Epidemiological aspects on renal impairment in patients with type 2 diabetes

Studies based on data from the Swedish National Diabetes Register

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Cover illustration: An Abstract painting of colliding Pancreas and Kidney with diabetes and renal impairment, by Ferechte Kazerouni

This is to all the women and men whom has made the difference in this world by devotion, passion and sincerity

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ABSTRACT

Diabetes is a leading cause of renal impairment (RI) and indication of the need for renal replacement therapy in many parts of the world. Albuminuria and RI are the two main forms of diabetic kidney disease. The overall aims of this thesis were to explore risk factors and consequences associated with albuminuria and RI in patients with type 2 diabetes (T2D), as well as to assess the relationship between blood pressure variables, cardiovascular events and all-cause mortality. The studies were based on data from the Swedish National Diabetes Register (NDR).

Study I followed 3,367 patients with T2D who did not exhibit signs of albuminuria or RI from 2002 to 2007 in order to evaluate the risk of developing them. A total of 20% of patients developed albuminuria and 11% developed RI. Among those with one of the two conditions, 62% had normoalbuminuric RI. Development of albuminuria or RI was independently associated with advanced older age, high systolic blood pressure and elevated triglycerides. The independent risk factors were obesity, poor glycemic control, smoking, low HDL- cholesterol and male gender for developing albuminuria, as opposed to elevated plasma creatinine at baseline and female gender for developing RI. Different sets of risk factors were associated with development of RI and albuminuria. High body mass index (BMI) was an independent risk factor for RI when renal function was calculated with the MDRD equation, while low BMI was a risk factor with when the Cockcroft-Gault equation was used. In other words, the equation chosen to estimate renal function is important when

interpreting data. Thus, patients with T2D face have distinct risk factors for albuminuria and RI.

Study II included 94,446 patients with T2D, including 19,330 with RI. The majority with T2D and RI were normoalbuminuric. Normoalbuminuric RI may be partly due to treatment with RAAS blockade, however, that only 25% of the patients with normoalbuminuric renal impairment had received RAAS blockade. The possibility that other underlying pathophysiological mechanisms play a role should be further evaluated.

Study III followed 33,356, and Study IV 27,732, patients with T2D and RI in 2005-2011 in order to evaluate correlations associations between systolic blood pressure (SBP) and all-cause mortality. We observed U-shaped relationships between various aspects of SBP and the risk of all-cause mortality. The greatest risks for cardiovascular events (CVEs) and all-cause mortality were at the highest and lowest blood pressure intervals. SBP of 135-139 and diastolic blood pressure (DBP) of 72-74 mmHg showed the lowest risks of CVEs and all-cause mortality.

Adjusting for presence of albuminuria or chronic heart failure did not significantly alter the results. A reduction in SBP during follow-up was associated with a greater risk of all-cause mortality.

In summary, this thesis shows that obesity and other traditional cardiovascular risk factors are associated with development of albuminuria and RI in patients with T2D. We also found that normoalbuminuric RI is common in patients with T2D. Finally, both the highest and lowest blood pressure intervals are associated with greater risks of cardiovascular events and all-cause mortality.

SAMMANFATTNING PÅ SVENSKA

Diabetisk njurskada är vanligaste orsaken till svår njursvikt och behov av dialysbehandling eller njurtransplantation i Sverige. Antalet nya patienter med typ 2-diabetes och behov av dialysbehandling eller njurtransplantation har fördubblats de senaste femton åren.

De viktigaste kända och behandlingsbara riskfaktorerna för diabetisk njurskada är högt blodsocker, högt blodtryck och rökning. Behandlingsbara riskfaktorer för försämring av njurfunktionen är högt blodtryck, förekomst av proteinuri/albuminuri, högt blodsocker, förhöjda lipider och rökning. Nedsatt njurfunktion innebär en ökad risk för insjuknande i hjärtkärlsjukdom och död hos patienter med diabetes.

Denna avhandling omfattar fyra observationsstudier baserade på data från Svenska Nationella Diabetesregistret (NDR). I studierna har vi undersökt förekomsten av njurskada och njurfunktionsnedsättning/njursvikt hos patienter med typ 2 diabetes i Sverige, vilket är av betydelse för bl.a. planering av diabetes- och njursjukvården. Vi har också identifierat kända, och potentiellt nya riskfaktorer för utveckling av njurskada vid typ 2 diabetes. Slutligen har vi också studerat sambanden mellan olika blodtrycks mått och insjuknande i hjärt-kärlsjukdom och död hos patienter med typ 2 diabetes och nedsatt njurfunktion.

I denna avhandling har vi kunnat visa att:

Albuminuri (äggvita i urinen) inte alltid föregår utveckling av nedsatt njurfunktion hos patienter med typ 2 diabetes, vilket talar för att mätning av enbart albuminuri inte räcker som mått på risk för utveckling av njurskada hos patienter med typ 2 diabetes.

Majoriteten av patienter med typ 2 diabetes och nedsatt njurfunktion har ingen albuminuri. De faktorer som var kopplade till utveckling av både albuminuri och nedsatt njurfunktion var hög ålder, höga blodfetter (triglycerider) och högt blodtryck. Manligt kön, bristande blodsockerkontroll, övervikt och lågt HDL-kolesterol var kopplade till utveckling av enbart albuminuri medan kvinnlig kön och ett högt kreatininvärde vid studiens början var kopplade till enbart utveckling av nedsatt njurfunktion.

Övervikt är en stark riskfaktor för utveckling av njurskada vid diabetes och att denna effekt kan inte enbart förklaras av kopplingen mellan övervikt och andra kända riskfaktorer som högt blodtryck och högt blodsocker.

Bara en fjärdedel av patienter med nedsatt njurfunktion utan albuminuri hade behandling med så kallad RAAS-blockerare som minskar albuminuri. Andra orsaker till nedsatt njurfunktion utan albuminuri är t ex åldrande och andra samtidiga sjukdomar som t ex högt blodtryck.

Hos patienter med typ 2 diabetes och nedsatt njurfunktion, var ett systoliskt blodtryck på 135-139 och ett diastoliskt blodtryck 72-74 mmHg kopplat till den lägsta risken för hjärt-kärlhändelser och död.

Risken för hjärt-kärlhändelser och död ökade med både ett högt och ett lågt blodtryck. Ett systoliskt blodtryck lägre än 130 mmHg och en minskning av det systoliska blodtrycket under studien var förknippade med en ökad dödlighet hos patienter med typ 2 diabetes och nedsatt njurfunktion.

Det är viktigt att påpeka att dessa fynd gäller observationsstudier och inte studier där blodtrycket aktivt behandlats till en viss blodtycksnivå. I observationsstudier kan ett lågt blodtryck även bero på andra samtidiga sjukdomar som t ex hjärtsvikt vilket kan bidar till resultaten. I detta sammanhang är det därför intressant att vi inte såg någon koppling mellan antalet blodtryckssänkande läkemedel som patienterna hade vid studiens början och risken för död vid studiens avslutning.

Sammanfattningsvis, visar vi i denna avhandling att traditionella kardiovaskulära riskfaktorer, inklusive fetma, är förknippade med utveckling av albuminuri och nedsatt njurfunktion hos patienter med typ 2 diabetes. Dessutom bekräftar vi att nedsatt njurfunktion utan samtidig albuminuri är vanligt hos patienter med typ 2 diabetes. Både höga och låga blodtryck är förknippade med högre risk för hjärt-kärlhändelser och död.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Afghahi H, Cederholm J, Eliasson B, Zethelius B, Gudbjörnsdottir S, Hadimeri H, Svensson MK. Risk factors for the development of albuminuria and renal impairment in type 2 diabetes- the Swedish National Diabetes. Nephrol Dial Transplant. 2011 Apr;26(4):1236-43.

II. Afghahi H, Miftaraj M, Svensson AM, Hadimeri H, Gudbjörnsdottir S, Eliasson B, Svensson MK. Ongoing treatment with RAAS-blockade does not predict normoalbuminuric renal impairment in a general type 2 diabetes population. Journal of Diabetes and its Complications. 2013 May-Jun;27(3):229-34.

III. Afghahi H, Svensson MK, Pirouzifard M, Eliasson B, Svensson AM. Optimal blood pressure levels and major cardiovascular events in patients with type 2 diabetes and renal impairment. Diabetologia. 2015 Jun;58(6):1203-11.

IV. Svensson MK, Afghahi H, Franzén S, Björck S, Gudbjörnsdottir S, Svensson AM, Eliasson B. Decreased in systolic blood pressure during follow up is associated with an increased risk of all-cause mortality in patients with type 2-diabetes and renal impairment-a nationwide longitudinal observational study of 27,732 patients based on the Swedish National Diabetes Register (NDR). Submitted

CONTENT

ABBREVIATIONS

BMI	Body mass index
BP	Blood Pressure
C-G	Cockcroft–Gault equations
CHD	Coronary heart disease
CHF	Chronic heart failure
CI	Confidence Interval
CKD	Chronic kidney disease
CVD	Cardiovascular disease
CVE	Cardiovascular events
DBP	Diastolic blood pressure
ESRD	End-stage renal disease
GFR	Glomerular filtration rate
eGFR	Estimated glomerular filtration rate
HR	Hazard ratio
MDRD	Modification of Diet by in Renal Disease equation
RI	Renal impairment
SBP	Systolic Blood pressure
T1D	Type 1 diabetes
T2D	Type 2 diabetes
UAER	Urinary albumin excretion rate

1 INTRODUCTION

1.1 Definitions and measurements

1.1.1 Diabetes and its long-term complications

Diabetes is characterized by chronic hyperglycemia, which is caused by defective insulin secretion or action [1]. Several pathogenic processes may be involved in the development of diabetes, ranging from autoimmune destruction of the insulin-producing β cells in the pancreas – primarily in type 1 diabetes (T1D) – to abnormalities that produce resistance to insulin action in the liver and other peripheral tissue – primarily in type 2 diabetes (T2D) [2]. The various forms of diabetes are classified in accordance with their etiology. T1D and T2D are the most common [2]. T1D occurs frequently in children and adolescents, whereas T2D predominates in adults, but no age is exempt from either form [3]. T2D accounts for 90-95% of cases [4]. The World Health Organization (WHO) diagnostic criteria are 1) two consecutive values of fasting plasma glucose ≥ 7.0 mmol/L or a 2-hour glucose value of ≥ 11.1 mmol/L following an oral glucose tolerance test (OGTT), or 2) a glycated hemoglobin A1c (HbA1c) value of ≥ 6.5% (48 mmol/mol). No single test is currently available for the diagnosis of T2D, but obesity, other signs of insulin resistance, metabolic syndrome or family history and a high-risk ethnic background are grounds for suspecting the disease [5].

Chronic hyperglycemia is associated with organ damage, particularly to the eyes, kidneys, nervous system (microvascular complications) and arteries (macrovascular complications). Such long-term complications seriously affect life expectancy and quality of life (QoL). Renal dysfunction (albuminuria and renal impairment) can progress to end-stage kidney disease and need for dialysis or transplant [6-9]. Renal dysfunction and end-stage kidney disease in

combination with diabetes both have a major impact on life expectancy and quality of life [10, 11].

1.1.2 Prevalence and incidence of diabetes

Estimates are that the prevalence of diabetes worldwide is currently 382 million (8.3%) and will increase to 592 million (10%) by 2035 [12]. The most important demographic factor impacting the prevalence of diabetes is the increase in the above-65 population [13, 14]. An estimated 4-6% of Swedes have diabetes [15] and 90% of them have T2D [16]. A population-based study in Laxå showed that incidence was relatively stable from 1988 to 2001 [17]. A recent nationwide study found that the prevalence of pharmacologically treated diabetes had increased in 2005-2013 from 42 to 51 per 1,000 men and 30 to 35 per 1,000 women, while incidence had decreased by 0.6% per year in men and 0.7% per year in women. Total prevalence is low compared to other countries [18].

1.1.3 Chronic kidney disease and renal impairment

Chronic kidney disease (CKD) includes abnormalities of kidney structure or function for three months or longer that affect health and manifest in various ways, depending upon etiology and severity [19]. Most causes of CKD are chronic and irreversible – treatment aims at slowing progression to end-stage renal disease [20] .

1.1.4 Measurement and estimation of renal function

Glomerular filtration rate (GFR) is a universal marker of renal function [21]. The most accurate methods for measuring GFR are inulin, iothalamate, iohexol, 51Cr-EDTA and other exogenous tracers. Because such approaches are cumbersome, time-consuming and relatively expensive, they are not used in epidemiological studies. As a result, several equations that estimate GFR (eGFR) on the basis of endogenous biomarkers have been developed [22-25]. The most used proxy for GFR is serum creatinine concentration. Serum creatinine is inversely related to renal function. Several creatinine-based equations to estimate eGFR are used in current clinical practice, epidemiological studies and treatment guidelines.

Serum cystatin C, which has been proposed as a better marker of GFR, is closely related to clearance of inulin, 51Cr EDTA and iohexol [26]. Cystatin C is not affected by muscle mass to the same degree as creatinine [27, 28] It is influenced, however, by steroid medication and other non-GFR related factors [29, 30]. Cystatin C has been evaluated as a marker of GFR in various populations, including patients with diabetes [31-33]. The American Diabetes Association (ADA) recommends measurement of serum creatinine, as a marker of renal function, at least once a year in all adults with diabetes, regardless of urinary albumin excretion [34].

1.1.5 Creatinine-based equations for estimating renal function

The most used creatinine-based equations are Cockcroft Gault (C-G), Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease and Epidemiology (CKD-EPI).

Cockcroft Gault (C-G)

C-G estimates creatinine clearance, which is a function of GFR and tubular secretion of creatinine, overestimating GFR by 10-40%, especially in subjects with impaired renal function. C-G is not currently used in clinical practice [35, 36].

Modification of Diet in Renal Disease (MDRD)

MDRD is the most popular equation for estimating GFR worldwide. It includes age, gender, and race as indicators of muscle mass [37]. MDRD was developed and validated on an adult U.S. population consisting primarily of Caucasians and African Americans [38, 39], but later a large bias has been found in for exemple Asian populations [40, 41]. The equation has been shown to systematically underestimate GFR in subjects with reduced renal function, leading to in overdiagnosis of CKD, particularly among young Caucasian women and the elderly [42, 43], while overestimating GFR in obese subjects [44].

Chronic Kidney Disease and Epidemiology (CKD-EPI)

CKD-EPI is more accurate for estimating renal function in subjects with normal or near-normal GFR, as well as chronic heart failure [45, 46].

Swedish Lund–Malmö revised

In addition to the above equations, the Swedish Lund–Malmö revised creatinine-based equations (LM Revised) are more accurate than MDRD or CKD-EPI in patients with suspected or known RI [47]. The finding, however, remains to be validated in patients with diabetes and RI.

This thesis generally used MDRD to estimate renal function, given that it is the most commonly used creatinine-based equation. Cystatin C values were not available

1.1.6   Quantifying albuminuria

Increased urinary excretion of albuminuria is an early clinical sign of renal damage or dysfunction in people with diabetes, as well as an important risk factor for progression of RI and development of ESRD [48, 49], cardiovascular disease (CVD) and all-cause mortality [50-52]. Albuminuria can be monitored qualitatively with a dipstick or quantitatively by assessing timed urine collections or spot samples for urinary albumin – albumin-creatinine ratio (ACR) [53, 54]. Current guidelines recommend that patients with T2D be monitored annually for urinary albumin as soon as diabetes is diagnosed [34]. Microalbuminuria is defined as a urine albumin excretion rate (UAER) of 20-200 µg/min or spot sample of 3-29 mg/µmol albumin-creatinine. Macroalbuminuria is defined as an UAER of > 200 µg/min or a spot sample of ≥30 mg/µmol albumin-creatinine. The results must be found in two out of three consecutive urine specimens, preferably collected over a period of six months. The urine should be sterile, and other causes of increased albumin excretion rate – such as various renal or urogenital conditions, physical activity and fever – should be ruled out. Obtaining 24-hour or overnight urine specimens may be cumbersome in clinical practice. Early morning spot samples are recommended instead [54]. Table 1 describes quantification and staging of albuminuria.

Table 1. Quantification and staging of albuminuria

Stages of albuminuria	Urinary albumin excretion rate (UAER) mg/24 hours	Albumin-to-creatinine ratio (ACR)		Description
		mg/mmol	mg/g	
A1	< 30	< 3	< 30	Normal to mild
A2	30-300	3-30	30-300	Moderate
A3	> 300	> 30	> 300	Severe

1.1.7 Staging of chronic kidney disease (CKD)

International guidelines have been adopted for the classification and staging of CKD in order to facilitate clinical trials, monitoring and treatment [20]. The five stages of CKD are based primarily on measured GFR or estimates as shown in Table 2 [55].

Table 2. Staging of Chronic Kidney Disease (CKD) according to measured or estimated glomerular filtration rate (GFR).

Chronic kidney disease (CKD) stages	Glomerular filtration rate (GFR) (ml/min/1.73 m2)	Description
G1	> 90	Normal or high
G2	60 to 89*	Mildly decreased
G3a	45 to 59	Mildly to moderately decreased
G3b	30 to 44	Moderately to severely decreased
G4	15 to 29	Severely decreased
G5	< 15	Kidney failure

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate. *In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD. Add D if treated by dialysis and add T to any of the stages if the patient has a kidney transplant.

The recent KDIGO guidelines combine CKD stage and albuminuria category to better predict the progression of renal impairment [55] as shown in Table 3.

Table 3. Risk of progression of chronic kidney disease (CKD) by combining chronic kidney disease (CKD) stage and albuminuria category classification.

Chronic kidney disease (CKD) stage*	Albuminuria category**		
	A1	A2	A3
G1	Low	Moderate	High
G2	Low	Moderate	High
G3a	Moderate	High	Very high
G3b	High	Very high	Very high
G4	Very high	Very high	Very high
G5	Very high	Very high	Very high

*as defined in Table 1, ** as defined in Table 2

In the absence of albuminuria or hematuria, patients with Stage 1 and 2 (G1 and G2) do not meet the formal criteria for CKD [20]. Because normal aging is associated with a decrease in renal function (GFR) and a slight increase in albuminuria, the role of pathological processes has been a controversial subject. Current KDOQI guidelines attribute all persistent reduction of GFR or elevation of albuminuria to CKD [20]. Regardless of GFR levels, a kidney transplant recipient is defined as having CKD [20].

1.2   Type 2 diabetes and renal disease

1.2.1   Incidence and prevalence of renal disease in patients with type 2 diabetes

Diabetes increases the risk of developing ESRD by an estimated 10-12 times [7, 10]. T2D is currently the main reason renal replacement therapy, dialysis

or kidney transplant, in many countries [11, 56]. Diabetes is the underlying cause of an estimated 40% or more of all incident cases of ESRD in the United States [10]. The number of Swedes with T2D who start on renal replacement therapy has doubled over the past 15-20 years to approximately 170 (18 per million) (www.snronline.se).

1.2.2 Renal pathology in patients with type 2 diabetes

Pathological lesions associated with T2D and kidney disease are similar to those associated with kidney disease in T1D. The traditional lesions of diabetic kidney disease are diffuse mesangial expansion, diffuse thickened glomerular basement membrane (GBM) and hyalinosis of afferent and efferent arterioles [57, 58]. Diffuse mesangial sclerosis or nodular sclerosis (Kimmelstiel-Wilson lesions) are not common nowadays [59]. Based on electron microscopy, loss of podocytes and hypertrophy is regarded as an early marker [60, 61]. These pathologies are used in a new classification system for diabetic kidney disease: Class I – GBM thickening only; Class II – mild to severe mesangial expansion; Class III – including nodular sclerosis; Class IV – all of the above changes and 50% globally sclerotic glomeruli [62]. In addition to the above glomerular lesions, tubular basement membrane thickening and interstitial fibrosis are strong predictors of the rate of decline of renal function in diabetes [58, 63]. Patients with T2D are usually older and often have hypertension, dyslipidemia or other comorbidities. The fact that the delay from onset of diabetes to diagnosis is often longer among them than among patients with T1D may impact renal pathology [64]. The renal lesions found in patients with T2D are frequently a combination of diabetic lesions, atherosclerosis in the renal arteries and nephrosclerosis. Nephrosclerosis, which develops in the small intrarenal blood vessels, is associated with both aging and hypertension [65, 66]. The renal pathology of patients with T2D is more heterogeneous but

biopsy data are scarce [67, 68]. Studies have shown that the typical pattern of glomerular lesions is less common in patients with diabetes and normoalbuminuric RI than in those with albuminuria [69]. These results are consistent with a more multifactorial pathogenesis of the renal lesions in T2D patients with normoalbuminuric RI [70].

1.2.3 Development of renal disease in patients with type 2 diabetes

Older studies concluded that the rate of decline and loss of renal function in patients with T2D was as much as 6 ml/min per year. With more intensive BP and glycemic control, however, the decline is only 1(-4) ml/min per year, which is almost similar to the general population [71-74]. The progression of kidney disease associated with T2D typically has three stages: microalbuminuria, proteinuria (macroalbuminuria) with declining GFR, and ESRD [75, 76]. Many patients already exhibit renal damage at diagnosis of T2D, and RI is common [77]. This type of renal damage is not regarded as entirely diabetes-related but rather a sign of nephrosclerosis. Normoalbuminuric RI is associated with gradual slower progression of renal impairment, as well as the lower risk of developing ESRD and CVEs compared to albuminuric RI [78].

1.2.4 Albuminuric renal impairment in patients with type 2 diabetes

Albuminuria is a sensitive clinical marker and predictor for identifying the risk of diabetic and non-diabetic RI, ESRD, CVEs and all-cause mortality [50, 79]. But albuminuria does not always precede development of RI in patients with T2D [76]. The risk of CVEs and all-cause mortality increases significantly, even with very low-grade albuminuria and normal GFR [80]. Though the etiology of the strong association between macrovascular complications and albuminuria is not completely understood, one potential, but highly

speculative, mechanism is a reduction of circulating adiponectin [81, 82]. Because adiponectin has been shown to be involved in regulating podocyte function, reduced adiponectin as found in the diabetes could be associated with the development of albuminuria [83].

1.2.5 Normoalbuminuric renal impairment in patients with type 2 diabetes

A total of 10-20% of patients with T2D have normoalbuminuric RI [77, 84, 85]. As shown in Table 4, the majority of patients with T2D and RI are normoalbuminuric [86-91]. The etiology of normoalbuminuric RI in T2D is considered to be multifactorial, including hypertension, aging, obesity and lipid toxicity. Glomerulosclerosis and nephrosclerosis may also contribute [77, 92, 93]. Distinct sets of cardiovascular risk factors have also been associated with the absence of albuminuria in patients with T2D and RI [91, 94], suggesting a more favorable cardiovascular risk profile. The hypothesis is also supported by prospective studies indicating that patients with T2D and normoalbuminuric RI face a lower risk of both CVEs and all-cause mortality [78, 88]. Ongoing RAAS-blockade has been proposed as another underlying reason for normoalbuminuric RI in patients with T2D but does not seem to be the sole explanation [77, 85, 95].

Table 4. Percentage of patients with type 2 diabetes (T2D) and normoalbuminuric or albuminuric renal impairment (RI) in various studies.

First author/year	Numbers of patients (n)	Type of study population	Proportion of normoalbuminuric vs. albuminuric RI* (%)	Women with normoalbuminuric RI (%)
MacIsaac 2004[85]	301	T2D with RI*	39 (61)	56
Rigalleau 2007[84]	89	T2D with RI	17 (83)	66
Ykoyama 2009[88]	3 297	T2D	52 (48)	47
Thomas 2009[86]	3 893	T2D	55 (45)	64
Ito 2010[89]	1 197	T2D	50 (50)	60
Penno 2011[90]	15 773	T2D	57 (43)	66
Mottl 2013[87]	2 798	T2D	52 (42)	58
Boronat* 2014[91]	78	T2D with RI	22 (78)	77

RI defined as eGFR< 60 ml/min/1.73 m^2.

*Included only patients with eGFR < 30 ml/min/1.73 m^2

1.2.6 Risk factors for development of renal impairment and albuminuria in patients with type 2 diabetes

Hyperglycemia is the most important risk factor for development of albuminuria, and intensive glycemic control has shown to reduce the risk. The Action in Diabetes and Vascular Disease (ADVANCE) study found that intensive glucose control (HbA1c 6.5%) reduced the risk of nephropathy by 21% in patients with T2D compared to standard control (HbA1c 7.3%) [96]. The association with hyperglycemia is not as strong for RI as for albuminuria [88, 91]. The importance of hypertension is well documented [97, 98]. Blood pressure control and antihypertensive treatment have been shown to reduce the

incidence of albuminuria [99, 100] and ESRD [101, 102]. Male gender is a risk factor for developing albuminuria [103-105]. Cross-sectional studies, however, have concluded that RI is more common in women, though possibly due to a biased estimate of renal function when using creatinine-based equations [70, 85, 89]. Independent of albuminuria, smoking is associated with a decrease of GFR in T2D patients with normal or near-normal renal function [106, 107]. Dyslipidemia is independently associated with a higher risk of developing RI and albuminuria in patients with diabetes [108, 109]. ApoE abnormalities and Apolipoprotein L1 (APOL1) gene variants have been associated with an increased risk of developing CKD [110-113]. The risk of developing albuminuria and RI is positively correlated with obesity [114, 115].

1.3   Type 2 diabetes and cardiovascular disease

Diabetes involves a 4-5 time higher risk of developing CVEs [116-118]. CVD mortality is 10-20 times higher in patients with RI than age-matched subjects in the general population [119]. Both T2D and RI further increase the risk of all-cause and CV mortality [120, 121]. The excess risk of both all-cause and CV mortality in patients with T2D is positively correlated with the severity of RI [122, 123]. Reduced renal function (eGFR) and albuminuria are predictors of CVEs in patients with T2D. Similarly, higher albuminuria levels are associated with greater risk of CVEs, CV and all-cause mortality in such patients [124-126]. Accelerated atherosclerosis is a plausible mechanism to explain the relationship between albuminuria, RI, CVEs and all-cause mortality [127].

1.3.1 Risk factors for development of cardiovascular disease

Depending on renal status, individual risk factors may have a variety of effects on the risk for CV outcomes. Hyperlipidemia, smoking and glycemic control have a significant impact on the risk for CVEs in patients with albuminuria and normal renal function. Evidence strongly suggests that high blood pressure, both systolic and diastolic, is associated with an increased risk of CVEs in patients with diabetes, either with or without RI. The UK Prospective Diabetes Study (UKPDS) found a 13% reduction of microvascular complications for every 10 mmHg [128]. Intensive treatment of hypertension has also been shown to reduce the risk of both microvascular and macrovascular complications in patients with T2D [129, 130]. High-risk patients seem to experience additional benefits from more intensive antihypertensive treatment [131, 132].

However, both hypertension and hypotension been associated with an increased risk of CVEs and all-cause mortality [133-135]. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study concluded that targeting SBP of 120 mmHg among patients with T2D did not reduce the rate of CVEs (with the exception of stroke) compared with targeting 140 mmHg [136]. The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET), which included patients both with and without diabetes, did not find any benefits for either fatal or nonfatal CVEs (with the exception of stroke) from reducing SBP to below 130 mmHg [137]. The Veterans Affairs Diabetes Trial (VADT) associated DBP below 70 mmHg in patients with T2D with elevated CVD risk [138]. A post hoc analysis of the Irbesartan in Diabetic Nephropathy Trial (IDNT) among patients with T2D and RI identified an increase in all-cause mortality, CVEs and CHF when SBP was lower than 120 mmHg [139]. Based on these data, researchers have described

a J-shaped or U-shaped relationship between BP and the risk of CVEs and all-cause mortality [140, 141]. Comorbidities, especially CHF, are a possible explanation for the increase in risk of CVEs or all-cause of mortality associated with low BP in observational studies. Thus, it is possible that the finding does not reflect antihypertensive treatment [142, 143]. Because the association between hypotension and increased all-cause mortality in patients with moderate to severe RI also stems from an interaction between renal function and atherosclerotic disease, hypotension may be a surrogate marker for comorbidities rather than play a causative role [144]. Intensive BP control was associated with an increased risk of elevated serum creatinine in patients with normal renal function or early stages of diabetic kidney disease [145]. As a result, the target BP in patients with T2D and RI is still under discussion.

The type of dyslipidemia that develops in patients with T2D and RI is characterized by hypertriglyceridemia, normal or elevated LDL-cholesterol, and low HDL-cholesterol [146, 147]. The Study of Heart and Renal Protection (SHARP) associated a combination of simvastatin 20 mg and ezetimibe daily in CKD patients, 23% of whom had diabetes, with a 21% reduction in LDL cholesterol and a 17% reduction in major atherosclerotic events [148]. Treating to New Targets (TNT), which included patients with a history of coronary artery disease (CAD), associated 80 mg of atorvastatin daily with a 32% decrease in CVEs when CKD was also present [149]. Deutsche Diabetes Dialyse Studie (4D) and Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis (AURORA) found, however, that a lipid lowering statin did not significantly reduce CVEs among patients on hemodialysis [150, 151]. The Assessment of Lescol in Renal Transplant (ALERT) study associated fluvastatin with a reduction of cardiac events among kidney transplant patients [152]. The current KDIGO guidelines recommend a lipid lowering statin for

non-dialysis patients with CKD, as well as post-transplant patients who are at risk for CVD but not for CKD patients on hemodialysis [153].

Hyperglycemia is a key risk factor for CVD among patients with diabetes, regardless of whether they have RI [154-156]. The UKPDS study concluded that intensive glycemic control with metformin for 10.7 years modestly reduced the risk of CVD [157]. The ADVANCE study found, however, that intensive treatment (HbA1c 6.5% vs. 7.3%) did not have a significant impact on major CVEs or CV mortality [96]. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study demonstrated that intensive glucose lowering treatment (HbA1c < 6%) did not significantly reduce major CVEs compared to conventional methods (HbA1c 7-7.9%) but increased the risk of mortality [158]. The VADT study among American veterans with T2D found that intensive glycemic control did not have a significant impact on the occurrence of major CVEs [159]. The impact of intensive glycemic control among patients who have severe RI or are on dialysis, as well as the risk of developing CVD has been widely discussed. The finding in observational studies that patients with severe RI face a higher risk of CVD and mortality when their HbA1c is low may be confounded by other factors such as anemia and malnutrition [160].

1.4 Guidelines and treatment recommendations for hypertension with diabetes and renal impairment

Several guidelines that contain treatment recommendations have been issued for patients with diabetes and RI. The Improving Global Outcomes work group (KDIGO) recommends a BP target of < 140/90 mmHg in the absence of albuminuria and < 130/80 mmHg in the presence of albuminuria as a means of reducing the risk of CVD. But the guidelines specify that age, cardiovascular

comorbidities and other factors also should be taken into account [161]. The ADA/EASD guidelines recommend a BP target of 140/90 mmHg for patients with diabetes, or < 130/80 mmHg if there are signs of albuminuria, retinopathy or other end-organ damage [162]. The Joint National Committee (JNC) recommended a BP target of < 140/90 mmHg but did not include patients age 70 or older [163].

RAAS blockade has been proposed as the standard first-line antihypertensive treatment in patients with diabetes and RI [164]. The Effects of Losartan on Renal and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Nephropathy (RENAAL) study found that losartan had significant renal benefits for patients with T2D and nephropathy but that the risk of morbidity and mortality from CVEs was similar to the placebo group [73]. The ONTARGET study concluded that a combination of telmisartan (ARB) and ramipril (ACE inhibitor) for high-risk T2D patients reduced proteinuria but was associated with an increase in major renal outcomes, chronic dialysis or doubling of creatinine [164]. The NEPHRON study did not show that combination therapy (ACEi plus ARB) had a beneficial impact on CVEs, but rather associated it with an increased risk of hyperkalemia and acute kidney injury among patients with diabetic nephropathy [165]. The Diabetes Using Cardio-Renal Endpoints (ALTITUDE) trial associated aliskiren (a direct renin inhibitor) treatment for RI with an increase in hypotension, hyperkalemia, renal failure and nonfatal stroke among T2D patients and was terminated early as a result [166]. The European Renal Best Practice (ERBP) group recently released Clinical Practice Guidelines for the management of patients with diabetes and CKD. The guidelines recommend treatment with an ACEi at the maximum tolerated dose in patients with GFR < 45 ml/min (stage 3b-5) and a cardiovascular indication (heart failure or ischemic heart disease) but not

combining different classes of RAAS blocking agents or direct renin inhibitors) [167].

2 AIMS

The overall aim of this thesis was to explore risk factors for development of albuminuria and RI in patients with T2D, as well as to assess the relationship between various BP variables and the risk of CVEs and all-cause of mortality in patients with T2D and RI.

The specific aims were to:

- Identify clinical risk factors associated with the development of albuminuria and RI in patients with T2D during a 5-year follow-up (Study I)

- Evaluate whether the use of various the MDRD and Cockcroft–Gault equations to estimate renal function – glomerular filtration rate (GFR) – impacts interpretation of data (Study I)

- Examine the prevalence of, and the clinical characteristics associated with, normoalbuminuric RI in an unselected general T2D population (Study II)

- Explore the use and impact of treatment with RAAS blockade in patients with T2D and normoalbuminuric RI (Study II)

- Assess the relationship between BP and risk of CVEs and all-cause mortality in unselected patients with T2D and RI, with and without albuminuria, who are treated in clinical practice (Study III)

- Evaluate the association among BP variables (baseline and time-dependent SBP, as well as change to SBP) during follow-up, along with the risk of all-cause mortality in patients with T2D and RI, with and without CHF (Study IV)
- Evaluate the potential association between the number of antihypertensive medication prescribed at baseline and the risk of all-cause mortality during follow-up in an unselected population with T2D and RI (Study IV)

3 PATIENTS AND METHODS

3.1 Sources of data

The National Diabetes Register (NDR) was the main source of data for all four studies. Studies II, III and IV also included data from the Hospital Discharge Register, the Cause of Death Register and the Prescribed Drug Register. All of them are maintained by Swedish National Board of Health and Welfare.

3.1.1 National Diabetes Register

The purpose of the NDR, which began in 1996, is to improve and ensure the quality of diabetes care. The Swedish Society of Diabetology is responsible for the register. The NDR is supported by the Swedish Diabetes Association and financed mainly by the Executive Committee of National Quality (National Board of Health and Welfare, Swedish Association of Local Authorities and Regions, and Swedish Society of Medicine). Data about patients with diabetes are reported to the NDR by doctors and nurses at primary care centers and medical clinics at least once a year on the basis of regular appointments. Data are transmitted online (www.ndr.nu) or by means of electronic charts and stored in a central database. Reporting to the NDR is not mandatory, but the number of entries has grown steadily from year to year. All medical clinics and more than 90% of primary care centers currently report [168]. As evaluated by previous studies, the data have been shown to be 94% valid (89-97%). The NDR may be linked directly to the Hospital Discharge Register, Cause of Death Register and Prescribed Drug Register.

3.1.2 Hospital Discharge Register

The Hospital Discharge Register, which is part of the National Patient Register, obtains records from each hospital. The physician proceeds from the ICD to code the diagnoses in the patient charts. The register includes the main

diagnosis, length of hospitalization, ward, the cause of any injury, and the codes for any surgery that has been performed. It has enjoyed complete nationwide coverage ever since 1987. The main diagnosis was missing for 1% of cases in 2006, indicating data validity with positive predictive value of 85-95% for most conditions [169].

3.1.3 Cause of Death Register

The Cause of Death Register, which was set up in 1961, covers everyone in the Population Register [170].

3.1.4 Prescribed Drug Register

The Prescribed Drug Register, which started in 2005, includes age, gender and a unique identifier, as well as all prescriptions that have been filled and picked up at pharmacy [171].
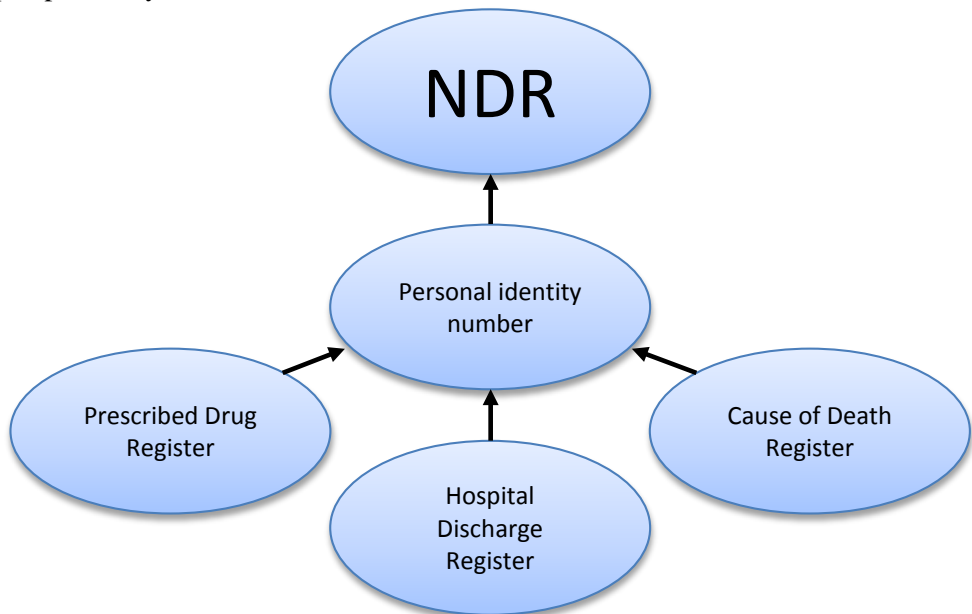
Figure 1. A schematic presentation of the linkages in this thesis between the National Diabetes Register and three other registers.

3.2   Study populations and design

The populations in all four studies were patients with T2D according to an epidemiological definition. Studies II, III and IV included individuals with T2D and RI. RI was defined as eGFR < 60 ml/min/1.73m^2 according to the MDRD equation. Study II was cross-sectional, whereas I, III and IV were longitudinal observational cohort studies. Study I included patients in the NDR who were alive at the end of the period and showed no signs of albuminuria or RI at baseline. Studies II, III and IV included patients who had at least one S-creatinine value entered in the NDR and who had picked up at least two prescriptions or 15 multi-dose dispensations.

Studies II, III, and IV excluded patients with a serum creatinine of < 20 or > 800 µmol/L. Patients with severe RI (eGFR < 15 ml/min/1.73 m^2) were also excluded because they had been reported to the NDR on a limited basis only. Studies III and IV excluded patients with extreme body composition (BMI ≤ 18 or ≥ 45 kg/m^2). There were no age restrictions in Studies II, III, and IV and all of the studies included patients with a history of CVD or CHF. Table 5 shows the study populations, designs and important variables at baseline.

Table 5. An overview of study populations, designs and important variables at baseline.

Study	I	II	III	IV
Study population	T2D without RI	T2D	T2D with RI	T2D with RI
Type of study	Longitudinal cohort	Cross-sectional	Longitudinal cohort	Longitudinal cohort
Number of patients	3 667	94 446 19 330 with RI	33 356	27 732
Baseline years	2002	2009	2005-2007	2005-2007
End of study (years)	2007	2009	2011	2011
Mean follow up (years)	5	-	5.3	4.7
eGFR at baseline (ml/min/1.73m2)*	80±16	88±20 without RI 47±10 with RI	48±9	48±9
Age at baseline	60±8	66±11 without RI 77±9 with RI	75±9	75±9
Male (%)	61	59 without RI 44 with RI	43	43
Diabetes duration at baseline (year)	7.6±6	7.8±7 without RI 11.1±8 with RI	10±8	10±8
Clinical characteristic at baseline	Age, gender, diabetes duration, BMI, smoking, SBP, DBP	Age, gender, diabetes duration, BMI, smoking, SBP, DBP	Age, gender, diabetes duration, BMI, smoking, SBP, DBP	Age, gender, diabetes duration, BMI, smoking, SBP, DBP
Biochemical characteristic at baseline	Creatinine, albuminuria, HbA1c, cholesterol, LDL, HDL, TG	Creatinine, albuminuria, HbA1c, cholesterol, LDL,HDL, TG	Creatinine, albuminuria, HbA1c, cholesterol, LDL, HDL, TG	Creatinine, albuminuria, HbA1c, cholesterol, LDL, HDL, TG
Disease at baseline	CVD**	CVD, CHF, retinopathy	CVD, CHF, retinopathy	CVD, CHF, retinopathy
Medication at baseline	Antihypertensive	Antihypertensive, glucose lowering, anticoagulants/platelets, lipid lowering	Antihypertensive, glucose lowering, lipid lowering	Antihypertensive, glucose lowering, lipid lowering
History of CVD (%)	20**	18 without RI 34 with RI	33	31
History of CHF (%)	-***	5 without RI 20 with RI	15	14
Statistics	χ^2 test Univariable and multivariable logistic regression	Linear and logistic regression	Unadjusted and adjusted Cox-regression, spline functions	Unadjusted and adjusted Cox-regression, spline functions
Outcomes	Prevalence and risk factors for albuminuria and RI with in pts with T2D	Prevalence of normoalbuminuric T2D with or without RAAS-blockade	BP and risk of CVEs and all-cause mortality	Change of SBP and risk of all-cause mortality

*According to MDRD

**Included only the diagnoses of coronary heart disease and stroke

***Data on previous history of CHF were not included

3.3 Definitions of main variables

3.3.1 Type 2 diabetes (T2D)

T2D was defined as reported treatment with diet only, oral glucose lowering agents only, or onset of diabetes at age 40 or older and treatment with insulin either alone or combined with oral glucose lowering agents [1].

3.3.2 Renal impairment (RI)

RI was defined as eGFR < 60 ml/min/1.73m^2 according to the MDRD equation – 175 × [plasma creatinine (μmol/L)/88.4] × age for men and 175 × [plasma creatinine (μmol/L)/88.4] × age × 0.742 for women [37]. In study I Cockcroft–Gault was also calculated as [140 − age × weight (kg) × 1.23/plasma creatinine (μmol/L)] for men and [140 − age × weight (kg) × 1.23 × 0.85/plasma creatinine (μmol/L)] (eCrCl) for women to define renal function [35].

3.3.3 Clinical and laboratory variables

Body mass index (BMI, kg/m^2) was calculated as weight/height^2. A smoker was defined as one or more cigarettes per day, or a pipe, within the past three months. The Swedish standard for BP recording is the average (mmHg) of two supine readings (Korotkoff I–V) with a cuff of an appropriate size following at least 5 minutes of rest. Hypertension was defined as treatment with antihypertensive medications or SBP ≥ 140 mmHg or DBP ≥ 90 mmHg. Laboratory analyses were performed locally. HbA1c was calibrated with the HPLC Mono-S method and converted to IFCC standard values with the following formula: HbA1c (DCCT) = [0.923 × HbA1c (Mono-S) + 1.345]; R2 = 0.998. LDL cholesterol values were calculated with Friedewald's formula: LDL cholesterol = total cholesterol − HDL cholesterol − (0.45 × triglycerides) if triglycerides < 4.0 mmol/L. Microalbuminuria was defined as UAER 20–200 μg/min, and macroalbuminuria as > 200 μg/min in two out of three consecutive tests within one year.

3.3.4 Cardiovascular disease, chronic heart failure and retinopathy

ICD-10 was used to define CVD and diabetic retinopathy [172, 173]. CVD was defined as composite of coronary heart disease (CHD), stroke or peripheral arterial disease (PAD), whichever came first. CHD was myocardial infarction (MI) (ICD-10 code I21), unstable angina (ICD-10 code I20.0), percutaneous coronary intervention or coronary artery bypass grafting. Fatal CHD was defined as ICD-10 codes I20–I25. Stroke was defined as non-fatal or fatal cerebral infarction, intracerebral hemorrhage or unspecified stroke (ICD-10 codes I61, I63, I64 and I67.9). PAD was defined as ICD-10 codes 173, I70.2, I73.1, I73.9, and I79.2. CHF was defined as ICD-10 code I50. Diabetic retinopathy was defined as ICD-9 codes 250.5 and 362.0 and ICD-10 codes H36.0, E10.3, E 11.3 and E14.3.

3.4 Statistical methods

3.4.1 General comments on study design

All of the studies used conventional statistical and epidemiological methods to address associations and covariate adjustments. All of them were observational in nature. Study I, III and IV were longitudinal observational cohort studies and II was a cross-sectional study.

Cross-sectional (or prevalence) studies: data are collected for a group of subjects all at once rather than over time. Surveys and polls are generally cross-sectional [174].

Cohort studies: the exposure variable is assessed at baseline and subjects are followed over time to monitor development of the end-point. They are sometimes referred to as prospective studies. Many of them are designed on

the basis of past information and described as longitudinal, retrospective or historical [175, 176].

3.4.2 Statistical methods
Study I

In order to follow albuminuria and RI over time, univariable and multivariable logistic regressions for each risk factor were performed as a means of estimating both unadjusted and adjusted odds ratios (ORs). Linear regression was used to analyze the relationship between two continuous variables.

A linear regression model describes the linear relationship of the outcome (dependent) variable to the predictor variable (independent variable). A multiple/multivariable linear regression analysis permits estimation of the linear effect of the independent variable on a dependent variable or outcome after controlling for the confounding effect of other variables or covariates [177, 178].

A univariable or multivariable logistic regression analysis describes the relationship between an independent variable and a dichotomic dependent or dummy variable [179].

The OR is the likelihood that a patient has been exposed to the risk factor divided by the likelihood that a control has been exposed [179].

Study II

To estimate risk factors associated with normoalbuminuric RI in T2D patients, currently (or not) under treatment with RAAS blockade, unadjusted and

adjusted univariable and multivariable logistic regression analyses were performed.

Study III

The relationship between SBP, DBP, pulse pressure and mean arterial pressure and the risk of CVEs and all-cause mortality were estimated with an adjusted time dependent cox regression model and predicted hazard ratios (HRs) with 95% CIs. Spline functions with nine knots and 95% CIs were also used to estimate the nonlinear relationship between SBP, DBP and the risk of CVEs.

A Cox proportional hazard model is a regression technique for simultaneously determining the impact of several risk factors on survival. The model can be used to assess the risk of each independent variable relative to the outcome variable, adjusted for the effect of all other variables in the equation [180].

A spline function is a complex statistical method for continuously specifying the correlation of independent variable X with dependent variable Y. Spline functions are formed by joining polynomials at fixed points called knots [181, 182].

Study IV

The associations of the baseline, time-updated mean and the change in SBP between the last two observations and the risk of all-cause mortality was evaluated in patients with T2D and RI, with or without a history of CHF, using a Cox proportional hazards regression model while adjusting for CV risk factors and antihypertensive treatment. The impact of the number of antihypertensive medications at baseline on the risk of all-cause mortality was also estimated using a Cox regression model.

A smoothing spline function with 3 degrees of freedom was used to estimate the influence of time-updated SBP, change in SBP between the last two observations and risk of all-cause mortality.

The study used time-updated mean SBPs. This type of analysis follows the mean SBP of each participant until the individual events. Time-updated values were chosen in order to reduce or eliminate the influence of known or unknown confounders such as age or comorbidities on SBP over time and thereby minimize error and bias. A simplified illustration of time-updated mean SBP appears below.
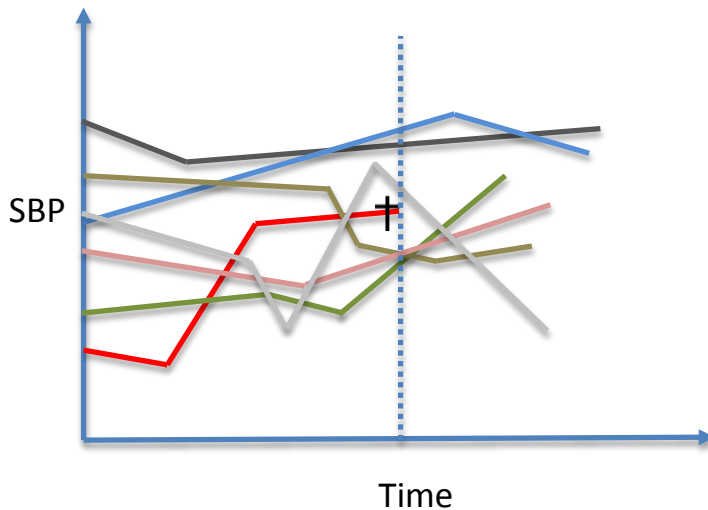
Figure 2. Simplified illustrations of time-updated1 SBP. Each colored line represents a patient. Red represents patients who died. The mean values of SBPs in all patients were followed until the patient in red died (blue streak line).

SAS versions 9.1 to 9.4 were employed to perform the statistical analyses for each study.

Ethical considerations

All patients approved entry of their data in the NDR. Each participant was entitled to request that the data be corrected or deleted at any point, as well as to be informed about how they had been used. The participants were notified that researchers would have access to the data. They did not, however, consent to any specific study. Identifying risk factors, as well as assessing associations between them and outcomes on an aggregate cohort level, was not deemed to be a violation of privacy. NDR stores data securely by means of unique usernames and passwords for each medical center.

The Regional Ethical Review Board at the University of Gothenburg approved the studies.

4 RESULTS

Key findings

Study I – risk factors for development of albuminuria and RI

A total of 3,667 T2D patients without albuminuria or RI at baseline were followed for 5 years. At the end of the period, 729 (20%) patients had developed albuminuria (4% per year) and 407 (11%) had developed RI (2.2% per year). A total of 16% of albuminuria patients had developed RI. The majority of patients developed normoalbuminuric RI, 6-7% after 5 years, as shown in Table 6.

Table 6. Development of albuminuria and RI in patients with T2D after 5-year follow-up (n= 3667).

	Albuminuria	Renal impairment (MDRD)[d]	Renal impairment (eCrCl)[e]
Total	729 (19.9%)	407 (11.1%)	241 (6.7%)
Albuminuria[a]	-	117 (3.1%)	76 (2.1%)
Microalbuminuria[b]	597 (16.3%)	84 (2.3%)	55 (1.5%)
Macroalbuminuria[c]	132 (3.6%)	33 (0.8%)	21 (0.6%)
Normoalbuminuric RI	-	290 (8.0%)	165 (5.6%)

[a]UAER 20–200 μg/min. [b]UAER > 200 μg/min. [c]Microalbuminuria or macroalbuminuria.
[d]eGFR according to MDRD. [e]Estimated creatinine clearance according to Cockcroft–Gault

The risk of developing both albuminuria and RI increased with age, high triglycerides, high SBP and antihypertensive treatment (Tables 7 and 8). Male gender, high HbA1c, high BMI, smoking and low HDL cholesterol were associated with a greater risk of developing albuminuria alone (Table 7). Female gender and high creatinine at baseline were associated with a greater risk of developing RI alone (Table 8).

Table 7. Adjusted odds ratios (95% CI) for baseline variables significantly associated with development of albuminuria after 5-year follow-up (n=3667).

Variables	OR	P-value
SBP (mmHg)	1.25 (1.15–1.37)	< 0.001
HbA1c (DCCT, %)	1.23 (1.13–1.33)	< 0.001
Age (years)	1.27 (1.16–1.40)	< 0.001
Female gender	0.65 (0.55–0.79)	< 0.001
Smoker (%)	1.50 (1.21–1.86)	< 0.001
BMI (kg/m2)	1.13 (1.04–1.24)	0.0064
Triglycerides (mmol/L)	1.12 (1.02–1.22)	0.016
HDL-cholesterol (mmol/L)	0.90 (0.82–0.99)	0.045

The odds ratio (OR) for each variable was adjusted for all other variables. Continuous variables were increased per 1 SD.CI, confidence interval. SBP; systolic blood pressure, BMI; body mass index.

Table 8. Adjusted odds ratios (95% CI) for baseline variables associated with the development of RI (eGFR < 60 mL/min/1.73 m^2 according to MDRD) at 5-year follow-up (n=3667).

Variable	OR	P-value
SBP (mmHg)	1.25 (1.15–1.37)	0.003
HbA1c (DCCT, %)	1.23 (1.13–1.33)	< 0.001
Age (years)	2.00 (1.75–2.28)	< 0.001
Female sex	4.03 (2.97–5.48)	< 0.001
Creatinine (μmol/L)	2.11 (1.80–2.46)	< 0.001
BMI (kg/m2)	1.19 (1.06–1.33)	0.0026
Triglycerides (mmol/L)	1.20 (1.07–1.34)	0.0013

The odds ratio (OR) for each variable was adjusted for all other variables. Continuous variables were increased per 1 SD.CI, confidence interval. SBP; systolic blood pressure, BMI; body mass index.

High BMI was associated with an increased risk of developing RI according to the MDRD equation. When RI was defined according to the Cockcroft-Gault (C-G) equation, however, low BMI was associated with an increased risk of developing RI. The adjusted multivariable analysis associated each 5 kg/m^2 increase on BMI with an OR 1.13 (95% CI 1.04-1.24) higher risk of developing albuminuria and an OR 1.16 (95% CI 1.04–1.31) risk of RI according to the MDRD equation.

Study II – clinical and biochemical characteristics of T2D and RI patients, with or without albuminuria

A total of 16,322 T2D patients in this observational cross-sectional study had RI. A total of 10,111 (62%) of them were normoalbuminuric, and 6,211 (38%) had albuminuric RI. Table 9 shows some of the variables that differed significantly between patients with normoalbuminuric and albuminuric RI. Normoalbuminuric patients tended to be women with a more favorable CV risk profile (lower BMI, HbA1c, triglycerides and SBP, as well as shorter diabetes duration), less history of CVD and CHF, and better renal function. A total of 20% of patients with normoalbuminuric RI had concomitant retinopathy, as opposed to 31% of patients with albuminuric RI.

Table 9. Clinical and biochemical characteristics in patients with T2D and RI, with or without albuminuria (n=16 322).

	Normoalbuminuric RI (n=10 111)	Albuminuric RI (n=6 211)
Age	76±9	76±9
Diabetes duration (years)	10±7.7	13±8.2
HbA1c (IFCC, mmol/mol)	52±8	56±13
BMI (kg/m2)	29.3±5.2	29.5±5.3
eGFR (ml/min/1.73 m2)	49±9	44±7
Male (%)	36	64
Smoker (%)	6	8
Retinopathy (%)	20	31
History of CVD (%)	31	39
History of CHF (%)	17	23
Antihypertensive treatment (%)	93	96

Data are means ± SD. P-value < 0.05 for all variables. Renal impairment (eGFR < 60 ml/min/1.73 m^2 according to MDRD).

A total of 2,774 (27%) of patients with normoalbuminuric RI were not receiving treatment with RAAS blockade. Patients with normoalbuminuric RI who were not receiving treatment with RAAS blockade had better renal function and were less likely to have a history of CVD, CHF or retinopathy

than those with normoalbuminuric RI and treatment with RAAS blockade (Table 10).

Table 10. Clinical and biochemical characteristic in patients with T2D and normoalbuminuric RI, with or without RAAS blockade treatment (n=10111).

	Normoalbuminuric RI with RAAS blockade (n=7 337)	Normoalbuminuric RI without RAAS blockade (n=2 774)
Age	76±8	77±9
Diabetes duration (years)	10±7.7	9±7.4
eGFR (ml/min/1.73 m^2)	49±9	50±8
Male (%)	38	31
Retinopathy (%)	23	15
History of CVD (%)	33	24
History of CHF (%)	19	10

Data are means ± SD. P-value< 0.05 for all variables. Renal impairment (eGFR < 60 ml/min/1.73 m^2 according to the MDRD equation), CVD; cardiovascular disease, CHF; chronic heart failure

Study III – association between SBP and CVEs and all-cause mortality in T2D and RI patients

A total of 33,356 patients with T2D and RI were followed for an average of 5.3 years. During the study period, 11,317 (34%), CVEs occurred and 10,738 (32%) patients died. CVD (34%) and cancer (18%) were the most common causes of death. The lowest and the highest SBP intervals of 80-120 and 160-230 mmHg showed the greatest risks of CVEs and all-cause mortality, while the SBP interval of 135-139 mmHg showed the smallest risks (Table 11).

Table 11. Incidence and hazard ratios of cardiovascular events and all-cause mortality in the highest and lowest SBP intervals compared to the reference interval (n=33 356).

Interval SBP (mmHg)	mean SBP ± SD	CVEs n (%)	CVEs HR 95% CI	All-cause mortality n (%)	All-cause mortality HR 95% CI
80-120	114±7	1 526 (46.0)	2.30 (2.03-2.60)	1 686 (50.8)	2.40 (2.11-2.73)
135-139	137±1	719 (21.7)	1 (ref. group)	678 (20.4)	1 (ref. group)
160-230	169±10	1 621 (48.8)	2.95 (2.62-3.34)	1 536 (46.3)	2.02 (1.78-2.30)

Hazard ratios (HR) with 95% confidence interval adjusted for age, diabetes duration, gender, HbA1c, BMI, presence/absence of albuminuria, smoking, LD -cholesterol, triglycerides/HDL, history of CVD, history of CHF, antihypertensive and lipid lowering treatment. SBP interval 135-139 mmHg was defined as the reference group. SBP; systolic blood pressure, CVEs; cardiovascular events

During the course of the study, 7,704 (23%) patients had a coronary event and 2,284 (6.8%) had a stroke. The greatest risk for CHD was in the lowest SBP interval of 80-120 mmHg (n=1211, 37%), whereas the greatest risk for stroke was in the highest SBP interval of 160-230 mmHg (n=376, 11.3%) (Table 12).

Table 12. Incidence and hazard ratios for stroke and coronary heart disease in the lowest and highest systolic blood pressure intervals compared with the reference interval (n=33 356).

Interval SBP (mmHg)	Means ± SD	Stroke n (%)	Stroke HR 95% CI	CHD n (%)	CHD HR 95% CI
80-120	114±7	198 (6.0)	1.79 (1.34-2.39)	1 211 (36.5)	2.60 (2.25-3.02)
135-139	137±1	169 (5.1)	1 (ref. group)	458 (13.8)	1 (ref. group)
160-230	169±10	376 (11.3)	2.65 (2.04-3.43)	1 000 (31.1)	2.93 (2.53-3.41)

Hazard ratios (HR) with 95% confidence interval adjusted for age, diabetes duration, gender, HbA1c, BMI, presence/absence of albuminuria, smoking, LDL cholesterol, triglycerides/HDL, history of cardiovascular disease (CVD), previous history of congestive heart failure (CHF), antihypertensive and lipid lowering treatment. SBP 135-139 mmHg was defined as the reference group. SBP; systolic blood pressure, CHD; coronary heart disease

Patients in the lowest (40-63 mmHg) and highest (83-125 mmHg) DBP intervals faced the greatest risks of CVEs and all-cause mortality. The DBP interval of 72-74 mmHg was associated with the smallest risk of CVD and all-cause mortality (Table 13).

Table 13. Incidence and hazard ratios of cardiovascular events and all-cause mortality in the lowest and highest diastolic blood pressure intervals compared to the reference interval (n=33 356).

DBP interval (mmHg)	Mean DBP ± SD	CVEs n (%)	CVEs HR 95% CI	All-cause mortality n (%)	All-cause mortality HR 95% CI
40-63	50±3	1 625 (49.0)	2.0 (1.80-2.22)	1 662 (50.1)	2.00 (1.78-2.24)
72-74	73±1	870 (26.2)	1 (ref. group)	801 (24.1)	1 (ref. group)
83-125	88±4	1 621 (48.8)	1235 (37.2)	1 151 (34.7)	2.30 (2.03-2.59)

Hazard ratios (HR) with 95% confidence interval adjusted for age, diabetes duration, gender, HbA1c, BMI, presence/absence of albuminuria, smoking, LDL cholesterol, triglycerides/HDL, history of cardiovascular event (CVE), previous history of congestive heart failure (CHF), antihypertensive and lipid lowering treatment. Diastolic blood pressure 72-74 mmHg was defined as the reference a group. DBP; diastolic blood pressure, CVEs; cardiovascular events

The highest risk of CHD was in the lowest DBP interval of 40-63 mmHg (1,197, 36.1%) and the highest risk of stroke was in the highest DBP interval of 83-125 mmHg (n=790, 24%) (Table 14).

Table 14. Incidence and hazard ratios for stroke and coronary heart disease in the lowest and highest mean diastolic blood pressure intervals compared to the reference interval (n=33 356).

DBP interval (mmHg)	Mean DBP ± SD	Stroke n (%)	Stroke HR 95% CI	CHD n (%)	CHD HR 95% CI
40-63	50±3	226 (6.8)	1.47 (1.18-1.95)	1 197 (36.1)	2.05 (1.78-2.34)
72-74	73±1	193 (5.8)	1 (ref. group)	575 (17.3)	1 (ref. group)
83-125	88±4	323 (9.7)	2.62 (2.03-3.38)	790 (23.80)	2.30 (2.03-2.59)

Hazard ratios (HR) with 95% confidence interval adjusted for age, diabetes duration, gender, HbA1c, BMI, presence/absence of albuminuria, smoking, LDL cholesterol, triglycerides/HDL, history of cardiovascular event (CVE), previous history of congestive heart failure (CHF), antihypertensive and lipid lowering treatment. Diastolic blood pressure 72-74 mmHg was defined as the reference a group. DBP; diastolic blood pressure, CHD; coronary heart disease

The highest incidence of CVEs and all-cause mortality was in the highest pulse pressure interval (85-154 mmHg), while the highest risk of mortality was in the lowest pulse pressure interval (15-49 mmHg) and the highest risk of CVEs was in the highest pulse pressure interval (Table 15).

Table 15. Incidence and hazard ratios for cardiovascular events and all-cause mortality in the lowest and highest pulse pressure intervals compared to the reference interval (n=33 356).

Pulse pressure interval (mmHg)	Mean pulse pressure ± SD	CVEs n (%)	CVEs HR 95% CI	All-cause mortality n (%)	All-cause mortality HR 95% CI
15-49	43±5	1 174 (35.4)	1.48 (1.31-1.66)	1 278 (38.5)	2.11 (1.85-2.40)
61-65	63±1	907 (27.3)	1 (ref. group)	774 (23.3)	1 (ref. group)
85-154	94±9	1 543 (46.5)	1.99 (1.77-2.22)	1 517 (45.7)	1.70 (1.50-1.94)

Hazard ratios (HR) with 95% confidence interval adjusted for age, diabetes duration, gender, HbA1c, BMI, presence/absence of albuminuria, smoking, LDL cholesterol, triglycerides/HDL, history of cardiovascular event (CVE), previous history of congestive heart failure (CHF), antihypertensive and lipid lowering treatment. Pulse pressure 61-65mmHg was defined as the reference a group. CVEs; cardiovascular events

Study IV – association between SBP at baseline, time-updated SBP and change in SBP and the risk of all-cause mortality during follow-up

A total of 27,732 patients with T2D and RI were followed for an average of 4.7 years. SBP was between 130 and 160 mmHg in 80% of the cases. Approximately one-third of the patients (31%, n=8580) had a history of CVD, and one-seventh (14%, n= 3933) of CHF, at baseline. Only 30% of them had albuminuria at baseline. CVD and CHF were more common in patients with SBP < 130 mmHg, who were younger − as well as having shorter diabetes duration, lower HbA1c and less frequent albuminuria − than the others. During the follow-up, 8,265 (30%) patients died − 2,268 (57%) of those with a history of CHF and 6,290 (26%) without. Patients with SBP < 130 mmHg at baseline faced a higher risk of all-cause mortality than the reference group (130-140

mmHg), though not significantly so when those with a history of CHF were excluded.

Compared to the reference group (130-140 mmHg), the risk of all-cause mortality was higher with time-updated SBP < 130 mmHg during follow-up, even when patients with a history of CHF were excluded. The risk of all-cause mortality was not significantly higher with time-updated SBP > 160 mmHg.

The change in SBP between the last two observations during follow-up and the risk of all-cause mortality were evaluated, and a time-updated change of +/-10 mmHg was used to define the reference group. A decrease of more than 10 mmHg was significantly associated with a higher risk of all-cause mortality, both with and without a history of CHF. An increase in time-updated SBP between the last two observations of between 25-50 mmHg was associated with a higher risk of all-cause mortality among patients without a history of CHF.

The number of antihypertensive drug classes at baseline and the risk of all-cause mortality were also evaluated. The reference group consisted of those who were taking two drug classes. The risk of all-cause mortality was significantly higher among patients without a history of CHF who were consuming no more than one hypertensive at baseline.

5 DISCUSSION

Main findings of the thesis

Albuminuria does not always develop before RI in patients with T2D.

Approximately one-fifth of the patients in Study I with T2D developed albuminuria during 5 years of follow-up (4% per year). The majority (16%) developed microalbuminuria and only 4% developed macroalbuminuria. A total of only 3% of patients developed both albuminuria and RI.

The UKPDS 74 study with a median of 15 years of follow-up found that 38% (2.5% per year) of patients developed albuminuria and 14% (1% per year) developed albuminuric RI [183]. The UKPDS 64 study concluded that approximately one-quarter of patients developed microalbuminuria within 10 years after being diagnosed with T2D, suggesting that many individuals do not necessarily progress to poorer renal outcomes, even after onset of microalbuminuria [184]. A study in Japan by Yamada et al demonstrated that 15% of patients with T2D and at least 8 years of follow-up developed albuminuria [185]. The fact that the participants in our study were older and had longer diabetes duration than previous studies may explain the slightly higher incidence of albuminuria and RI. None of the patients in our study developed severe RI or ESRD. That risk is relatively small among patients with T2D since many die before developing ESRD [186].

The risk factors that T2D patients will develop albuminuria or RI are not the same.

We found that the factors differed somewhat. Study I found that the risk of developing albuminuria and RI was associated with age and diabetes duration.

Other studies have reached the same conclusion [183, 187]. In addition, we demonstrated that high SBP at baseline increased the risk of developing albuminuria and RI.

The finding is in line with UKPDS and other studies [56, 188, 189]. Previous studies have also shown that BP < 130/80 mmHg does not reduce the risk of developing RI and that only patients with severe proteinuria may benefit [139]. The risk of developing albuminuria was greater with male gender, high HbA1c and smoking. As previously demonstrated, female gender is associated with a higher risk of developing RI [104, 183]. The greater risk of RI in women may be due to misclassification when using creatinine and creatinine-based equations as a markers of renal function [190]. Our study associated high HbA1c with an elevated risk of developing albuminuria but not RI. UKPDS reached the same conclusion [183]. A study by Murussi et al showed that only patients with T2D who developed microalbuminuria experienced a pronounced decline in GFR during 10-year follow-up and that it was primarily related to poor glycemic control at baseline. The researchers suggested that development of normoalbuminuric RI may be attributable to the aging process [191].

Experimental studies have shown that dyslipidemia may contribute to podocyte injury among patients with diabetic kidney disease [192, 193]. Study I associated high triglyceride levels with a greater risk of developing both albuminuria and RI. Other epidemiological studies have also identified a relationship between serum triglycerides and kidney disease [194]. Elevated triglycerides are associated with both poor glycemic control and insulin resistance [195].

Obesity is associated with the development of albuminuria and RI in patients with T2D.

Study I associated high BMI with the development of albuminuria and RI in patients with T2D. When BMI increased from normal to obesity, the risk of developing albuminuria became 2.3 times as great [115]. Once the statistical models had been adjusted for HbA1c, SBP, triglycerides, HDL-cholesterol and LDL-cholesterol, the increase was less pronounced but still significant [196].

Previous studies have identified an association between obesity and the development of renal dysfunction. A large study that followed young adults for 15-34 years associated morbid obesity with 6 times as great a risk of ESRD as compared to normal weight [197]. Another study associated $BMI > 30 \, kg/m^2$ with double the risk of developing ESRD, though only among those with metabolic syndrome [198]. Recent studies of patients with diabetes have found a link between high BMI and progression of diabetic nephropathy [199]. The mechanisms explaining the association between obesity and CKD are not completely understood, but hyperfiltration and glomerular hypertrophy mediated by obesity may lead to glomerular capillary injury and sclerosis and probably play an important role [200].

Our study associated high BMI with an increased risk of developing RI according to the MDRD equation. When RI was defined according to the Cockcroft-Gault (C-G) equation, however, low BMI was associated with an increased risk of developing RI. Thus, we highlighted the need for additional research on methods of determining renal function in population-based studies, considering that the current equations (MDRD and C–G) generate different results, especially with regard to BMI and gender [201, 202].

The majority of patients with T2D and RI have normoalbuminuric RI.

A total of 6-7% of patients in Study I developed normoalbuminuric RI during follow-up. A total of 62% of patients in Study II had normoalbuminuric RI. A total of 70% of patients with RI in Studies III and IV had normoalbuminuric RI at baseline.

Normoalbuminuric RI is frequently observed in patients with T2D and RI [85, 86]. Several studies have shown that the majority of patients with T2D and RI are normoalbuminuric [90, 93]. Multifactorial pathogenesis has been hypothesized as the underlying mechanism for development of normoalbuminuric RI in patients with T2D [69, 77]. RAAS blockade, which is prescribed for a considerable percentage of patients with diabetes, may reduce albuminuria [91]. Only one-quarter of patients with normoalbuminuric RI in Study III were being treated with RAAS blockade. However, we cannot rule out the possibility that albuminuria became normoalbuminuria before baseline. Genetic susceptibility may also contribute to the development of normoalbuminuric RI, and genetic polymorphisms of the protein kinase C-beta gene have been associated with accelerated decline of eGFR in patients with T2D who do not have overt albuminuria [203]. Aging, dyslipidemia and hypertension can also contribute to the pathogenesis of normoalbuminuric RI among patients with T2D [92].

Patients with normoalbuminuric RI in the studies covered by this thesis were more often women, had shorter diabetes duration, lower HbA1c and less propensity to smoke than those with albuminuric RI. These findings are similar to a previous study [91]. Patients with normoalbuminuric RI also had better renal function than patients with albuminuric RI. In line with previous studies, we observed that a history of CVD and retinopathy was less common in patients with normoalbuminuric RI [78]. Study II associated female gender and

non-smoking with normoalbuminuric RI. A multivariable analysis concluded that treatment with RAAS-blockade was not significantly associated with normoalbuminuric RI. Patients who had normoalbuminuric RI and were not receiving treatment with RAAS blockade were less likely to have a history of CVD, CHF or retinopathy and had better renal function. Our results show that patients with normoalbuminuric RI who were not receiving RAAS blockade had a more favorable cardiovascular profile than those who were receiving RAAS blockade.

BP variables and the risk of CVD and all-cause mortality in patients with T2D and RI

Studies III and IV evaluated the relationship between BP and the risk of CVD and all-cause mortality. The risk of CVEs and all-cause mortality in patients with T2D and RI is very high, even more so among those with a history of CVD and CHF. More than 50% of patients in Study IV with a history of CVD died during the 5 years of follow-up. Previous studies have shown that albuminuria and RI considerably increase the risk of CVD and all-cause mortality among patients with T2D [121, 204].

The Appropriate Blood Pressure Control in Diabetes (ABCD) study evaluated the role of intensive versus standard BP control for T2D patients. After five years of follow-up, both hypertensive and normotensive patients in the intensive BP control group showed a significant reduction in mortality [205]. UKPDS followed patients with T2D between 1977 and 1991 and concluded that the risk of diabetic complications was positively correlated with elevated BP. The lowest risk of complications was observed in patients with SBP < 120 mmHg [206]. The UKPDS study followed 75 patients newly diagnosed with T2D for a median of 10.4 years. Glycemic control (HbA1c) and SBP were

independently associated with an increased risk of diabetic complications, along with additive effects of hyperglycemia and hypertension [155].

The recent Systolic Blood Pressure Intervention Trial (SPRINT) of patients without diabetes found that targeting SBP below 120 mmHg led to lower rates of fatal and nonfatal major CVEs and all-cause mortality than targeting SBP below 140 mmHg. However, no benefit of intensive treatment was found for patients with CKD [207]. A systematic review and meta-analysis associated antihypertensive treatment for T2D patients with reduced mortality and other clinical outcomes. Lower risk ratio was observed among those with SBP of 140 mmHg or greater at baseline. Again, no benefit of intensive treatment was found for patients with CKD [208].

Study III identified a U-shaped relationship between BP and the risk of CVEs or all-cause mortality, while SBP of 135-139 mmHg and DBP of 72-74 mmHg were associated with the lowest risk. The hypothesis that both hypotension and hypertension in patients with T2D, RI and other comorbidities increases the likelihood of CVEs and mortality has been discussed and disputed [135, 209-211]. An observational study of American veterans with CKD, 43% of whom had diabetes, concluded that optimal BP was 130-159/70-89 mmHg. The highest mortality rates were seen in patients for whom both SBP and DBP were low. Even among those with normal SBP, DBP below 70 mm Hg increased the risk of mortality [212]. Another study found that intensive BP control targeting 130/78 mmHg had no effect on mortality or the progression of kidney disease in patients with CKD compared to a control group those mean BP was 141/86 mmHg [213].

The elevated risk of CVD and mortality associated with low BP may be due to CHF, RI and other preexisting conditions [144, 214]. Study III showed that the risk of CVEs and all-cause mortality remained high in the lowest SBP and DBP

intervals ($80 \leq$ SBP ≤ 120 and $40 \leq$ DBP ≤ 63 mmHg), even after excluding patients with a history of CHF. Study IV found that the risk of all-cause mortality was not significantly higher among patients with SBP < 130 mmHg who did not have a history of CHF at baseline than the reference group. A greater risk was identified; however, when the time-updated SBP was below 130 mmHg, which (rather than baseline SBP) thereby increased the risk of all-cause mortality. Previous studies have also shown that the risk of CVD and mortality is primarily associated with variables that also reflect BP after baseline [133, 208, 215].

Study IV evaluated the relationship between SBP change or variability and the risk of all-cause mortality. A reduction in SBP of more than 10 mmHg between the last two observations significantly increased the risk of all-cause mortality among patients both with and without a previous history of CHF. Recent studies have reported that visit-to-visit BP variability correlates positively with the risk of CVD and all-cause mortality [216-218]. Short-term, long-term and ultra-long-term BP variability increased the risk of both CVD and mortality [219]. The correlation of BP variability with CVD and all-cause mortality has also been observed in patients with T2D, independent of SBP [220]. Greater vascular stiffness, autonomic nervous system dysfunction and inconsistent compliance with medication regimens are possible explanations for visit-to-visit BP variability and greater risk of all-cause mortality [221].

Study III associated the highest (85-154 mmHg) and lowest (15-49 mmHg) pulse pressure intervals with the greatest risk of CVD and all-cause mortality when using 61-65 mmHg as the reference. Previous studies have shown a positive correlation between pulse pressure and risk of CVEs and mortality [222, 223]. Arterial stiffness and poor vascular compliance among patients with T2D and RI often lead to greater pulse pressure [224-227]. Higher SBP

and lower DBP are strongly correlated with the risk of CVEs and mortality among older CKD patients [228, 229]. The mean age in our study was 75±9, and almost 50% of patients in the highest pulse pressure interval died after baseline. Our results also showed that low pulse pressure increased the risk of CVD and all-cause mortality, perhaps due to low SBP or isolated diastolic hypertension. Patients in Study III with the lowest (53-85 mm Hg) and highest (107-153 mmHg) MAP intervals also faced the greatest risk of CVE and mortality.

Only one out of ten patients in Study IV with SBP ≥160 mmHg at baseline were receiving treatment with at least four antihypertensive agents. Patients with CKD, for whom an average of three medications are needed, had poorer BP control than those without CKD [230, 231]. Study IV found no significant association between the number of antihypertensive agents and attainment of optimal BP control. A total of 6% of patients with SBP < 130 mmHg were receiving at least four antihypertensive drug classes. It has previously been shown that adding antihypertensive medication lowers DBP in CKD patients, increasing and widening pulse pressure, which elevates the risk of CVEs [232]. A recent systematic review and meta-analysis of the effect of antihypertensive treatment at various BP levels in patients with T2D concluded that it reduced the risk of mortality and CV morbidity in those with SBP > 140 mmHg but increased the risk of CV mortality in those with SBP < 140 mmHg [233] .

Our study used patients who were taking two antihypertensive drug classes at baseline as a reference group. Those who were taking no more than one antihypertensive faced a slightly higher risk of all-cause mortality. After patients with a history of CHF had been excluded, however, the risk was no longer significant. Patients who were receiving three or four antihypertensive drug classes at baseline did not face a greater risk of all-cause mortality. This

result may indicate that a combination of antihypertensive agents is beneficial for patients with T2D and RI, particularly those with a history of CHF. One factor may be that RAAS blockade, diuretics, aldosterone inhibitors and other antihypertensive drug classes also have a direct, favorable impact on the kidneys and heart (heart failure) [234].

Our studies were subject to certain overall limitations. The fact that data were obtained from various medical centers and local laboratories may have compromised accuracy and increased the risk of bias. While all of the studies used BP data from medical appointments, it has been shown that ambulatory measurements are stronger predictors of CV risk in patients both with and without diabetes [235-237]. Although BMI is a widely accepted indicator, some findings suggest that central adiposity is more strongly associated with risk of CVD and all-cause mortality [238, 239]. The studies did not include waist measurements or data on physical activity or adjust for them as potential confounders.

6 CONCLUSIONS

Albuminuria did not always develop prior to RI in patients with T2D.

RI in the majority of patients with T2D was normoalbuminuric.

The risk factors for development of albuminuria or RI differed somewhat in patients with T2D.

Male gender was a risk factor for development of albuminuria, whereas female gender was associated with a greater risk of developing RI. The finding, however, probably stems from misleading creatinine-based estimates of renal function in women.

Obesity was a risk factor for development of both RI and albuminuria in patients with T2D. This was not entirely explained by other risk factors associated to obesity such as high BP and hyperglycemia.

Patients with T2D and normoalbuminuric RI had a potentially more favorable cardiovascular risk profile than those with albuminuric RI.

A total of 25% of patients with T2D and normoalbuminuric RI 25% were not receiving treatment with RAAS blockade.

A U-shaped relationship was observed between BP and cardiovascular events and all-cause mortality in patients with both T2D and RI.

An SBP interval of 135-139 and a DBP interval of 72-74 mmHg were associated with the lowest risk of CVEs and all-cause mortality.

SBP < 130 mmHg at baseline among patients who did not have a previous history of CHF and SBP < 130 mmHg during follow-up, both with and without CHF, was associated with an increased risk of all-cause mortality.

A reduction in SBP of more than 10 mmHg was associated with an increased risk of all-cause mortality in patients with both T2D and RI.

Receiving treatment with more than one antihypertensive at baseline was not associated with a greater risk of all-cause mortality.

7 FUTURE PROSPECTIVE

This thesis has examined risk factors associated with the development of mild to moderate RI in patients with T2D. The length of time associated with progression from mild to severe RI and the need for renal replacement therapy varies widely. Partly due to the competing risk of CVD and mortality, many individuals with mild to moderate RI may never develop severe RI and ESRD. Risk factors associated with progression from mild to severe RI need to be further evaluated as part of future longitudinal studies.

The U-shaped relationship between BP and CVD and all-cause mortality should be additionally assessed in various groups of patients, including young vs. old, mild vs. severe RI, and with or without a history of CVD or CHF.

The impact of the intensity and type of antihypertensive treatment and the reduction in BP among T2D patients and the RI risk of all-cause or cardiovascular mortality should be further evaluated, especially for the impact of diuretics vs. vasodilators.

Previous studies have shown a J-shape relationship between glycemic control, CVD and all-cause mortality in patients with diabetes. The possibility of a similar relationship should be evaluated among patients with various severities of RI.

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