
IN THE NAME OFGOD

Diabetic Nephropathy

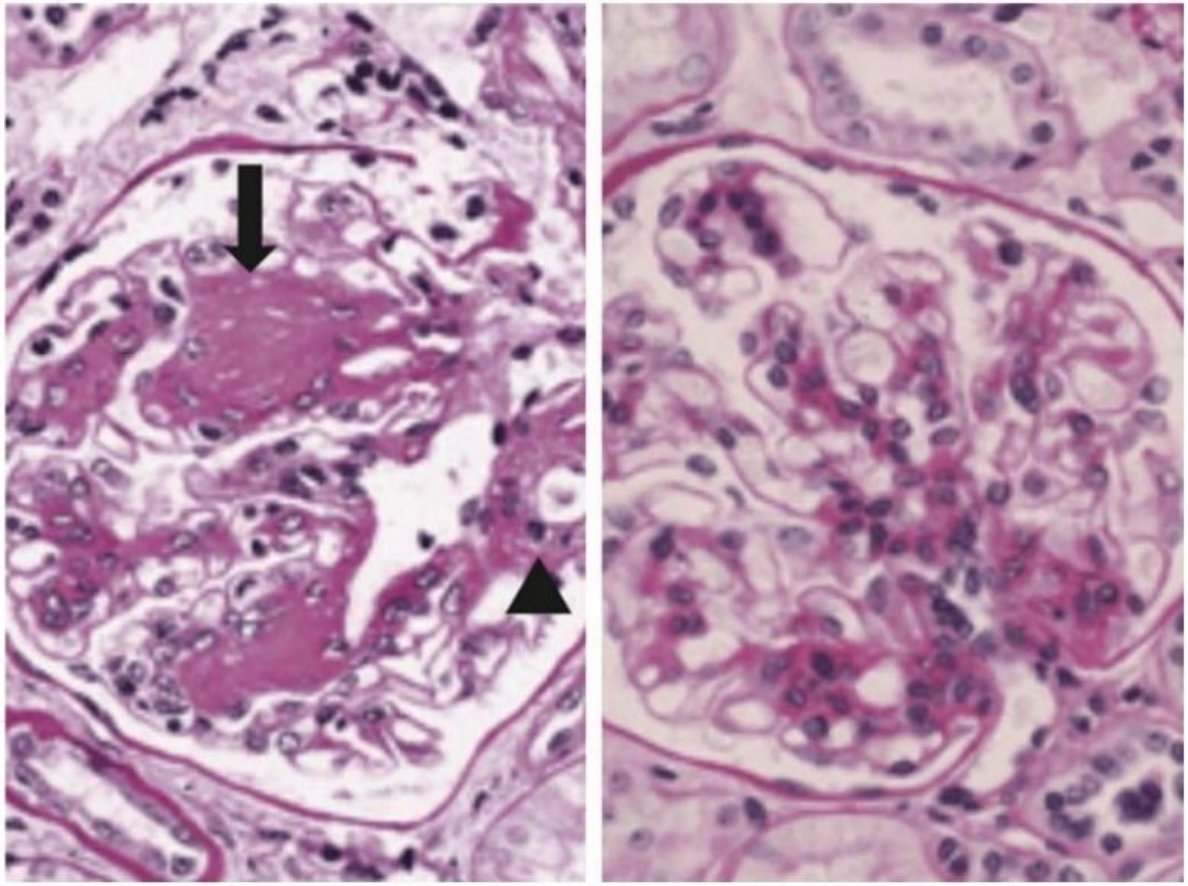


FIGURE 405-4 Diabetic glomerular changes in a patient with type 1 diabetes are reversed by 10 years of normoglycemia as a result of pancreas transplantation. Left panel shows diabetic glomerulosclerosis (*arrow*) and arteriolar hyalinosis (*arrowhead*) on kidney biopsy. Right panel shows a near-normal glomerulus in the same patient after 10 years of normoglycemia from pancreas transplantation. *(Reproduced with permission from P Fioretto et al: Reversal of lesions of diabetic nephropathy after pancreas transplantation. N Engl J Med 339:69, 1998.)*

Definition and criteria for chronic kidney disease

Definition:

Chronic kidney disease is defined based on the presence of either kidney damage or decreased kidney function for three or more months, irrespective of cause.

Criteria	Comment
Duration ≥3 months, based on documentation or inference	Duration is necessary to distinguish chronic from acute kidney diseases. ▪ Clinical evaluation can often suggest duration ▪ Documentation of duration is usually not available in epidemiologic studies
Glomerular filtration rate (GFR) <60 mL/min/1.73 m^2	GFR is the best overall index of kidney function in health and disease. ▪ The normal GFR in young adults is approximately 125 mL/min/1.73 m^2; GFR <15 mL/min/1.73 m^2 is defined as kidney failure ▪ Decreased GFR can be detected by current estimating equations for GFR based on serum creatinine (estimated GFR) but not by serum creatinine alone ▪ Decreased estimated GFR can be confirmed by measured GFR, measured creatinine clearance, or estimated GFR using cystatin C

Kidney damage, as defined by structural abnormalities or functional abnormalities other than decreased GFR	Pathologic abnormalities (examples). Cause is based on underlying illness and pathology. Markers of kidney damage may reflect pathology. ▪ Glomerular diseases (diabetes, autoimmune diseases, systemic infections, drugs, neoplasia) ▪ Vascular diseases (atherosclerosis, hypertension, ischemia, vasculitis, thrombotic microangiopathy) ▪ Tubulointerstitial diseases (urinary tract infections, stones, obstruction, drug toxicity) ▪ Cystic disease (polycystic kidney disease)
	History of kidney transplantation. In addition to pathologic abnormalities observed in native kidneys, common pathologic abnormalities include the following: ▪ Chronic allograft nephropathy (non-specific findings of tubular atrophy, interstitial fibrosis, vascular and glomerular sclerosis) ▪ Rejection ▪ Drug toxicity (calcineurin inhibitors) ▪ BK virus nephropathy ▪ Recurrent disease (glomerular disease, oxalosis, Fabry disease)
	Albuminuria as a marker of kidney damage (increased glomerular permeability, urine albumin-to-creatinine ratio [ACR] >30 mg/g).* ▪ The normal urine ACR in young adults is <10 mg/g. Urine ACR categories 10-29, 30-300 and >300 mg are termed "mildly increased,

Compared with levels for the general population, *DKD confers a threefold higher risk of all-cause mortality and a 16-year loss in life expectancy*. Reduced eGFR and albuminuria independently predict increased CV morbidity and mortality, and the presence of both exerts multiplicative effects on CV mortality risk.

Nothing beyond glycemic and blood pressure control was available to halt CKD progression until a trial of captopril in 1993 in people with type 1 diabetes . Results from this trial revealed a key role of the renin-angiotensin system (RAS) blockade for slowing DKD by approximately 5–7 mL/min/year.

However, substantial residual risk for DKD progression persisted, as *the rate of decline with RAS blockers was estimated to be between 4 and 6 mL/min/year and* the normal annual decline is approximately 0.7–0.9 mL/min/year.

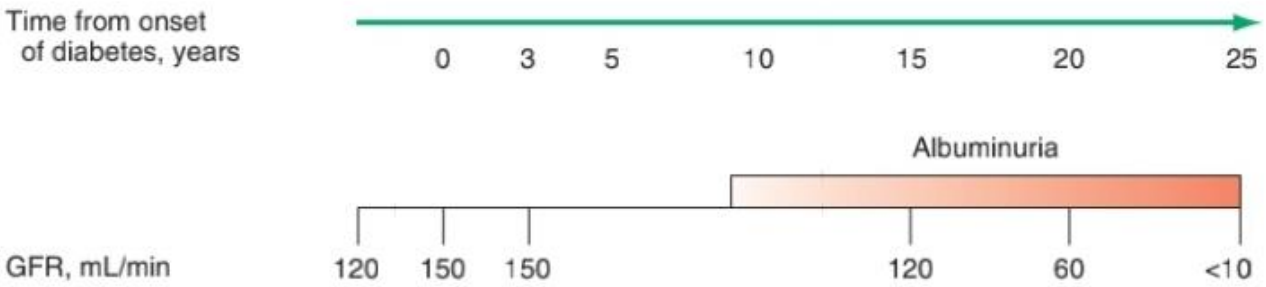
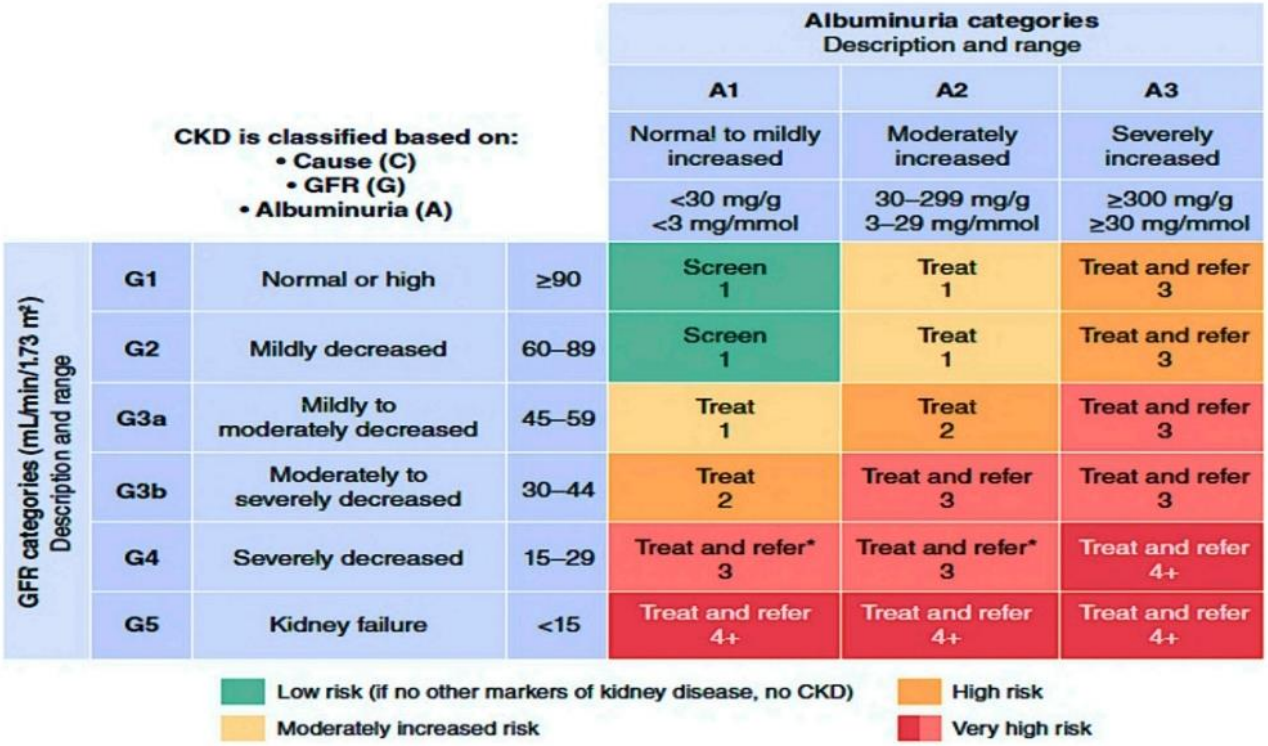


FIGURE 405-3 Time course of development of diabetic nephropathy. The relationship of time from onset of diabetes, albuminuria, and the glomerular filtration rate (GFR) are shown. This figure is typical for type 1 diabetes; individuals with type 2 diabetes may present with a lower GFR at the time of diagnosis.



CKD is classified based on: • Cause (C) • GFR (G) • Albuminuria (A)				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–299 mg/g 3–29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73 m²) Description and range	G1	Normal or high	≥90	Screen 1	Treat 1	Treat and refer 3
	G2	Mildly decreased	60–89	Screen 1	Treat 1	Treat and refer 3
	G3a	Mildly to moderately decreased	45–59	Treat 1	Treat 2	Treat and refer 3
	G3b	Moderately to severely decreased	30–44	Treat 2	Treat and refer 3	Treat and refer 3
	G4	Severely decreased	15–29	Treat and refer* 3	Treat and refer* 3	Treat and refer 4+
	G5	Kidney failure	<15	Treat and refer 4+	Treat and refer 4+	Treat and refer 4+

Low risk (if no other markers of kidney disease, no CKD)
Moderately increased risk
High risk
Very high risk

In 2014, the serendipitous discovery of sodium–glucose cotransporter 2 *(SGLT2) inhibitors provided hope that DKD progression could be further slowed*. This has clearly been shown in multiple outcomes trials. Around the same time as the discovery of SGLT2 inhibitors, trials were started on a novel class of agents, the *nonsteroidal mineralocorticoid receptor antagonists (NS-MRAs), specifically finerenone.*

Finerenone was distinctly different from spironolactone and also slowed DKD, independent of SGLT2 inhibitor use .

We now have two evidence based medications, which, when combined with RAS inhibition, are proven to *slow DKD progression to approximately 2.5–3 mL/min/year,* provided blood pressure and glucose levels are at guideline goals.

The mechanisms underlying DKD can be broadly conceptualized as stemming from an interplay of three key processes, each with variable contributions depending on the genetic makeup of an individual, which accounts for heterogeneity in the *hemodynamic, metabolic, and inflammatory components* .

Hemodynamic effects are central to the maintenance of nephron homeostasis and center around the renin-angiotensin aldosterone system. The enzyme renin is key to the activation of the RAS. Produced by the juxtaglomerular cells of the nephron, renin is found in the area adjacent to the afferent arterioles. Angiotensin II, which is generated by activation of the RAS, binds avidly to two specific receptors, designated AT1 and AT2, that exert pleiotropic effects .

AT1 activation mediates increased efferent arteriolar resistance of the nephron, which increases intraglomerular pressure to maintain the renal filtration rate . AT2 receptor activation, in contrast, modulates renal vasodilating prostaglandin release, thereby exerting protective counterregulatory action on blood pressure regulation, which opposes AT1 receptor action .

High angiotensin II levels exert several nonhemodynamic effects that contribute to renal injury, including increased adrenal aldosterone secretion, induction of fibrogenic chemokine (monocyte chemoattractant protein-1 [MCP-1] and transforming growth factor-b [TGF-b]), and macrophage activation, which creates an inflammatory milieu.

Increases in intraglomerular pressure induced by RAS activation are among the early and well-characterized findings noted in up to 75% and 40% of individuals with type 1 and type 2 diabetes, respectively .Angiotensin II and endothelin contribute to the earliest changes in glomeruli exposed to hyperglycemia, which results in *a mesangial expansion .These changes, along with inflammation, contribute to glomerulosclerosis over time* .

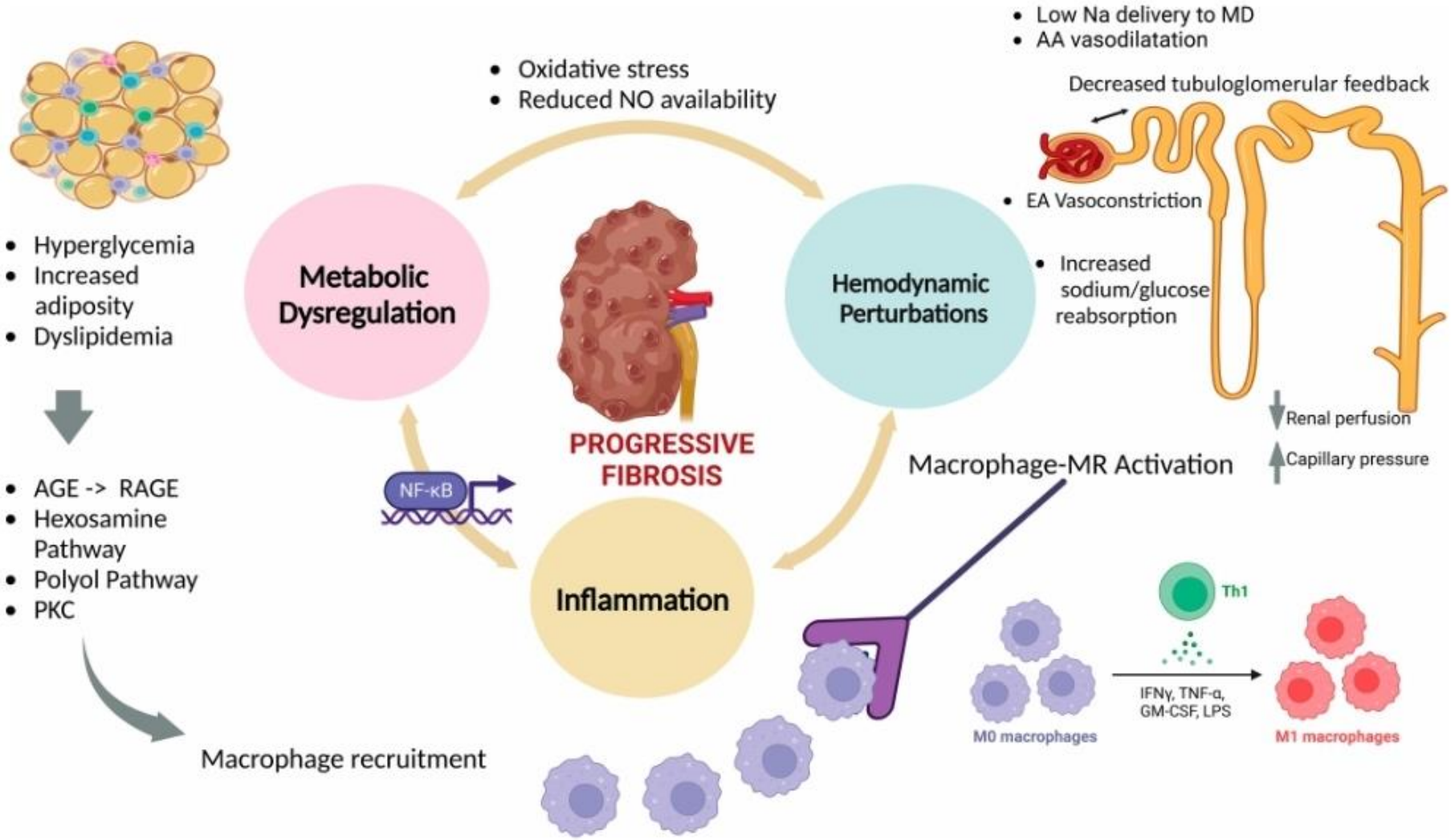


Figure 2—Metabolic, hemodynamic, and inflammatory pathways implicated in the underlying pathophysiology of DKD, underscoring the need for multitargeted therapies to halt disease progression. MR is a pervasive ligand-activated transcription factor that exerts injury beyond the kidney to endothelial cells, adipocytes, smooth muscle cells, and immune cells (55,136). Once released in local tissue, inflammatory cytokines exert pleiotropic effects, setting in motion inflammatory and profibrotic processes that affect adjacent compartments and contribute to increased adverse cross talk between glomeruli, which contributes further to increased scarring (137). AA, afferent arteriole; AGE, advanced glycation end products; EA, efferent arteriole; GM-CSF, granulocyte macrophage colony-stimulating factor; IFNγ, γ-interferon; LPS, lipopolysaccharide; MD, macula densa; NO, nitric oxide; NF-κB, nuclear factor κ light-chain enhancer of activated β-cell; RAGE, receptor-bound advanced glycation end products.

Changes in tubular function can trigger glomerular hemodynamic changes via impaired tubuloglomerular feedback .In diabetes, supraphysiologic levels of glucose delivered to the proximal tubule upregulate SGLT1 and SGLT2 to maximize the reabsorption of glucose and sodium .

Reduced sodium delivery to the distal nephron results in negative tubuloglomerular feedback. Studies of individuals with type 1 diabetes demonstrate that to increase glomerular perfusion, local angiotensin production is upregulated, which triggers afferent arteriole dilatation and efferent arteriole constriction. This explains, in part, the renoprotective role of SGLT2 inhibitors under conditions of normal kidney function.

By blocking glucose reabsorption at the proximal tubule and diverting it into the urine, tubuloglomerular balance is restored, with the net effect of lowering intraglomerular pressure and reducing hyperfiltration. Hyperglycemia, insulin resistance, and dyslipidemia commonly coexist, which sets in motion several dysregulated metabolic pathways inextricably related to oxidative stress and inflammatory processes, ultimately creating a vicious cycle where one process potentiates another .

Most notable are the polyol and protein kinase C (PKC) pathways, which augment oxidative stress and deplete endothelial nitric oxide synthase, respectively, leading to higher endothelin-1 and vascular endothelial growth factor levels. Endothelial instability and nuclear factor-kB (NF-kB)–mediated cytokines (tumor necrosis factor-a [TNF-a] and interleukin-6 [IL-6]) favor an inflammatory response. The hyperglycemic milieu also encourages the accumulation of advanced glycation end products (AGEs).

AGEs are a heterogeneous group of nonenzymatically glycated molecules. Upon engaging with their receptors (RAGEs), which are found throughout the kidney, they trigger cellular function perturbations, including NF-kB upregulation, which induces a cascade of proinflammatory cytokines (TNF-a and IL-6). AGEs reduce the bioavailability of endothelium-derived nitric oxide and increase reactive oxygen species production, which is linked to impaired vasodilatation in diabetes.

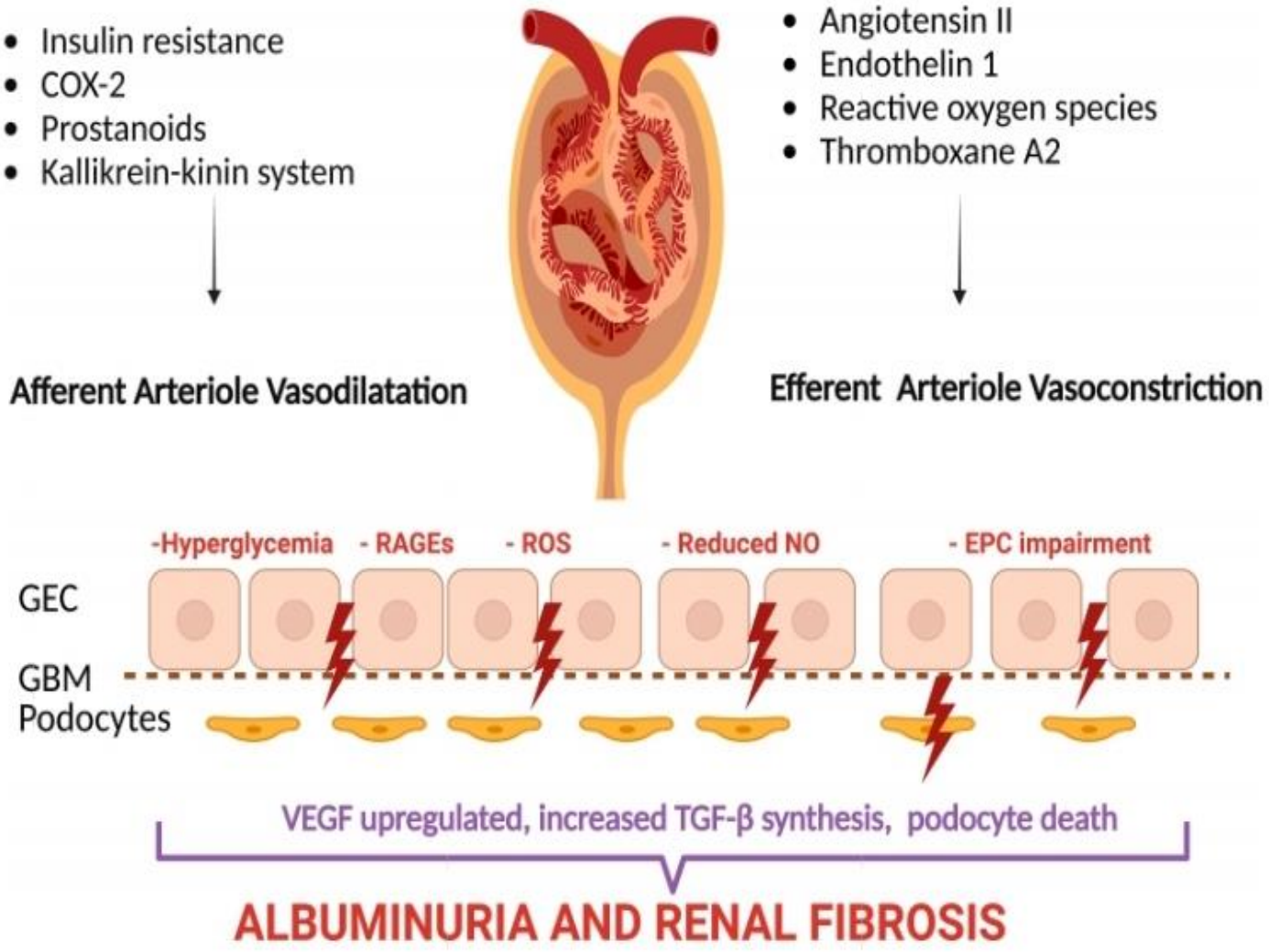


Figure 3—Local mechanisms underlying glomerular hypertension. Endothelin 1, reactive oxygen species, and thromboxane A2 increase efferent vessel tone, whereas insulin resistance upregulates cyclooxygenase 2 (COX-2), prostanoids, and the kallikrein-kinin system, resulting in afferent arteriole dilatation (138). RAS activation damages glomerular endothelial cells (GEC), which increases fenestrations and induces apoptosis. Hyperglycemia leads to advanced glycation end products (AGEs), which bind to their receptors (RAGEs), which decreases nitric oxide (NO) availability and stimulates transforming growth factor-β (TGF-β), a profibrotic factor. Diabetes further accelerates endothelial progenitor cell (EPC) aging, which reduces their reparative function. Vascular endothelial growth factor (VEGF) synthesis by podocytes is dysregulated. Podocyte injury leads to foot process effacement and podocyte loss, the unifying mechanism underlying albuminuria in diabetes (33–37).

MR activation occurs in the aldosterone-responsive distal nephron, causing sodium reabsorption and potassium excretion. Aldosterone secretion is stimulated by RAS activation in response to decreased circulating plasma volume or significant increases in serum potassium levels. While critical for survival in states of low sodium intake, it becomes pathologic in the setting of persistently high sodium intake ,as exemplified by Western and many Asian diets.

Inappropriate aldosterone signaling combined with high sodium intake results in hypertension, a direct contributor to glomerular injury and fibrosis. The MR possesses a binding affinity for cortisol and corticosterone similar to that of aldosterone. These cells typically coexpress 11Bdehydrogenase isoenzyme 2 (11B-HSD2), which neutralizes cortisol and thereby mitigates MR overactivation. Outside the distal nephron, MRs are expressed on other cell types, including podocytes, fibroblasts, vascular cells, and macrophages; these cells, however, do not uniformly coexpress the steroid-blunting effects of 11B-HSD2, which permits unbridled MR activation .

MR is upregulated in hyperglycemia, insulin resistance, dyslipidemia, and obesity. This results in increased gene transcription of profibrotic factors plasminogen activator inhibitor-1 (PAI-1) and TGF-b1, connective tissue growth factor, and extracellular matrix proteins, all of which contribute to progressive DKD .

Briefly*, macrophage infiltration has been identified as one of the hallmarks of DKD*, the burden of which is associated with worse disease . Hyperglycemia, endothelial cell dysfunction, angiotensin II, AGEs, and oxidized LDL recruit macrophages . Macrophage-MR activation polarizes *macrophage differentiation toward the M1 phenotype, which promotes inflammation via a cascade of injurious cytokines .*

In contrast, the NSMRAs in the phase 2 trials of the Mineralocorticoid Receptor Antagonist Tolerability Study-Diabetic Nephropathy (ARTS-DN) and ARTS-DN Japan demonstrate up to *38% albuminuria reduction with finerenone compared with placebo in patients with albuminuric DKD* .Other NS-MRAs, namely, finerenone, esaxerenone, and apararenone, also have demonstrated significant albuminuria reduction and a very low adverse effect profile in advanced DKD.

Albuminuria is an established continuous variable, where levels exceeding 30 mg/day predict adverse CV outcomes and those exceeding 300 mg/day are typically diagnostic of underlying kidney disease and are associated with accelerated decline in DKD .Many trials have established that a reduction in albuminuria is associated with slowed DKD progression and reduced CV event rates .

people at high risk for DKD progression, defined by eGFR< 60 and UACR> 300 mg/day. This does not imply that those with high albuminuria, formerly called microalbuminuria, do not derive benefit from treatment—in fact, they do, and the benefits are predominantly CV. However, the slowing of the DKD trajectory in these cohorts was detected in post hoc analyses

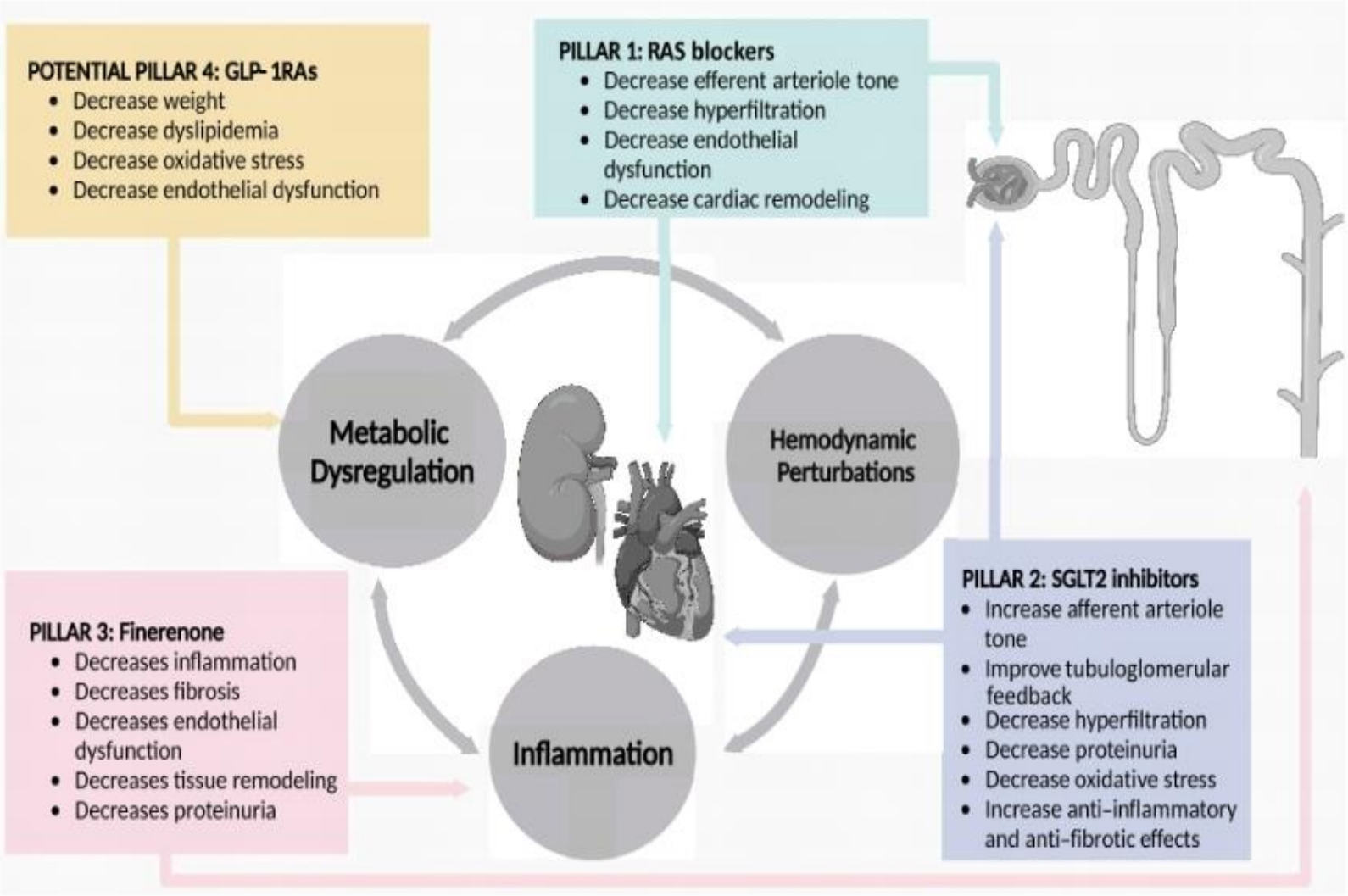


Figure 6—The manifold pathophysiological mechanisms involved in end-organ damage argue for a pillared approach with targeted t
have distinct pharmacodynamic actions (135).

The captopril trial was the first study to conclusively establish the value of ACE inhibition in delaying DKD, in patients with type 1 diabetes, where using an angiotensin I converting enzyme (ACEI) achieved a slower rate of decline in creatinine clearance (11% vs. 17% in placebo) and a striking 50% risk reduction in combined renal end points (dialysis, transplantation, or death) independent of blood pressure, which was managed with agents other than the experimental drug .

Mechanistically, blocking angiotensin II generation or action should partially inhibit aldosterone secretion, yet this is not long-standing due to “aldosterone escape,” which is the upstream accumulation of renin in the setting of long-term ACEI/ARB therapy, resulting in plasma aldosterone rise by overcoming RAS inhibition or by alternative pathways that bypass RAS. In one study using UACR as an indicator of the renoprotective effects of trandolapril (the longest-acting ACEI), aldosterone breakthrough was observed in 40% of patients at 40 weeks, when UACR started to increase during a relatively long period of ACEI use .

Over 2 years' median duration, empagliflozin reduced the risk of ESKD progression or CV death by 28% compared with placebo (hazard ratio [HR] 0.72; 95% CI 0.64–0.82; P < 0.001), findings that generalized to patients with and without diabetes. Additionally, the empagliflozin group evidenced a 14% risk reduction in hospitalization from any cause compared with placebo (HR 0.86; 95% CI 0.78–0.95; P = 0.003). It should further be noted that there were many people with normal and high albuminuria in this trial.

Steroid-based MRAs, including first- and second-generation spironolactone and eplerenone, respectively, continue to be used extensively in symptomatic heart failure patients .Use in DKD has been much more limited given the scarcity of supporting data and concern about hyperkalemia and further declines in kidney function, particularly if given in addition to ACEI/ARBs.

Finerenone, apararenone, esaxerenone, and ocedurenone are members of a new class of NS-MRAs with pharmacologic properties distinct from those of their distant cousins, the steroidal agents. *Finerenone is the only one developed and approved for cardiorenal risk reduction*, whereas the others are approved only for blood pressure control, with no outcome data supporting use in DKD.

Finerenone demonstrates superior anti-inflammatory and antifibrotic outcomes compared with its steroidal counterparts in preclinical studies .Unlike the steroidal MRAs, the NS-MRAs achieve balanced tissue distribution between the heart and kidney rather than affecting the kidney alone.

Finerenone was studied in two complementary phase 3 randomized, double-blinded, placebo-controlled clinical trials that included over 13,000 participants with type 2 diabetes optimized on maximally tolerated RAS blockade before randomization to the NS-MRA or placebo .

These trials were developed with the same protocol but different inclusion criteria, which allowed for an individual pooled patient analysis in the Finerenone in Chronic Kidney Disease and Type 2 Diabetes: Combined FIDELIO-DKD and FIGARO-DKD Trial Programme Analysis (FIDELITY) .

The FIDELITY individual pooled patient analysis included 13,026 patients with type 2 diabetes and a wide range of CKD stages, from 1 to 4, and high to very high albuminuria. In this analysis, there was a 23% reduction in doubling of creatinine, ESKD, and renal death, with a significant 20% reduction in ESKD alone.

GLP-1 RAs are recommended for patients with DKD who have not met their glycemic targets despite optimization with metformin and SGLT2 inhibitors . A wave of CV outcome trials (CVOT) have demonstrated a significant reduction in atherosclerotic CV events by GLP-1 RAs and led to guideline revisions in 2020 that recommend the integration of GLP-1 RAs in the setting of type 2 diabetes, atherosclerotic disease, and/or high risk for CV events .

Compared with placebo, semaglutide and liraglutide evidenced a 24% reduction in albuminuria from baseline to 2 years (95% CI 20–27%; $P < 0.001$). Semaglutide and liraglutide were associated with significant slowing of annual eGFR decline, 0.87 and 0.26 mL/min/1.73 m2 /year ($P < 0.0001$ and $P < 0.001$), respectively, compared with placebo.

The substantial and sustained weight loss, reaching 20% with some GLP-1 RAs, is important to note. Abdominal obesity is independently associated with albuminuria despite normoglycemia and normotension and addresses an important subgroup of patients who have obesity-related glomerulopathy and who, by conventional screening, may be classified as metabolically healthy yet are still at risk for developing ESKD .This is not surprising given the inflammatory milieu engendered by excess adiposity .

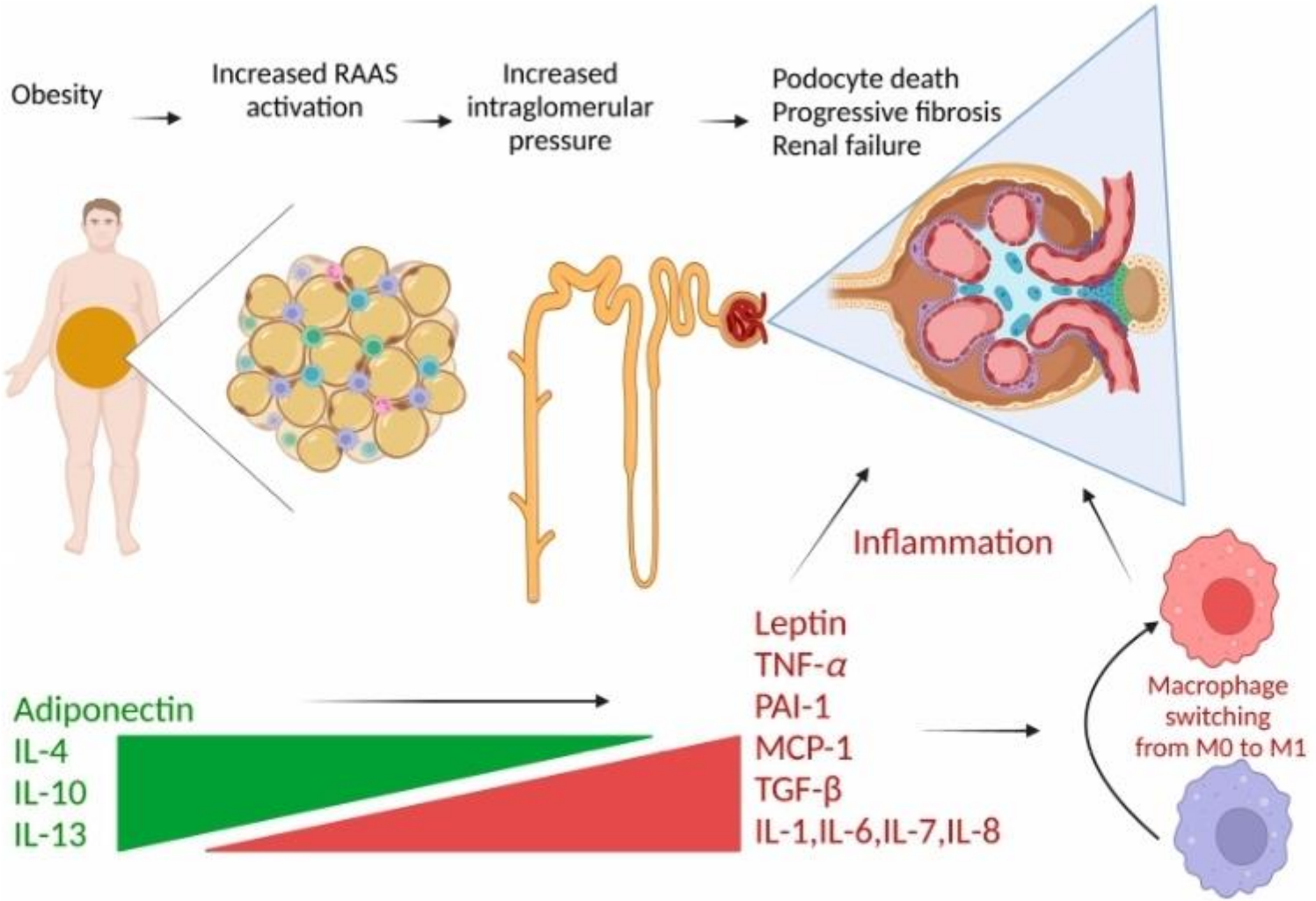


Figure 5—Obesity reduces the production of adiponectin in favor of leptin. Gene transcription of inflammatory mediators such as IL-1, IL-6, IL IL-8, and TNF-α is increased, which creates a proinflammatory state and oxidative stress. Profibrotic factors plasminogen activator inhibito (PAI-1) and TGF-β1, connective tissue growth factor, and extracellular matrix proteins are increased, all contributing to progressive diabe nephropathy. IL, interleukin; TNF-α, tumor necrosis factor-α; MCP-1, monocyte chemoattractant protein-1.

CLINICAL APPLICATION

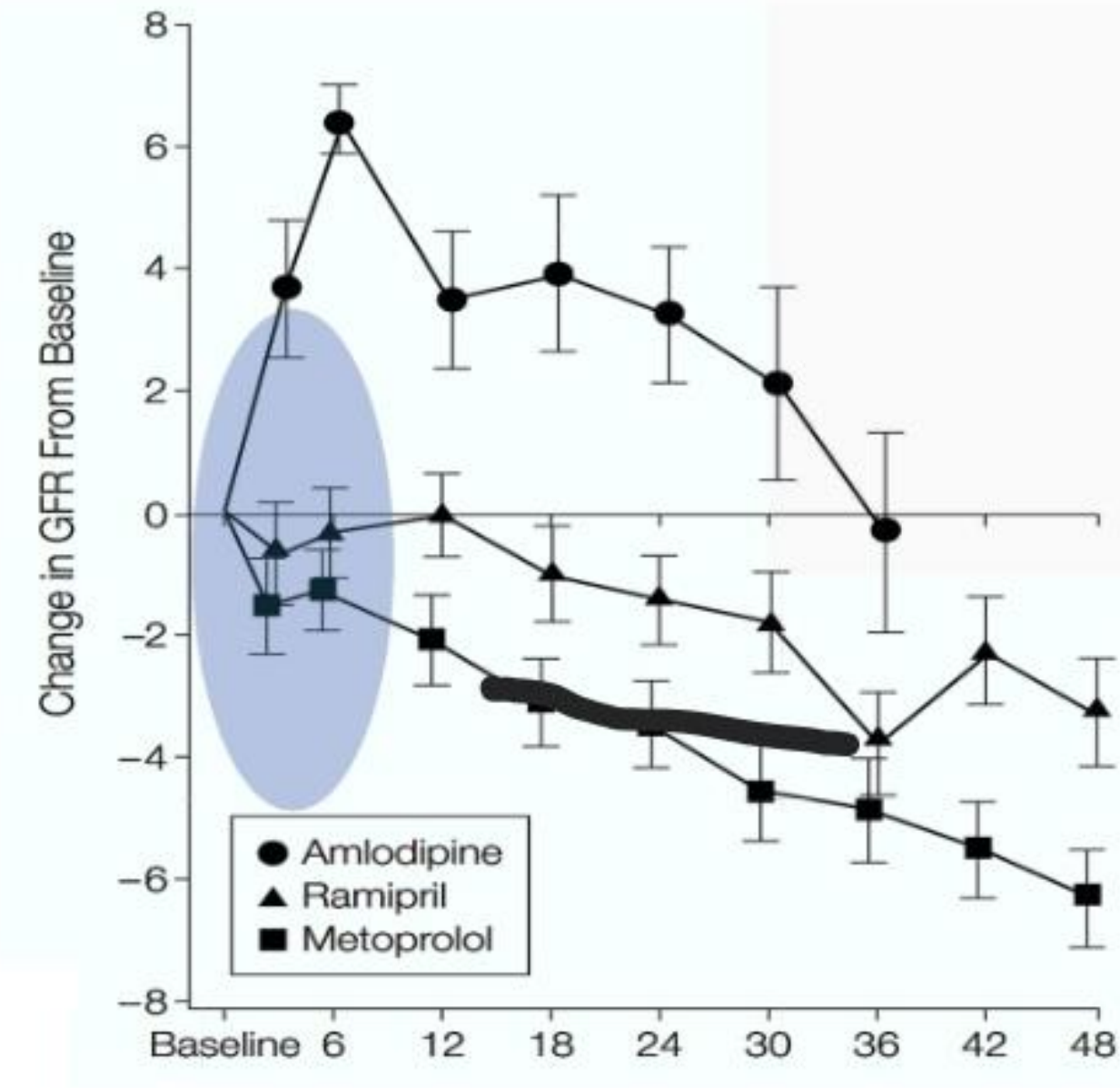
DKD management should start with maximally dosed RAS blockade; this is based on the doses used in the original RAS blocking trials, wherein dose reduction to avoid hyperkalemia resulted in markedly reduced protection against DKD decline. This was observed in a large analysis (N = 205,108) *showing that submaximal ACEI/ ARB dosing was associated with worse cardiorenal outcomes.*

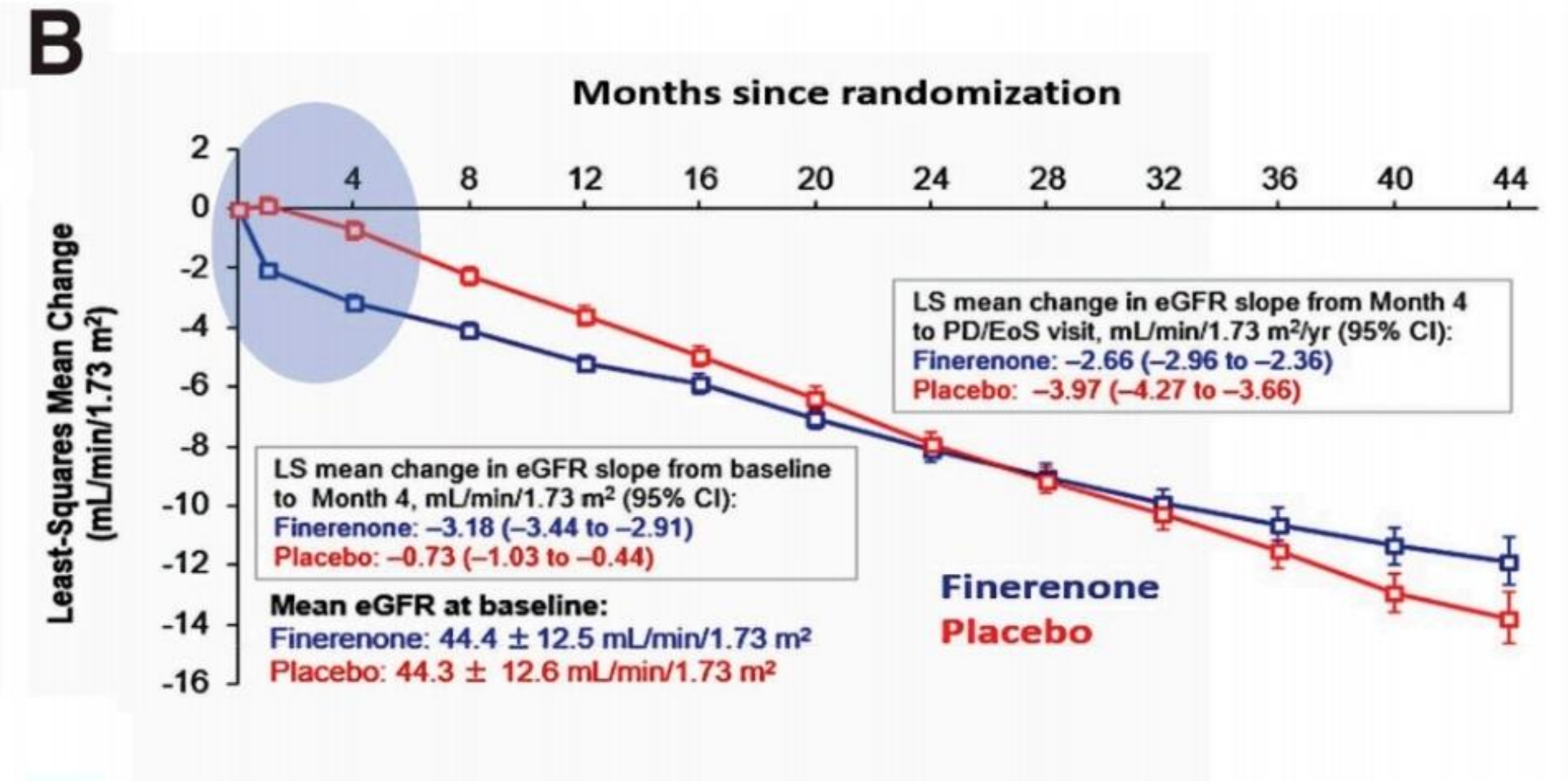
practice guidelines articulate that clinicians should start first by titrating to maximally tolerated RAS blockade before introducing these medications (SGLT2 inhibitors, NS-MRAs, and GLP-1 RAs), as was done in pivotal clinical trials .This is challenging for many clinicians due to eGFR dipping observed at treatment initiation, reaching 10–30% .depending on hydration status and duration of suboptimally controlled hypertension, but this response is reassuring .

THE ADDITIVE VALUE OF DRUG COMBINATION

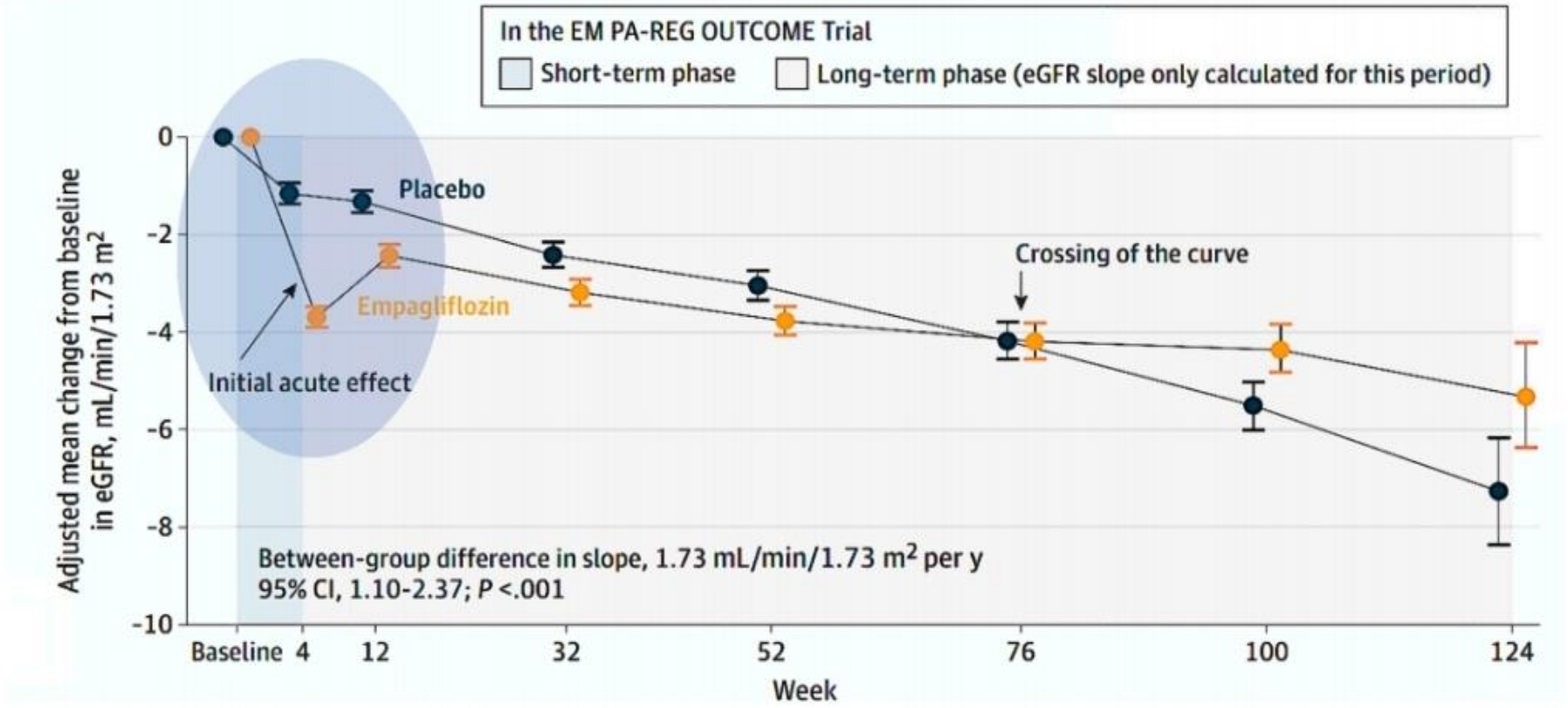
An elegant study that used an animal model of preclinical hypertension–induced cardiorenal disease with a *low-dose combination therapy of finerenone and empagliflozin revealed additive cardiorenal benefit above that of the respective dose-dependent monotherapy, as measured by reductions in blood pressure, proteinuria, cardiac fibrosis, vasculopathy, and mortality* .These findings further argue strongly for distinct harmacodynamic actions that counteract the manifold pathophysiological mechanisms involved in end-organ damage .

When combined with finerenone, SGLT2 inhibitors reduced hyperkalemic events compared with levels found in nonusers (8.1% vs. 18.7%). These are separate retrospective analyses of renal outcome trials clearly showing a protective effect of SGLT2 inhibitors from hyperkalemia in the setting of NS-MRA and MRA use .The Study to Learn How Well the Treatment Combination of Finerenone an Empagliflozin Works and How Safe It Is Compared to Each Treatment Alone in Adult Participants With Long-term Kidney Disease (Chronic Kidney Disease) and Type 2 Diabetes


Change in GFR From Baseline
8
6
4
2
0
−2
−4
−6
−8
Baseline
6
12
18
24
30
36
42
48
Amlodipine
Ramipril
Metoprolol


B
Months since randomization
Least-Squares Mean Change (mL/min/1.73 m²)
2
0
-2
-4
-6
-8
-10
-12
-14
-16
4
8
12
16
20
24
28
32
36
40
44
LS mean change in eGFR slope from Month 4 to PD/EoS visit, mL/min/1.73 m²/yr (95% CI):
Finerenone: –2.66 (–2.96 to –2.36)
Placebo: –3.97 (–4.27 to –3.66)
LS mean change in eGFR slope from baseline to Month 4, mL/min/1.73 m² (95% CI):
Finerenone: –3.18 (–3.44 to –2.91)
Placebo: –0.73 (–1.03 to –0.44)
Mean eGFR at baseline:
Finerenone: 44.4 ± 12.5 mL/min/1.73 m²
Placebo: 44.3 ± 12.6 mL/min/1.73 m²
Finerenone
Placebo

C


In the EM PA-REG OUTCOME Trial
Short-term phase
Long-term phase (eGFR slope only calculated for this period)
Adjusted mean change from baseline in eGFR, mL/min/1.73 m²
0
-2
-4
-6
-8
-10
Placebo
Empagliflozin
Initial acute effect
Crossing of the curve
Between-group difference in slope, 1.73 mL/min/1.73 m² per y
95% CI, 1.10-2.37; P <.001
Baseline
4
12
32
52
76
100
124
Week

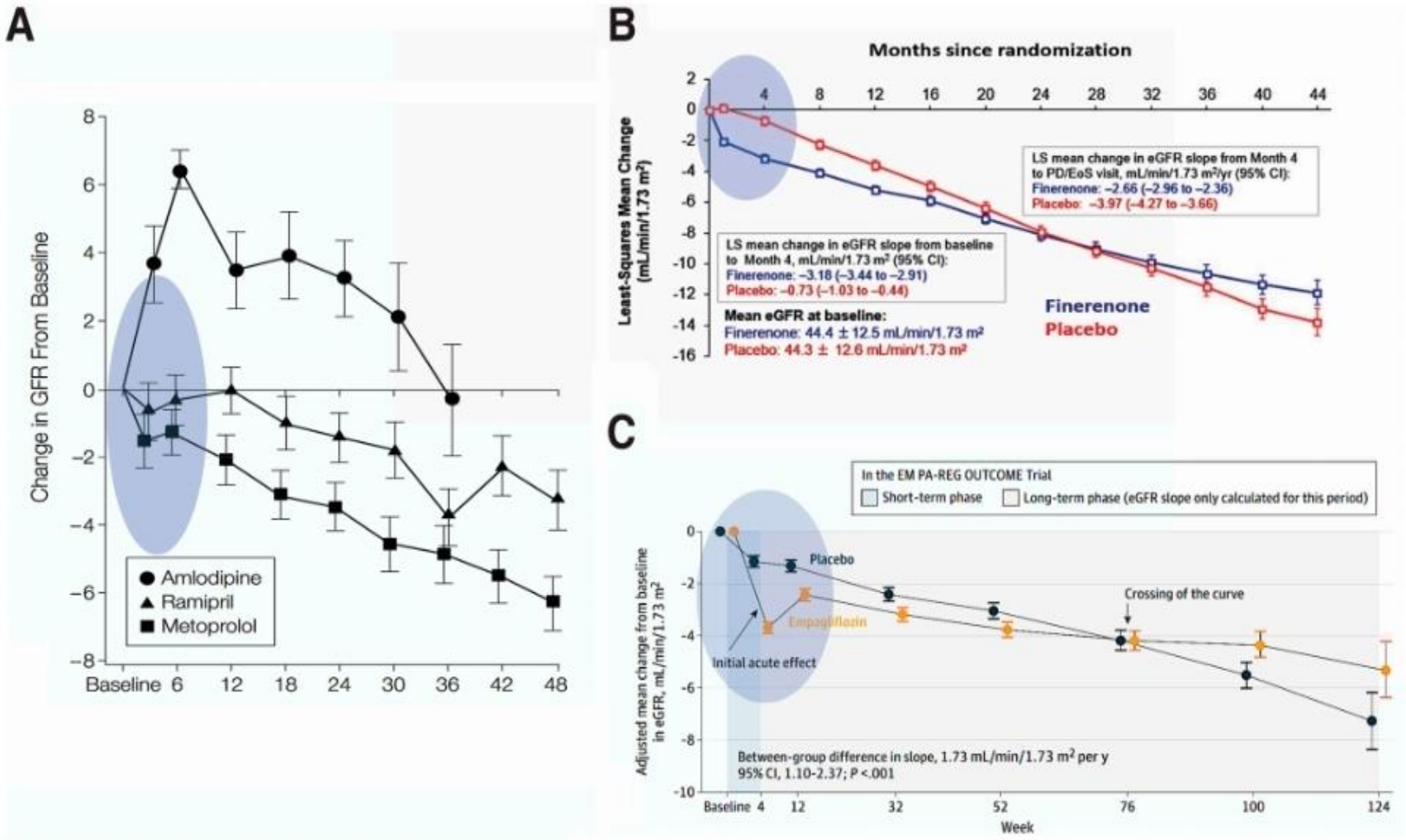


Figure 7—Acute changes in GFR slopes with three distinct classes of drugs with unique mechanisms that slow kidney disease progression associated diabetes. *A*: Estimated mean changes (SE) in GFR (mL/min/1.73 m^2) from baseline through follow-up in three drug interventions (127). *B*: Rate of eGFR decline between finerenone and placebo. Despite equivalent GFR at baseline, the finerenone group shows stabilization of slowed GFR declines (96) and higher GFR declines at 4 months, which are associated with better long-term outcomes. *C*: Initial decline in GFR decline in the empagliflozin group compared with placebo at month 4 (128). The slopes eventually cross over at week 76, and analyses of the slopes in the long-term phase shows higher GFR decline in the placebo group than the empagliflozin group, $P < 0.05$. EMPA-REG Outcome, BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; LS, least squares.

At least annually, urinary albumin (e.g., spot urinary albumin-to-creatinine ratio [UACR]) and estimated glomerular filtration rate [eGFR] should be assessed in people with type 1 diabetes with duration of 5 years and in all people with type 2 diabetes regardless of treatment.

In people with established chronic kidney disease (CKD), urinary albu-min (e.g., spot UACR) and eGFR should be monitored 1–4 times per year de-pending on the stage of the kidney disease .

Optimize glucose management to reduce the risk or slow the progression of CKD. Optimize blood pressure control and reduce blood pressure variability to reduce the risk or slow the progression of CKD and reduce cardiovascular risk. In nonpregnant people with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker (ARB) is recommended for those with moderately increased albuminuria (UACR 30–299 mg/g creatinine) and is strongly recommended.

for those with severely increased albuminuria (UACR 300 mg/g creatinine) and/or eGFR <60 mL/min/1.73 m2 to prevent the progression of kidney disease and reduce cardiovascular events. A Periodically monitor for increased serum creatinine and potassium levels when ACE inhibitors, ARBs, and miner alocorticoid receptor antagonists are used, or for hypokalemia when diuretics are used.

An ACE inhibitor or an ARB is not recommended for the primary prevention of CKD in people with diabetes who have normal blood pressure, normal UACR (<30 mg/g creatinine), and normal eGFR.

Do not discontinue renin angiotensin system blockade for mild to moderate increases in serum create nine (#30%) in the absence of signs of extracellular fluid volume depletion.
For people with type 2 diabetes and CKD, use of a sodium–glucose cotransporter 2 (SGLT2) inhibitor is recommended to reduce CKD progression and cardiovascular events in individuals with eGFR >20 mL/min/1.73 m2 and urinary albumin >200 mg/g creatinine.

For people with type 2 diabetes and CKD, use of an SGLT2 inhibitor is recommended to reduce CKD progression and cardiovascular events in individuals with eGFR >20 mL/min/1.73 m2 and urinary albumin ranging from normal to 200 mg/g creatinine. For cardiovascular risk reduction in people with type 2 diabetes and CKD, consider use of an SGLT2 inhibitor (if eGFR is >20 mL/min/1.73 m2), a glucagon-like peptide 1 agonist, or a nonsteroidal mineralocorticoid receptor antagonist (if eGFR is >25 mL/min/1.73 m2).

As people with CKD and albuminuria are at increased risk for cardiovascular events and CKD progression, a nonsteroidal mineralocorticoid receptor antagonist that has been shown to be effective in clinical trials is recommended to reduce cardiovascular events and CKD progression (if eGFR is >25 mL/min/1.73 m2 . people with CKD who have >300 mg/g urinary albumin, a reduction of 30% or greater in mg/g urinary albumin is recommended to slow CKD progression.

For people with non–dialysis dependent stage G3 or higher CKD, dietary protein intake should be aimed to a target level of 0.8 g/kg body weight per day. AFor individuals on dialysis, 1.0–1.2 g/kg/day of dietary protein intake should be considered since protein energy wasting is a major problem in some individuals on dialysis. Individuals should be referred for evaluation by a nephrologist if they have continuously increasing urinary albumin levels and/or continuously decreasing eGFR and/or if the eGFR is <30 mL/min/1.73 m2 . Promptly refer to a nephrologist for uncertainty about the etiology.

normal level of urine albumin excretion is defined as <30 mg/g creatinine, moderately elevated albuminuria is defined as >30–300 mg/g creatinine, and severely elevated albuminuria is defined as >300 mg/g creatinine. However, UACR is a continuous measurement, and differences within the normal and abnormal ranges are associated with kidney and cardiovascular outcomes . Furthermore, because of high biological variability of >20% between measurements in urinary albumin excretion*, two of three specimens of UACR collected within a 3- to 6-month period should be abnormal before considering an individual to have moderately or severely elevated albuminuria* .

Exercise within 24 h, infection, fever, congestive heart failure, marked hyperglycemia, menstruation, and marked hypertension may elevate UACR independently of kidney damage .The only proven primary prevention interventions for CKD in people with diabetes are blood glucose (A1C goal of 7%) and blood pressure control (blood pressure <130/80 mmHg). There is no evidence that renin-angiotensin-aldosterone system inhibitors or any other interventions prevent the development of diabetic kidney disease in the absence of hypertension or albuminuria.

There is a clear need for annual quantitative assessment of urinary albumin excretion. This is especially true after a diagnosis of albuminuria, institution of ACE inhibitors or ARB therapy to maximurated doses, and achievement of blood pressure targets. Early changes in kidney function may be detected by increases in albuminuria before changes in eGFR , and this also significantly affects cardiovascular risk. Moreover, an initial reduction of >30% from baseline, subsequently maintained over at least 2 years, is considered a valid surrogate for renal benefit by the Division of Cardiology and Nephrology of the U.S. Food and Drug Administration (FDA) .

Continued surveillance can assess both response to therapy and disease progression and may aid in assessing participation in ACE inhibitor or ARB therapy. In addition, in clinical trials of ACE inhibitors or ARB therapy in people with type 2 diabetes, *reducing albuminuria to levels <300 mg/g creatinine or by >30% from baseline has been associated with improved renal and cardiovascular outcomes*.

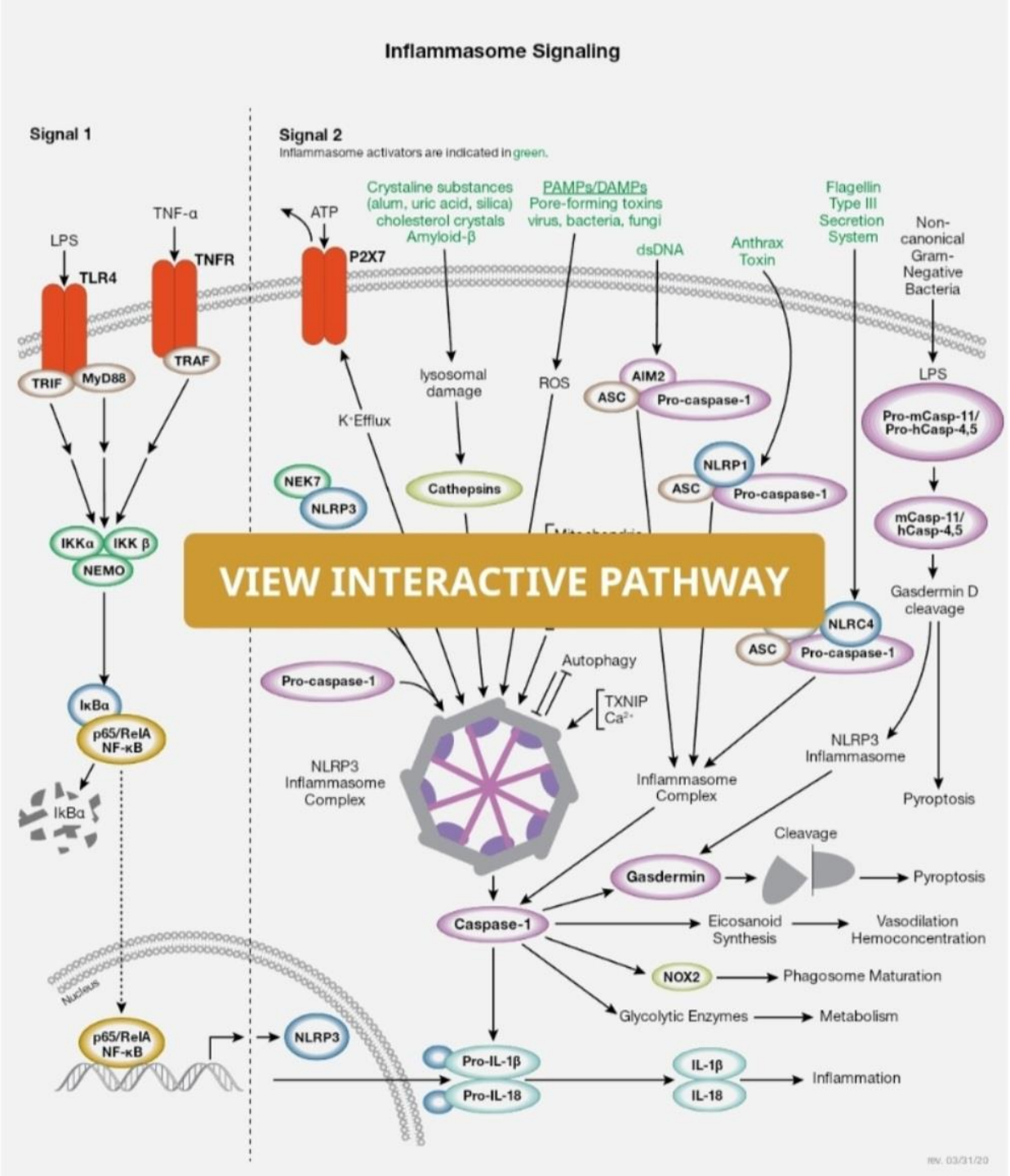
Higher levels of dietary pro-tein intake (>20% of daily calories from protein or >1.3 g/kg/day) have been associated with increased albuminuria,more rapid kidney function loss, and CVD mortality and therefore should be avoided. Reducing the amount of dietary protein below the recommended daily allowance of 0.8 g/kg/day is not recommended because it does not alter blood glucose levels, cardiovascular risk measures, or the course of GFR decline blood Pressure .

ACE Inhibitors and Angiotensin Receptor Blockers ACE inhibitors and ARBs remain a mainstay of management for people with CKD with albuminuria and for the treatment of hypertension in people with diabetes (with or without diabetic kidney disease).

antihypertensive therapy reduces the risk of cardiovascular events ACE inhibitors or ARBs are the preferred first-line agents for blood pressure treatment among people with diabetes, hypertension, eGFR <60 mL/min/1.73 m2 and UACR >300 mg/g creatinine because of their proven benefits for prevention of CKD progression. ACE inhibitors and ARBs are considered to have similar benefits and risks. In the setting of lower levels of albuminuria (30–299 mg/g creatinine), ACE inhibitor or ARB therapy at maximum tolerated doses in trials has reduced progression to more advanced albuminuria (>300 mg/g creatinine), slowed CKD progression, and reduced cardiovascular events but has not reduced progression to ESKD .

Direct Renal Effects of Glucose-Lowering Medications

Some glucose-lowering medications also have effects on the kidney that are direct, i.e., not mediated through glycemia. For example, SGLT2 inhibitors reduce renal tubular glucose reabsorption, weight,systemic blood pressure, intraglomerular pressure, and albuminuria and slow GFR loss through mechanisms that appear independent of glycemia. *Moreover, recent data support the notion that SGLT2 inhibitors reduce oxidative stress in the kidney by >50% and blunt increases in angiotensinogen as well as reduce NLRP3 inflammasome activity .*


Inflammasome Signaling
Signal 1
Signal 2
Inflammasome activators are indicated in green.
LPS
TLR4
TRIF
MyD88
TNF-α
TNFR
TRAF
ATP
P2X7
K+ Efflux
Crystaline substances (alum, uric acid, silica) cholesterol crystals Amyloid-β
lysosomal damage
Cathepsins
PAMPs/DAMPs Pore-forming toxins virus, bacteria, fungi
ROS
dsDNA
AIM2
ASC
Pro-caspase-1
Anthrax Toxin
NLRP1
ASC
Pro-caspase-1
Flagellin Type III Secretion System
Non-canonical Gram-Negative Bacteria
LPS
Pro-mCasp-11/ Pro-hCasp-4,5
mCasp-11/ hCasp-4,5
Gasdermin D cleavage
NLRC4
ASC
Pro-caspase-1
NEK7
NLRP3
IKKα
IKK β
NEMO
VIEW INTERACTIVE PATHWAY
Autophagy
TXNIP
Ca2+
Pro-caspase-1
IκBα
p65/RelA NF-κB
IκBα
NLRP3 Inflammasome Complex
Inflammasome Complex
NLRP3 Inflammasome
Pyroptosis
Cleavage
Gasdermin
Pyroptosis
Caspase-1
Eicosanoid Synthesis
Vasodilation Hemoconcentration
NOX2
Phagosome Maturation
Glycolytic Enzymes
Metabolism
Nucleus
p65/RelA NF-κB
NLRP3
Pro-IL-1β
Pro-IL-18
IL-1β
IL-18
Inflammation
rev. 03/31/20

Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) also have direct effects on the kidney and have been reported to improve renal outcomes compared with placebo,although a definitive resolution as to the renoprotective effects of GLP-1 RAs is yet to be determined.

The FDA revised its guidance for the use of metformin in CKD in 2016 recommending use of eGFR instead of serum creatinine to guide treatment and expanding the pool of people with kidney disease for whom metformin treatment should be considered. The revised FDA guidance states that

1 metformin is contraindicated in individuals with an eGFR <30 mL/min/1.73 m2,

2 eGFR should be monitored while taking metformin,

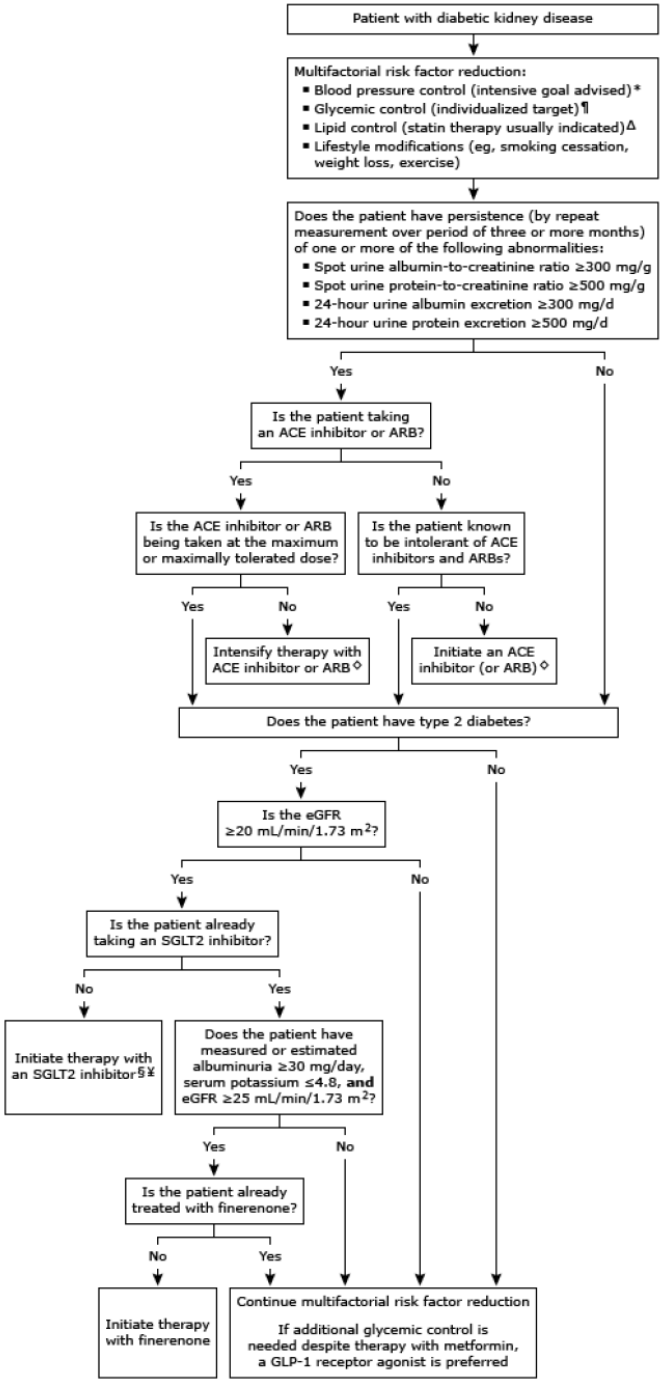
3 the benefits and risks of continuing treatment should be reassessed when eGFR falls to <45 mL/min/1.73 m2,

4 metformin shouldnot be initiated for individuals with an eGFR <45 mL/min/1.73 m2, and

5 metformin should be temporarily discontinued at the time of or before iodinated contrast imaging procedures in individuals with eGFR 30–60 mL/min/1.73 m2 .

A number of recent studies have shown cardiovascular protection from SGLT2 inhibitors and GLP-1 RAs as well as renal protection from SGLT2 inhibitors and possibly from GLP-1 RAs. Selection of which glucose-lowering medications to use should be based on the usual criteria of an individual's risks (cardiovascular and renal in addition to glucose control) as well as convenience and cost

SGLT2 inhibitors are recommended for people with eGFR >20 mL/min/1.73 m2 and type 2 diabetes, as they slow CKD progression and reduce heart failure risk independent of glucose management. GLP-1 RAs are suggested for cardiovascular risk reduction if such risk is a predominant problem, as they reduce risks of CVD events and hypoglycemia and appear to possibly slow CKD progression .


Patient with diabetic kidney disease
Multifactorial risk factor reduction:
Blood pressure control (intensive goal advised)*
Glycemic control (individualized target)¶
Lipid control (statin therapy usually indicated)Δ
Lifestyle modifications (eg, smoking cessation, weight loss, exercise)
Does the patient have persistence (by repeat measurement over period of three or more months) of one or more of the following abnormalities:
Spot urine albumin-to-creatinine ratio ≥300 mg/g
Spot urine protein-to-creatinine ratio ≥500 mg/g
24-hour urine albumin excretion ≥300 mg/d
24-hour urine protein excretion ≥500 mg/d
Yes
No
Is the patient taking an ACE inhibitor or ARB?
Yes
No
Is the ACE inhibitor or ARB being taken at the maximum or maximally tolerated dose?
Is the patient known to be intolerant of ACE inhibitors and ARBs?
Yes
No
Yes
No
Intensify therapy with ACE inhibitor or ARB◇
Initiate an ACE inhibitor (or ARB)◇
Does the patient have type 2 diabetes?
Yes
No
Is the eGFR ≥20 mL/min/1.73 m2?
Yes
No
Is the patient already taking an SGLT2 inhibitor?
No
Yes
Initiate therapy with an SGLT2 inhibitor§¥
Does the patient have measured or estimated albuminuria ≥30 mg/day, serum potassium ≤4.8, and eGFR ≥25 mL/min/1.73 m2?
Yes
No
Is the patient already treated with finerenone?
No
Yes
Initiate therapy with finerenone
Continue multifactorial risk factor reduction
If additional glycemic control is needed despite therapy with metformin, a GLP-1 receptor agonist is preferred

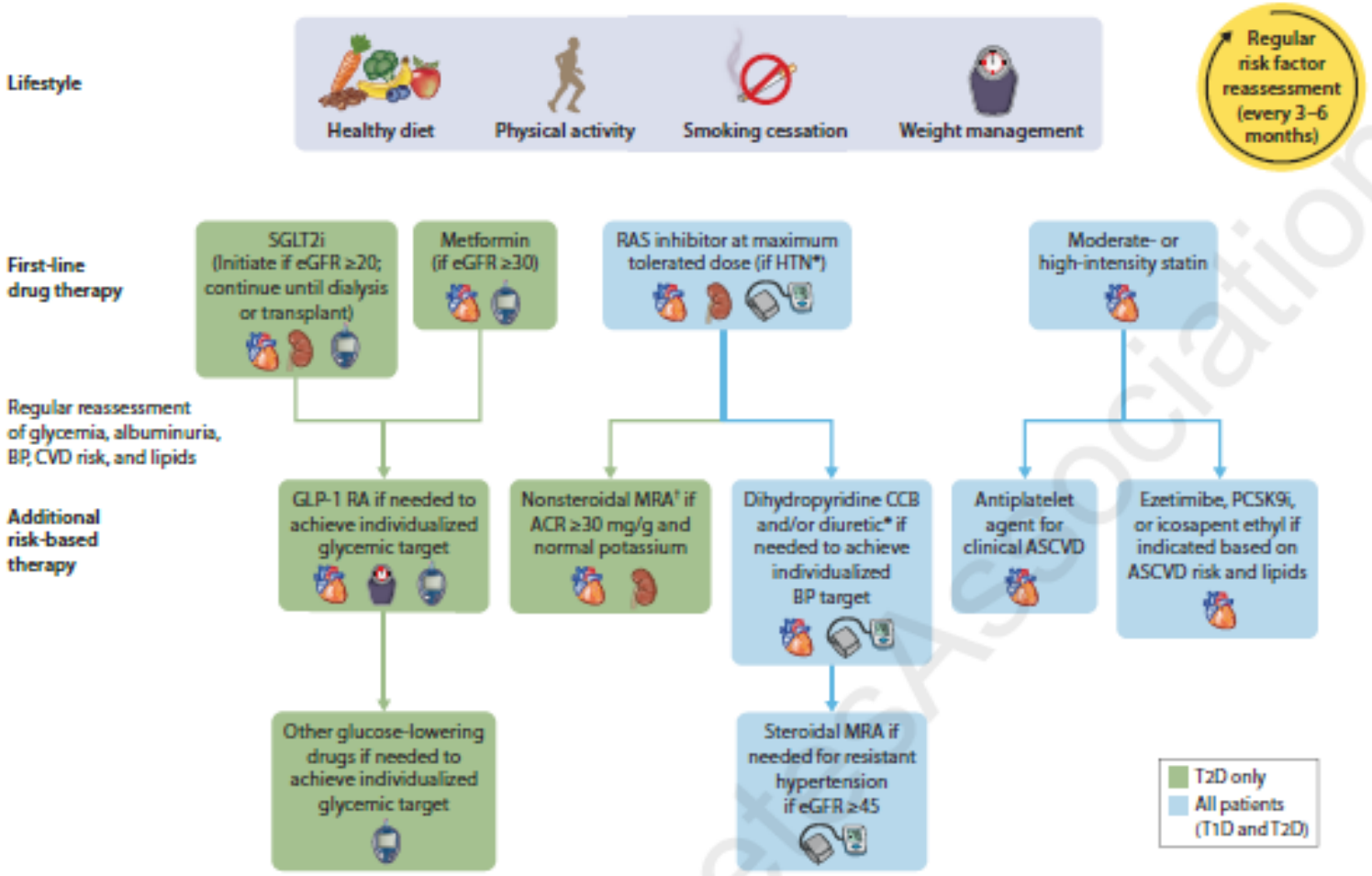


Figure 11.2—Holistic approach for improving outcomes in people with diabetes and CKD. Icons presented indicate the following benefits: BP cuff, BP lowering; glucometer, glucose lowering; heart, cardioprotection; kidney, kidney protection; scale, weight management. eGFR is presented in units of mL/min/1.73 m^2. *ACEi or ARB (at maximal tolerated doses) should be first-line therapy for hypertension when albuminuria is present. Otherwise, dihydropyridine calcium channel blocker or diuretic can also be considered; all three classes are often needed to attain BP targets. †Finerenone is currently the only ns-MRA with proven clinical kidney and cardiovascular benefits. ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to creatinine ratio; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CCB, calcium channel blocker; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HTN, hypertension; MRA, mineralocorticoid receptor antagonist; ns-MRA, nonsteroidal mineralocorticoid receptor antagonist; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; RAS, renin-angiotensin system; SGLT2i, sodium–glucose cotransporter 2 inhibitor; T1D, type 1 diabetes; T2D, type 2 diabetes. Reprinted from de Boer et al. (1).