although the research in this thesis is only a first step towards further understanding the pathophysiological mechanisms involved, it does contribute already. For example, we demonstrated that renin secretion is not increased in kidneys with multifocal fibromuscular dysplasia (Chapters 6 and 7). Until recently, the clinical decision to perform balloon angioplasty in kidneys with fibromuscular dysplasia was often guided by the presence or absence of increased renin secretion: e.g. balloon angioplasty was only performed in kidneys with increased renin secretion. This practice was based on previous studies in patients with atherosclerotic renal artery stenosis and animal models, but not on research in patients with fibromuscular dysplasia. In our study, however, systemic renin levels were below the upper limit of normal in all 58 patients, while 48% of the patients had a decrease in blood pressure in response to balloon angioplasty. Moreover, no differences in renin secretion were found between responders and non-responders. This indicates that using renin secretion as a predictor for the effectiveness of balloon angioplasty is not a good strategy.

We furthermore demonstrated that the microvascular function in kidneys with fibromuscular dysplasia is better preserved as compared to kidneys with atherosclerotic renal artery stenosis. We hypothesized that this difference in microvascular function may be responsible for the difference in response to revascularization between patients with fibromuscular dysplasia and atherosclerotic renal artery stenosis. If this is indeed the case, this opens up opportunities for improving the selection of patients who will benefit from revascularization. If we will be able to develop a test that identifies the patients with sufficiently preserved renal microvascular function, we can select those patients for balloon angioplasty. The patients with too much loss of kidney tissue and/or severe microvascular dysfunction (e.g. due to too long exposure to high blood pressure) would probably not respond

anymore and should be withheld from balloon angioplasty and, consequently, treated in a different way.

Improving cost-effectiveness

The abovementioned change in patient selection could improve cost-effectiveness in two ways:

First, rejecting patients with fibromuscular dysplasia for balloon angioplasty because of low renin levels leads to undertreatment. Based on the incorrect assumption that patients would only respond in case of increase renin secretion, balloon angioplasty was withheld in many patients. Since those patients did not receive a possibly curative intervention (based on unjustified grounds) they continue to be at risk for cardiovascular and kidney disease on the long term. Moreover, undertreatment leads to substantial economic burden due to additional costs for antihypertensive drugs and hospital visits.

Second, better selection of the patients improves the success rate of revascularization and reduces the number of unnecessary procedure-related complications and, probably even more importantly, the costs: Currently, the estimated costs for a balloon angioplasty without complications are € 3233: € 2154 procedure-related costs, € 946 for hospital admission, and € 133 for other costs such as laboratory tests, travel costs, and productivity losses [costs were derived from a previous study²³ and adjusted for annual inflation in the Netherlands (Statline, Statistics Netherlands)]. Given that 52% of the patients with fibromuscular dysplasia did not respond to balloon angioplasty (Chapter 6), a test that is able to identify the responders before balloon angioplasty is performed could already have saved almost € 100,000 in our cohort of 58 patients only. If such test is not too expensive, it is very likely that cost-effectiveness will improve, especially when this can be applied on a larger scale, for example in patients with atherosclerotic renal artery stenosis as well.

Conclusion

In this thesis we performed research on the renin-angiotensin system in kidneys from hypertensive patients. In this way, we improved our knowledge in pathophysiological changes that occur in these kidneys. Although further research is required, the increased knowledge of the kidneys from patients with hypertension could lead to changes in diagnostic and therapeutic strategies. This research contributes to society as it eventually could lead to improved cost-effectiveness of current treatment strategies and to new strategies that potentially reduce death and morbidity in patients with hypertension, cardiovascular diseases, and kidney failure.

References

1. Ezzati M, Riboli E. Behavioral and dietary risk factors for noncommunicable diseases. *N Engl J Med*. 2013;369:954-964
2. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Judd SE, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Mackey RH, Magid DJ, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER, 3rd, Moy CS, Mussolino ME, Neumar RW, Nichol G, Pandey DK, Paynter NP, Reeves MJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Wong ND, Woo D, Turner MB. Heart disease and stroke statistics--2014 update: A report from the american heart association. *Circulation*. 2014;129:e28-e292
3. Leal J, Luengo-Fernandez R, Gray A, Petersen S, Rayner M. Economic burden of cardiovascular diseases in the enlarged european union. *Eur Heart J*. 2006;27:1610-1619
4. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: A systematic analysis for the global burden of disease study 2010. *Lancet*. 2012;380:2224-2260
5. Weaver CG, Clement FM, Campbell NR, James MT, Klarenbach SW, Hemmelgarn BR, Tonelli M, McBrien KA, Alberta Kidney Disease N, the Interdisciplinary Chronic Disease C. Healthcare costs attributable to hypertension: Canadian population-based cohort study. *Hypertension*. 2015;66:502-508
6. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: Analysis of worldwide data. *Lancet*. 2005;365:217-223
7. Allen N, Berry JD, Ning H, Van Horn L, Dyer A, Lloyd-Jones DM. Impact of blood pressure and blood pressure change during middle age on the remaining lifetime risk for cardiovascular disease: The cardiovascular lifetime risk pooling project. *Circulation*. 2012;125:37-44
8. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: A systematic analysis for the global burden of disease study 2010. *Lancet*. 2012;380:2095-2128
9. Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mm hg. *JAMA*. 1967;202:1028-1034
10. van Vark LC, Bertrand M, Akkerhuis KM, Brugts JJ, Fox K, Mourad JJ, Boersma E. Angiotensin-converting enzyme inhibitors reduce mortality in hypertension: A meta-analysis of randomized clinical trials of renin-angiotensin-aldosterone system inhibitors involving 158,998 patients. *Eur Heart J*. 2012;33:2088-2097
11. Banegas JR, Lopez-Garcia E, Dallongeville J, Guallar E, Halcox JP, Borghi C, Masso-Gonzalez EL, Jimenez FJ, Perk J, Steg PG, De Backer G, Rodriguez-Artalejo F. Achievement of treatment goals for primary prevention of cardiovascular disease in clinical practice across europe: The eurika study. *Eur Heart J*. 2011;32:2143-2152
12. Prugger C, Keil U, Wellmann J, de Bacquer D, de Backer G, Ambrosio GB, Reiner Z, Gaita D, Wood D, Kotseva K, Heidrich J, Group EIS. Blood pressure control and knowledge of target blood pressure in coronary patients across europe: Results from the euroaspire iii survey. *J Hypertens*. 2011;29:1641-1648
13. Singh Y, Singh K, Sharma PL. Effect of combination of renin inhibitor and mas-receptor agonist in doca-salt-induced hypertension in rats. *Mol Cell Biochem*. 2013;373:189-194
14. Cunha TM, Lima WG, Silva ME, Souza Santos RA, Campagnole-Santos MJ, Alzamora AC. The nonpeptide ang-(1-7) mimic ave 0991 attenuates cardiac remodeling and improves baroreflex sensitivity in renovascular hypertensive rats. *Life Sci*. 2013;92:266-275
15. Bertagnolli M, Casali KR, De Sousa FB, Rigatto K, Becker L, Santos SH, Dias LD, Pinto G, Dartora DR, Schaan BD, Milan RD, Irigoyen MC, Santos RA. An orally active angiotensin-(1-7) inclusion compound and exercise training produce similar cardiovascular effects in spontaneously hypertensive rats. *Peptides*. 2013;51C:65-73
16. Fraga-Silva RA, Savergnini SQ, Montecucco F, Nencioni A, Caffa I, Soncini D, Costa-Fraga FP, De Sousa FB, Sinisterra RD, Capetini LA, Lenglet S, Galan K, Pelli G, Bertolotto M, Pende A, Spinella G, Pane B, Dallegrì F, Palombo D, Mach F, Stergiopoulos N, Santos RA, da Silva RF. Treatment with angiotensin-(1-7) reduces inflammation in carotid atherosclerotic plaques. *Thromb Haemost*. 2014;111

17. Yang JM, Dong M, Meng X, Zhao YX, Yang XY, Liu XL, Hao PP, Li JJ, Wang XP, Zhang K, Gao F, Zhao XQ, Zhang MX, Zhang Y, Zhang C. Angiotensin-(1-7) dose-dependently inhibits atherosclerotic lesion formation and enhances plaque stability by targeting vascular cells. *Arterioscler Thromb Vasc Biol.* 2013;33:1978-1985
18. Qi Y, Zhang J, Cole-Jeffrey CT, Shenoy V, Espejo A, Hanna M, Song C, Pepine CJ, Katovich MJ, Raizada MK. Diminazene aceturate enhances angiotensin-converting enzyme 2 activity and attenuates ischemia-induced cardiac pathophysiology. *Hypertension.* 2013;62:746-752
19. Haber PK, Ye M, Wysocki J, Maier C, Haque SK, Battle D. Angiotensin-converting enzyme 2-independent action of presumed angiotensin-converting enzyme 2 activators: Studies in vivo, ex vivo, and in vitro. *Hypertension.* 2014
20. Fraga-Silva RA, Costa-Fraga FP, Murca TM, Moraes PL, Martins Lima A, Lautner RQ, Castro CH, Soares CM, Borges CL, Nadu AP, Oliveira ML, Shenoy V, Katovich MJ, Santos RA, Raizada MK, Ferreira AJ. Angiotensin-converting enzyme 2 activation improves endothelial function. *Hypertension.* 2013;61:1233-1238
21. Hendricks NJ, Matsumoto AH, Angle JF, Baheti A, Sabri SS, Park AW, Stone JR, Patrie JT, Dworkin L, Cooper CJ, Murphy TP, Cutlip DE. Is fibromuscular dysplasia underdiagnosed? A comparison of the prevalence of fmd seen in coral trial participants versus a single institution population of renal donor candidates. *Vasc Med.* 2014;19:363-367
22. Kuczera P, Wloszczynska E, Adamczak M, Pencak P, Chudek J, Wiecek A. Frequency of renal artery stenosis and variants of renal vascularization in hypertensive patients: Analysis of 1550 angiographies in one centre. *J Hum Hypertens.* 2009;23:396-401
23. van Helvoort-Postulart D, Dirksen CD, Nelemans PJ, Kroon AA, Kessels AG, de Leeuw PW, Vasbinder GB, van Engelshoven JM, Hunink MG. Renal artery stenosis: Cost-effectiveness of diagnosis and treatment. *Radiology.* 2007;244:505-513