Diabetes and the kidney disease risk

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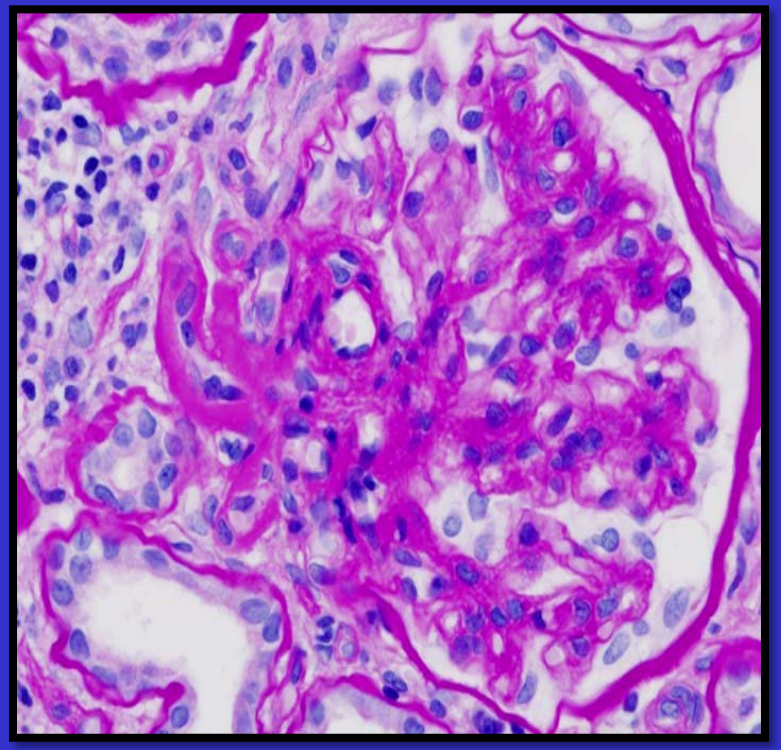
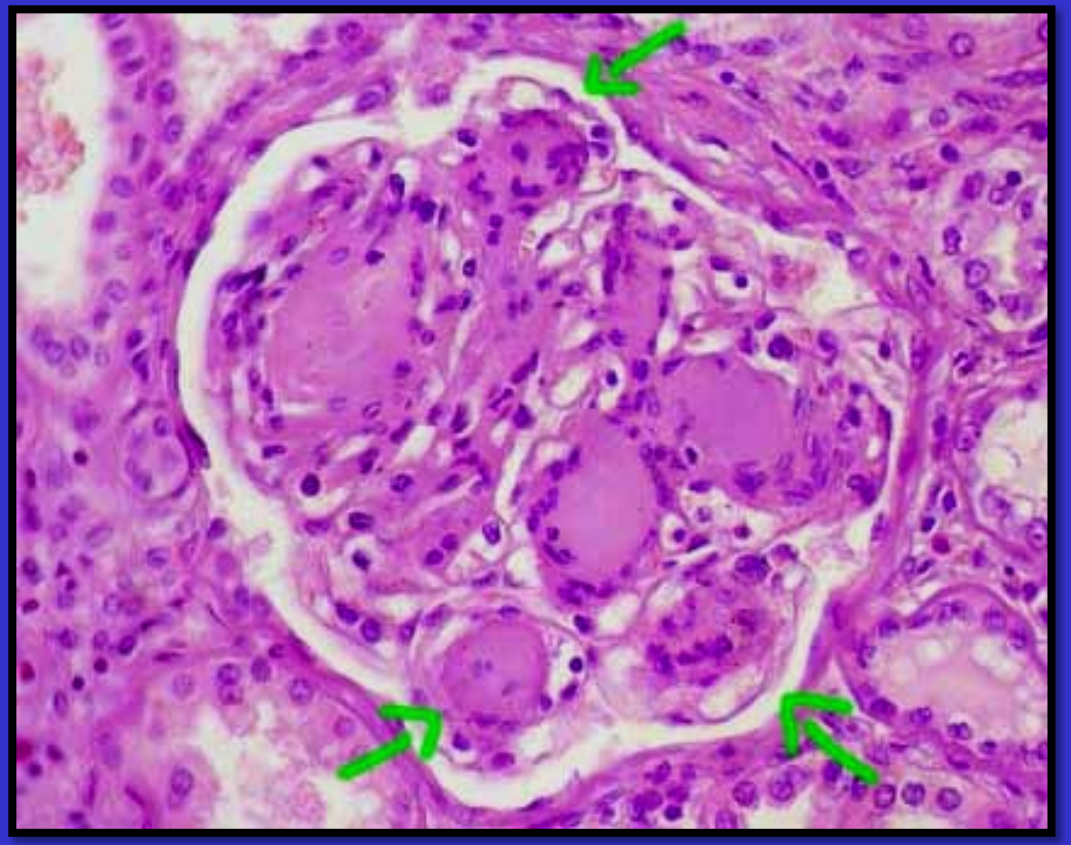
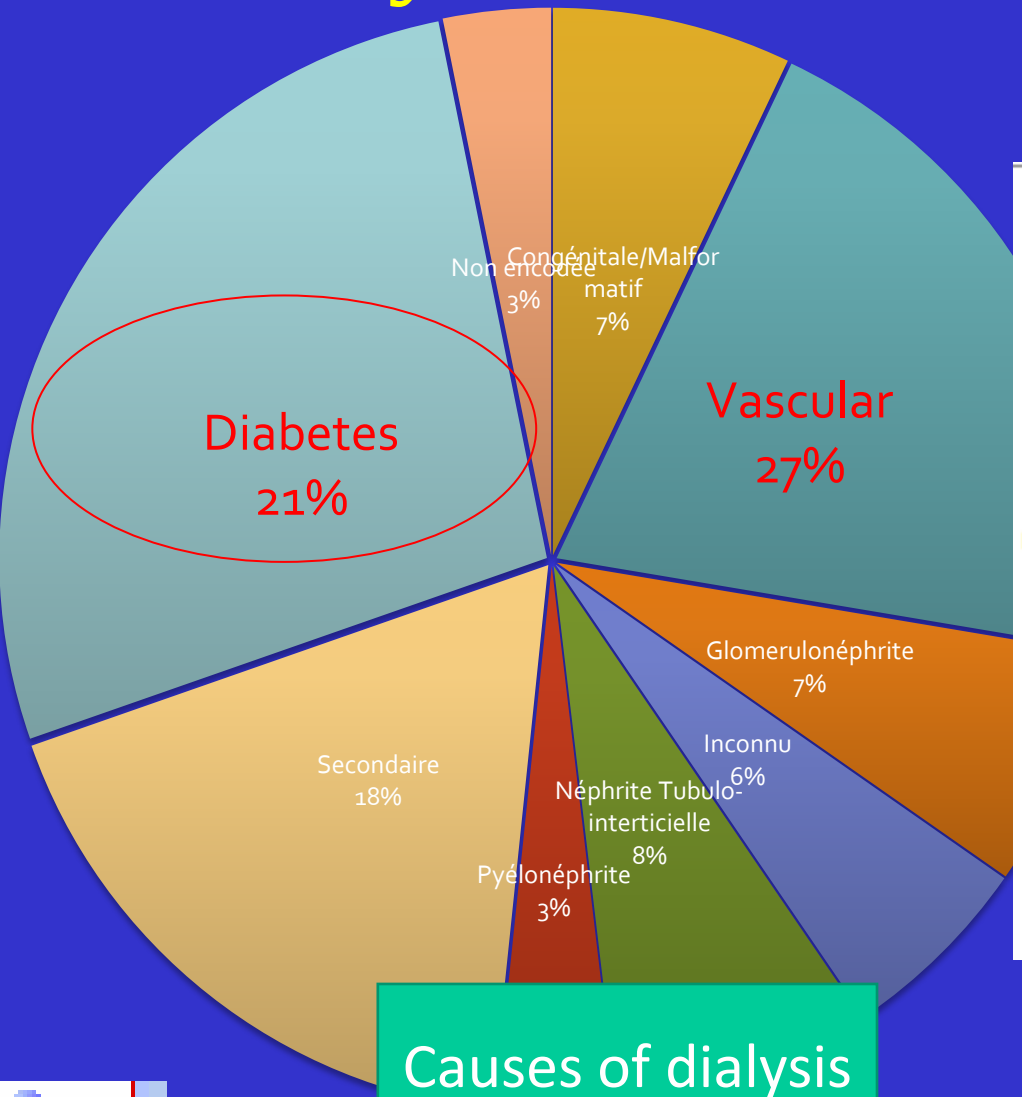
DIABETIC NEPHROPATHY

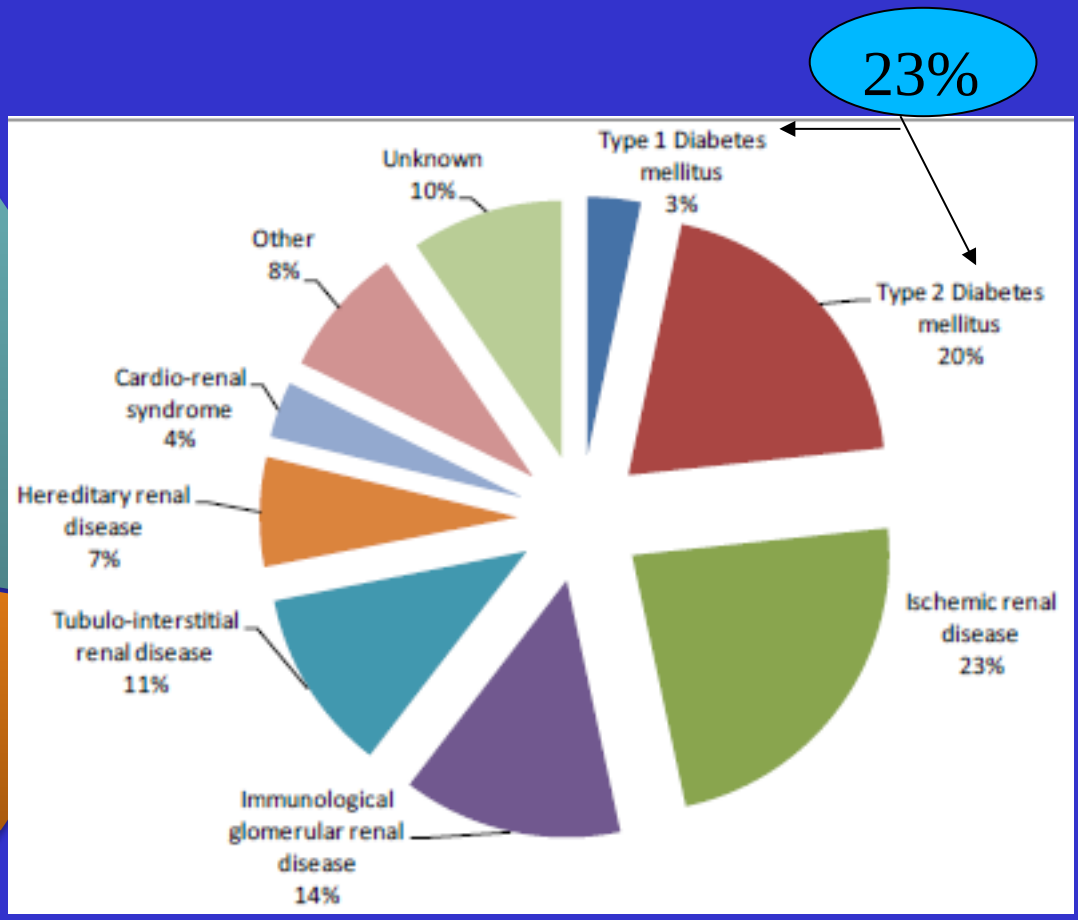
First cause of ESRD in the XXst century





Dialysis: Incident causes of ESRD (2013) in Belgiun

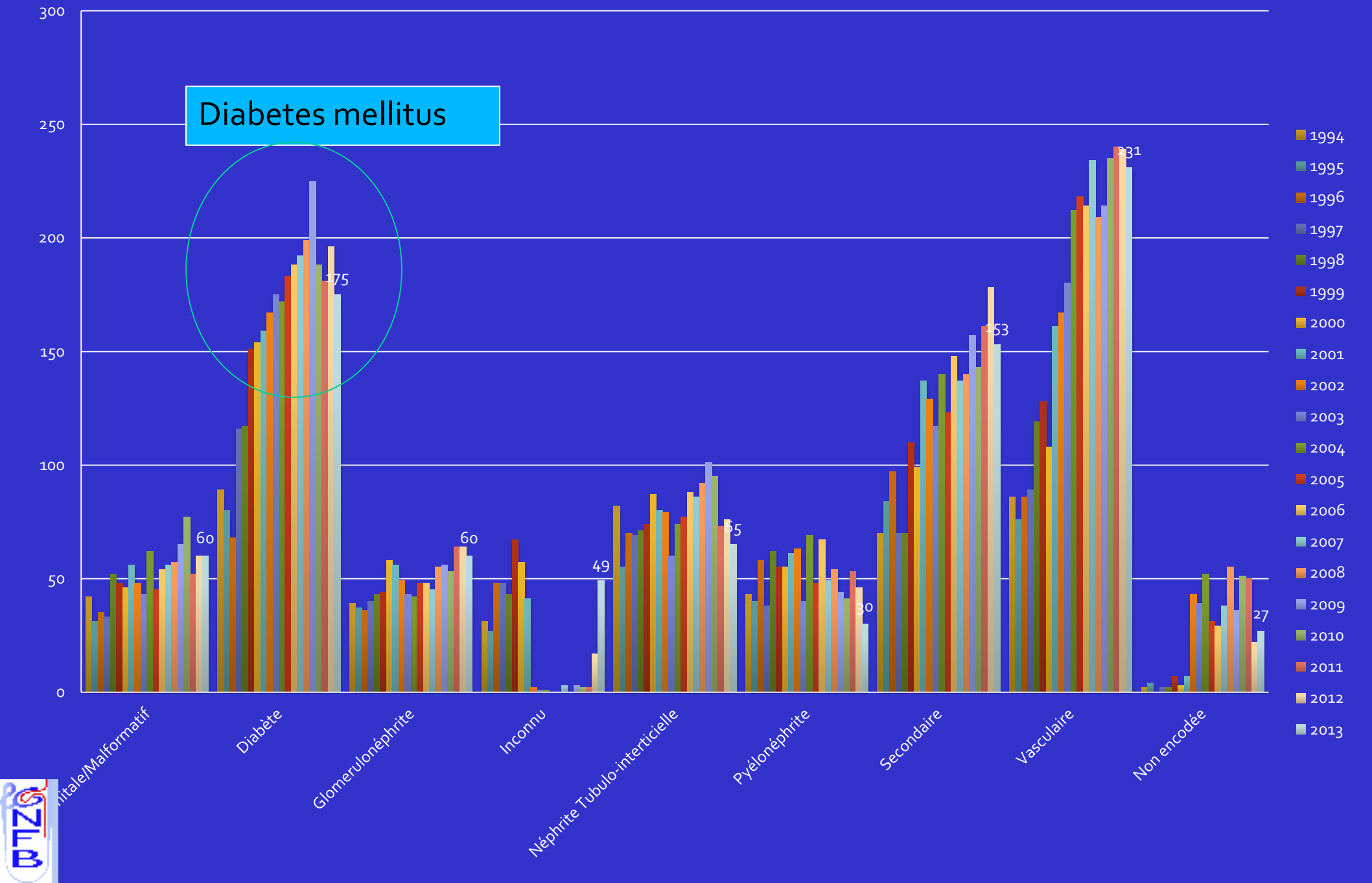




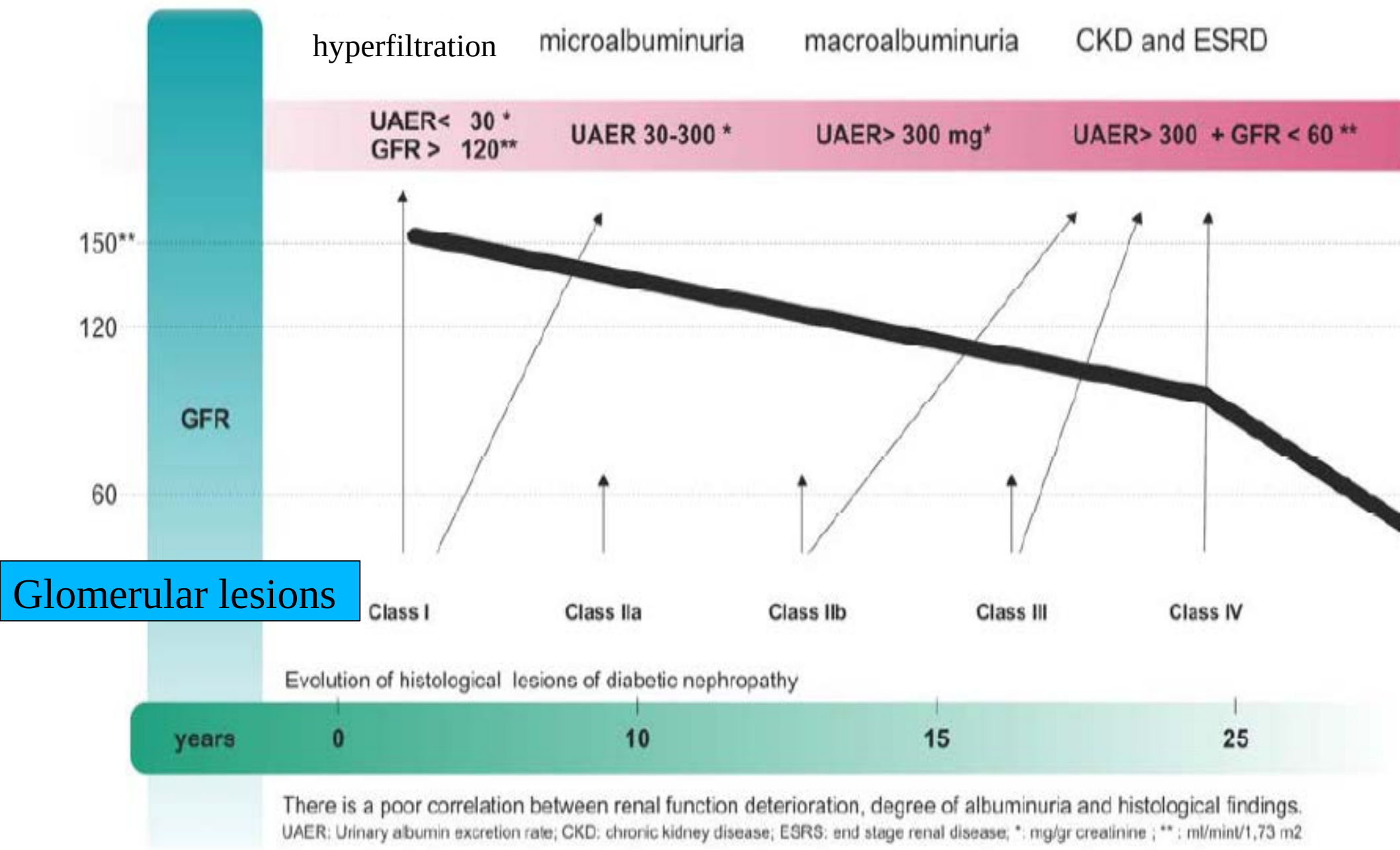
Causes of dialysis due to DM:
in USA 40%
in Asia 50%

Nederlandstalige Belgische Vereniging voor Nefrologie

Incident patients: Distribution according to nephropathy from 1994 - 2013



J. Clin. Med. **2015**, *4*



Glomerular lesions

Importance of TI lesions on the rate of progression

New paradigm of Diabetic kidney disease in the 21st century?

- In type 2 DM, kidney disease lesions could be quite different:

- Association between classical DN and a mixture of different patterns (including other primary glomerular diseases)

The Modern Spectrum of Renal Biopsy Findings in Patients with Diabetes

Shree G. Sharma, Andrew S. Bomback,† Jai Radhakrishnan,† Leal C. Herlitz,‡ Michael B. Stokes,‡ Glen S. Markowitz,‡ and Vivette D. D'Agati‡*

Table 1. Key demographic and clinical data at time of kidney biopsy

Among 611 type 2 DM

Characteristics	DN Alone	DN Plus NDRD	NDRD Alone
Participants (*n*)	227	164	220
Age (yr)	59 (49–65)	63 (55–72)[a]	63 (54–70)[b]
Male sex	129 (56.8)	100 (61.0)	142 (64.6)
Race			
Unknown	108 (47.6)	57 (34.8)[a]	104 (47.3)[c]
White	62 (27.3)	63 (38.4)[a]	70 (31.8)
African American	39 (17.2)	33 (20.1)	29 (13.2)
Hispanic	12 (5.3)	7 (4.3)	8 (3.6)
Asian	4 (1.8)	4 (2.4)	7 (3.2)
Other	2 (0.9)	0 (0.0)	2 (0.9)
DM type 1	9 (4.0)	5 (3.1)	2 (0.9)[b]
Duration of DM (yr)	13 (8–17)	10 (7–18)	5 (3–10)[b,c]
Serum creatinine (mg/dl)	2.3 (1.6–3.8)	3.1 (1.7–5.2)[a]	2.3 (1.5–4.4)[c]
eGFR (ml/min per 1.73 m^2)	31.3 (17.5–55.2)	21.4 (12.5–46.6)[a]	32.5 (14.3–60.0)[c]
Proteinuria (g/d)	5.0 (2.8–8.8)	5.0 (2.0–8.0)	2.9 (1.4–7.1)[b,c]

37% 27% 36%

Clin J Am Soc Nephrol 8: 1718–1724, October, 2013

New paradigm of Diabetic kidney disease in the 21st century?

- In type 2 DM, kidney disease lesions could be quite different:

- Association between classical DN and a mixture of different patterns (including other primary glomerular diseases) or

- Presence of decreased GFR but no proteinuria.

JAMA | Original Investigation

Clinical Manifestations of Kidney Disease Among US Adults With Diabetes, 1988-2014

JAMA. 2016;316(6):602-61

Table 4. Prevalence of Albuminuria and Reduced Estimated Glomerular Filtration Rate Among US Adults With Diabetes by Race/Ethnicity, 1988 Through 2014

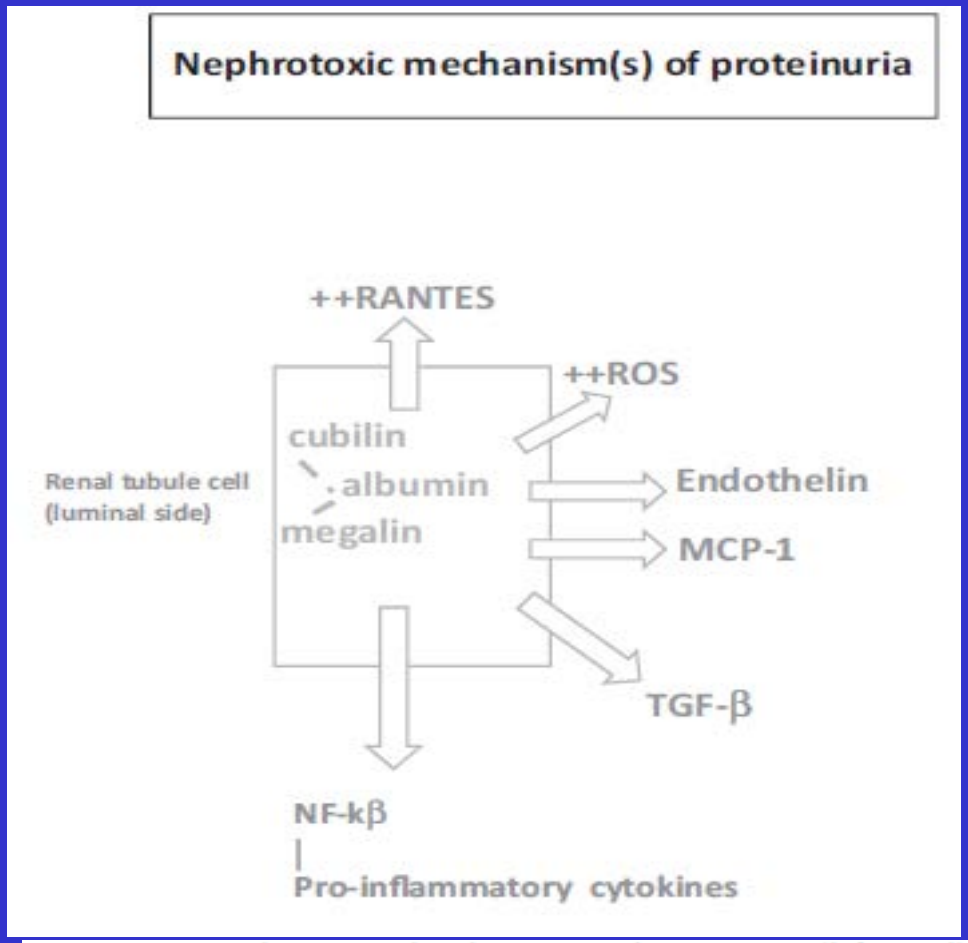
NHANES Period	No. With Diabetes	Unadjusted Prevalence, % (95% CI)		Adjusted Prevalence Ratio (95% CI)[b]	*P* Value for Trend
		Based on a Single Laboratory Value	Accounting for Persistence[a]		
Albuminuria (ACR ≥30 mg/g)[c]					
Non-Hispanic white					
1988-1994	179	35.9 (30.6-41.5)	21.2 (14.9-27.5)	1 [Reference]	.001
1999-2004	179	28.5 (24.6-32.8)	17.1 (12.8-21.4)	0.81 (0.65-0.99)	
2005-2008	169	28.9 (25.3-32.8)	17.4 (12.8-22.1)	0.82 (0.68-1.00)	
2009-2014	204	24.1 (20.0-28.7)	14.2 (9.9-18.5)	0.67 (0.53-0.85)	
Reduced Estimated Glomerular Filtration Rate (eGFR <60 mL/min/1.73 m^2)[d]					
Non-Hispanic white					
1988-1994	102	14.2 (11.4-17.7)	9.8 (5.5-14.0)	1 [Reference]	<.001
1999-2004	138	18.6 (16.1-21.3)	12.9 (8.7-17.1)	1.36 (1.06-1.73)	
2005-2008	123	19.0 (15.1-23.8)	13.3 (8.1-18.6)	1.42 (1.05-1.92)	
2009-2014	206	23.4 (21.2-25.7)	16.1 (12.1-20.0)	1.65 (1.32-2.06)	

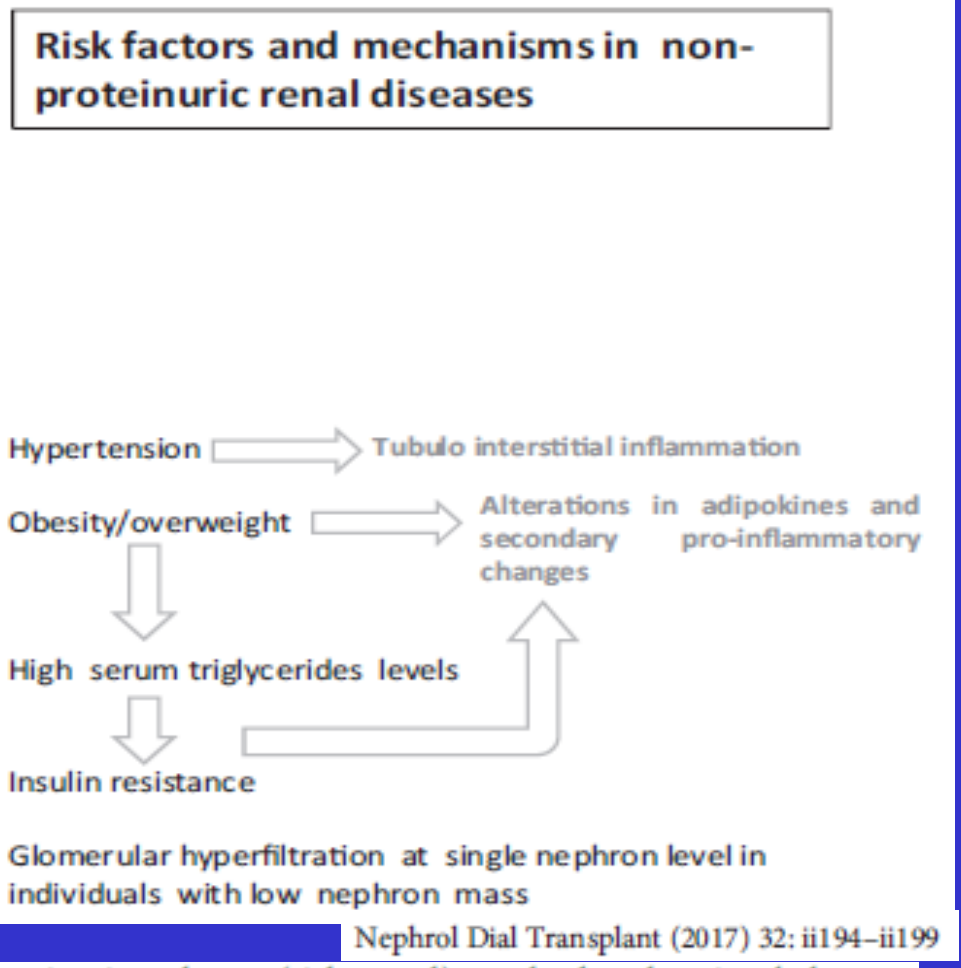
Non-Proteinuric Diabetic Nephropathy

Among 301 Type 2 diabetic patients attending an outpatient clinic in Australia [20] and 1197 patients from the Third National Health and Nutrition Examination Survey (NHANES III) [21,22], of patients with GFR less than 60 mL/min, 39% and 36%, respectively, were normoalbuminuric. Recently, a nonalbuminuric renal impairment syndrome was described in Type 2 diabetic patients, which has distinct clinical features that are not clearly associated with poor glycemic control and that are correlated less closely with retinopathy and high blood pressure [23]. This entity is associated with a higher prevalence of cardiovascular diseases (CVD); therefore a predominance of macroangiopathy as the underlying renal pathology has been suggested, which has yet to be demonstrated.

J. Clin. Med. **2015**, *4*, 1761-1773;

Non-proteinuric rather than proteinuric renal diseases are the leading cause of end-stage kidney disease





Nephrol Dial Transplant (2017) 32: ii194–ii199

FIGURE 1: Mechanisms whereby sustained proteinuria (left panel) and non-proteinuric pathways (right panel) may lead to chronic tubulo-interstitial damage. Nephrotoxicity of proteinuria: albumin escaped from the glomerular filter is taken up by the cubilin–megalin complex in tubular cells. The complex cubilin–megalin–albumin triggers local production of ROS and activates regulated on activation, normal T cell expressed and secreted (RANTES), a fundamental chemotactic cytokine. Monochemotactic protein 1 (MCP-1), another chemo-attractant of inflammatory cells, is also activated and these factors trigger macrophage accumulation at the tubular level and in the interstitium. Nuclear factor κB (NF-κB) and the cytokine cascade recruited by this factor are also activated in parallel with TGF-β, a factor that stimulates the proliferation of fibrocytes and collagen accumulation. The cubilin–megalin–albumin complex also activates endothelin synthesis, which eventually results in vasoconstriction and parallel inflammatory changes in the vascular endothelium. Non-proteinuric pathways that may be conducive to kidney damage include hypertension, obesity/overweight, high serum triglycerides and hyperfiltration at the single nephron level. As for diabetes, these pathways are discussed in some detail in Porrini *et al.* [3].

Different patterns of DN according to GFR changes

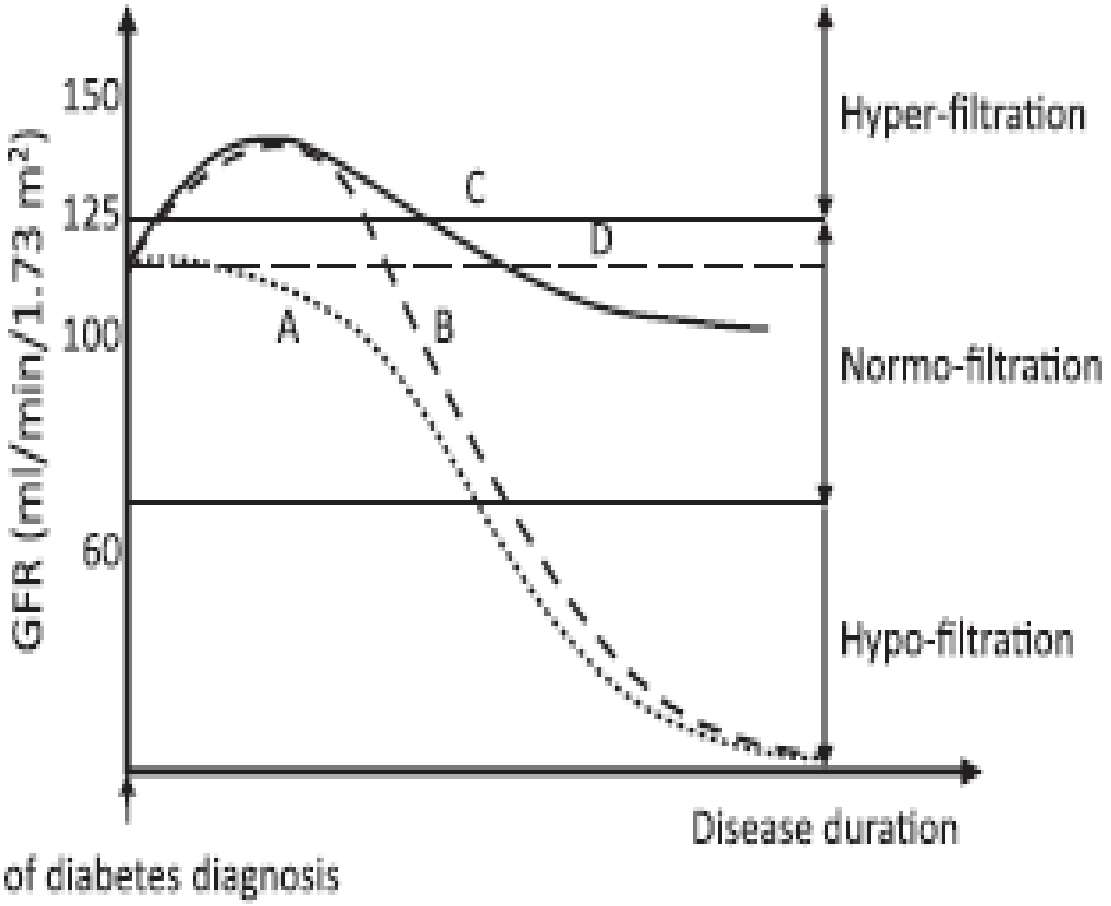


Figure 1. Clinical patterns of diabetic kidney disease. (A) Normo-hypofiltration; (B) normo-hyper-normo-hypofiltration; (C) normo-hyper-normofiltration; and (D) persistent normofiltration. Abbreviation: GFR, glomerular filtration rate.

How identifying patients with slow or fast renal decline function trajectories?

Progressive Renal Decline: The New Paradigm of Diabetic Nephropathy in Type 1 Diabetes

Andrzej S. Krolewski

Diabetes Care 2015;38:954–962 | DOI: 10.2337/dc15-0184

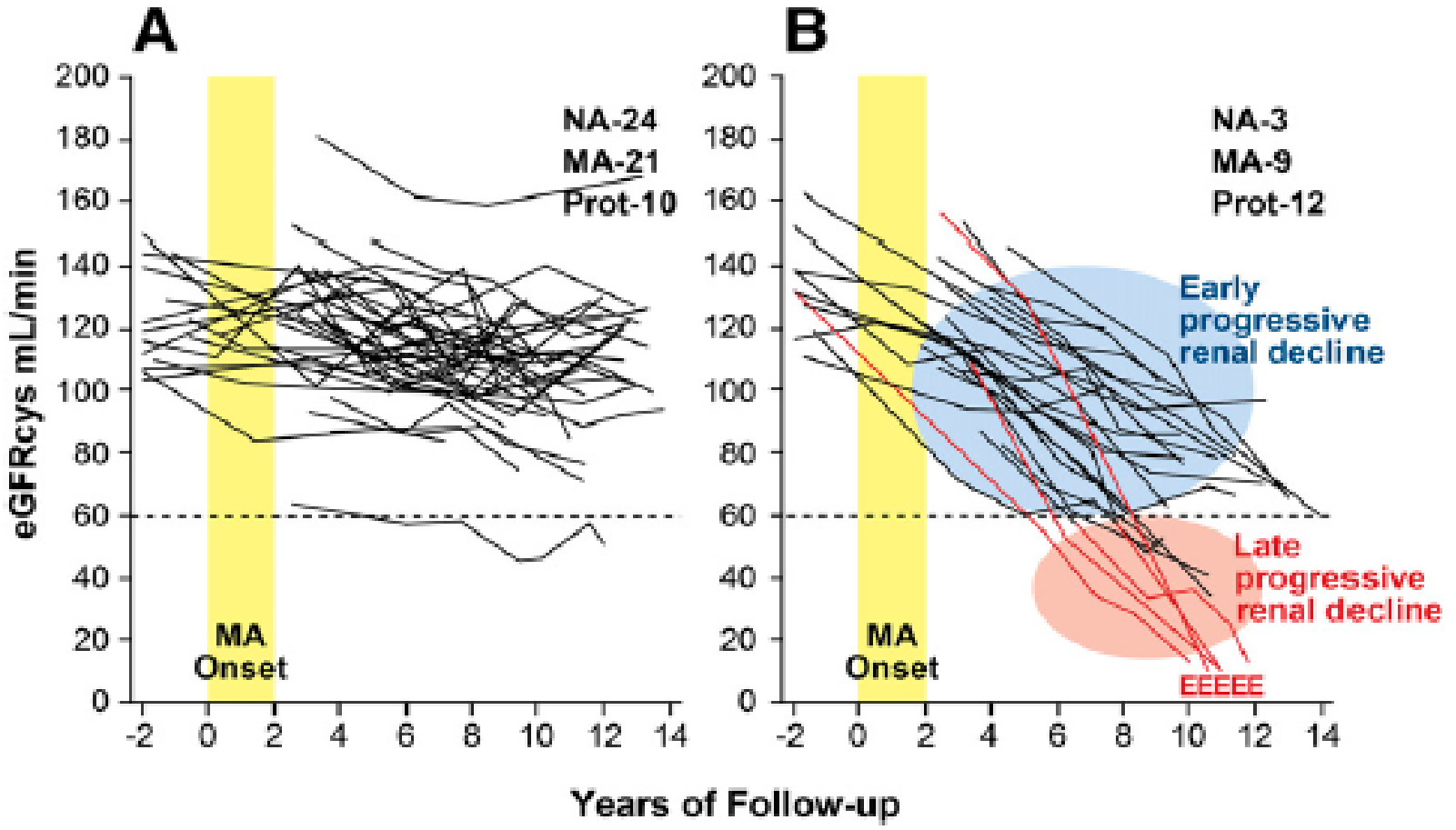


Figure 3—Trajectories of eGFRcys in patients with T1D and new-onset MA who were followed for 12 years. *A*: Patients with stable renal function (nondecliners). The eGFRcys slopes of these patients reflect a loss of <3.3%/year. *B*: Patients with early progressive renal decline (decliners). The eGFRcys slopes of these patients reflect a loss ≥3.3%/year. MA onset indicates the 2-year interval when multiple determinations of ACR became elevated; E indicates the date of ESRD diagnosis. Insets: The numbers of patients at the end of follow-up according to category of albumin excretion rate: NA, MA, and proteinuria (Prot). Figure adapted with permission from

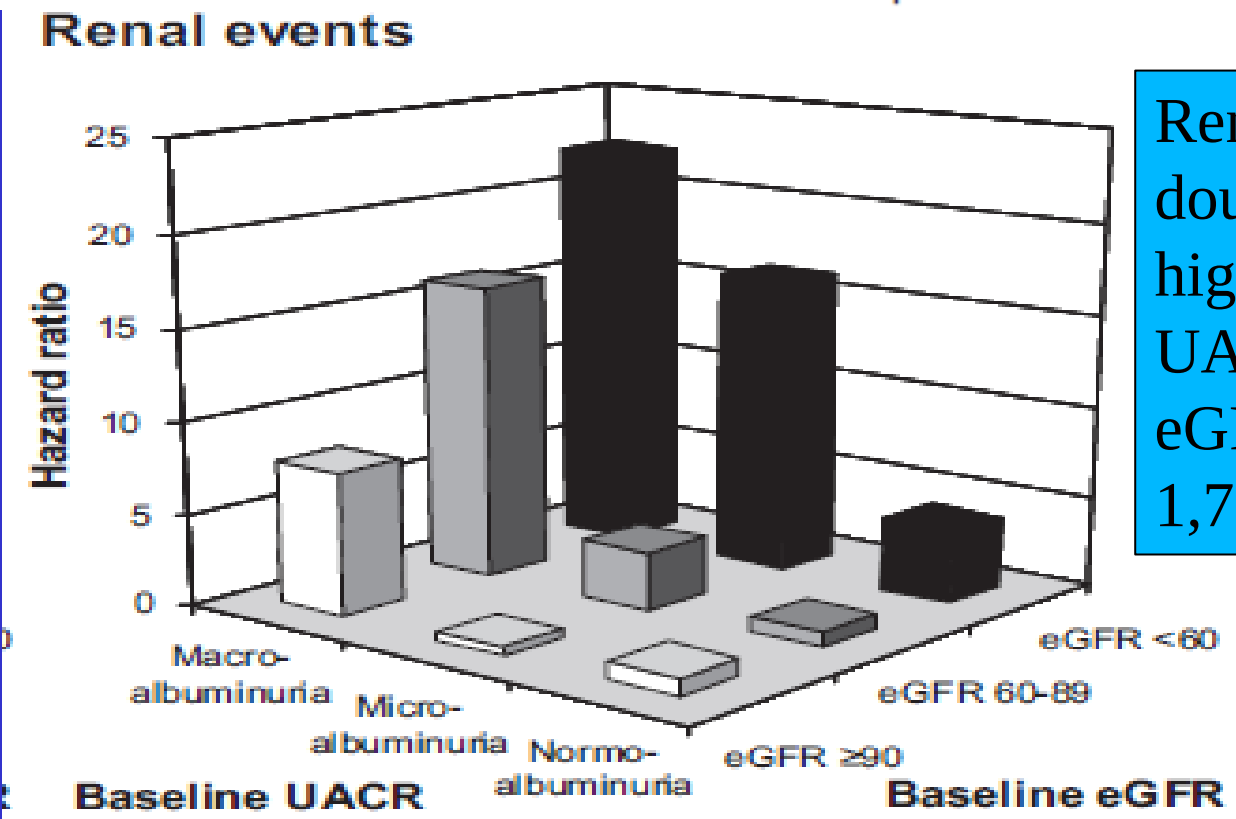
Am J Kidney Dis. 2014;63(2)(suppl 2):S39-S62

Table 1. Summary of the Usefulness of Various Markers for the Development and Progression of DKD

Marker for DKD	Advantages	Disadvantages
Albuminuria	Urinary albumin levels within the microalbuminuric range predict ESRD	High variability, low specificity for DKD; spontaneous regression and ΔAER within the microalbuminuric range ≠ ΔGFR
GFR	Best measure of kidney function	Routine methods for accurately estimating GFR in the normal-high range are still lacking
Glucose	An important marker because hyperglycemia is the initiator of DKD	Targets still to be optimally defined; evidence documenting that intensive glycemic control prevents ESRD is sparse
Blood pressure	An important promoter of DKD; also important in CV risk reduction	Targets are still to be optimally defined
Lipids	Important in CV risk reduction; lipid-modifying agents may have renal-protective effects independent of changes in lipid profile	The relationship between components of the lipid profile and risk for DKD progression is not optimally defined
Soluble TNF receptors	Circulating levels of TNF receptors have been shown to predict ESRD and possibly have a more powerful predictive ability than proteinuria	The relationship between TNF receptors and ESRD remains to be confirmed in various patient populations attending different centers
Uric acid	Easy to measure; levels also may relate to CV risk	Kidney disease outcome intervention studies to target uric acid levels are still required
Tubular markers	Easy to measure in urine sample	The prognostic significance of their measurement over and above established risk factors remains to be fully defined
Urinary proteome	The appearance of the CKD273 biomarker classifier is an earlier marker for the risk of the development of proteinuria, even prior to the onset of microalbuminuria	Clinical assays are lacking
Serum cystatin C	Predicts ESRD better than creatinine-based eGFR methods and possibly directly measured GFR	Expensive and the standardization of assays is not yet universal

Albuminuria and Kidney Function Independently Predict Cardiovascular and Renal Outcomes in Diabetes

Toshiharu Ninomiya,* Vlado Perkovic,* Bastiaan E. de Galan,*† Sophia Zoungas,* Avinesh Pillai,* Meg Jardine,* Anushka Patel,* Alan Cass,* Bruce Neal,* Neil Poulter,‡ Carl-Erik Mogensen,§ Mark Cooper,‖ Michel Marre,¶ Bryan Williams,** Pavel Hamet,†† Giuseppe Mancia,‡‡ Mark Woodward,*§§ Stephen MacMahon,* and John Chalmers,* on behalf of the ADVANCE Collaborative Group



Renal events (dialysis, Tx, doubling s creat) 22X higher when combining UACR >300 mg/g and eGFR <60 ml/min per 1,73m²

J Am Soc Nephrol 20: 1813–1821, 2009.

	Baseline eGFR (ml/min/1.73 m²)		
	GFR ≥90	GFR 60-89	GFR <60
Baseline UACR			
Normoalbuminuria	1.00 (Reference)	0.89 (0.31-2.58)	3.95 (1.38-11.34)
Microalbuminuria	0.45 (0.05-3.83)	3.17 (1.15-8.74)	16.19 (6.16-42.54)
Macroalbuminuria	7.82 (1.51-40.53)	16.13 (5.49-47.42)	22.20 (7.62-64.72)

Table 2 | Distribution of categories of progressive renal decline during 6–10 years of follow-up in patients with type 1 diabetes and type 2 diabetes in the Joslin Kidney Studies according to category of albuminuria at entry[a] into follow-up

eGFR decline per ml/yr[b]	Normo-albuminuria % (N)	Micro-albuminuria % (N)	Proteinuria % (N)	Total % (N)
Patients with type 1 diabetes				
<2.9	91%	78%	49%	81%
3–4.9	6%	11%	16%	8%
5–9.9	2%	7%	19%	7%
> 10	1%	4%	16%	4%
Total	100% (932)[b]	100% (525)[c]	100% (275)[d]	100% (1732)
Patients with type 2 diabetes				
<2.9	80%	67%	32%	72%
3–4.9	13%	18%	17%	15%
5–9.9	6%	12%	30%	10%
> 10	1%	3%	21%	3%
Total	100% (681)	100% (418)	100% (82)	100% (1181)[e]

10%

20%

68%

Fast decliner

Fast decliner

Kidney International (2017) ■, ■–■; http://dx.doi.org/10.1016/j.kint.2016.10.046

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Serum cystatin C	Predicts ESRD better than creatinine-based eGFR methods and possibly directly measured GFR	Expensive and the standardization of assays is not yet universal

Serum Concentration of Cystatin C and Risk of End-Stage Renal Disease in Diabetes

Table 4—*Analysis of time to onset of ESRD in each cohort according to CKD stage defined by eGFRcreat and partitioned by eGFRcyst stage*

	Cohort		
CKD stages	Joslin T1D	FinnDiane T1D	Joslin T2D
eGFRcyst higher than eGFRcreat stage*	2.2 (1.5–3.9)	2.2 (1.3–3.8)	3.2 (1.8–5.9)
Stages the same	1.0 (ref)	1.0 (ref)	1.0 (ref)
eGFRcyst lower than eGFRcreat stage†	0.4 (0.1–1.3)	0.3 (0.1–0.9)	Indeterminate

Data are HR (95% CI) unless otherwise indicated. Adjusted for CKD stage and albumin-to-creatinine ratio and albumin excretion rate. *$P < 0.001$ for Joslin, $P = 0.0025$ for FinnDiane. †$P = 0.1$ for Joslin T1D, $P = 0.03$ for FinnDiane.

Krolewski A et al. Diabetes Care 2012;35:2311-2316

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Kidney International (2017) ■, ■–■; http://dx.doi.org/10.1016/j.kint.2016.10.046

ESRD

Fast decliners

Slow decliners

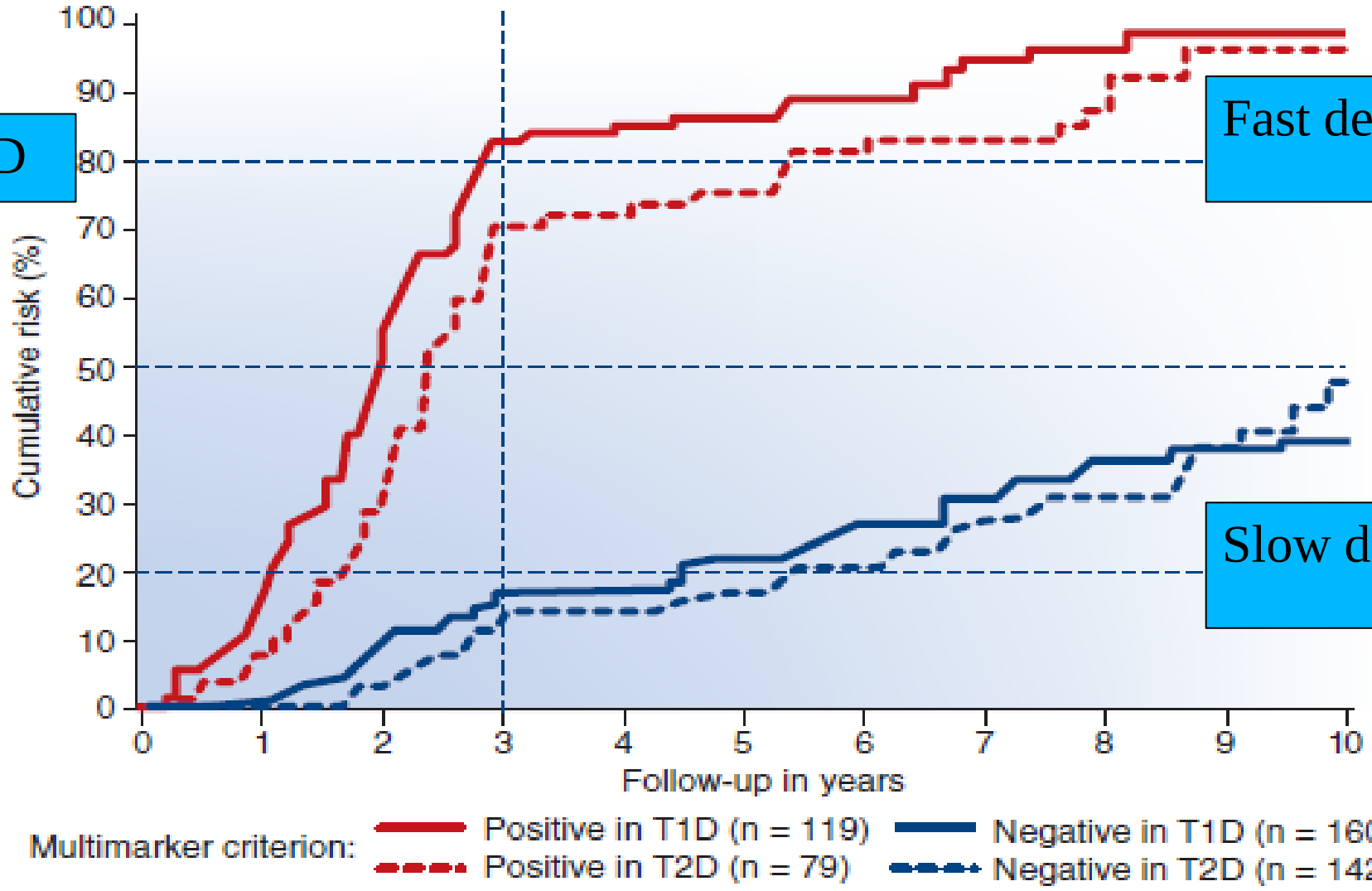

Figure 5 | Cumulative risk of end-stage renal disease (ESRD) during 10-year follow-up in the two Joslin cohorts with chronic kidney disease according to value of multimarker criterion at entry into the follow-up period. The following markers at baseline were considered: albumin-to-creatinine ratio (ACR), estimated glomerular filtration rate (eGFR), tumor necrosis factor receptor 1 (TNFR1), and tumor necrosis factor receptor 2 (TNFR2) to develop the multimarker criterion to identify patients (fast decliners) at risk for ESRD during the first 3 years of follow-up using data from the type 1 diabetes (T1D) cohort. The performance of the criterion was replicated in the data from the type 2 diabetes (T2D) cohort. Positive criterion: at baseline, serum TNFR1 >4.3 ng/ml without regard to other markers or serum TNFR1 between 2.9 and 4.3 ng/ml and ACR >1.9 g albumin/g creatinine in urine. Negative criterion: At baseline, serum TNFR1 <4.3 ng/ml and ACR <1.9 g albumin/1 g creatinine in urine or serum TNFR1 <2.9 ng/ml without regard to values of other markers. It was extraordinary that the multimarker criterion that was developed in the T1D cohort produced almost identical stratification according to ESRD risk in the T2D cohort. The T2D cohort had very different clinical characteristics than the T1D cohort. Data were obtained from the study by Yamanouchi M *et al.*[44] and reanalyzed.

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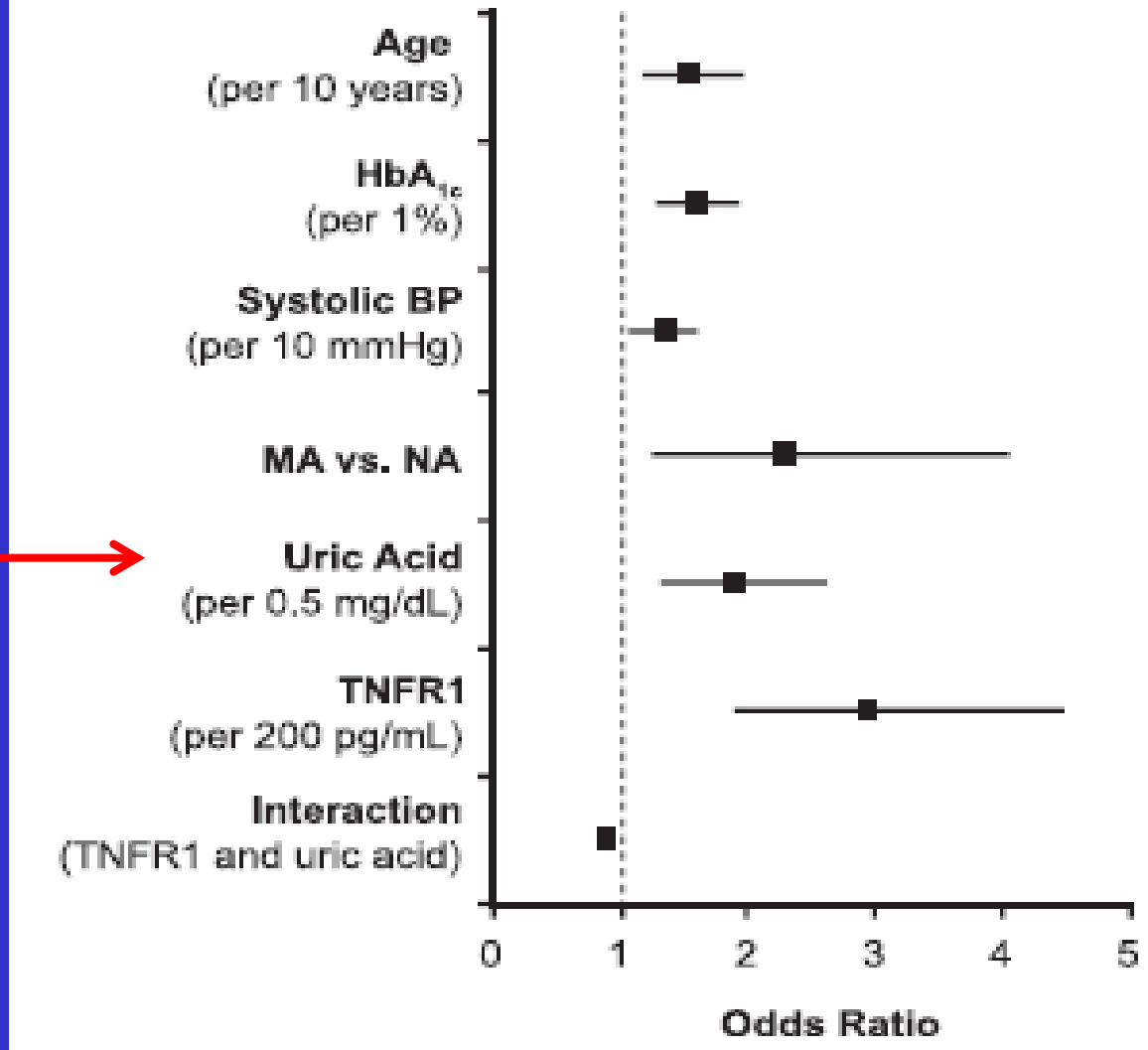


Figure 6—Risk of progressive renal decline according to baseline clinical characteristics and serum markers in a cohort of patients with NA and MA enrolled in the 2nd Joslin Kidney Study and followed for 4–10 years. The results of multiple logistic analyses are presented. Data are derived from Krolewski

physicians face not only the challenge of identifying patients in whom progressive renal decline will develop from those who will be spared but also the challenge within the affected group of distinguishing rapid from moderate and slow decliners for estimating the time to onset of ESRD

DM patients
Stage 1 or 2 CKD:
prediction of risk for progressive renal decline!

At present, two tests are used to diagnose diabetic nephropathy in T1D: urinary albumin excretion (a measure of glomerular damage) and serum creatinine concentration (a measure of renal function loss). Positive results of these tests indicate the presence and extent of kidney damage at the time of examination. A recommendation has been made to use a combination of these tests in clinical practice to diagnose diabetic nephropathy , despite the fact that the results give no information about the rate of renal function loss or allow estimation of the time to ESRD.

recently, we showed that the serum concentration of TNFR1 or TNFR2 is a very good predictor of the future development of CKD stage ≥3 and ESRD in patients with T1D (18,21) and is similarly effective in predicting ESRD in patients with type 2 diabetes (31). Similar findings were obtained by other authors in different populations (47,48). Accordingly, we postulate that a suite of determinations, including urinary albumin excretion and serum concentrations of creatinine, cystatin C, and TNFR1, may be sufficient to construct an index for stratifying patients with T1D according to their risk of progressive renal decline and time of onset of ESRD (A.S.K.,

Diabetes Care Volume 38, June 2015

Biomarkers of rapid chronic kidney disease progression in type 2 diabetes

Helen C. Looker[1,12], Marco Colombo[2,12], Sibylle Hess[3,13], Mary J. Brosnan[4,13], Bassam Farran[1], R. Neil Dalton[5], Max C. Wong[6], Charles Turner[5], Colin N.A. Palmer[7], Everson Nogoceke[8], Leif Groop[9], Veikko Salomaa[10], David B. Dunger[6], Felix Agakov[2,11], Paul M. McKeigue[2,15] and Helen M. Colhoun[1,12,15] on behalf of the SUMMIT Investigators

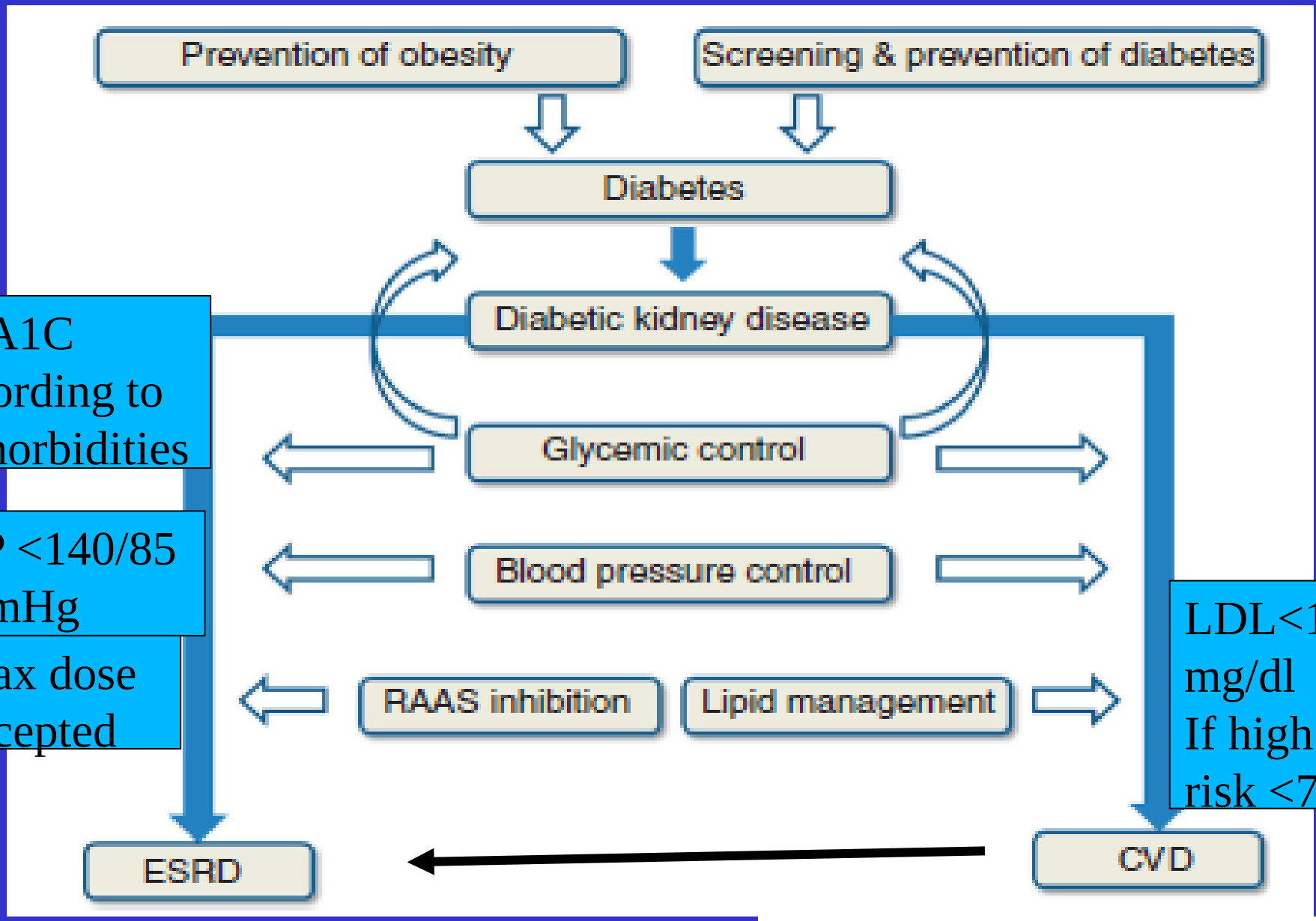
Here we evaluated the performance of a large set of serum biomarkers for the prediction of rapid progression of chronic kidney disease (CKD) in patients with type 2 diabetes. We used a case–control design nested within a prospective cohort of patients with baseline eGFR 30–60 ml/min per 1.73 m^2. Within a 3.5-year period of Go-DARTS study patients, 154 had over a 40% eGFR decline and 153 controls maintained over 95% of baseline eGFR. A total of 207 serum biomarkers were measured and logistic regression was used with forward selection to choose a subset that were maximized on top of clinical variables including age, gender, hemoglobin A1c, eGFR, and albuminuria. Nested cross-

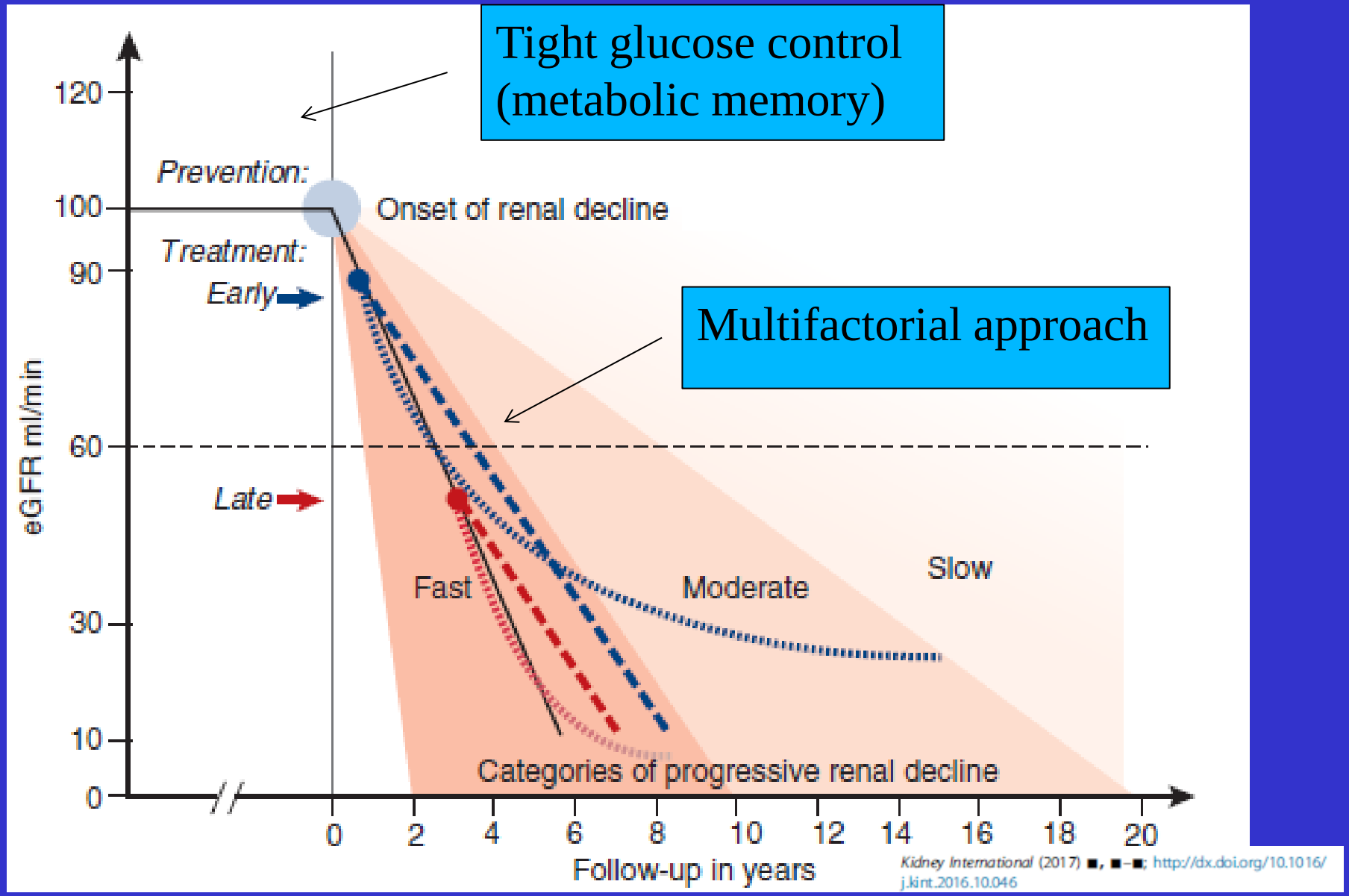
biomarkers showed significant associations with rapid progression and adjusted for clinical characteristics. A panel of 14 biomarkers increased the area under the ROC curve from 0.706 (clinical data alone) to 0.868. Biomarkers selected included fibroblast growth factor-21, the symmetric to asymmetric dimethylarginine ratio, β2-microglobulin, C16-acylcarnitine, and kidney injury molecule-1.

DM patients
Stage 3 or higher CKD

Kidney International (2015) **88,** 888–896;

Management of diabetes





Kidney International (2017) ■, ■–■; http://dx.doi.org/10.1016/j.kint.2016.10.046

Figure 6 | Schematic representation of estimated glomerular filtration rate (eGFR) trajectories in fast decliners and their modifications in response to different interventions to reduce the rate of decline and postpone the development of ESRD. Intervention with a treatment that effectively reduces the rate of decline will postpone the onset of ESRD by a longer interval, depending on how soon after the onset of decline the intervention occurs (dashed red and blue lines). Evidence of an effective treatment may not be seen until after a lag interval (as described by Skupien *et al.*[31]). That effect will not be realized, however, if the treatment is initiated too late (dotted red and blue lines). In moderate and slow decliners, the effects of the treatments illustrated will be more pronounced. An immediate treatment effect (straight lines) would result in a greater delay in ESRD, and a lagged treatment effect (curves) would result in a higher residual eGFR. However, demonstrating these effects would require clinical trials longer than 3 years and different definitions of end-point measures (e.g., deceleration of eGFR slopes or other more sensitive surrogates).

Intensified multifactorial intervention in type 2 diabetics with microalbuminuria leads to long-term renal benefits

Kidney International (2017)

STENO2

Jens Oellgaard[1,2,3], Peter Gæde[1,2], Peter Rossing[3,4,5], Frederik Persson[3], Hans-Henrik Parving[5,6] and Oluf Pedersen[7]

Table 1 | Baseline clinical, anthropometric, and biochemical data

Variable	Baseline (1993) Intensive (n = 80)	Standard (n = 80)
Age (yr)	54.9 ± 7.2	55.2 ± 7.2
Age range (yr)	37–67	42–67
Proportion male sex (%)	79	70
Diabetes duration (yr)	4 (0–30)	6 (0–29)
BMI (kg/m^2)		
Men	29.3 ± 3.6	30.3 ± 5.3
Women	31.1 ± 4.5	28.9 ± 3.8
Waist circumference (cm)		
Men	105 ± 10	107 ± 14
Women	100 ± 14	101 ± 13
Blood pressure (mm Hg)		
Systolic	146 ± 11	149 ± 19
Diastolic	85 ± 10	86 ± 11
Fasting glucose (mmol/L)	10.1 ± 3.1	10.5 ± 3.0
HbA_{1c}		
IFCC (mmol/mol)	68 ± 6	73 ± 5
DCCT (%)	8.4 ± 2.7	8.8 ± 2.6
Total cholesterol (mmol/L)	5.4 ± 1.1	6.0 ± 1.3
LDL cholesterol (mmol/L)	3.4 ± 0.9	3.5 ± 1.0
GFR (ml/min/1.73 m^2)	116 ± 2.7	118 ± 2.8
p-Creatinine (μmol/L[a])	78 ± 17	76 ± 16
u-AER (mg/24 h)	78 (61–120)	69 (47–113)

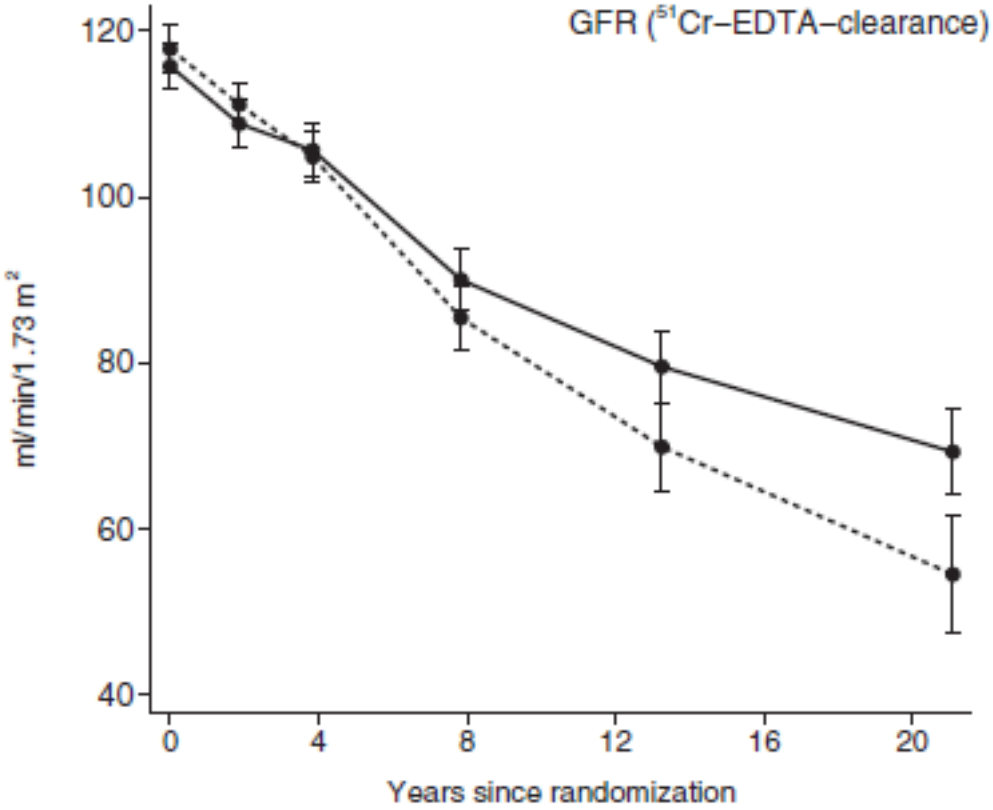


Figure 3 | Glomerular filtration rate (GFR) trajectories (mean ± SEM) by treatment allocation. Solid line: intensive therapy group. Dashed line: conventional therapy group. The yearly decline rate in the conventional therapy group was 28% higher than that in the intensive therapy group. 51-Cr-EDTA, 51-chrome ethylenediamine tetraacetic acid.

Table 3 | Treatment targets

	Conventional Therapy		Intensive Therapy	
	1993–1999	2000–2001	1993–1999	2000–2001
Systolic blood pressure (mm Hg)	<160	<135	<140	<130
Diastolic blood pressure (mm Hg)	<95	<85	<85	<80
HbA_{1c} (%)	<58	<48	<48	<48
Fasting serum total cholesterol (mmol/L)	<6.5	<4.9	<4.9	<4.5
Fasting serum triglycerides (mmol/L)	<2.2	<2.0	<1.7	<1.7
Treatment with RAS-inhibitor irrespective of BP	No	Yes	Yes	Yes
Aspirin therapy				
Known ischemia	Yes	Yes	Yes	Yes
Peripheral vascular disease	No	No	Yes	Yes
No known vascular disease	No	No	No	Yes

7.5%

6.5%

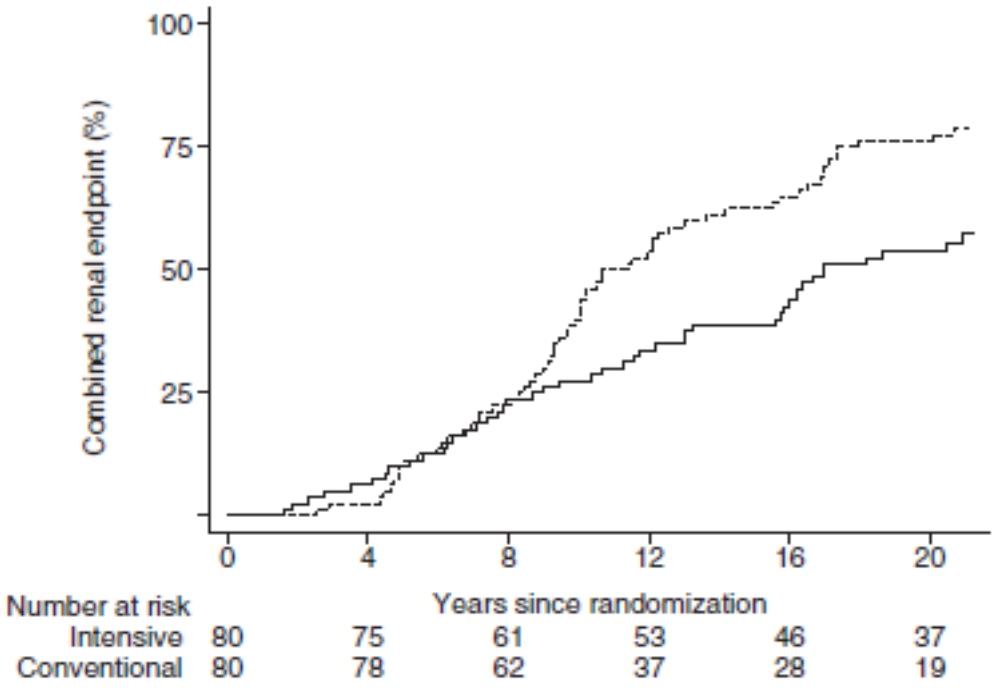
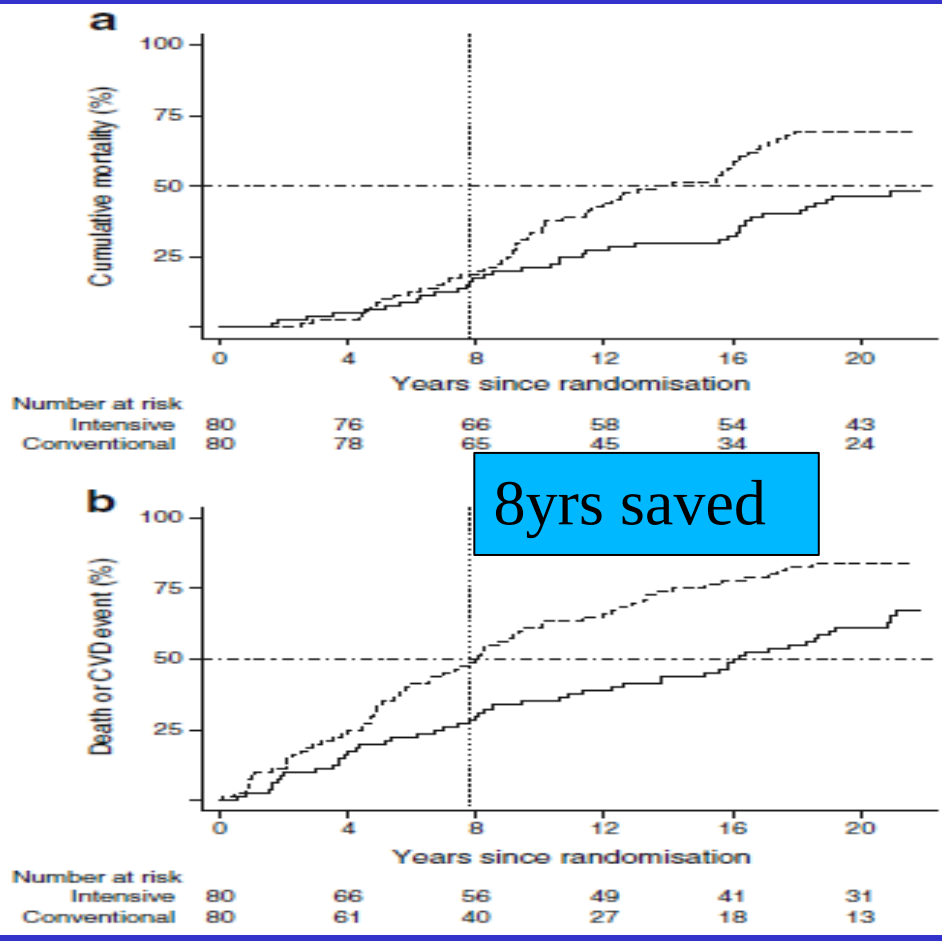


Figure 5 | Kaplan-Meier estimates of the combined renal endpoint of progression to glomerular filtration rate <45, end-stage renal disease, or death. Solid line: intensive therapy group. Dashed line: conventional therapy group. Adjusted hazard ratio of 0.55 (95% confidence interval: 0.37–0.81; $P = 0.003$; model 2).



8yrs saved

Diabetic nephropathy: landmark clinical trials and tribulations

Nephrol Dial Transplant (2016) 31: 359–368

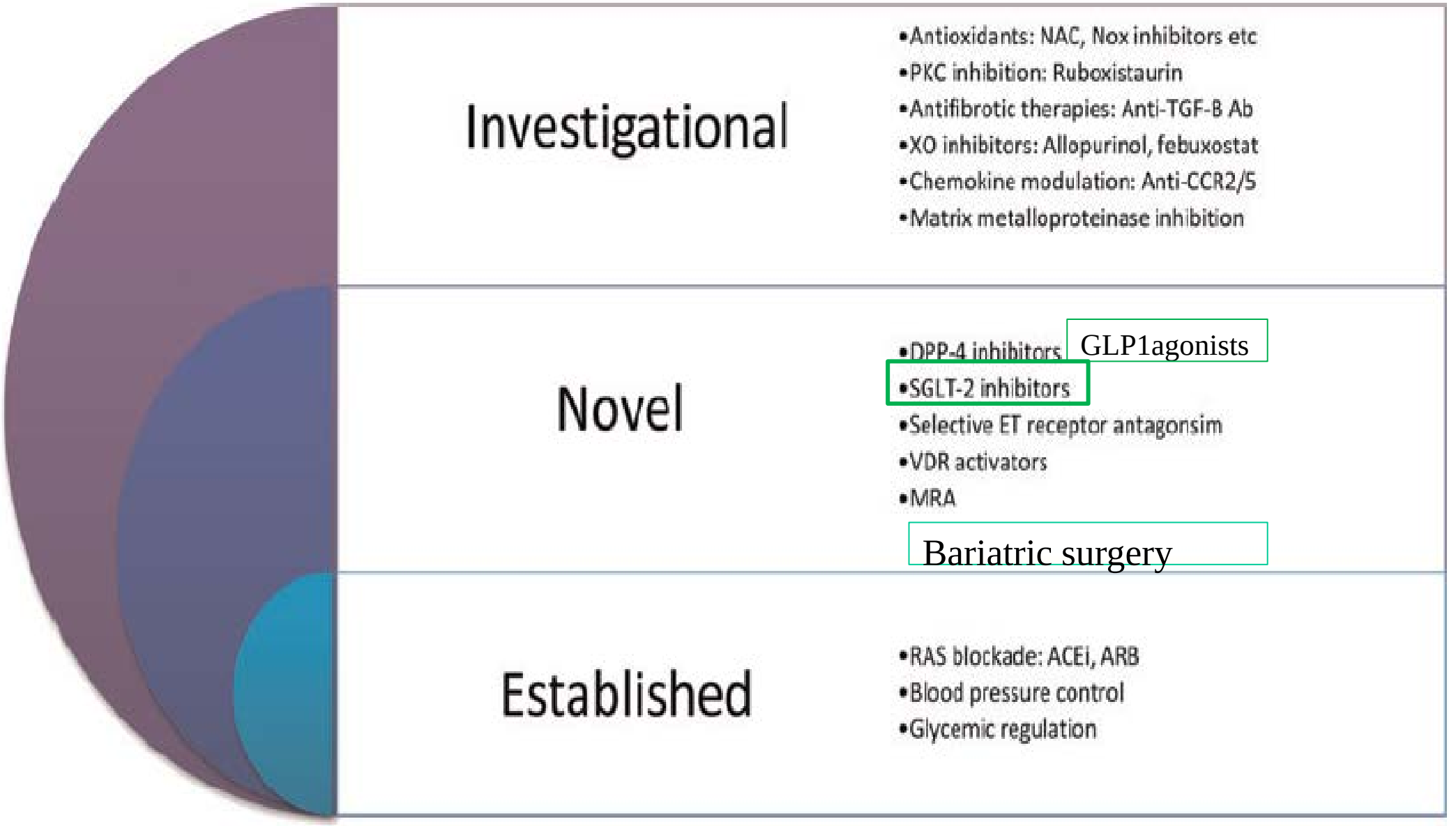


FIGURE 1: Current status of diabetic nephropathy treatment. RAS, renin–angiotensin system; ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; DPP-4, dipeptidyl peptidase-4; SGLT-2, sodium-glucose co-transporter 2; ET, endothelin; VDR, vitamin D receptor; MRA, mineralocorticoid receptor antagonists; NAC, *N*-acetylcysteine; Nox, NADPH oxidase; Anti-TGF B Ab, anti-transforming growth factor beta antibody.

SGLT2 inhibitors might halt progression of diabetic nephropathy

Hala Yamout and George L. Bakris

Blood pressure lowering slows the progression of diabetic nephropathy whereas the effects of glycaemic control are smaller and slower. New findings from the EMA-REG OUTCOME investigators indicate that SGLT2 inhibition slows the progression of kidney disease by lowering glucose and blood pressure, thereby lowering the risk of adverse renal outcomes in this patient group.

Refers to Wanner, C. *et al.* Empagliflozin and progression of kidney disease in type 2 diabetes. *N. Engl. J Med.* http://dx.doi.org/10.1056/NEJMoa1515920 (2016)

High CV DM risk population
63y, 72 % Males
Most with history of CVE
>75% with RASI and statins

Table 1 | Selected renal outcomes and adverse events in the EMPA-REG OUTCOME study

Outcome	Empagliflozin (%)	Placebo (%)
Renal outcome measures (all participants)		
Incident or worsening nephropathy or cardiovascular death	16.2	23.6
Incident or worsening nephropathy	12.7	18.8
Doubling of SCr accompanied by eGFR ≤45 ml/min/1.73 m^2	1.5	2.6
Initiation of RRT	0.3	0.6
Doubling of SCr accompanied by eGFR ≤45 ml/ min/1.73 m^2; initiation of RRT or death from renal disease	1.7	3.1

Potential protective mechanisms of SGlT2 inhibition

Kidney International (2016) **89,** 524–526;

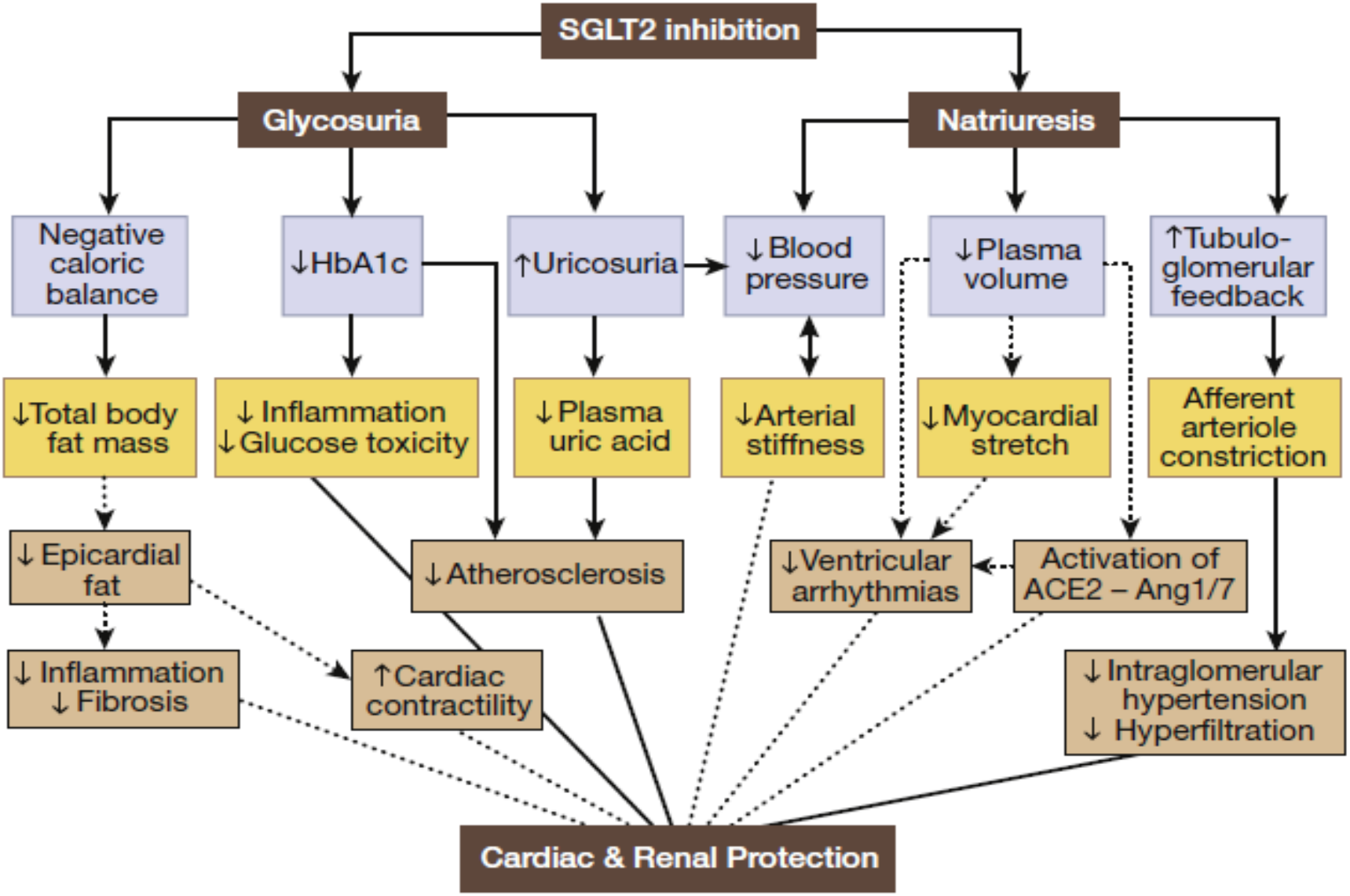


Figure 1 | Possible mechanisms responsible for cardiovascular and renal protection with sodium–glucose cotransporter 2 (SGLT2) inhibition. Solid lines represent pathways supported by existing data; dashed lines represent possible areas for future research. ACE2, angiotensin-converting enzyme-2; Ang1/7, angiotensin 1/7;

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

9340 high CV risk type 2 DM, median FU 3.8y

N Engl J Med 2016;375:311-22

CONCLUSIONS

In the time-to-event analysis, the rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke among patients with type 2 diabetes mellitus was lower with liraglutide than with placebo. (Funded by Novo Nordisk and the National Institutes of Health; LEADER ClinicalTrials.gov number,

MICROVASCULAR OUTCOMES

The incidence of a composite outcome of renal or retinal microvascular events was lower in the liraglutide group than in the placebo group (hazard ratio, 0.84; 95% CI, 0.73 to 0.97; P=0.02), a difference that was driven by a lower rate of nephropathy events in the liraglutide group (1.5 vs. 1.9 events per 100 patient-years of observation; hazard ratio, 0.78; 95% CI, 0.67 to 0.92; P=0.003)

Liraglutide (GlP1 agonist) decreases the nephropathy risk, mainly in eGFR group < 60 ml/min per 1,73 m²

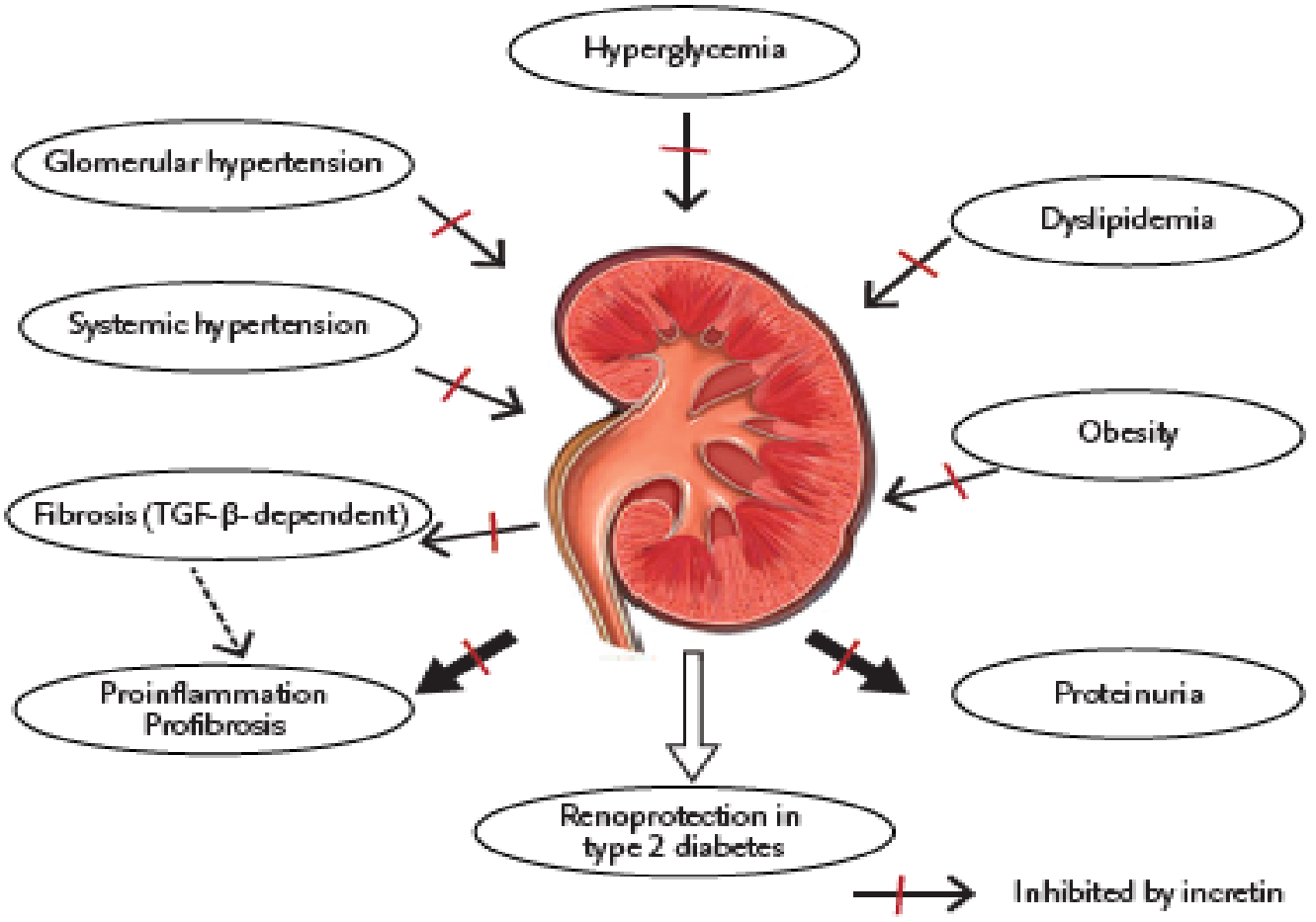
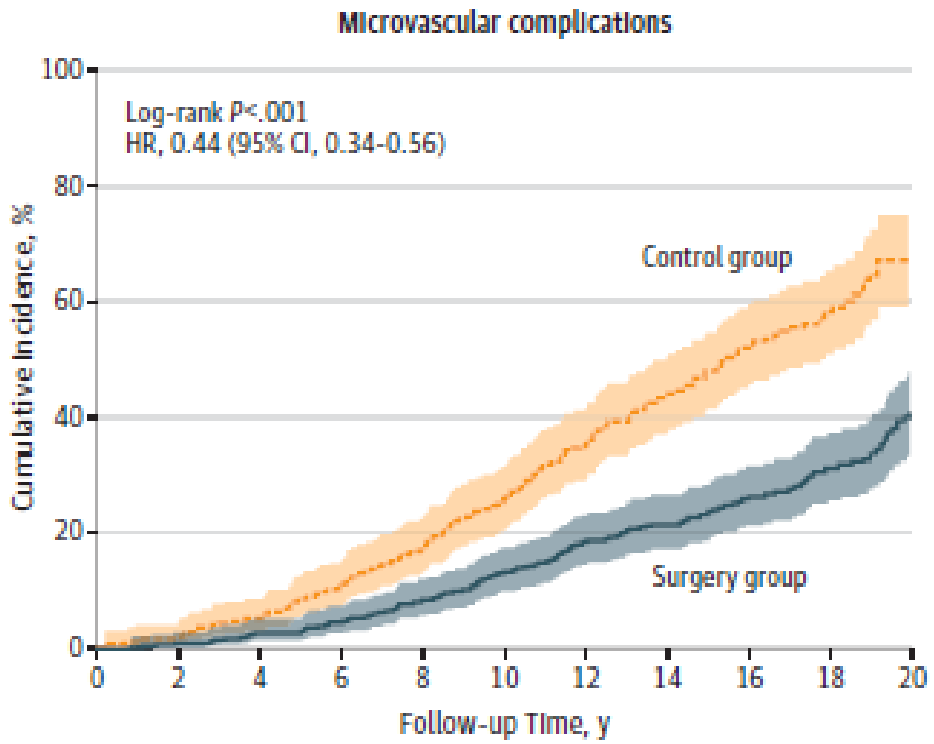
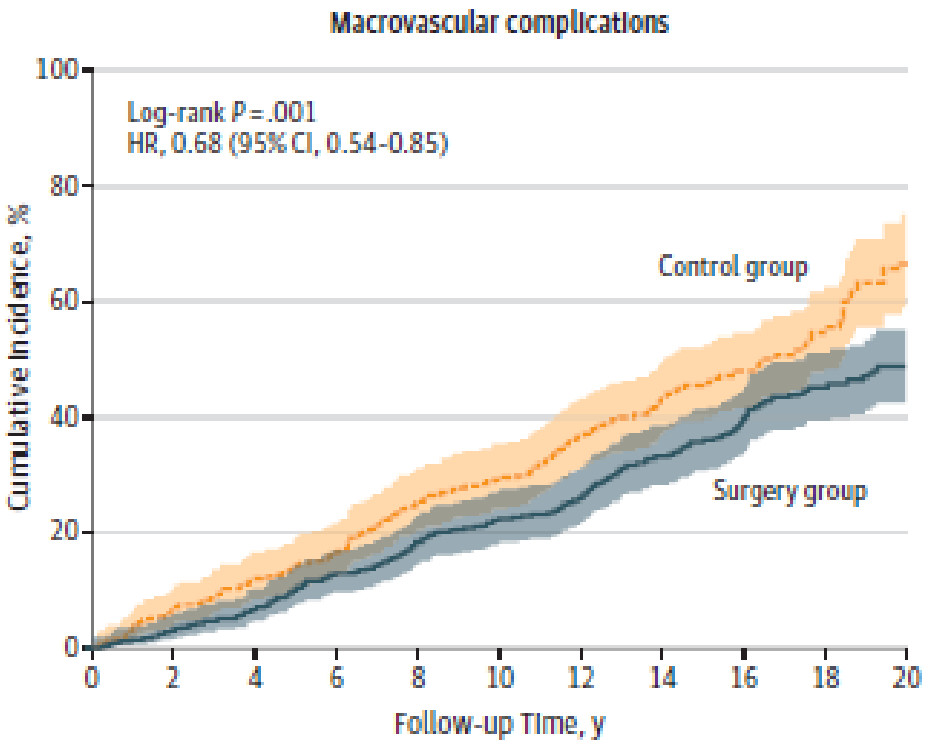


Figure 2. Favorable renal outcome achieved by incretin in diabetic nephropathy. Glucagon-like peptide 1 receptor agonists mimic favorable actions of incretin. Its glycemic effect via improving insulin secretion and inhibiting glucagon secretion, antihypertensive effect in both systemic and glomerular hypertension with attenuated dyslipidemia and obesity collectively ameliorate proteinuria and blocks proinflammatory and profibrotic pathways through transforming growth factor β (TGF-β)-dependent anti-fibrotic effect. These results comprehensively contribute to the renoprotection in type 2 diabetes.

Association of Bariatric Surgery With Long-term Remission of Type 2 Diabetes and With Microvascular and Macrovascular Complications

Figure 3. Cumulative Incidence of Microvascular and Macrovascular Diabetes Complications in the Surgery and Control Groups





No. at risk

Control	260	251	239	222	201	177	146	104	68	46	19
Surgery	343	336	326	318	301	280	257	207	160	112	63

260	240	225	214	191	178	155	116	80	53	20
343	330	315	294	270	254	238	186	142	92	54

Mean Age 50 y; mean BMI 40; DM mean duration 3y

JAMA. 2014;311(22):2297-2304.

Conclusions

- Incidence of DM is growing and brings CV and renal risk
- An early identification of those who will be fast decliners and early multifactorial treatment approach is necessary, before development of complications.
- New treatments are urgently resquested, according to the DN development mechanisms.
- The most interesting protecting drugs come from new glucose management therapies.
- Don’t forget to apply lifestyle and diet approaches (or bariatric surgery in severe obesity).

Nephrol Dial Transplant (2016) 0: 1–8
doi: 10.1093/ndt/gfw292

ndt
Nephrology Dialysis Transplantation

Original Article

Urinary proteomics predict onset of microalbuminuria in normoalbuminuric type 2 diabetic patients, a sub-study of the DIRECT-Protect 2 study

Morten Lindhardt[1], Frederik Persson[1], Petra Zürbig[2], Angelique Stalmach[3], Harald Mischak[2,3], Dick de Zeeuw[4], Hiddo Lambers Heerspink[4], Ronald Klein[5], Trevor Orchard[6], Massimo Porta[7], John Fuller[8], Rudolf Bilous[9,10], Nish Chaturvedi[11], Hans-Henrik Parving[12] and Peter Rossing[1,13,14]

Conclusions. In this cohort of patients with type 2 diabetes and normoalbuminuria from a large intervention study, the CKD273-classifier was an independent predictor of microalbuminuria. This may help identify high-risk normoalbuminuric patients for preventive strategies for diabetic nephropathy.

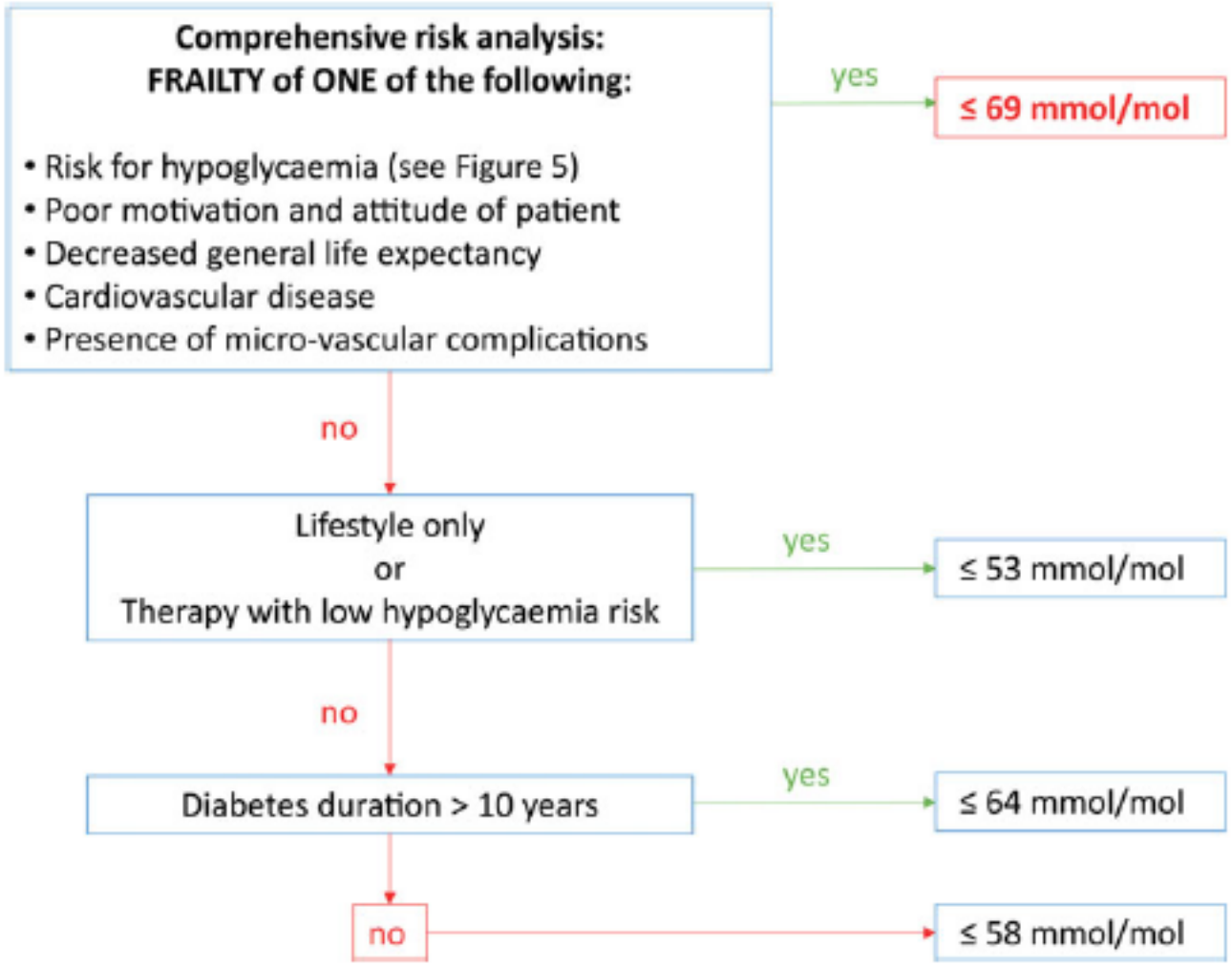
8. CHAPTER 2. ISSUES RELATED TO GLYCAEMIC CONTROL IN PATIENTS WITH DIABETES AND CKD STAGE 3B OR HIGHER (eGFR <45 mL/min)

NDT 2015 Clinical practice guidelines

Chapter 2.2. Are there better alternatives than HbA1c to estimate glycaemic control in patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2)?

Statements

2.2.1 We recommend the use of HbA1C as a routine reference to assess longer term glycaemic control in patients with CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2) (1C).



NDT 2015 Clinical practice guidelines

In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2), should we aim at lower blood pressure targets than in the general population?

Statements

3.4.1 We suggest against applying lower blood pressure targets in patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2) than in the general population (2C).

3.4.2 We suggest that in patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2) but without proteinuria, all blood pressure-lowering drugs can be used equally to lower blood pressure (2C).

Chapter 3.5

In patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min/1.73 m^2) or on dialysis, should we prescribe lipid-lowering therapy in primary prevention?

Statements

3.5.1 We recommend starting a statin in patients with diabetes and CKD stage 3b and 4 (1B).

3.5.2 We suggest a statin be considered in patients with diabetes and CKD stage 5 (2C).

3.5.3 We recommend against starting a statin in patients with diabetes and CKD stage 5D (1A).

3.5.4 There was no consensus in the guideline development group on whether or not statins should be stopped in patients with diabetes with CKD stage 5D.

3.5.5 We suggest fibrates can replace statins in patients with CKD stage 3b who do not tolerate statins (2B).

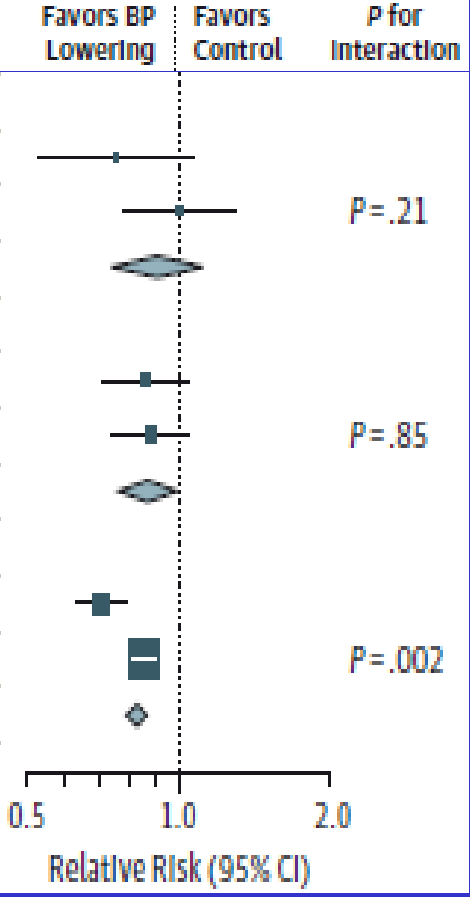
Blood Pressure Lowering in Type 2 Diabetes
A Systematic Review and Meta-analysis

Connor A. Emdin, HBSc; Kazem Rahimi, DM, MSc; Bruce Neal, PhD; Thomas Callender, MBChB; Vlado Perkovic, PhD; Anushka Patel, PhD

JAMA. 2015;313(6):603-615.

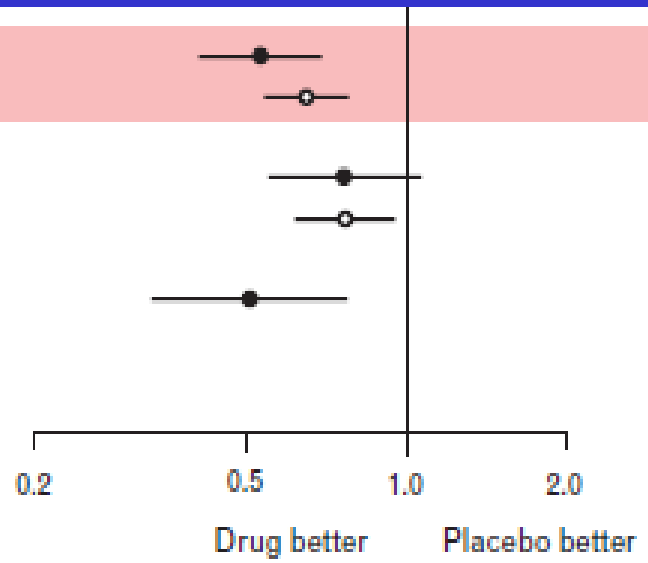
Figure 3. Standardized Associations Between 10-mm Hg Lower Systolic BP and All-Cause Mortality, Macrovascular Outcomes, and Microvascular Outcomes Stratified by Mean Systolic BP of Trial Participants at Entry

Outcome	No. of Studies	Baseline SBP, Mean, mm Hg	BP Lowering, No.		Control, No.		Relative Risk (95% CI)	P for Interaction
			Events	Participants	Events	Participants		
Renal failure, mm Hg								
≥140[16, 18, 29, 30, 35, 40, 41, 64, 65]	6	147	389	12475	346	11530	0.75 (0.52-1.08)	
<140[31, 58-60]	3	138	207	7360	214	7382	1.00 (0.77-1.29)	P = .21
Overall							0.91 (0.74-1.12)	
Retinopathy, mm Hg								
≥140[16, 29, 30, 64, 65, 77-80]	4	146	564	7946	586	7753	0.86 (0.70-1.04)	
<140[36-38, 59, 60, 80, 81]	3	137	280	1835	319	1813	0.88 (0.74-1.05)	P = .85
Overall							0.87 (0.76-0.99)	
Albuminuria, mm Hg								
≥140[16, 28-30, 64, 65]	4	146	1681	8447	1898	7647	0.71 (0.63-0.79)	
<140[17, 36-38, 59, 60]	3	137	1118	5357	1265	5174	0.86 (0.81-0.90)	P = .002
Overall							0.83 (0.79-0.87)	



Relative risk of major cardiovascular events, all death and end-stage renal disease (ESRD) in trials of BP lowering by different classes of drugs (vs. placebo).

RASB	Stroke + CHD	DM	13	0.53 (0.41–0.69)	0.021
		noDM	6	0.65 (0.54–0.77)	
	All Death	DM	12	0.76 (0.54–1.09)	0.91
		noDM	5	0.77 (0.62–0.95)	
	ESRD	DM	7	0.50 (0.32–0.76)	NA
		noDM	-	---	



Journal of Hypertension 2017, 35:922–944

7. CHAPTER 1: ISSUES RELATED TO RENAL REPLACEMENT MODALITY SELECTION IN PATIENTS WITH DIABETES AND END-STAGE RENAL DISEASE

Chapter 1.1. Should patients with diabetes and CKD stage 5 start with peritoneal dialysis or haemodialysis as a first modality?

Statements

1.1.1 We recommend giving priority to the patient's general status and preference in selecting renal replacement therapy as there is an absence of evidence of superiority of one modality over another in patients with diabetes and CKD stage 5 (1C).

1.1.2 We recommend providing patients with unbiased information about the different available treatment options (1A).

1.1.3 In patients opting to start haemodialysis (HD), we suggest prefering high flux over low flux when this is available (2C).

1.1.4 We suggest diabetes has no influence on the choice between HD or haemodiafiltration (HDF) (2B).

Chapter 1.2. Should patients with diabetes and CKD stage 5 start dialysis earlier, i.e. before becoming symptomatic, than patients without diabetes?

Statements

1.2.1 We recommend initiating dialysis in patients with diabetes on the same criteria as in patients without diabetes (1A).

Chapter 1.3. In patients with diabetes and CKD stage 5, should a native fistula, graft or tunnelled catheter be preferred as initial access?

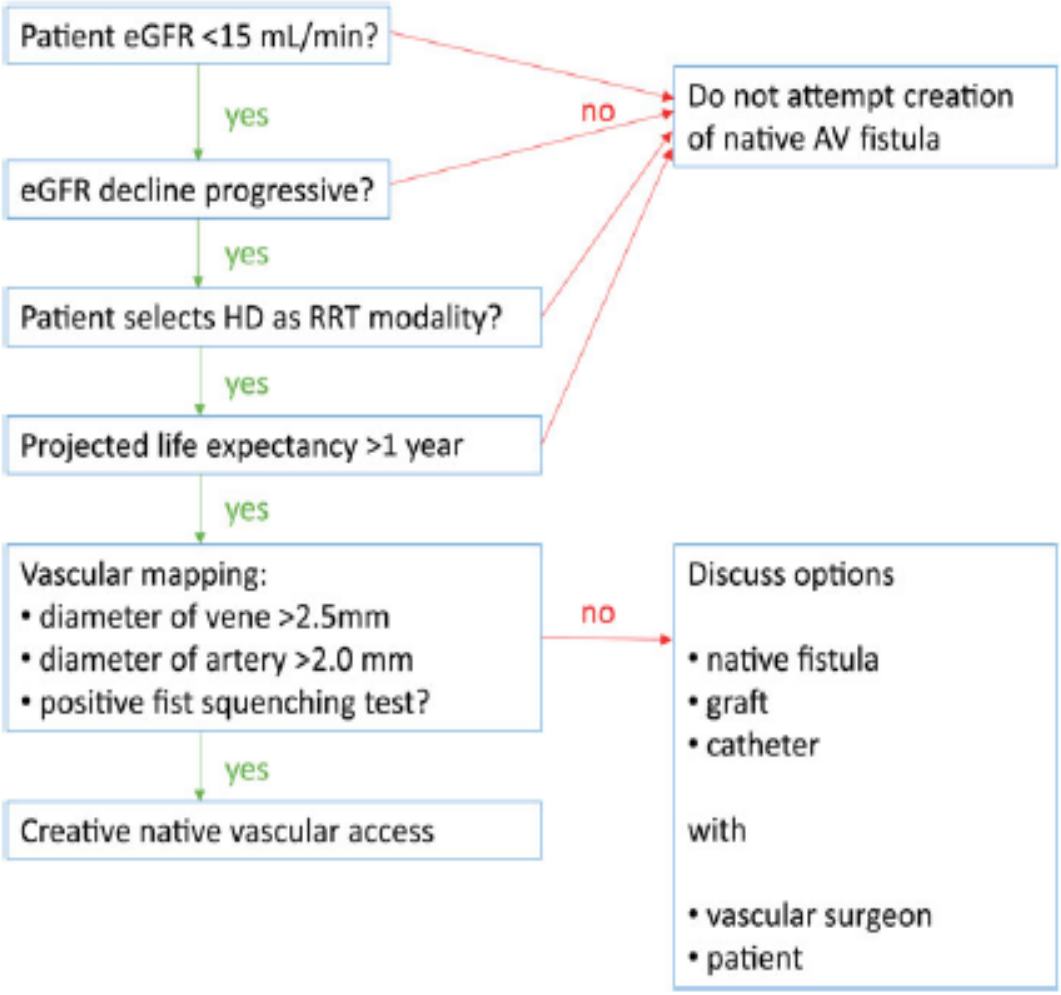


FIGURE 2: Decision flow chart for vascular access in patients with diabetes.

Chapter 1.4 Is there a benefit to undergoing renal transplantation for patients with diabetes and CKD stage 5?

1.4.1 We recommend providing education on the different options of transplantation and their expected outcomes for patients with diabetes and CKD stage 4 or 5 who are deemed suitable for transplantation (Table 5) (**1D**).

Statements only for patients with type 1 diabetes and CKD stage 5

1.4.2 We suggest living donation kidney transplantation or simultaneous pancreas kidney transplantation to improve survival of suitable patients (**2C**).

1.4.3 We suggest against islet transplantation after kidney transplantation with the aim to improve survival (**2C**).

1.4.4 We suggest pancreas grafting to improve survival after kidney transplantation (**2C**).

Statements only for patients with type 2 diabetes and CKD stage 5

1.4.5 We recommend against pancreas or simultaneous kidney pancreas transplantation (**1D**).

1.4.6 We recommend diabetes in itself should not be considered a contraindication to kidney transplantation in patients who otherwise comply with inclusion and exclusion criteria for transplantation (**1C**).

Fast renal decline to end-stage renal disease: an unrecognized feature of nephropathy in diabetes

Andrzej S. Krolewski[1,2], Jan Skupien[3], Peter Rossing[4,5] and James H. Warram[1]

Kidney International (2017) ■, ■–■; http://dx.doi.org/10.1016/j.kint.2016.10.046

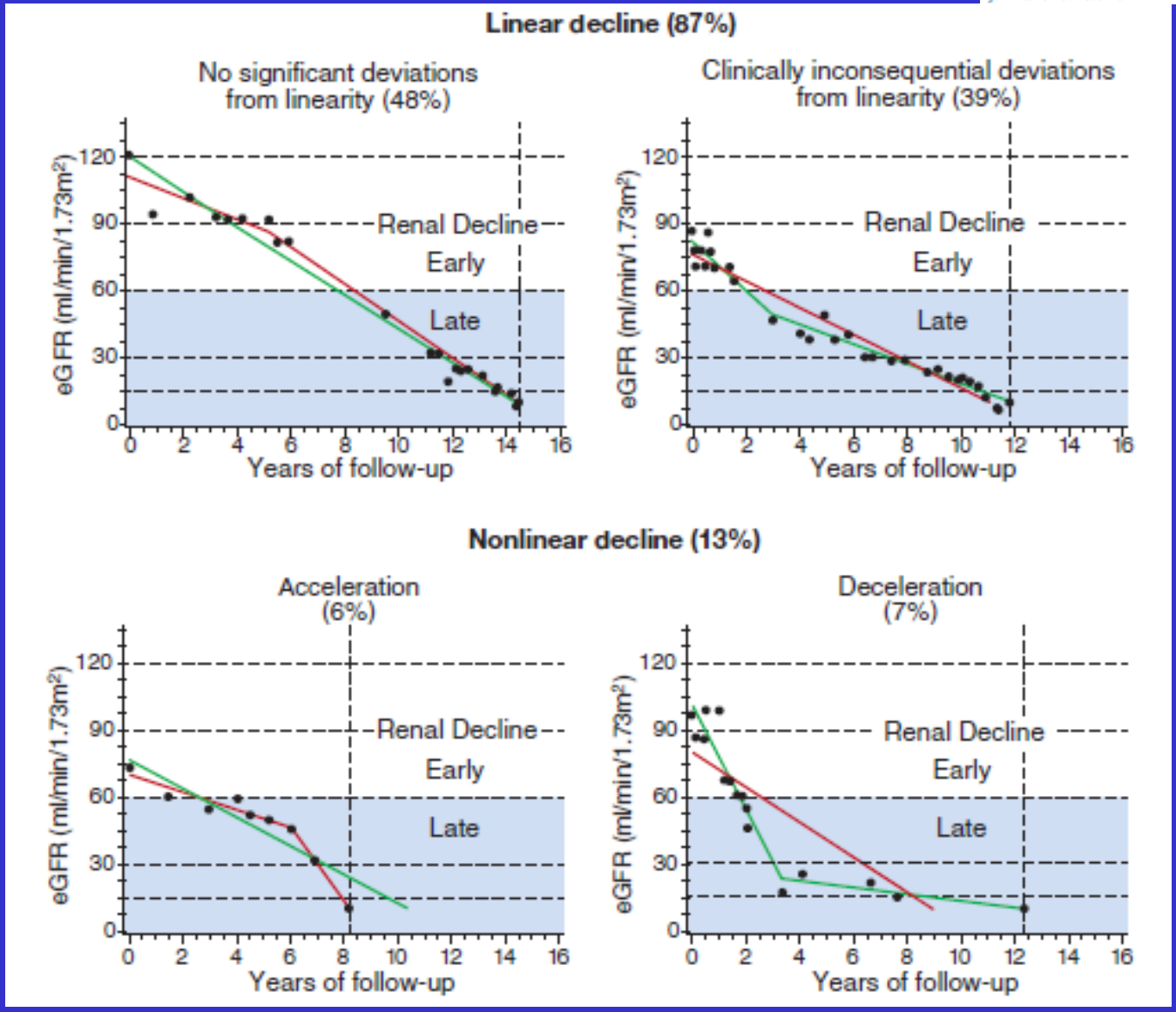


Figure 2 | Examples and frequencies of trajectories of estimated glomerular filtration rate (eGFR) decline in the Joslin end-stage renal disease (ESRD) cohort, classified as linear or nonlinear by a linear spline approach. Trajectories were classified by comparing linear (solid

Renal decline to ESRD

- KDIGO guidelines have defined rapid progression by a rate of eGFR decline >5 ml/min/y.
- There are indeed fast (renal function loss with an interval of 2 to less than 10y between normal function and ESRD), moderate (between 10-20y) and slow (between 20 and 45y) decline of Kidney function.
- In type 1(but also 2) DM, role of high HbA1C, urinary albumin-to-creatinine ratio values, and eGFR (cystatine C) and circulating TNF1R
- In type 2 DM, 14 biomarkers have been identified in those with stage 3 and higher CKD who will have a rapid decline of GFR .

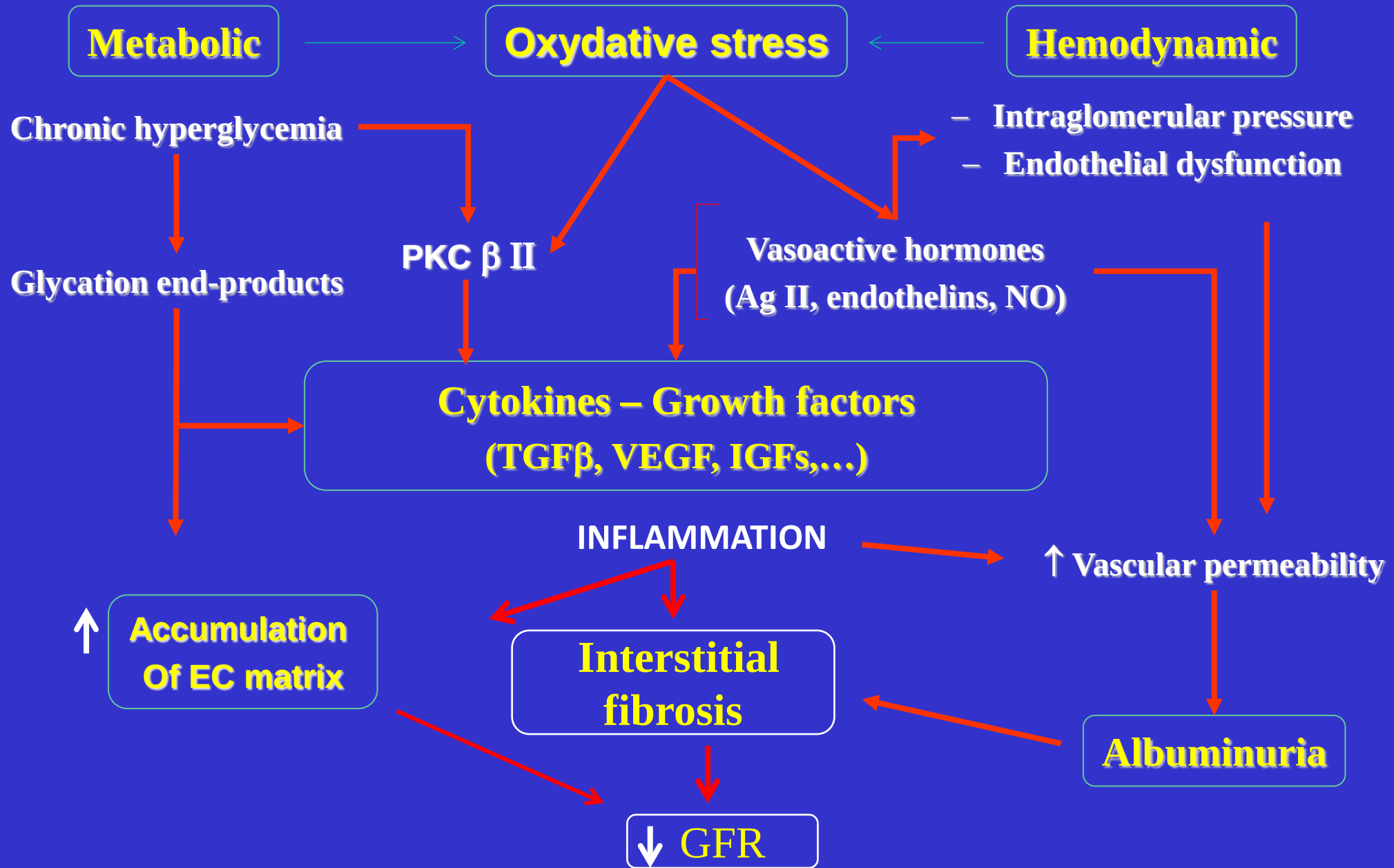
Strict control of glycemia and protection

- Positive results for microvascular complications
- It postpones their onsets by several years if applied early
- Less convincing results for CV protection
- The benefit on CV disease of a HbA1C < 7% rather than 8% decreases with - age,

  - diabetes duration and

  - comorbidities.

Pathophysiology of classical DN



Box 2. Candidate Genes Implicated in the Susceptibility for the Development of DKD

- Angiotensin-converting enzyme (ACE)
- Angiotensinogen
- Angiotensin II receptor (type 1)
- Aldose reductase
- Apolipoprotein E
- Atrial natriuretic peptide
- Heparin sulfate
- Intercellular adhesion molecule 1 (ICAM)
- Matrix metalloproteinase
- Methylene metalloproteinase 9 (MM-9)
- Na/H exchanger
- Nitric oxide synthase
- Plasminogen activator inhibitor 1 (PAI-1)
- Peroxisome proliferator-activated receptor (PPAR)
- Type 4 collagen
- 3-Adrenergic receptor
- Vascular endothelial growth factor (VEGF)
- Engulfment and cell motility 1 (ELMO1)

Am J Kidney Dis. 2014;63(2)(suppl 2):S39-S62