Optimal cardiovascular treatment strategies in kidney disease: casual inference from observational data

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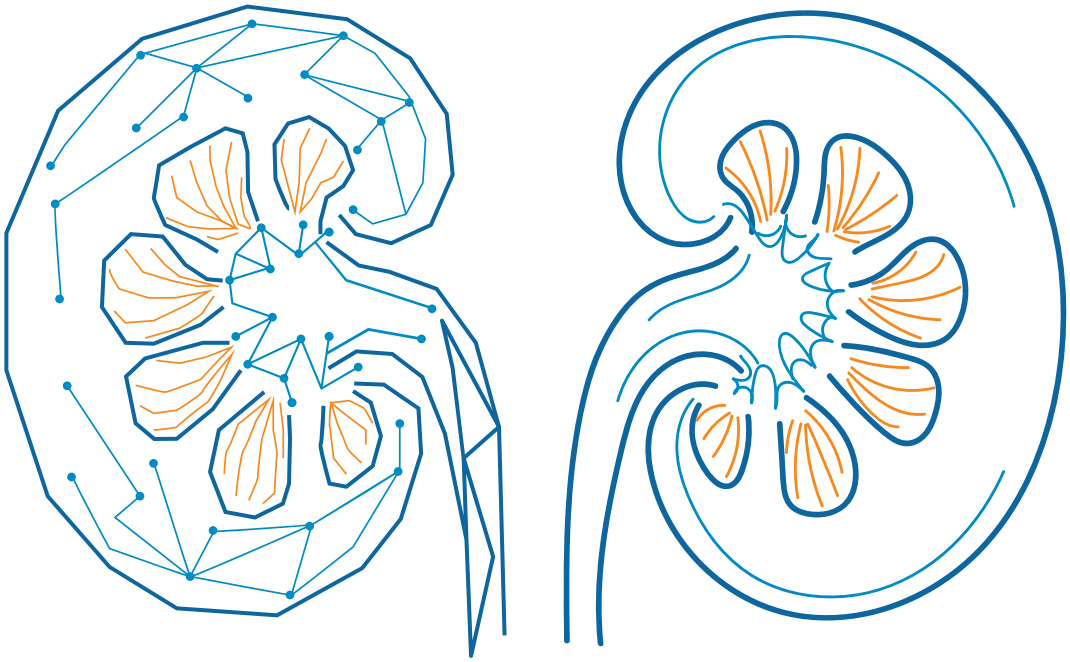

CHAPTER 1

General introduction and outline of the thesis

The kidneys in health and disease

The kidneys play a central role in body homeostasis. They remove waste products and toxins from the body, regulate fluid balance, acid-base homeostasis, bone mineralization and blood pressure and produce hormones such as erythropoietin and renin (1-5). Each kidney contains around 1 million nephrons, the functional units of the kidney, which consist of a glomerulus and a renal tubule. The glomerulus is a network of capillaries (small blood vessels), which are surrounded by Bowman's capsule. Blood is filtered across the capillary walls into Bowman's space, which yields a filtrate of water, small solutes and low-molecular-weight proteins (6). Next, this ultrafiltrate is modified along the tubular segments of the nephron, where reabsorption and secretion take place. Although the kidneys produce only 1.5 L of urine per day, they receive 20% of the cardiac output and form 180 L of ultrafiltrate daily.

Current international guidelines define chronic kidney disease (CKD) as a heterogeneous group of disorders leading to decreased kidney function or abnormalities in kidney structure (proteinuria or abnormalities in urinary sediment, histology or imaging) that are present for at least 3 months (7). The glomerular filtration rate is the recommended form of assessment for overall kidney function. It can be measured via exogenous markers (e.g. using iohexol), but is usually estimated based on creatinine in routine clinical practice (eGFR) (8). Proteinuria is preferably measured by the urinary albumin-to-creatinine ratio. Based on these two measurements, CKD is classified into six stages of eGFR and three stages of proteinuria (**Table 1**) (7). When eGFR is less than 15 ml/min/1.73m^2 (CKD G5), a person has kidney failure and kidney replacement therapy (either dialysis or kidney transplantation) is necessary for survival.

The classification and definition of CKD are based on large-scale epidemiological studies, which have shown strong, graded and consistent associations between eGFR or albuminuria with adverse outcomes, which are independent of age, sex, ethnicity or traditional cardiovascular risk factors (9-17). The lower the kidney function and the higher the albuminuria, the higher the risk for mortality, cardiovascular events, or end stage kidney disease. The association between CKD and cardiovascular abnormalities was first described in 1836 by the British physician Richard Bright (18). Since then, many epidemiological studies have confirmed and extended this finding. For instance, 50% of patients with CKD G4-5 have cardiovascular disease (19, 20). Compared with individuals with a normal kidney function, the risk for cardiovascular mortality is twice as high for individuals with CKD G3, and three times as high for individuals with CKD G4, even after adjustment for traditional cardiovascular risk factors and albuminuria (10, 17). Furthermore, the risks of heart failure, stroke, peripheral arterial disease, coronary artery disease and atrial fibrillation are roughly doubled in patients with an eGFR <60 ml/min/1.73m^2

compared to individuals with a preserved kidney function (21-25). Similarly, the risk of cardiovascular death is doubled in individuals with albuminuria of 300 mg/g, compared with individuals with normal albuminuria (10, 17).

Chronic kidney disease (CKD) is a significant public health problem. Estimates suggest that CKD affects around 850 million individuals (26), corresponding to 8-16% of the worldwide population (27-30). In developed countries the main causes of CKD are hypertension and diabetes, which are increasing in prevalence due to the rise in obesity (31). Like other chronic diseases, the prevalence of CKD increases with age. Among individuals above the age of 60 years the prevalence exceeds 20%, and among those older than 70 years, 35% have CKD (32). CKD was responsible for 1.2 million deaths and 35.8 million disability-adjusted life-years worldwide in 2017 (27, 28), and leads to significant healthcare costs (33, 34). Investigating the effectiveness of therapies to reduce the cardiovascular burden and prevent progression to kidney failure in CKD patients is therefore of high importance.

Table 1: CKD classification based on eGFR and albuminuria.

				Persistent albuminuria categories, description, and ACR range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g	30-300 mg/g	≥300 mg/g
GFR categories, description, and eGFR range (ml/min/1.73m²)	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Data from the KDIGO CKD Work Group clinical practice guidelines (7). Colors indicate the prognosis by eGFR and albuminuria category. Green, low risk; Yellow, moderately increased risk; Orange, high risk; Red, very high risk.

Management of chronic kidney disease

Currently, optimal management of CKD patients includes cardiovascular risk reduction (lipid and blood pressure management), drug dosage adjustments and avoidance of nephrotoxic agents, as well as treating complications that may arise due to CKD, such as anemia, electrolyte abnormalities and mineral and bone disorders (35). Renin-angiotensin system inhibitors (RASi; i.e. ACE inhibitors and angiotensin-II receptor blockers) are indicated in patients with diabetes and ACR >30 mg/g and in all CKD patients with ACR >300 mg/g. In patients with diabetes, glycemic control can delay CKD progression and adjustment of oral antihyperglycemic agents may be necessary. Recently, sodium-glucose cotransporter-2 inhibitors have been shown to reduce major adverse cardiovascular events and in particular CKD progression and heart failure in various patient populations, including individuals with diabetes, heart failure or CKD (36-39).

Promises and perils of "real-world evidence" in CKD

To establish the causal effects of treatments and guide decision making, we prefer data from randomized controlled trials (RCT). Due to randomization, treatment allocation depends only on chance, and not on the decision of the clinician or patient. Any differences in outcomes that are larger than we could expect from chance can then be interpreted as a causal effect of the treatment itself.

Unfortunately, evidence from randomized trials is not always available, which has led to uncertainty about the effects of therapies in patients with kidney disease. One of the reasons for this is that fewer trials are conducted in nephrology, and the quality of trials is often lower compared with other specialties (40-42). Second, patients with kidney disease have historically been excluded from many RCTs in the field of cardiovascular disease or cancer (43-45), and continue to be underrepresented in recent cardiovascular trials, especially those with CKD G4-5 (46). Besides the fact that few RCTs are performed, they also have a number of important limitations. RCTs are costly, may be unethical to conduct, and can take a long time to complete (47). Furthermore, they are often conducted in selected populations, whereas a much wider population is likely to receive these treatments in clinical practice (48, 49). For instance, a meta-analysis of 186 trials conducted in the dialysis population showed that trial participants are younger, have a different pattern of comorbidities and a lower mortality rate than the overall population of dialysis patients (48). Findings from RCTs can therefore not be readily translated to effectiveness and safety profiles of patients from routine clinical practice. Lastly, the number of clinical questions greatly outpaces the number of RCTs that can be performed.

For these reasons, there is growing interest from regulators, insurance companies and physicians in using observational data to supplement trial evidence and aid in clinical decision-making (50, 51). Vast amounts of observational data are generated each day as patients interact with the healthcare system and are stored in the form of administrative claims databases, electronic health records and registries (52). These data sources can be used relatively fast and at a fraction of the cost of RCTs to study how treatments work in routine clinical care. Indeed, many observational studies are published every year and there has been a trend towards greater reliance by regulators on such "real-world evidence" (RWE), which is defined as evidence coming from data sources other than the traditional highly controlled RCTs (53, 54). In 2019, 60% of new drug approvals to the US Food and Drug Administration (FDA) had observational evidence as part of their submission, of which 12% was considered essential evidence (55).

However, drawing causal conclusions from routinely collected healthcare data is not an easy task. Because treatment has not been randomized, there can be systematic differences between the treatment groups, known in the epidemiology literature as confounding (56). After all, in observational data we just observe what happens in every day care, where treatments are often given to individuals with a worse prognosis, or in the case of preventive treatments to health-seeking individuals. In addition to this confounding, selection bias (57-59) and information bias (60, 61) can also affect the validity of observational studies. Because data are widely available while the knowledge to properly analyse these is not, observational studies can easily yield associations that are precise (due to the large sample size) but not causal. A notable example is the debacle surrounding postmenopausal hormone therapy and coronary heart disease (62). Observational studies had shown that women using postmenopausal hormone replacement therapy had a markedly lower risk of coronary heart disease compared with women who did not use these medications (63, 64). As a consequence, this therapy was widely promoted in postmenopausal women to prevent heart disease (65, 66). However, a subsequent large randomized trial showed completely opposite results: a 24% increased risk of coronary heart disease (67). This example illustrates that making mistakes in observational data is not without costs and can have grave consequences (62).

Fortunately, in the past four decades there have been tremendous developments in the field of causal inference, the discipline that investigates the assumptions, study designs and methods that are needed to draw causal conclusions based on data (68). A theoretical framework for causality has been developed such that we are able to ask better causal questions, and novel methods increase the validity of findings from observational data (47, 69, 70). Our understanding of how the various biases arise and how they can be addressed has vastly improved. At the same time, databases are becoming larger and more detailed, including longitudinal patient-level information on medications, lab tests, procedures and diagnoses. As the flourishing of the field of causal inference coincides with the upcoming of big data, this combination provides immense opportunities to contribute valuable evidence for decision making in nephrology.

Aims and outline

The aim of this thesis is to answer a number of clinical questions on the effectiveness and safety of treatments in the field of kidney disease by using observational data from routine clinical care in combination with causal inference methods. This thesis is structured in two parts. In **part I** we explore the methodological aspects of using routinely collected observational data to establish causal effects. In **part II** we apply state-of-the-art statistical and epidemiological methods to answer a number of pressing clinical questions in nephrology.

Part I: Methodological considerations

A number of biases threaten the validity of observational studies that try to estimate the causal effects of treatments. Some of these biases can be prevented by applying a sound study design, whereas others need to be addressed in the statistical analysis. In **Chapter 2** we specifically discuss confounding, prevalent user bias, immortal time bias, missing data and measurement error and methods to handle these biases, including active comparator new user designs, target trial emulation, propensity scores, marginal structural models and multiple imputation.

Different methods exist to adjust for measured confounding in the statistical analysis. **Chapter 3** discusses the merits and caveats of propensity scores, a commonly used method to adjust for confounding. We discuss four types of propensity score methods, including propensity score matching, stratification, adjustment and weighting, and illustrate these with a clinical example. We also provide guidance when to choose propensity score methods versus conventional multivariable regression. In **Chapter 4** we point out immortal time bias in a published observational study which aimed to estimate the causal effect of metformin on kidney outcomes, and discuss how this could have been prevented with an appropriate study design or statistical analysis.

Part II: Clinical applications

RASi (i.e., ACE inhibitors and angiotensin-II receptor blockers) are widely prescribed drugs that are a cornerstone in the treatment of hypertension, heart failure and proteinuric kidney disease. Acute increases in creatinine (reflecting a drop in kidney function) are often observed after initiation of RASi, but the clinical significance of such increases is controversial. **Chapter 5** investigates the significance of this acute creatinine increase by studying the association between the magnitude of increase and the outcomes mortality, cardiovascular events and end-stage kidney disease using standard multivariable regression to adjust for confounding. Since guidelines recommend to monitor creatinine, we also investigate which proportion of patients receive this monitoring.

We do not know the best antihypertensive medications to use in patients with advanced CKD (stage 4/5), because they have not been included in many trials. In **Chapter 6** we compare the effects of RASi versus calcium channel blockers, two of the most widely used antihypertensive drugs in this population. An active comparator new user design in combination with propensity score weighting is applied to reduce confounding and other biases. Since ample evidence is available on the efficacy of RASi in moderate CKD (stage 3) from randomized trials, we replicate our analyses in a positive control cohort of patients with stage 3 CKD to compare the trial findings against our observational estimates.

Between 10-15% of patients with heart failure have advanced CKD. Although β-blockers are a cornerstone in the treatment of patients with heart failure with reduced ejection fraction, we do not know whether they are effective in individuals with advanced CKD, a population at an extremely high risk of complications and (cardiovascular) death. **Chapter 7** investigates the effect of β-blocker use in patients with heart failure and advanced CKD on cardiovascular and all-cause mortality and heart failure hospitalization. Results are reported for reduced, midrange and preserved ejection fraction. Similar to the previous chapter, a positive control cohort of heart failure patients with moderate CKD is used to benchmark the observational findings against trial evidence.

Small single-center studies have suggested that stopping RASi in patients with advanced CKD can postpone dialysis. However, few studies have addressed the cardiovascular and kidney effects of this decision. In **Chapter 8** we therefore investigate the effect of stopping versus continuing RASi in patients with advanced CKD on mortality, cardiovascular events and kidney replacement therapy using the target trial emulation framework and the cloning, censoring and weighting method. In addition, results are replicated by modelling RASi as a time-varying exposure using a marginal structural model.

Chapter 9 investigates the optimal kidney function to initiate dialysis with respect to mortality and cardiovascular outcomes using the target trial emulation framework. Although the randomized IDEAL trial showed no differences in outcomes between early and late dialysis initiation, only two treatment strategies were compared, and the realized eGFR values were within a narrow range (7.2 vs. 9.0 ml/min/1.73m^2). As a randomized trial testing many different treatment strategies is unfeasible, observational data need to be used to answer this question. Since this question involves dynamic treatment strategies a cloning, censoring and weighting approach is used. We also investigate the influence of lead time bias, selection bias and immortal time bias in previous observational studies. The last two chapters calculate restricted mean survival time to easily interpret how long an average patient would live by following a particular treatment strategy.

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