Diagnosing Diabetic Kidney Disease: Screening, methodology, and role of guidelines

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Disclosure Slide

Scientific Advisor: Johnson and Johnson, AstraZeneca, Merck, Bayer, Vifor, Boehringer-Ingelheim, NovoNordisk, Akebia

Grant Funding: NIDDK: R01 DK120886, U01 DK116095, R01 DK 132271, U01 DK106102, U01 DK129884

Overview

- Screening
- Methodology
- Guidelines

Perspective

- CKD affects 37 million American adults who experience high rates of cardiovascular events and are at risk of kidney failure.

- Mortality is under-recognized as a competing event versus end-stage kidney disease (ESKD).

- Recent evaluation of US population-level care for individuals with eGFR below 60 ml/min per 1.73 m2 reveals that
- Approximately 40% receive UACR testing
- Only 12% to 20% have evidence of a CKD diagnosis
- Less than 50% have controlled hypertension
- 40% have controlled diabetes
- 29% to 31% use statins to reduce cardiovascular events,6 less than 50% are treated with angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) drugs,6 and nephrology services are delivered to only approximately 50% of patients with CKD G4 and G5

USRDS 2021
CJASN 2019; 14: 1142
PLOS One 2014; 9:e110535

Primary Care Implementation of CKD Testing

- Routine primary care case finding for CKD with eGFR and UACR should focus on risk conditions:
  - Diabetes
  - Hypertension
  - Cardiovascular disease
  - Family history of kidney disease

Perspective

- Annual UACR testing is approximately 40% for diabetes and less than 10% for hypertension in national data sets from Medicare, commercial insurance, health systems, and clinical laboratories, supporting the need for interventions to improve targeted albuminuria testing
- There are some challenges for clinicians to order UACR
- Laboratories do not universally offer the test
- Reporting formats vary, introducing inconsistencies and complexity in the interpretation of the results.

Diabetic Care 2021;44:2000-2009
Diabetic Care 2021;44:2025-2032

- Clinicians are unlikely to order tests that they are not sure how to interpret, suggesting low rates of albuminuria testing may simply reflect an underappreciation in the utility of the results or challenges in the interpretation.

Kidney Int Reports 2020;5:392-395

Definitions of Proteinuria

Urine Collection Method	Normal	Microalbuminuria	Albuminuria or Clinical Proteinuria
Total protein			
24-Hour excretion (varies with method)	< 300 mg/d	NA	≥ 300 mg/d
Spot urine dipstick	< 30 mg/dL	NA	≥ 30 mg/dL
Spot urine protein-to-creatinine (varies with method)	< 200 mg/g	NA	≥ 200 mg/g
Albumin			
24-Hour excretion	< 30 mg/d	30–300 mg/d	> 300 mg/d
Spot urine albumin-specific dipstick	< 3 mg/dL	> 3 mg/dL	NA
Spot urine albumin-to-creatinine ratio	< 17 mg/g (men)	17–250 mg/g (men)	> 250 mg/g (men)
(varies by sex)	< 25 mg/g (women)	25–355 mg/g (women)	> 355 mg/g (women)

NA indicates not applicable.

* Sex-specific cutoff values are from a single study. Use of the same cutoff value for men and women leads to higher values of prevalence for women than men. Current recommendations from the American Diabetes Association define cutoff values for spot urine albumin-to-creatinine ratio for microalbuminuria and albuminuria as 30 and 300 mg/g, respectively, without regard to sex.

Primary Care CKD Detection

- Detection of CKD using CKD diagnosis codes remains low in primary care practice, although chart review or natural language processing analysis more accurately reflects clinician diagnosis.
- The ADD-CKD study of more than 9 thousand US patients with type 2 diabetes managed by 466 primary care clinicians revealed a CKD detection in only 12% of the population with laboratory evidence for the condition.
- Importantly, awareness or patient self-reported CKD was 81.1% with practitioner detection versus 2.6% in the absence of diagnosis.

Plos One 2014;26e110535

Clinical Evaluation of Patients at Increased Risk of CKD

- All patients
  - Blood pressure
  - Serum creatinine
  - RBC or WBC in urine samples
  - Protein in urine
  - Serum glucose and lipids
  - Serum electrolytes
- Selected patients, depending on risk factors
  - Ultrasound imaging (polycystic kidney, infection, obstruction of stones)
  - Urine Protein:Creatinine or albumin:creatinine ratio
  - Urinary microalbumin
  - Urinary concentration or dilution
  - Urinary acidification

Percentage of individuals in the various CKD (eGFR and albuminuria) risk categories (KDIGO 2012)

				Albuminuria categories		
				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
GFR categories (ml/min/1.73 m²)	G1	Normal to high	≥ 90	54.7	4.3	0.4
	G2	Mildly decreased	60-89	30.4	2.6	0.3
	G3a	Mildly to moderately decreased	45-59	3.9	0.9	0.2
	G3b	Moderately to severely decreased	30-44	1.0	0.5	0.2
	G4	Severely decreased	15-29	0.1	0.1	0.2
	G5	Kidney failure	< 15	<0.001	0.001	0.01

2016 Annual Data Report, Vol 1, CKD, Ch 1

Outcomes Associated with CKD

All-cause mortality

	ACR <10	ACR 10–29	ACR 30–299	ACR ⩾300
eGFR >105	1.1	1.5	2.2	5.0
eGFR 90–105	Ref	1.4	1.5	3.1
eGFR 75–90	1.0	1.3	1.7	2.3
eGFR 60–75	1.0	1.4	1.8	2.7
eGFR 45–60	1.3	1.7	2.2	3.6
eGFR 30–45	1.9	2.3	3.3	4.9
eGFR 15–30	5.3	3.6	4.7	6.6

Kidney failure (ESRD)

	ACR <10	ACR 10–29	ACR 30–299	ACR ⩾300
eGFR >105	Ref	Ref	7.8	18
eGFR 90–105	Ref	Ref	11	20
eGFR 75–90	Ref	Ref	3.8	48
eGFR 60–75	Ref	Ref	7.4	67
eGFR 45–60	5.2	22	40	147
eGFR 30–45	56	74	294	763
eGFR 15–30	433	1044	1056	2286

Acute kidney injury (AKI)

	ACR <10	ACR 10–29	ACR 30–299	ACR ⩾300
eGFR >105	Ref	Ref	2.7	8.4
eGFR 90–105	Ref	Ref	2.4	5.8
eGFR 75–90	Ref	Ref	2.5	4.1
eGFR 60–75	Ref	Ref	3.3	6.4
eGFR 45–60	2.2	4.9	6.4	5.9
eGFR 30–45	7.3	10	12	20
eGFR 15–30	17	17	21	29

Levey et al., Kidney Int 2011; 80: 17-28

SCREENING

*Estimate GFR
*Quantitate albuminuria/proteinuria
*Measure longitudinal changes over time

Decreased GFR has consistently been found to be an independent risk factor for CVD outcomes and all cause mortality!

The key understanding is that patients with CKD benefit as much as non-CKD patients with appropriate medications and therapies, if not more, because of their increased risk!

Diabetes Management in Chronic Kidney Disease: A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease Improving Global Outcomes (KDIGO)

DeBoer et al. Diabetes Care. 2022 Oct 3;dci220027. Online ahead of print.

CKD screening and diagnosis for people living with diabetes

Who and when to screen?

T1D Yearly starting 5 years after diagnosis

T2D Yearly starting at diagnosis

How to screen?

Spot urine ACR

and

eGFR

What to do with a positive result?

Repeat and confirm:

- Evaluate possible temporary or spurious causes
- Consider using cystatin C and creatinine to more precisely estimate GFR
- Only persistent abnormalities define CKD

Initiate evidence-based treatments

What defines CKD diagnosis?

Persistent urine ACR ≥30 mg/g

and/or

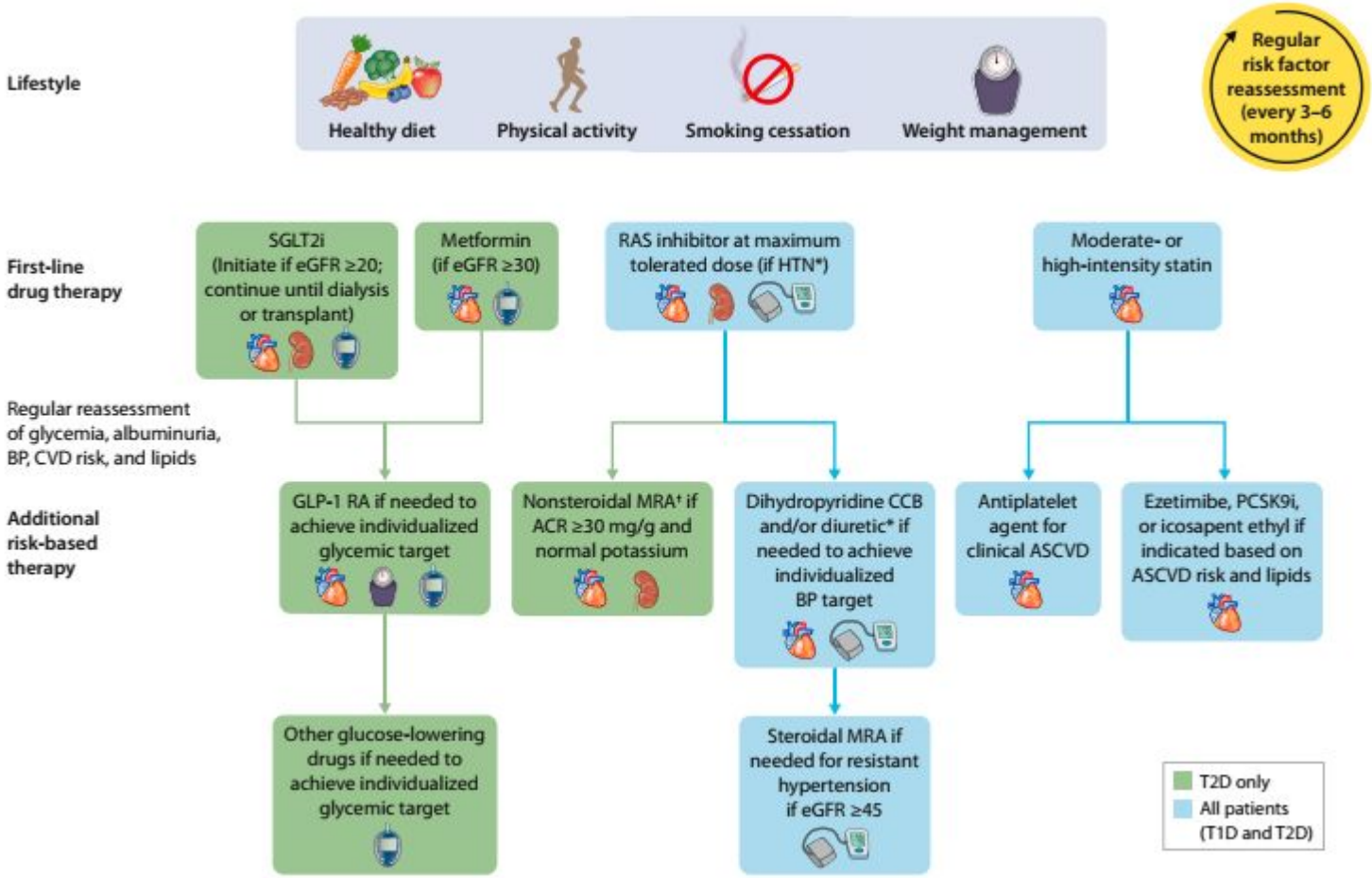
Persistent eGFR <60 mL/min/1.73 m^2

and/or

Other evidence of kidney damage

DeBoer et al. Diabetes Care. 2022 Oct 3;dci220027. Online ahead of print.

Holistic approach for improving outcomes in patients with diabetes and CKD. Icons presented indicate the following benefits: BP cuff, BP lowering; glucometer, glucose lowering; heart, cardioprotection; kidney, kidney protection; scale, weight management



DeBoer et al. Diabetes Care. 2022 Oct 3;dci220027. Online ahead of print.

AACE Recommendations for the Management of CKD In Diabetes

Recommendation		Level of evidence
R 6.3	Renin-angiotensin-aldosterone system blockade with an ARB or an ACE inhibitor is recommended for persons with albuminuria (T1D or T2D) to reduce the risk of DKD or CKD in DM progression.	Grade A; BEL 1
R 6.4	An SGLT2 inhibitor with proven benefit is recommended as foundational therapy for persons with T2D and CKD with eGFR ≥20 mL/min/1.73 m ^{2} to reduce progression of CKD and risk of CVD.	Grade A; BEL 1
R 6.5	A GLP-1 RA with proven benefit is recommended for persons with T2D and DKD or CKD in DM with eGFR ≥15 mL/min/1.73 m ^{2} for glycemic control and to reduce risk of ASCVD and progression of albuminuria.	Grade A; BEL 1
R 6.6	A non-steroidal MRA (finerenone) with proven kidney and CVD benefit is recommended for persons with T2D, an eGFR ≥25 mL/min/1.73 m ^{2}, normal serum potassium concentration, and albuminuria (ACR ≥30 mg/g) despite a maximum tolerated dose of a renin -angiotensin-system inhibitor.	Grade A; BEL 1

Grade A: Strong recommendation; BEL 1: Strong Evidence Level
AACE, American Association of Clinical Endocrinology; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BEL, Best Evidence Level; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GLP, glucagon-like peptide-1; T1D, type 1 diabetes; T2D, type 2 diabetes

1. Blonde L et al. *Endocr Pract* 2022;28:835-922. [published online ahead of print, September 27, 2022]. Doi: https://doi.org/10.1016/j.eprac.2022.08.002

RAASIs ARE RECOMMENDED BY MULTIPLE ORGANIZATIONS FOR THE PREVENTION OF HEART FAILURE AND KIDNEY FUNCTION DECLINE

Class IA recommendation

- ACEi is recommended, in addition to a BB, for symptomatic patients with HF[1–3]*
- ACEi/ARB is recommended for treatment of hypertension[4,5]† and ACEi/MRA for HF in patients with DM[4]
- ARB is recommended when ACEi is not tolerated[1,2]
- MRA is recommended for patients with HF*, who remain symptomatic despite treatment with an ACEi, and a BB[2]

Highest tolerated targeted doses recommended[1,2]

Slow the progression of kidney disease[4]

- Reduce proteinuria[6,7]
- Valuable in CKD and indicated in proteinuria[6–8]
- More effective at reducing kidney function decline than other BP-lowering drugs[6]

* With reduced ejection fraction; † Class A level of evidence.

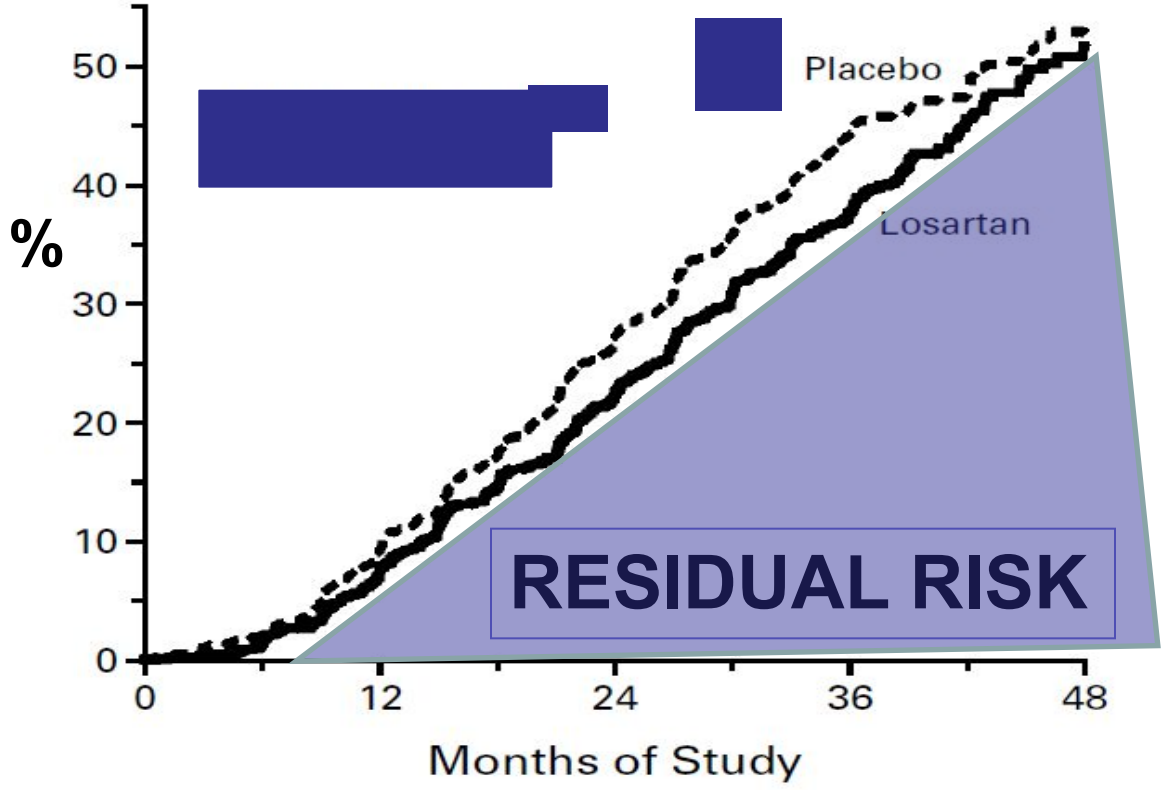
1. Yancy CW *et al. Circulation* 2017;136:e137–61; 2. Ponikowski P *et al. Eur J Heart Fail* 2016;18:891–975; 3. Lindenfeld J *et al. J Card Fail* 2010;16:475–539;
4. Cosentino F, *et al. Eur Heart J* 2020;41:255–323; 5. American Diabetes Association. *Diabetes Care* 2020;43:S111–34; 6. KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl* 2013;3:1–150; 7. National Kidney Foundation. K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease. 2004. Available at: kidneyfoundation.cachefly.net/professionals/KDOQI/guidelines_bp/index.htm (accessed July 2020);
8. National Institute for Health and Care Excellence. Chronic kidney disease in adults: assessment and management. 2014 (updated 2015). Available at: nice.org.uk/CG182 (accessed July 2020).

The Only Proven Treatment for Renoprotection in T2DM: RENAAL & IDNT

Doubling of serum creatinine, ESKD, or death

Risk reduction, 16%
P = 0.02

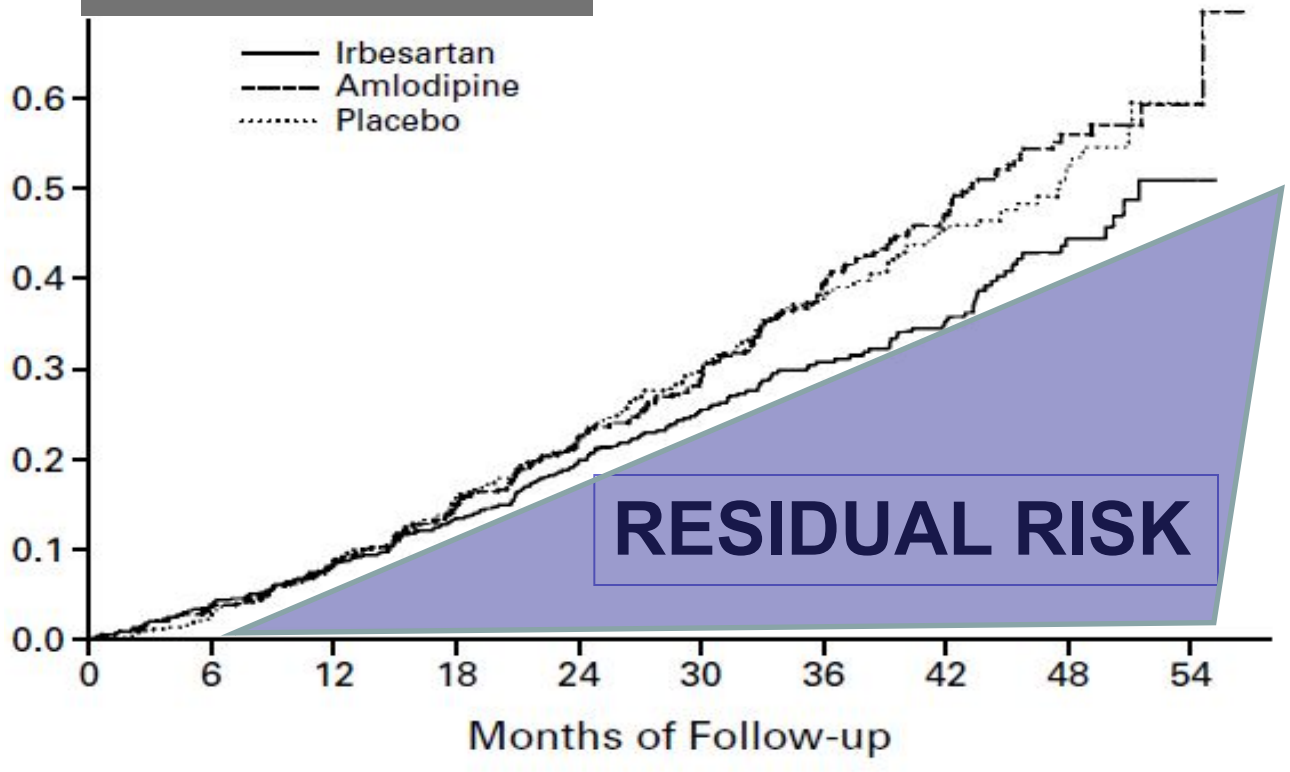
RENAAL



Brenner B, et al. *N Engl J Med*. 2001;345(12):861-869.

Risk reduction, 20%
P = 0.02

IDN T

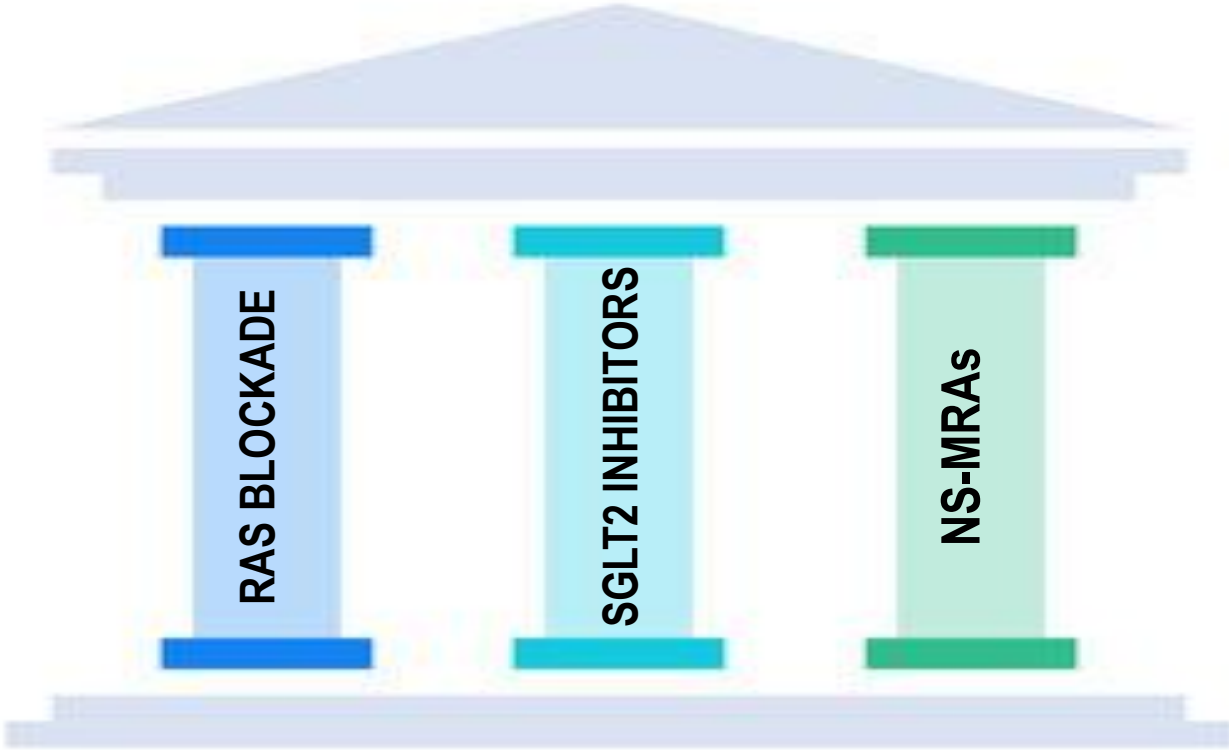


Lewis EJ, et al. *N Eng J Med*. 2001;345(12):851-860.

Perspective

- We still need intensification of traditional treatment goals
- Newer treatment approaches are a step in the right direction
- Has the “playing field” changed with the results of CREDENCE, DAPA-CKD, and FIDELIO-DKD studies?
- The “standard of care” for people at risk for CVD and CKD has now changed!
- We need to evaluate the benefit: risk ratio for all therapies, both traditional and newer.

Pillars of Therapy to Reduce CardioRenal Risk



Slowing DKD Progression and Reduce CV Risk

Benefit supported by primary and secondary outcome data

	Progression of CKD	ASCVD	Heart failure	Glucose-lowering efficacy	Hypoglycemia risk	Weight effects	Cost
Metformin	Neutral	Potential benefit	Potential benefit	High	Low	Neutral	Low
SGLT2 inhibitors	Benefit[a]	Benefit[c]	Benefit	Intermediate	Low	Loss	High
GLP-1 receptor agonists	Benefit[b]	Benefit[c]	Potential benefit	High	Low	Loss	High
DPP-4 inhibitors	Neutral	Neutral	Potential risk[c] (saxagliptin)	Intermediate	Low	Neutral	High
Insulin	Neutral	Neutral	Neutral	Highest	High	Gain	High (analogs) Low (human)
Sulfonylureas	Neutral	Neutral	Neutral	High	High	Gain	Low
Thiazolidinediones	Neutral	Potential benefit (pioglitazone)	Increased risk	High	Low	Gain	Low
α-Glucosidase inhibitors	Neutral	Neutral	Neutral	Intermediate	Low	Neutral	Low

Neutral

Potential benefit or intermediate glucose-lowering efficacy

Benefit (organ protection, high efficacy, low hypoglycemia risk, weight loss, or low cost)

Potential risk or high cost to patient

Increased risk for adverse effects

DeBoer et al. Diabetes Care. 2022 Oct 3;dci220027. Online ahead of print.

APPROACHES TO MANAGEMENT OF PATIENTS WITH DIABETES AND CKD

Recommendation 5.1.1: We recommend that a structured self-management educational program be implemented for care of people with diabetes and CKD (Figure 28) *(1C)*.

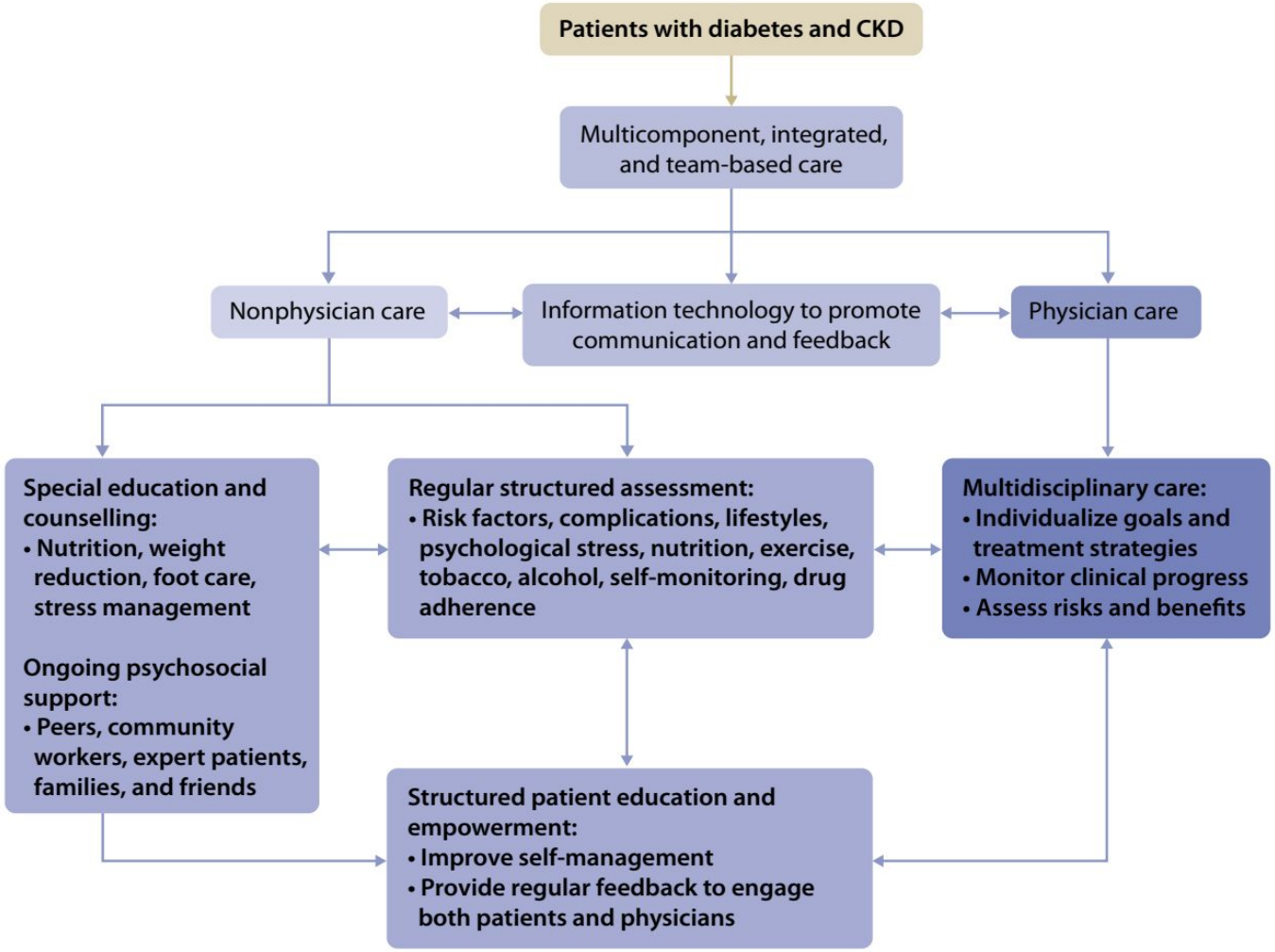
Practice Point 5.1.1: Health care systems should consider implementing a structured self-management program for patients with diabetes and CKD, taking into consideration local context, cultures, and availability of resources.

Key objectives are to:

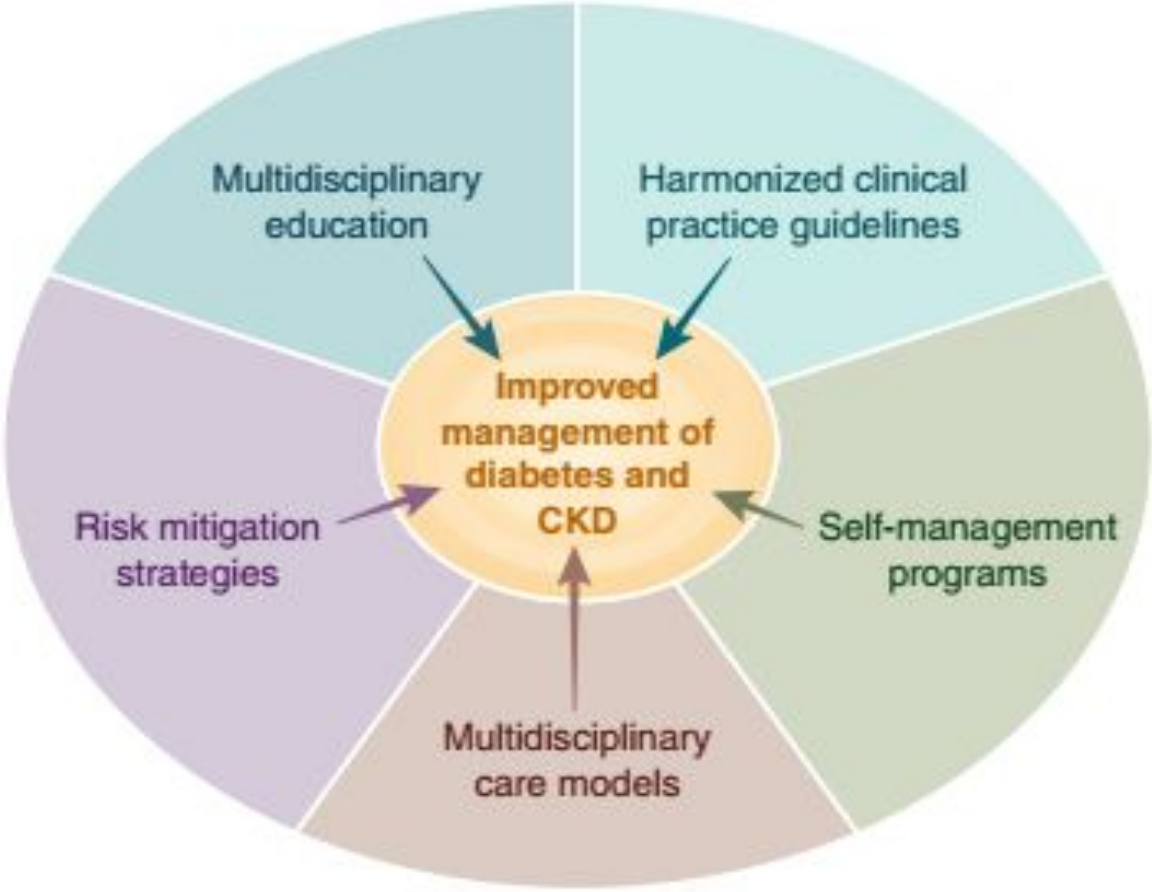
Improve diabetes-related knowledge, beliefs, and skills
Improve self-management and self-motivation
Encourage adoption and maintenance of healthy lifestyles
Improve vascular risk factors
Increase engagement with medication, glucose monitoring, and complication screening programs
Reduce risk to prevent (or better manage) diabetes-related complications
Improve emotional and mental well-being, treatment satisfaction, and quality of life

APPROACHES TO MANAGEMENT OF PATIENTS WITH DIABETES AND CKD

Recommendation 5.2.1: We suggest that policymakers and institutional decision-makers should implement team-based, integrated care focused on risk evaluation and patient empowerment to provide comprehensive care in patients with diabetes and CKD



Overcoming barriers to management of CKD in patients with diabetes



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Current Consideration for Treatment:

- ACEI or ARB (preferably in highest possible tolerated dose with potassium mitigation if needed)
- SGLT2i and nsMRA (preferably both)
- A good prescription plan!

We need to evaluate the benefit: risk ratio for all therapies, both traditional and non-traditional