Chapter 1

Introduction and scope of the thesis
Introduction

“Tonight, I’m launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes – and to give all of us access to the personalized information we need to keep ourselves and our families healthier” (President Barack Obama, State of the Union Address, January 20, 2015).

In October 2016 the median age of the population of the European Union has reached the marking point of 80 years for the first time in its history. Although the average human life expectancy has increased over the past decades and is still on the rise, healthy and quality years do not keep up with this trend. Around the age of 60, the prevalence of chronic diseases increases and pose a burden on quality of life of individual patients and health care expenditures. The most common chronic diseases are cardiovascular and renal including diabetes. Cardiovascular disease is the global leading cause of death. To reduce the burden of chronic disease, the Worldwide Health Organization has launched a campaign to combat cardiovascular disease which is the number one health priority for 2016.[1] From this prospective, the explosive global increase of diabetes, with its associated cardiovascular and renal disease, is highly alarming.[2]

In the past two decades the prevalence of diabetes has been continuously increasing and it is becoming one of the greatest contributors to the global burden of human disease.[3] Worrying is the fact that end-stage renal disease, which is an important microvascular consequence of diabetes, causes more deaths than various types of cancer such as prostate and long cancer according to USRDS data from 2008. Forecasts for 2030 indicate that the number of patients who are diagnosed with diabetes will exceed 550 million, and the number of patients who require renal replacement therapies will more than double.[4]

In diabetic population significant progress has been made in the treatment of cardiovascular disease leading to a marked decrease in the incident rates lower-extremity amputation, acute myocardial infarction and stroke, the incidence of end-stage renal disease did not change over time (Figure 1).[5] These data undoubtedly illustrate the high risk and unmet need in diabetic kidney disease.
Figure 1: In patients with type 2 diabetes the incidence in Myocardial Infarction, Stroke and Amputation but not ESRD decreases over time. Adapted from Gregg et.al. New Engl. J. Med 2014

Part 1: Individual drug response to established interventions

What could be the explanation for the high unmet need and the failure to decrease the incidence of ESRD? One explanation could be that many patients with diabetic kidney disease do not respond to the guideline recommended therapy. Intervention in the renin-angiotensin-aldosterone system (RAASi) is the mainstay of renoprotective therapy in both diabetic and non-diabetic patients. ACE-inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs) have been shown on a population level to slow the progression of kidney function decline. However, the response to RAASi is highly variable between individual patients (Figure 2).

Figure 2: Cumulative distribution of changes in albuminuria after 6 months treatment with losartan or placebo in the RENAAL trial. The figure shows that approximately 70% of patients during losartan therapy show a reduction in albuminuria and 30% an increase. Adapted from Heerspink et.al. NDT 2016

Thus, while clinical trials and clinical practice guidelines recommend a “one-size-fits-all” approach based on broad population averages from clinical trials, only a proportion of patients in daily practice follows the average patient and benefit from ACEIs and ARBs.
Indeed, a marked variability in response exists when looked at the variability of eGFR slope during treatment with the angiotensin receptor blocker losartan. This variability is mirrored by a similar variability in the 6-month albuminuria response to losartan. These data illustrate that approximately one-third of patients do not respond at all to the cornerstone of treatment. Accordingly, a large proportion of patients remains at a high risk to progress to ESRD.

Despite many scientists, clinicians, and professional medical associations recognize that individual patients show a wide variability in their response to many drugs, questions have been raised as to whether drug response variability represents a true response variability or is merely the result of methodological flaws in the analysis and interpretation of clinical trials or technical measurement error. For instance, Senn questions the consistency of individual response and stated that the existence of individual response “is founded on a largely untested assumption”. Additionally, Bell suggested that most of the variation in individual treatment responses are due to measurement error in the risk factor (for example blood pressure) rather than representing a true variability in treatment response.

These concerns are directly applicable to the treatment of diabetes and kidney disease as well. Albuminuria is often used to monitor disease progression and response to ACEIs and ARBs. However, albuminuria is highly variable within an individual over time and although the change in albuminuria is measured to monitor the efficacy of the drug one could question whether changes in albuminuria after start of renoprotective therapy represents a true drug response or are merely a results of biological or measurement variations in albuminuria over time.

**Part 2: Individual drug response to novel interventions**

In addition to developing strategies for more effective drug use of well-established drugs like RAASi to decrease the burden of diabetic kidney disease, novel drugs are also desired to improve the current therapeutic armamentarium. In this respect, sodium-glucose co-transport inhibitors (SGLT2i) are of particular interest. SGLT2i lower plasma glucose through blockade of SGLT-2 transporters in the proximal tubule of the kidney. Inhibition of SGLT2 transporters results in increased urinary glucose and sodium excretion. As a result of increased glucose excretion, HbA1c decreases by approximately 0.7%. Perhaps more important than the metabolic effects are the non-glycemic effects induced by SGLT2i. SGLT2i exert important reductions in blood pressure, body weight, and uric acid. In addition, post-hoc analyses from clinical trials have suggested that SGLT2i ameliorate glomerular hypertension and decrease albuminuria, although most data on the albuminuria lowering effects are derived from post-hoc analyses. The pattern of eGFR changes seen with SGLT2 inhibitors (i.e. acute fall in eGFR and stabilization of long-term renal function) are reminiscent
of ACEIs and ARBs. Inhibitors of the RAAS reduce intraglomerular pressure through efferent arterial vasodilatation, leading to reductions in intraglomerular pressure and resulting in nephroprotection.[13] The initial decline observed with SGLT2 inhibitors is also most likely reflecting a reduction in intra-glomerular pressure. Unlike RAASi, SGLT2 inhibitors cause afferent vasoconstriction secondary to restoration of tubuloglomerular feedback.[14] The hemodynamic effects of SGLT2i may also explain the reduction in albuminuria, although non-hemodynamic pathways such as suppression of oxidative stress, inflammation, and fibrosis may also reduce albuminuria. However, distinguishing hemodynamic and non-hemodynamic pathways is complex given the lack of human data.

As mentioned above, various studies have suggested that SGLT2 inhibitors appear to decrease albuminuria but all studies were based on post-hoc analyses in selected subgroups of patients.[15-17] A prospective randomized controlled clinical trial is required to confirm (or refute) effects of SGLT2 inhibitors on albuminuria.

At least as important as characterizing the effect on albuminuria, is to understand how individual patients respond to SGLT2 inhibition. There is little information about individual responses to SGLT2 inhibition, but it is likely that some patients show a good response whereas others do not. Moreover, SGLT2 inhibitors exert effects on multiple renal and cardiovascular risk markers, as described above. There are no data how the individual patient responds in each of these risk markers and whether a beneficial response in HbA1c, the main target parameter, is linked to beneficial responses in other cardiovascular risk markers, such as blood pressure or body weight. Previous studies on this topic with ACEi and ARBs have suggested that the response in blood pressure, the main target parameter for ACEi and ARBs, is uncoupled from the response in albuminuria, potassium and other renal and cardiovascular risk markers. In other words, a patient can have a reduction in blood pressure but not in albuminuria or vice versa, a reduction in albuminuria but not in blood pressure.[18-20] This suggests that the ultimate responder patient is the patient with a beneficial response in all cardiovascular risk markers. Thus in the context of precision medicine, it is crucial to understand how individual patients respond to SGLT2 inhibitors in terms of the multiple effects on cardiovascular risk markers. To date, there are no data available on this topic.
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Scope of the thesis

Precision medicine is an emerging research area which has gained significant interests in various areas of medicine. In the area of diabetes and kidney disease there is, relative to other areas such as oncology, limited data available on the degree of individual response variability and strategies as to how to improve individual response variability to current and new interventions. This thesis aims to address these aspects in order to improve the treatment of diabetes and kidney disease with a focus on the individual patient.

The first part of the thesis starts in chapter two with an assessment whether the response variability to renoprotective treatment is reproducible or represents random measurement variability. If it is a true reproducible response variability, it is relevant to determine how therapy resistance to established renoprotective interventions can be overcome. Therefore, chapter three seeks to identify strategies to enhance the response in patients not responding to renoprotective drugs. Part 1 of this thesis mainly focuses on ACEIs and ARBs as these are guideline recommended drugs and most data are available for these agents. However, other interventions, such as NSAIDs, diuretics, or dietary sodium restrictions, are also considered.

The second part of the thesis focuses on the individual drug response to the SGLT2i dapagliflozin. Chapter four describes the result of a randomized controlled cross-over trial in patients with diabetes and high albuminuria already being treated with an ACEI or ARB. The study, IMPROVE trial, uses a unique design in which half of all patients are exposed twice to dapagliflozin in order to assess in a prospective fashion whether the individual drug response is reproducible upon re-exposure of the same patient to dapagliflozin. In chapter five we assessed whether therapy resistance in albuminuria response to ACEi or ARB therapy could be overcome by the SGLT2i dapagliflozin. Chapter four and five focus on the variation in response between individual patients.

In chapter six, a pooled analysis of multiple phase 3 trials with dapagliflozin was conducted and analyses the response to dapagliflozin on multiple cardiovascular risk markers according to renal function. Moreover, the individual response in multiple cardiovascular risk markers within an individual is also assessed.

This thesis ends by summarizing the conducted studies and providing future perspectives in order to change the current treatment paradigm from a “one-size-fits-all” to an individual focused therapy approach.
References


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