Risk factors of chronic kidney disease progression: Dutch cohort studies

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Chapter 9 –

Discussion

In this thesis we aimed to investigate the role of a variety of risk factors for chronic kidney disease (CKD) progression, mainly focused on patients at high cardiovascular risk. These risk factors encompass both traditional cardiovascular risk factors, as well as lifestyle factors such as obesity and diet, acute kidney injury, and the role of low birth weight. Research on (modifiable) risk factors in cardiovascular compromised patients is relatively scarce. The trends of population ageing and unhealthier lifestyle, lead to a growing population with CKD, which is the rationale of this thesis. Additionally, we assessed the beneficial renal effects of use of cholesterol-lowering medication (statins) for secondary prevention. Globally, statins are among the most prescribed drugs, also in CKD patients. We therefore not only investigated the effect of statins as a whole, but additionally aimed to assess whether certain types of statins may be preferable from a renal perspective. This chapter briefly discusses the main findings of this thesis, and incorporates these into clinical implications and recommendations.

MAIN FINDINGS IN CONTEXT

In **Chapter 2, 3, and 4**, we investigated the role of different risk factors on CKD progression in post-myocardial infarction (MI) patients of the Alpha Omega Cohort. In **Chapter 2** we showed that diabetes and hypertension are the strongest drivers for the accelerated kidney function decline in post-MI patients, which in is line with previous publications.[1–3] To a lesser extent, obesity and smoking were also associated with faster kidney decline. Most importantly, we found that patients with a higher compared to lower number of cardiovascular risk factors have a faster progression of kidney function decline. Post-MI patients with optimally treated cardiovascular risk factors had an annual eGFR decline of 0.90 mL/min/1.73m^2, which is comparable to the general population. In contrast, patients with at least three cardiovascular risk factors had a three-fold faster rate of kidney function decline. In **Chapter 3** we investigated the role of obesity more in detail. Both body mass index and waist circumference were associated with faster eGFR decline. Our results underline the importance of a healthy weight, as recommended in current guidelines, and argue against the so called "obesity paradox".[4] The obesity paradox propagates for a variety of chronic diseases that overweight and obesity compared to normal weight lead to improved survival.[5, 6] However, this phenomenon is based on selection bias, and such results should be interpreted with caution.[7] In **Chapter 4** we showed a strong linear relation between protein intake and faster eGFR decline. Our findings are in agreement with current KDIGO guidelines, which recommend

to limit daily total protein intake to <1.30 g/kg body weight, and restrict intake to 0.60-0.80 g/kg per day in patients with diabetes or CKD stage 4B or higher.[4] Our results were in line with results from the Singapore Chinese Health Study.[8] However, in several Dutch and US community based cohorts no association was found between dietary protein intake and CKD risk.[9-11] Importantly, participants in the latter studies were relatively healthy and 20 years younger than the post-myocardial infarction patients described in this thesis. We found comparable associations for dietary protein from animal and plant sources, thereby not supporting the hypothesis that protein derived from plant sources is healthier compared to animal sources.

In **Chapter 5** we showed that for type 1 diabetes patients with end-stage renal disease (ESRD) a simultaneous pancreas-kidney transplantation led to 15% and 33% reduced 10-year mortality compared to those who received only a kidney transplantation from a living or deceased donor. Previous studies showed that a simultaneous pancreas-kidney transplantation is associated with improved survival compared to a kidney transplant alone from a deceased donor.[12, 13] However, only a few studies compared survival after a simultaneous pancreas-kidney transplantation with a kidney transplant alone from a living donor. Although a recent study showed that the 10-year survival benefit for a pancreas-kidney transplantation compared to a kidney transplant alone from a living donor is clinically irrelevant,[14] the majority of studies showed that short-term survival was similar and long-term survival was better in patients receiving both a pancreas and kidney, compared to a kidney from a living donor.[15] Moreover, using regional differences in preferred treatment, we showed that a treatment strategy that preferably transplants both a pancreas and kidney resulted in a 44% reduced 10-year mortality compared to a treatment strategy that favoured transplantation of a kidney alone.

In **Chapter 6** the renal effects of statins were examined, in a pair-wise and network meta-analysis of randomized controlled trials. In pair-wise meta-analysis, pooling all statins, statins compared to control treatment led to a 0.57 mL/min/1.73m^2 reduction in annual eGFR decline. These figures are comparable to another meta-analysis from 2016.[16] Likewise, statins compared to control led to a small reduction in proteinuria after one year, although in this case there was significant evidence for publication bias. In a subsequent network meta-analysis, generally all statins performed better than control, though confidence intervals were very wide and substantially overlapped. Due to a lack of power, it is therefore impossible to draw firm conclusions of superiority of certain statins regarding CKD progression.

In **Chapter 7** we addressed the potential of two novel biomarkers, TIMP-2 and IGFBP7, for the early diagnosis of acute kidney injury (AKI) in patients

undergoing elective cardiac surgery. Cardiac surgery may cause an episode of AKI, which increases the risk of CKD and mortality. We found that both biomarkers were at most of minor added value in the early prediction of AKI after elective cardiac surgery.

In **Chapter 8** we investigated the Brenner hypothesis, in relation to kidney function.[17] According to this hypothesis individuals with low compared to normal birth weight develop less glomeruli, making them more susceptible to develop CKD later in life. In the Netherlands Epidemiology of Obesity (NEO) study, we found no evidence of an association between self-reported birth weight and kidney function at middle age. Two-sample Mendelian randomization analyses, using a genetic score for birth weight, showed a 3.8 mL/min/1.73m^2 lower kidney function per 500 gram genetically lower birth weight at middle age in the NEO study.[18] In two-sample Mendelian randomization analyses in 133,814 individuals from the CKDgen consortium, we found that each 500 gram genetically decreased birth weight was non-significantly associated with a 1% lower eGFR.[19] We thus concluded that the effect of low birth weight on kidney function at middle age is small. Our results are different from a meta-analysis of 31 studies, showing that low birth weight was associated with a 70% higher risk to develop CKD.[20] Importantly, the included studies consisted of highly selected populations, not representative for the general population. The HUNT-2 study explored the association between birth weight and kidney function in 7457 individuals aged 20-30y, and measured birth weight accurately, using birth weight registry data.[21] They found a relatively small effect of low birth weight only in men, which disappeared after adjustment for maternal factors. Importantly, all previous studies were observation cohort studies, and were therefore sensitive to confounding. Our study was the first to use Mendelian randomization analyses to address the association between birth weight and kidney function.

Limitations and strengths of this research

In each chapter the main study limitations and strengths are reported. In the current section, we therefore report the general limitations of the research described in this thesis, and a brief overview of strengths per chapter.

Limitations

First, observational research is sensitive to confounding, resulting from differences in patient characteristics with regard to the exposure of interest. Apart from the analyses in **Chapter 6**, all chapters report the results of observational cohort studies. Due to the non-randomized nature of observational studies, patients in one stratum of the exposure are usually not similar to, or

exchangeable with, patients in another stratum. Lack of exchangeability may lead to incorrect results, because any association between the exposure and outcome of interest may in fact be wholly or partly explained by other factors for which groups based on the exposure differ.[22] The effect of such confounding may be reduced by adjusting the analyses for factors that differ across strata of the exposure, and are also associated with the outcome. However, one can never be sure that all confounding is corrected, e.g. because confounders may have been unmeasured or unknown, or they may have been measured imprecisely. In the present thesis, although all reported research was adjusted for the most important confounding factors, we can therefore not exclude the possibility of any residual confounding. Notably, often observational research is more feasible than performing a randomized controlled trial, in terms of time, costs, and ethics. For example, investigating the effect of obesity or low birth weight is no possible in a randomized controlled trial. It is both practically infeasible and ethically objectionable to allocate the exposure "obesity" or "low birth weight" to a patient group. Therefore, the limitations of observational research should be acknowledged balanced against the benefits.

Second, for several chapters we measured data by questionnaires. In **Chapter 4** validated food frequency questionnaires were used to measure dietary intake. In **Chapter 8** birth weight was collected using questionnaires. Furthermore, data on comorbidity, medical history, and medication use is often collected by questionnaires. Though in general questionnaires yield valid results, depending on the questions they are sensitive to measurement error, recall bias, and missing data. In **Chapter 8** we showed that a large proportion of birth weight data was missing. Using food frequency questionnaires to measure food intake may result in under- or overestimation of food intake.[23] However, when conducting a study including many patients, questionnaires are often preferred and may even be the only possibility, both in terms of time, cost-effectiveness and logistics.

Strengths

In **Chapter 2, 3, and 4** we used data from the Alpha Omega Cohort, which is the largest post-myocardial infarction patient cohort to date. Additionally, due to very strict data collection, the number of missing data was negligible. The Alpha Omega Cohort therefore provided an ideal opportunity to investigate potential modifiable risk factors for kidney function decline in patients at high cardiovascular risk. In **Chapter 5** we used registry data of all type 1 diabetes patients requiring renal replacement therapy in the Netherlands over a 30-year follow-up period. The nationwide nature of the data prevented any selective in- or exclusion of patients. Moreover, we used regional differences in treatment

strategies within The Netherlands. Using an intention-to-treat like analysis, we aimed to maximally reduce the influence of confounding. In **Chapter 6** we used state-of-the-art methodology to conduct a network meta-analysis on the effect of statins on renal outcomes, to provide evidence on which statins should be preferred from a kidney perspective. Network meta-analyses incorporate both direct and indirect evidence of all connections in a treatment network, to provide a hierarchical overview of all treatments. In **Chapter 7** we used data of a large cohort of elective cardiac surgery patients, to investigate the potential value of two novel urinary biomarkers in the prediction of acute kidney injury. In addition to estimating discrimination of both biomarkers univariably, as is done in most current publications, we assessed the added value to simple multivariable models. Finally, in **Chapter 8**, we used three different methods and three different data sources, to investigate the effect of low birth weight on kidney function at middle age. For two analyses we used as instrumental variable for birth weight an instrument based on 59 genetic variants that were associated with birth weight in a previously published genome-wide association study.

CONCLUSIONS, IMPLICATIONS AND RECOMMENDATIONS

Cardiovascular and lifestyle risk factors in cardiovascular patients

With this thesis, we provide nuance in the general idea that post-myocardial infarction patients have compared to the general population have a two-fold faster kidney function decline. We showed that, depending on the number of risk factors, kidney function decline may be comparable to the average decline in the general population. We furthermore found that diabetes and hypertension are the most important drivers of CKD progression. Therefore, we recommend that optimization of these, and other, risk factors is important to prevent CKD progression. We showed that obesity is a risk factor rather than a protective factor in post-MI patients, which underlines current KDIGO guidelines recommending an ideal body mass index lower than 25 kg/m^2.

Furthermore, dietary protein restriction is a potentially effective preventive intervention. Importantly, since nutrients are part of a dietary pattern, simply reducing intake of one component such as protein is unrealistic. Randomized controlled intervention studies evaluating a dietary pattern as a whole, for a timespan of several years, would provide the most solid evidence on the effectiveness of dietary interventions. Notably, such studies are complex. First, defining the interventions is difficult, since these may vary from person to person. More importantly, since blinding of participants is difficult

to maintain, there may be contamination in the control groups. Patients are willing to participate in the study to become healthier, increasing the chance that patients randomized to the control intervention will change their behaviour nonetheless.[24] Finally, since dietary pattern is difficult to change, compliance may pose a problem, especially over longer periods of time. Despite these challenges in the design of nutritional intervention studies, nutrition is warranted to play an increasingly important role in the prevention of chronic (cardiovascular) diseases.

Finally, we showed that prescribing a statin for cardiovascular prevention, led to slower annual eGFR decline and a reduction of proteinuria. However, we cannot provide a strong recommendation as to which statin should preferably be prescribed to attenuate CKD progression. In line with our results, current KDIGO guidelines recommend a statin in all non-dialysis dependent CKD patients 50y and older with an eGFR lower than 60 mL/min/1.73m^2, or at least 30 mg/g albuminuria, independent of serum cholesterol levels.[25] Finally, KDIGO guidelines do not specify which statin should be used, which is underlined by our study.[25]

Transplantation in type 1 diabetes patients with ESRD

We showed that type 1 diabetes mellitus patients with renal failure who received a simultaneous pancreas-kidney transplantation had the best survival, compared to patients who received a kidney transplantation alone. The difference was most pronounced compared to a kidney from a deceased donor, but 10-year survival in pancreas-kidney transplanted patients was also 15% better compared to patients receiving a living donor kidney. In general, a treatment strategy with a preference for simultaneous pancreas-kidney transplantation, rather than a kidney transplantation alone, resulted in a 44% and 31% lower 10- and 20-year mortality risk. For type 1 diabetes patients with ESRD, a simultaneous pancreas-kidney transplantation should therefore be the first choice.

Prediction of AKI

The relatively novel urinary biomarkers TIMP-2 and IGFBP7 appeared of minor value in the prediction of AKI in a relatively healthy ICU population of elective cardiac surgery patients. Our results do not argue against the use of these biomarkers in general ICU populations. However, in elective cardiac surgery patients, both markers poorly predicted AKI stage 2 or 3, and at best moderately predicted the need for renal replacement therapy after surgery. Most importantly, on top of a multivariable model of clinical parameters, the added value of either biomarker was limited. Future studies should focus on

the value of these biomarkers as part of a biomarker panel, which may more adequately predict AKI, or on their potential role in other populations at high risk of AKI.

Birth weight and kidney function

Finally, in middle-aged individuals of the general population, low birth weight has only a small effect on kidney function in middle aged individuals. It is plausible that in middle-aged individuals other risk factors or diseases during life have had more impact on kidney function than a person's birth weight. Low birth weight may be more important as a risk factor for CKD in younger patients. Given our results, low birth weight is at most weakly associated with kidney function at middle age, and as such may be irrelevant for risk stratification of middle-aged adults with regards to kidney disease.

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