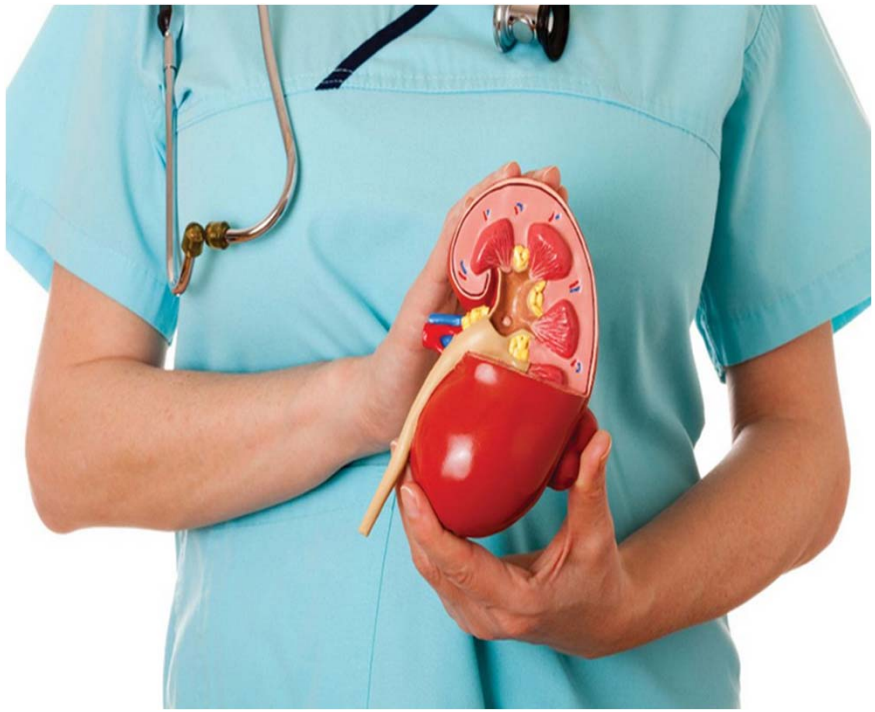
Endocrinology perspective of Diabetic nephropathy



Dr. KYAR NYO SOE MTINT

Consultant Physician

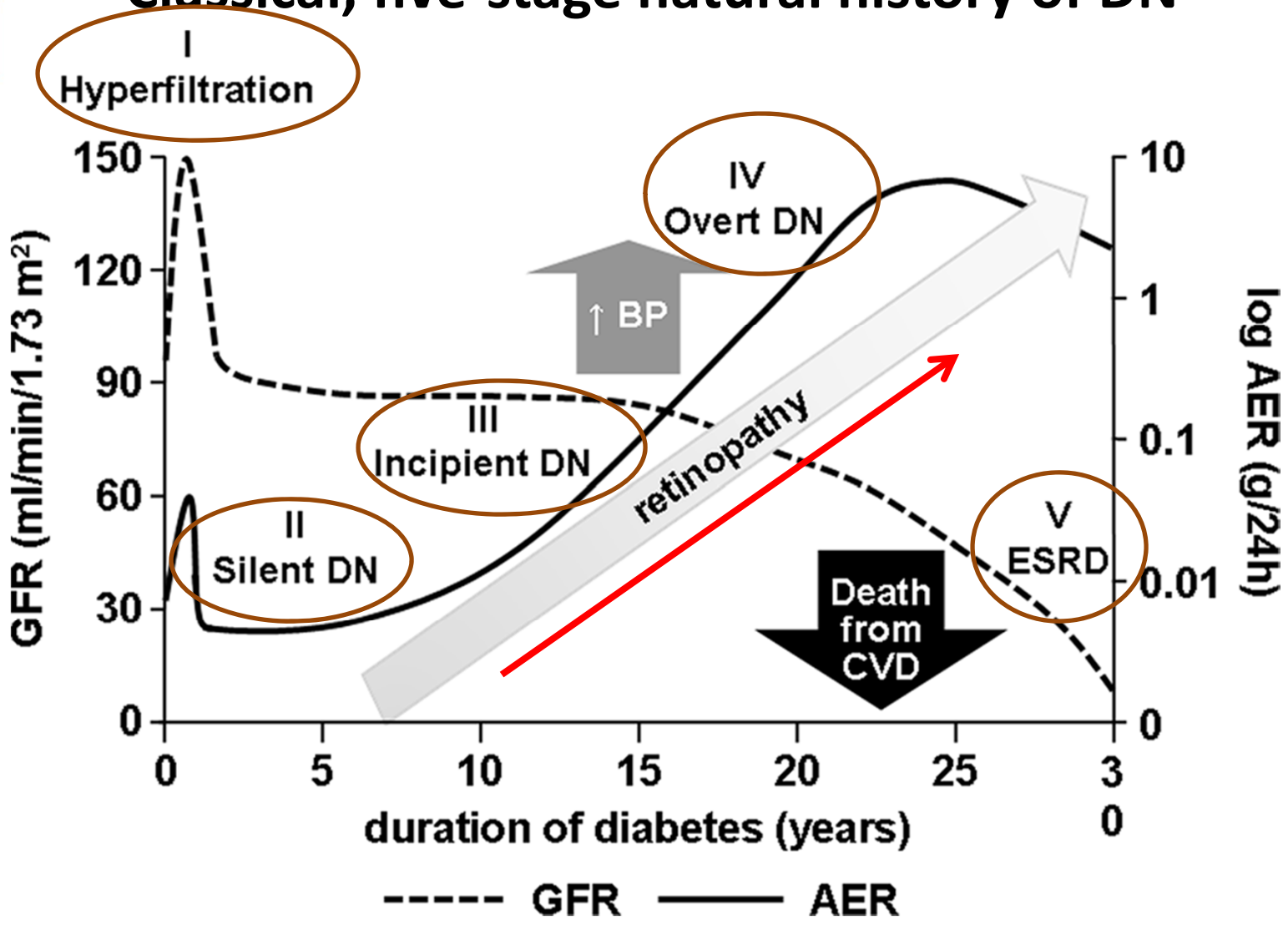
Department od Diabetes and Endocrinology, NOGH

21-1-2018

Outlines

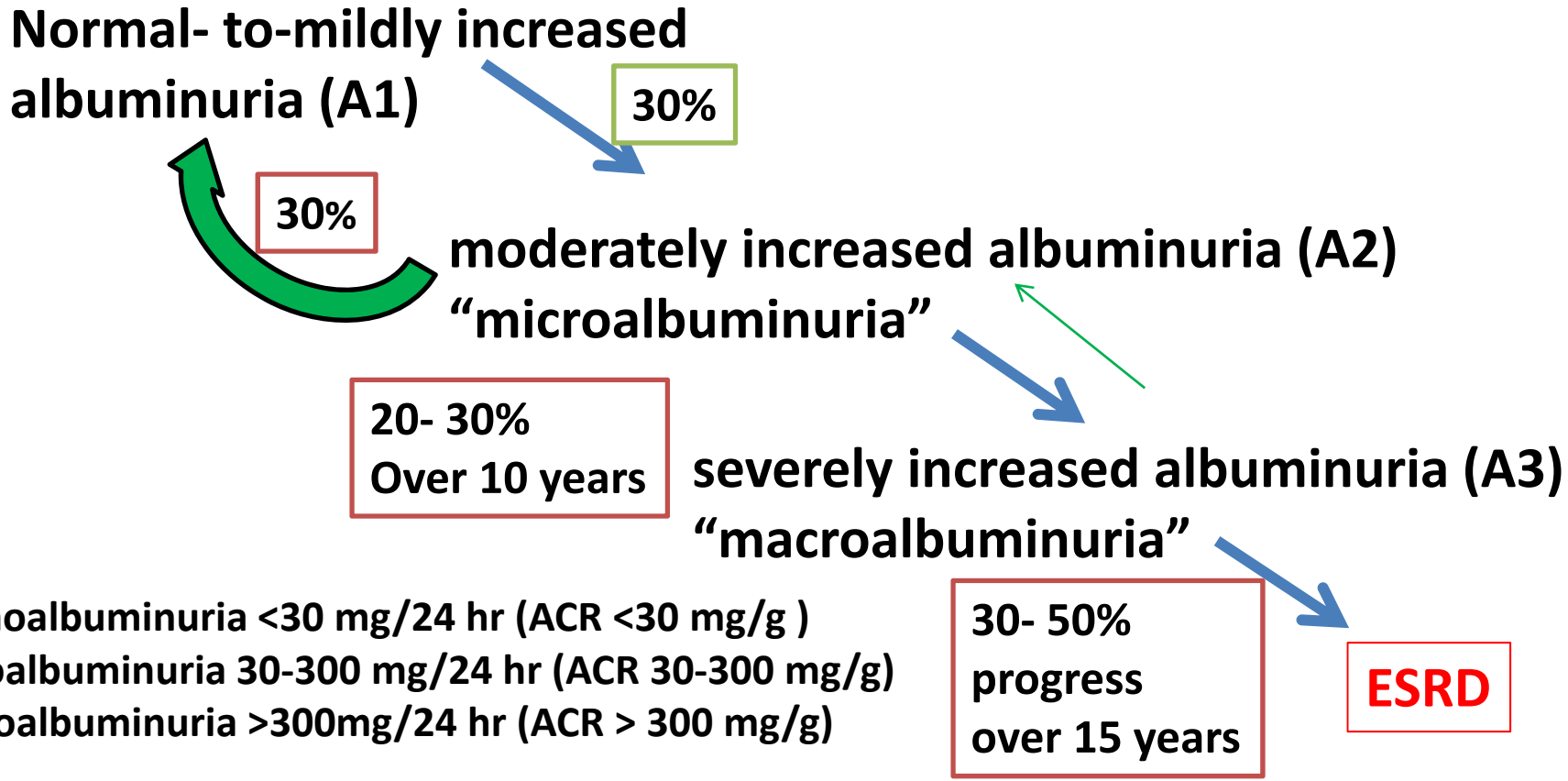
1. Current landscape and natural history of diabetic nephropathy
2. Importance of multifactorial management including BP management and brief overview of pathophysiology of diabetic nephropathy
3. Highlight on therapies
4. Emerging data for SGLT 2 inhibitors and GLP1 receptor agonist as novel Reno protective agents.

Classical, five-stage natural history of DN



Mogensen CE (1999), Giuseppe Pugliese, 2014,Acta Diabetol (2014) 51:905–915

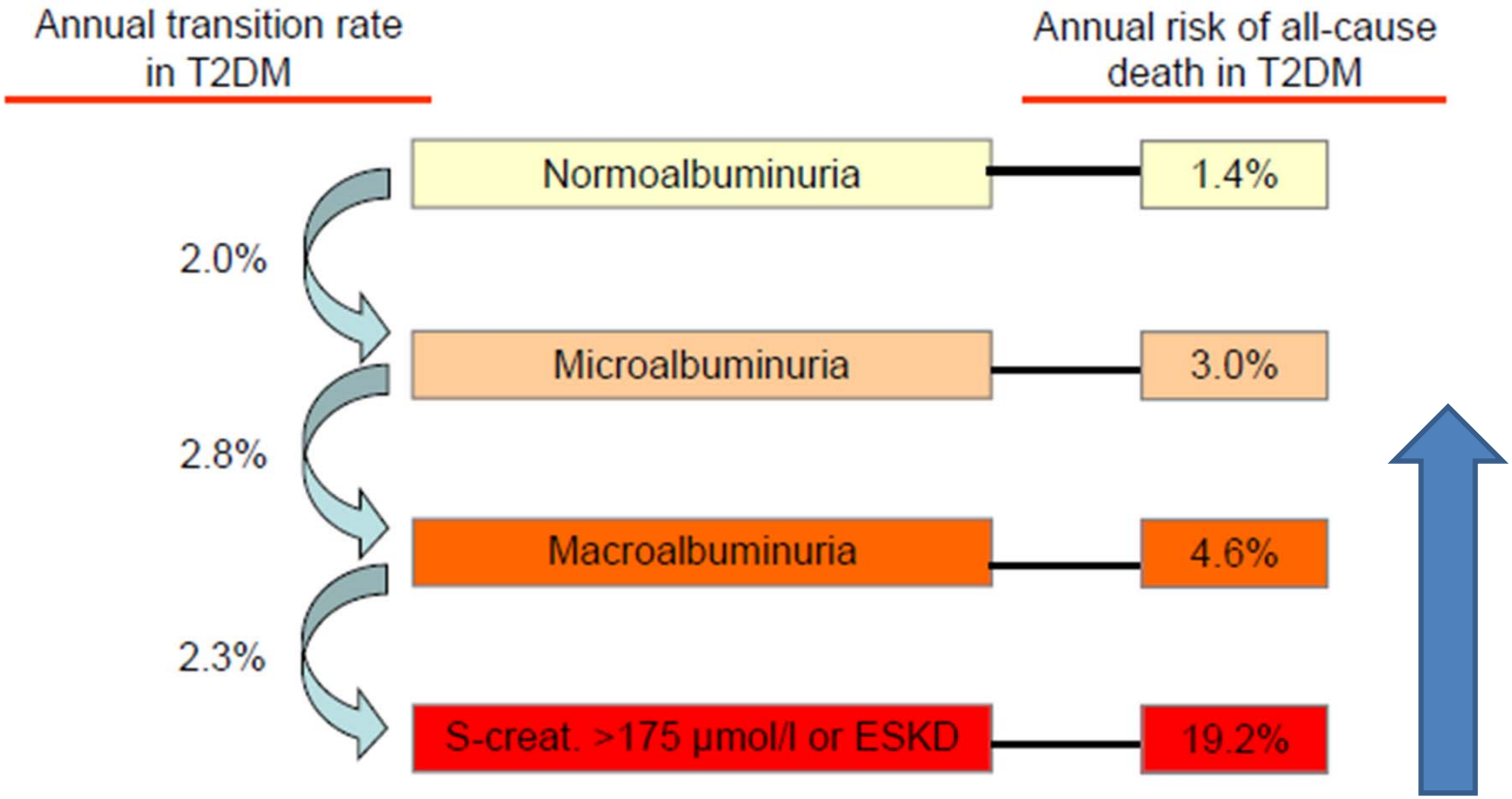
Developing Diabetic nephropathy



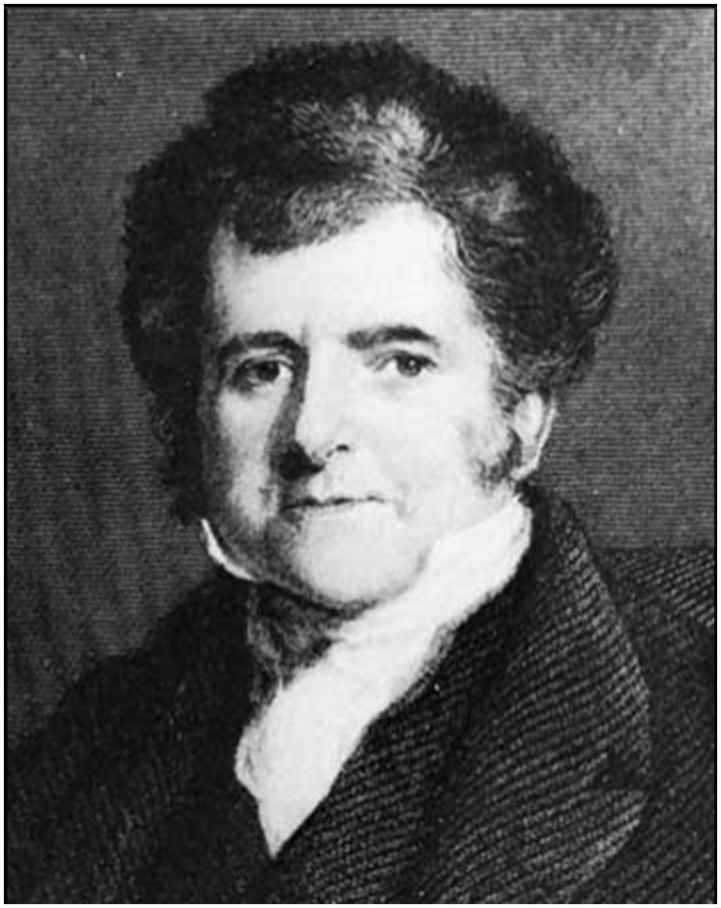
Normoalbuminuria <30 mg/24 hr (ACR <30 mg/g)
Microalbuminuria 30-300 mg/24 hr (ACR 30-300 mg/g)
Macroalbuminuria >300mg/24 hr (ACR > 300 mg/g)

Diabetic nephropathy in Oxford Texbook of Endocrinology 2011

Stages of nephropathy in Diabetes



Adapted from: UKPDS 64. Kidney Int 2003; 63: 225-32



Richard Bright

(1836)

British physician, (1789-1858)

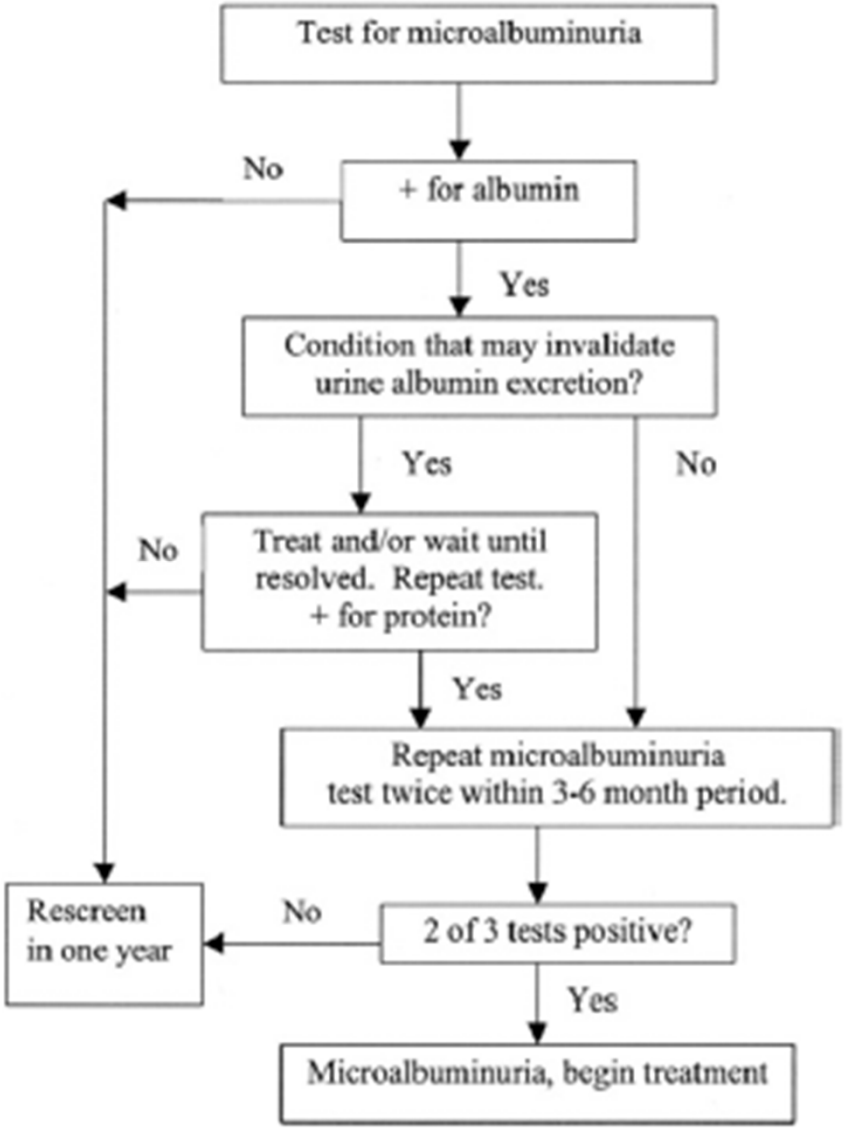
established edema (swelling) and proteinuria (the presence of albumin in the urine) as the primary clinical symptoms of the serious kidney disorder

- Easily preformed - urinary albumin–to– creatinine ratio (UACR) random spot urine collection
- two of three specimens of UACR collected within a 3- to 6-month period should be abnormal before considering a patient to have albuminuria.
- Measurement of serum creatinine and estimation of GFR

www.kidney.org/GFR

Diabetes Care Volume 41, Supplement 1, January 2018. KDOQI 2007

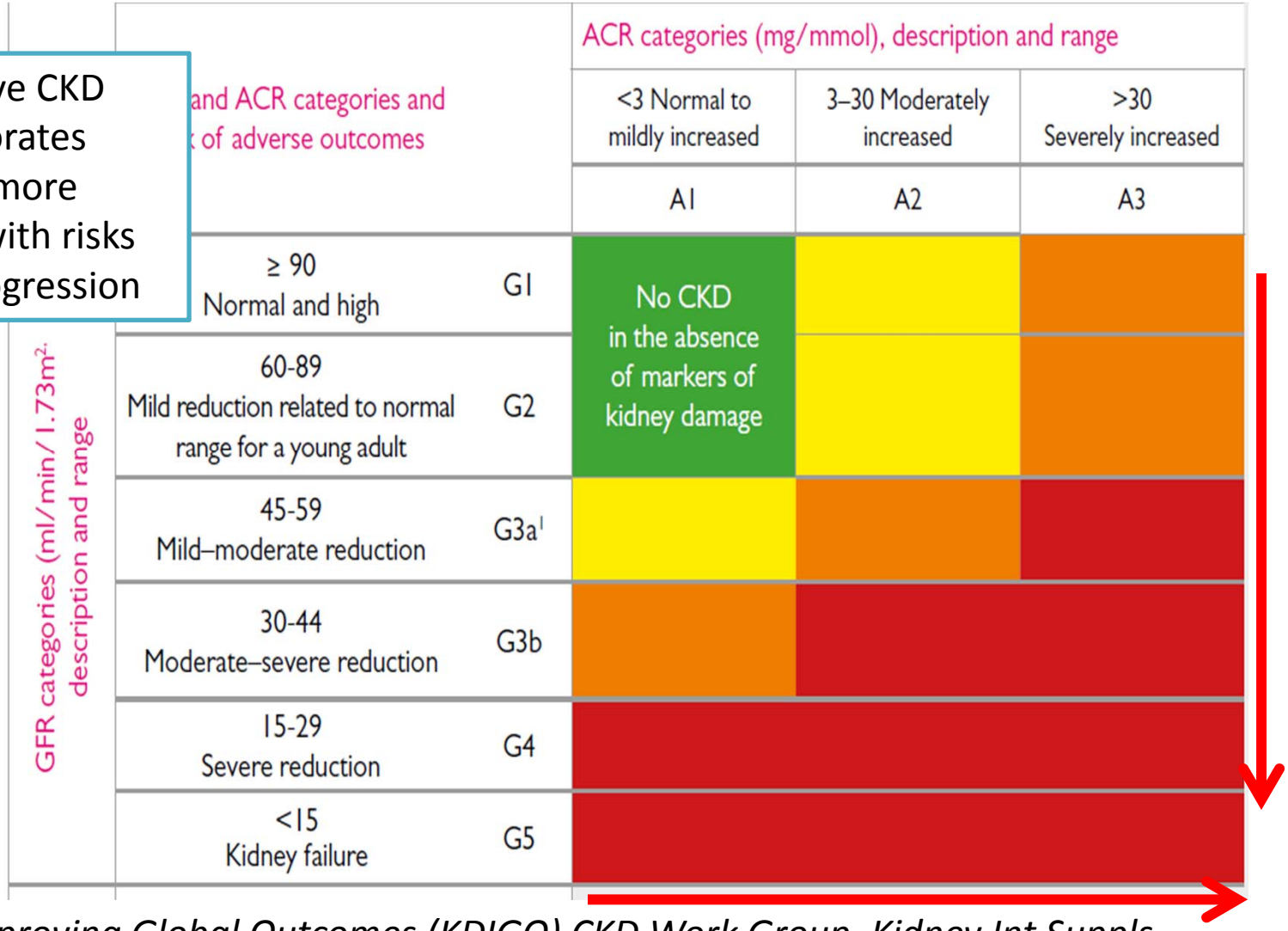
Screening for microalbuminuria



KDOQI 2007

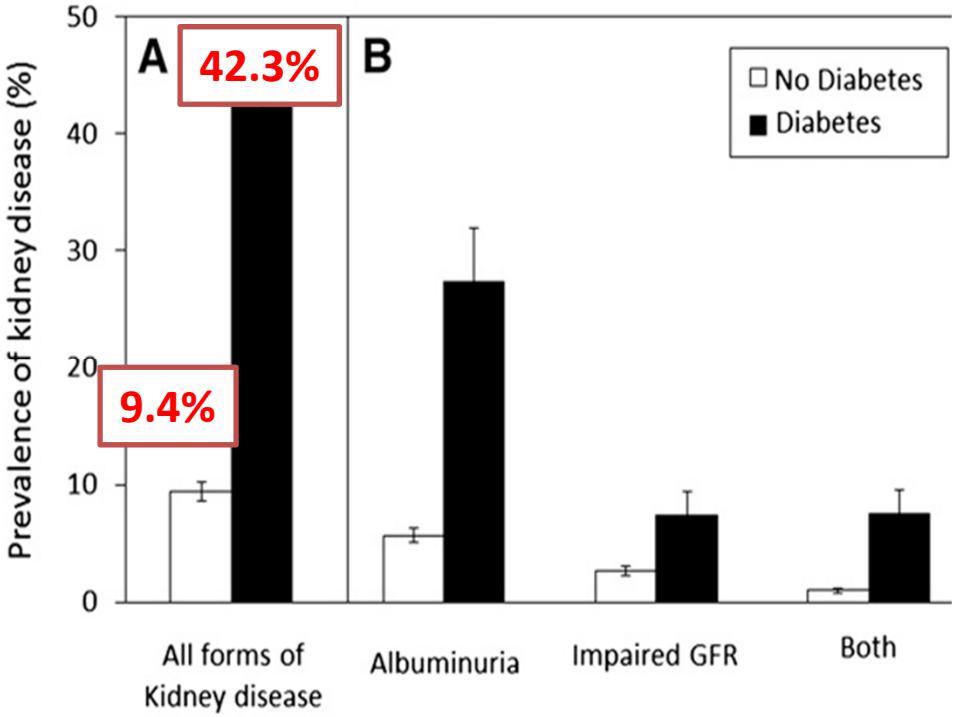
Prognosis of CKD by GFR and albuminuria category

More comprehensive CKD staging that incorporates albuminuria and is more closely associated with risks of CVD and CKD progression

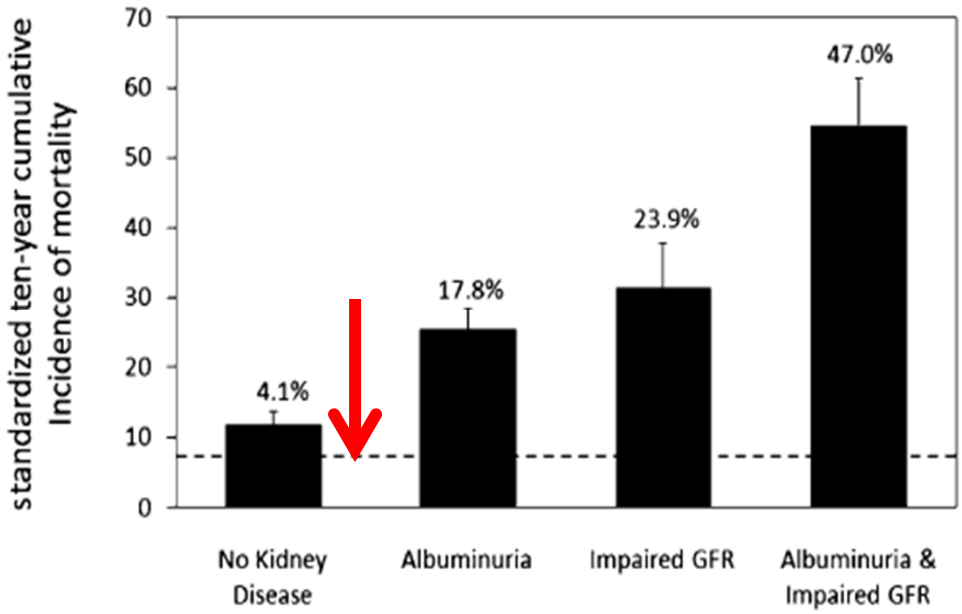


Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. Kidney Int Suppls. 2013;3:1-150.

Kidney Disease and Increased Mortality Risk in Type 2 Diabetes



Prevalence (A) and manifestations (B) of kidney disease in diabetic and nondiabetic subpopulations

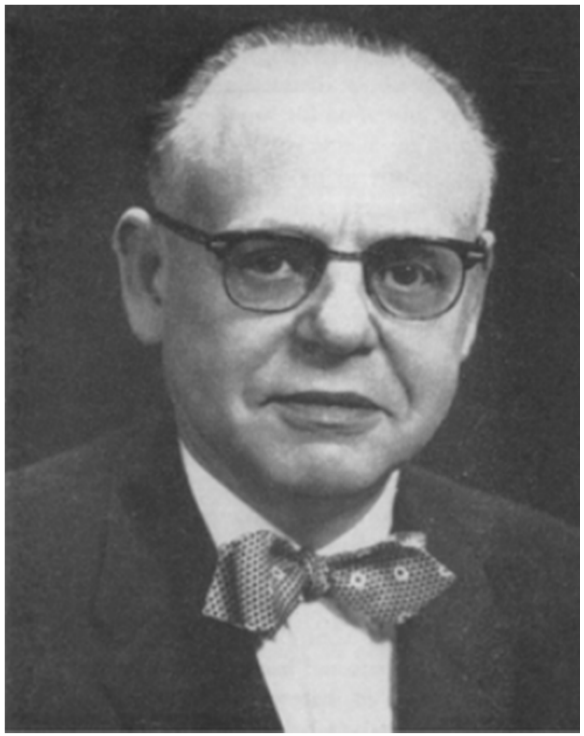


Ten-year mortality in type 2 diabetes by kidney disease manifestation

Maryam Afkarian et al, J Am Soc Nephrol 24: 302–308, 2013.

Kimmelstiel and Wilson (1936)

Paul Kimmelstein (1900-70)

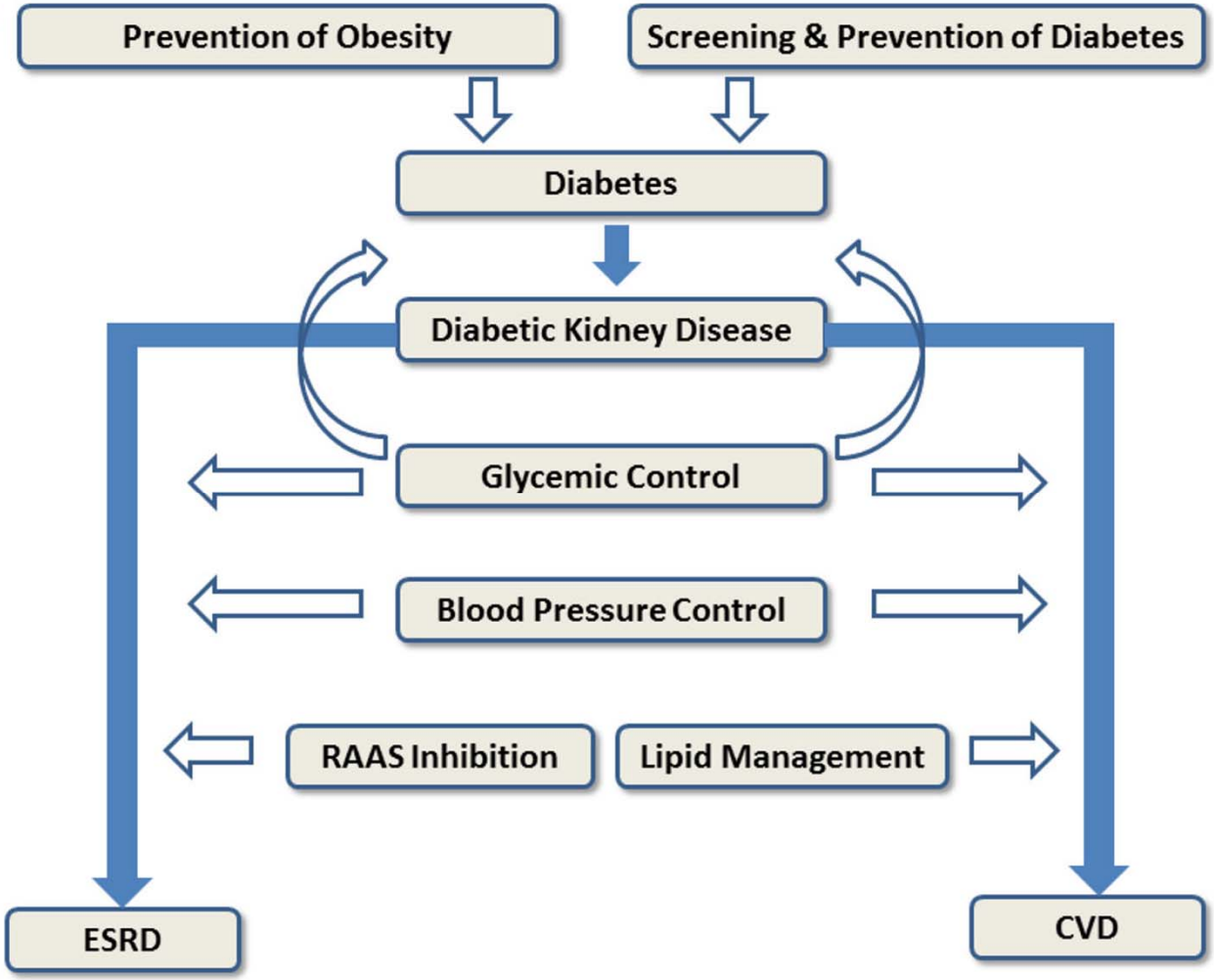


German-born pathologist in the U.S

Clifford Wilson (1906-1997)

English physician

Approaches to improving outcomes related to diabetic kidney disease.

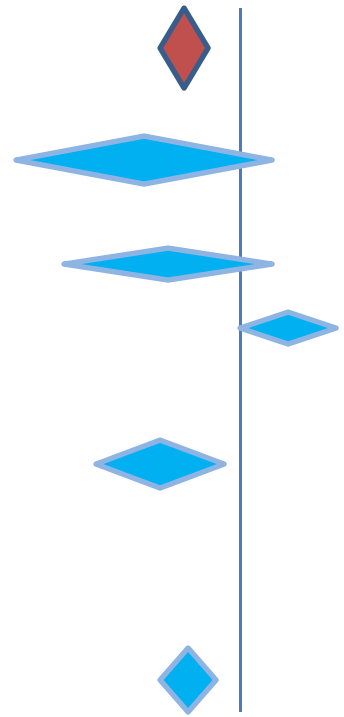


Mark E. Molitch et al, Kidney Int. 2015 January ; 87(1): 20–30

Effects of intensive glucose control on renal outcomes in patients with type 2 diabetes

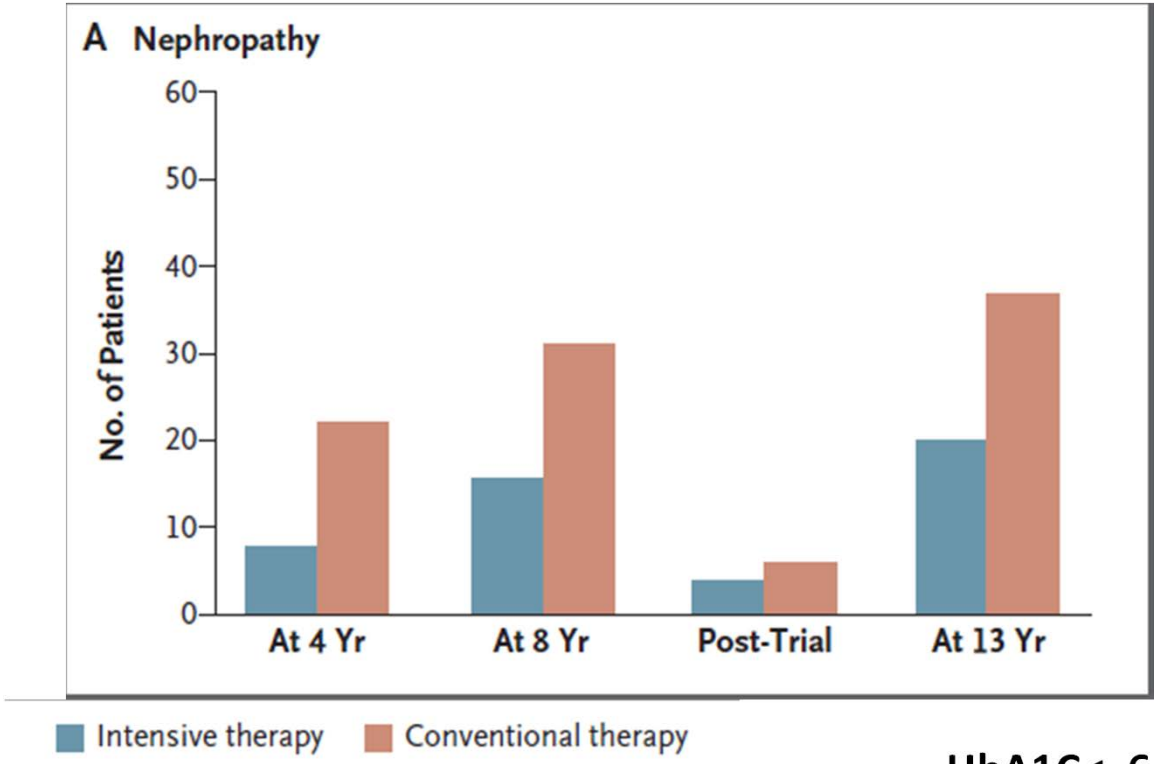
(ACCORD, ADVANCE, UKPDS, and VADT) 27 049 participants. 1626 kidney events

	Events per year , n (%)		
	Intense control	Less intense control	HR (95% CI)
Primary renal outcome	**761 (1.2)**	**865 (1.6)**	**0.8 (0.7,0.88)**
ESRD	**113 (0.2)**	**143 (0.2**	**0.61 (0.26,1.44)**
Renal death	**18 (0**	**22 (0.1)**	**0.77 (0.41 1.46)**
GFR <30 ml/min/1.73m²	**175 (0.3)**	**149 (0.3)**	**1.16 (0.93, 1.44)**
macroablunimuria	**509 (0.9)**	**603 (1.2)**	**0.74 (0.61, 0.90)**
Secondary outcome			
microalbuminuria	**2121 (5.2)**	**2210 (6.3)**	**0.90 (0.84, 0.95)**



Zoungas et al, Lancet Diabetes Endocrinol. 2017 Jun;5(6):431-437

STENO 2 Study: Intensive Multifactorial Care Reduce the relative risk of microvascular Disease and CVD mortality in patients with T2DM and Microalbuminuria



Diabetic nephropathy developed in20 patients in the intensive- therapy group, as compared with 37 patients in the conventional-therapy group (relative risk, 0.44; 95% CI, 0.25 to 0.77; **P = 0.004**)

HbA1C< 6.5%,
fasting serum TC < 175 mg /dl (4.5 mmol/ L),
fasting serum TG <150 mg /dl (1.7 mmol/ L),
SBP < 130 mm Hg, DBP < 80 mm Hg
Asprin

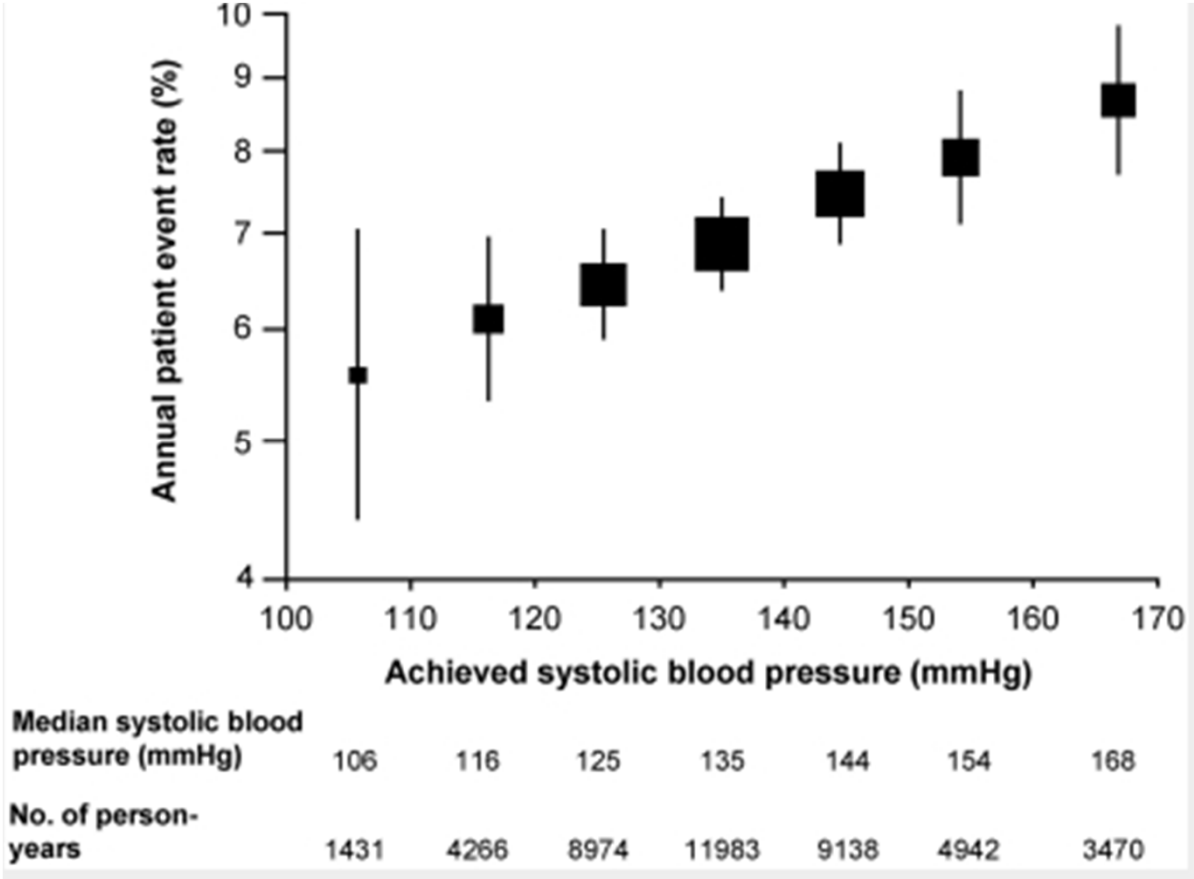
Gaede P et al, N E J Med, 2003; 348, 383-393

Multifactorial interventions strategy is recommended for patients with T2DM and Nephropathy

GLYCEMIA	**SMOKING CESSATION**
individualized, **A1C** mostly **~7%**	†cessation
BP LOWERING	**NUTRITION**
Generally **< 140/90** mmHg Individual risk benefit **< 130/80**	dietary protein intake ~ **0.8 g**/kg /day (non HD)
LIPID †	**WEIGHT CONTROL**
reduces risk of major atherosclerotic events not initiating statin therapy in patients with diabetes who are treated by dialysis	BMI (18.5 to 24.9 kg/m2) Diet, physical activity, achieved weight loss

BP lowering is associated with reduction of all renal events in T2DM

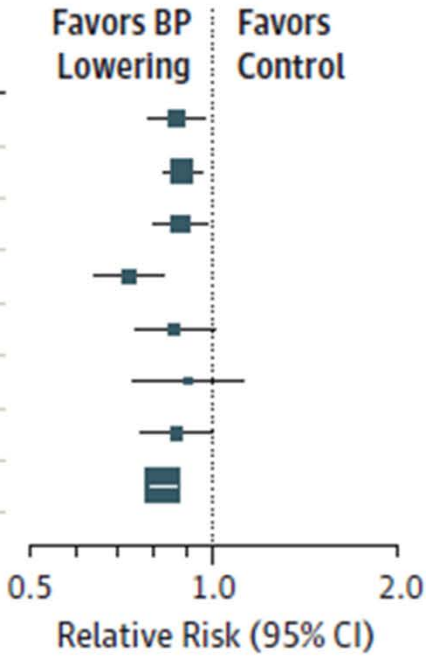
In ADVANCED BP study, rate of all renal events significantly associated with SBP level



Bastiaan E. de Galan et al, J Am Soc Nephrol. 2009 Apr; 20(4): 883–892.

Standardized Associations Between 10–mm Hg Lower Systolic BP and All-Cause Mortality, Macrovascular Outcomes, and Microvascular Outcomes in Diabetic Patients

Outcome	No. of Studies	BP Lowering		Control		Relative Risk (95% CI)
		Events	Participants	Events	Participants	
Mortality	20	2334	27693	2319	25864	0.87 (0.78-0.96)
Cardiovascular disease	17	3230	25756	3280	24862	0.89 (0.83-0.95)
Coronary heart disease	17	1390	26150	1449	24761	0.88 (0.80-0.98)
Stroke	19	1350	27614	1475	26447	0.73 (0.64-0.83)
Heart failure	13	1235	21684	1348	20791	0.86 (0.74-1.00)
Renal failure	9	596	19835	560	18912	0.91 (0.74-1.12)
Retinopathy	7	844	9781	905	9566	0.87 (0.76-0.99)
Albuminuria	7	2799	13804	3163	12821	0.83 (0.79-0.87)



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

Connor A et al, JAMA. 2015;313(6):603-615. doi:10.1001/jama.2014.18574

Harry Goldblatt (1891-1977)

Pathologist

Renin and hypertension 1934

Eduardo Braun-Menéndez (1903 –1959)

Argentine physiologist

Angiotensin 1939

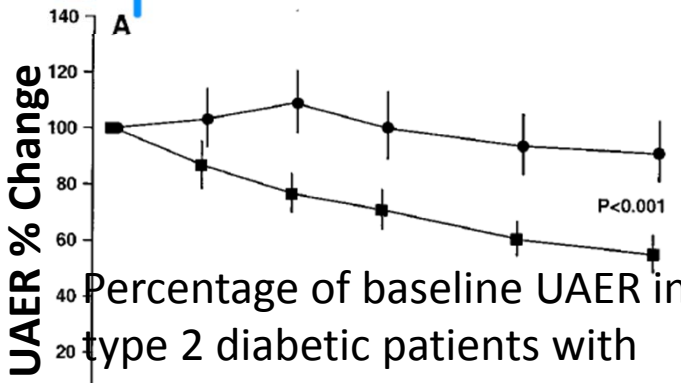
Choice of antihypertensive drugs

- ACE inhibitors or ARBs are the preferred *first-line agent* for blood pressure treatment among patients with diabetes, hypertension, eGFR< 60mL/min/1.73m², and UACR≥ 300mg/g Cr
- their proven benefits for prevention of CKD progression

- recommend not using an (ACE-I) or an(ARB) for the primary prevention of DKD in *normotensive normo-albuminuric* patients with diabetes

KDOQI Diabetes Guideline: 2012 Update, ADA 2018

Reno protective benefits beyond simply regulation of blood pressure

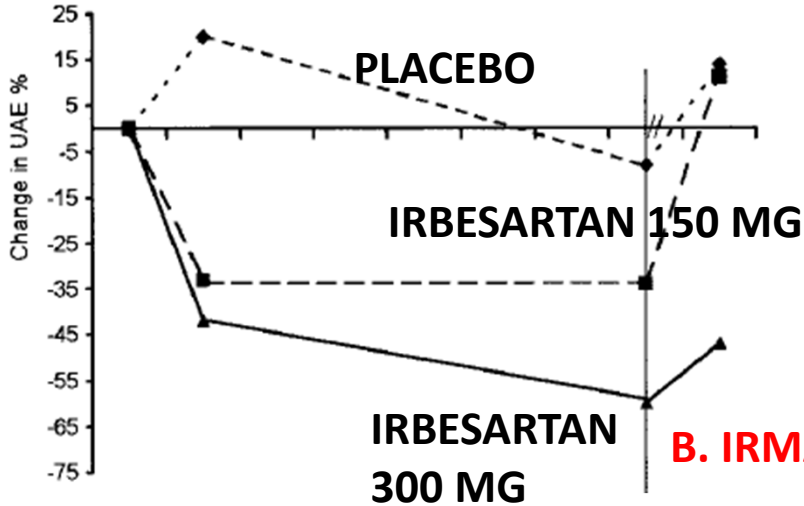


AMLODIPINE

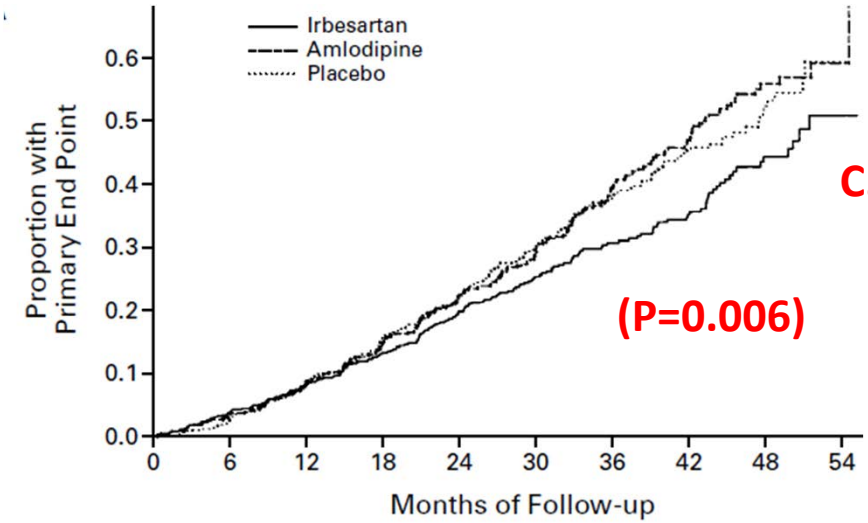
VALSARTAN

Percentage of baseline UAER in type 2 diabetic patients with microalbuminuria

A. MARVAL



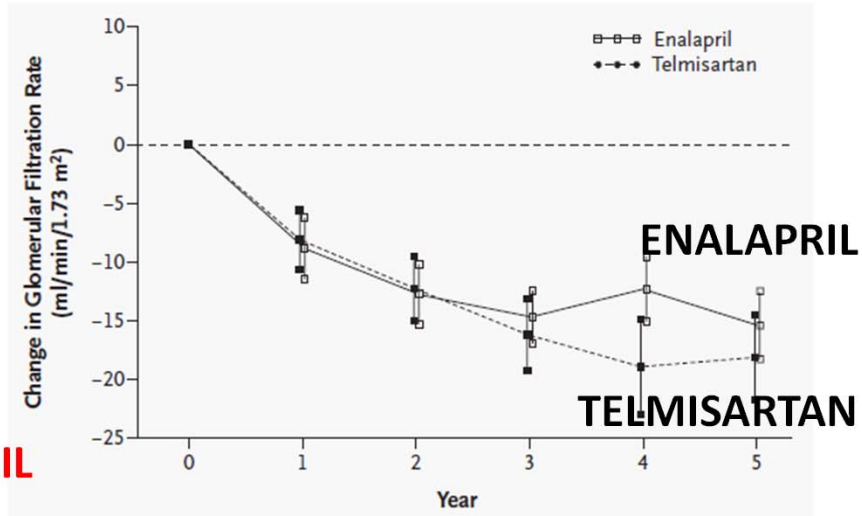
B. IRMA-2



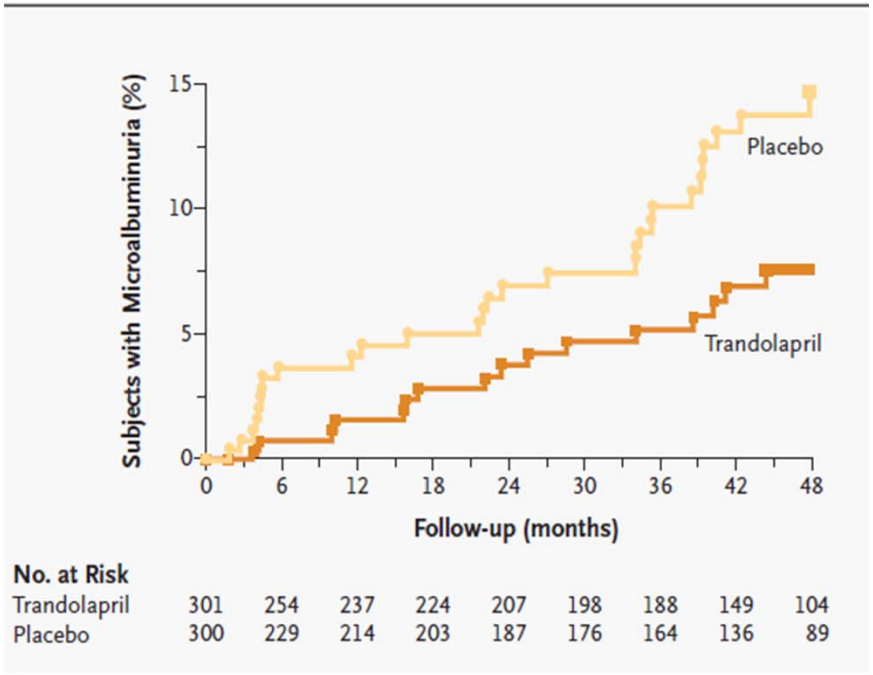
C. IDNT

(P=0.006)

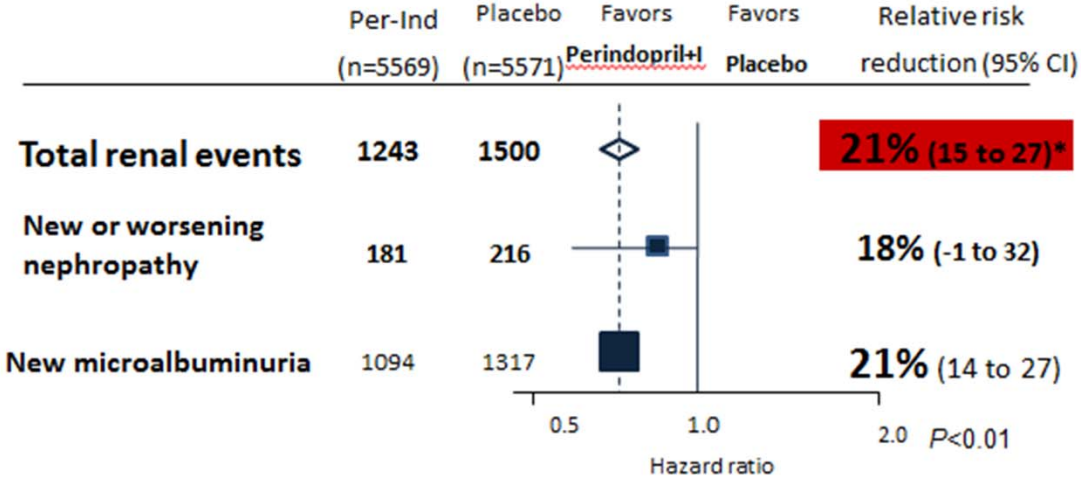
A. *Viberti G, Circulation, 2002; 106(6): 672–8*
B. *Steen Andersen et al, Diabetes Care 26:3296–3302, 2003*
C. *Lewis EJ, et al, N Engl J Med. 2001; 345(12): 851–60*



A. DETAIL



C. BENEDICT



B. ADVANCE

A. Barnett, A. et al. N Engl J Med 2004;351:1952-1961
B. ADVANCE Collaborative Group. N Engl J Med 2008;358:24.
3. BENEDICT. N Engl J Med 2004;351:1941-51.

What is the BP treatment target?

ADA 2018

- BP <140/90 mmHg are generally recommended
- < 130/80mmHg may be considered for patients based on individual anticipated benefits and risks

JNC 8 <140/90 mmHg

KDIGO Clinical Practice

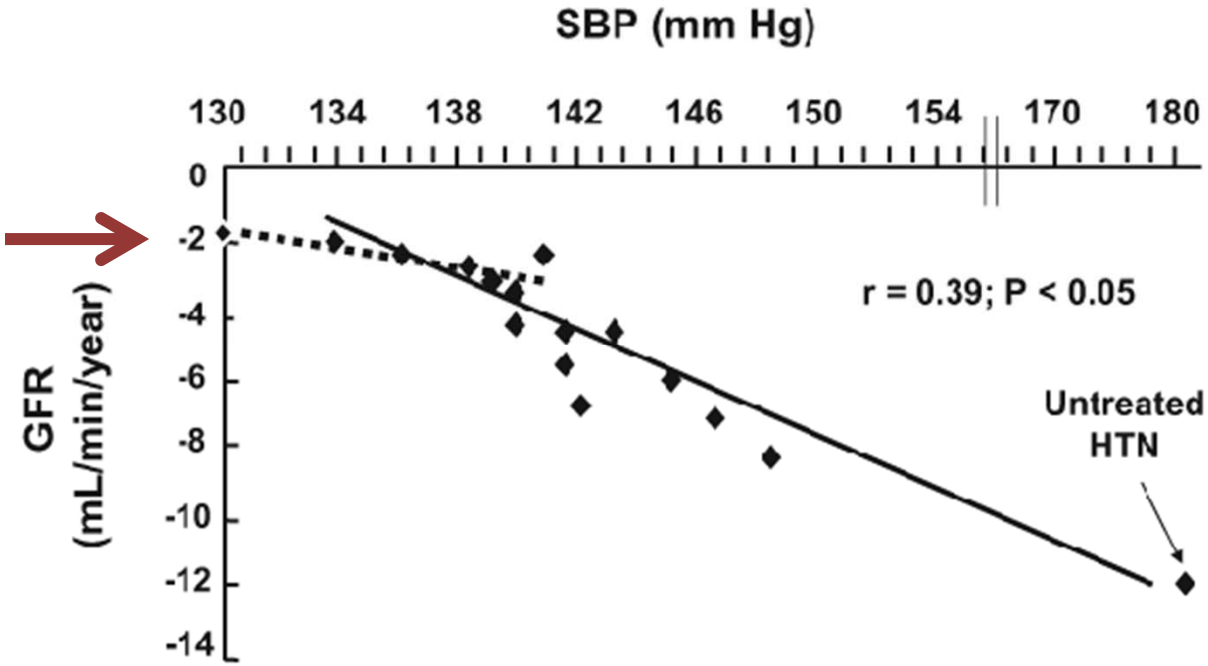
- urine albumin excretion < 30 mg /24 hr (SBP < 140mmHg DBP< 90mmHg) (1B)
- urine albumin excretion > 30 mg per 24 hour SBP < 130mmHg and DBP < 80mmHg (2D)

KDOQI 2007, AHA 2017

- CKD stage 1-4< 130/80 mmHg (B)

Kidney International Supplements (2012) 2, 343–346

Blood Pressure Level and Rate of GFR Decline in Controlled Trials of DKD



Diamonds represent the mean achieved systolic blood pressure (SBP) and mean rate of calculated or directly measured GFR decline in the studies of DKD. The dotted line represents a flattening of possible benefit of blood pressure lowering at blood pressure levels less than 140 mmHg.

Hart PD, Bakris GL,. Philadelphia, PA, Hanley & Belfus, 2004, pp 249-252

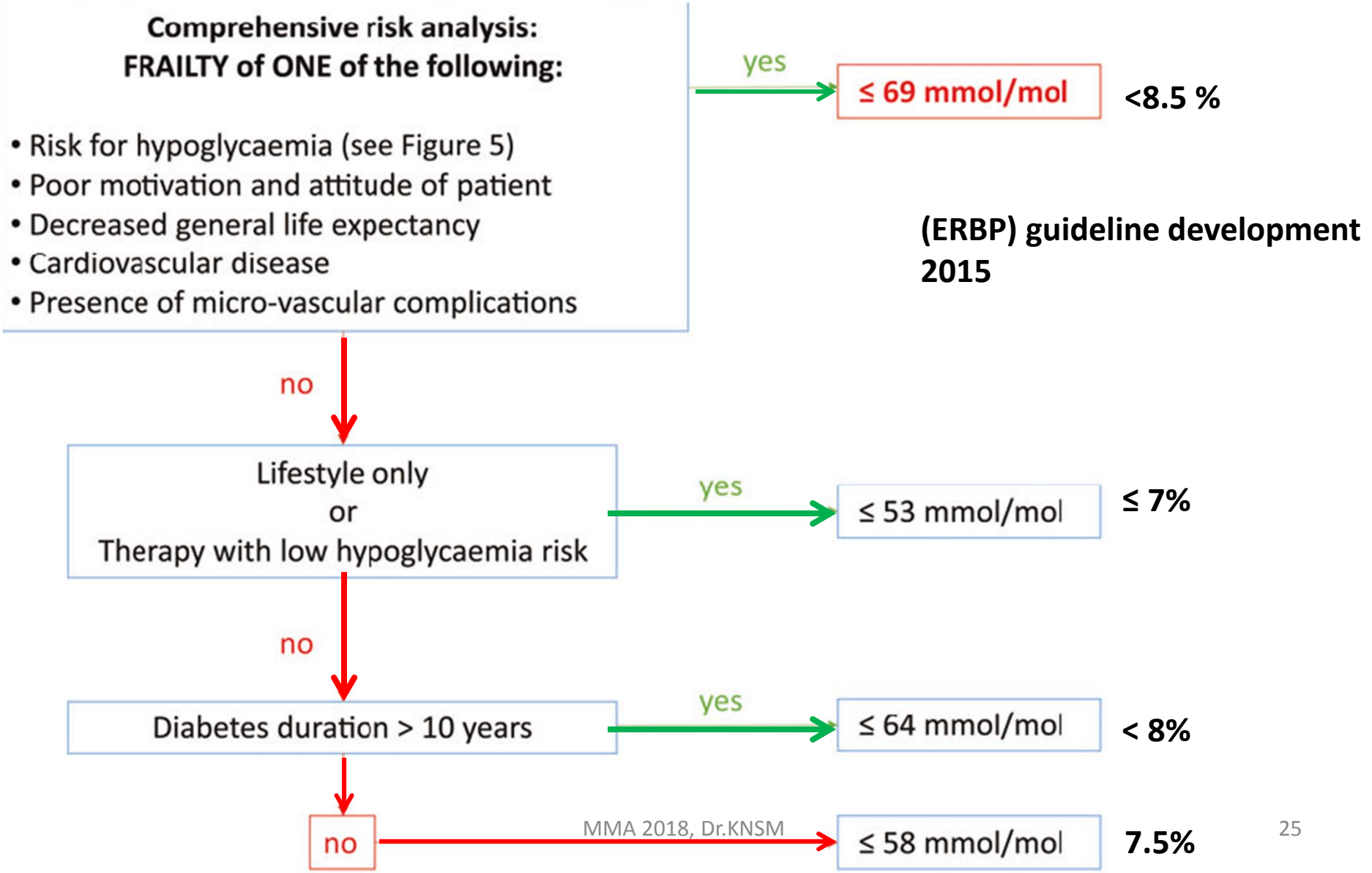
A1C targets

GUIDELINE	TARGET
ADA 2018	A1C of < 7% Goals should be individualized (duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations)
KDOQI Diabetes Guideline: 2012	(HbA1c) of ~7.0% to prevent or delay progression of the microvascular complications HbA1c be extended above 7.0% in individuals with co-morbidities
European-renal-best-practice (ERBP) 2015	Stage 3 b >7% and < 8.5%

ESRD patients with diabetes benefit from maintaining their A1c between 7–8 %, as A1c levels above 8 % or below 7 % carry increased risks of all-cause and cardiovascular death

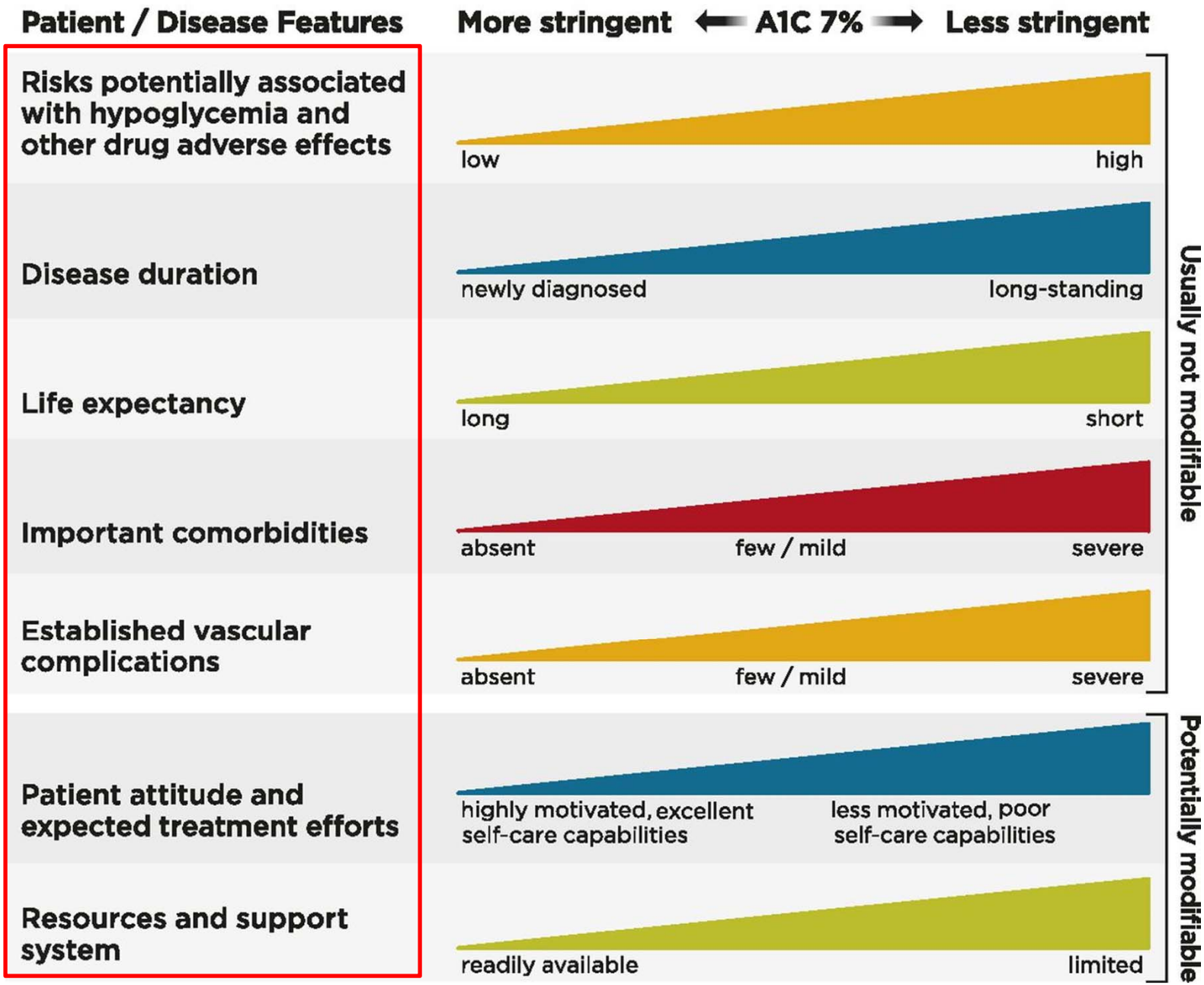
Ricks J, et al, Glycemic control and cardiovascular mortality in hemodialysis patients with diabetes: a 6-year cohort study. Diabetes. 2012;61:708–15.

Flowchart of management targets for HbA1C in patients with diabetes and CKD stage 3b or higher (eGFR <30 mL/min)



(ERBP) guideline development 2015

Approach to the Management of Hyperglycemia

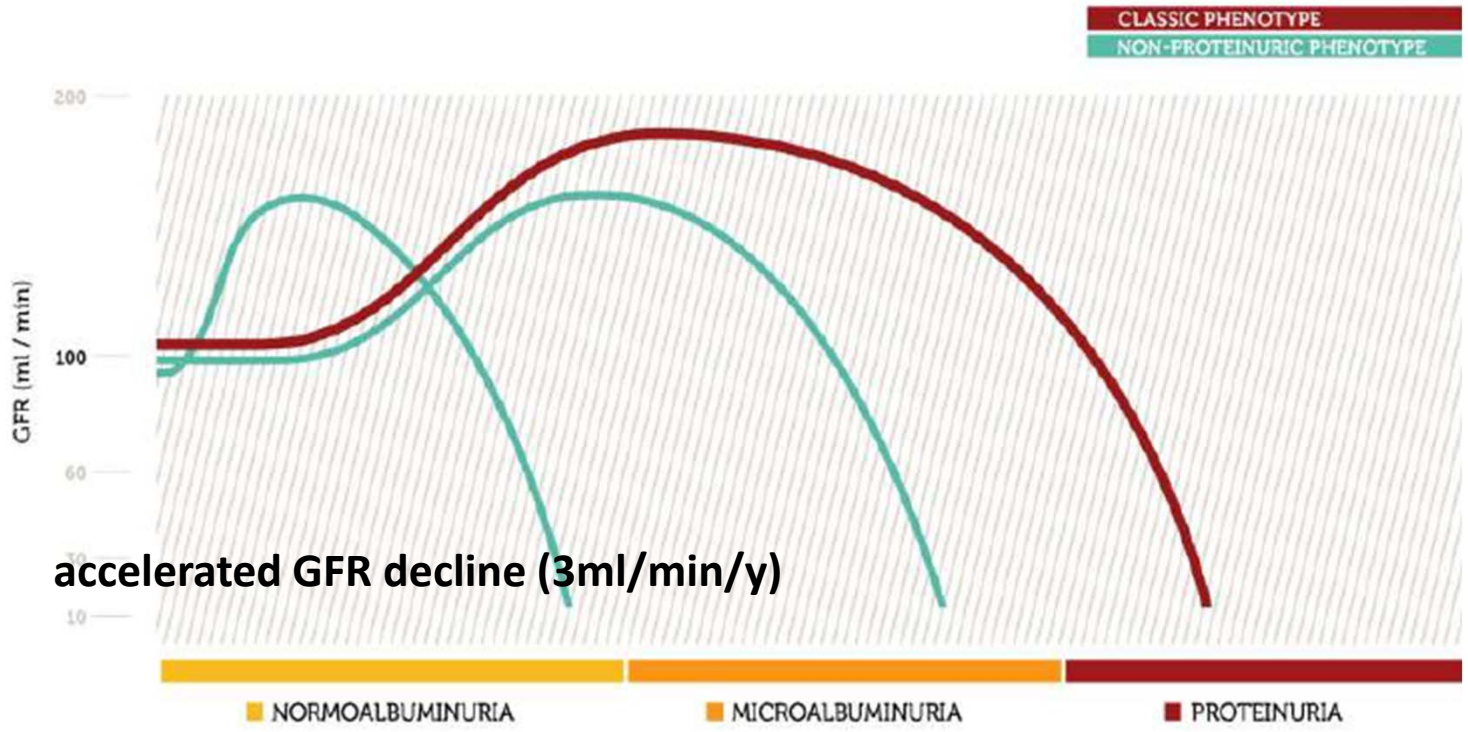


Harry Keen (1925-2013)

the measurement of small quantities of albumin in the urine in 1963, it was predictive of diabetic nephropathy and its consequences.

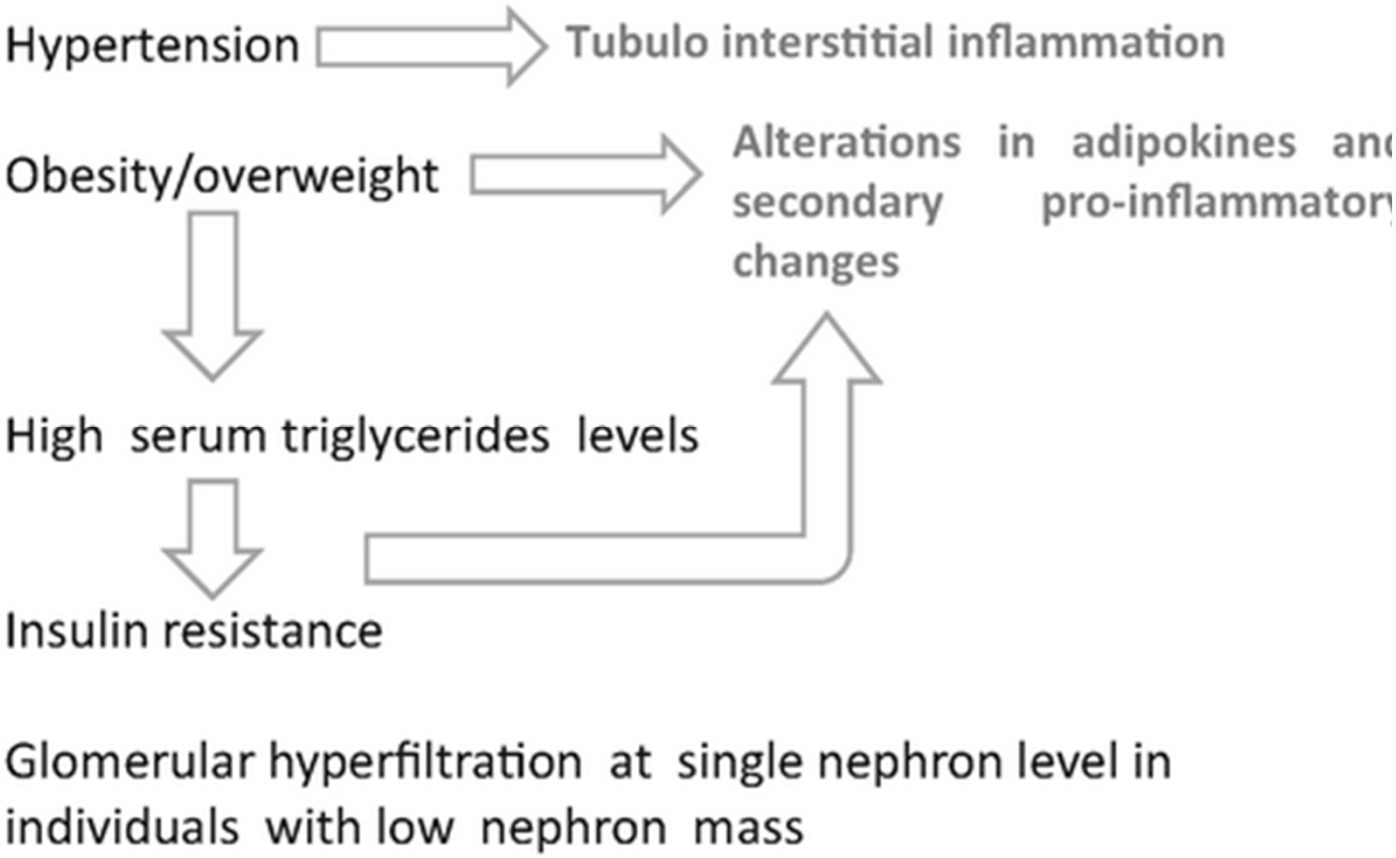
Progression of kidney dysfunction may be independent of proteinuria

Renal dysfunction may evolve through a classic or non-proteinuric phenotype



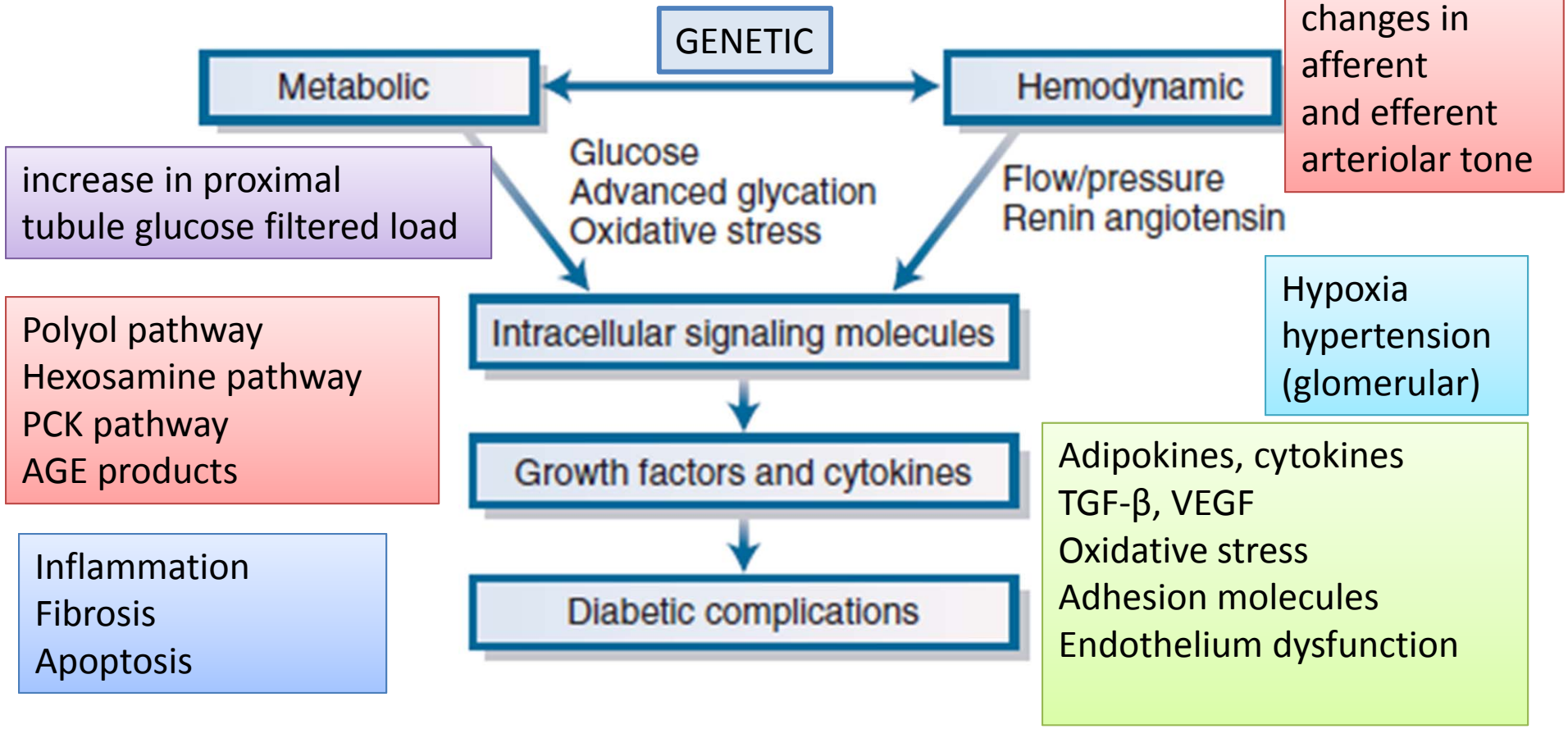
E s t e b a n po r r i n i, Volume 3, No. 5, p382–391, May 2015

Risk factors and mechanisms in non-proteinuric renal disease



Davide Bolignano Carmine Zoccali, Nephrology Dialysis Transplantation, Volume 32, Issue suppl_2, 1 April 2017, Pages ii194–ii199,

Interactions between metabolic and hemodynamic factors in promoting diabetic complications including nephropathy



Williams Text Book Of Endcrinology 13th Edition ,Nature (2001) ;414:813-820

Focusing renal and CVD outcomes in choosing medications ADA 2018

activates adenosine monophosphate kinase (AMPK) Inhibits hyperglycemia-induced podocyte apoptosis

	on of CKD	Dose consideration
METFO		CI eGFR < 30
SGLT2	Benefit- Canagliflozin, Empagliflozin	Cana eGFR < 45 Empa eGFR < 30
GLP1 AGONIST	Benefit - Liraglutide	Liraglutide eGFR< 30
DPP4 INHIBITORS	Neutral	Dose adjustment
TZD	al	No dose adjustment
SU	al	Glyburide - avoid
INSULIN	Neutral	Lower dose

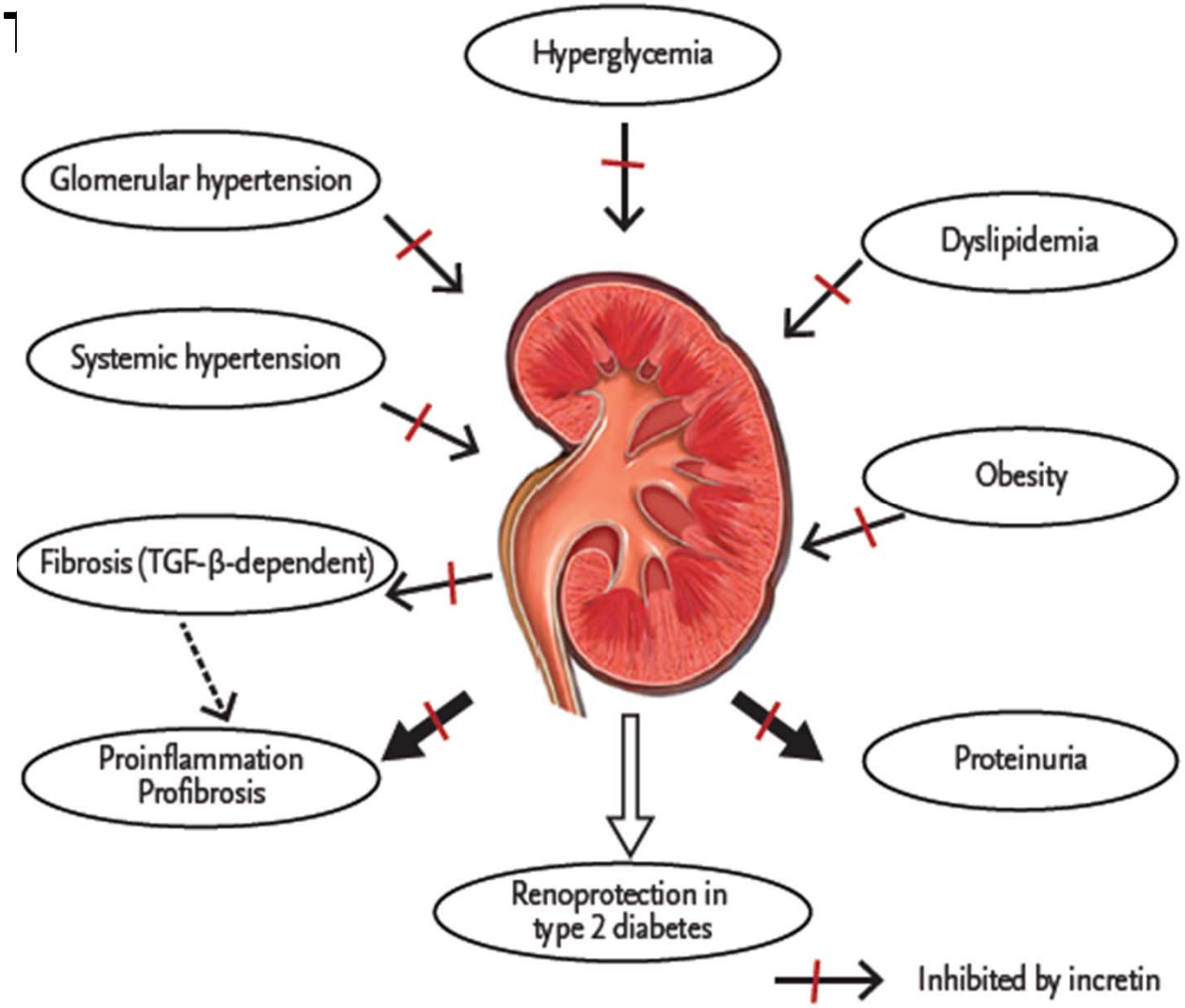
amelioration of glucose-induced oxidative stress, downregulation of MCP1, ICAM1, NF-κB, and TGF β

Diabetes Care Volume 41, Supplement 1, January 2018

	eGFR (ml/min/1.73m²)		
Drug	**15–29**	**30–59**	**60–89**
Metformin		Dose reduction if eGFR <45	
Sulfonylureas	Risk of hypoglycaemia with renal impairment		
Pioglitazone			
DPP-4 inhibitors			
Alogliptin	Further dose reduction if eGFR <30	Dose reduction if eGFR <50	
Linagliptin			
Sitagliptin	Further dose reduction if eGFR <30	Dose reduction if eGFR <50	
Saxagliptin	Use with caution	Dose reduction if eGFR <50	
Vildagliptin	Use with caution	Dose reduction if eGFR <50	
GLP-1 agonists			
Dulaglutide			
Exenatide standard-release		Dose reduction if eGFR <50	
Exenatide modified-release			
Liraglutide			
Lixisenatide		Use with caution	
SGLT2 inhibitors			
Canagliflozin	Avoid if eGFR <45	Dose reduction if eGFR <60	
Dapagliflozin		Avoid if eGFR <60	
Empagliflozin	Avoid if eGFR <45	Dose reduction if eGFR <60	
Use freely	Restricted use	Not recommended	

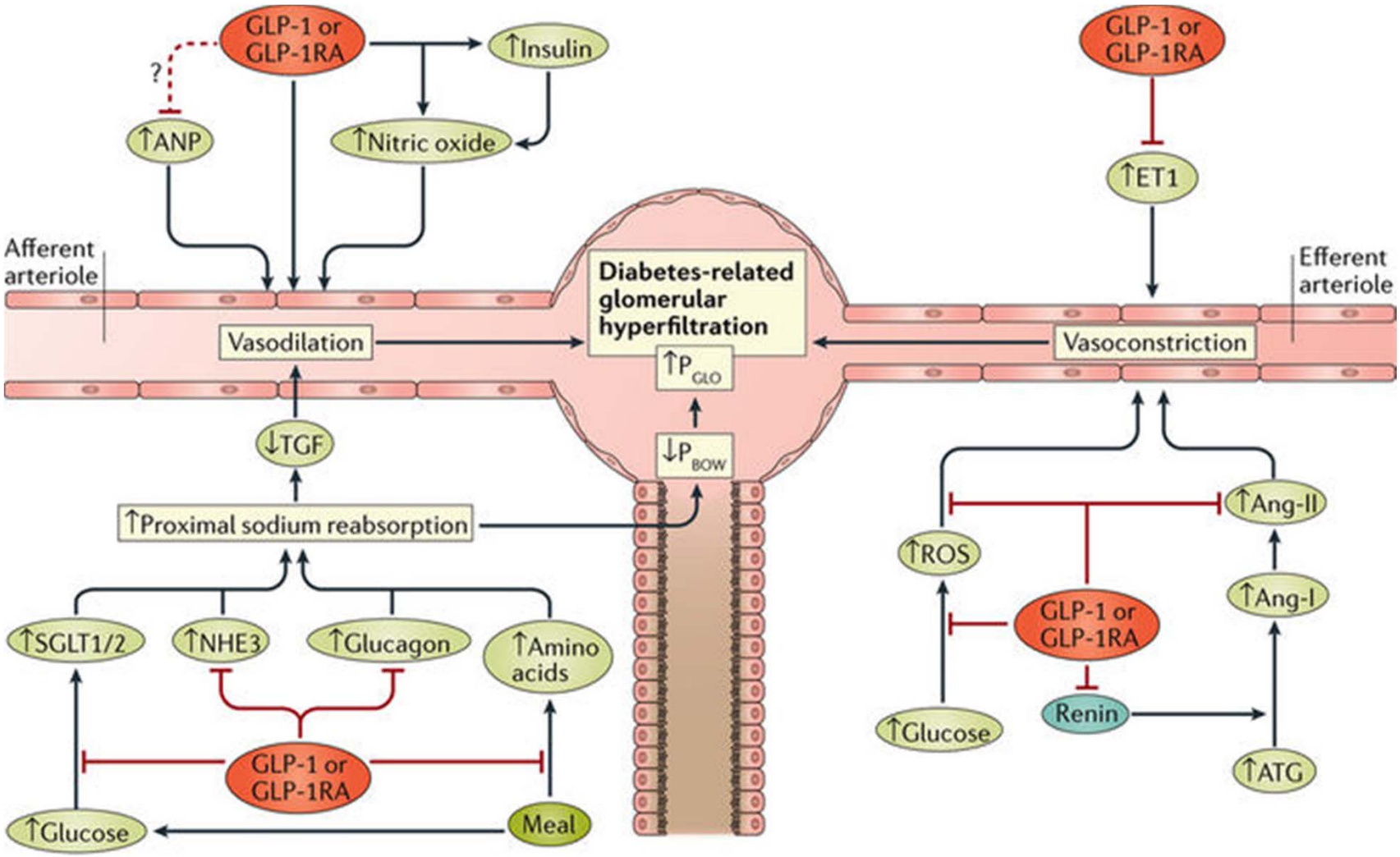
BNF 72. September 2016–March 2017.

Effects of Incretin-based therapies on renal risk factors in



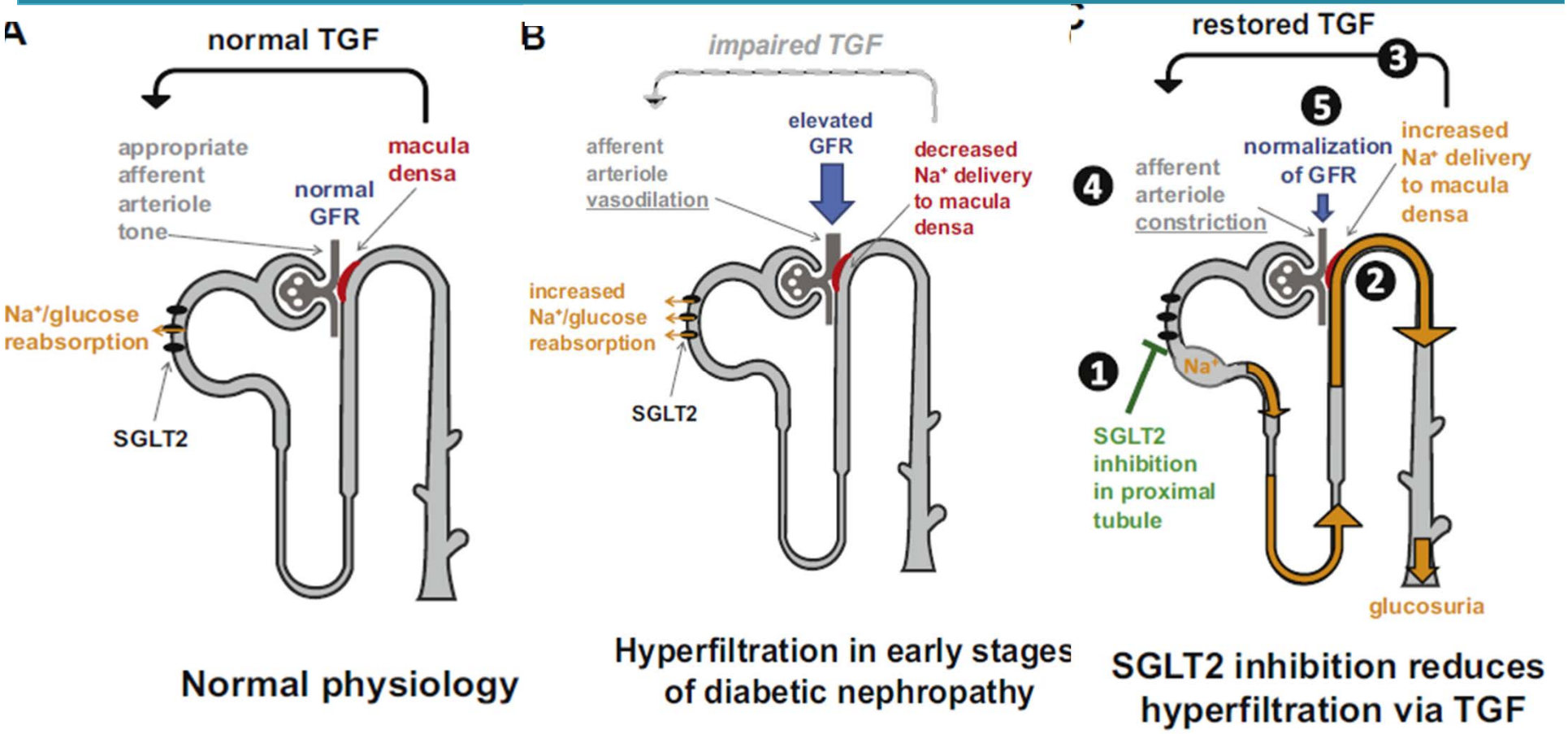
Marcel HA Muskiet et al, Nature Reviews Nephrology 10, 88–103 (2014)
Yaeni Kim and Cheol Whee Park, Korean J Intern Med 2017;32:11-25

Effects of glucagon-like peptide 1 (GLP-1) and GLP-1 receptor agonists (GLP-1RAs) on renal haemodynamics in diabetes mellitus



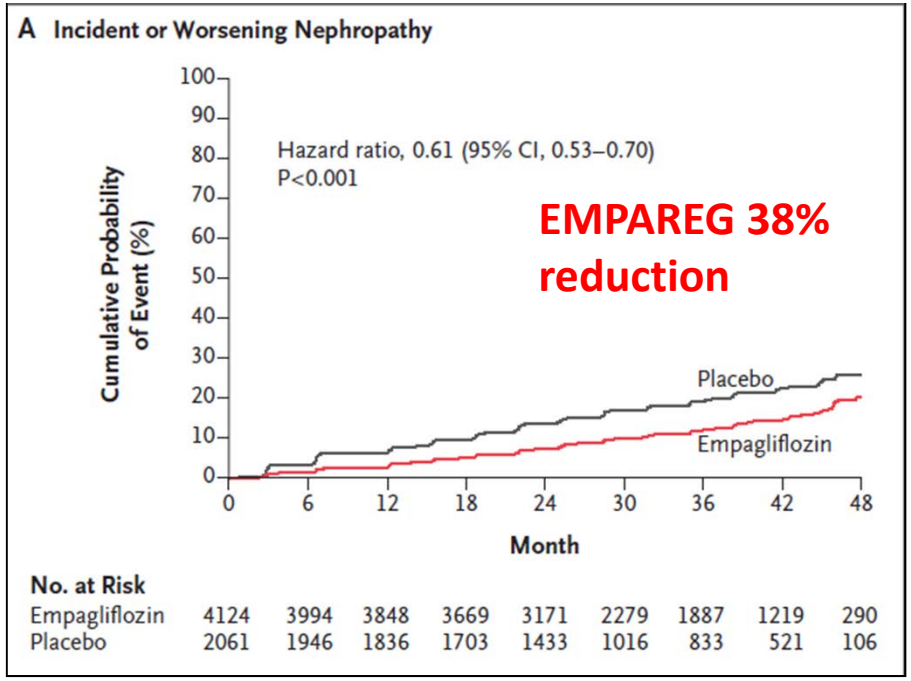
Marcel HA Muskiet et al, Nature Reviews Nephrology 13, 605–628 (2017)

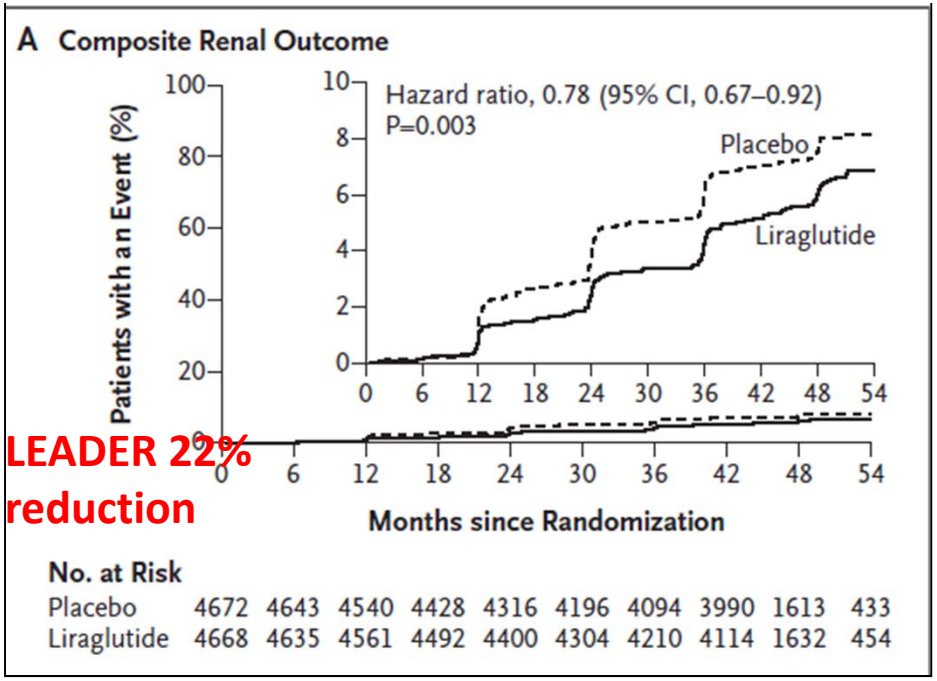
Possible renal hemodynamic effects with SGLT2 inhibition

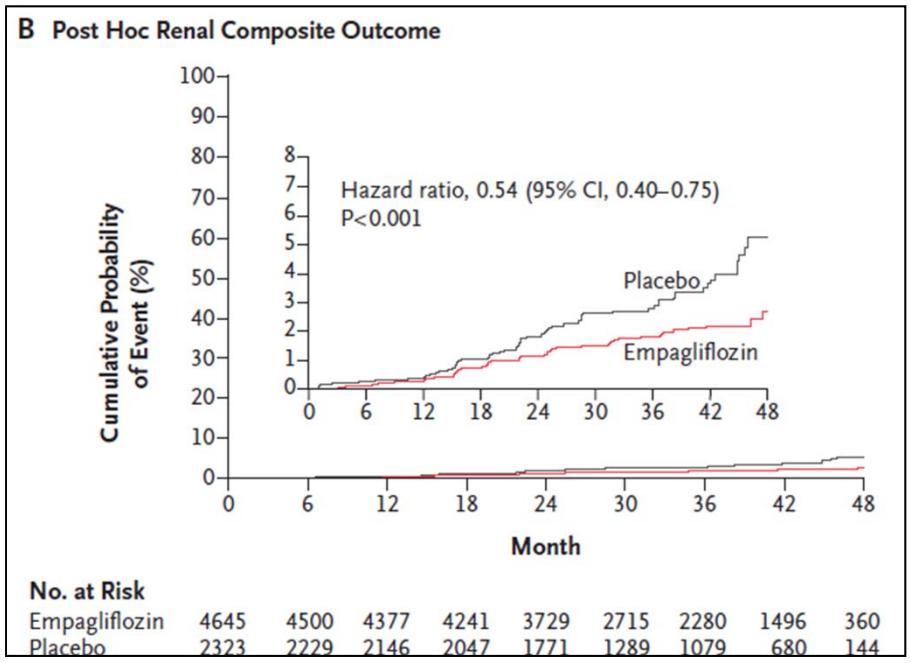


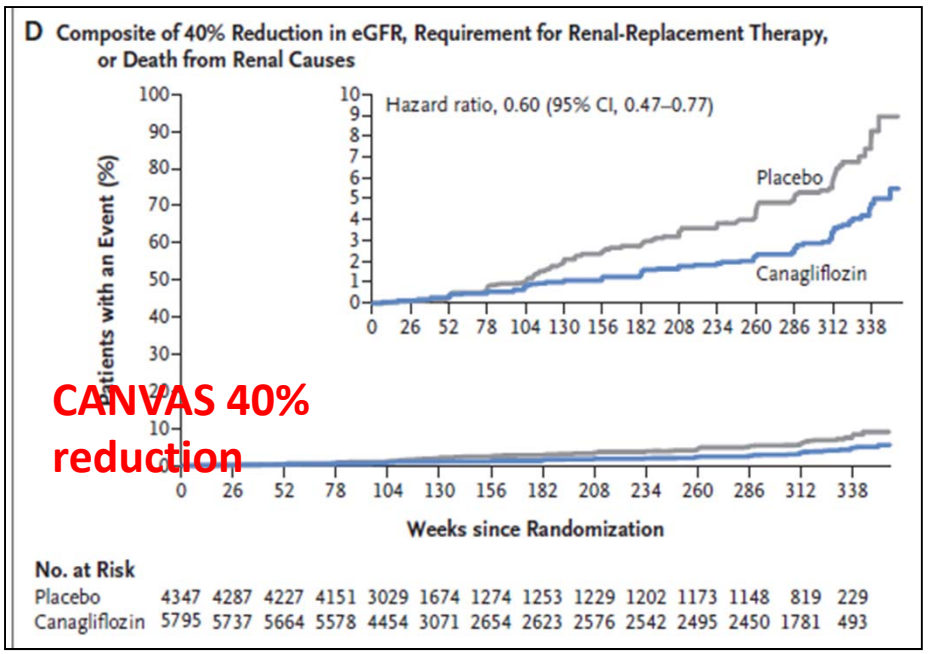
Circulation. (2014) ;129:587-597

Increased renal tubular Na reabsorption due to increased sodium-glucose cotransport leads to the increase in extracellular fluid volume, which then increases GFR


A Incident or Worsening Nephropathy
Cumulative Probability of Event (%)
Hazard ratio, 0.61 (95% CI, 0.53–0.70)
P<0.001
EMPAREG 38% reduction
Placebo
Empagliflozin
Month
No. at Risk
Empagliflozin 4124 3994 3848 3669 3171 2279 1887 1219 290
Placebo 2061 1946 1836 1703 1433 1016 833 521 106


A Composite Renal Outcome
Patients with an Event (%)
Hazard ratio, 0.78 (95% CI, 0.67–0.92)
P=0.003
Placebo
Liraglutide
LEADER 22% reduction
Months since Randomization
No. at Risk
Placebo 4672 4643 4540 4428 4316 4196 4094 3990 1613 433
Liraglutide 4668 4635 4561 4492 4400 4304 4210 4114 1632 454


B Post Hoc Renal Composite Outcome
Cumulative Probability of Event (%)
Hazard ratio, 0.54 (95% CI, 0.40–0.75)
P<0.001
Placebo
Empagliflozin
Month
No. at Risk
Empagliflozin 4645 4500 4377 4241 3729 2715 2280 1496 360
Placebo 2323 2229 2146 2047 1771 1289 1079 680 144


D Composite of 40% Reduction in eGFR, Requirement for Renal-Replacement Therapy, or Death from Renal Causes
Patients with an Event (%)
Hazard ratio, 0.60 (95% CI, 0.47–0.77)
Placebo
Canagliflozin
CANVAS 40% reduction
Weeks since Randomization
No. at Risk
Placebo 4347 4287 4227 4151 3029 1674 1274 1253 1229 1202 1173 1148 819 229
Canagliflozin 5795 5737 5664 5578 4454 3071 2654 2623 2576 2542 2495 2450 1781 493

Key renal outcome from EMPA-REG, LEADER and CANVAS

	EMPA-REG † Empagliflozin		**LEADER‡** Liraglutide		**CANVAS*** Canagliflozin	
	HR	P	HR	p	HR	p
Renal endpoint	0.61 (0.55–0.69)	<0.001	0.78 (0.67–0.92)	0.003	0.60 (95% CI, 0.47–0.77)	NA
Progression to macroalbuminuria	0.62 (0.54–0.72)	<0.001	0.74 (0.60–0.91)	0.004	0.73 (95% CI, 0.67–0.79)	NA
Doubling of serum Cr	0.56 (0.39–0.79)	<0.001	0.89 (0.67–1.19)	0.4	NA	
Initiation of RRT	0.45 (0.21–0.97)	<0.001	0.87 (0.61–1.24)	0.44	NA	

Renal Outcome †‡=incident or worsening nephropathy (progression to macroalbuminuria, doubling of the serum creatinine level, initiation of renal-replacement therapy, or death from renal disease) and incident albuminuria

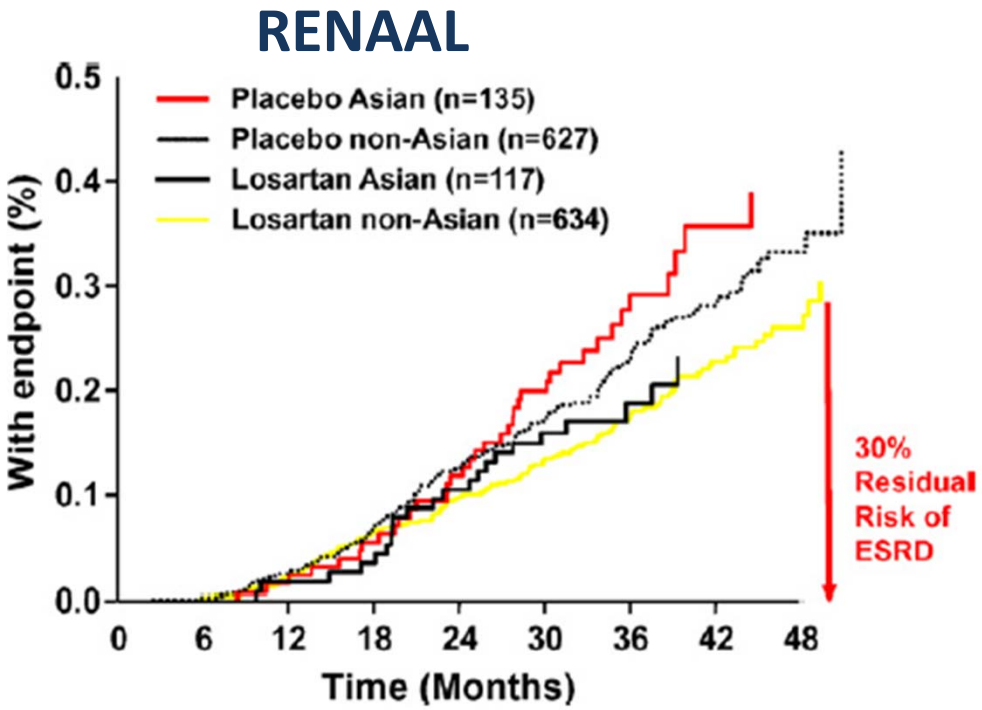
Renal outcome*= sustained 40% reduction in the estimated glomerular filtration rate, the need for renal-replacement therapy, or death from renal causes

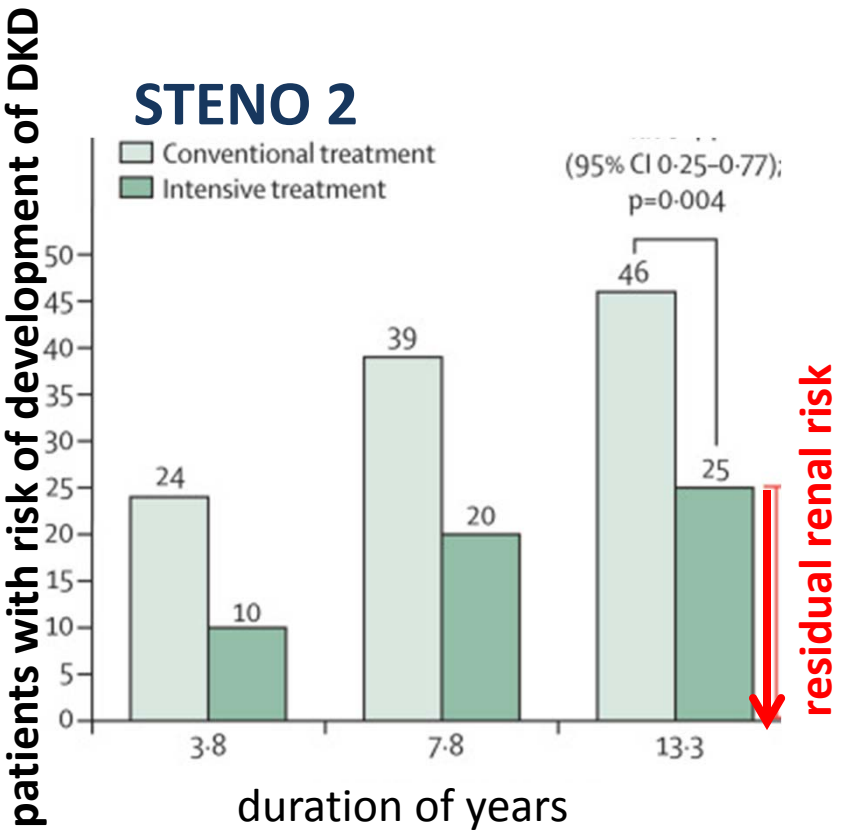
Dr. Elliot Proctor Joslin (1869-1962)

Diet, exercise, insulin

Joslin medical center

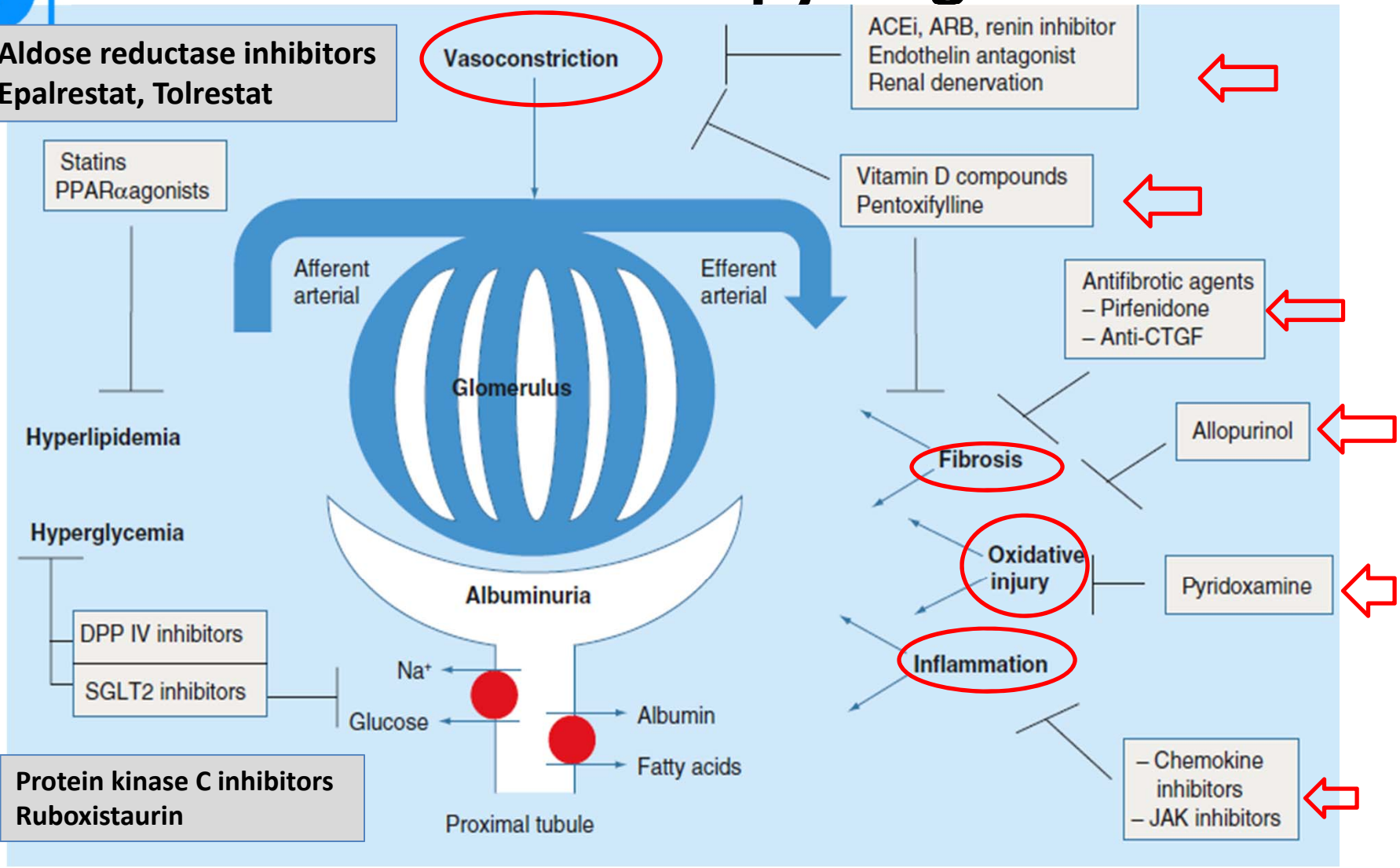
Residual renal risk in patients with T2DM





Andrea Luk, diabetesresearch and clinical practice 82s (2008) s 15– s20
Marcel H A Muskiet, Volume 3, No. 5 ,p367–381, May 2015

Possible novel therapy targets in DN



Edward J Horwitz & Jeffrey R Schelling, Clin. Invest. (2014) 4(4), 327–341

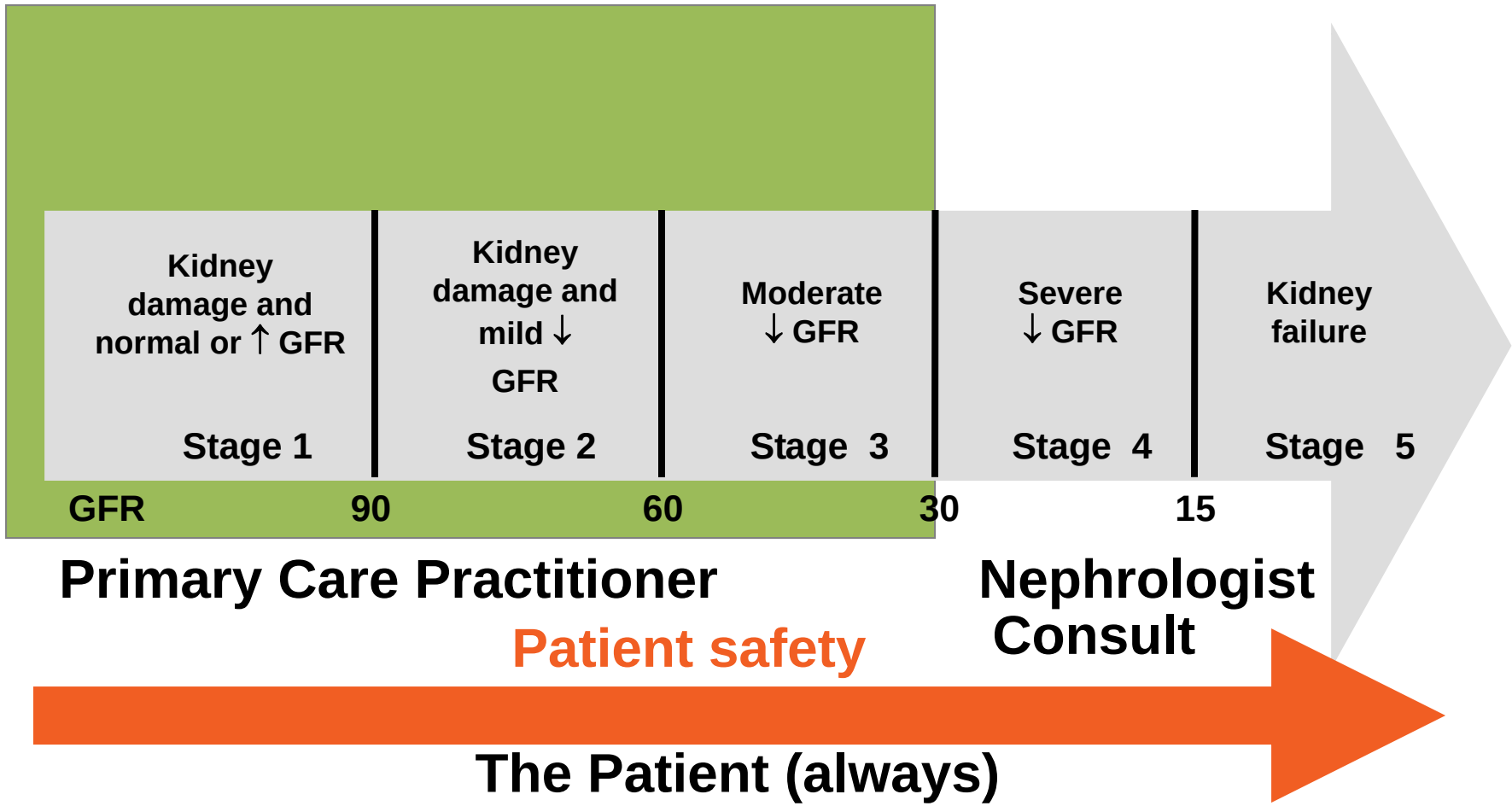
When to refer nephrologist

- When eGFR < 60 mL/min/1.73 m², evaluate and manage potential complications of chronic kidney disease. E
- Patients should be referred for evaluation for RRT if they have an eGFR < 30 mL/min/1.73 m². A
- Promptly refer to a physician experienced in the care of kidney disease for uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease. B

ADA 2018, National kidney Foundation 2002

- difficult management issues
  - anemia,
  - secondary hyperparathyroidism,
  - metabolic bone disease,
  - resistant hypertension, or
  - electrolyte disturbances

Who Should be Involved in the Patient Safety Approach to CKD?



Summary

- *Multifactorial interventions* are required to prevent the progression of DKD and associated CVD
- Patients with DM & CKD are at increased risk of *hypoglycemia* and treatment that promote hypoglycemia should be used with cautious monitoring and patient education
- Individualized glycemic and BP *targets* are required in treatment of patients with Diabetic nephropathy
- *GLP1 agonist & SGLT2 inhibitors* have demonstrated promising renal protective outcomes and which are being explored further in dedicated renal outcome trials

Protect your kidneys, save your heart