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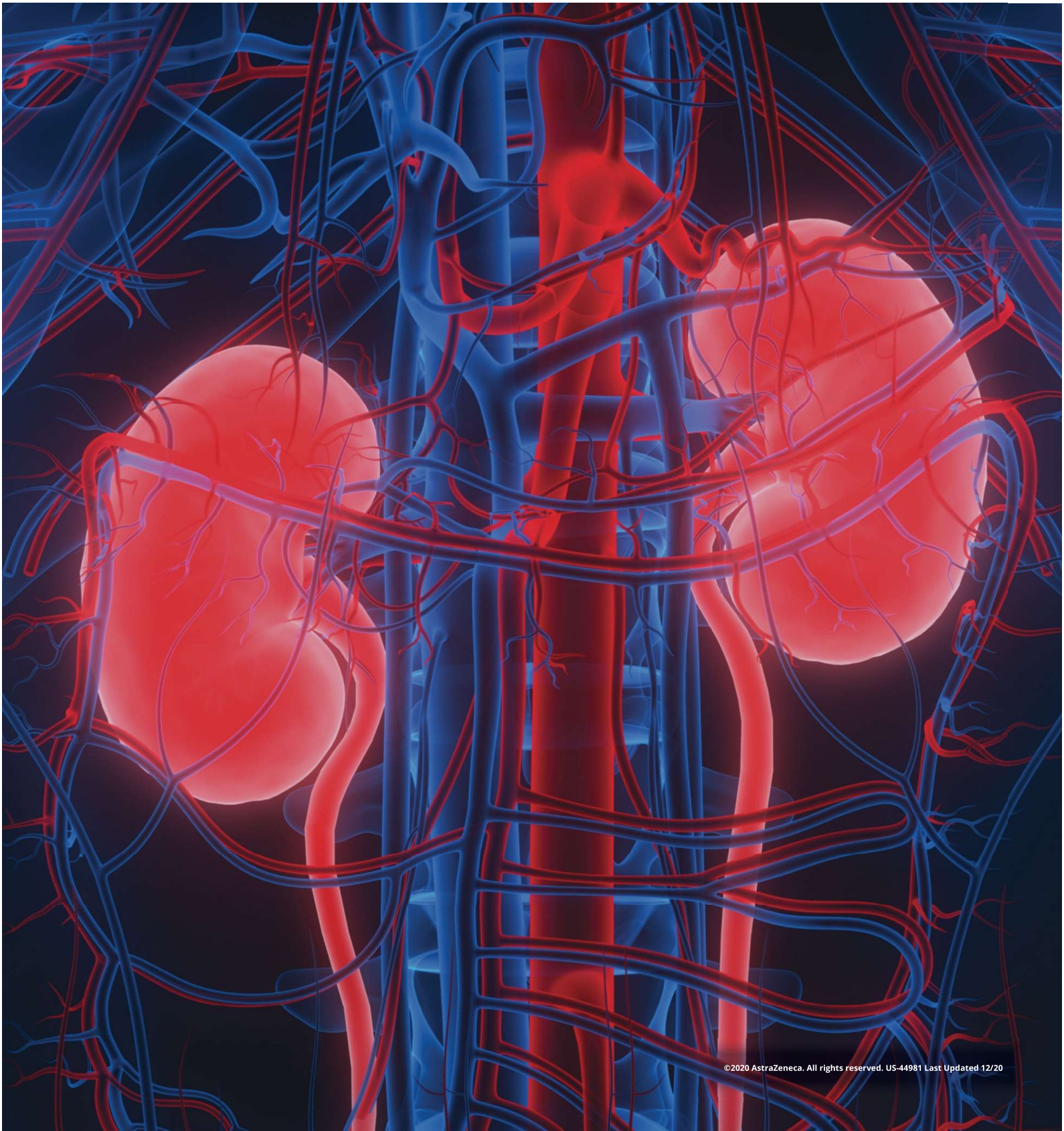
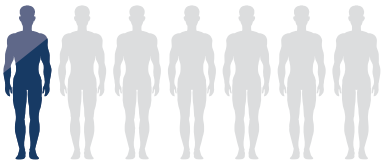
Progression of Chronic Kidney Disease:
Drivers of Disease and Opportunities for Earlier Diagnosis and Intervention



Burden of Chronic Kidney Disease in the US



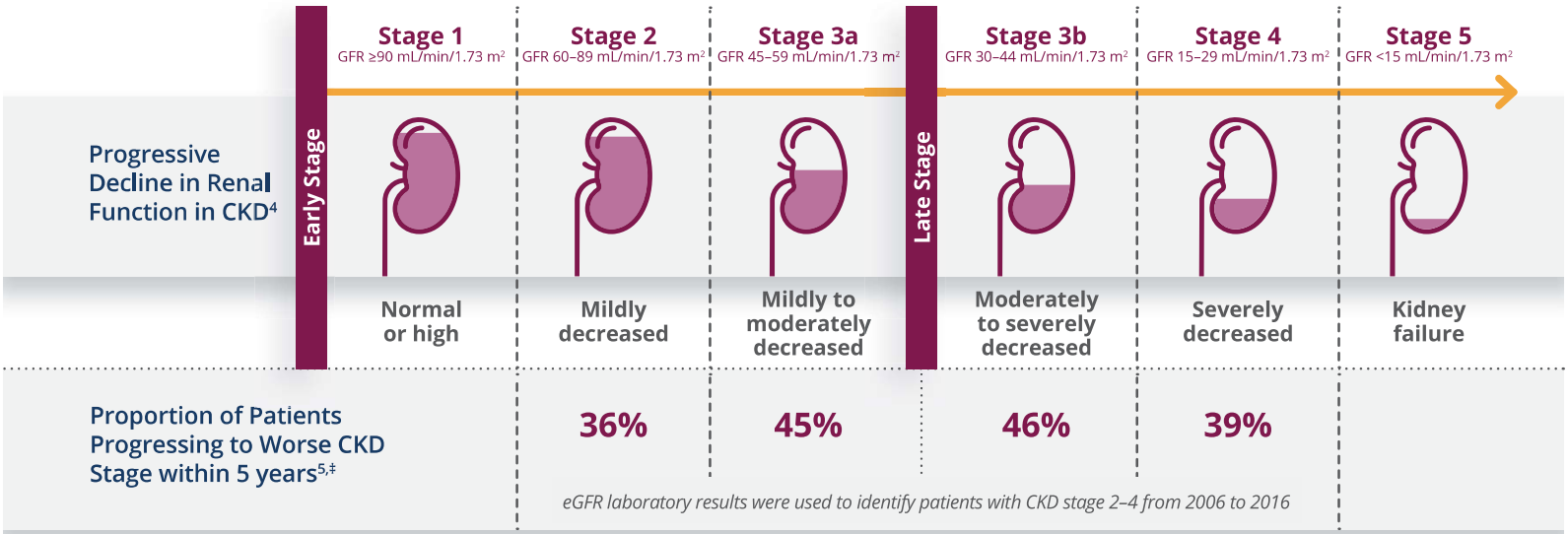
Approximately **1 in 7 adults** in the US are living with CKD[1,*]

$72 billion

CKD expenditure represents **25% of overall spending** for Medicare patients[2,†]

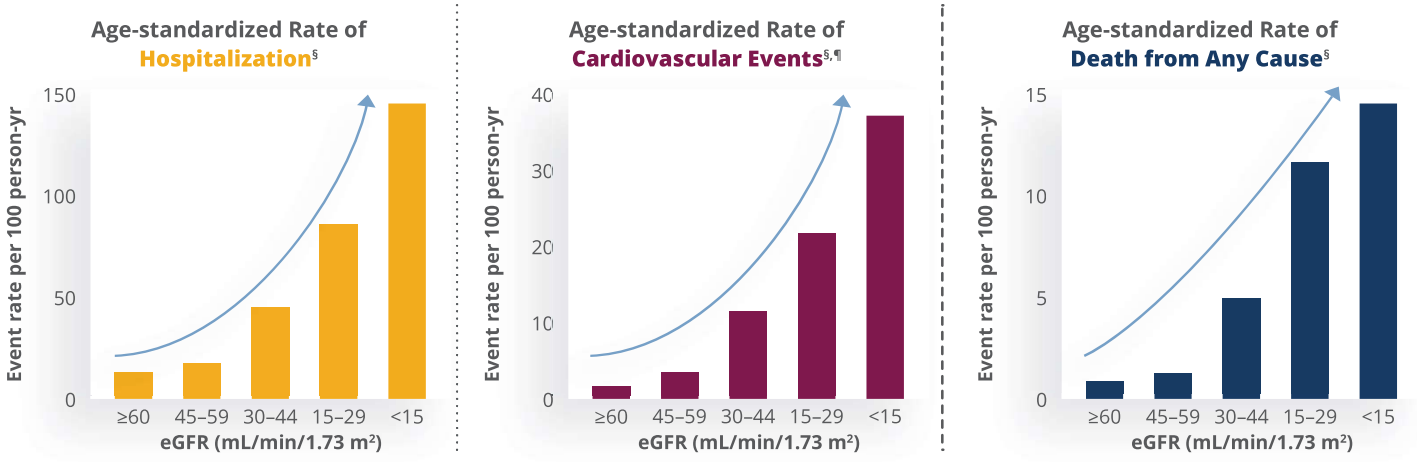
Overall life expectancy was shortened by 6 years with early CKD and by **16 years with CKD and comorbid T2D[3]**

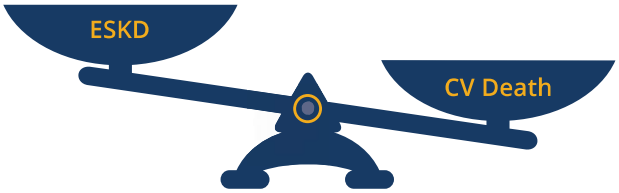
Progressive Nature of Chronic Kidney Disease



eGFR laboratory results were used to identify patients with CKD stage 2–4 from 2006 to 2016

Progression of CKD Increases the Risk for Adverse Outcomes[6]





Older adults with CKD are **6-fold more likely** to die from CV causes than develop ESKD[7,#]

eGFR and ACR are strong and independent predictors of CV mortality[8,‖]

*Prevalence of CKD in US adults using NHANES 2013-2016 data. CKD may be overestimated as persistence of albuminuria or creatinine was not accounted for based on KDIGO recommendations. †Based on 2017 data. ‡This data comes from a retrospective, observational cohort study (N=29,303) using administrative data in the Henry Ford Health System (HFHS). Outcomes for CKD progression included progression to a higher stage of CKD based on eGFR and ESRD, defined as a composite outcome of CKD stage 5 (eGFR <15 mL/min), renal transplant or dialysis. §N=1,120,295. ¶Cardiovascular event was defined as hospitalization for coronary heart disease, heart failure, ischemic stroke, and peripheral arterial disease. #Based on a cohort study including 1268 participants 65 years and older with eGFR <60. ‖n=24,777; 15 studies; 1879 cases of CV mortality.

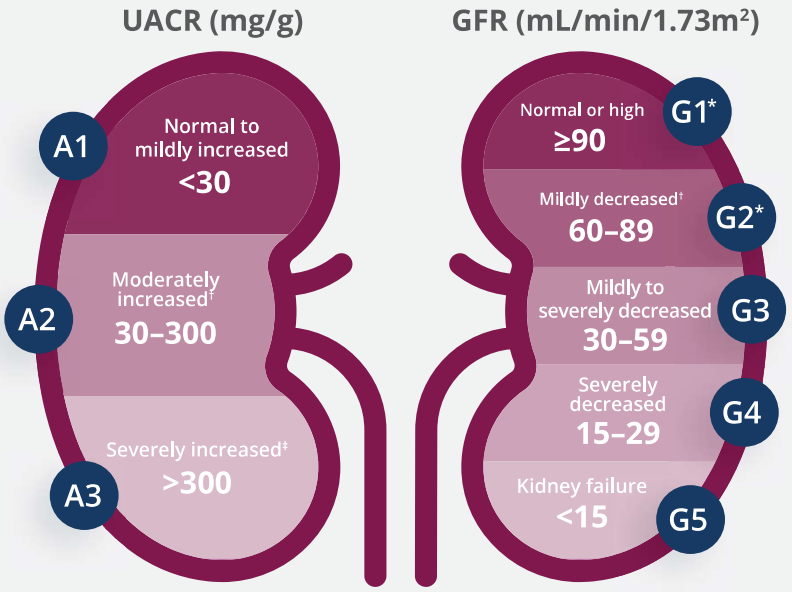
ACR = albumin-to-creatinine ratio; **CKD** = chronic kidney disease; **CV** = cardiovascular; **eGFR** = estimated glomerular filtration rate; **ESKD** = end-stage kidney disease; **GFR** = glomerular filtration rate; **T2D** = type 2 diabetes; **US** = United States

Importance of Screening and Monitoring

CKD is classified based on GFR category and albuminuria category[4]

Function
- Decreased eGFR
  - eGFR <60 mL/min/1.73 m² (Stage 3–5)

Damage
- Albuminuria
  - UACR ≥30 mg/g [≥3 mg/mmol]
- Urine sediment abnormalities
- Electrolyte abnormalities
- Abnormalities detected by histology
- Structural abnormalities
- History of kidney transplant



Screening for CKD using GFR and UACR testing should be carried out annually in patients with T2D[9]

Documented proteinuria, a reflection of underlying structural kidney damage, **is a strong predictor of short-term, fast CKD progression[10,§]**

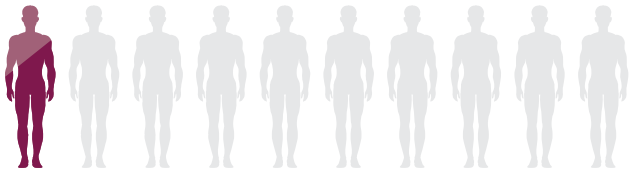
Monitoring of CKD Should Intensify as Renal Function Declines[4]

Recommended frequency of monitoring¶
(number of times per year) by GFR and albuminuria category

GFR categories (mL/min/1.73m²)		Persistent albuminuria categories: A1 <30 mg/g <3 mg/mmol	A2 30-300 mg/g 3-30 mg/mmol	A3 >300 mg/g >30 mg/mmol
G1	>90	1/year if CKD	1/year	2/year
G2	60-89			
G3a	45-59	1/year	2/year	3/year
G3b	30-44	2/year	3/year	
G4	15-29	3/year		4+/year
G5	<15	4+/year		

KDIGO recommends referral to a nephrologist for advanced CKD

Diagnosis of CKD in Patients with T2D Needs Improvement[1]



Only 1 in 10

adults with CKD are aware of their diagnosis

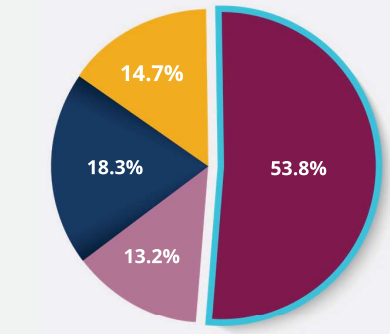
*Does not fulfill the criteria for CKD in the absence of evidence of kidney damage. †Relative to young adult level. ‡Including nephrotic syndrome (albumin excretion usually >2200 mg/24 hours [UACR >2220 mg/g; >220 mg/mmol]). §Patients were classified as fast progressors if they lost >4 mL/min/1.73 m² per year in eGFR in a large cohort of patients with mild-moderate CKD. ¶green = low risk (if no other markers of kidney disease, no CKD); yellow = moderately increased risk; orange = high risk; red = very high risk.

CKD = chronic kidney disease; **eGFR =** estimated glomerular filtration rate; **GFR =** glomerular filtration rate; **KDIGO =** Kidney Disease Improving Global Outcomes; **T2D =** type 2 diabetes; **UACR =** urine albumin-to-creatinine ratio

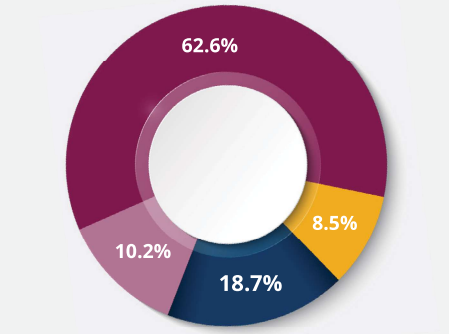
Diabetes as a Driver of Chronic Kidney Disease

Diabetes is the **leading cause of ESKD**[2]

Diabetes is the Leading Cause of CKD in the US[11,*]



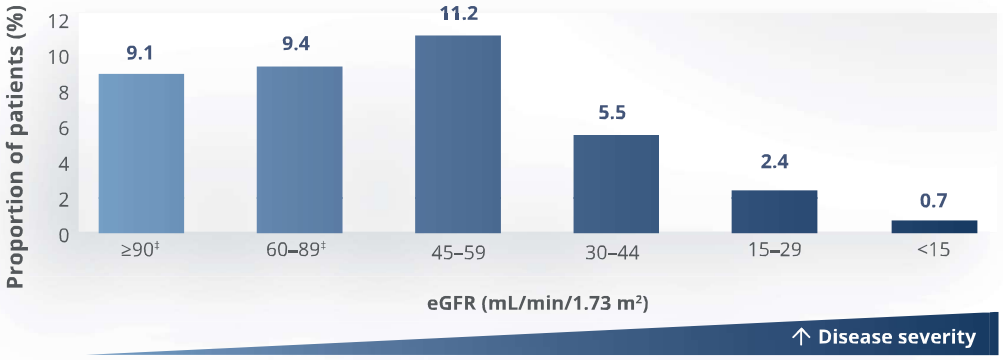
Most Patients with T2D Do Not Have Significantly Reduced Renal Function or Proteinuria[12,†]



In patients with T2D, CKD stages 1–3b combined are **10x more prevalent** than stage 4–5 combined[13]

In Patients with T2D, Early Stages of CKD are Most Prevalent[13]

Prevalence of CKD in patients with T2D
NHANES, 2007–2012



In newly diagnosed patients with T2D...

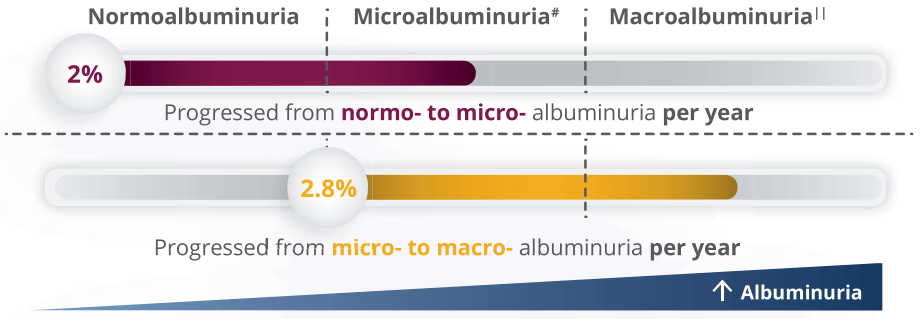
38%
Developed albuminuria[§]

28%
Developed eGFR <60 mL/min/1.73 m²
(CKD stage 3–5)

over a median of 15 years[14]

Long-term Progression of Kidney Disease in Patients with T2D

United Kingdom Prospective Diabetes Study (UKPDS)[15]
5102 patients with T2D[¶]



Estimated Time per CKD Stage

Poorly Controlled T2D[16,**]

1.8 fewer years in CKD **stage 3a**

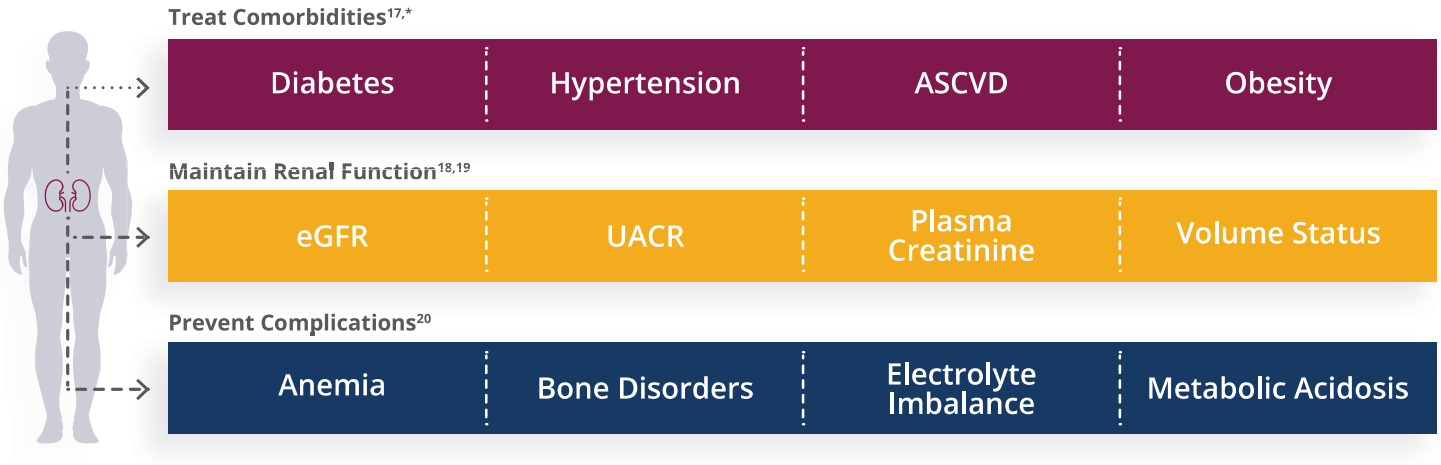
1.4 fewer years in CKD **stage 3b**

*Age-standardized US prevalence of CKD by cause in 2016. †Distribution of markers of CKD in NHANES participants with diabetes in 2013–2016. CKD defined as UACR ≥30 mg/g or eGFR <60 mL/min/1.73 m². ‡In addition, UACR ≥30 mg/g. §Defined as urinary albumin concentration ≥50 mg/L. ¶The UKPDS enrolled patients with newly diagnosed T2D. #Defined as a urinary albumin concentration 50–299 mg/L. ||Defined as a urinary albumin concentration ≥300 mg/L. **Data from 9.5 years of median follow-up in 3682 participants (48% with diabetes) of the Chronic Renal Insufficiency Cohort study utilizing mixed model estimates of time spent in each CKD stage prior to progression or death in patients with A1c ≥7.5% compared to patients with A1c <7.5%.

CKD = chronic kidney disease; **eGFR** = estimated glomerular filtration rate; **ESKD** = end-stage kidney disease; **NHANES** = National Health and Nutrition Examination Survey; **T2D** = type 2 diabetes; **UACR** = urine albumin-to-creatinine ratio; **US** = United States

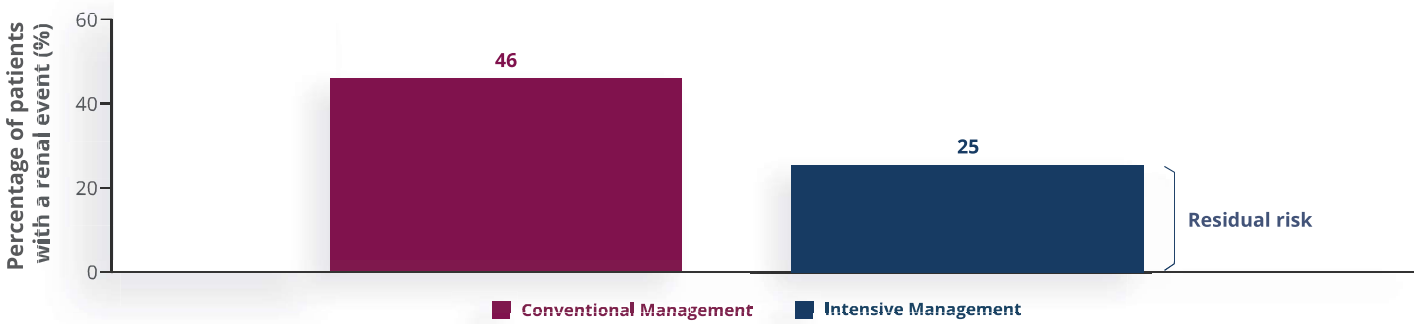
Current Approaches to Management

Targets for Therapeutic Intervention in CKD



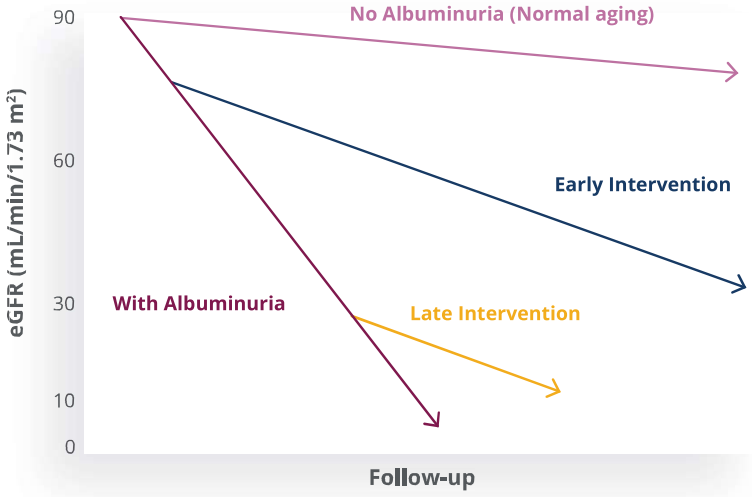
Optimal Risk Factor Management Does Not Eliminate Risk of Diabetic Nephropathy[21,22,†]

Residual Nephropathy Risk in Patients with T2D and Microalbuminuria Randomized to Multifactorial Intensive Medical Therapy After 13 Years



Conventional and intensive management based on treatment goals for BP, HbA1c, and cholesterol in the 1999 Steno-2 trial over a mean follow up of 3.8 years.

Potential Impact of Early Intervention to Maintain Renal Function[23]



Guidelines Recommend Routine Screening for CKD in Patients with Cardiorenal-metabolic Disease

KDIGO[4,24]

Regular testing of high-risk groups (including those with T2D, HTN, CVD) can give early indication of kidney damage. A team-based and integrated approach to manage these patients should focus on regular assessment, control of multiple risk factors, and self-management to protect kidney function and reduce risk of complications.

ADA[9]

Annually assess urinary albumin and eGFR in patients with T2D.

*This is not an exhaustive list of treatable risk factors. †Diabetic nephropathy was defined as a urinary albumin excretion of more than 300 mg/24 hours in at least one of the two-yearly examinations.

ADA = American Diabetes Association; **ASCVD** = atherosclerotic cardiovascular disease; **BP** = blood pressure; **CKD** = chronic kidney disease; **CVD** = cardiovascular disease; **eGFR** = estimated glomerular filtration rate; **HbA1c** = hemoglobin A1c; **HTN** = hypertension; **KDIGO** = Kidney Disease Improving Global Outcomes; **T2D** = type 2 diabetes

Summary

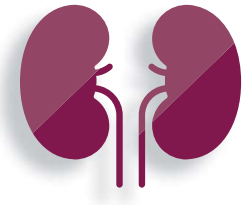
Burden of CKD is Significant

- 1 in 7 adults in the US is living with CKD, and increases in the prevalence of CKD risk factors are anticipated to increase the burden of ESKD[1,25]
- Progressive deteriorations in renal function increase the risk of adverse outcomes, such as risk of hospitalizations, CV events, mortality, and healthcare costs[2,10]
- CKD significantly shortens life span which is further reduced with comorbid T2D[3]

Screen, Diagnose, and Manage Early

Several guidelines recommend to regularly screen patients at increased risk[4,9]

- Roughly 10% of patients with CKD and T2D receive a diagnosis[26]
- In patients with T2D, earlier stages (1–3) of CKD are more common than late stages[13]
- 35 – 45% of patients with CKD (stages 2 – 4) will progress to a worse stage of kidney disease within 5 years[5]



Monitor Renal Function

Engage patients in risk factor reduction and use multifactorial interventions to tailor treatment regimens to the individual

- KDIGO recommends routine CKD monitoring with increasing frequency as renal function declines[4]
- Lower eGFR and higher albuminuria are independently associated with increased adverse CV outcomes and premature death, which is worse in patients with T2D[27]

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