LOUISIANA DEPARTMENT OF HEALTH

Diabetes-Related Kidney Disease

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Dr. Robey is Associate Chief of Staff for Research at the Southeast Louisiana Veterans Health Care System (SLVHCS) and is Professor of Medicine at both Tulane University and LSU Health New Orleans. In addition to his administrative responsibilities overseeing the research operations at SLVHCS, he is an active practicing Nephrologist and participates in the full spectrum of undergraduate and graduate medical education activities. He is board-certified in both Internal Medicine and Nephrology and is a certified Specialist in Clinical Hypertension. He also holds a number of national leadership positions and is both current New Orleans Regional Councilor for the Louisiana Chapter of the American College of Physicians and President of the Medical Advisory Board of the National Kidney Foundation of Louisiana. Prior to his relocation to Louisiana, Dr. Robey was Associate Chief of Staff for Research and Founding Chief of the Section of Nephrology and Hypertension at the White River Junction VA Medical Center and a member of the faculty of Medicine, of Physiology and Biophysics, and of Medical Education at the Geisel School of Medicine at Dartmouth. At Geisel, he was heavily involved in curricular redesign and co-designed & co-directed their new preclinical Renal Medicine curriculum. Previously, he was on the faculty of the University of Illinois at Chicago College of Medicine.

Disclosure

In the past 24 months, I have NOT had any financial relationships with any ineligible companies.

Disclaimer

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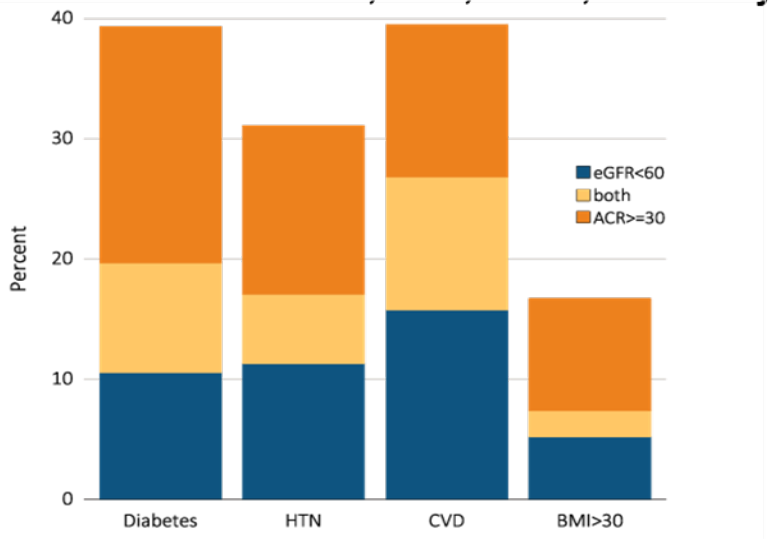
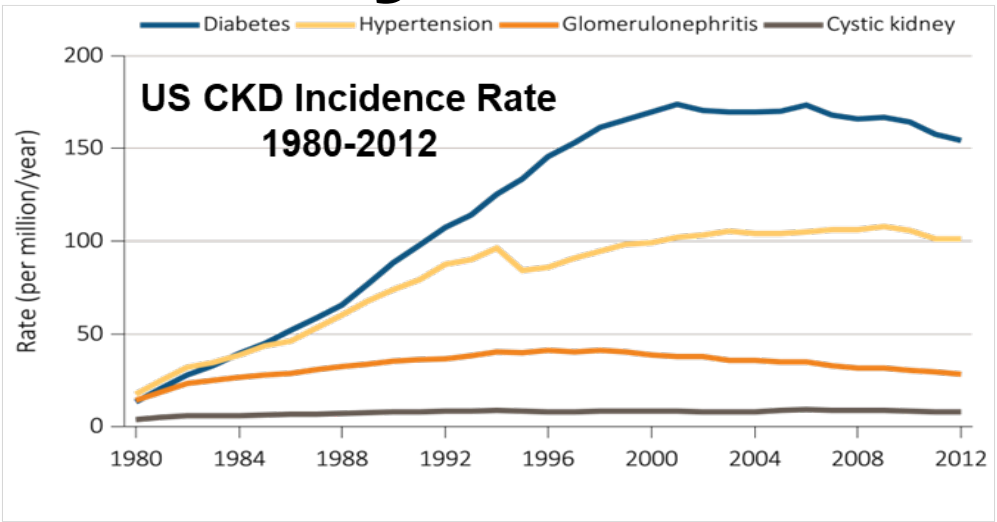
Clinical Features & Natural History

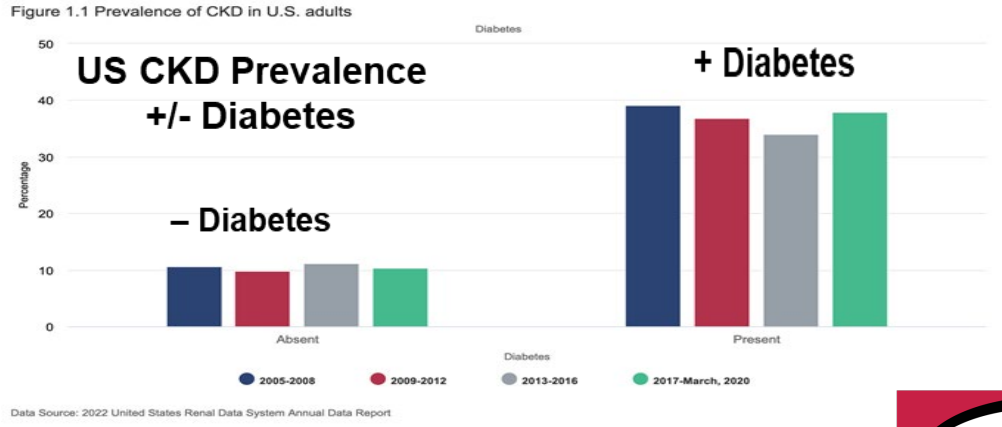
Diabetes-Associated Kidney Disease

- **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



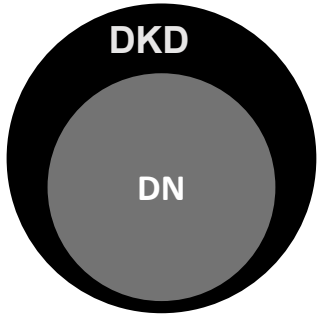




Diabetes-Associated Kidney Disease

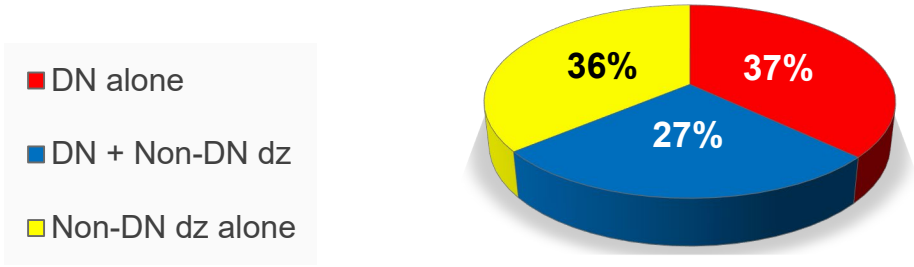
Terminology

- **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



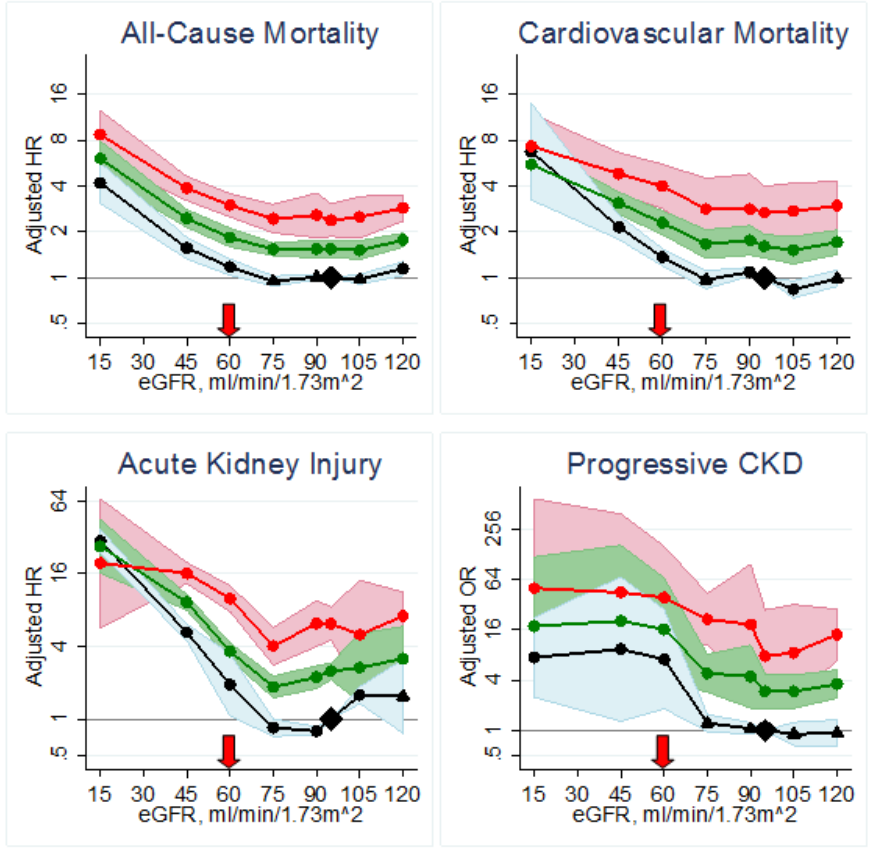
Data from Sharma, *CJASN*, 2013

Duration of DM – best predictor of DN alone.

General Albuminuria-Associated Risks

- **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***

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.

Prognosis of CKD by GFR and Albuminuria Categories

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

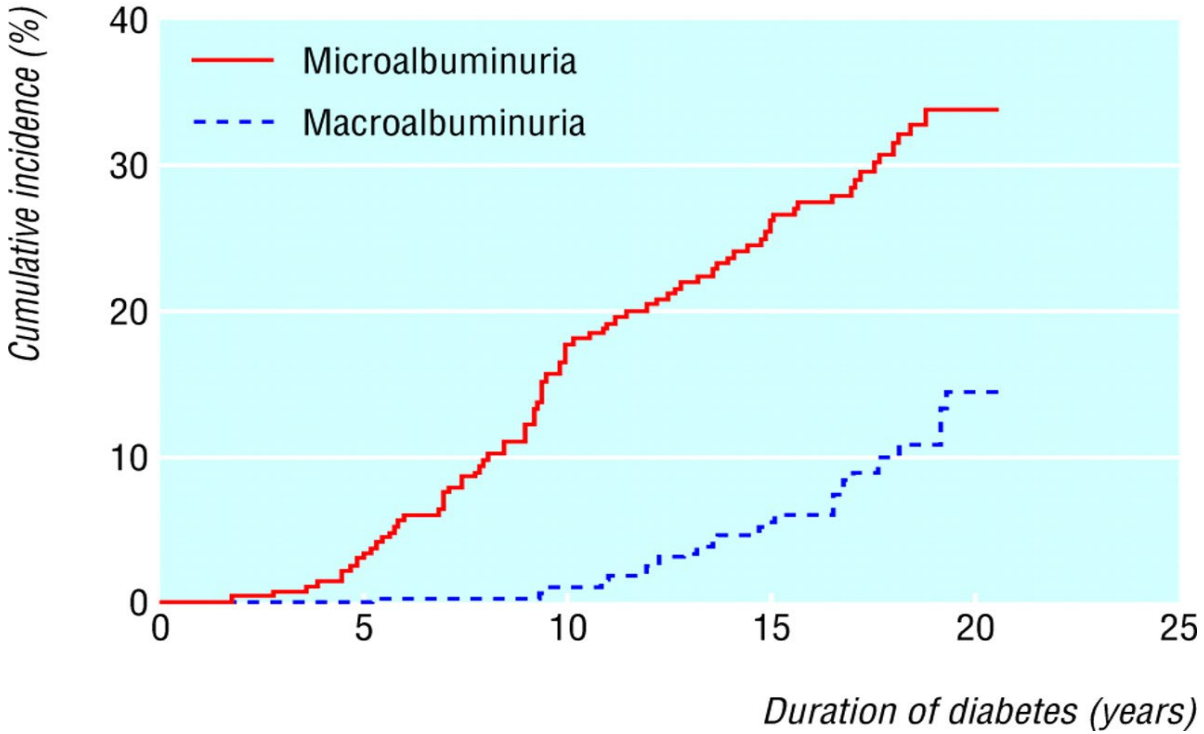
GFR categories (ml/min/1.73m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly 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.

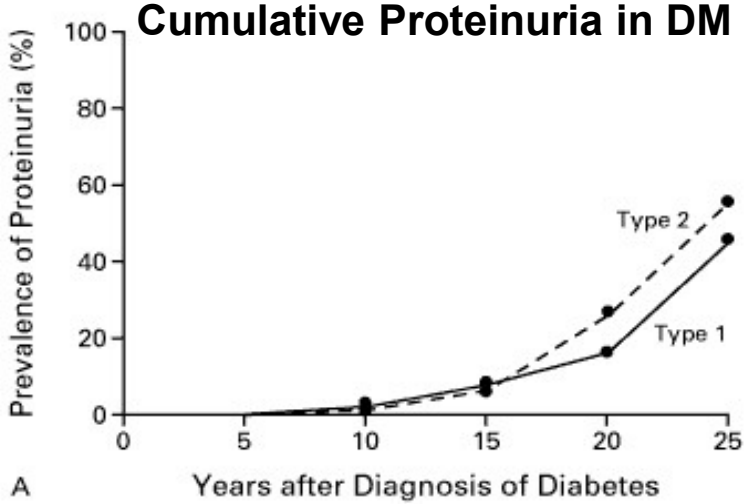
Natural History – Proteinuria & CKD in DKD

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

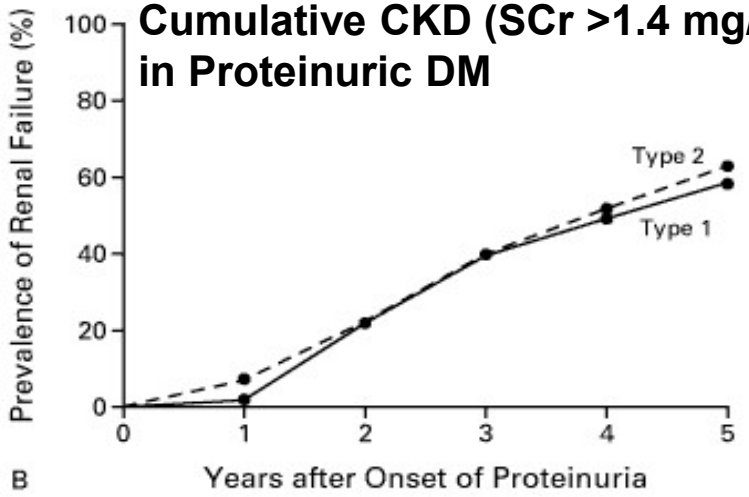


Hovind, *BMJ,* 2004

Cumulative Proteinuria in DM

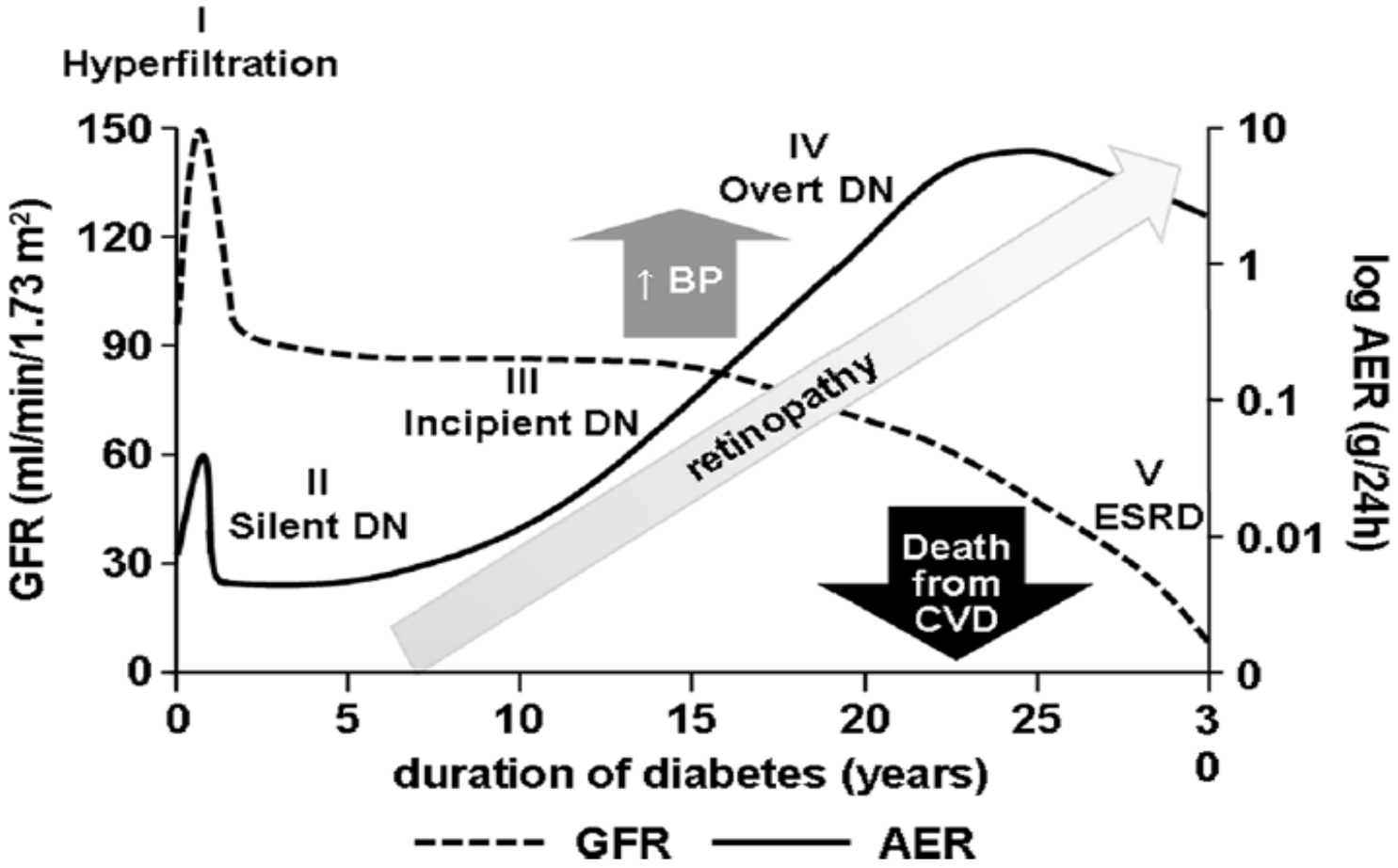


Cumulative CKD (SCr >1.4 mg/dL) in Proteinuric DM

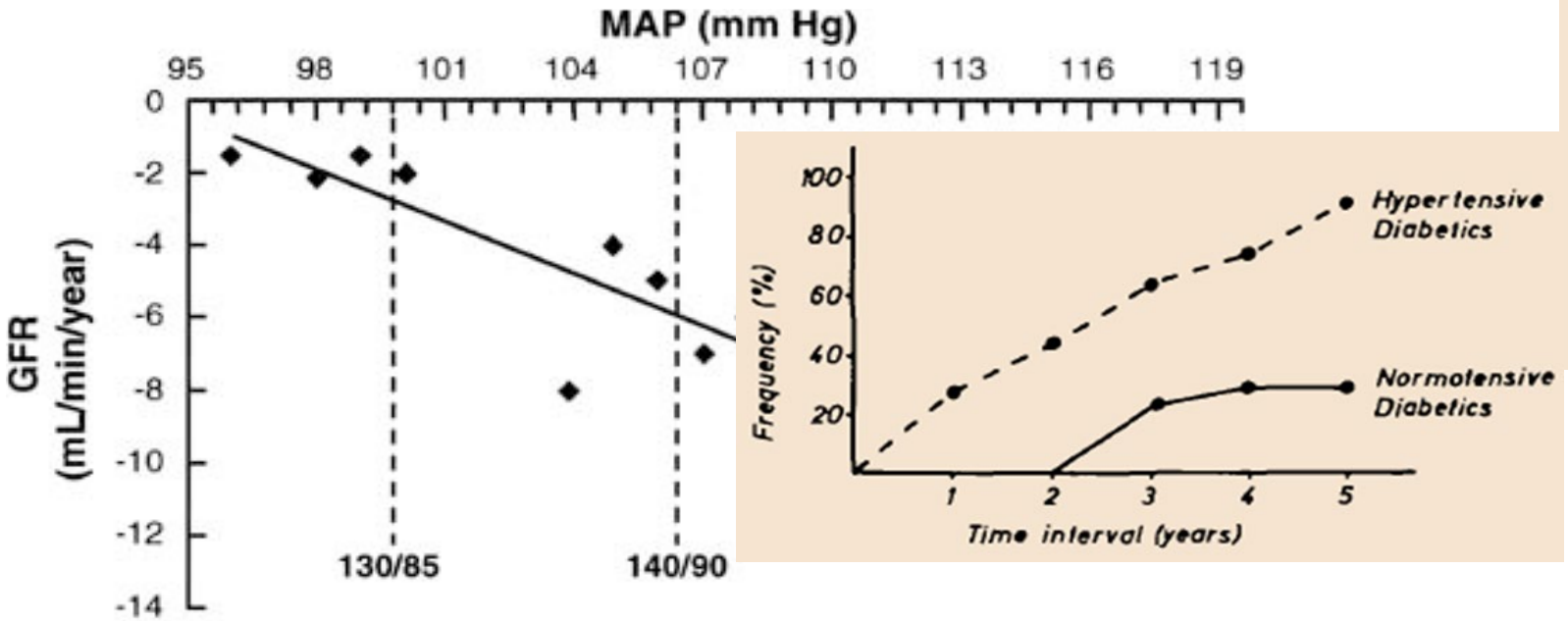


Ritz, *NEJM*, 1999

Natural History of Diabetic Nephropathy – Classic Clinical Stages



BP & CKD Onset/Progression

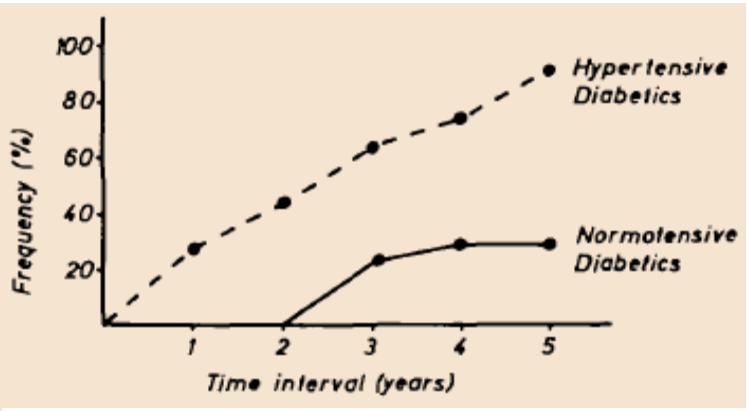


Summary of studies on nephropathy progression used in figure

- 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*

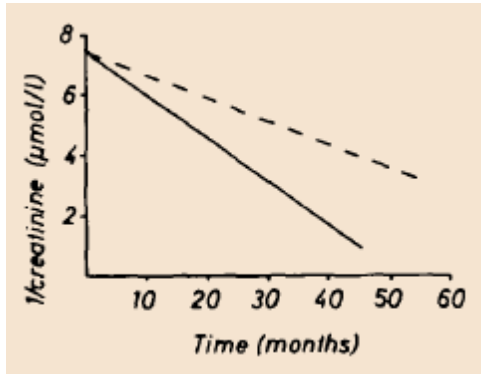
Bakris, *AJKD*, 2000

CKD in Proteinuric T1DM



Hasslacher, *Hypertension*, 1985

Renal Functional Decline in Hypertensive DM



Hasslacher, *Hypertension*, 1985

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

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]

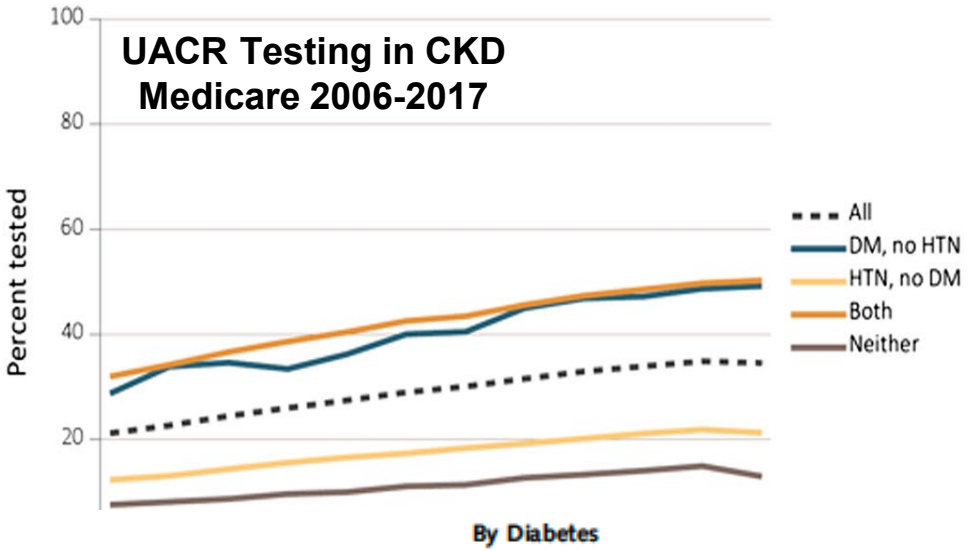
Tuttle, *AJKD*, 2014

Screening & Management

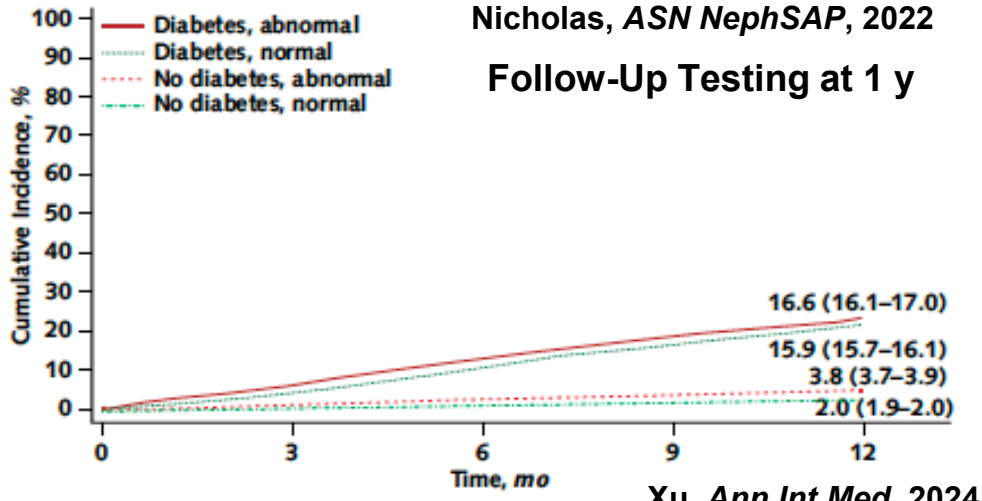
DKD Screening

- 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

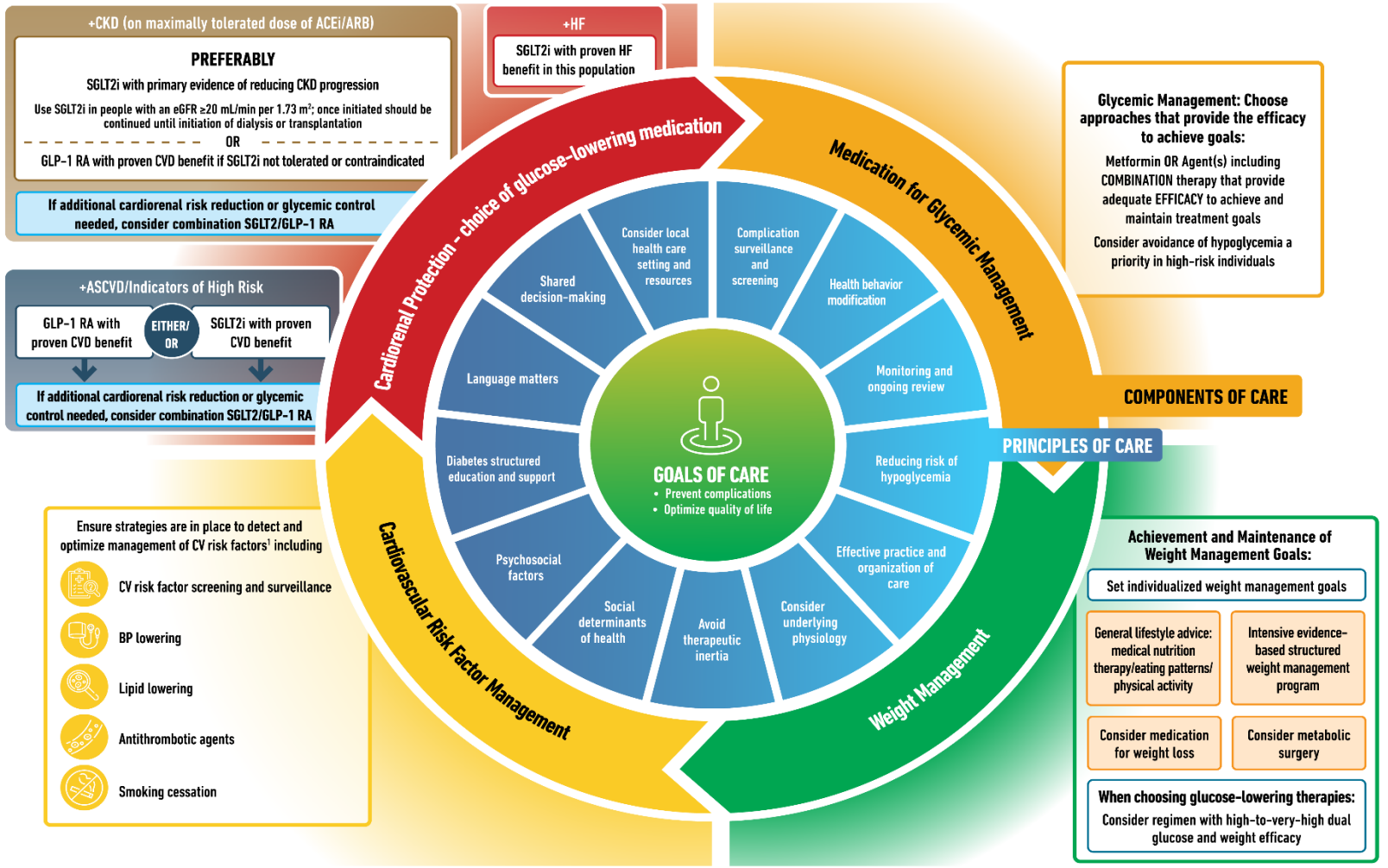


Nicholas, *ASN NephSAP*, 2022



Xu, *Ann Int Med*, 2024

HOLISTIC PERSON-CENTERED APPROACH TO T2DM MANAGEMENT

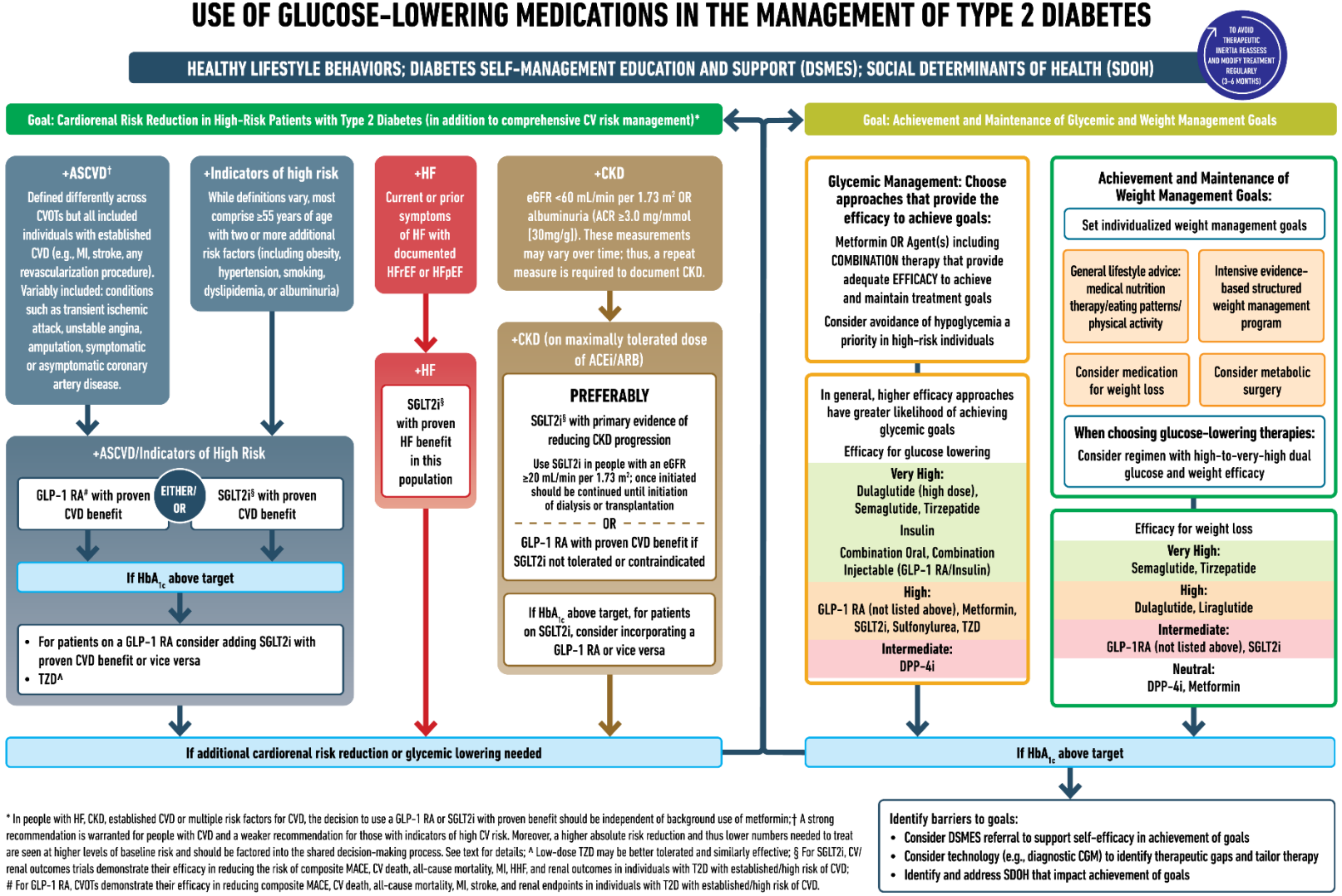


2022 ADA-EASD Consensus

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

2022 ADA-EASD Consensus

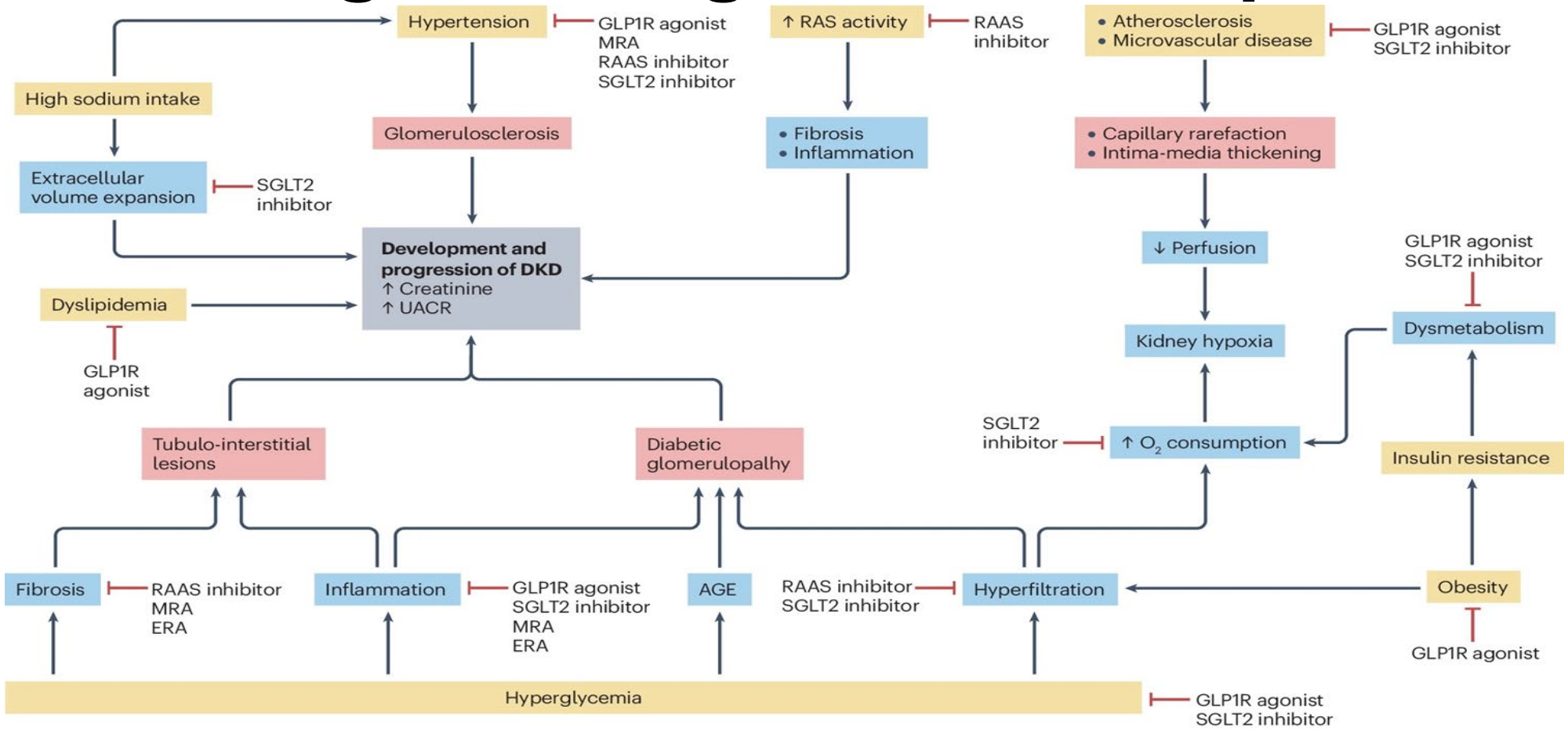
USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES



* 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)

DKD Pathogenic Targets for Renoprotection



Van Raalte, *Nat Rev Nephrol*, 2024

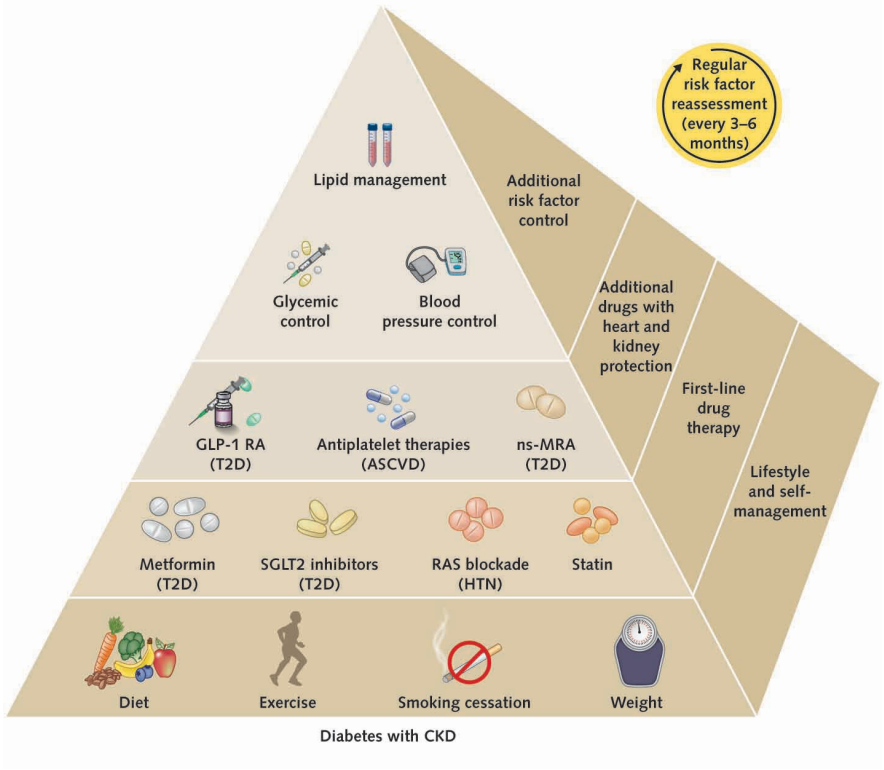
Table 1 | Large cardiovascular outcome trials of kidney-protective therapies

Study (year)	Intervention	Population (*n*)	Primary outcome	Result (HR [95% CI])
Renin–angiotensin–aldosterone system inhibitors				
Captopril (1993)	Captopril (ACE inhibitor)	Insulin-dependent diabetes, DKD (409)	Doubling of baseline serum creatinine to >177 μmol/l	0.48 [0.16–0.69]
IDNT (2001)	Irbesartan (ARB)	T2DM, DKD (1,715)	Composite of doubling of baseline serum creatinine, onset of kidney failure and death from any cause	0.80 [0.66–0.97] versus placebo; 0.77 [0.63–0.93] versus amlodipine
RENAAL (2001)	Losartan (ARB)	T2DM, DKD (1,513)	Composite of doubling of baseline serum creatinine, onset of kidney failure and death from any cause	0.84 [0.72–0.98]
Sodium glucose cotransporter-2 inhibitors				
CREDENCE (2019)	Canagliflozin	T2DM, DKD (4,401)	Composite of doubling of baseline serum creatinine, onset of kidney failure and death from renal or cardiovascular disease	0.70 [0.59–0.82]
DAPA-CKD (2020)	Dapagliflozin	T2DM, non-diabetic CKD (4,304)	Composite of 50% reduction in eGFR, onset of kidney failure and death from renal or cardiovascular causes	0.61 [0.51–0.72]
EMPA-KIDNEY (2023)	Empagliflozin	T2DM, non-diabetic CKD (6,609)	Composite of 40% reduction in eGFR, onset of kidney failure, death from renal causes and death from cardiovascular causes	0.72 [0.64–0.82]
Mineralocorticoid antagonist				
FIDELIO-DKD (2020)	Finerenone	T2DM, DKD (5,734)	Composite of 40% reduction in eGFR, onset of kidney failure and death from renal causes	0.82 [0.73–0.93]
Endothelin receptor antagonist				
SONAR (2019)	Atrasentan	T2DM, DKD (2,648)	40% reduction in eGFR or onset of kidney failure including renal death	0.65 [0.49–0.88]

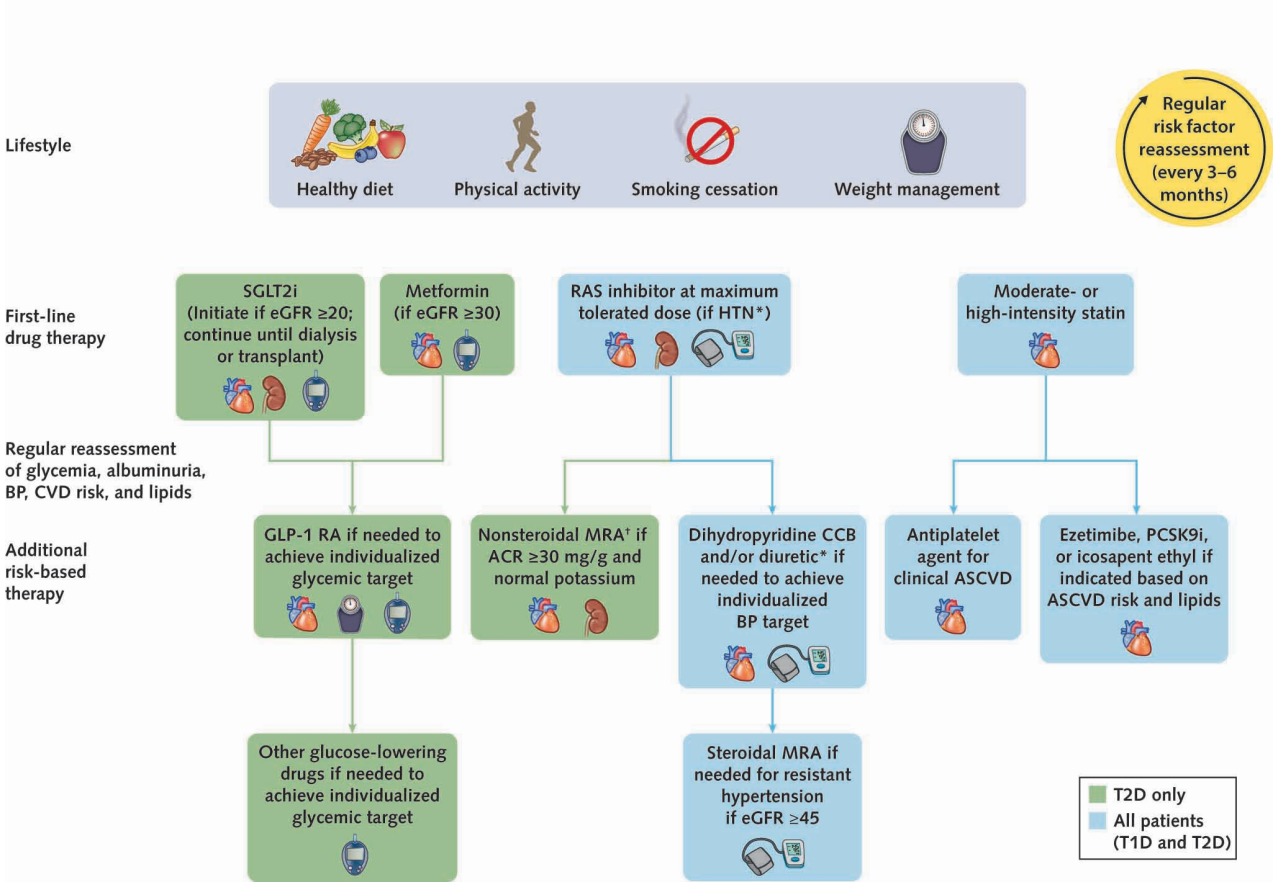
ACE, angiotensin converter enzyme; ARB, angiotensin receptor blocker; CI, confidence interval; CKD, chronic kidney disease; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; T2DM, type 2 diabetes mellitus.

Van Raalte, *Nat Rev Nephrol*, 2024

KDIGO 2022 Clinical Practice Guidelines – Diabetes Management in CKD



Navaneethan, *Ann Int Med*, 2023



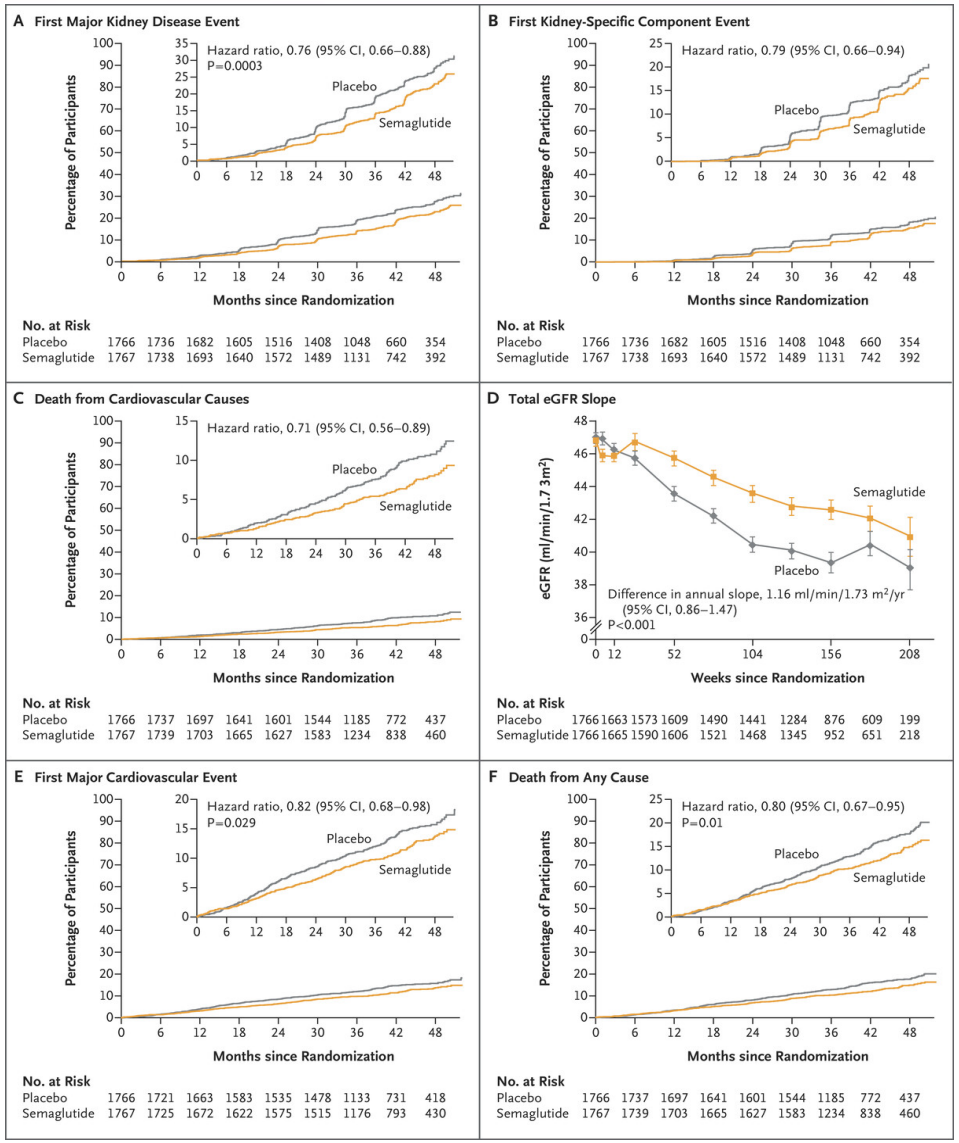
Navaneethan, *Ann Int Med*, 2023

FLOW Trial

Semaglutide in T2DM & CKD (2024)

↓ CV Mortality

↓ 1st Major CV Event



↓ 1st Kidney Events
- Major
- Kidney-Specific

↓ eGFR Decline Rate

↓ All Cause Mortality

Perkovic, *NEJM*, 2024

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!
- 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 if detected early!
  - ACEi/ARB
  - SGLT2i
  - GLP1R Agonists
  - MRA
- Dietary protein restriction (0.8 g/kg/d) may offer additional benefits.
- Consider interactive comorbidities when managing patients with DKD (e.g. HTN & ApoL1 risk allele status).

Questions?

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