Maladies rénales et diabète, place des gliflozines

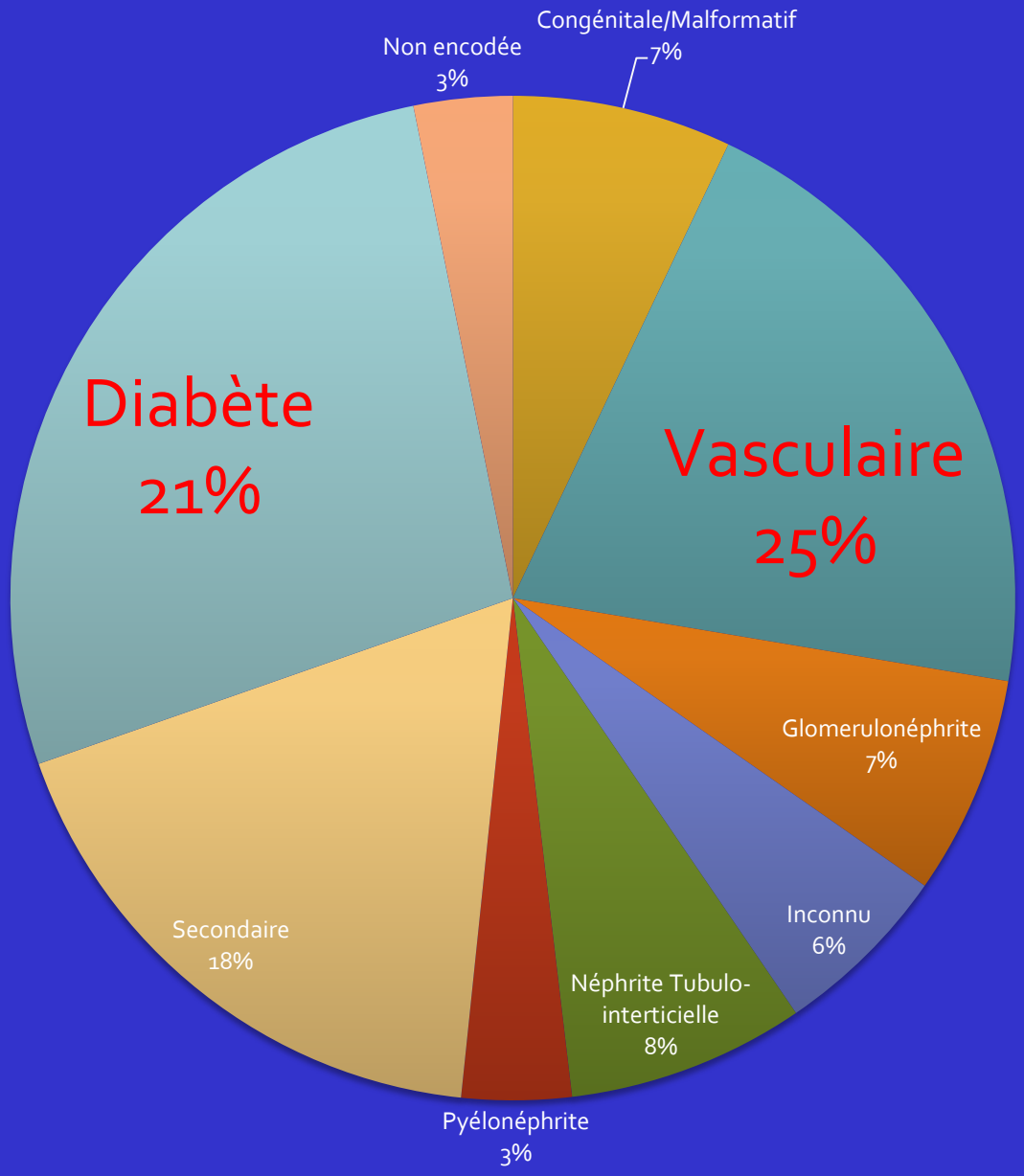
JM Krzesinski

ULg-CHU Liège

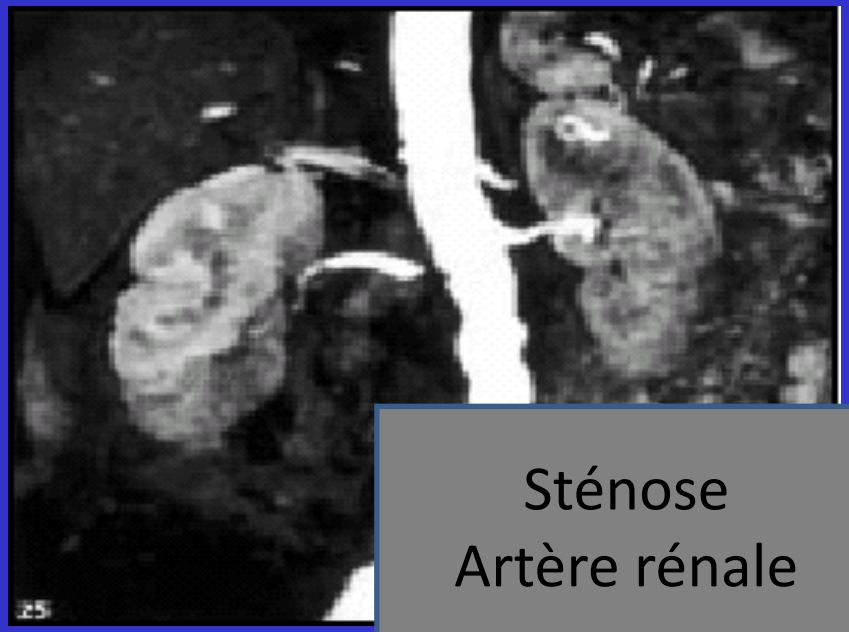
Service de Néphrologie- Dialyse-Transplantation

Dialyse: Les Néphropathies incidentes en 2013

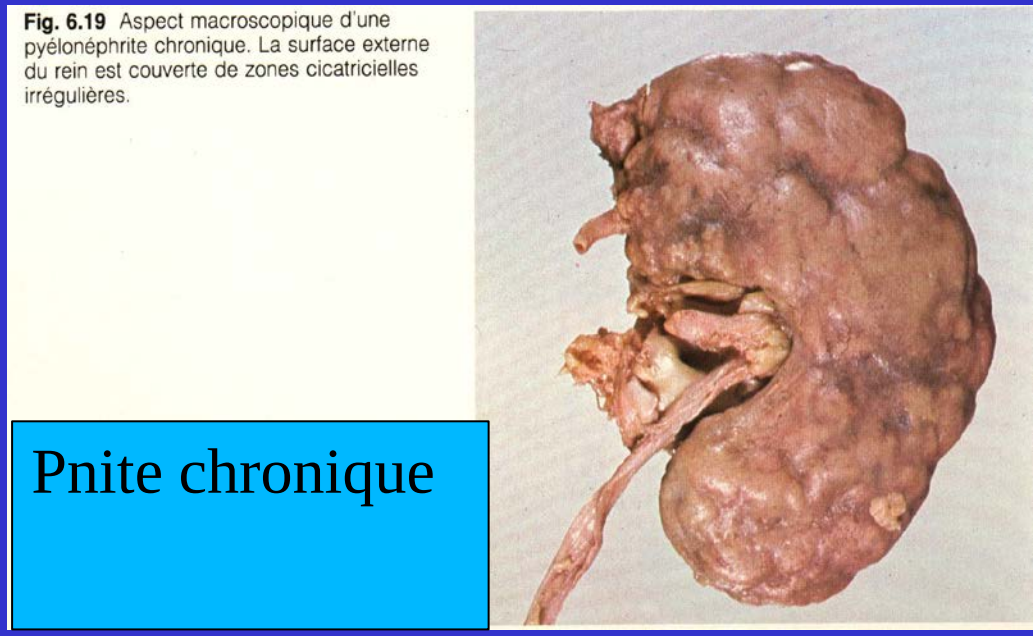
Causes de dialyse liées à DM USA: 30%
DM Asie: 50%



Multiple causes of nephropathy in type 2 diabetes



Sténose
Artère rénale

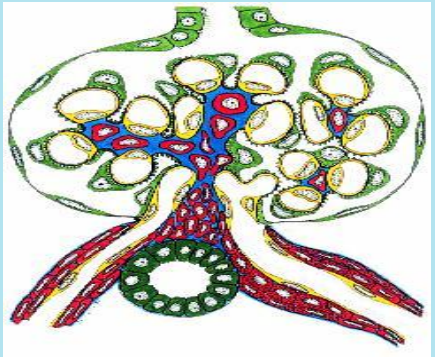


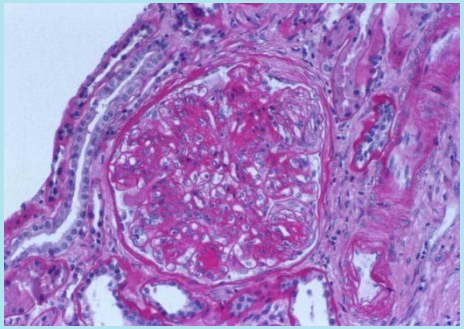
Pnite chronique

- **classical DN (> 10 y DM, Proteinuria with retinopathy)**
- **hypertensive nephropathy (complications of HTA)**
- **ischaemic renal disease (atherosclerosis)**
- **Pyelonephritis, T/I disease (HyperK risk, role of infection, drugs, hyperuricemia)**

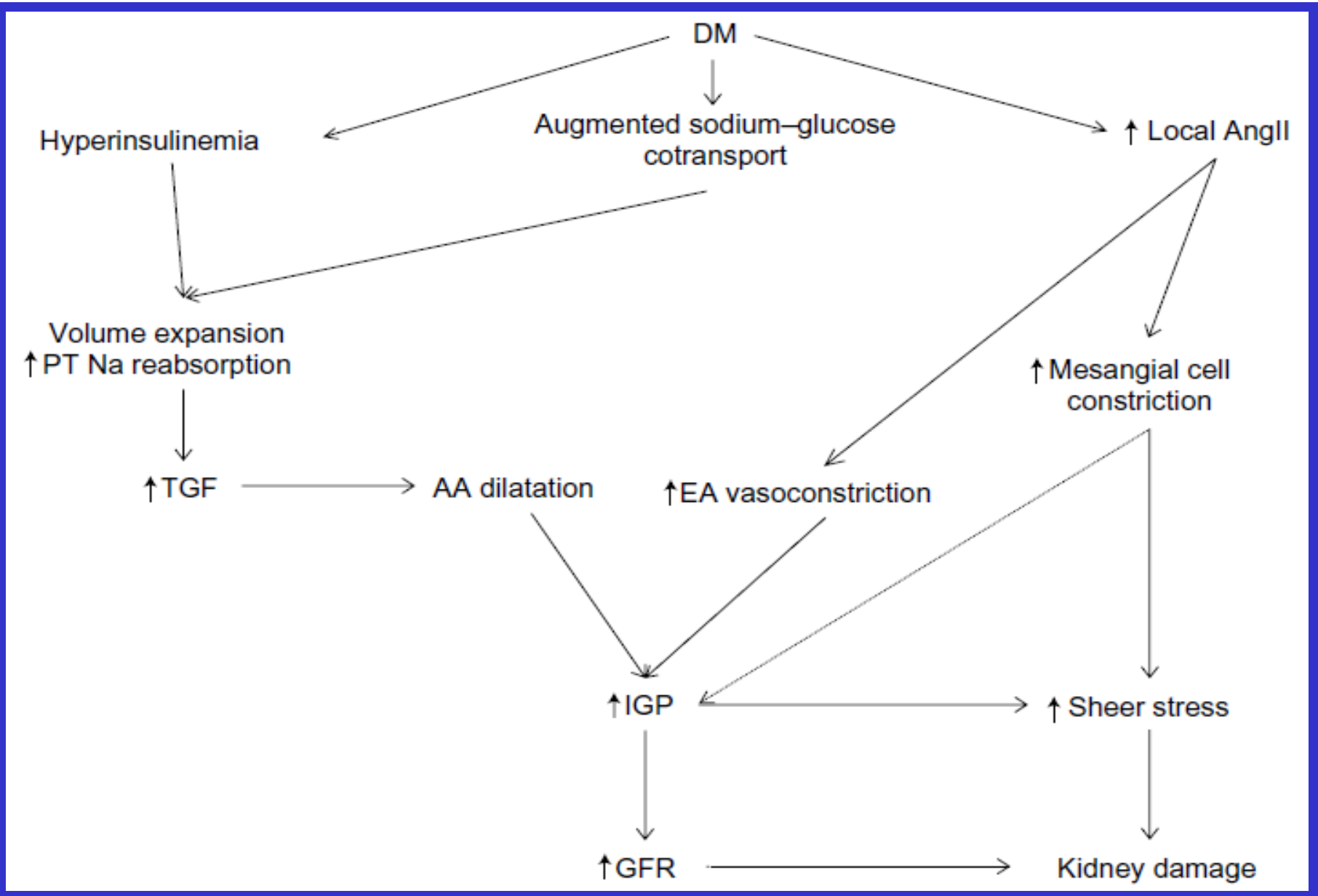
If no proteinuria, check for another cause than classical DN

Diabetic Nephropathy





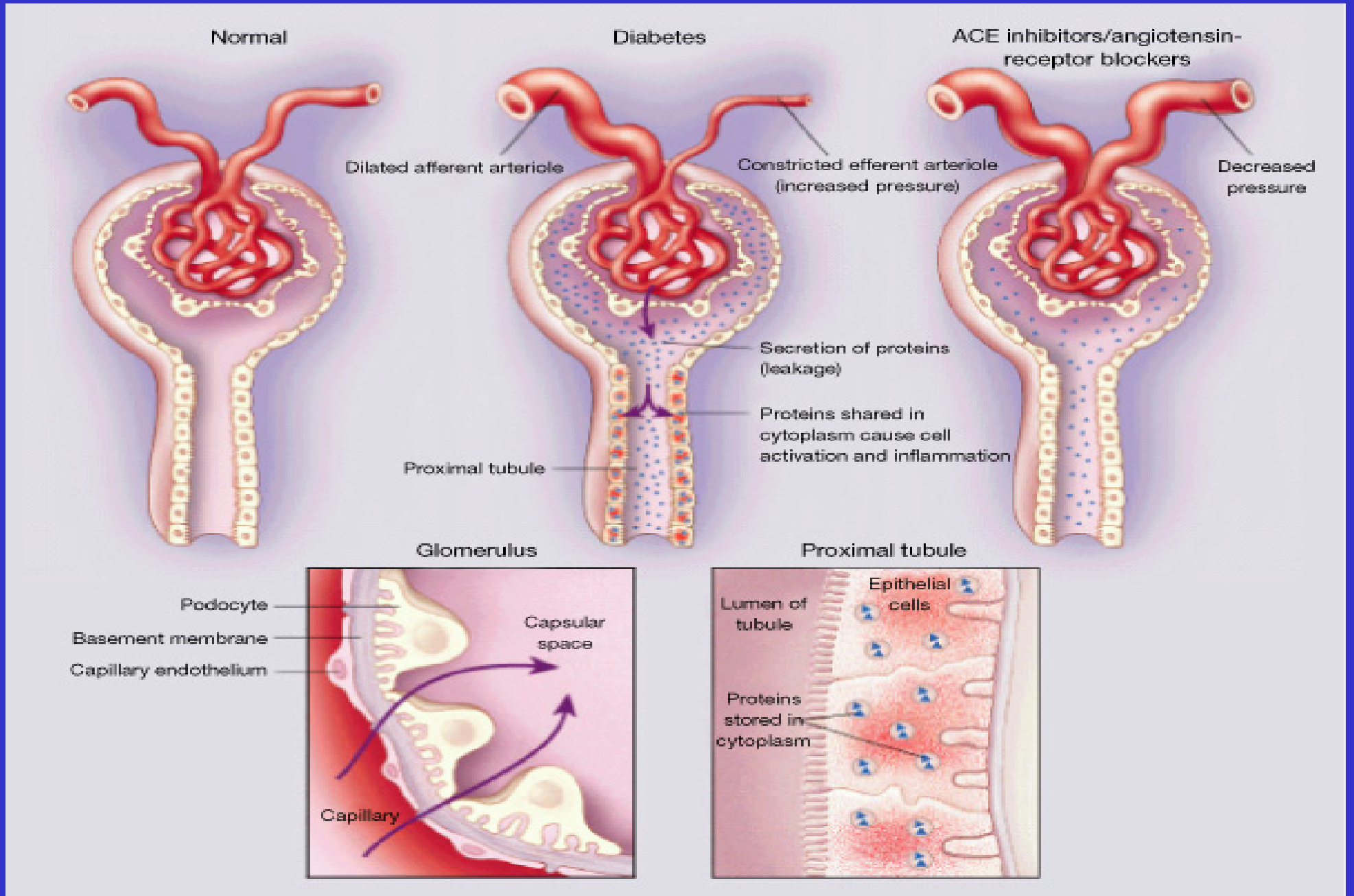
Inhibition of RAS in diabetic nephropathy



Hemodynamic changes in diabetic kidney disease

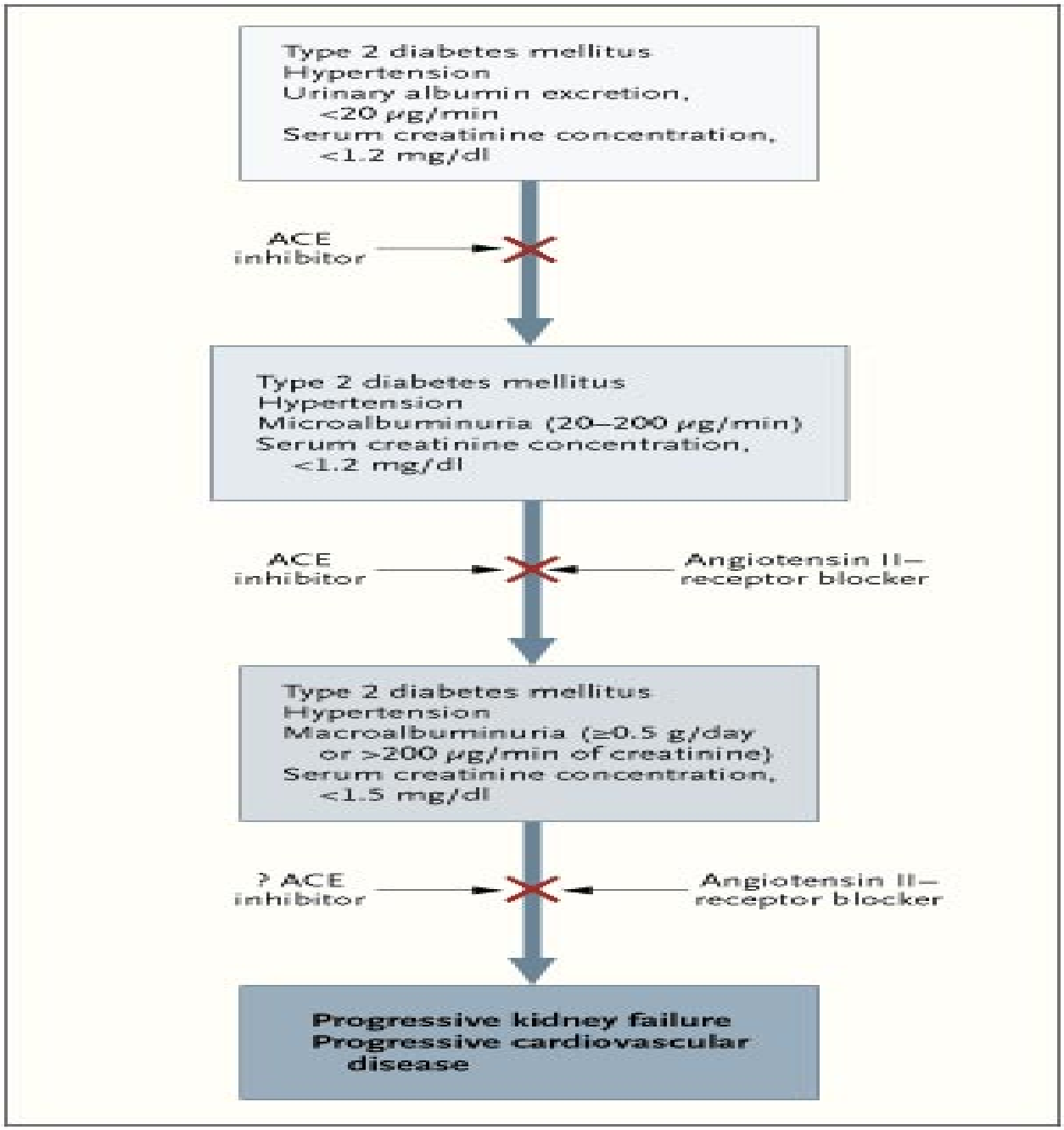
International Journal of Nephrology and Renovascular Disease 2015:

Diabetic nephropathy: physiopathology



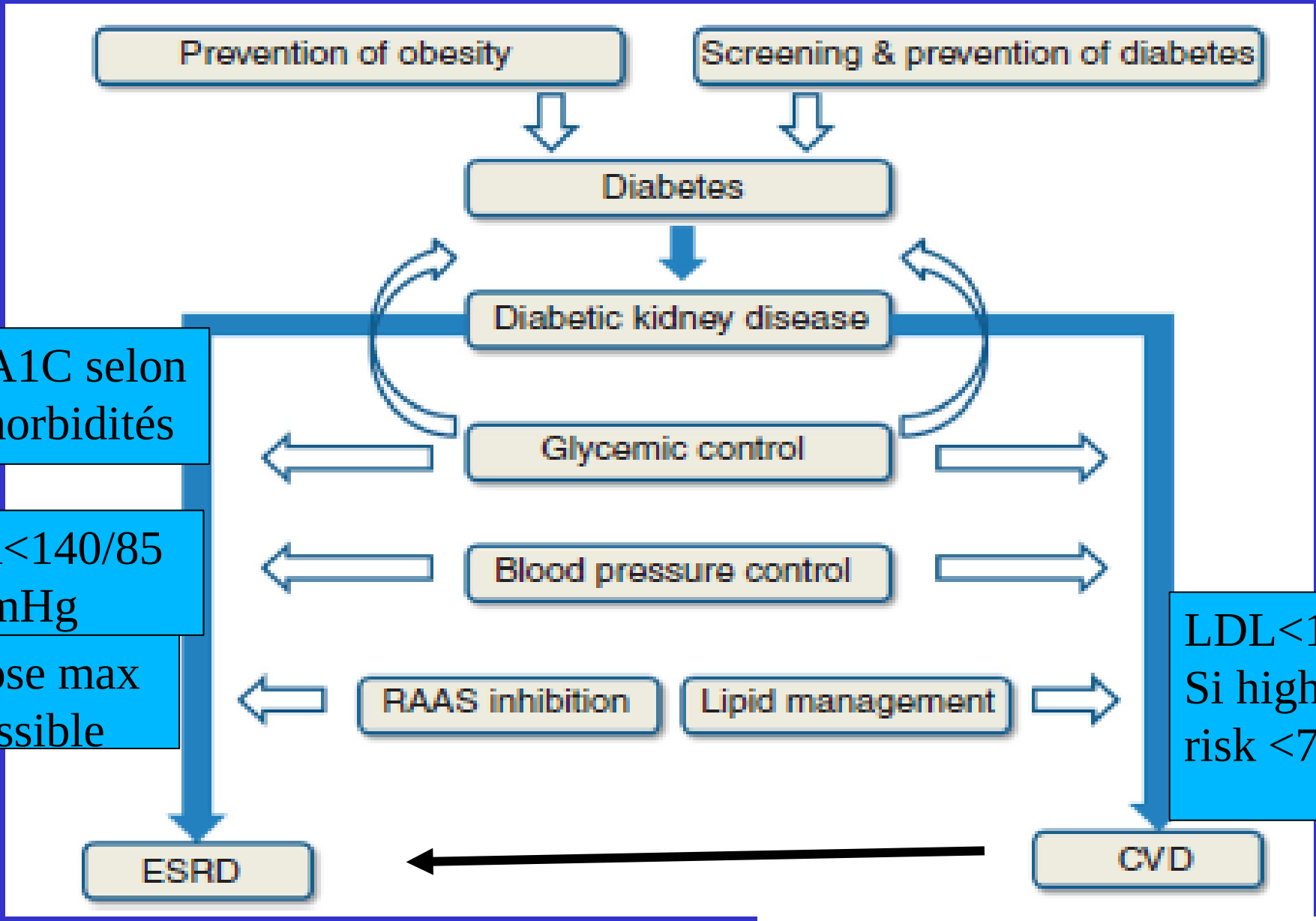
ACE Inhibition or Angiotensin-Receptor Blockade in Progressive Nephropathy Associated with Type 2 Diabetes

Ne PLUS utiliser un double blocage SRA!!



Mitch, W. E. N Engl J Med 2004;

Prise en charge du diabète



HbA1C selon comorbidités

PA<140/85 mmHg

Dose max possible

LDL<100
Si high CV risk <70

Kidney International (2015) **87**, 20–30

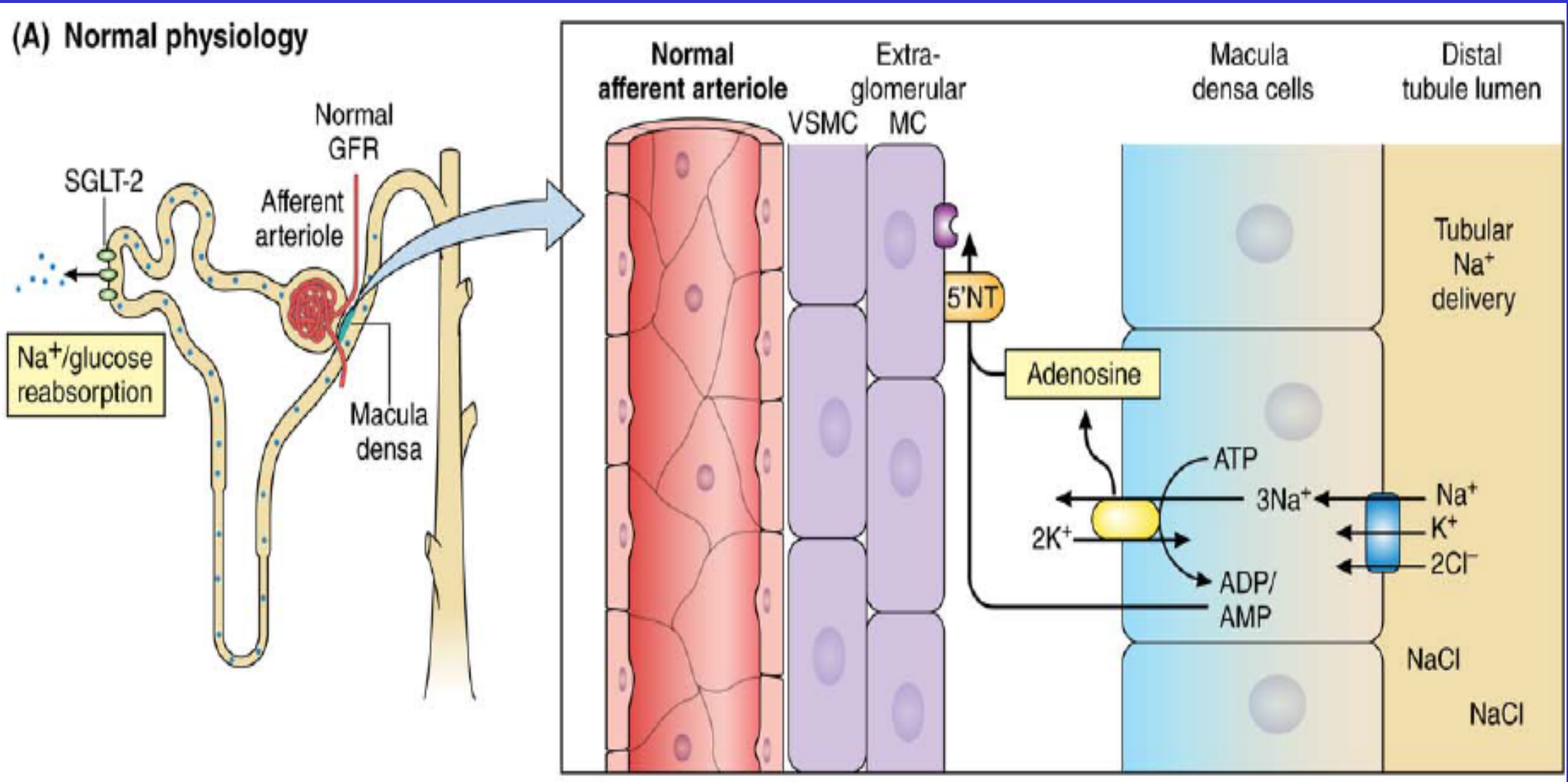
Diabetic nephropathy: landmark clinical trials and tribulations

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.

Sodium Glucose Cotransporter 2 Inhibitors in the Treatment of Diabetes: Cardiovascular and Kidney Effects, Potential Mechanisms and Clinical Applications

Heerspink et al: Cardiovascular Risk and SGLT2 Inhibition



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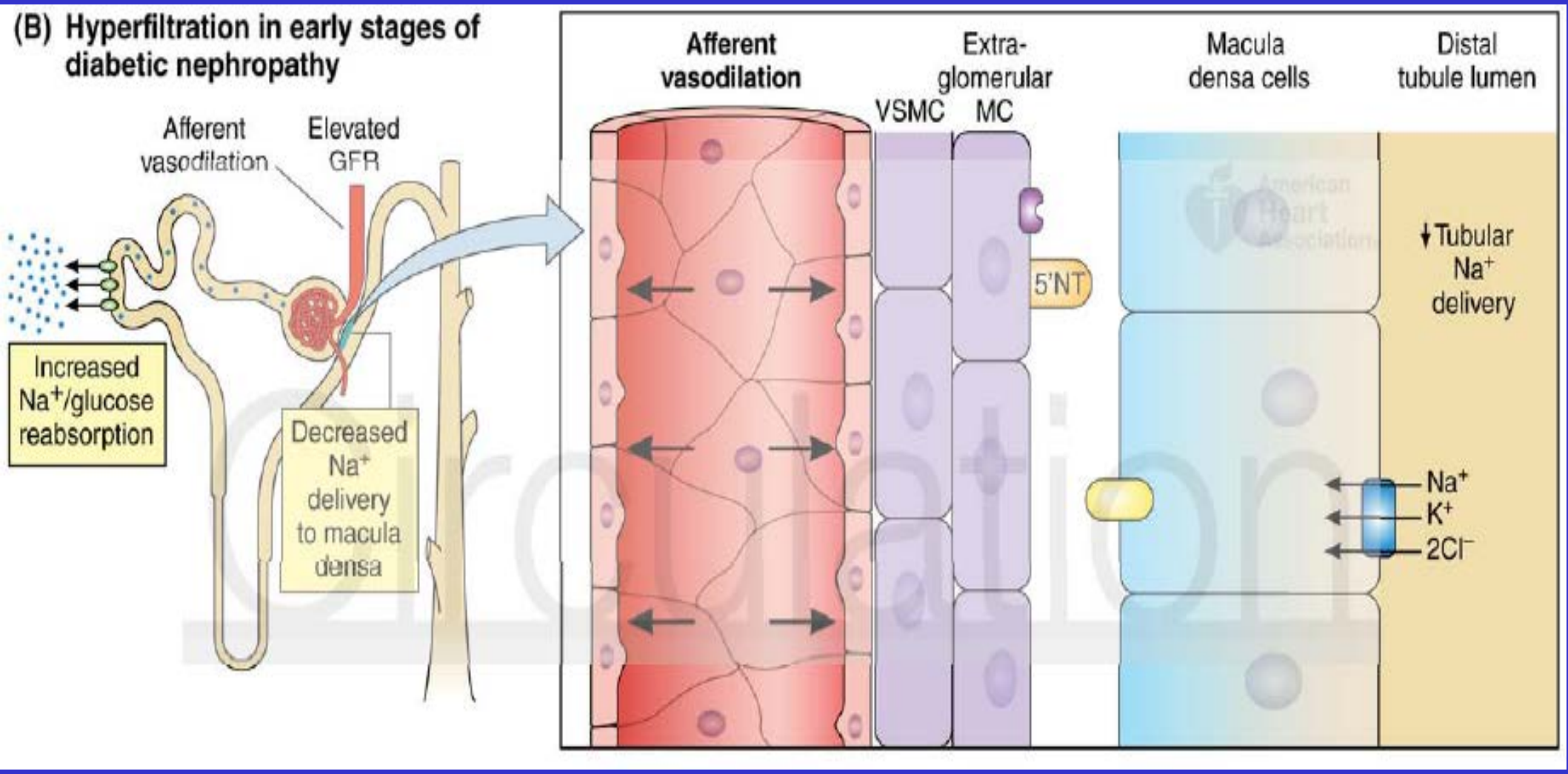

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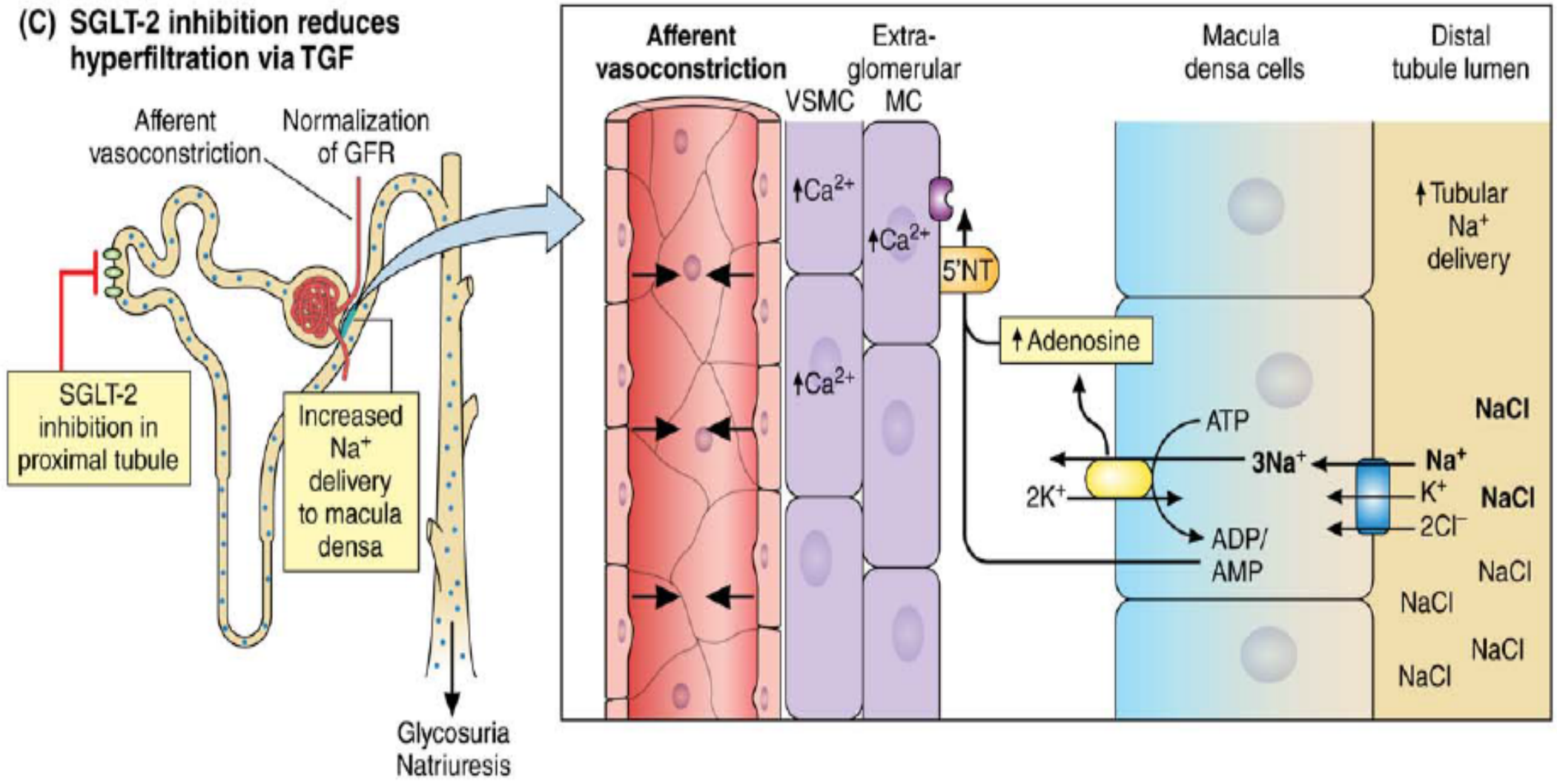

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

Christoph Wanner, M.D., Silvio E. Inzucchi, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Maximilian von Eynatten, M.D., Michaela Mattheus, Dipl. Biomath., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Bernard Zinman, M.D., for the EMPA-REG OUTCOME Investigators*

This article was published on June 14, 2016, at NEJM.org.

CONCLUSIONS

In patients with type 2 diabetes at high cardiovascular risk, empagliflozin was associated with slower progression of kidney disease and lower rates of clinically relevant renal events than was placebo when added to standard care. (Funded by the Boehringer Ingelheim and Eli Lilly and Company Diabetes Alliance; EMPA-REG OUTCOME ClinicalTrials.gov number, NCT01131676.)

Caractéristiques de base de la population
Pas de différence entre les 2 groupes (pl vs E)

- Age: 63 ans, 72% H, Caucasiens: 72%
- IMC 30,7%
- HbA1C: 8,1%
- Maladies coronaires: 75%
- AVC: 23%
- Artériopathie MI: 21%
- PA 135/77 mmHg
- ISRA: 81% et Statines: 77%

Etude Empaglifozine: fonction rénale de départ

	Placebo	Empaglifozine:
Estimated glomerular filtration rate – mL/min/1.73m[2][‡‡]	73.8 ± 21.1	74.2 ± 21.6
Estimated glomerular filtration rate – no. (%)[‡‡]		
≥90 mL/min/1.73m^2	488 (20.9)	1050 (22.4)
60 to <90 mL/min/1.73m^2	1238 (53.1)	2423 (51.7)
<60 mL/min/1.73m^2	607 (26.0)	1212 (25.9)
Urine albumin-to-creatinine ratio – no. (%)[§§]		
<30 mg/g	1382 (59.2)	2789 (59.5)
30 to 300 mg/g	675 (28.9)	1338 (28.5)
>300 mg/g	260 (11.1)	509 (10.9)

Empagliflozine et protection rénale (Empa-Reg)

- Réduction de risque de :
- 39% de survenue ou d'aggaravation d'une IR
- 55% de démarrer un RRT
- 44% du doublement du taux de créatinine avec DFG < 45 ml/min
- 38% de progression vers Macroalbuminurie
- Protection rapide, indépendante de la dose, du niveau de fonction rénale initial, de l'âge, du sexe, de la race, du nombre d'années de diabète!

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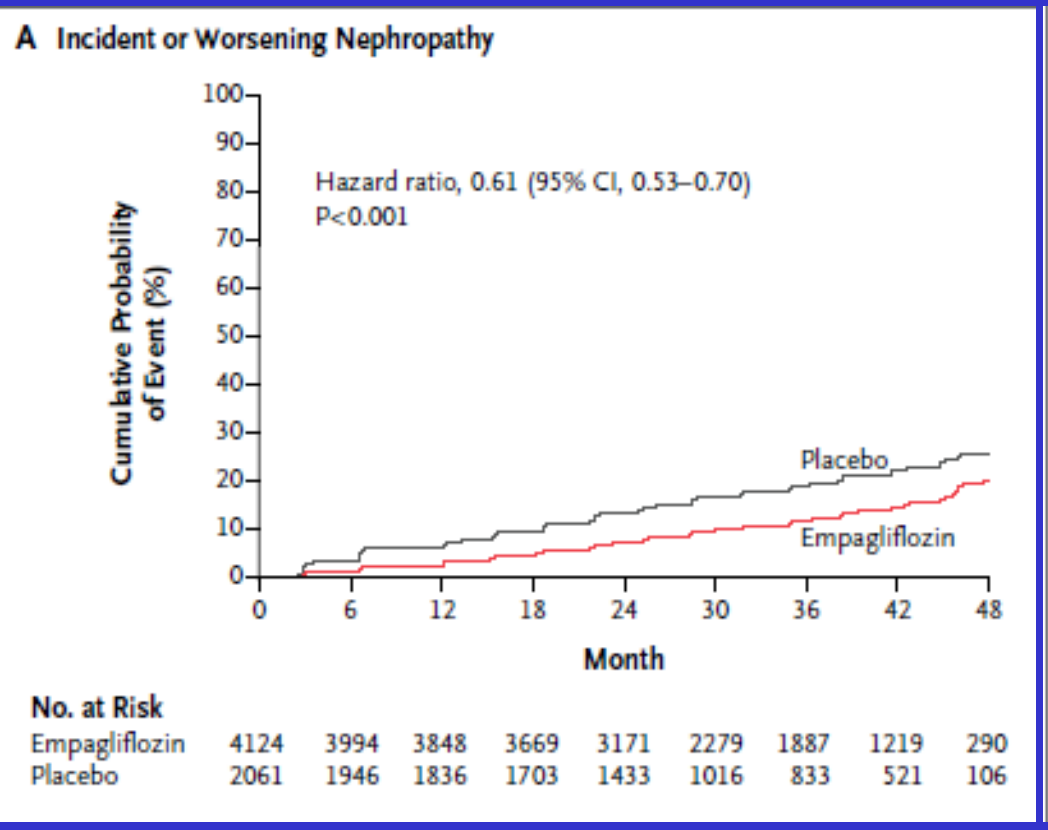

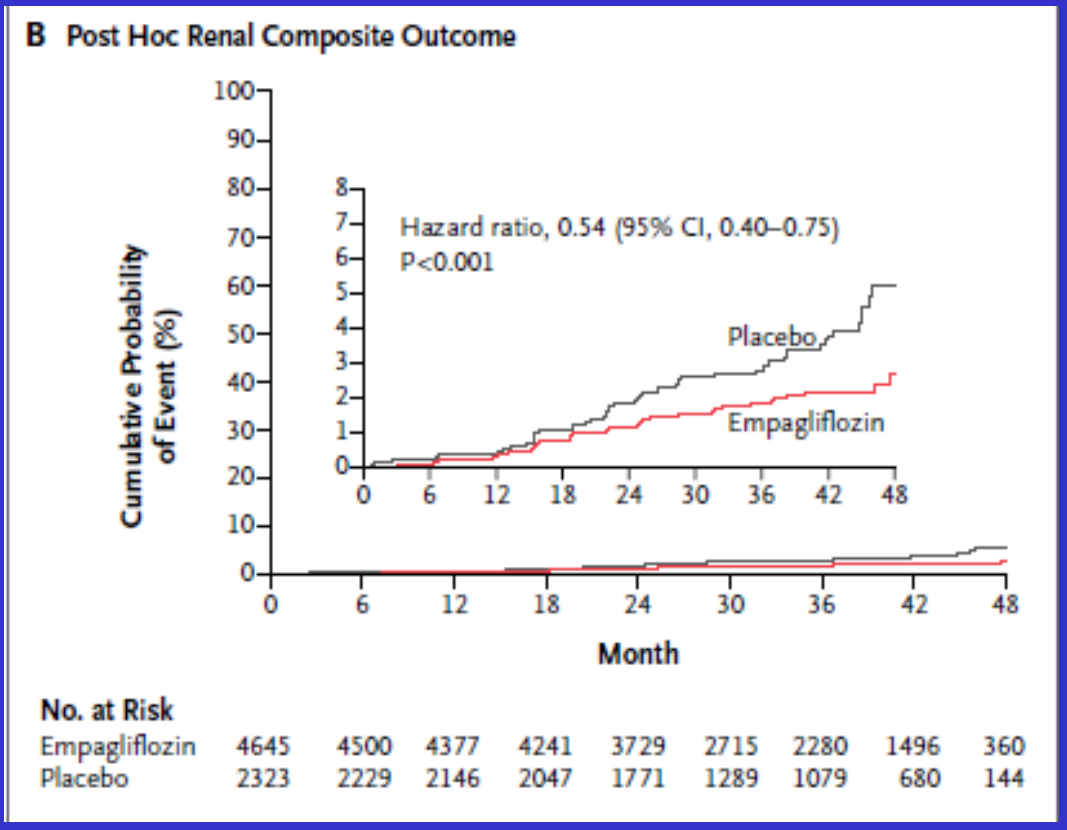

Figure 1. Kaplan–Meier Analysis of Two Key Renal Outcomes.

Shown are estimates of the probability of a first occurrence of a prespecified renal composite outcome of incident or worsening nephropathy (Panel A) and of a post hoc renal composite outcome (a doubling of the serum creatinine level, the initiation of renal-replacement therapy, or death from renal disease) (Panel B) among patients who received at least one dose of either empagliflozin or placebo. The inset in Panel B shows the data on an

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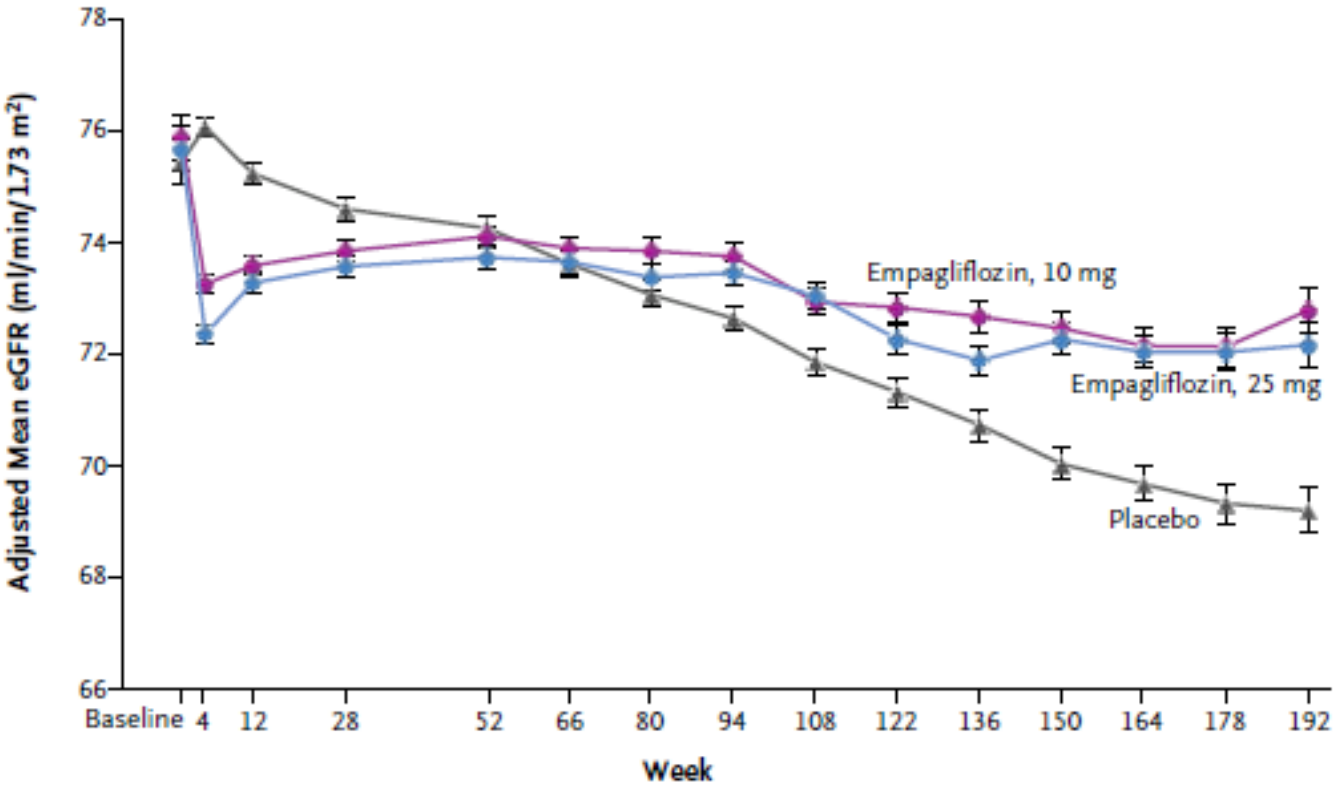
A Change in eGFR over 192 Wk



No. at Risk															
Placebo	2323	2295	2267	2205	2121	2064	1927	1981	1763	1479	1262	1123	977	731	448
Empagliflozin, 10 mg	2322	2290	2264	2235	2162	2114	2012	2064	1839	1540	1314	1180	1024	785	513
Empagliflozin, 25 mg	2322	2288	2269	2216	2156	2111	2006	2067	1871	1563	1340	1207	1063	838	524
No. in Follow-up Analysis															
Total	7020	7020	6996	6931	6864	6765	6696	6651	6068	5114	4443	3961	3488	2707	1703

Sodium–glucose cotransporter 2 inhibition and cardiovascular risk reduction in patients with type 2 diabetes: the emerging role of natriuresis

Harindra Rajasekeran[1,3], Yuliya Lytvyn[1,2,3] and David Z.I. Cherney[1]

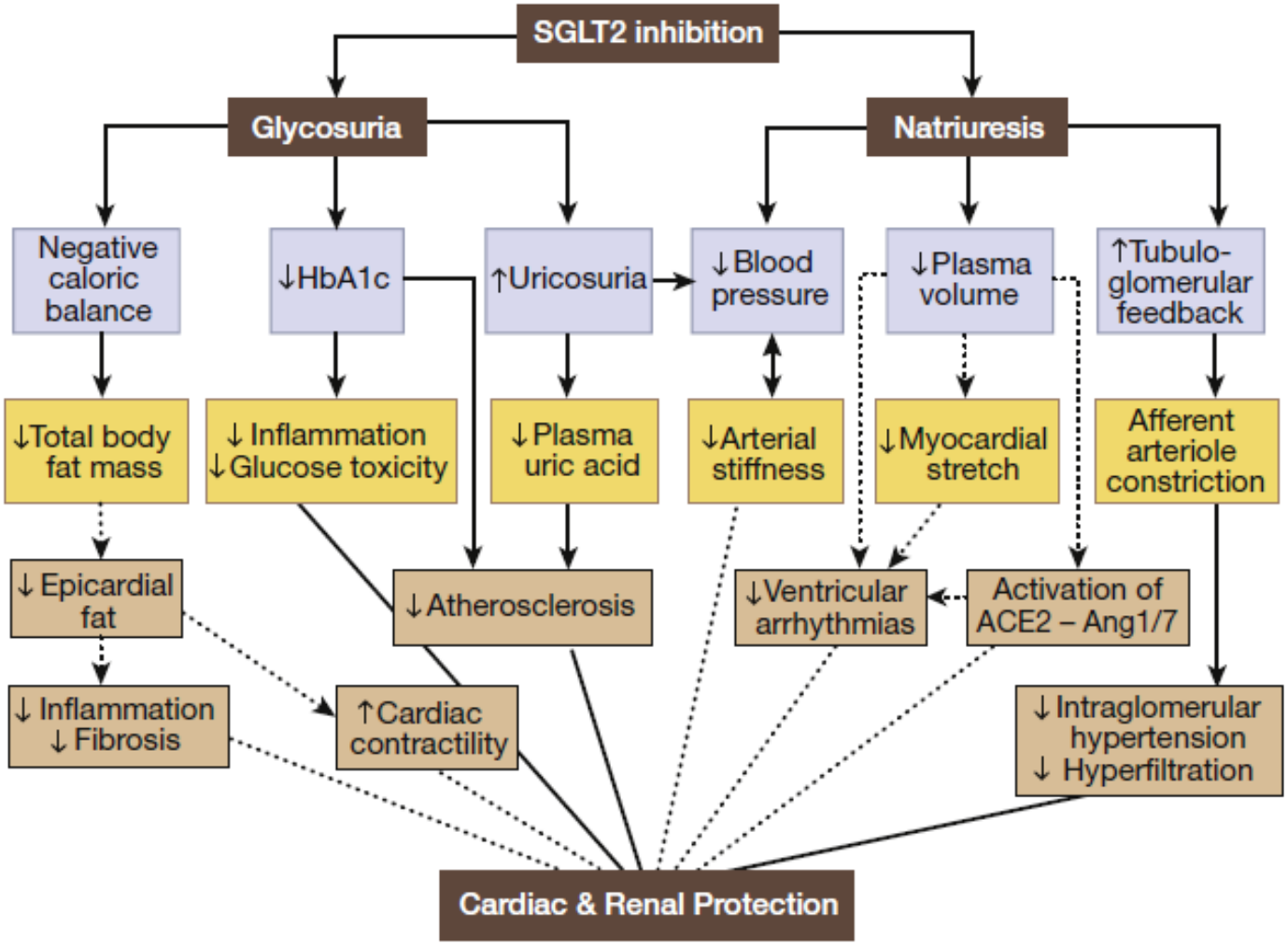


Figure 1 | Possible mechanisms responsible for cardiovascular and renal protection with sodium–glucose cotransporter 2 (SGLT2) inhibition. Solid lines represent pathways supported by existing data; dashed lines represent possible areas for future research. ACE2, angiotensin-converting enzyme-2; Ang1/7,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

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

Conclusions

- Diabète = grand risque Maladie rénale
- Maladie rénale = risque CV>
- Approche multifactorielle nécessaire
- Dépistage précoce nécessaire
- Rôle majeur joué par le MG!
- Collaboration multidisciplinaire indispensable!
- Place potentielle des gliflozines chez les patients DM à haut risque CV.

Canagliflozin Slows Progression of Renal Function Decline Independently of Glycemic Effects

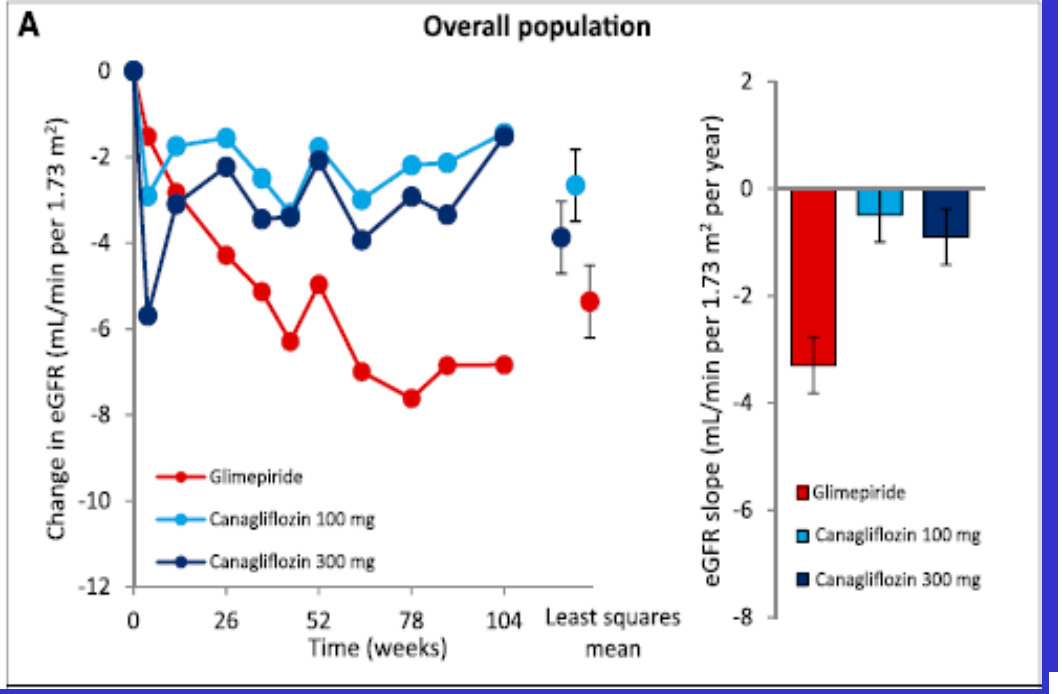
Hiddo J. L. Heerspink,* Mehul Desai,† Meg Jardine,‡ Dainius Balis,† Gary Meininger,† and Vlado Perkovic‡

*Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; †Janssen Research & Development, LLC, Raritan, New Jersey; and ‡The George Institute for Global Health, University of Sydney, Sydney, Australia

J Am Soc Nephrol 28: ●●●–●●●, 2016. doi: 10.1681/ASN.2016030278

ABSTRACT

Sodium-glucose cotransporter 2 inhibition with canagliflozin decreases HbA1c, body weight, BP, and albuminuria, implying that canagliflozin confers renoprotection. We determined whether canagliflozin decreases albuminuria and reduces renal function decline independently of its glycemic effects in a secondary analysis of a clinical trial in 1450 patients with type 2 diabetes receiving metformin and randomly assigned to either once-daily canagliflozin 100 mg, canagliflozin 300 mg, or glimepiride uptitrated to 6–8 mg. End points were annual change in eGFR and albuminuria over 2 years of follow-up. Glimepiride, canagliflozin 100 mg, and canagliflozin 300 mg groups had eGFR declines of 3.3 ml/min per 1.73 m^2 per year (95% confidence interval [95% CI], 2.8 to 3.8), 0.5 ml/min per 1.73 m^2 per year (95% CI, 0.0 to 1.0), and 0.9 ml/min per 1.73 m^2 per year (95% CI, 0.4 to 1.4), respectively ($P<0.01$ for each canagliflozin group versus glimepiride). In the subgroup of patients with baseline urinary albumin-to-creatinine ratio ≥30 mg/g, urinary albumin-to-creatinine ratio decreased more with canagliflozin 100 mg (31.7%; 95% CI, 8.6% to 48.9%; $P=0.01$) or canagliflozin 300 mg (49.3%; 95% CI, 31.9% to 62.2%; $P<0.001$) than with glimepiride. Patients receiving glimepiride, canagliflozin 100 mg, or canagliflozin 300 mg had reductions in HbA1c of 0.81%, 0.82%, and 0.93%, respectively, at 1 year and 0.55%, 0.65%, and 0.74%, respectively, at 2 years. In conclusion, canagliflozin 100 or 300 mg/d, compared with glimepiride, slowed the progression of renal disease over 2 years in patients with type 2 diabetes, and canagliflozin may confer renoprotective effects independently of its glycemic effects.



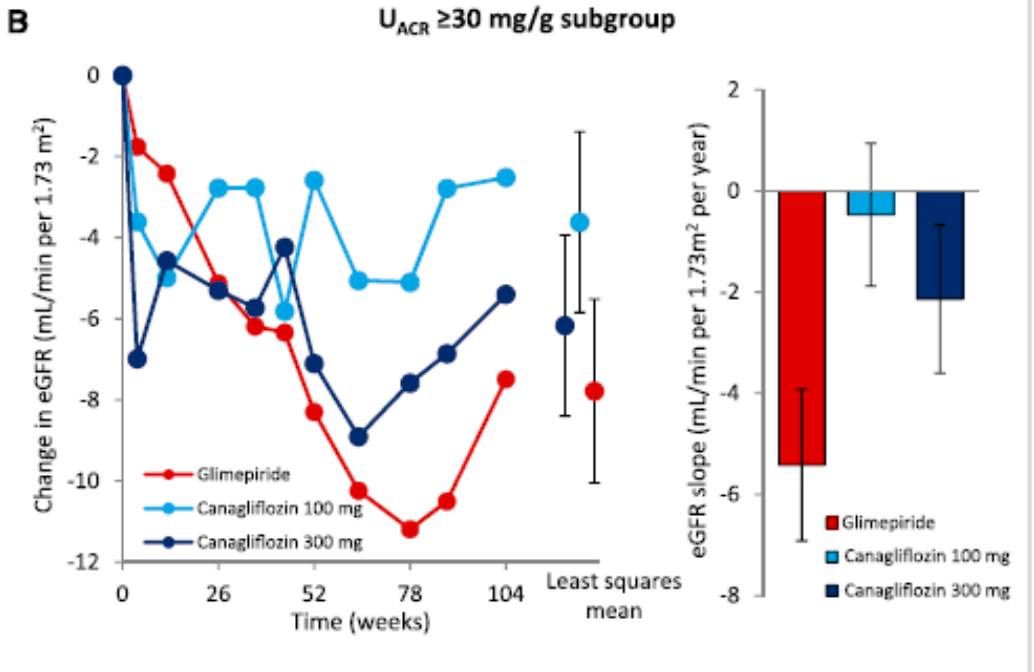
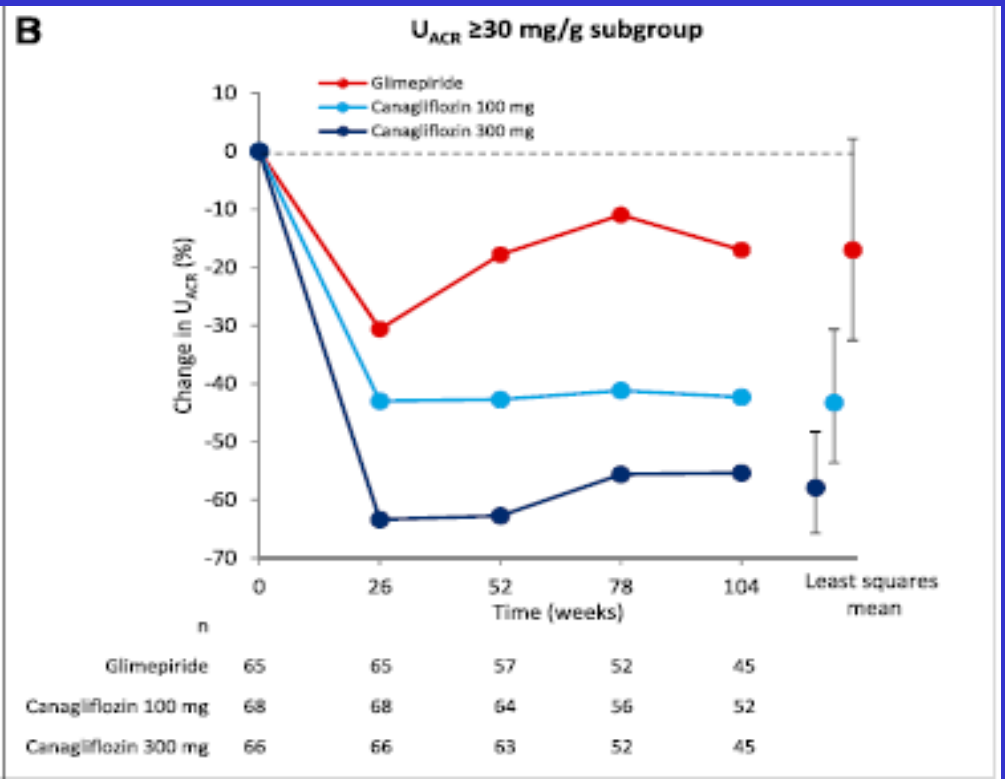


Figure 1. Canagliflozin slows the progression of eGFR decline in patients with type 2 diabetes compared with glimepiride. (A) Changes in eGFR in the canagliflozin and glimepiride treatment arms in the overall population, and the rate of eGFR decline per year. (B) Changes in eGFR in the canagliflozin and glimepiride treatment arms in patients with U_{ACR}≥30 mg/g, and the rate of eGFR decline per year in patients with U_{ACR}≥30 mg/g

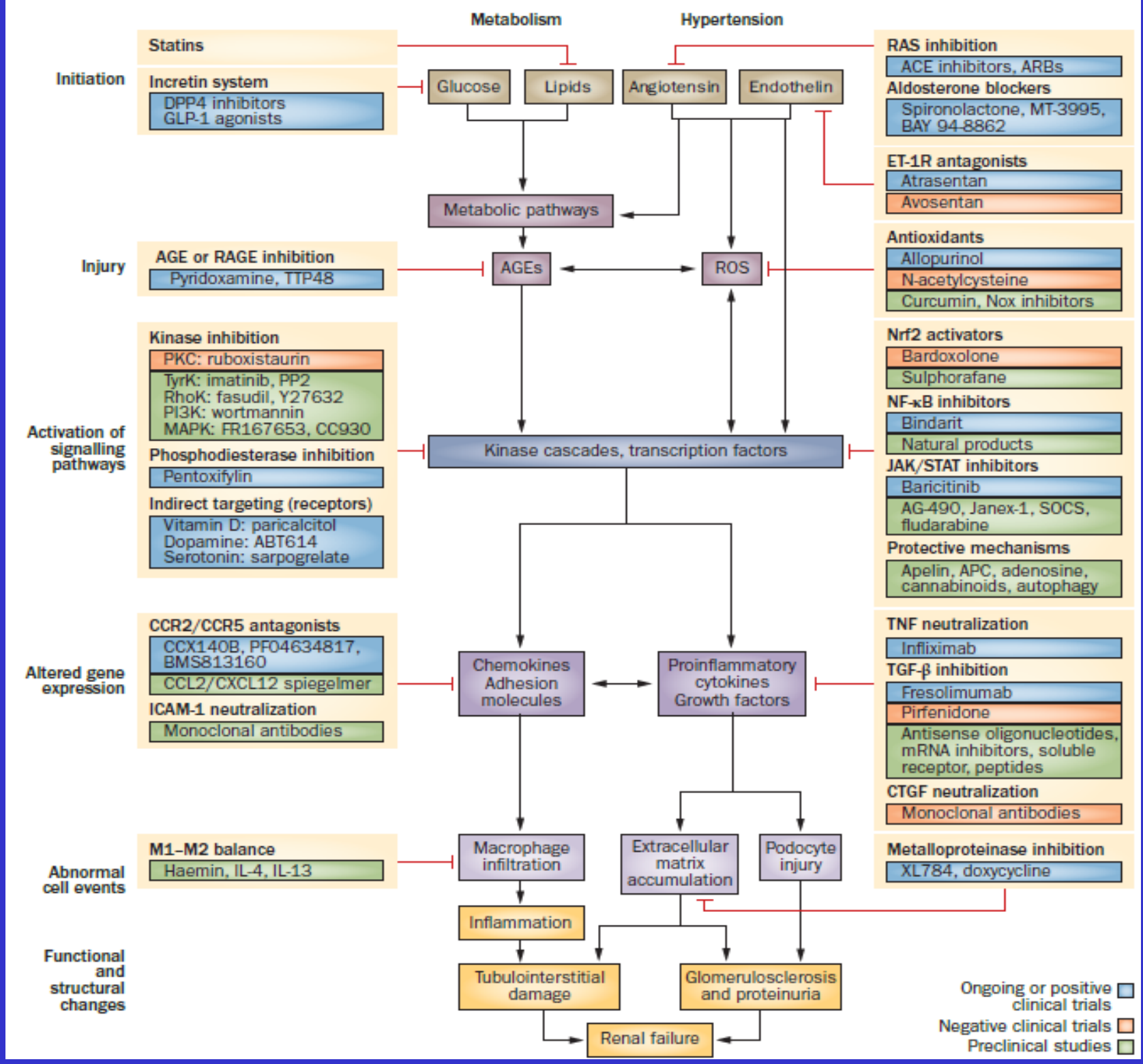


J Am Soc Nephrol 28: ●●●–●●●, 2016. doi: 10.1681/ASN.2016030278

FIGURE 2: Suggested use and dose adaptation of glucose-lowering drugs according to the CKD stages (see also Table 1 for details)

		CKD-1	CKD-2	CKD-3	CKD-4	CKD-5ND	CKD-5D
	Metformin	No adjustments		1,5g-850 mg/day*	500 mg/day**	Consider carefully/Awaiting further data	
Sulfonylureas	Chlorpropamide	No adjustments		100-125 mg/day	To be avoided		
	Acetohexamide	To be avoided					
	Tolazamide	To be avoided					
	Tolbutamide	250mg, 1-3 times/day				To be avoided	
	Glipizide	No adjustments					
	Glicazide	Start at low doses and dose titration every 1-4 weeks					
	Glyburide	To be avoided					
	Glimepiride	Recude dosage to 1 mg/day				To be avoided	
	Gliquidone	No adjustments					
Meglitinides	Repaglinide	No adjustments				Limited experience available	
	Nateglinide	No adjustments				Start at 60 mg/day	To be avoided
α-gluc inhibitors	Acarbose	No adjustments			Avoid if GFR<25mL/min	To be avoided	
	Miglitol	Limited experience available					
	Pioglitazone	No adjustments					
DPP-IV inhibitors	Sitagliptin	No adjustments		Reduce to 50 mg/day	Reduce to 25 mg/day		
	Vildagliptin	No adjustments		Reduce to 50 mg/once daily			
	Saxagliptin	No adjustments		Reduce to 2,5 mg/once daily			
	Linagliptin	No adjustments					
	Alogliptin	No adjustments		Reduce to 12,5 mg/daily			
Incretin Mimetics	Exenatide	No adjustments	Reduce dose to 5 mcg/once to twice daily		To be avoided		
	Liraglutide	Limited experience available					
	Lixisenatide	No adjustments	Careful use if GFR 80-50 mL/min				No experience available
	Pramlintide	Limited experience available					
SGLT-2 inhibitors	Dapagliflozin	Limited experience available					
	Canagliflozin	Reduced efficacy		Careful monitoring		To be avoided	
	Empagliflozin	Limited experience available					

FIGURE 2: Suggested use and dose adaptation of glucose-lowering drugs according to the CKD stages (see also Table 1 for details)

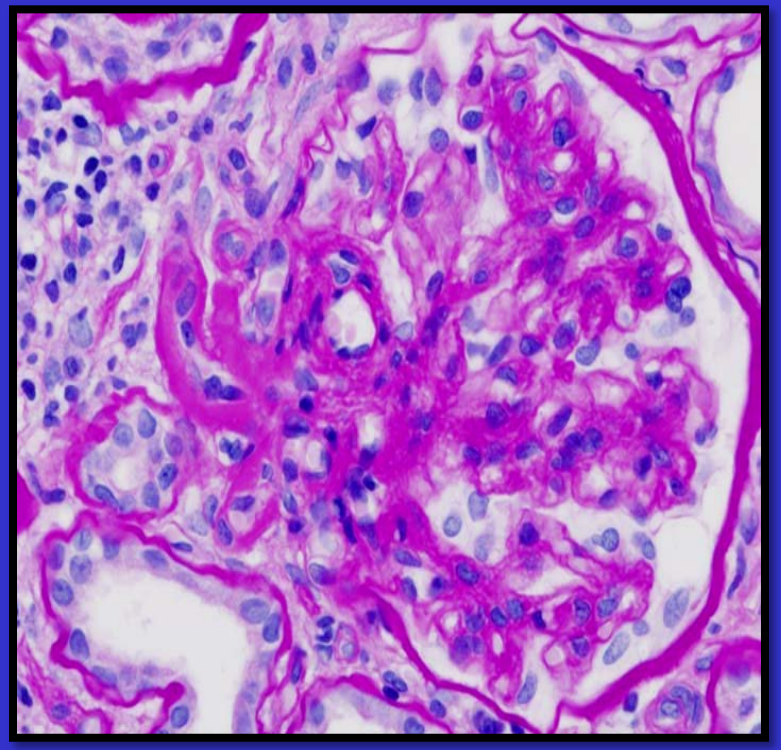


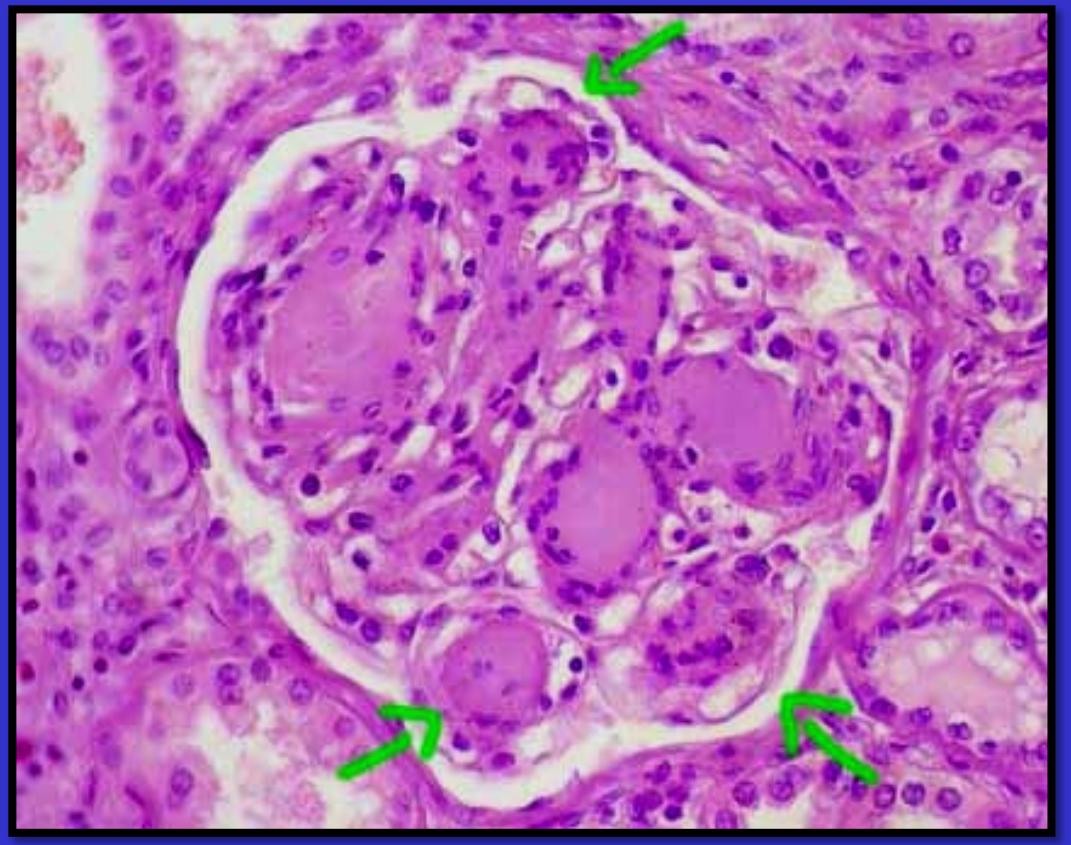
Nat. Rev. Nephrol. 10, 225–246 (2014); published online 6 May 2014;

DIABETIC NEPHROPATHY

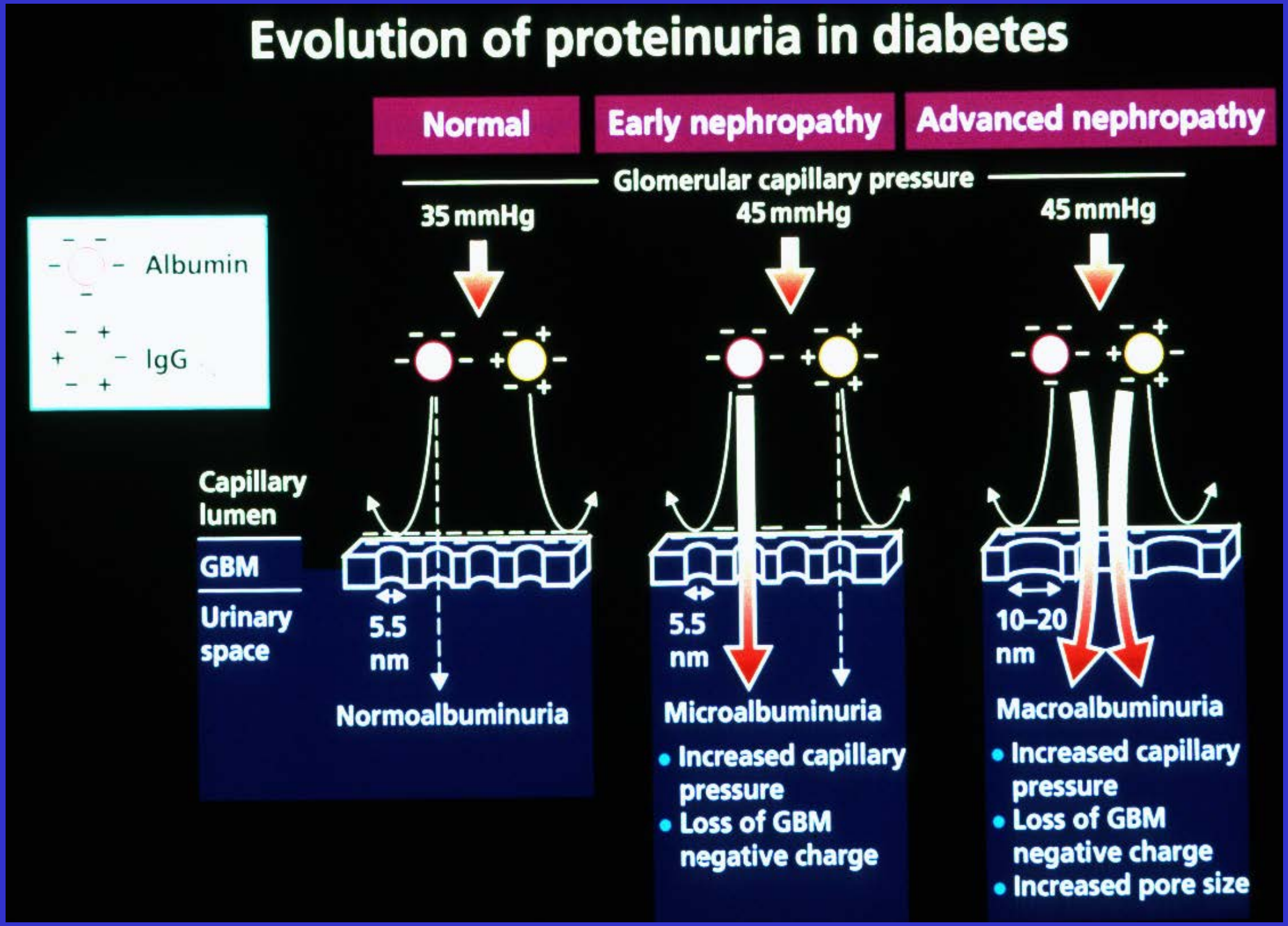
Mesangial expansion progressing to Nodules of Kimmelstiel-Wilson

First cause of ESRD in the XXst century

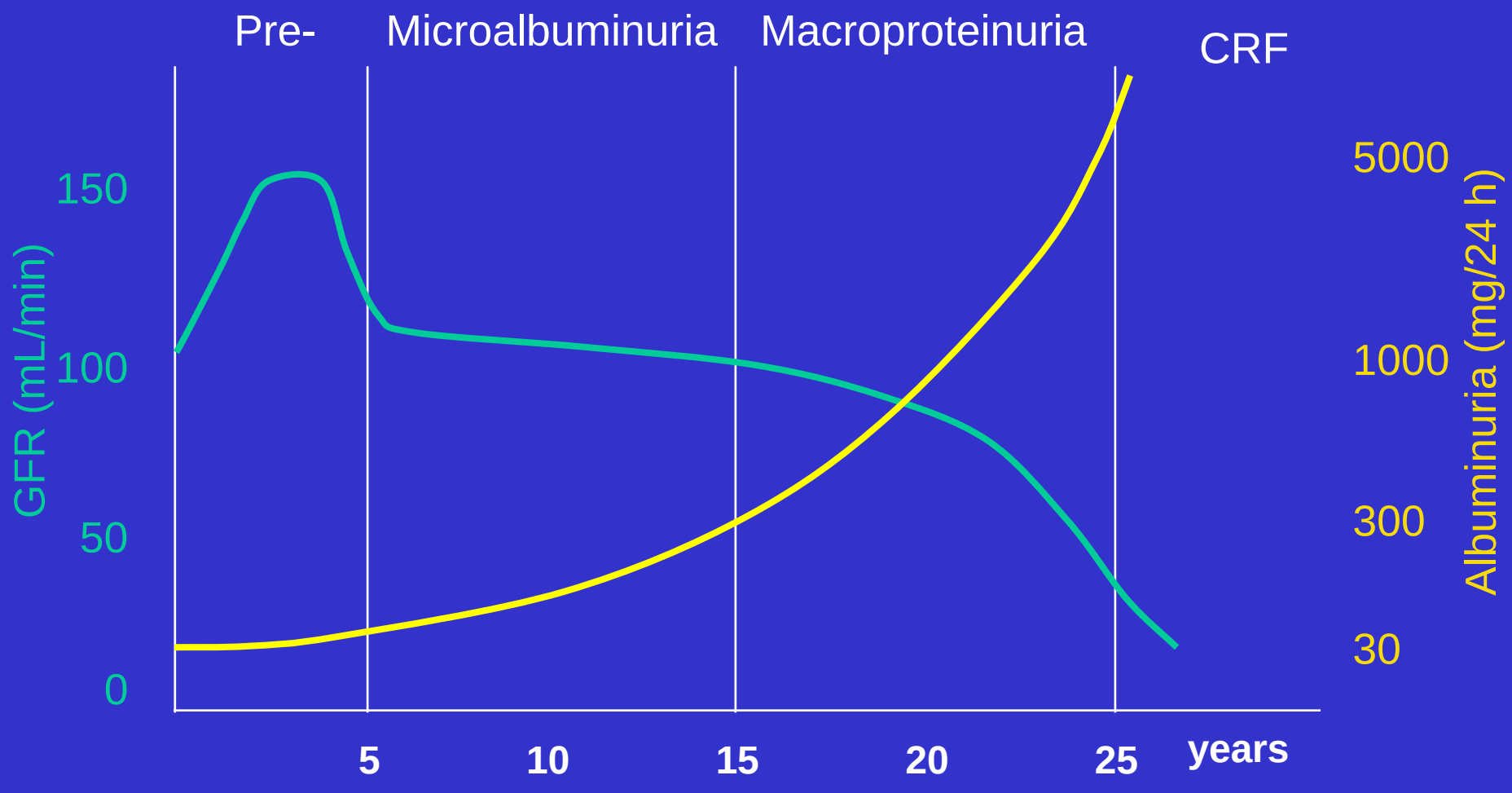




Evolution of proteinuria in diabetes



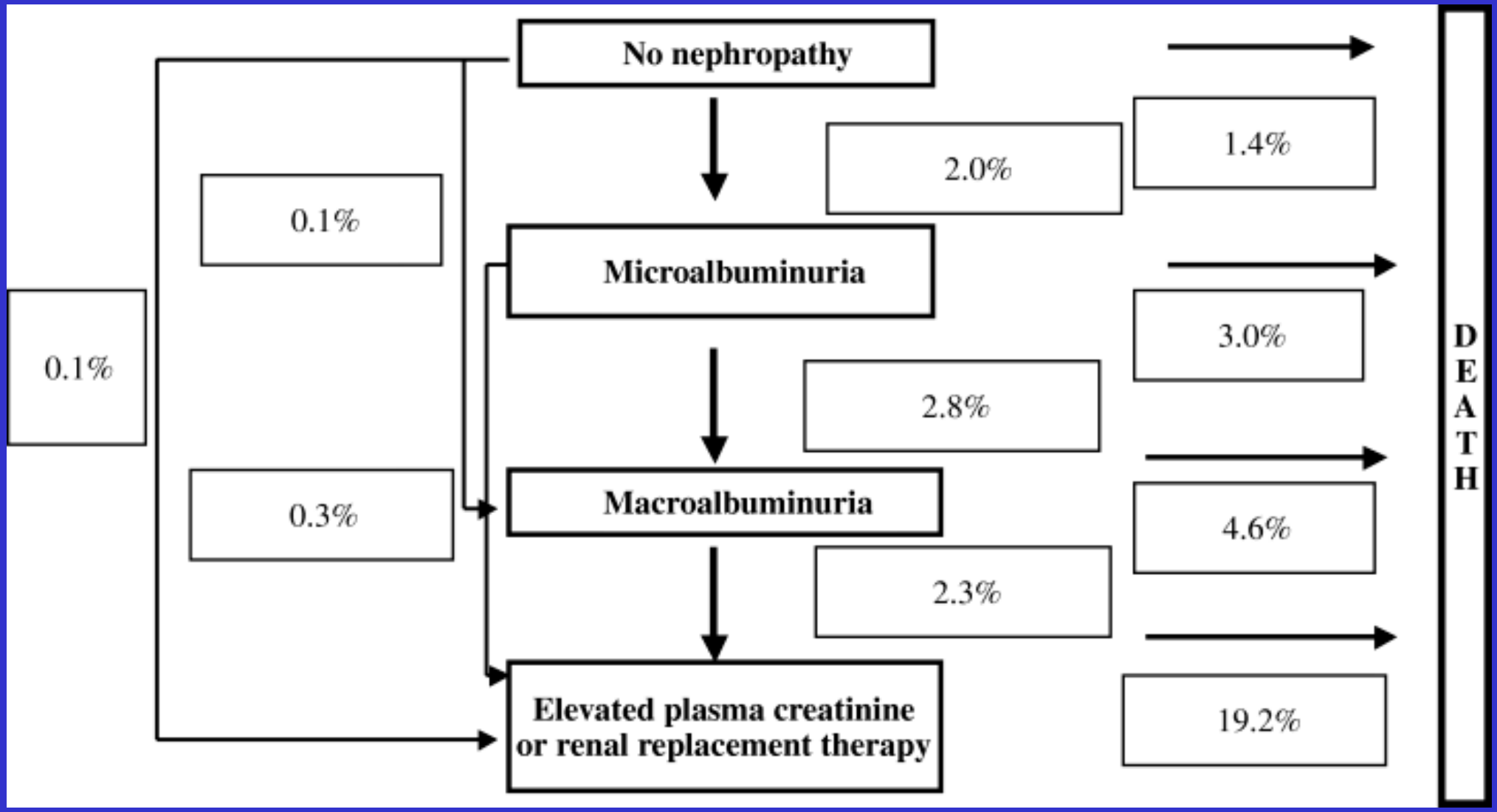
Progression of the Diabetic Nephropathy



GFR: measured by MDRD or 24h creat clearance

Strippoli et al. *J Nephrol* 2003;16:487–499

NATURAL HISTORY OF DIABETIC NEPHROPATHY IN TYPE 2 DIABETES



2 goals : Prevent 1) End-stage renal disease 2) Death (cardiovascular)

Adler et al (UKPDS Group). Kidney Int 2003, 63, 225-32.

JAMA | Original Investigation

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

JAMA. 2016;316(6):602-610.

Table 2. Clinical Manifestations of Kidney Disease Among US Adults With Diabetes, 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]		
Any diabetic kidney disease[c]					
1988-1994	640	42.5 (38.4-46.6)	28.4 (23.8-32.9)	1 [Reference]	.39
1999-2004	659	40.5 (37.5-43.6)	27.3 (23.1-31.4)	1.00 (0.90-1.11)	
2005-2008	573	39.3 (36.0-42.7)	27.1 (22.6-31.4)	0.99 (0.88-1.10)	
2009-2014	874	38.1 (35.3-41.0)	26.2 (22.6-29.9)	0.95 (0.86-1.06)	
Albuminuria (ACR ≥30 mg/g)					
1988-1994	534	35.2 (31.1-39.5)	20.8 (16.3-25.3)	1 [Reference]	<.001
1999-2004	531	32.1 (29.0-35.3)	18.9 (15.3-22.4)	0.93 (0.79-1.06)	
2005-2008	447	30.4 (27.6-33.4)	17.9 (14.0-21.9)	0.86 (0.75-1.01)	
2009-2014	645	27.1 (24.1-30.3)	15.9 (12.7-19.0)	0.76 (0.65-0.89)	
Macroalbuminuria (ACR ≥300 mg/g)					
1988-1994	155	7.9 (6.0-10.4)	5.6 (2.8-8.4)	1 [Reference]	.22
1999-2004	141	7.4 (5.9-9.2)	5.4 (3.1-7.7)	0.93 (0.65-1.31)	
2005-2008	111	6.9 (5.4-8.7)	4.9 (2.7-7.1)	0.86 (0.60-1.23)	
2009-2014	171	6.7 (5.6-8.2)	5.0 (3.3-6.6)	0.82 (0.59-1.14)	
Estimated GFR <60 mL/min/1.73 m^2					
1988-1994	214	13.1 (10.9-15.7)	9.2 (6.2-12.2)	1 [Reference]	<.001
1999-2004	273	16.0 (14.1-18.2)	11.6 (8.5-14.6)	1.33 (1.09-1.63)	
2005-2008	242	16.6 (14.2-19.4)	11.8 (8.4-15.1)	1.38 (1.09-1.75)	
2009-2014	450	20.1 (18.5-21.8)	14.1 (11.3-17.0)	1.61 (1.33-1.95)	

Empaglifozine et progression de la maladie rénale chez le Diabétique type 2 (juillet NEJM 2016)

Table 1. Characteristics of the Patients at Baseline, According to the Estimated Glomerular Filtration Rate (eGFR).*

Characteristic	Patients with eGFR of 59 ml per Minute per 1.73 m^2 or Less		Patients with eGFR of 60 ml per Minute per 1.73 m^2 or More	
	Placebo (N=607)	Empagliflozin (N=1212)	Placebo (N=1726)	Empagliflozin (N=3473)
Age — yr	67.1±8.2	67.1±7.6	61.9±8.6	61.7±8.5
Male sex — no. (%)	418 (68.9)	816 (67.3)	1262 (73.1)	2518 (72.5)
Body-mass index†	30.9±5.4	31.0±5.5	30.6±5.2	30.5±5.2
Glycated hemoglobin — %‡	8.03±0.85	8.07±0.86	8.10±0.84	8.07±0.84
Interval of >10 yr since diagnosis of type 2 diabetes — no. (%)	422 (69.5)	794 (65.5)	917 (53.1)	1876 (54.0)
Blood pressure — mm Hg				
Systolic	136.4±18.7	136.1±18.0	135.6±16.7	135.0±16.6
Diastolic	74.6±10.3	74.5±9.9	77.6±10.0	77.4±9.5
Estimated glomerular filtration rate — ml/min/1.73 m^2	48.6±7.8	48.4±8.2	82.7±16.6	83.1±17.1
Urinary albumin-to-creatinine ratio — no. (%)§				
<30	283 (46.6)	566 (46.7)	1099 (63.7)	2223 (64.0)
30 to 300	205 (33.8)	411 (33.9)	470 (27.2)	926 (26.7)
>300	115 (18.9)	223 (18.4)	145 (8.4)	286 (8.2)
Concomitant medication — no. (%)				
Angiotensin-converting–enzyme inhibitor or angiotensin-receptor blocker	502 (82.7)	1031 (85.1)	1366 (79.1)	2766 (79.6)
Beta-blocker	415 (68.4)	829 (68.4)	1083 (62.7)	2226 (64.1)
Diuretic	355 (58.5)	710 (58.6)	633 (36.7)	1336 (38.5)
Calcium-channel blocker	227 (37.4)	446 (36.8)	561 (32.5)	1082 (31.2)
Statin	461 (75.9)	966 (79.7)	1312 (76.0)	2663 (76.7)
Aspirin	495 (81.5)	981 (80.9)	1432 (83.0)	2894 (83.3)
Metformin	369 (60.8)	711 (58.7)	1365 (79.1)	2746 (79.1)
Sulfonylurea	234 (38.6)	480 (39.6)	758 (43.9)	1534 (44.2)
Insulin	357 (58.8)	699 (57.7)	778 (45.1)	1551 (44.7)

The Effects of Dipeptidyl Peptidase-4 Inhibition on Microvascular Diabetes Complications

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Table 1—Summary of the effects of DPP4-I on microvascular end points at the various sites of diabetes complications

	Experimental		Clinical	
Complication	Model	Effects	Drug and patients	End point
Nephropathy	STZ diabetic DPP-4–deficient (F344/DuCrlCrlj) rats (86)	↓ GFR	Sitagliptin in 36 T2D patients (96)	↓ hs-CRP, ICAM-1 ↓ Albuminuria
	Sitagliptin in Zucker diabetic rats (87)	↓ Glomerular, tubulointerstitial, and vascular lesions	Alogliptin vs. sitagliptin (crossover) in 12 T2D patients (97)	↓ Albuminuria
	Sitagliptin in Zucker diabetic fatty rats (88)	↓ Tubulointerstitial and glomerular lesions ↓ Apoptosis	Vildagliptin in 47 T2D patients (98)	↓ Albuminuria
	Sitagliptin in ischemia reperfusion injury in nicotinamide/STZ diabetic rats (89)	↑ GFR ↓ Oxidative stress ↓ Tissue damage	Linagliptin vs. placebo in 217 T2D patients with micro-/macroalbuminuria (pooled analysis) (99)	↓ Albuminuria
	Linagliptin + telmisartan in STZ eNOS$^{-/-}$ mice (90)	↓ Albuminuria ↓ Glomerulosclerosis	Saxagliptin vs. placebo in >16,000 T2D patients (23)	↓ Microalbuminuria
	Linagliptin in STZ diabetic rats (91)	↓ AGE and RAGE ↓ Oxidative stress ↓ Albuminuria ↓ Glomerulosclerosis		
	Vildagliptin in STZ diabetic rats (92)	↑ GFR ↓ Albuminuria ↓ Glomerulosclerosis ↓ Interstitial fibrosis		
	Vildagliptin in Zucker diabetic fatty rats (93)	↓ Glomerulosclerosis ↑ Arteriolar function ↓ Oxidative stress		