Epidemiological aspects on nephropathy in type 2 diabetes-

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Prevalence and incidence of diabetes

- *The prevalence of diabetes worldwide is currently estimated to be 382 million people (8.3%) and has been estimated to increase to 592 million (~ 10%) in 2035.*

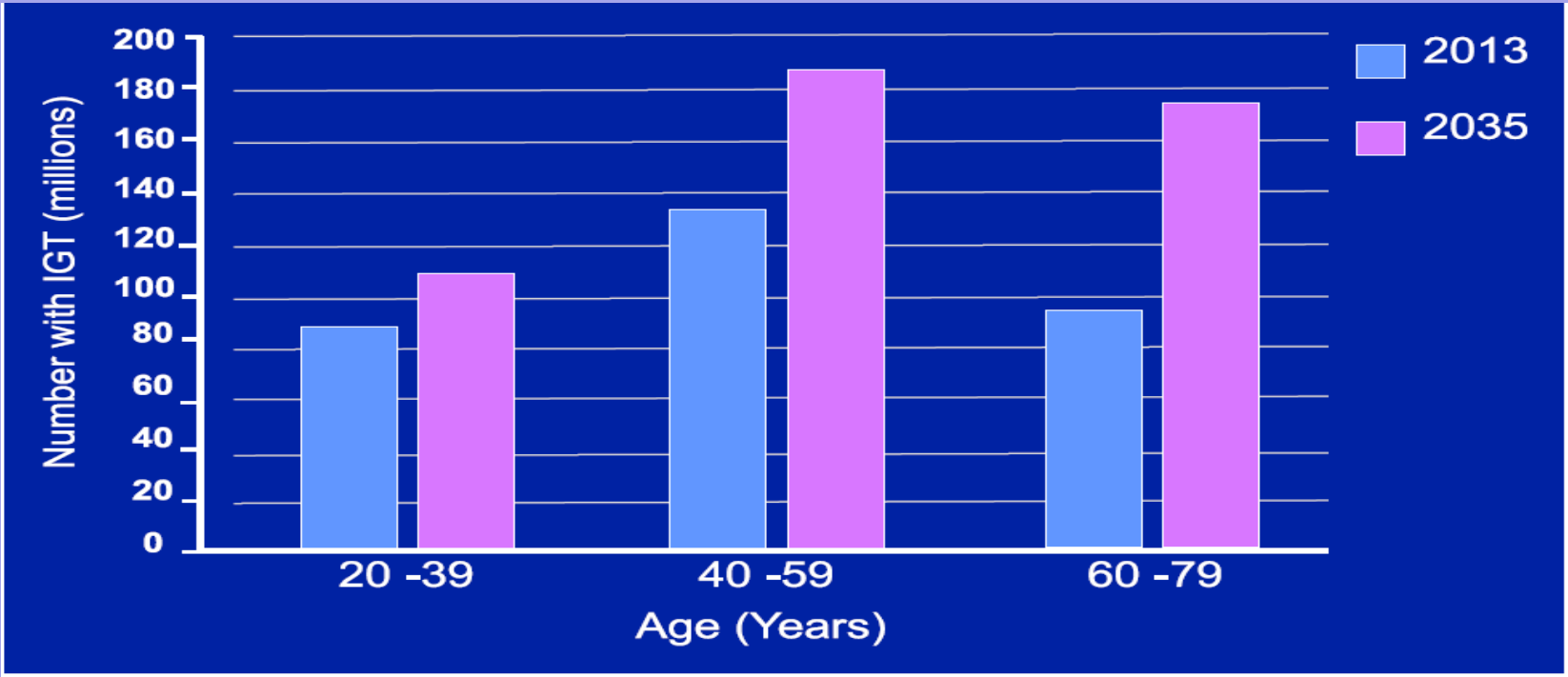
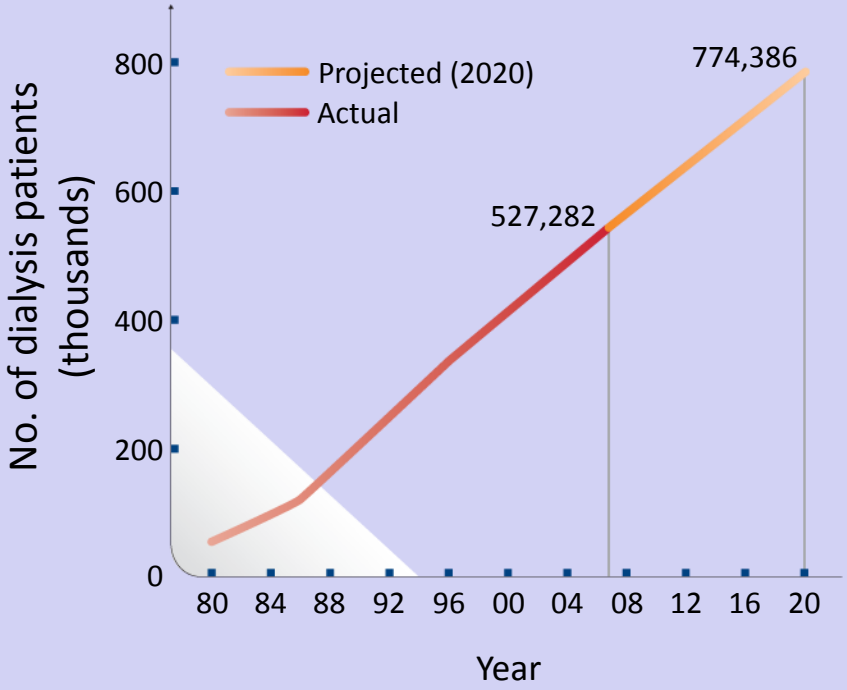


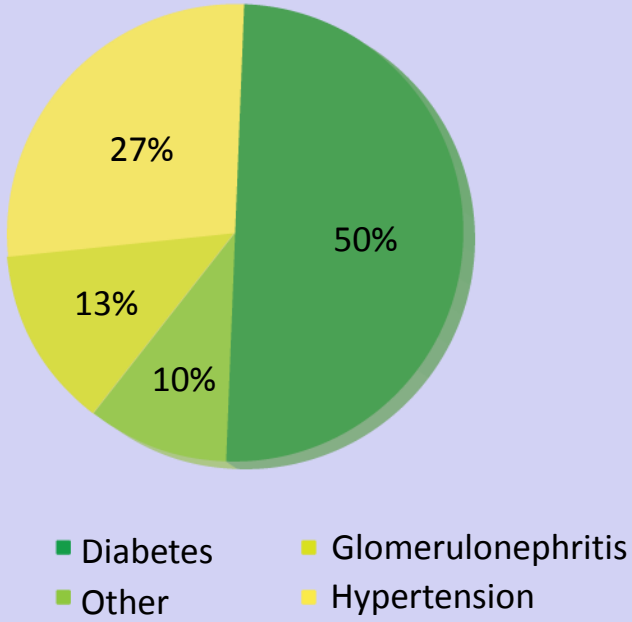
Figure 5—Global burden of prediabetes, or the number of people with impaired glucose tolerance (IGT). Source: International Diabetes Federation. *IDF Diabetes Atlas*. 6th ed. Brussels, Belgium, International Diabetes Federation, 2013, p. 40.

Diabetes is the leading cause of end-stage renal disease in the US

- ***Incidence is rising dramatically***

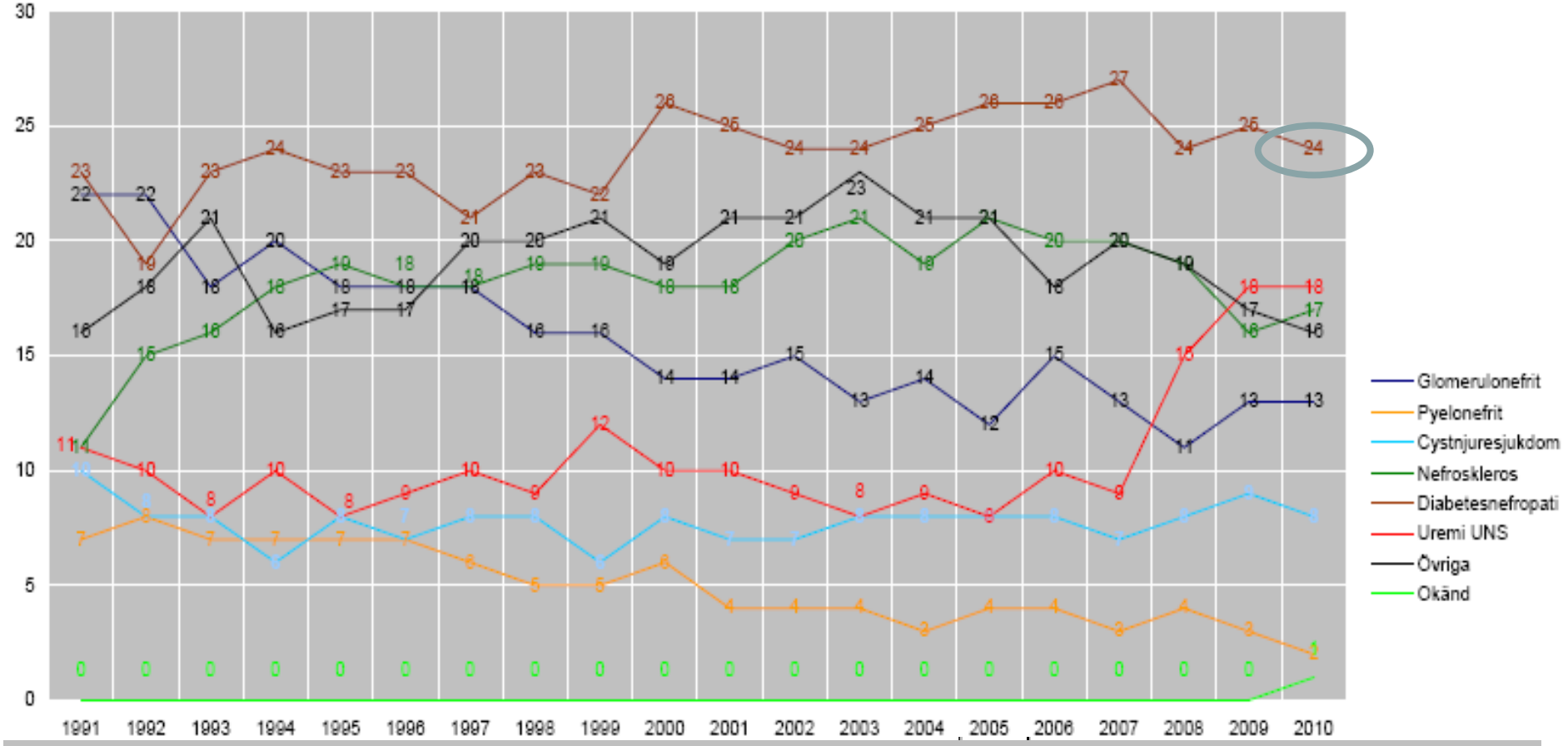


- ***Primary diagnosis for patients who start dialysis***



United States Renal Data System. Annual data report. 2000, 2007. http://www.usrds.org/atlas.htm , http://www.usrds.org/adr_2000.htm. Accessed 10 January 2011.

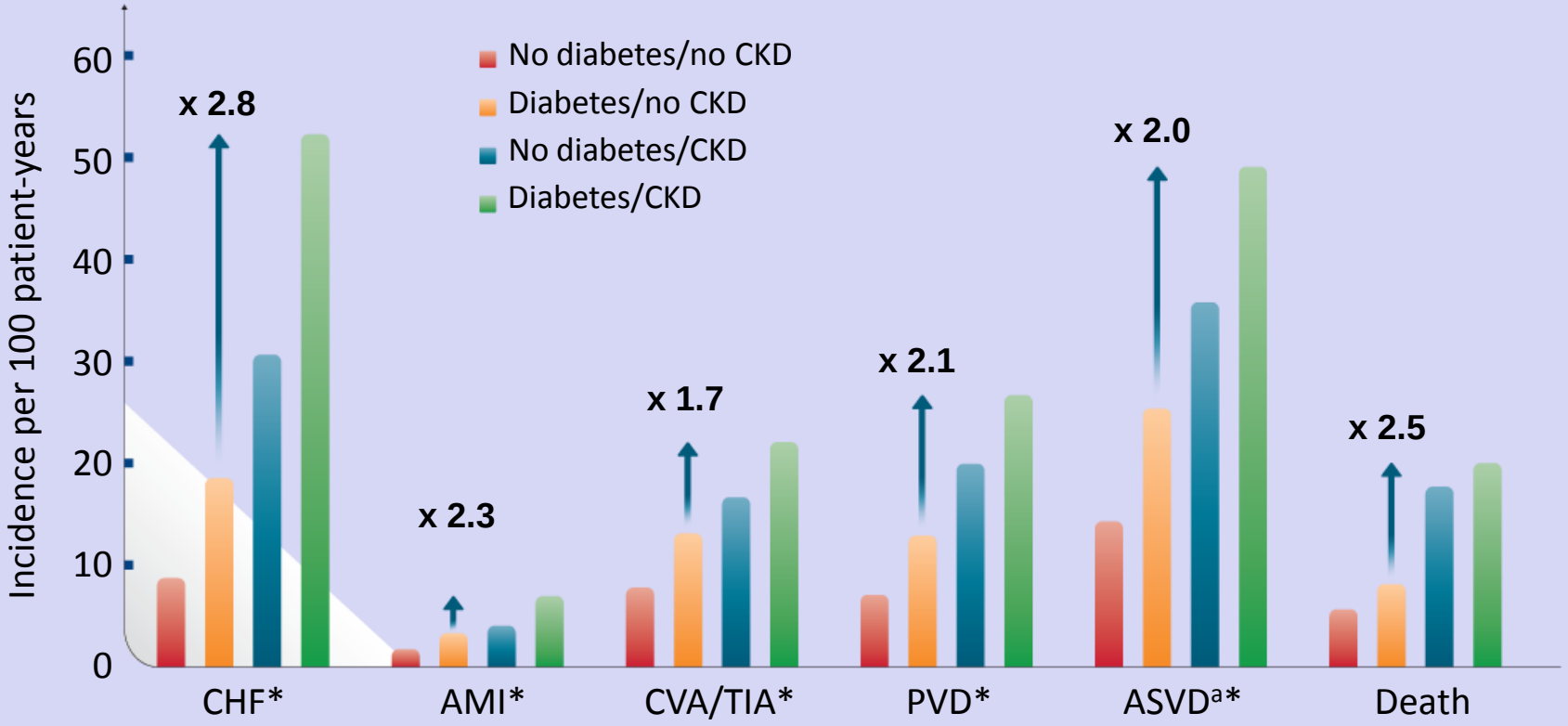
Diabetes is also the leading cause of end-stage renal disease in Sweden



	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
D M typ I	113	95	135	129	122	122	133	117	120	120	121	118	107	105	106	116	115	102	124	99
D M typ II	94	71	103	99	115	118	95	142	119	174	165	156	155	171	177	192	208	164	170	167
D M totalt	207	166	238	228	237	240	228	259	239	294	286	274	262	276	283	308	323	266	294	266

SNR rapport 2011

Risk for CV events is greatest when both diabetes and CKD are present



* CHF=congestive heart failure; AMI=acute myocardial infarction; CVA/TIA=cerebrovascular accident/transient ischemic attack; PVD=peripheral vascular disease; ASVD=atherosclerotic vascular disease. [a]ASVD was defined as the first occurrence of AMI, CVD/TIA, or PVD.

Foley RN, *et al*. *J Am Soc Nephrol* 2005;16:489–95.

Renal Impairment with type 2 diabetes

- *Renal impairment with type 2 diabetes is more complex than type 1.*
- *Natural history:*
  - *Renal damage can be found already at diagnosis of diabetes.*
  - *Normoalbuminuric renal impairment is common with type 2 diabetes.*

- *Pathological findings:*
  - *More heterogeneity in renal pathology.*
  - *Combination of diabetic lesions and nephrosclerosis.*

Definitions

- Type 2 diabetes: dietary treatment, treated with insulin either alone or in combination with oral glucose lowering agents. Debut of diabetes 40 years or older.

- Renal impairment : eGFR < 60 ml/min/1.73m ^{2} according MDRD

- Albuminuria:
- Microalbuminuria: urine albumin secretion 20–200 µg/min
- Macroalbuminuri:urine albumin secretion >200 µg/min

Overall patients and methods

Patients from

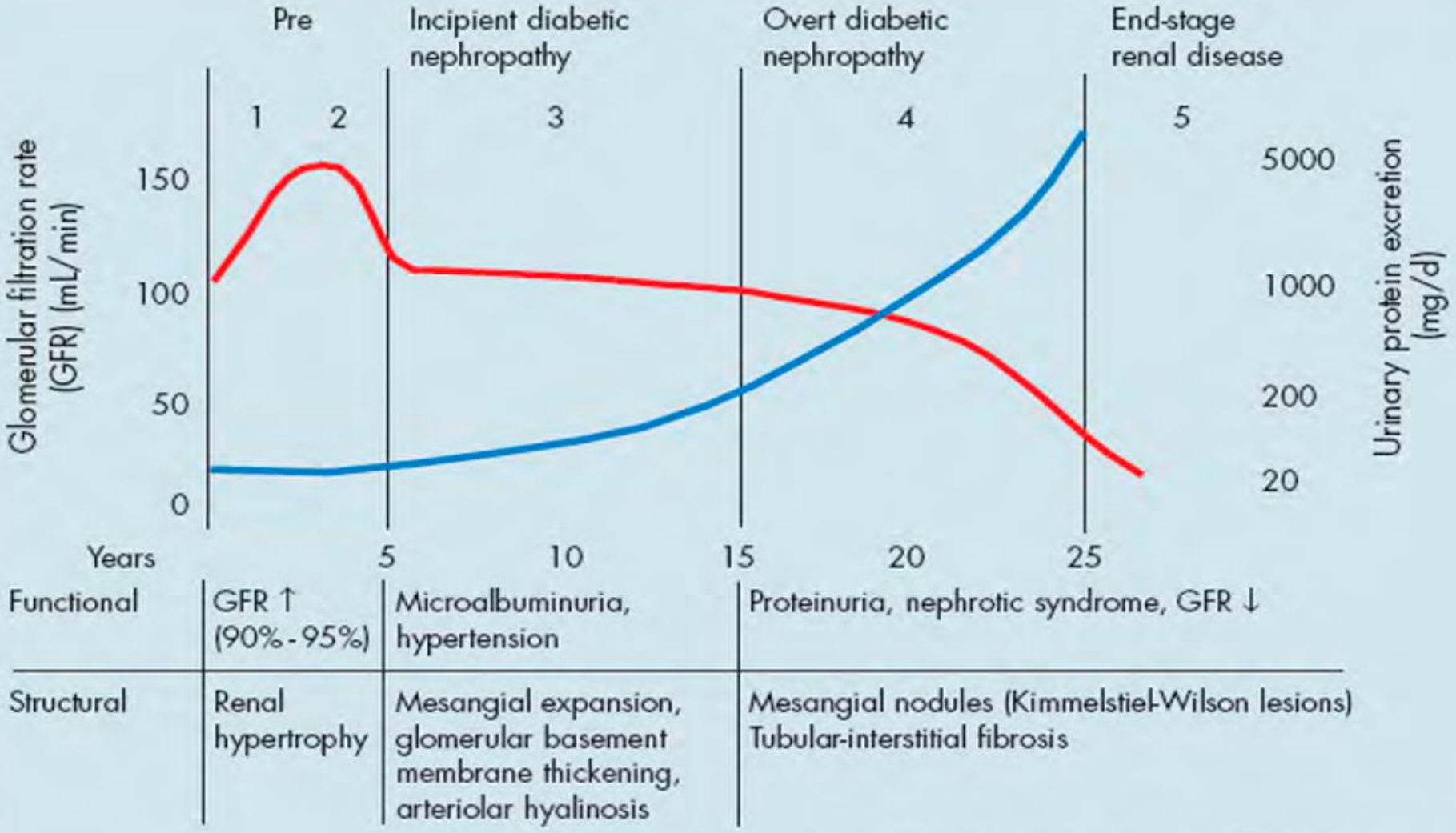
- *The Swedish National Diabetes Register (NDR)*

Data from

- *The Swedish National Diabetes Register (NDR)*
- *The Cause of Death Register (National Board of Health and Welfare)*
- *The Hospital Discharge Register*
- *The Swedish Prescribed Drug Register*

RISK FACTORS FOR THE DEVELOPMENT OF ALBUMINURIA AND RENAL IMPAIRMENT IN TYPE 2 DIABETES

Natural history of type 1 diabetic nephropathy



From Vora JP et al. *Comprehensive Clinical Nephrology*. 2000.[53] Used with permission.

- *Vora JP, Chattington PD, Ibrahin H: Clinical manifestations and natural history of diabetic nephropathy. In: Comprehensive Clinical Nephrology, Copyright Elsevier (2000).*

Background

Risk factors for development of Albuminuria or RI

- *Traditional risk factors :*

Age, diabetes duration, gender, BP, HbA1c, Obesity, dyslipidaemia, smoking.

- ***The same risk factors for development of albumniura or RI ?***

- *Non traditional risk factors (do not discuss)*

Background
Incidence of albuminuria /RI

- ***Rossing Parving 2004***
- *227 T2D + albuminuria> 120mg/dygn) were followed (3-17 år)*
- *GFR har minskat 5.2/ml/min/year*
- ***Risk RI at baseline** : Albuminuria, SBP, HbA1C, retinopathy,*
- ***Risk RI over the time of study**: Albuminuria, SBP, HbA1c, Hb, smoking*

**Source :Progression of nephropathy in type 2 diabetic patients KASPER ROSSING, PER K. CHRISTENSEN, PETER HOVIND, LISE TARNOW, PETER ROSSING,and HANS-HENRIK PARVING.*

Background
Incidence of albuminuria /RI

- ***UKPDS 64*, 5097 T2D***

Microalbuminuria 2.0%/year ➡ Macroalbuminuria 2.8%/year ➡ RI 2.3%/year

After 10 years : Microalbuminuria, 24.9%,
Macroalbuminuria 5.3%,
Elevated plasma creatinine or RRT was 0.8%

- ***UKPDS 74** 4,006 T2D***
- *After 15 years 38% albuminuria, 28% RI. 51% nonalbuminuic RI.*

**Source :Adler, A. I. Stevens, R. J. Manley, S. E. Bilous, R. W. Cull, C. A. Holman, R. R. UKPDS Group .* Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney Int 2003.
**Source: Retnakaran, R. Cull, C. A. Thorne, K. I. Adler, A. I. Holman, R. R. UKPDA Study Group. Risk factors for renal dysfunction in type 2 diabetes: U.K. Prospective Diabetes Study 74. Diabetes 2006

Aims of study

- To study the **occurence** renal dysfunction in patients with T2D during 5 years of follow-up.
- To identify **clinical risk factors** associated with the development of renal dysfunction.
- To evaluate if the currently used **equations to estimate renal function**, i.e. MDRD vs Cockcroft-Gault , have an impact on interpretation of data.

Patients and methods

- *Prospective cohort study (2002-2007)*

- *3667 patients with T2D with no signs of renal dysfunction at baseline*
  - no renal impairment eGFR>60 ml/min/1.73m² (MDRD)
  - no albuminuria (UAE<20 µg/min)

- *Development of albuminuria and/or renal impairment during 5 years follow-up*
  - albuminuria (UAE≥20 µg/min)

  and/or
  - eGFR≤60 ml/min/1.73m² (MDRD)
  - eCrCl ≤ 60 mL/min by Cockgroft–Gault (C–G)

Afghahi H et al Nephrol Dial Transplant. 2011 Apr;26(4):1236-43.

Baseline clinical characteristics (n=3667)

Age (years)	60±8
Men/Women (%)	61/39
Diabetes duration (years)	7.5±6.2
HbA1c (DCCT, %)	7.1±1.1
Systolic blood pressure (mmHg)	140±17
Diastolic blood pressure (mmHg)	79±9
Body Mass Index; BMI (kg/m^2)	29±4.8
Total-cholesterol (mmol/L)	5.1±1.0
LDL cholesterol (mmol/L)	3.0±0.9
Triglycerides (mmol/L)	1.6±0.7
HDL cholesterol (mmol/L)	1.3±0.4
Estimated Glomerular filtration rate (eGFR; MDRD; ml/min/1.73 m^2)	80±16
Estimated Creatinine clearance (eCrCl; C-G; ml/min)	103 ±30

Development of albuminuria after 5 years

	All patients (n=3667)	Albuminuria (n=729)
Microalbuminuria[a] (%)	16.3	
Macroalbuminuria[b] (%)	3.6	
Albuminuria[c] (%)	**19.9**	
eGFR[d] <60 (%)		16.1
eCrCl[e] <60 (%)		10.4

[a] U-albumin excretion 20-200 µg/min.
[b] U-albumin excretion >200 µg/min
[c] Micro- or macroalbuminuria.
[d] Estimated glomerular filtration rate <60 ml/min/1.73m^2 according to MDRD.
[e] Estimated creatinine clearance <60 ml/min/1.73m^2 according to Cockcroft-Gault

Development of renal impairment after 5 years

	All patients (n=3667)	eGFR <60 (n=407)	eCrCl <60 (n=241)
eGFR[d] <60 (%)	**11.1**		68.5
eCrCl[e] <60 (%)	**6.7**	40.5	
Microalbuminuria[a] (%)		20.6	22.8
Macroalbuminuria[b] (%)		8.1	8.7
Albuminuria[c] (%)		28.7	31.5

[a] U-albumin excretion 20-200 µg/min.
[b] U-albumin excretion >200 µg/min
[c] Micro- or macroalbuminuria.
[d] Estimated glomerular filtration rate <60 ml/min/1.73m^2 according to MDRD.
[e] Estimated creatinine clearance <60 ml/min/1.73m^2 according to Cockcroft-Gault

Predictors for development of albumiuria and renal dysfunction

	Albuminuria (micro or macroalbuminuria)		**Glomerular filtration rate (MDRD) <60 ml/min**	
	Adj OR (95% CI)	p-value	Adj OR (95% CI)	p-value
Systolic BP	1.25 (1.15-1.36)	<0.001	1.18 (1.06-1.31)	0.003
HbA1c	**1.22 (1.12-1.32)**	**<0.001**	-	-
Male sex	1.59 (1.33-1.89)	<0.001	0.25 (0.18-0.34)	<0.001
Triglycerides	1.15 (1.06-1.25)	0.001	1.20 (1.07-1.34)	0.0013
Age	1.27 (1.16-1.40)	<0.001	2.00 (1.75-2.28)	<0.001
Smoker	**1.52 (1.22-1.88)**	**<0.001**	-	-
BMI	1.15 (1.06-1.26)	0.001	1.19 (1.06-1.33)	0.0026
Creatinine	-	-	**2.11 (1.80-2.46)**	**<0.001**

Adverse effects of BMI on renal function

	Albuminuria (micro- or macroalbuminuria)		Glomerular filtration rate (MDRD) <60 ml/min/1.73m^2	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Model 1[a]				
BMI	1.26 (1.16-1.37)	<0.001	1.27 (1.14-1.42)	<0.001
Model 2[b]				
BMI	1.13 (1.04-1.24)	0.007	1.16 (1.04-1.31)	0.011

[a] Model 1: BMI adjusted for age, sex, diabetes duration, creatinine, smoking.

[b] Model 2: BMI adjusted as in Model 1 and also for HbA1c, systolic BP, triglycerides, HDL and LDL cholesterol.

Adverse effects of BMI on renal function and different estimates of renal function

	Glomerular filtration rate (MDRD) <60 ml/min/1.73m^2		Creatinine clearance (Cockcroft-Gault) <60 ml/min	
	Adj OR (95% CI)	p-value	Adj OR (95% CI)	p-value
BMI	**1.19 (1.06-1.33)**	**0.0026**	**0.33 (0.27-0.41)**	**<0.001**

MDRD →high BMI as a predictor of renal impairment

Cockcroft-Gault → low BMI as a predictor of renal impairment

.

[1]Retnakaran R et al, Risk Factors for Renal Dysfunction in Type 2 Diabetes, U.K. Prospective Diabetes Study 74. Diabetes 2006; 55: 1832–1839.

Conclusions

- With T2D development and risk factors for albuminuria and renal impairment are not entirely linked .

- High BMI by unknown pathways other than hyperglycaemia, high blood pressure and lipids increase the risk of RI.

- Other markers, such as eGFR, are therefore warranted when monitoring of renal function in these patients.

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Original Article

Risk factors for the development of albuminuria and renal impairment in type 2 diabetes—the Swedish National Diabetes Register (NDR)

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Non-albuminuric renal impairment with type 2 diabetes

Background

- ✓ Albuminuria and renal impairment are not entirely linked in patients with type 2-diabetes
- ✓ Recent studies have shown that non-albuminuric renal impairment is common in patients with type 2-diabetes.
- ✓ Non-albuminuric renal impairment could be explained by
  - ✓ Ongoing RAAS-inhibition
  - ✓ Other underlying renal conditions, i.e. primary hypertension and nephrosclerosis and obesity-related glomerulopathy

Prevalence of normoalbuminuric renal impairment by different studies

First author/year	*Numbers of patients (n)*	*Type of study population*	*Proportion of Normoalbuminuric (%)*	*Women (%)*
MacIsaac 2004	*301*	*T2D with RI**	*39*	*56*
Rigalleau 2007	*89*	*T2D with RI*	*17*	*66*
Ykoyama 2009	*3297*	*T2D*	*52*	*47*
Thomas2009	*3893*	*T2D*	*55*	*64*
Ito 2010	*1197*	*T2D*	*50*	*60*
Penno 2011	*15773*	*T2D*	*57*	*66*
Mottl 2013	*2798*	*T2D*	*52*	*58*
Boronat 2014*	*78*	*T2D with RI*	*22*	*77*

*Included only patients with eGFR <30min/ml

Objectives

- ✓ To study the prevalence of albuminuric and non-albuminuric renal impairment in patients with type 2-diabetes
- ✓ To describe and evaluate the clinical characteristics associated with non-albuminuric renal impairment
- ✓ To study the use and impact of treatment with RAAS-blockade in patients with non-albuminuric renal impairment

Patients and Methods

In total, 81 315 patients with type 2-diabetes and data on renal function (serum creatinine and albuminuria) and clinical characteristics reported to NDR in 2009 were included.

Cross-sectional study

Registry linkages between

Swedish National Diabetes Register (NDR)

Hospital Discharge Register

Swedish Prescribed Drug Register

The majority of patients with type 2-diabetes and renal impairment are non-albuminuric

All patients (n=81 315)	
Renal impairment, %	20.0
Albuminuria, %	27.4
-Microalbuminuria, %	18.6
-Macroalbuminuria, %	8.8

All patients with renal impairment (n=16 322)	
Albuminuria, %	38.0
-Microalbuminuria, %	20.4
-Macroalbuminuria, %	17.6
Non-albuminuric renal impairment , %	62.0

Clinical characteristics of patients with type 2-diabetes and renal impairment (eGFR<60 ml/min/1.73m^2)

	Non-albuminuric (n=10111)	Albuminuric (n=6211)	p-value
Age (years)	76.4±8.7	76.4 ±8.8	n.s
Male (%)	36	58	<0.001
Diab duration (years)	10.1±7.7	13.0 ±8.2	<0.001
HbA1c (DCCT, %)	7.0±1.0	7.2 ±1.2	<0.001
BMI (kg/m^2)	29.3 ±5.2	29.5 ±5.3	n.s
Systolic BP (mmHg)	136±17	139 ±19	<0.001
eGFR (ml/min/1.73m^2*)	49±9	44±12	<0.001
Smokers (%)	6	8	<0.001
Retinopathy (%)	20	31	<0.001
History of CVD (%)	31	39	<0.001
History of CHF (%)	17	23	<0.001

Data are crude means±SD or frequencies(%), *eGFR according to MDRD

Clinical characteristics of patients with type 2-diabetes, renal impairment (eGFR<60 ml/min/1.73m^2) and normoalbuminuria

	RAAS-blockade (n=7337)	No RAAS-blockade (n=2774)	p-value
Age (years)	76.0±8.4	77.5±9.5	<0.001
Male (%)	38	31	<0.01
Diabetes duration (years)	10.5±7.7	8.9±8.9	<0.001
HbA1c (DCCT, %)	7.0±1.0	6.9±1.0	<0.001
BMI (kg/m^2)	29.5±5.2	28.6±5.2	<0.001
Systolic BP (mmHg)	137±18	136±16	<0.001
eGFR (ml/min/1.73m^2*)	48.9±8.6	50.0±8.4	<0.001
Smokers (%)	6	7	0.09
Retinopathy (%)	22	15	<0.001
History of CVD (%)	33	24	<0.001
History of CHF (%)	19	10	<0.001

Data are crude means±SD or frequencies(%), *eGFR according to MDRD

CONCLUSIONS

The majority of patients with type 2-diabetes and renal impairment are non-albuminuric (62%) and they had the had more favourable.

Interestingly, 28% of patients with type 2-diabetes and non-albuminuric renal impairment had no ongoing treatment with any RAAS-blocking agent.

A larger proportion of women, indicate the MDRD equation may underestimate renal function (eGFR) in women.

The current findings support the concept of other underlying renal disease mechanisms than diabetic nephropathy

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Ongoing treatment with renin-angiotensin-aldosterone-blocking agents does not predict normoalbuminuric renal impairment in a general type 2 diabetes population ☆

Hanri Afghahi [a], Mervete Miftaraj [b], Ann-Marie Svensson [b], Henrik Hadimeri [a], Soffia Gudbjörnsdottir [c], Björn Eliasson [c], Maria K. Svensson [d,*]
on behalf of the Swedish National Diabetes Register (NDR)

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Relationship between blood pressure and risk of cardiovascular events and all cause of mortality in patients with type 2 diabetes and renal impairment

Background

- Hypertension is present in 20-55% of patients at the time of diagnosis of type 2-diabetes.

- Elevated blood pressure is associated with an increase in risk of cardiovascular disease and death in the general population and when hypertension is combined with diabetes the risk increases additionally.

- The optimal blood pressure targets in high risk patients with diabetes and renal impairment is not known .

Current guidelines for the management of blood pressure in patients with diabetes and renal impairment.

	Renal impairment without albuminuria	Renal impairment with albuminuria
KDIGO 2012	**140/90 mm Hg**	**130/80 mm Hg**
EHS/ESC 2013	**140/90 mmHg**	**130/80 mmHg**
ADA 2013	**140/80 mmHg**	**140/80 mmHg**
JNC 2014 < 70 years*	**140/90 mmHg**	**140/90 mm Hg**

- **JNC does not give an recommendation for BP goal in patients aged 70 years or older**

BP targets and cardiovascular outcomes in different RCT Studies

	Patients	Outcomes
Progress	6 501 with TIA and stroke	A mean reduction of 9/4 mmHg a significant reduction in stroke
Ontarget	22,1024	SBP <130mmhg increase risk of CV mortality
HOT	19 193 with DBP 100-115 mmHg	The benefit of BP<140/90 mmHg.
ACCORD	4 733 with T2D	Increase adverse events with intensive therapy SBP<120mmHg
HOPE	18 890 with HT	Reduction CVE and stroke in Ramipril groupBP 136/77 mmHg
ABCD	950 with T2D	Aggressive BP control, in both hypertensive 132/78mm Hg and normotensive patients 128/75, reduce means complications caused by type 2 diabetes mellitus.
UKPDS 36	4801 with T2D	lowest risk being in those with systolic blood pressure less than 120 mm Hg.
ADVANCE	11140 with T2D	BP 145/81 mmHg→ 135/75 mmHg, 9% reduction in micro/macrovascular events.
Invest Subgroup	6400 with DM and CAD	Tight control of SBP<130 mmHg was not associated with improved cardiovascular outcomes.
IDNT post hoc	1590 with T2D and DN(urine protein	BP <120/85 may be associated with an increase in CV events.

Aims of study

- The relationship between blood pressure level and risk of cardiovascular events or all- cause of mortality in patients with type 2-diabetes (T2D) and renal impairment.

- To evaluate if the risk pattern for cardiovascular events differ between coronary heart disease and stroke.

Patients and methods

- 33 356 patients with type 2-diabetes and renal impairment (eGFR <60ml/min/1.73m^2 according to MDRD)
- Median follow up time 5.3 years.
- Blood pressure values (BPs) were the mean of all reported values during the follow-up period (baseline to first event or end of study).
- The relationships between mean BPs, CV events were examined by time-dependent Cox models, to estimate hazard ratios (HR), adjusting for CV risk factors and medications.

Clinical and biochemical characteristics at baseline

	No renal impairment (eGFR ≥ 60 ml/min/1,73m^2) (n = 117 323)	Renal impairment (eGFR < 60 ml/min/1,73m^2) (n = 33 356)
Age (years)	65 ±11	75 ±9
Diabetes duration (years)	7.2±7	10 ±8
HbA1c (mmol/mol)	54 ±13	54 ±13
Syst blood pressure (mmHg)	140 ±17	141 ±19
Diast blood pressure (mmHg)	78 ±9.5	75 ±10
BMI (kg/m^2)	29 ±4.8	29±4.8
eGFR MDRD (ml/min/1.73m^2)	86±19	48±9.4
Male (%)	60	43
Smokers (%)	14	7
Any retinopathy (%)	17	23
History of CVD/CHF (%)	18/3.8	33/15
Antihypertensive treatment (%)	72	88
Albuminuria (%)	18	30
Micro vs Macro (%)	13/5	16/14

Prevalence and hazard ratios of CVD and all-cause mortality by SBP

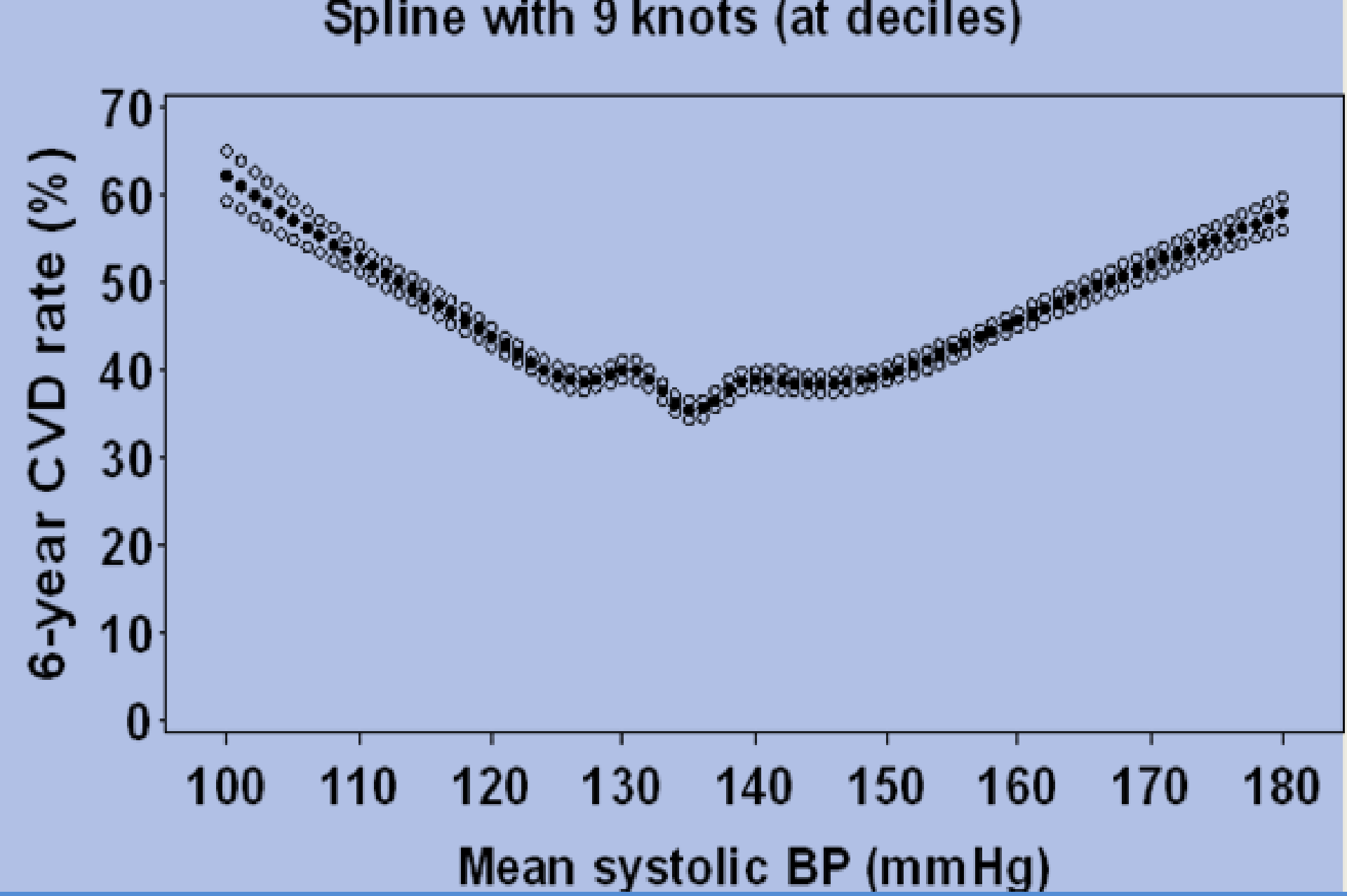
Systolic blood pressure mmHg (mean± SD)	CVD number/%	All-cause mortality number/%	CVD HR 95% CI	All-cause mortality (HR 95% CI)
80-120 (114±7)	1526/46.0	1686/50.8	2.30 (2.03-2.60)	2.40 (2.11-2.73)
120-127 (124±2)	1001/30.2	963/29.0	1.37 (1.20-1.55)	1.40 (1.22-1.60)
128-131 (130±1)	1128/34.0	1057/31.8	1.64 (144-1.86)	1.53 (1.35-1.76)
131-135 (134±1)	956/28.8	837/25.2	1.36 (1.20-1.55)	1.22 (1.05-1.41)
135-139 (137±1)	719/21.7	678/20.4	1	1
139-142 (140±1)	1201/36.2	1118/33.7	1.78 (1.57-2.02)	1.61 (1.40-1.84)
142-146 (144±1)	994/30.0	893/26.9	1.39 (1.22-1.58)	1.23 (1.07-1.42)
146-151 (149±2)	1153/34.7	983/29.6	1.77 (1.56-2.01)	1.30 (1.13-1.50)
151-160 (155±3)	1018/30.7	987/29.6	1.46 (1.28-1.66)	1.27 (1.10-1.46)
160-230 (169±10)	1621/48.8	1536/46.3	2.95 (2.62-3.34)	2.02 (1.78-2.30)

Hazard ratios were adjusted for age, diabetes duration, gender, HbA1c, BMI, albuminuria , smoking, cholesterol/HDL(cholesterol,HDL ratio), Triglicirde/HDL(cholesterol,HDL ratio), history of cardiovascular disease (CVD), history of congestive heart disease(CHF), anti hypertension and lipid lower treatment. Mean arterial pressure 97-100 mm Hg as a reference group.

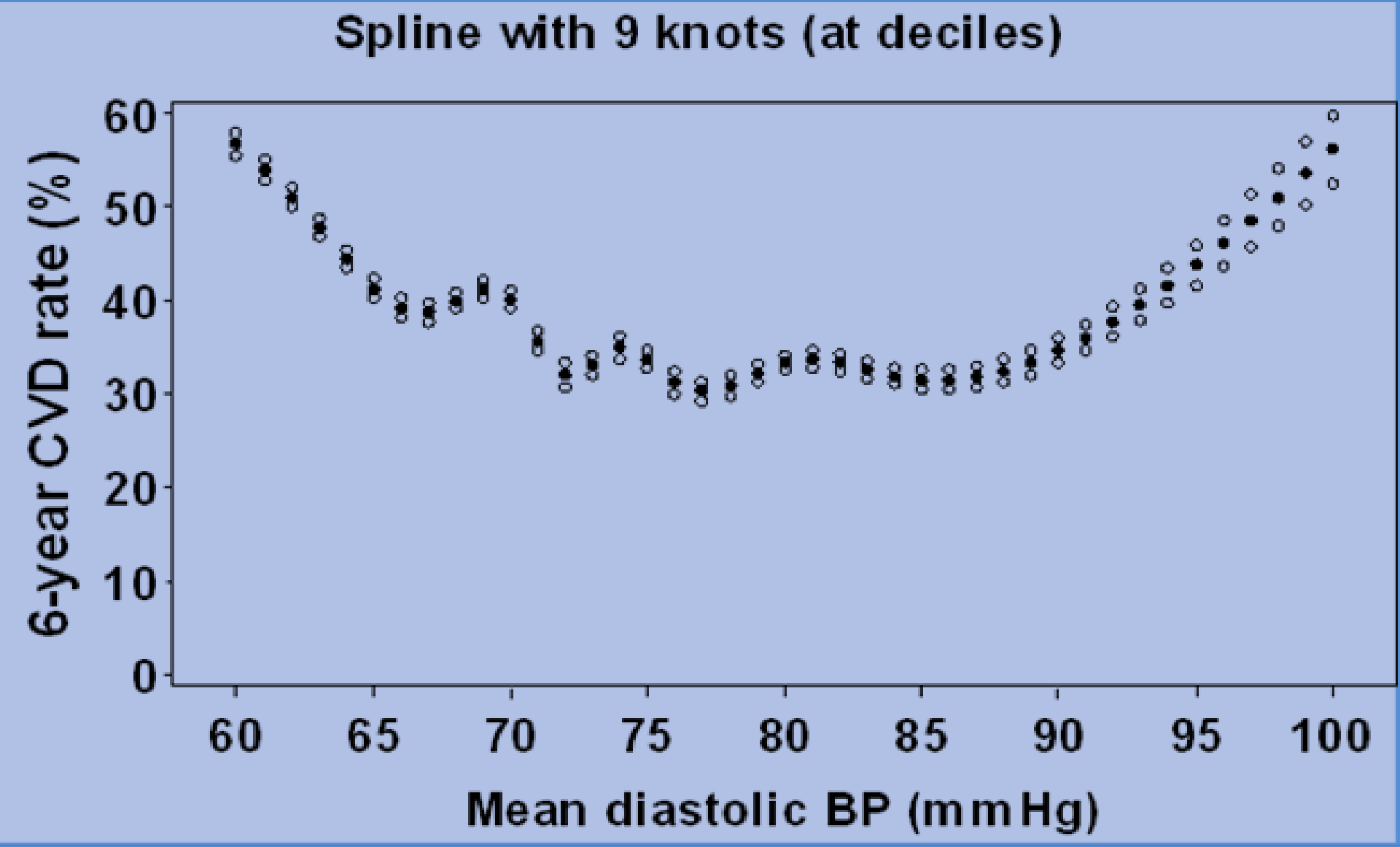
Prevalence and hazard ratios of CVD and all cause mortality by DBP

Diastolic blood pressure mmHg (Mean± SD)	CVDc number/%	All cause of mortality number/%	CVD HR 95% CI	All cause of mortality HR 95% CI
40-63 (50±3)	1526/46.0	1662/50.1	2.00 (1.80-2.22)	2.00 (1.78-2.24)
63-67 (65±1)	1001/30.2	1116/33.6	1.21 (1.07-1.37)	1.21 (1.07-1.37)
67-70 (68±1)	1128/34.0	911/27.4	1.15 (1.01-1.30)	1.14 (1.03-1.30)
70-72 (70±0.5)	956/28.8	1311/39.5	1.88 (1.67-2.11)	1.92 (1.67-2.14)
72-74 (73±1)	719/21.7	801/24.1	1	1
74-76 (75±0.5)	1201/36.2	1007/30.3	1.43 (1.26-1.62)	1.44 (1.28-1.63)
76-78 (77±1)	994/30.0	706/21.3	1.23 (1.08-1.40)	1.24 (1.01-1.41)
78-80 (79±1)	1153/34.7	1091/32.9	1.78 (1.58-2.01)	1.81 (1.60-2.04)
80-83 (81±1)	1018/30.7	982/29.6	1.60 (1.40-1.80)	1.62 (1.47-1.82)
83-125 (88±4)	1621/48.8	1151/34.7	2.26 (2.00-2.54)	2.30 (2.03-2.59)

Hazard ratios were adjusted for age, diabetes duration, gender, HbA1c, BMI, albuminuria , smoking, cholesterol/HDL(cholesterol,HDL ratio), Trigliciride/HDL(cholesterol,HDL ratio), history of cardiovascular disease (CVD), history of congestive heart disease(CHF), anti hypertension and lipid lower treatment. Mean arterial pressure 97-100 mm Hg as a reference group.



Splines with nine knots at deciles (filled circles) and 95% confidence intervals (unfilled circles) in patients with T2D and RI. SBP as a continuous variable and square of SBP for analysis of nonlinear relationship in a Cox regression model, adjustment for covariates .



Splines with nine knots at deciles (filled circles) and 95% confidence intervals (unfilled circles) in patients with T2D and RI. DBP as a continuous variable and square of DBP for analysis of nonlinear relationship in a Cox regression model, adjustment for covariates.

CONCLUSIONS

- A U-shaped relationship was observed between blood pressure and the overall risk of cardiovascular events and mortality.
- Both high and low blood pressure increased the risk of coronary heart disease and stroke but for stroke mainly a high blood pressure >160/88 mmHg increased the risk of stroke significantly.
- More than half the number of patients with systolic blood pressure <120 mmHg and >160 mmHg died during the study period (median 5.3 years).
- Adjustments for presence of albuminuria did not markedly alter the results.

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ARTICLE

Blood pressure level and risk of major cardiovascular events and all-cause of mortality in patients with type 2 diabetes and renal impairment: an observational study from the Swedish National Diabetes Register

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Change in blood pressure and risk of all cause of mortality in patients with type 2 diabetes and renal impairment

Background

- In our previous studies, we have seen a U-shape relationship between blood pressure and risk of death.
- Coexisting disease such as heart failure could be the cause of a higher risk of death at low blood pressure.
- It is unclear whether low blood pressure due to intensive antihypertensive treatment increases the risk of death.
- Previous studies have shown change in blood pressure level increases the risk of cardiovascular events and death. (BP variability)

Aims

- *Study the connection between: different blood pressure measurement*

  - Time-adjusted mean systolic blood pressure during study time
  - Change in systolic blood pressure between two last observations
  - The number of blood pressure lowering drugs classifies at baseline

and

- *The risk of death in patients with type 2 diabetes and impaired renal function with and without heart failure.*

Patients and methods

- 27,732 patients with type 2 diabetes and renal impairment were followed for 4.7 mean y*ears*

- Patients were divided based on baseline and time-adjusted systolic blood pressure in four groups from SBT <130 to SBT> 160 mmHg. A systolic blood pressure range of 130-140 mmHg was used as a reference group.

- Patients were divided according to change in systolic blood pressure between two last observations in 7 groups, from -50 mmHg to +50 mmHg. A blood pressure change of +/- 10 mmHg was used as a reference group.

Clinical characteristics at baseline

	Without CHF (n=23 799)	With CHF (n=3933)
Age (year)	74±9	77±8
Diabetes duration (år)	10±8	11 ±8
HbA1c (mmol/mol)	55 ±13	55 ±13
SBP (mmHg)	140 ±18	132 ±20
DBP (mmHg)	73 ±10	70 ±10
BMI (kg/m^2)	29 ±4.8	29±4.8
eGFR MDRD (ml/min/1.73m^2)	49±9	44±10
Man (%)	41	53
cholesterol (mmol/L)	4.9±1.0	4.6±1.0
LDL-C (mmol/L)	2.7±0.9	2.5±0.9
Tidigare CVD (%)	25	65
Blood pressure lowering agents (%)	80	93
Albuminuria (%)	29	36
Micro vs Macro (%)	16/13	18/14

Association between time updated systolic blood pressure and risk of mortality

Update Mean SBP (mmHg)	All patients HR 95% CI	P-value	Patients without previous CHF HR 95% CI	P-value
<130	1.28 (1.21-1.38)	<0.0001	1.26 (1.17-1.36)	<0.0001
130-140	1 (ref)	-	1 (ref)	-
141-160	0.91 (0.86-0.97)	0.002	0.92 (0.87-0.99)	0.017
>160	1.01 (0.93-1.09)	0.84	1.01 (0.92-1.10)	0.90

Hazard ratios (HR) with 95% confidence interval adjusted for age, diabetes duration, gender, HbA1c, BMI, albuminuria , smoking, LDL-cholesterol, triglycerides/HDL, history of cardiovascular disease (CVD), previous history of chronic heart failure (CHF), antihypertensive treatment and lipid-lowering treatment and diastolic blood pressure. SBP; systolic blood pressure

Change in systolic blood pressure between the two last observations and risk of mortality

Change in SBP (mmHg)	All patients HR 95% CI	P-value	Patients without previous CHF HR 95% CI	P-value
(-50, -25]	1.44 (1.33-1.56)	<0.0001	1.44 (1.32-1.58)	<0.0001
(-25, -10]	1.24 (1.17-1.32)	<0.0001	1.21 (1.13-1.31)	<0.0001
(-10, +10]	1 (ref)	-	1 (ref)	-
(+10, +25]	1.04 (0.98-1.10)	0.24	1.01 (0.94-1.09)	0.69
(+25, +50]	1.17 (1.07-1.29)	<0.0001	1.24 (1.11-1.38)	<0.0001

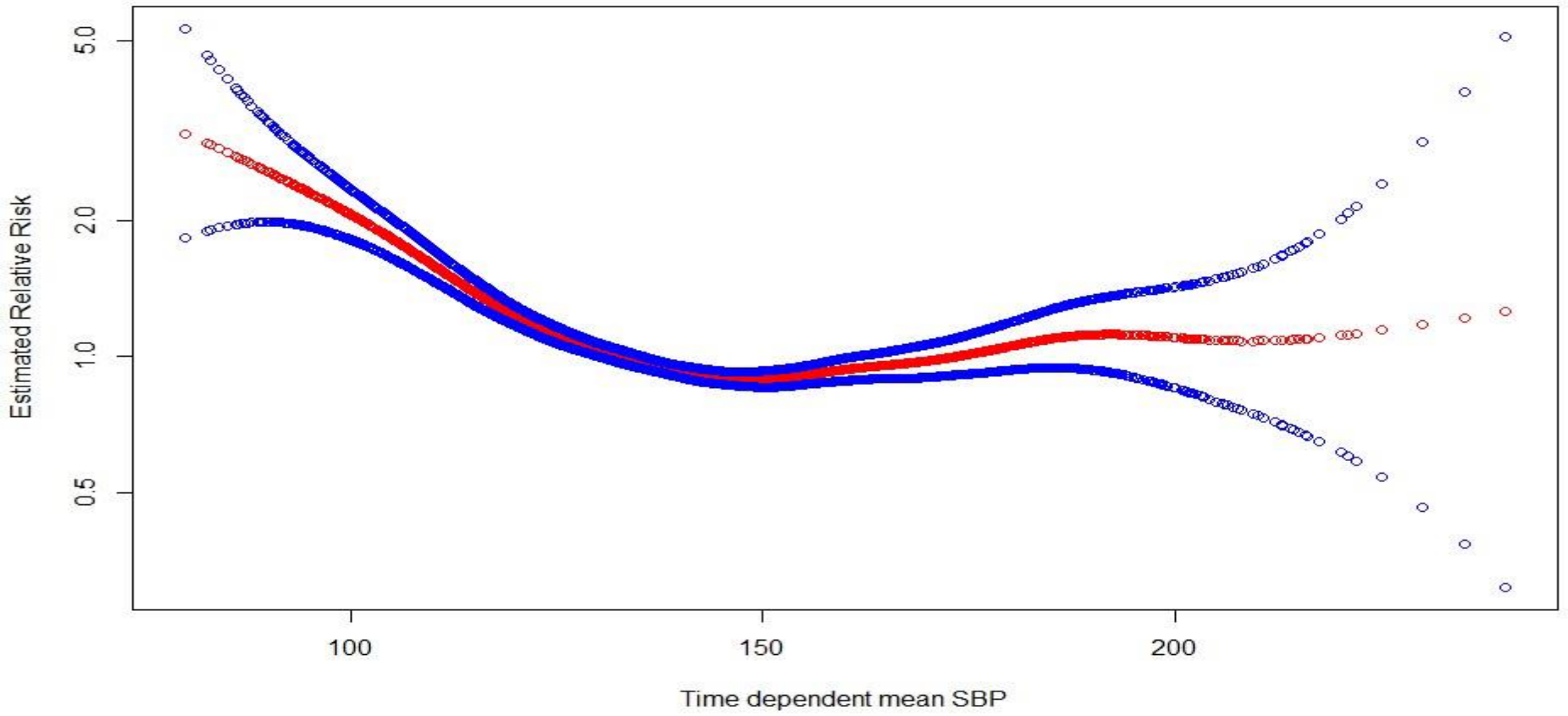
Hazard ratios (HR) with 95% confidence interval adjusted for age, diabetes duration, gender, HbA1c, BMI, albuminuria , smoking, LDL-cholesterol, triglycerides/HDL, history of cardiovascular disease (CVD), previous history of chronic heart failure (CHF), antihypertensive treatment and lipid-lowering treatment and diastolic blood pressure. SBP; systolic blood pressure,

Number of blood pressure lowering classes at baseline and risk of mortality

Numbers of antihypertensive	All patients HR 95% CI	P-value	Patients without previous CHF HR 95% CI	P-value
0	1.08 (1.00-1.17)	0.049	1.08 (0.99 ,1.17)	0.09
1	1.07 (1.01-1.14)	0.02	1.08 (1.01 ,1.15)	0.03
2	1 (ref)	-	1 (ref)	-
3	0.99 (0.94 -1.05)	0.79	0.99 (0.92 ,1.06)	0.68
4	0.93 P(0.86-1.02)	0.133	0.94 (0.85 ,1.03)	0.20

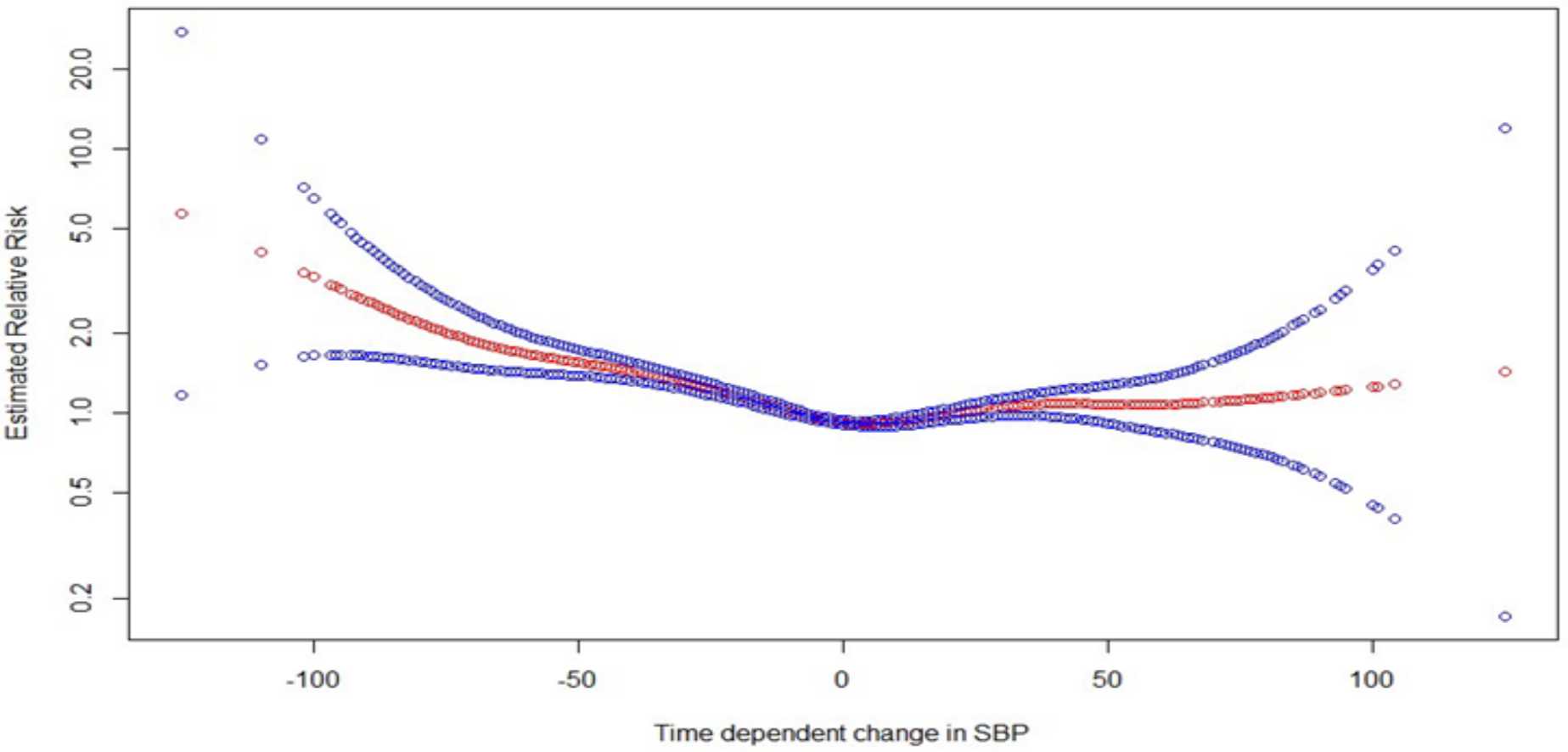
Hazard ratios (HR) with 95% confidence interval adjusted for age, diabetes duration, gender, HbA1c, BMI, albuminuria , smoking, LDL-cholesterol, triglycerides/HDL, history of cardiovascular disease (CVD), previous history of chronic heart failure (CHF), antihypertensive treatment and lipid-lowering treatment and diastolic blood pressure. SBP; systolic blood pressure,.

Relationship between time-adjusted systolic blood pressure as a continuous variable and relative risk (RR) for death



Splines 95% confidence intervals (unfilled circles) in patients with T2D and RI. SBP as a continuous variable and square of SBP for analysis of nonlinear relationship in a Cox regression model, adjustment for covariates

Relationship between change in systolic blood pressure between the last two observations and the risk of death



Splines 95% confidence intervals (unfilled circles) in patients with T2D and RI. SBP as a continuous variable and square of SBP for analysis of nonlinear relationship in a Cox regression model, adjustment for covariates

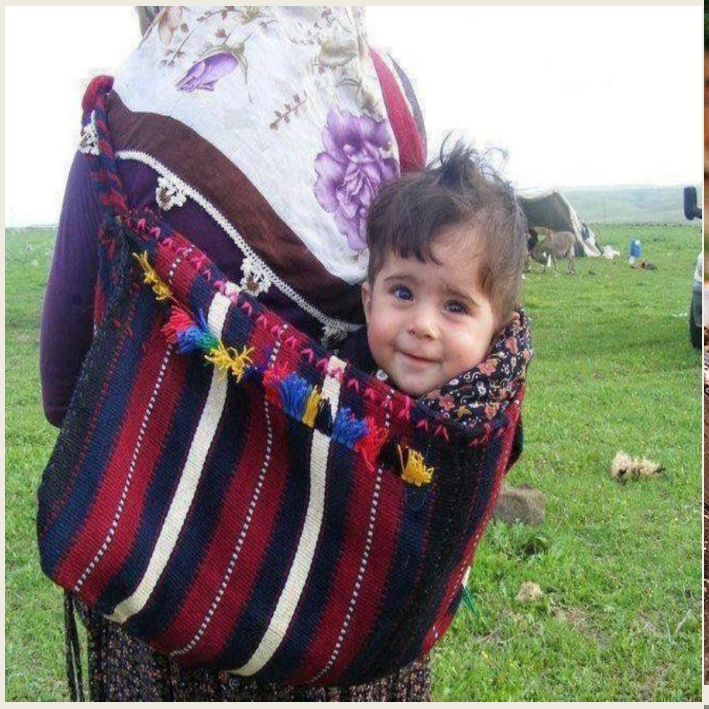
CONCLUSIONS

- 30% of all patients and 57% of patients with previous heart failure died during the follow-up (4.7 years)

- Both low systolic blood pressure and a decrease in systolic blood pressure during follow-up with or without previous heart failure were associated with a higher risk of death.

- The use of more classes of antihypertensive drugs at the baseline was not associated with a higher risk of death .

Association between HbA1c and risk of all cause of mortality in patients with diabetes and maintenance dialysis.



Thank for your attention!

Background

- Glycated hemoglobin (HbA1c) is mostly used as long-term glycemic control in diabetes
- Most of the studies indicated HbA1c is a strong marker for long term glycemic control in patients with diabetes and maintenance dialysis treatment.
- A U-shape correlation between HbA1c and mortality in patients with diabetes on dialysis treatment has been suggested .
- In Patients with diabetes and normal kidney function glycaemic variability identified as risk factor for mortality but is not well studies in patients with advance CKD or dialysis treatment .

Patients and methods

- 3930 patients with diabetes dialysis treatment [hemodialysis (HD), n = 2487 (63%); peritoneal dialysis (PD), n = 796 (20%); and both HD and PD, n = 647 (17%)] were followed between 2008-2017

- HbA1c was defined as the mean value
- HbA1c variability was determined by the coefficient of variation CV),SE(HbA1c)/mean(HbA1c).

- Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using time-dependent Cox models, which included adjustments for demographics, laboratory findings and comorbidity.

Hazard ratios (HR; 95% CI) for mean HbA1c

Mean HbA1C (%)	Univariate analyses HR 95% CI	Multivariate analyses HR 95% CI
HbA1c≤5	0.97 (0.82-1.16)	1.06 (0.88-1.28)
5< HbA1c≤6	1 (ref group)	1 (ref group)
6<HbA1c≤6.9	1.21 (1.08-1.36)	1.26 (1.12-1.42)
6.9<HbA1c≤7.8	1.11 (0.97-1.26)	1.22 (1.06-1.41)
7.8<HbA1c≤8.7	1.18 (1.01-1.34)	1.39 (1.17-1.09)
8.7< HbA1c≤9.7	1.33 (1.08-1.66)	1.69 (1.34-2.12)
9.7<HbA1c	1.46 (1.14-1.86)	2.03 (1.56-2.64)

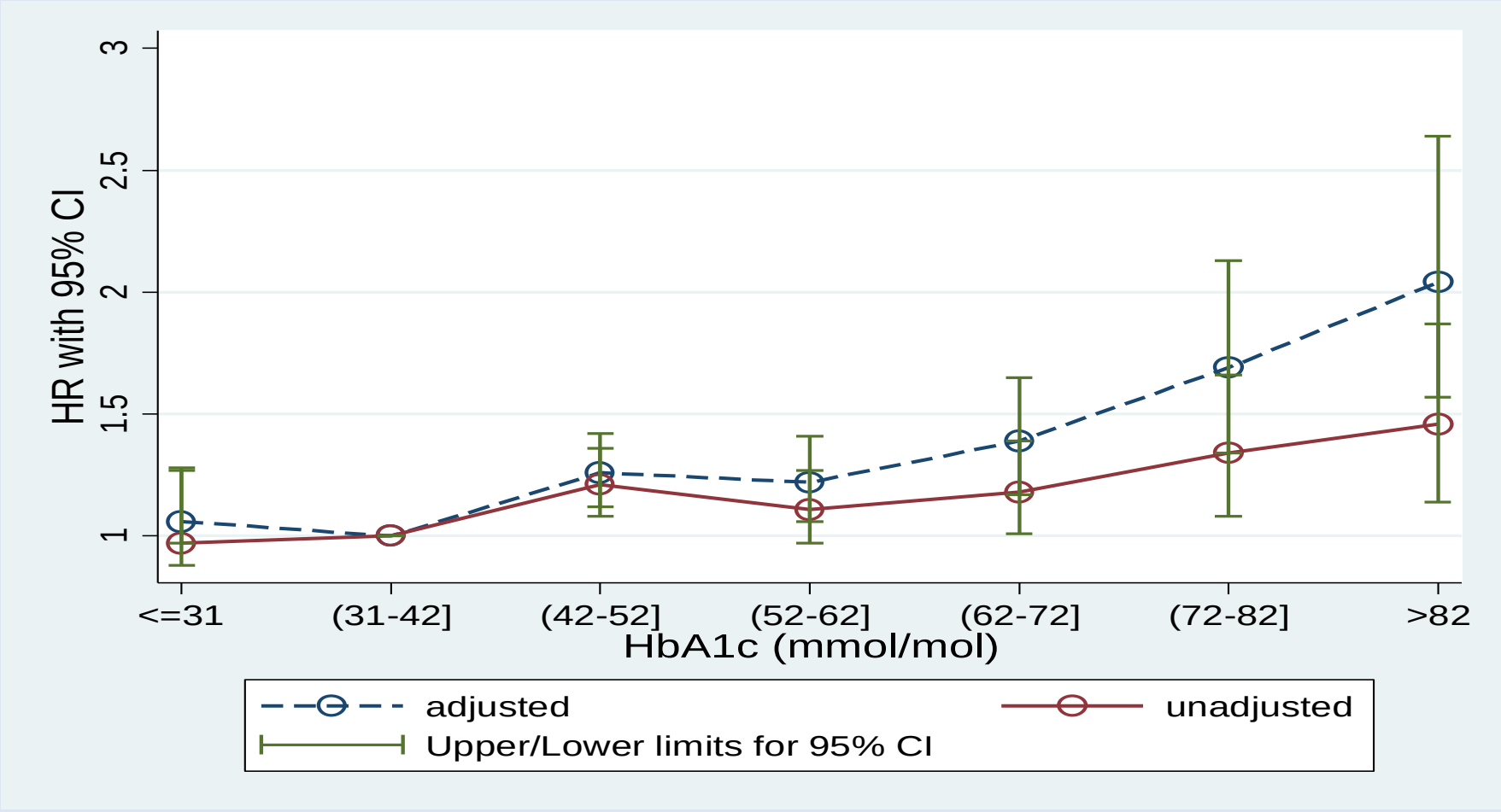
Hazard ratios (HR) with 95% confidence interval adjusted for for age, gender, BMI, LDL-cholesterol, triglycerides,systolic blood pressure, diastolic blood pressure, CRP, S-albumin, haemoglobin,PTH, history of cardiovascular disease (CVD) and malignancy, antihypertensive treatment,.5<HbA1c ≤6 is a reference group.

Hazard ratios (HR; 95% CI) for HbA1c variability,

Mean HbA1C (%)	Univariate analyses HR 95% CI	Multivariate analyses HR 95% CI
CV ≤0.51	1 (ref)	1.06 (0.88-1.28)
0.51< CV≤0.77	1.09 (0.87-1.34)	1.14 (0.90-1.43)
0.77<CV≤1.32	1.14 (0.92-1.14)	1.15 (0.93-1.42)
1.32<CV≤1.77	1.33 (1.07-1.68)	1.29 (1.02-1.63)
1.77<CV≤2.83	1.58 (1.27-1.98)	1.45 (1.15-1.82)
2.83< CV≤4.60	1.87 (1.52-2.32)	1.98 (1.59-2.47)
4.60<CV	1.83 (1.43-2.43)	1.98 (1.53-2.57)

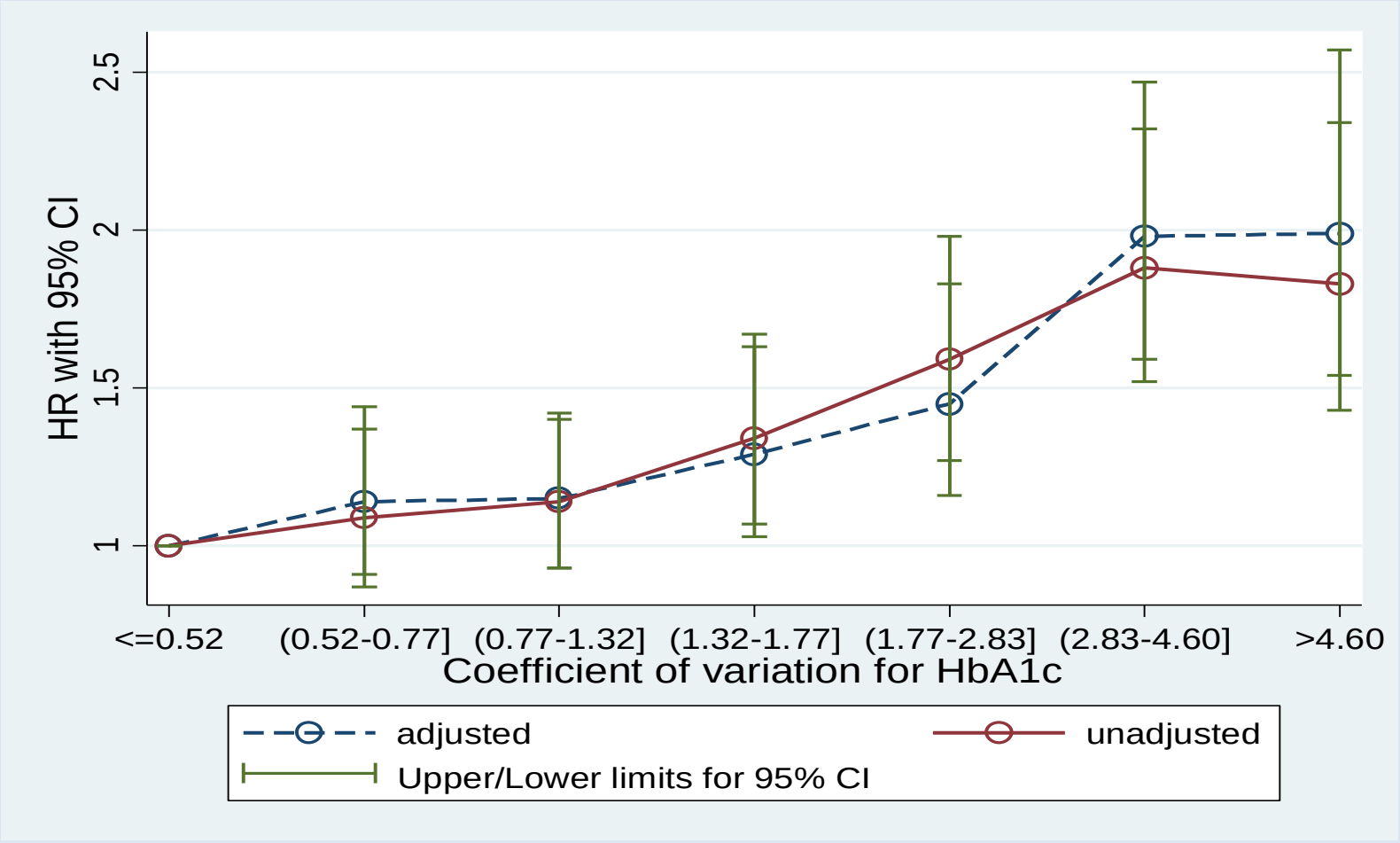
Hazard ratios (HR) with 95% confidence interval adjusted for for age, gender, BMI, LDL-cholesterol, triglycerides,systolic blood pressure, diastolic blood pressure, CRP, S-albumin, haemoglobin,PTH, history of cardiovascular disease (CVD) and malignancy, antihypertensive treatment,.5<HbA1c ≤6 is a reference group.

Hazard ratio (HR) of all-cause mortality according to mean HbA1c-level.



Reference category: 31-42 mmol/mol (5%),Adjusted model is adjusted for age, BMI, MAP, albumin, CRP, Hb, PTH, HD/PD, CVD, BP-medicine. Reference category: 31-42 mmol/mol

Hazard ratio (HR) of all-cause mortality according to HbA1c-variability.



Reference category:Reference category: ≤0.52,Adjusted model is adjusted for age, BMI, MAP, albumin, CRP, Hb, PTH, HD/PD, CVD, BP-medicine. Reference category: 31-42 mmol/mol

General aims of thesis

- *To study the prevalence and incidence of albuminuria and renal impairment in a general population with type 2 diabetes.*

- *To assess and study the occurrence of cardiovascular risk factors in a population with type 2 diabetes and renal impairment.*

- *To evaluate cardiovascular disease (CVD) as well as cardiovascular and all-cause mortality in a population with type 2 diabetes and renal impairment.*

Risk factors at UKPDS 74

Albuminuria and renal impairemnt

- High urin albumin
- High creatinine at baseline
- Indian ethnicity
- High systolic blood pressure (SBP)

Albuminuria only

- Male gender
- High HbA1c
- High waist cirumfrence
- Smoking
- Retinopathy
- High WBC

Renal impiremnt only

- Female gender
- Low waist cirumfrence
- Insulin sensitive

Prevalence and hazard ratios of stroke and coronary heart disease (CHD) by SBP

Systolic blood pressure mmHg (Mean± SD)	Stroke (number/%)	CHD (number/%)	Stroke (HR 95% CI)	CHD (HR 95% CI)
80-120 (114±7)	198/6.0	1211/36.5	1.79 (1.34-2.39)	2.60 (2.25-3.02)
120-127 (124±2)	193/5.8	719/21.7	1.40 (1.05-1.86)	1.45 (1.24-1.69)
128-131 (130±1)	200/6.0	808/24.3	1.36 (1.02-1.82)	1.76 (1.51-2.05)
131-135 (134±1)	186/5.6	673/20.3	1.26 (0.94-1.67)	1.46 (1.25-1.71)
135-139 (137±1)	169/5.1	458/13.8	1	1
139-142 (140±1)	250/7.5	826/24.9	1.67 (1.27-2.20)	1.89 (1.62-2.21)
142-146 (144±1)	209/6.3	662/19.7	1.42 (1.08-1.87)	1.43 (122-168)
146-151 (149±2)	254/7.6	718/21.6	1.78 (1.36-2.33)	1.67 (1.42-1.96)
151-160 (155±3)	249/7.5	629/18.9	1.48 (1.12-1.94)	1.46 (1.24-1.71)
160-230 (169±10)	376/11.3	1000/31.1	2.65 (2.04-3.43)	2.93 (2.53-3.41)

Hazard ratios were adjusted for age, diabetes duration, gender, HbA1c, BMI, albuminuria , smoking, cholesterol/HDL(cholesterol,HDL ratio), Trigliciride/HDL(cholesterol,HDL ratio), history of cardiovascular disease (CVD), history of congestive heart disease(CHF), anti hypertension and lipid lower treatment. Mean arterial pressure 97-100 mm Hg as a reference group.

Prevalence and hazard ratios of stroke and coronary heart disease (CHD) by DBP

Diastolic blood pressure mmHg (Mean± SD)	Stroke number/%	CHD number/%	Stroke HR 95% CI	CHD HR 95% CI
40-63 (50±3)	226/6.8	1197/36.1	1.47 (1.18-1.95)	2.05 (1.78-2.34)
63-67 (65±1)	168/5.1	857/25.8	0.89 (0.66-1.21)	1.28 (1.11-1.48)
67-70 (68±1)	202/6.1	658/19.8	1.06 (0.80-1.41)	1.09 (0.93-1.26)
70-72 (70±0.5)	246/7.4	952/28.7	1.72 (1.31-2.25)	1.92 (1.67-2.14)
72-74 (73±1)	193/5.8	575/17.3	1	1
74-76 (75±0.5)	222/6.7	726/21.9	1.34 (1.02-1.77)	1.40 (1.21-1.63)
76-78 (77±1)	197/5.9	541/16.3	1.41 (1.08-1.85)	1.15 (0.99-1.35)
78-80 (79±1)	261/7.9	753/22.7	1.80 (1.38-2.35)	1.72 (1.49-1.99)
80-83 (81±1)	246/7.4	655/19.7	1.86 (1.43-2.42)	1.48 (1.27-1.73)
83-125 (88±4)	323/9.7	790/23.80	2.62 (2.03-3.38)	2.18 (1.88-2.51)

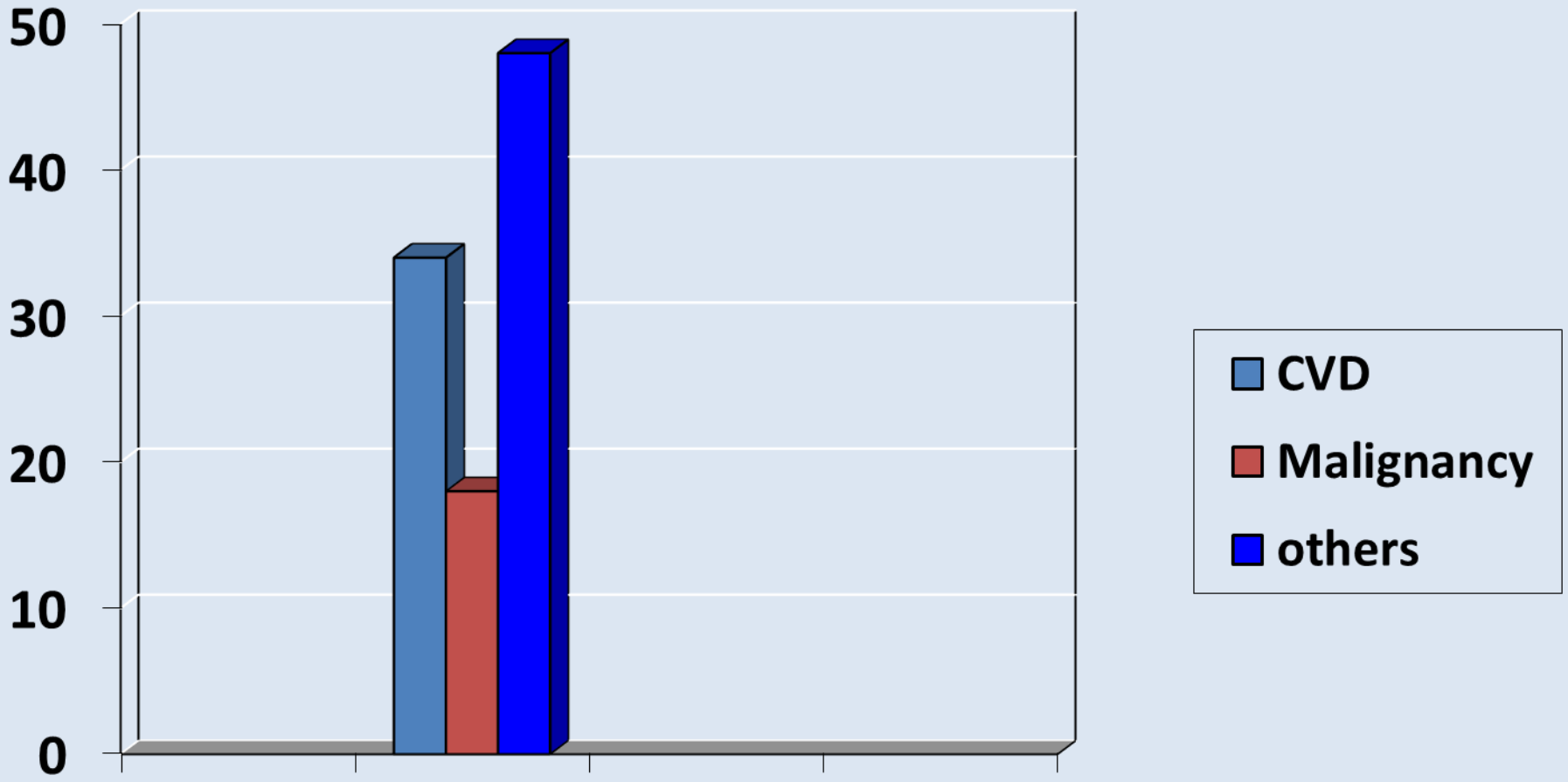
Hazard ratios were adjusted for age, diabetes duration, gender, HbA1c, BMI, albuminuria , smoking, cholesterol/HDL(cholesterol,HDL ratio), Trigliciride/HDL(cholesterol,HDL ratio), history of cardiovascular disease (CVD), history of congestive heart disease(CHF), anti hypertension and lipid lower treatment. Mean arterial pressure 97-100 mm Hg as a reference group.

Association between baseline systolic blood pressure and riskt of mortality

Baseline SBP (mmHg)	All patients HR 95% CI	P-value	Patients without previous CHF HR 95% CI	P-value
<130	1.10 (1.04-1.18)	0.003	1.06 (0.98-1.14)	0.16
130-140	1 (ref)	-	1 (ref)	-
141-160	0.96 (0.90-1.03)	0.30	0.96 (0.89-1.04)	0.31
>160	1.03 (0.96-1.11)	0.40	1.03 (0.94-1.12)	0.56

Hazard ratios (HR) with 95% confidence interval adjusted for age, diabetes duration, gender, HbA1c, BMI, albuminuria, smoking, LDL-cholesterol, triglycerides/HDL, history of cardiovascular disease (CVD), previous history of chronic heart failure (CHF), antihypertensive medication, lipid-lowering treatment and diastolic blood pressure. SBP; systolic blood pressure,

Cause of mortalitiy



Systolic Blood Pressure Intervention Trial (SPRINT)

Aim: Risk of cardiovascular events with target:

SBP< 120 mm Hg (intensive treatment)

or

SBP< 140 mmHg (standard treatment).

Methods:9361 persons without diabetes and SBP> 130 mm Hg. 2646(28%) had RI (eGFR<60ml/min)

Result and Conclusions:

After 1 year: lower rates of CVE and death with SBP<120 mmHg compare to SBP<140 mmHg but significantly.

Higher rates of some adverse events in intensive treatment. Not significantly risk reduction on main outcomes with patients with renal impairment (mean eGFR 47 ml/min at base line) with intensive treatment.