Diabetes-Related Kidney Disease

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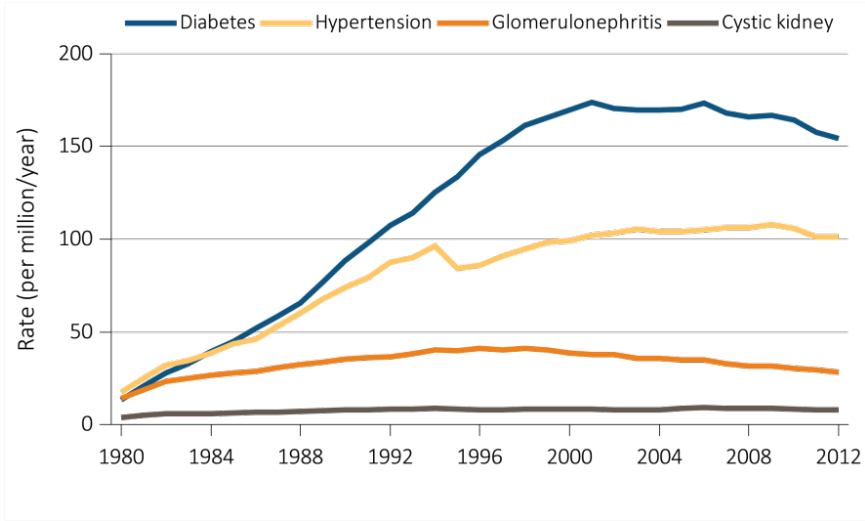
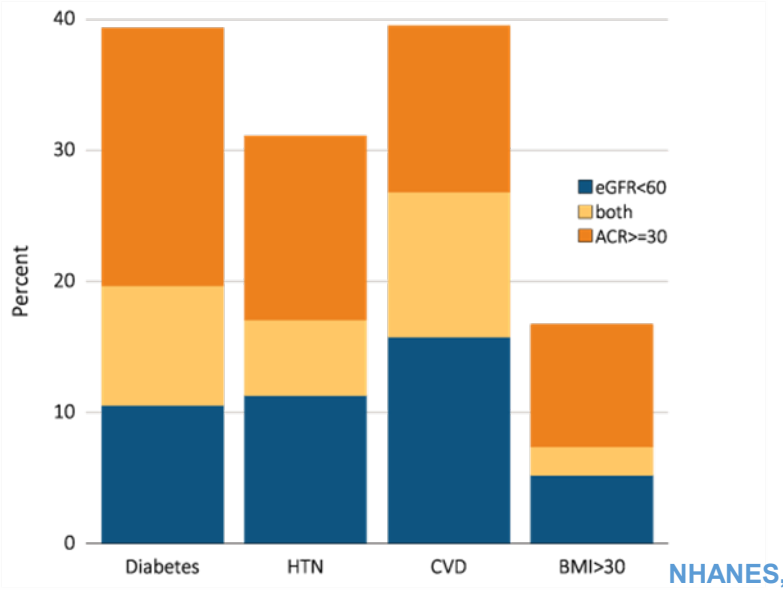
Clinical Features & Natural History

Diabetes-Associated Kidney Disease

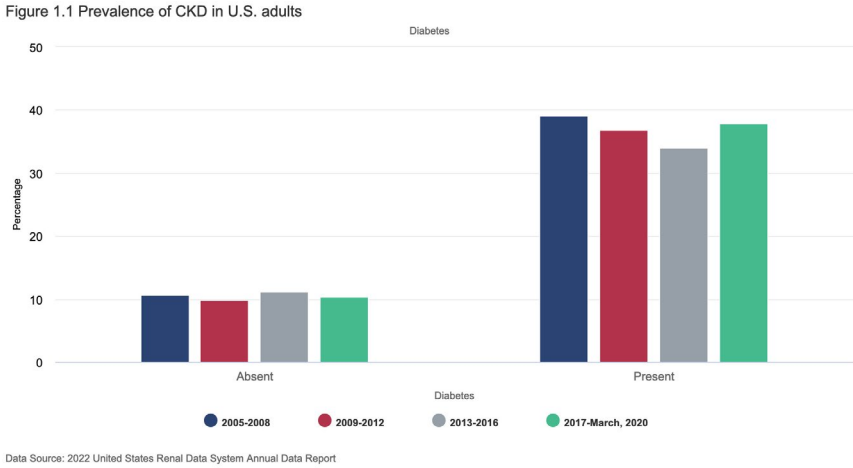
- **Diabetes – most common primary cause of ESRD in the US**
- **CKD prevalence ↑~4X in Diabetes**
  - **↑ in non-white & older cohorts**



CKD Markers in DM, HTN, CVDz, & Obesity



NHANES, 2007-2012



Diabetes-Associated Kidney Disease

Terminology

Diabetic Nephropathy (DN)

Diabetic glomerulopathy

Histopathological diagnosis

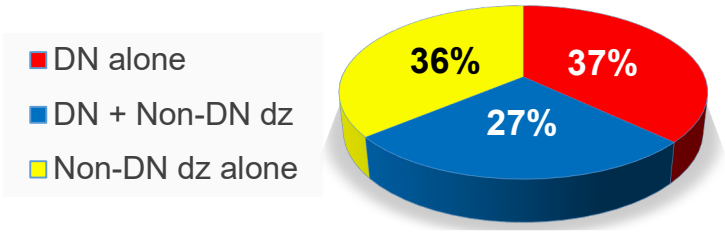
Diabetic Kidney Disease (DKD)

Presumptive *clinical diagnosis*

- CKD
- Albuminuria
- Late manifestation of disease
  - Association with other diabetic end-organ complications
  - Steadily progressive course

Diabetes-Associated Pathology

- 2642 consecutive native kidney Bxs – Columbia Renal Pathology Laboratory
  - 23.5% in pts w/ DM

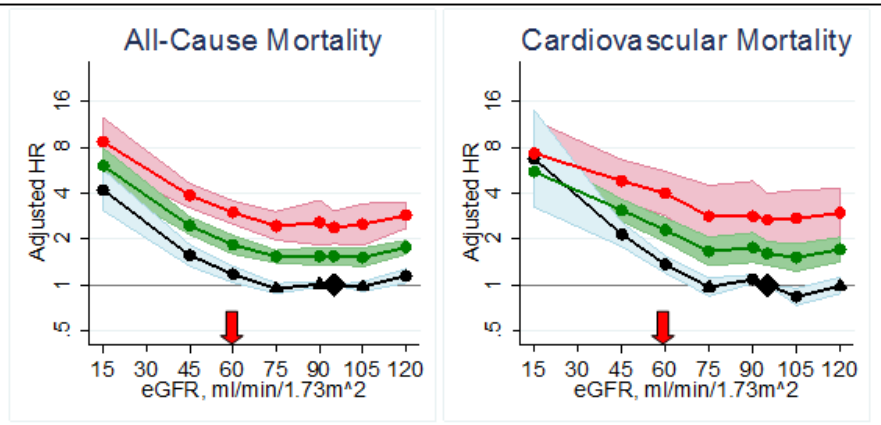


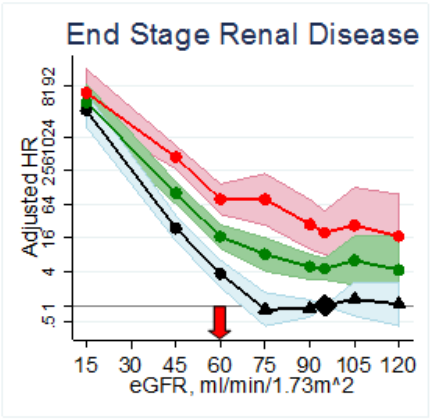
Duration of DM – best predictor of DN alone.

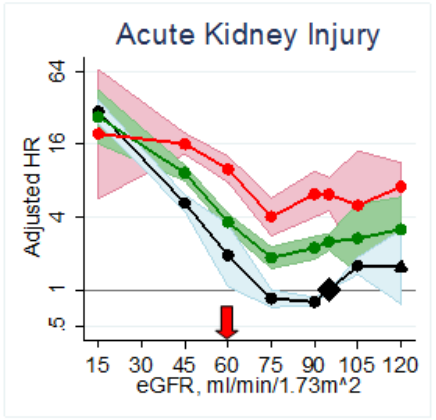
Data from Sharma, *CJASN*, 2013

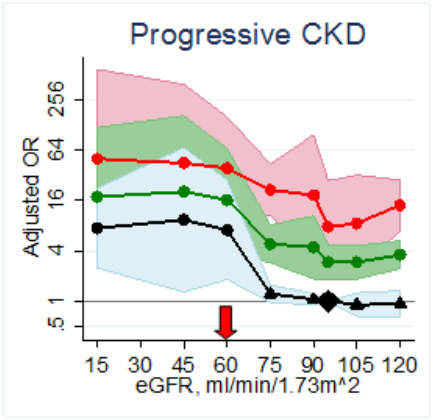
General Albuminuria-Associated Risks

Summary of Relative Risks from Continuous Meta-Analysis









National Kidney Foundation™

Modified with permission from Macmillan Publishers Ltd. Levey AS, de Jong PE. Coresh J, et. al. Kidney Int 2011; 80: 17-28.

- **Increased risk for all-cause & CV mortality**
- **Increased risk for ESRD, AKI, & CKD progression**
- **Risks additive to those associated w/ reduced GFR alone**
- **Unlike GFR, risks associated with albuminuria demonstrate *no threshold effect***

Prognosis of CKD by GFR and Albuminuria Categories

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

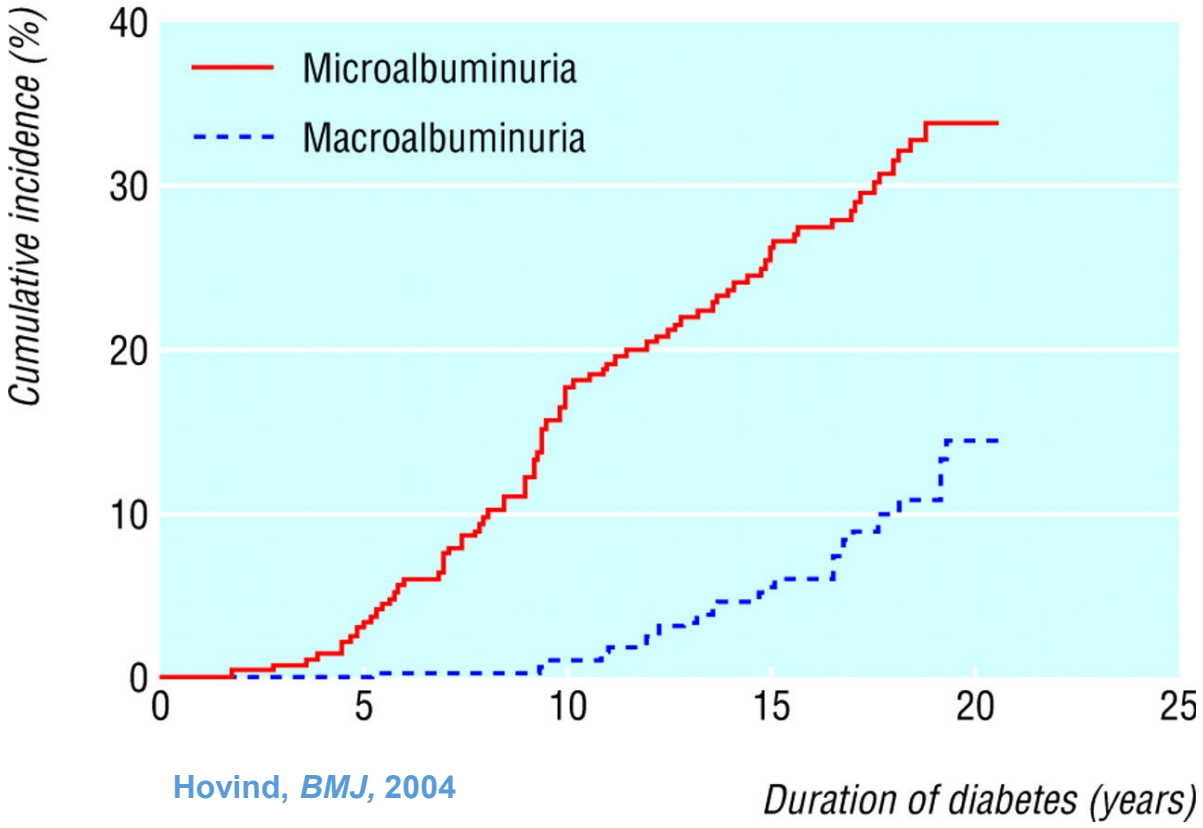
GFR categories (ml/min/1.73m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

National Kidney Foundation™

Modified with permission from Macmillan Publishers Ltd. Levey AS, de Jong PE. Coresh J, et. al. Kidney Int 2011; 80: 17-28.

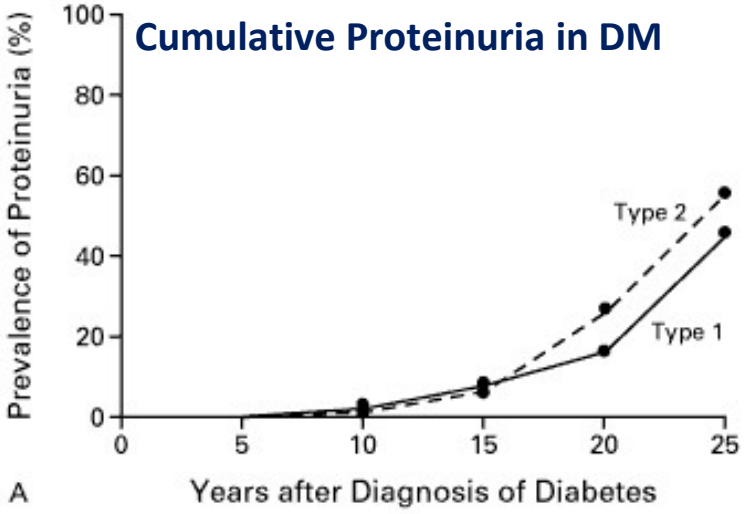
Natural History – Proteinuria & CKD in DKD

Cumulative "Microalbuminuria"& Progression to "Macroalbuminuria" in T1DM, 1979-1984

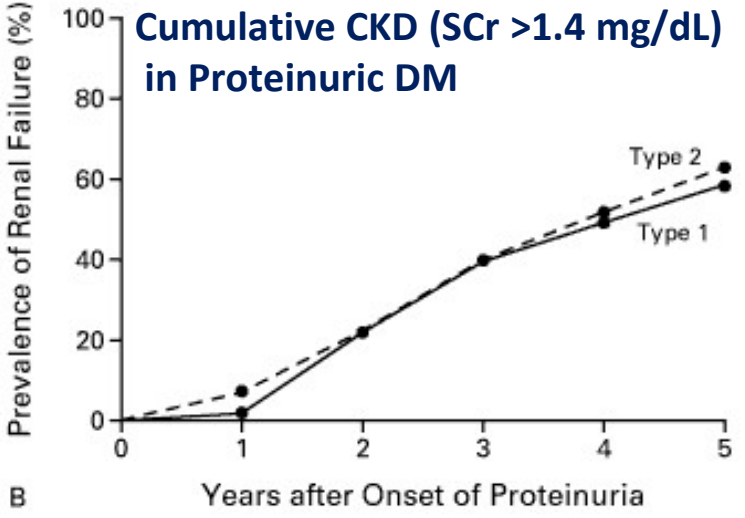


Hovind, *BMJ*, 2004

Cumulative Proteinuria in DM

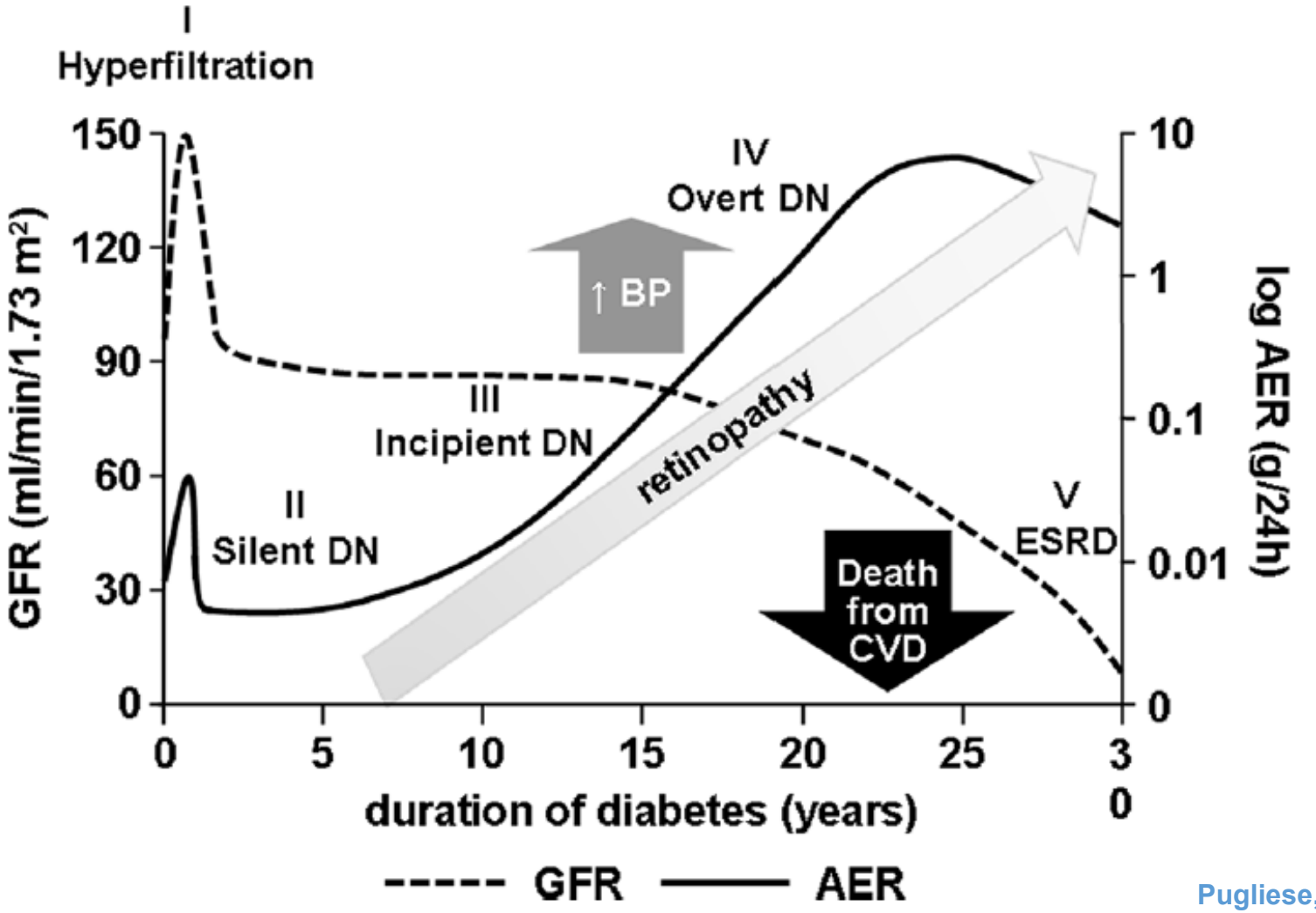


Cumulative CKD (SCr >1.4 mg/dL) in Proteinuric DM



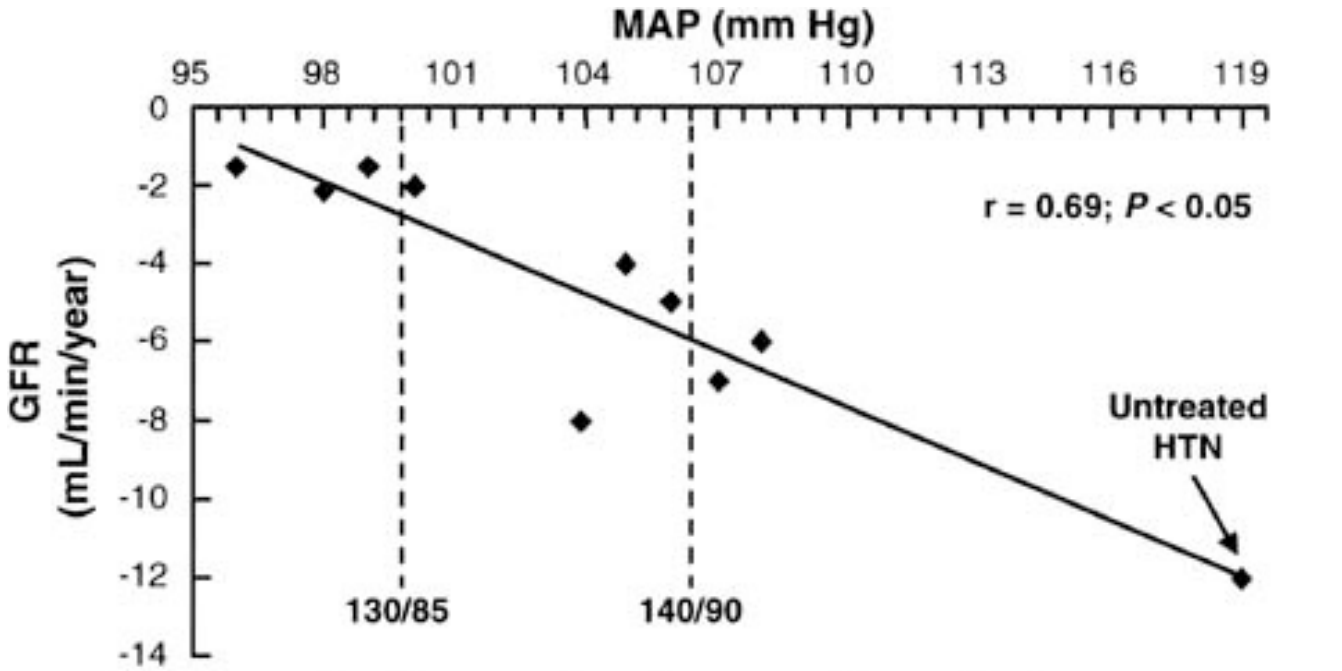
Ritz, *NEJM*, 1999

Natural History of Diabetic Nephropathy –Classic Clinical Stages



Pugliese, *Acta Diabetol*, 2014

HTN Amplification of CKD Onset/Progression

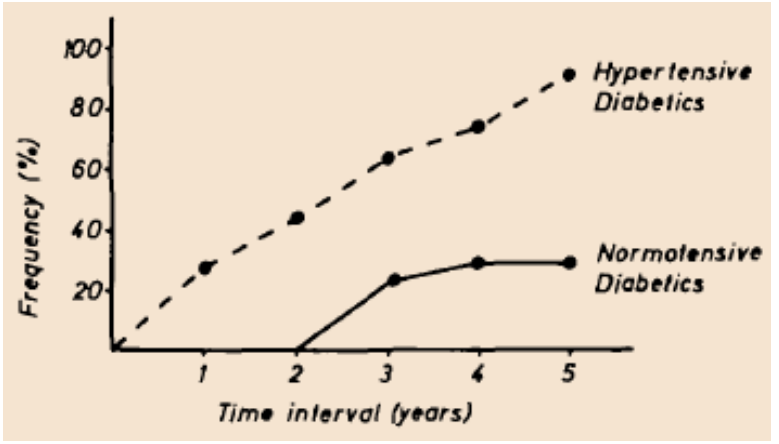


Summary of studies on nephropathy progression used in figure

- Parving HH et al. *Br Med J*, 1989
- Viberti GC et al. *JAMA*, 1993
- Klaur S et al. *N Eng J Med*, 1993*
- Hebert L et al. *Kidney Int*, 1994
- Lebovitz H et al. *Kidney Int*, 1994
- Moschio G et al. *N Engl J Med*, 1996*
- Bakris GL et al. *Kidney Int*, 1996
- Bakris GL. *Hypertension*, 1997
- GISEN Group, *Lancet*, 1997*

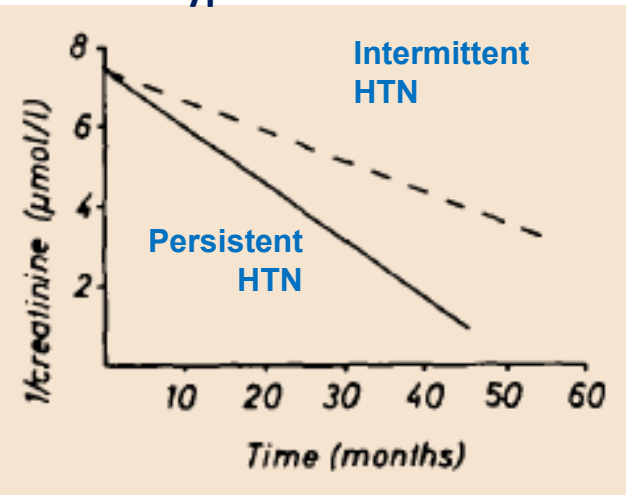
Bakris, *AJKD*, 2000

CKD in Proteinuric T1DM

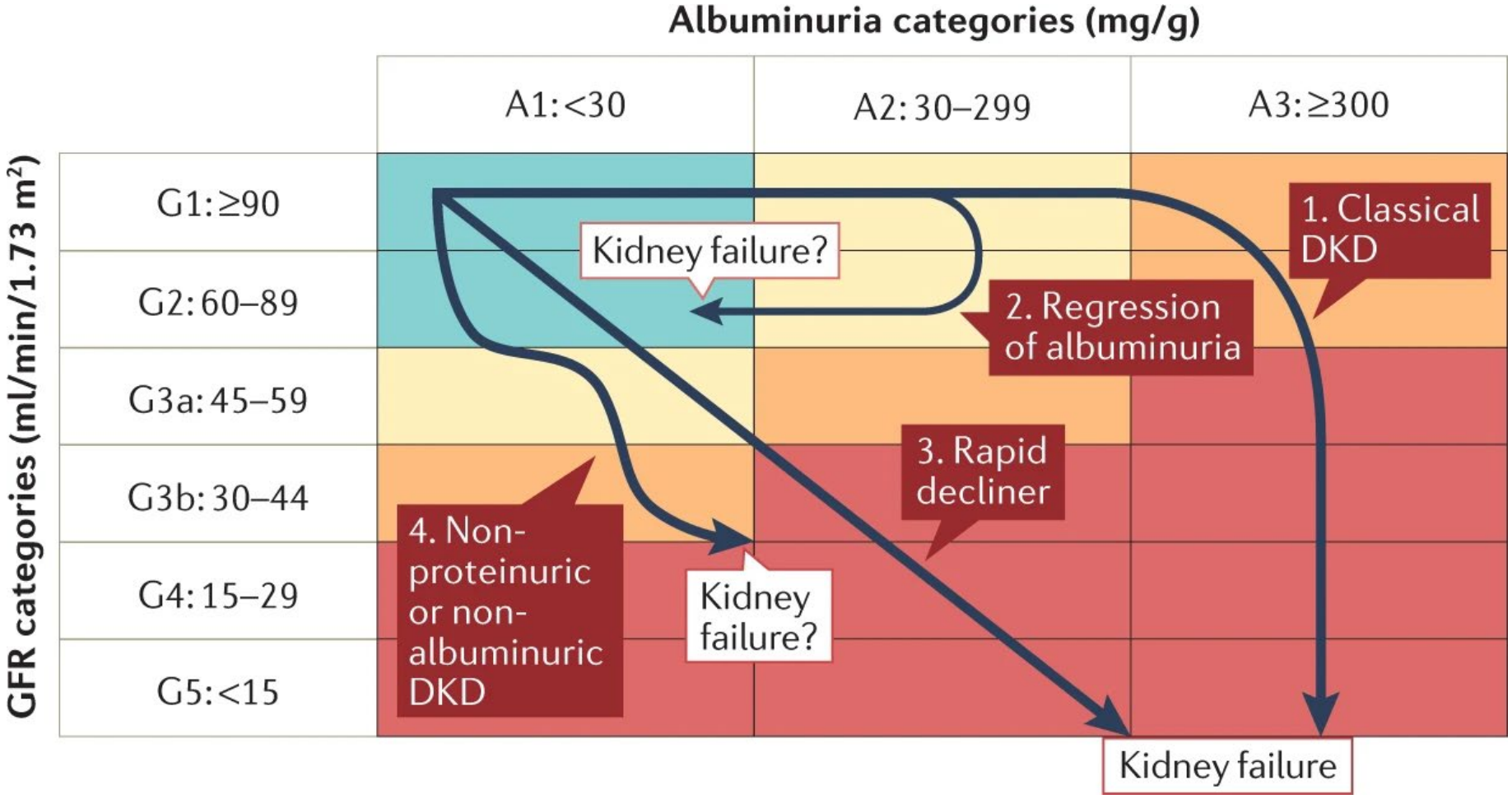


Hasslacher, *Hypertension*, 1985

Renal Functional Decline in Hypertensive DM



Heterogeneity of DKD Progression



Oshima, *Nat Rev Nephrol*, 2021

Diabetes is a Systemic Disease!

Diabetic Kidney Disease is typically associated with other end-organ sequelae of DM.

TABLE 5. COMMON PROBLEMS IN PATIENTS WITH TYPE 2 DIABETES AND ADVANCED DIABETIC NEPHROPATHY.

Microvascular complications

Retinopathy (nonproliferative and proliferative)
Polyneuropathy (including autonomic polyneuropathy)
- Cystopathy (detrusor paresis)
- Gastroparesis
- Diarrhea or constipation
- Impotence
- Foot (neuropathic) problems

Macrovascular (atherosclerotic) complications

Coronary heart disease
Cerebrovascular disease (ischemic)
Arterio-occlusive disease (legs and distal arteries)
Ischemic nephropathy (renal-artery stenosis and cholesterol embolism)

Ritz, *NEJM*, 1999

Non-Diabetic Kidney Disease in T2DM

T2DM in 538/5485 Kidney Bxs 2005-2022

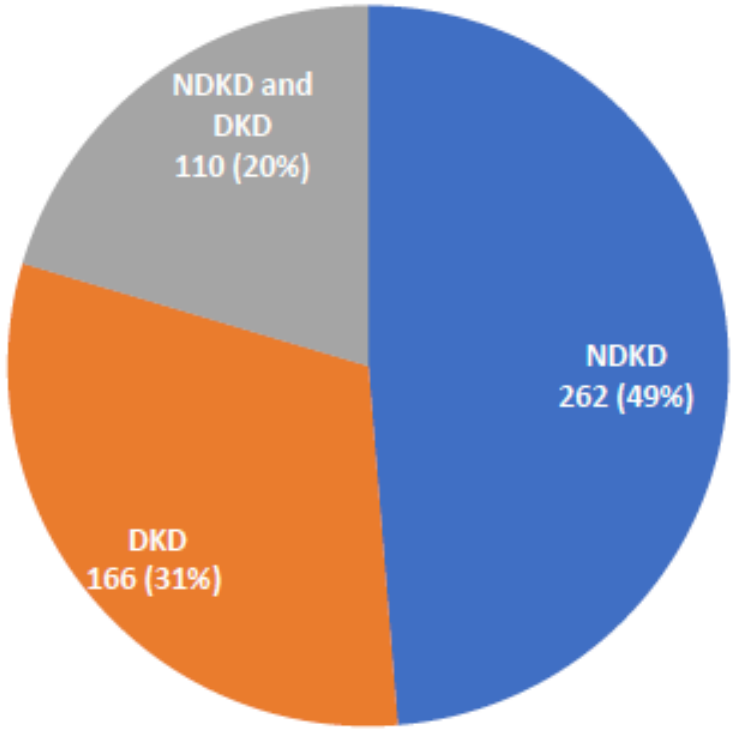


Figure 3. Frequencies of Various histological classes on Kidney biopsy. DKD: Diabetic Kidney disease; NDKD: Non-diabetic kidney disease.

Table 4. Multivariate logistic regression analysis showing predictor of NDKD.

Variable	*p*-Value	Odds Ratio (95% Confidence Interval)
Duration of DM ≤5 years	**0.003**	**1.9 (1.26–3.14)**
Hypertension	0.22	0.73 (0.3–2.11)
Hypertension onset after diabetes	0.94	0.11 (0.03–1.86)
Absence of CAD	**0.05**	**2.1 (1.11–4.96)**
Absence of DR	**<0.001**	**4.9 (2.9–8.4)**
Oliguria	**0.02**	**1.8 (1.1–3.1)**
Evidence of infection (ongoing/recent past)	0.63	1.2 (0.52–1.44)
Presence of extra-renal manifestations	0.64	1.8 (0.82–2.26)
Acute kidney Injury/Acute on Chronic kidney disease	**<0.001**	**6.2 (3.4–11.0)**
Rapidly progressive renal failure	0.58	1.23 (0.6–2.68)
Dialysis requiring renal failure at presentation	0.06	1.79 (0.96–3.3)
Microscopic hematuria	0.07	1.51 (0.95–2.41)
Nephrotic range proteinuria	0.66	0.48 (0.2–1.8)
Sub-nephrotic proteinuria	0.52	1.18 (0.4–3.1)
Low serum C3 level	**<0.001**	**4.9 (2.08–11.6)**
Low serum C4 level	0.77	1.6 (0.8–4.6)

CAD: Coronary artery disease; DR: Diabetic retinopathy; Evidence of active infection/infection within recent past of 4–6 weeks—history or examination evidence supported by laboratory evidence (e.g., Anti-streptolysin titer). Acute rise in creatinine (AKI)—Defined as per the KDIGO 2012 guidelines of AKI i.e., Increase in serum creatinine by ≥0.3 mg/dL within 48 h (or) increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days.

Prasad, *J Clin Med*, 2023

Diabetic vs. Non-Diabetic Kidney Disease?

Box 2. Other Cause(s) of CKD Should Be Considered in the Presence of Any of the Following Circumstances

- Absence of diabetic retinopathy;
- Low or rapidly decreasing GFR;
- Rapidly increasing proteinuria or nephrotic syndrome;
- Refractory hypertension;
- Presence of active urinary sediment;
- Signs or symptoms of other systemic disease; or
- >30% reduction in GFR within 2-3 months after initiation of an ACE inhibitor or ARB.

Reproduced with permission of NKF from KDOQI diabetes and CKD guideline.[4]

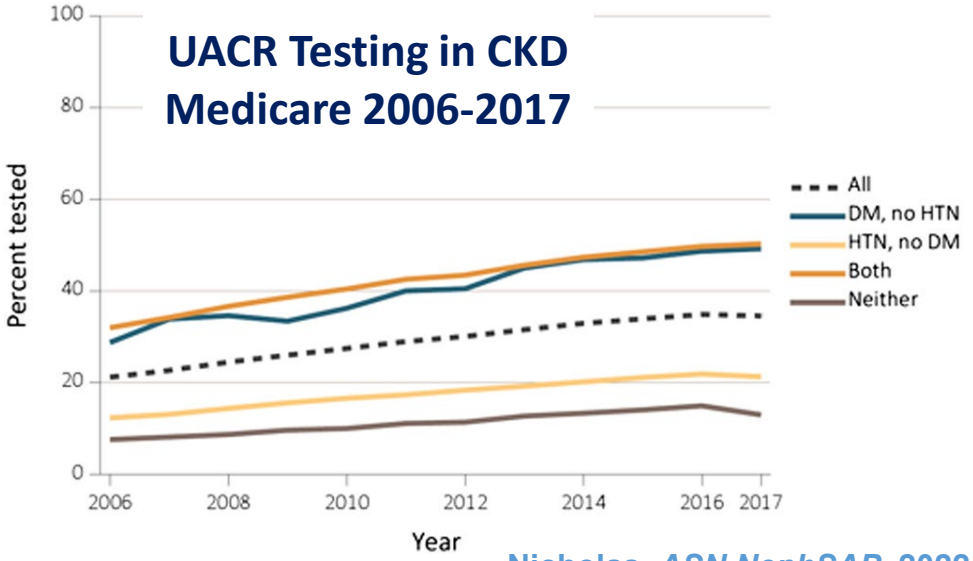
Tuttle, *AJKD*, 2014

Screening & Management

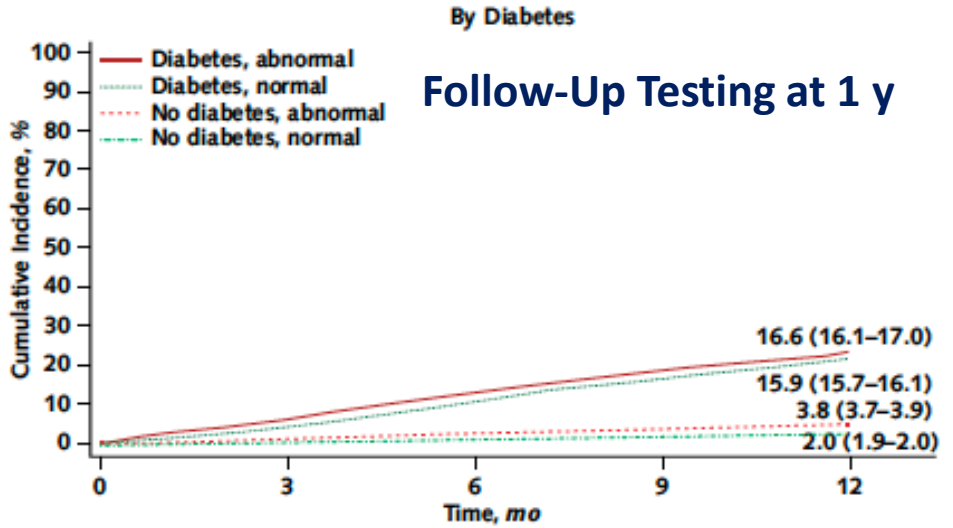
DKD Screening

- Low CKD awareness in both patients & health care providers
- New renoprotective therapies available to alter the course of disease if implemented in a timely manner

- <u>Screening</u>
  - T1DM – Annually, starting 5 y s/p Dx
  - T2DM – Annually, starting at Dx
- <u>Screening Tests</u>
  - Albuminuria (UACR)
    - SCr & eGFR

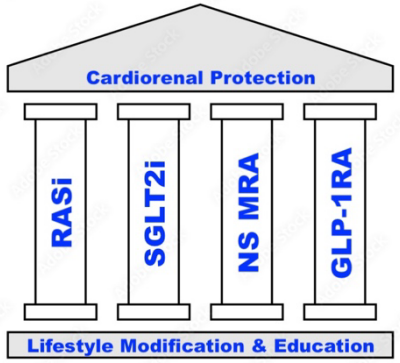


Nicholas, *ASN NephSAP*, 2022



Xu, *Ann Int Med*, 2024

Four Pillars of Cardiorenal Protection



Zheng, *Medicine Today*, 2024

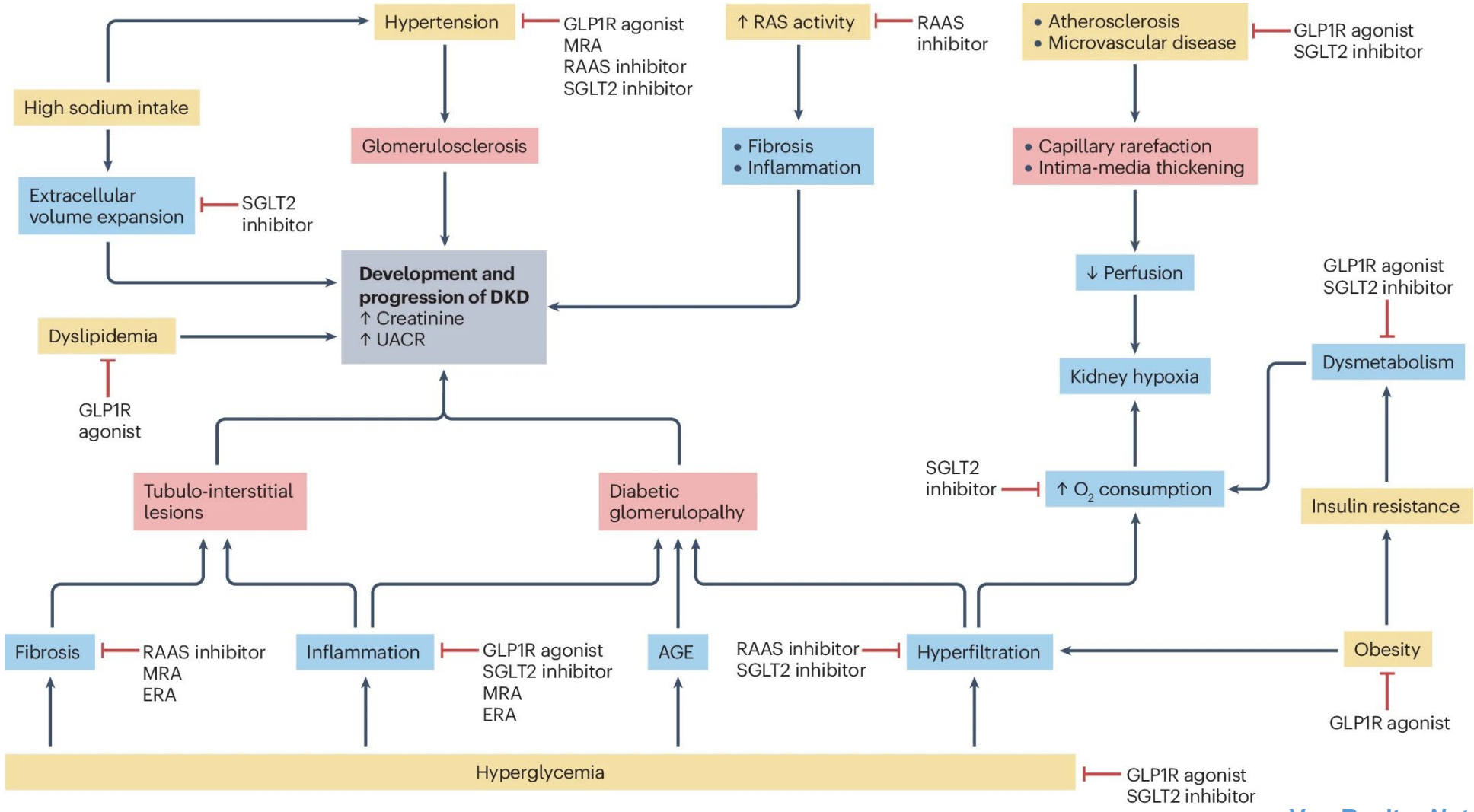
Table 1 Assembling the four pillars of therapy for cardiorenal protection in patients with chronic kidney disease (CKD) associated with type 2 diabetes (T2D)

Pillar	Dedicated trials in DKD	Clinical outcomes	Guideline-directed indication [7, 8]
(1) RAS-blockade *ACEIs or ARBs*	• RENAAL [5] • IDNT [6]	• Reduce risks of sustained eGFR decline, kidney failure, and heart failure hospitalization	• Initiation of an ACEI or an ARB for people with T2D and CKD with moderately-to-severely increased albuminuria • Avoiding any combination of ACEI, ARB and a direct renin inhibitor therapy in people with CKD • Continue therapy with a RAS-blocker in people with CKD, even when eGFR falls below 30 ml/min/1.73 m^2
(2) SGLT-2 inhibitors *Canagliflozin* *Dapagliflozin* *Empagliflozin*	• CREDENCE [15] • DAPA-CKD [16] • EMPA-KIDNEY [18]	• Reduce risks of sustained eGFR decline, kidney failure, heart failure hospitalization, and death attributable to kidney or cardiovascular causes • Glucose-lowering efficacy attenuated at low eGFR	• Initiation of an SGLT-2 inhibitor in patients with T2D, CKD, and an eGFR ≥ 20 ml/min/1.73 m^2 • Continue treatment with an SGLT-2 inhibitor even when eGFR falls below 20 ml/min/1.73 m^2, unless this is not tolerated or dialysis is initiated
(3) Non-steroidal MRAs *Finerenone*	• FIDELIO-DKD [31] • FIGARO-DKD [32] • FIDELITY [33]	• Reduce risks of sustained eGFR decline, kidney failure, heart failure hospitalization, atherosclerotic cardiovascular events as well as death from kidney and cardiovascular causes	• Initiation of finerenone in patients with T2D, an eGFR ≥ 20 ml/min/1.73 m^2, normal serum potassium concentration, and UACR ≥30 mg/g, despite treatment with a maximally tolerated dose of a RAS blocker
(4) GLP-1RAs *Semaglutide*	• FLOW [39]	• Reduce risks of sustained eGFR decline, kidney failure, atherosclerotic cardiovascular events, and death from kidney or cardiovascular causes • Glucose-lowering efficacy preserved at low eGFR • Weight loss	• The exact indication of semaglutide remains to be established, after the publication of FLOW trial

ACEI angiotensin-converting-enzyme inhibitor, *ARB* angiotensin-receptor blocker, *CKD* chronic kidney disease, *DKD* diabetic kidney disease, *eGFR* estimated glomerular filtration rate, *GLP-1-RA* glucagon-like peptide-1 receptor agonist, *MRA* mineralocorticoid-receptor antagonist, *RAS* renin-angiotensin-system, *SGLT-2* sodium-glucose co-transporter type 2, *T2D* type 2 diabetes, *UACR* urinary albumin-to-creatinine ratio

Georgianos, *Drugs*, 2024

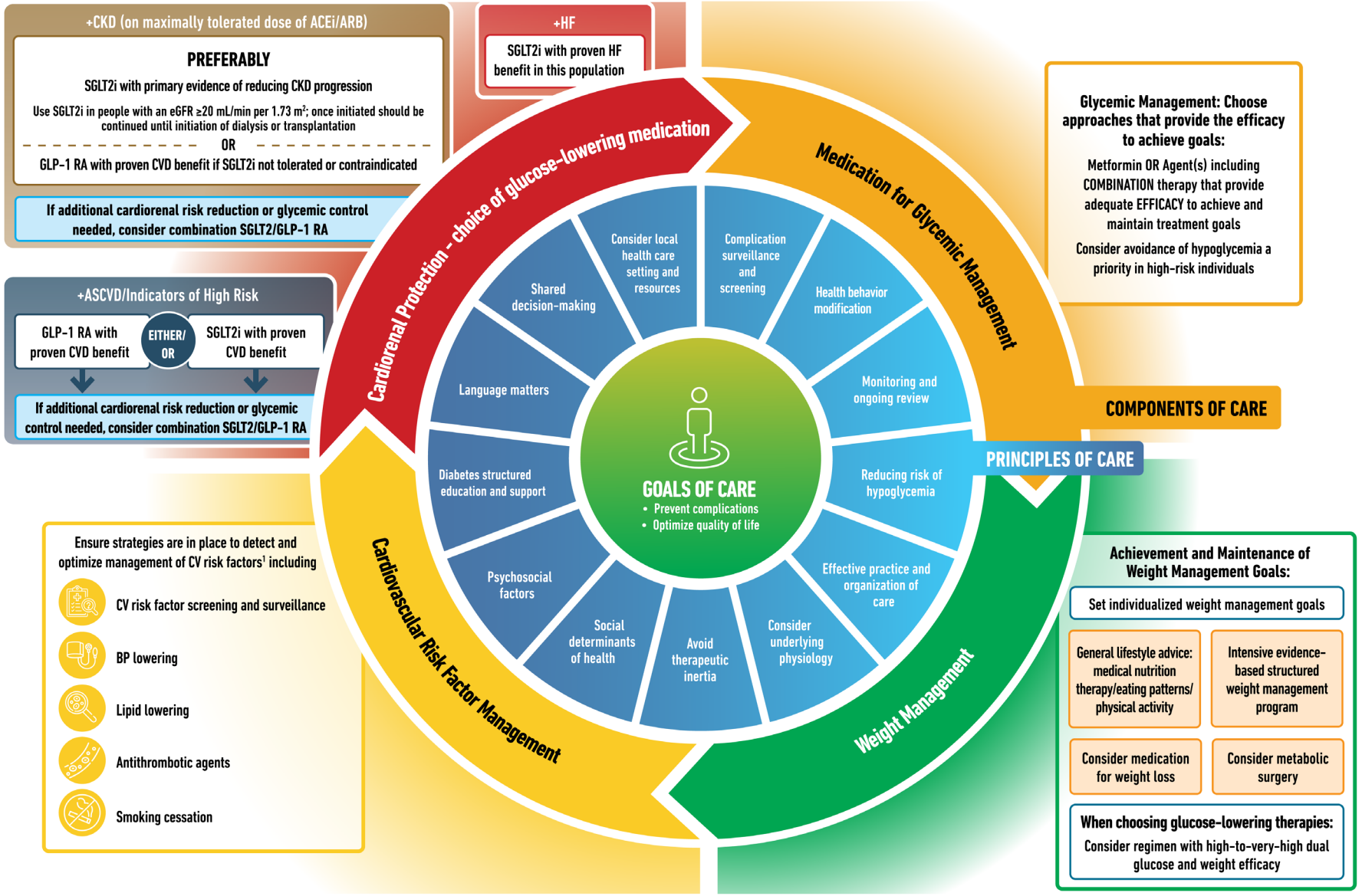
DKD Pathogenic Targets for Renoprotection



Van Raalte, *Nat Rev Nephrol*, 2024

2022 ADA-EASD Consensus

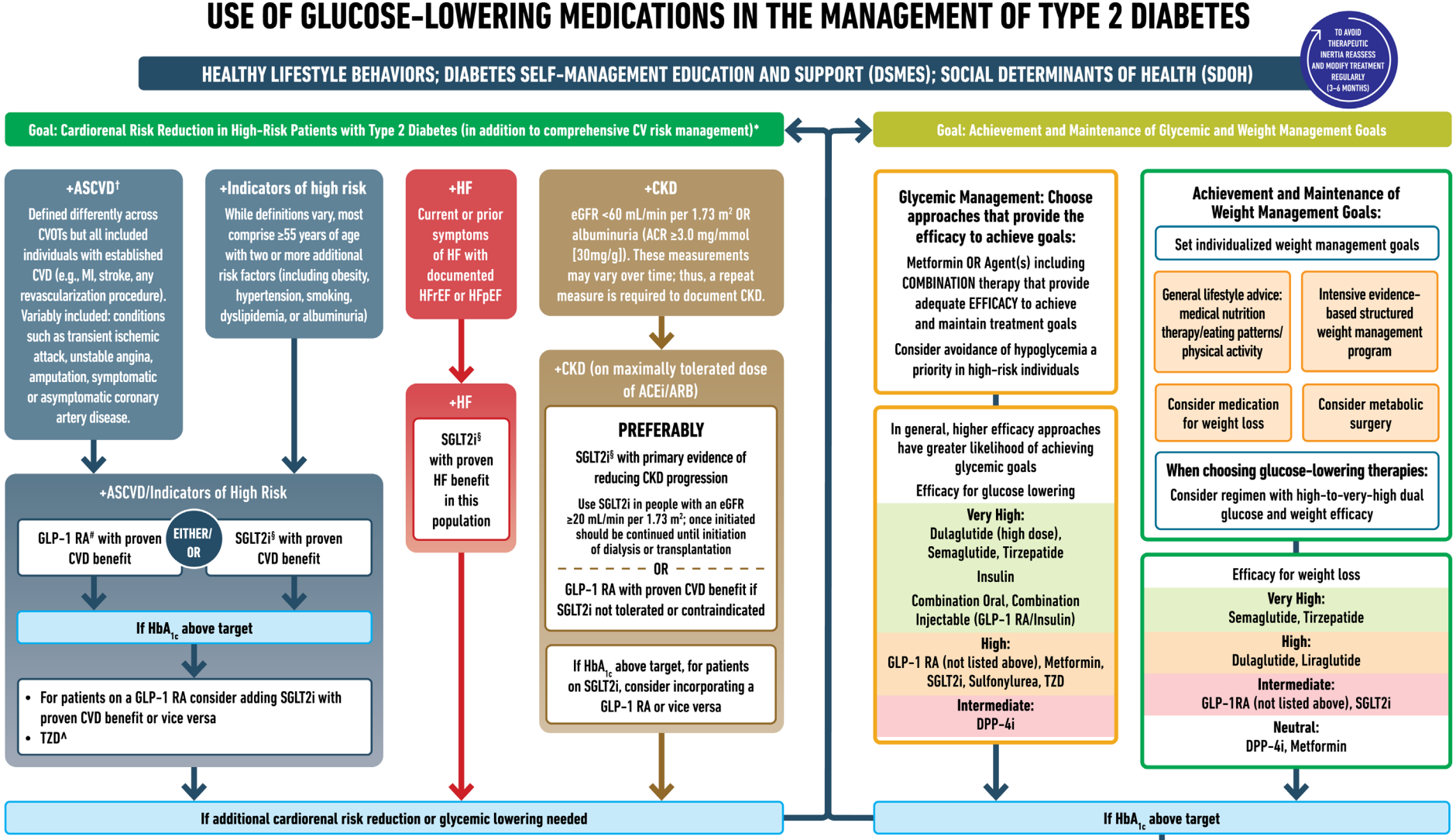
HOLISTIC PERSON-CENTERED APPROACH TO T2DM MANAGEMENT



Davies, *Diabetes Care*, 2022
(2022 ADA-EASD Consensus)

USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

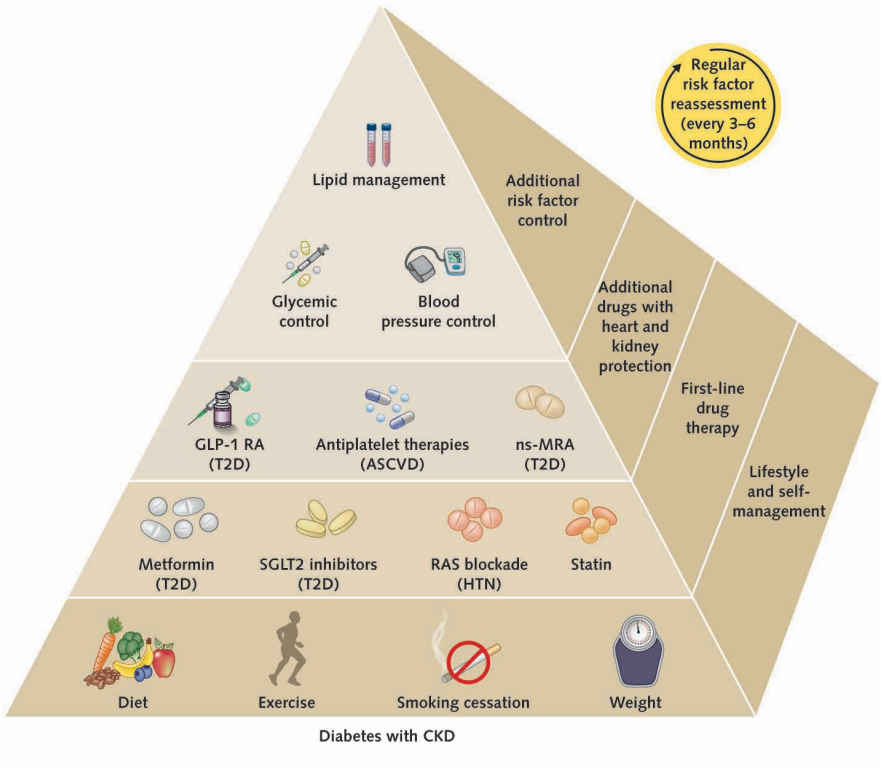
2022 ADA-EASD Consensus



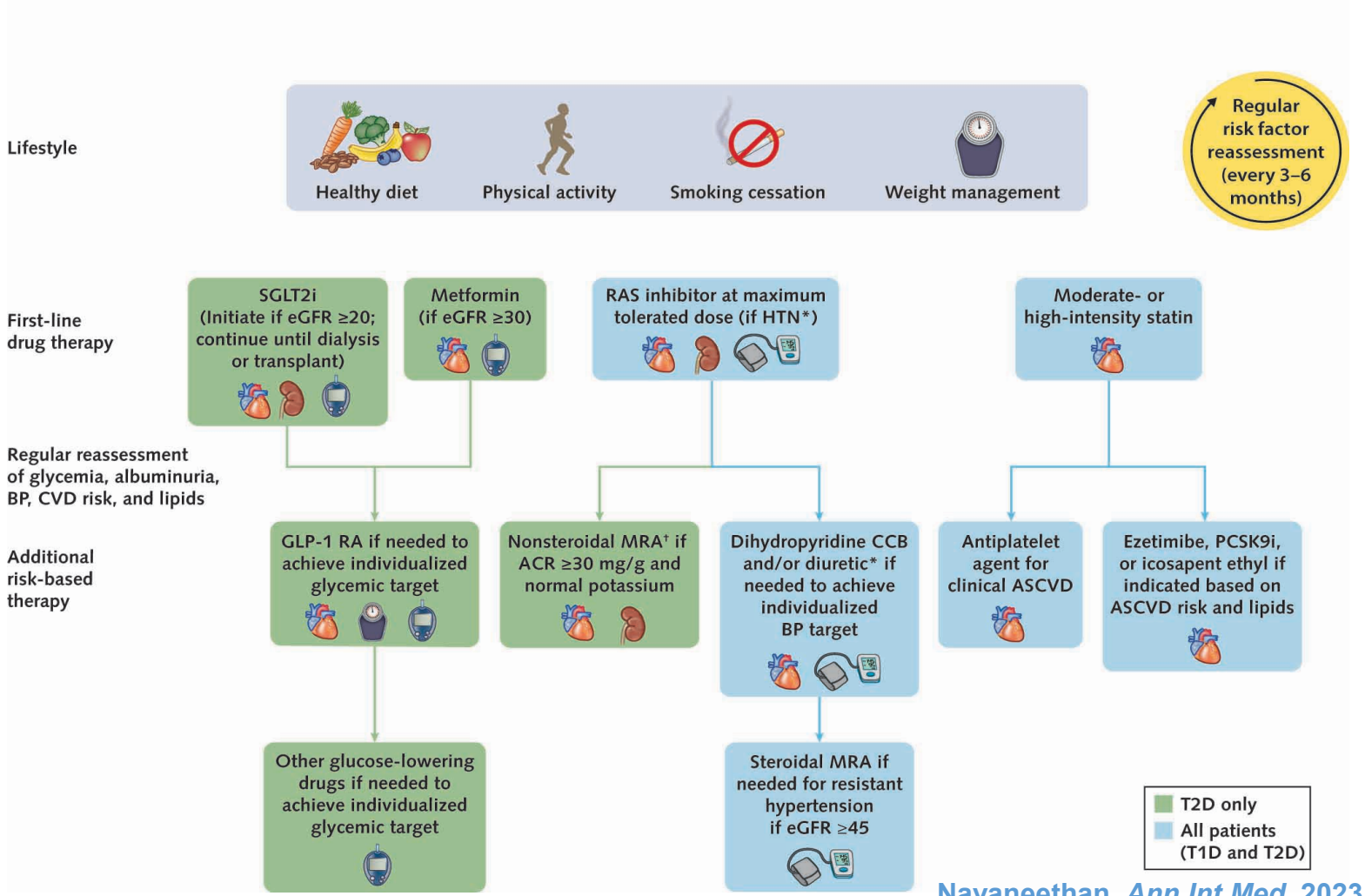
* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin;† A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF, and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.

Davies, *Diabetes Care*, 2022 (2022 ADA-EASD Consensus)

KDIGO 2022 Clinical Practice Guidelines – Diabetes Management in CKD



Navaneethan, *Ann Int Med*, 2023

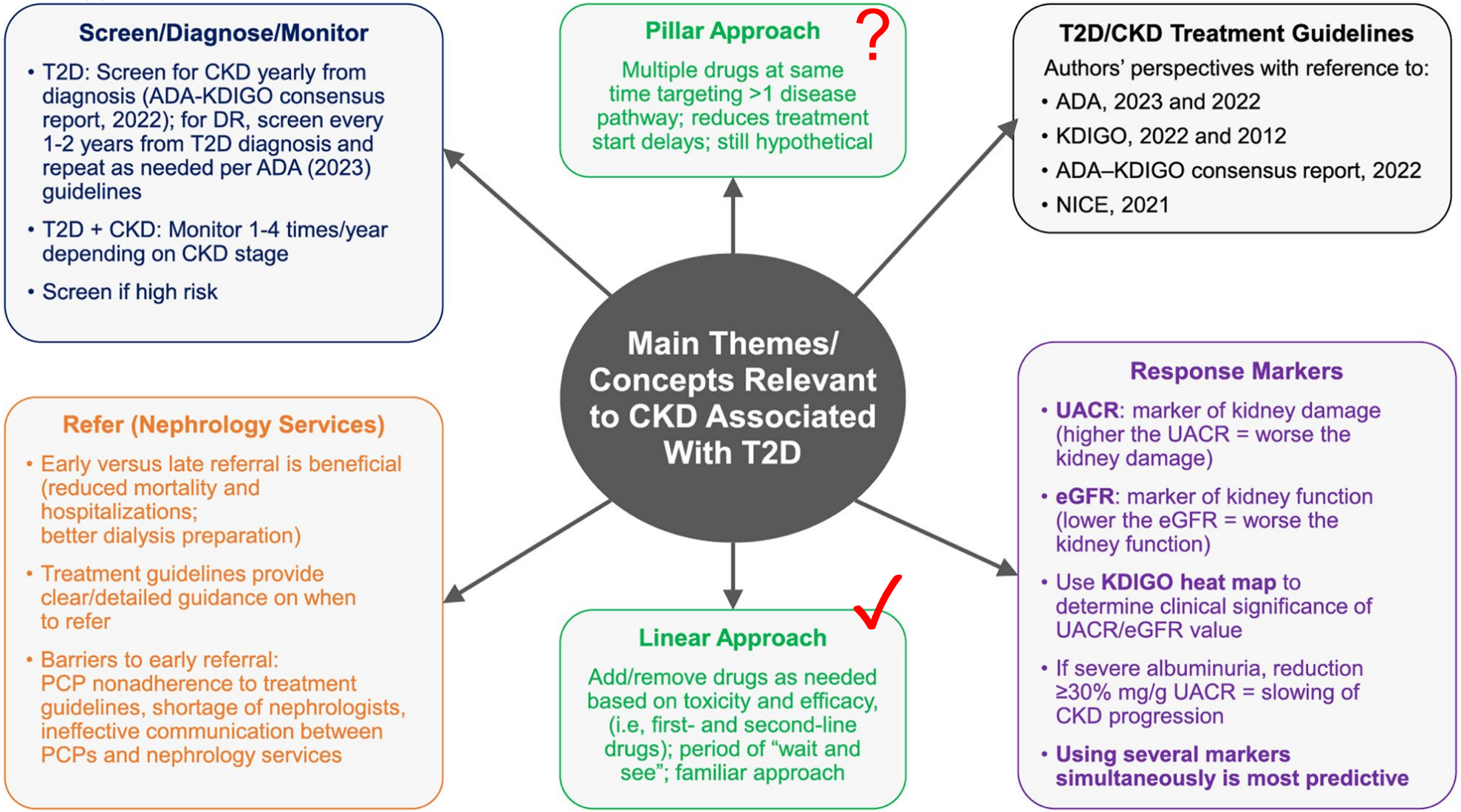


Navaneethan, *Ann Int Med*, 2023

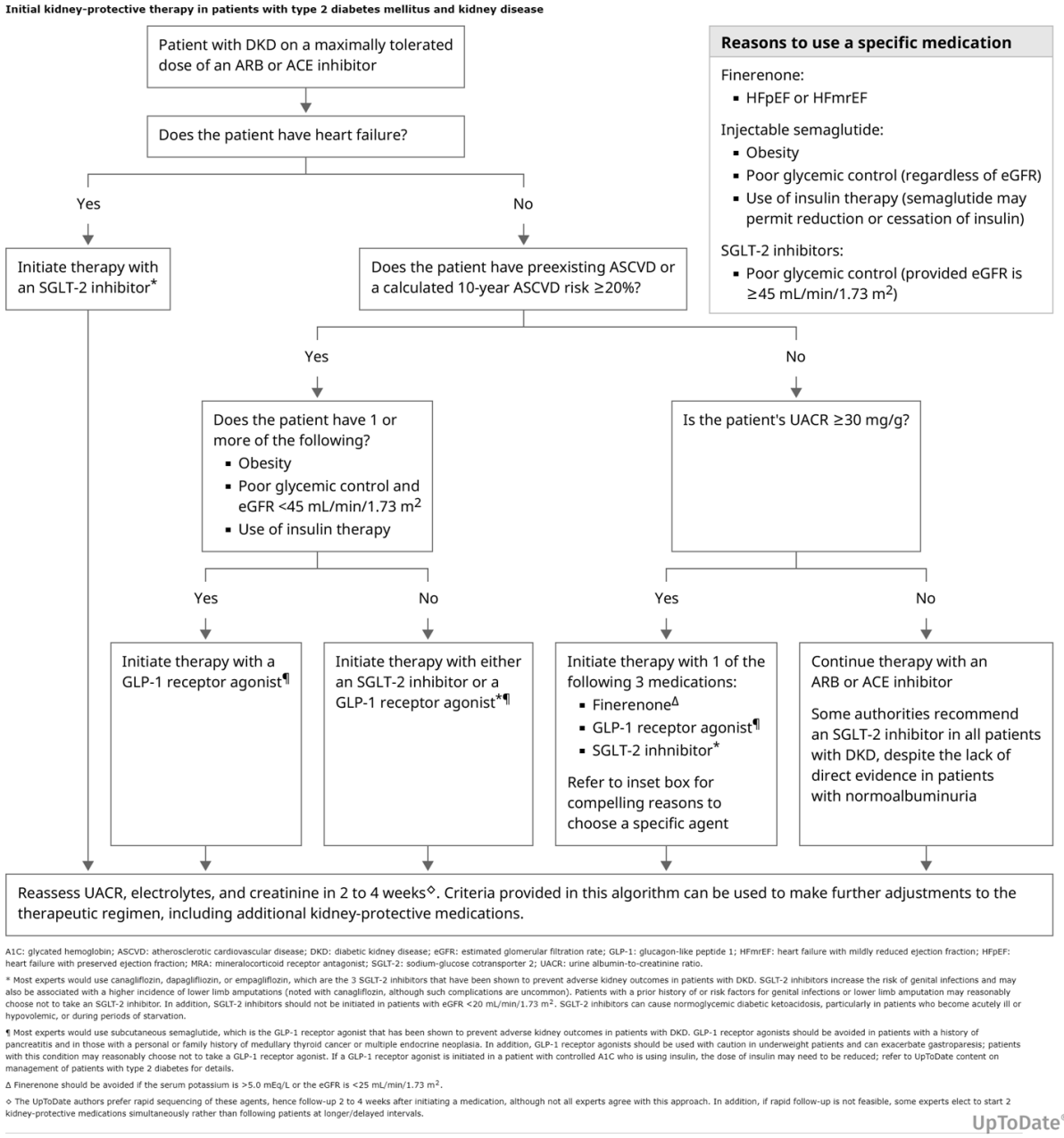
American Diabetes Association®

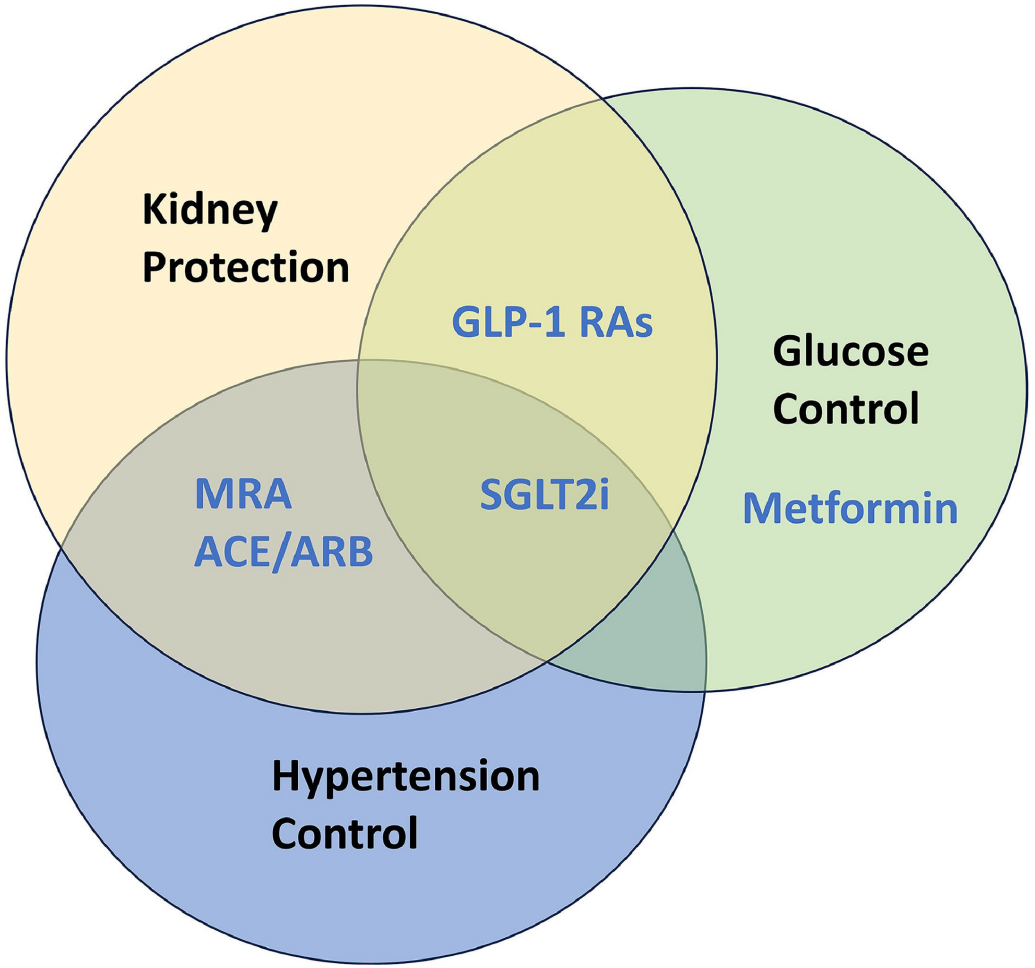
From: **Perspectives on Chronic Kidney Disease With Type 2 Diabetes and Risk Management: Practical Viewpoints and a Paradigm Shift Using a Pillar Approach**

Clin Diabetes. 2023;41(4):553-566. doi:10.2337/cd22-0110



A General Rx Approach





Gaddy, *Disease-a-Month*, 2025

Take Home Points

- Not every subject with DM gets DKD, but albuminuria largely identifies & prognosticates those that do. – *Screen!*
- DKD is a relatively late systemic complication of systemic disease. – *Look for other end-organ complications of DM!*
- Higher albuminuria levels are associated with faster eGFR decline & worse CV outcomes!
- DKD is typically diagnosed clinically – *Refer subjects with atypical clincal features to Nephrology for evaluation & possible biopsy!*
- BP & Glc control remain mainstays of management!
- Renoprotective interventions offer the opportunity to alter the course of disease!
  - ACEi/ARB
  - + SGLT2i
  - + GLP1R Agonists
  - + Nonsteroidal MRA
- Dietary protein restriction may offer additional benefits.
- Consider interactive comorbidities when managing patients with DKD (e.g. HTN & ApoL1 risk allele status).

KIDNEY FAILURE RISK EQUATION (KFRE)

https://kidneyfailurerisk.com/

ONLINE FIRST

A Predictive Model for Progression of Chronic Kidney Disease to Kidney Failure

Tangri, *JAMA*, 2011

Original Investigation

Multinational Assessment of Accuracy of Equations for Predicting Risk of Kidney Failure
A Meta-analysis

Tangri, *JAMA*, 2016