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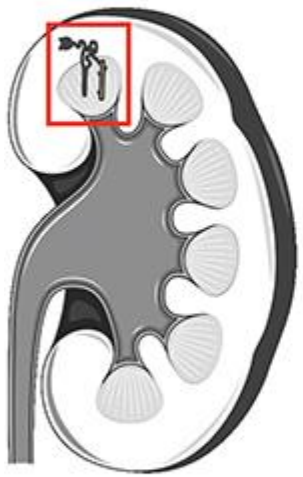
Pathophysiology and Epidemiology of Chronic Kidney Disease

George Bakris, MD
Professor of Medicine
University of Chicago Medicine

Kidney Function: An Overview



Renal corpuscle

- Generates the glomerular filtrate composed by water, ions, and small molecules

Proximal convoluted tubule

- Reabsorbs sodium, chloride, potassium, water, glucose, amino acids, bicarbonate, calcium and phosphate
- Secretes ammonium and creatinine

Loop of Henle (thin descending limb)

- Reabsorbs water

Loop of Henle (thin ascending limb)

- Reabsorbs sodium and chloride

Loop of Henle (thick ascending limb)

- Reabsorbs ammonium, sodium, chloride

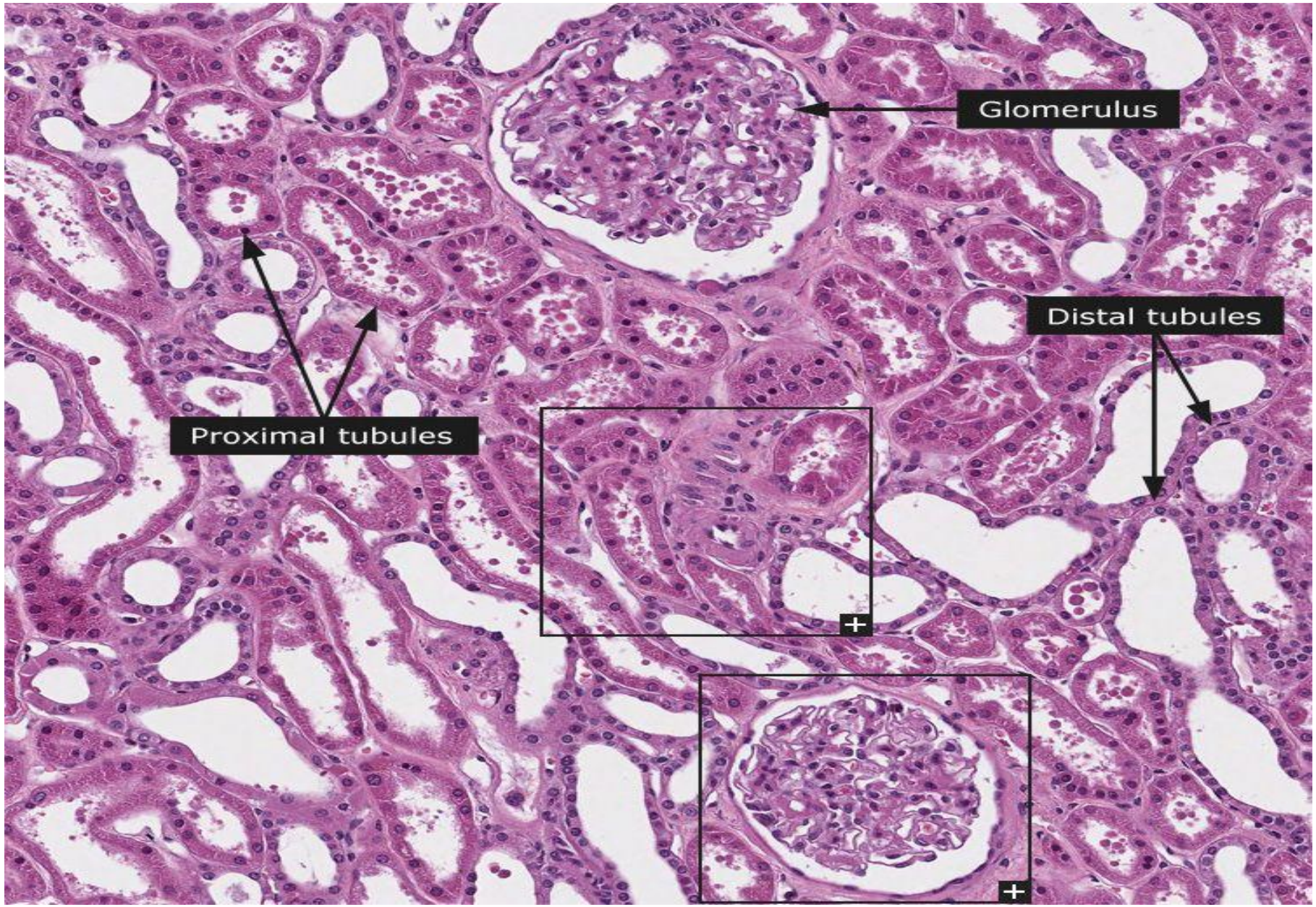
Distal convoluted tubule

- Reabsorbs sodium and chloride

Collecting duct

- Reabsorbs sodium, chloride and water
- Secretes ammonium, hydrogen ions and potassium

Cocchiaro P et al. Front Cell Dev Biol 2017; 5:114


Glomerulus
Distal tubules
Proximal tubules

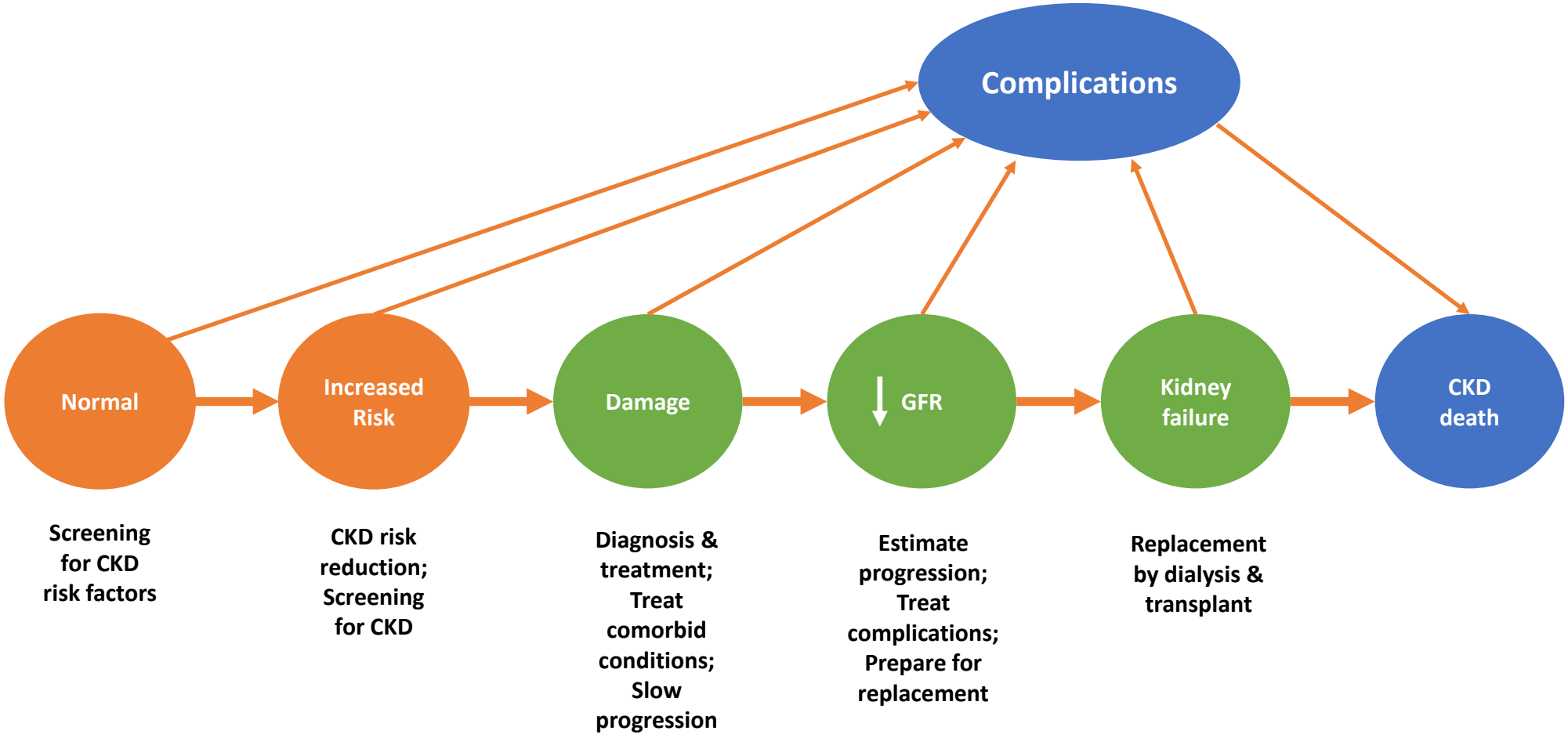
Overview of Pathophysiology

- Can’t Discuss Pathophysiology of Kidney Disease in General BECAUSE unique to each disease that causes it.

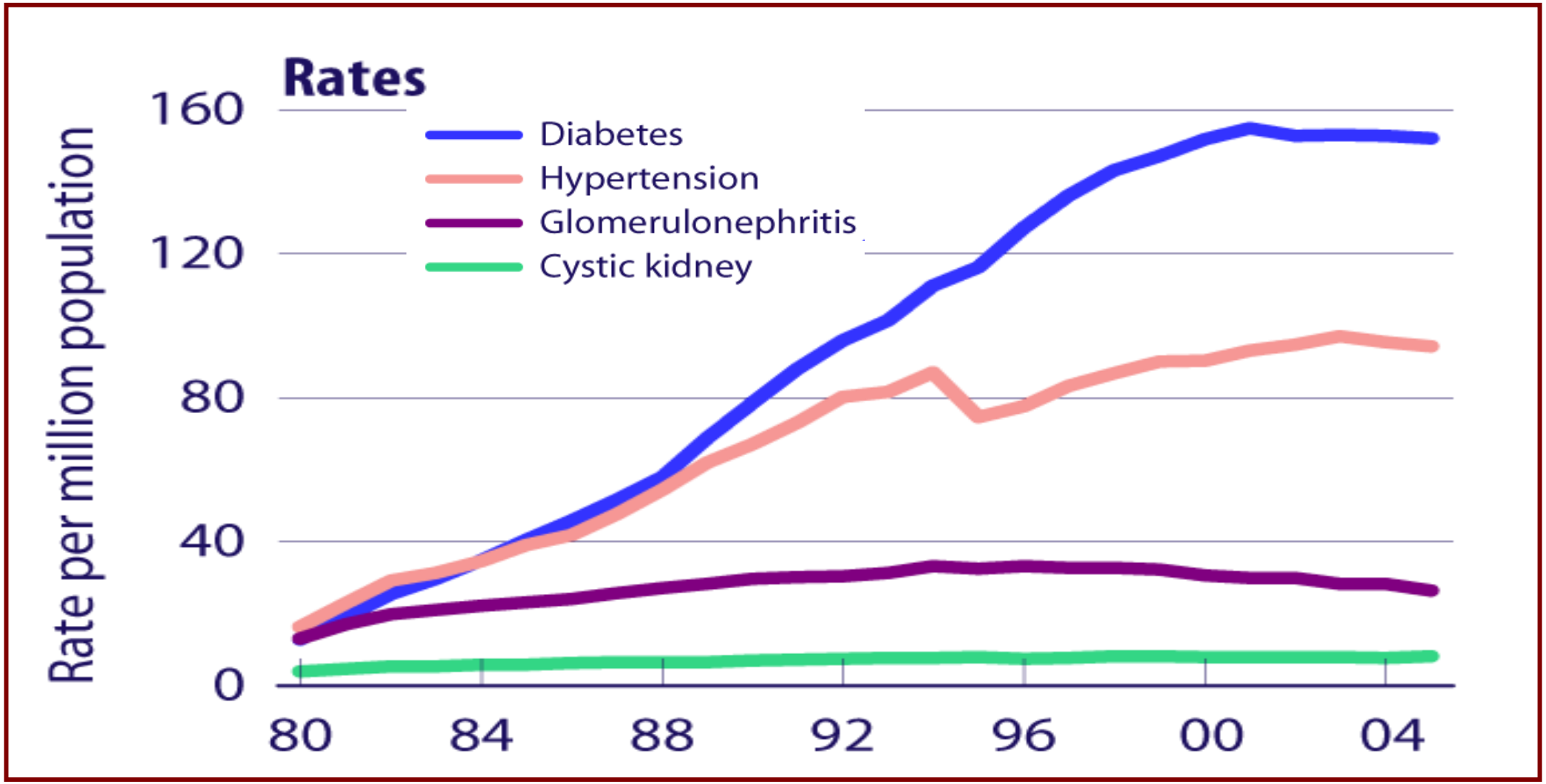
Commonalities among causes of CKD include:

- Inflammation resulting in nephron loss
- Inflammation resulting in loss of interstitium
- Ischemia resulting in limited blood flow to parts of the nephron

Stages in Progression of Chronic Kidney Disease and Therapeutic Strategies

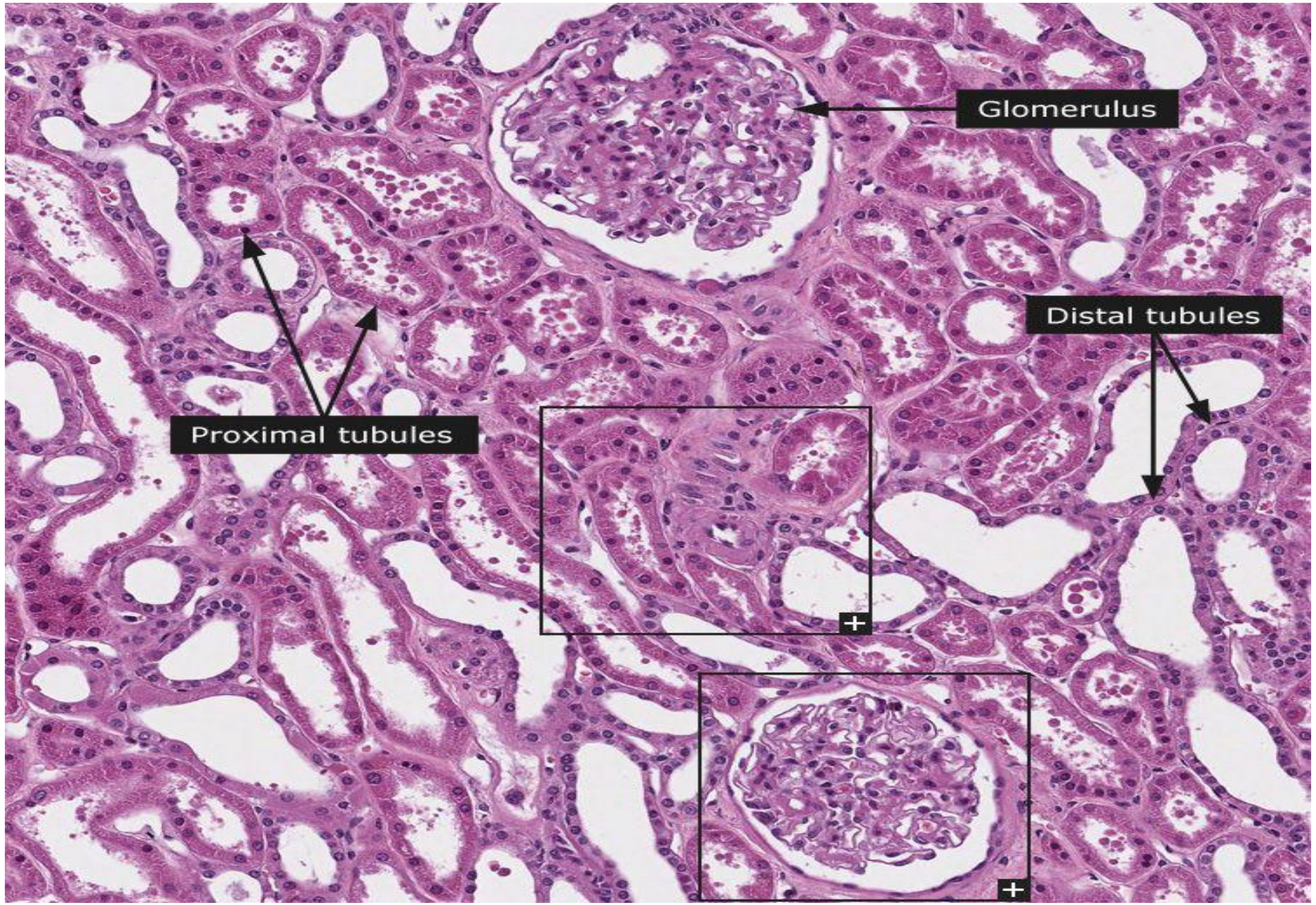


Diabetes and Hypertension are Leading Causes of Kidney Failure

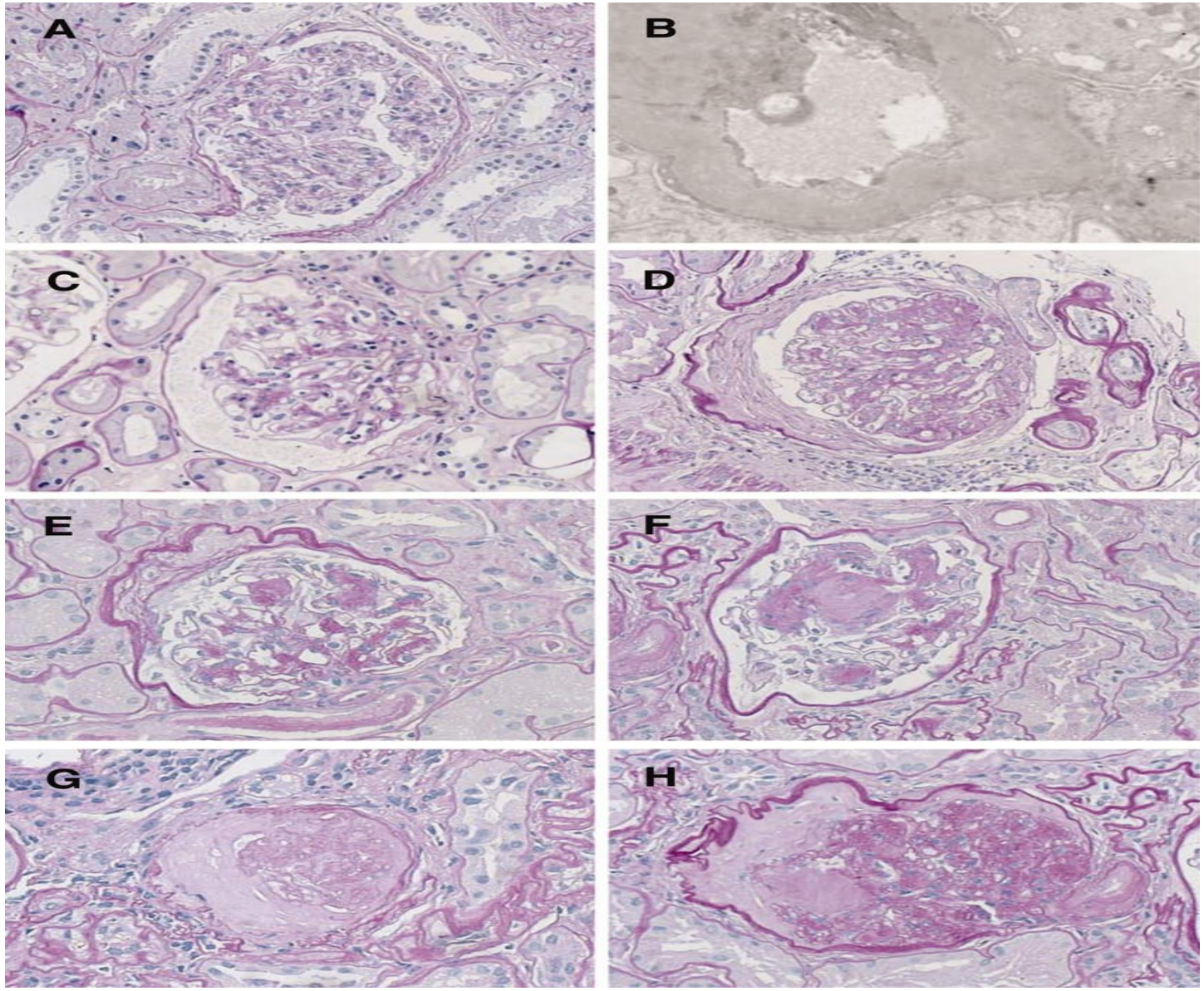


Incident ESRD rates, by primary diagnosis, adjusted for age, gender, & race.

ESRD, end stage renal disease; USRDS ADR, 2007


Glomerulus
Distal tubules
Proximal tubules

Representative examples of the morphologic lesions in DN. (A) Glomerulus showing only mild ischemic changes, with splitting of Bowman's capsule.



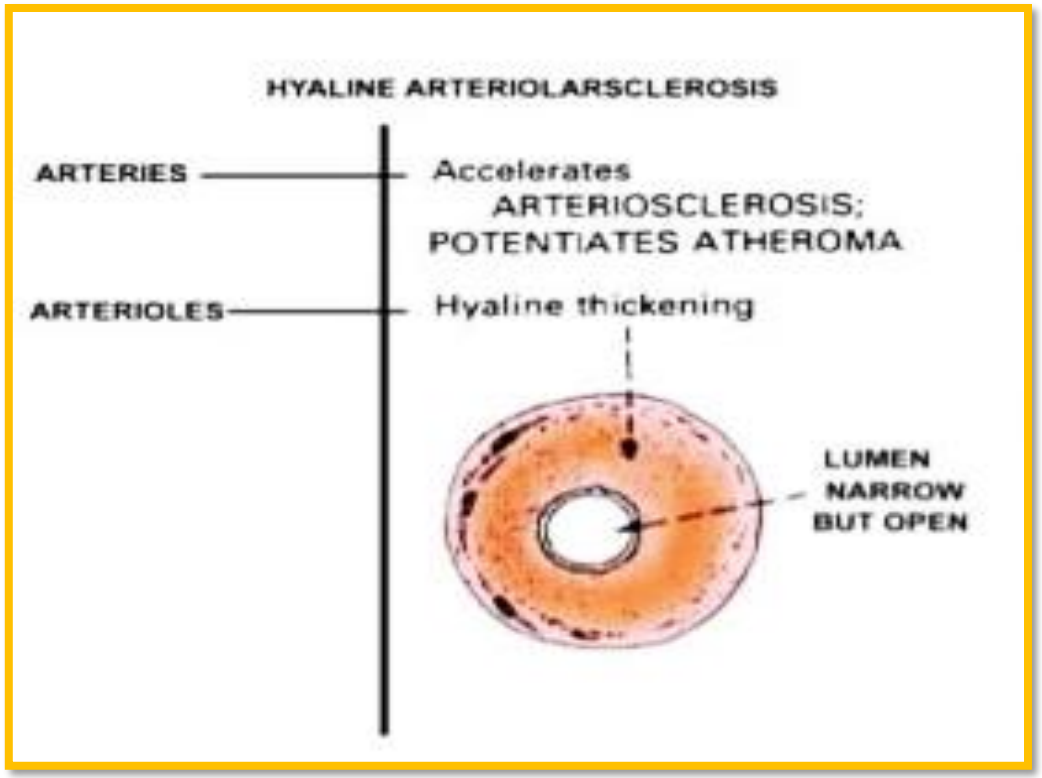
Thijs W. Cohen Tervaert et al. JASN 2010;21:556-563

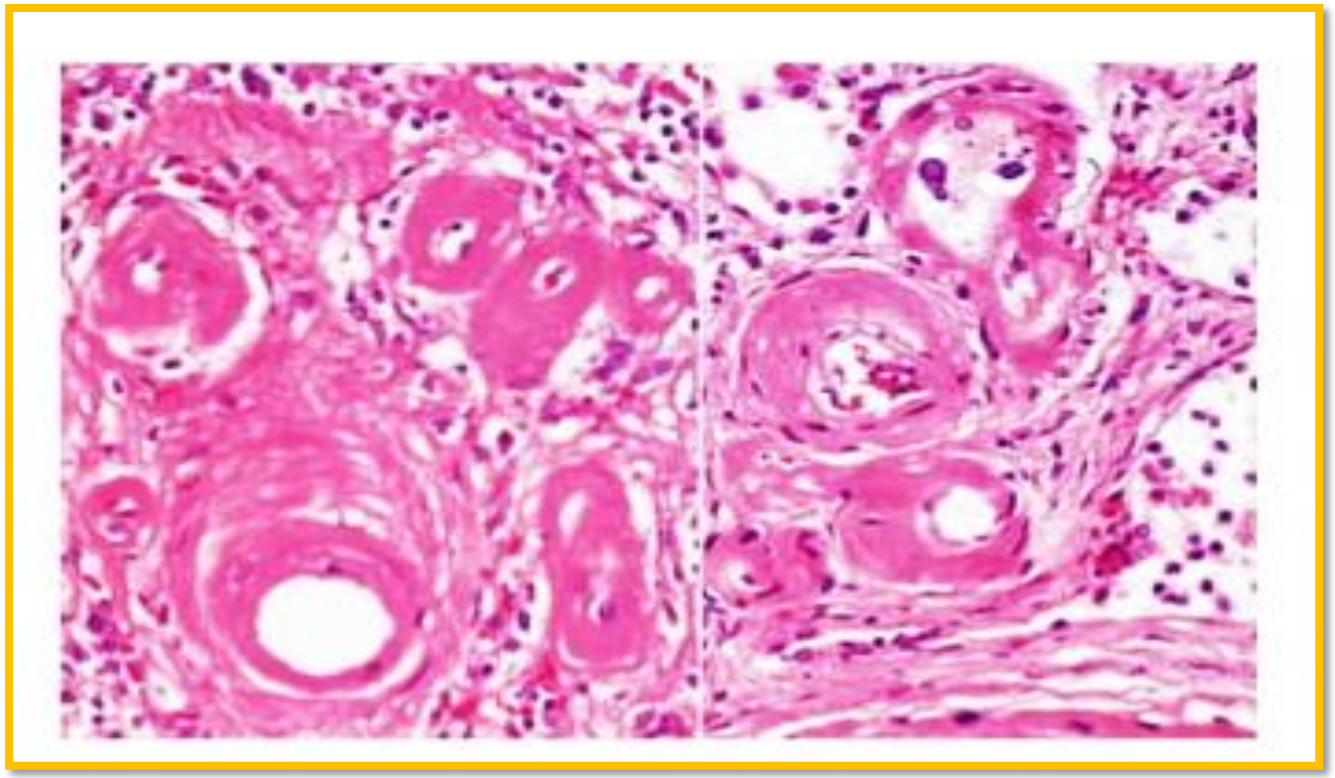
Effects on The Kidneys

- Glomerular sclerosis leading to impaired kidney function and finally end stage
  kidney disease

- Ischemic kidney disease especially when renal artery stenosis is the cause of HTN

Benign Nephrosclerosis: Hyaline Arteriolosclerosis



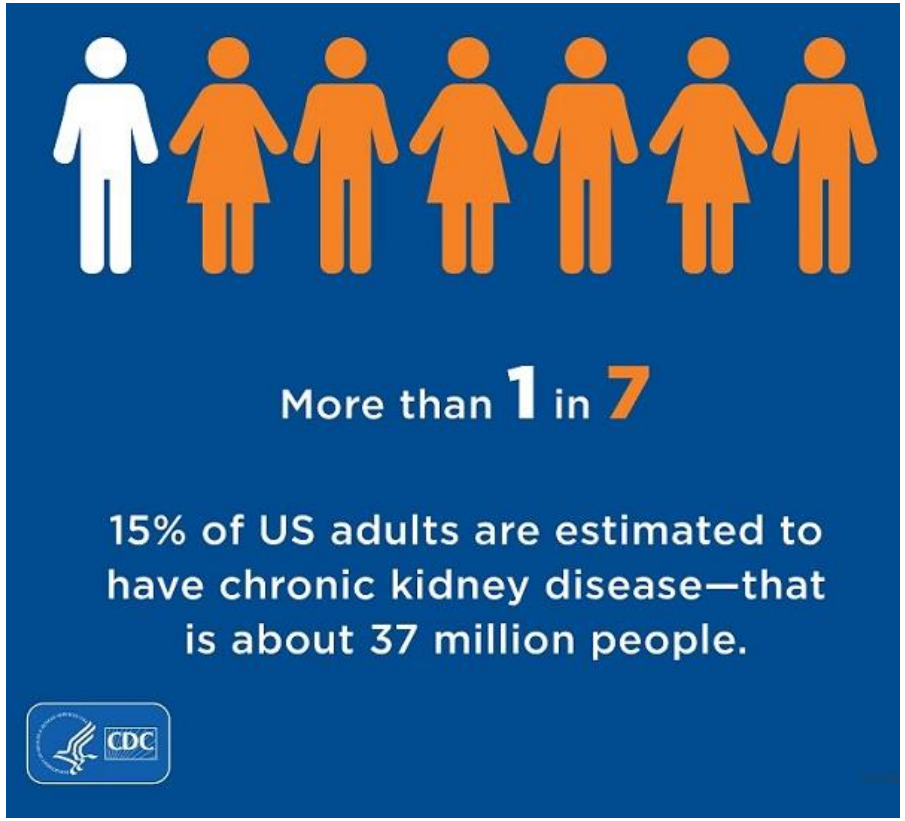


Gamble CN. Am J Pathol 1986;122(3): 410-420

CKD is Common Among US Adults

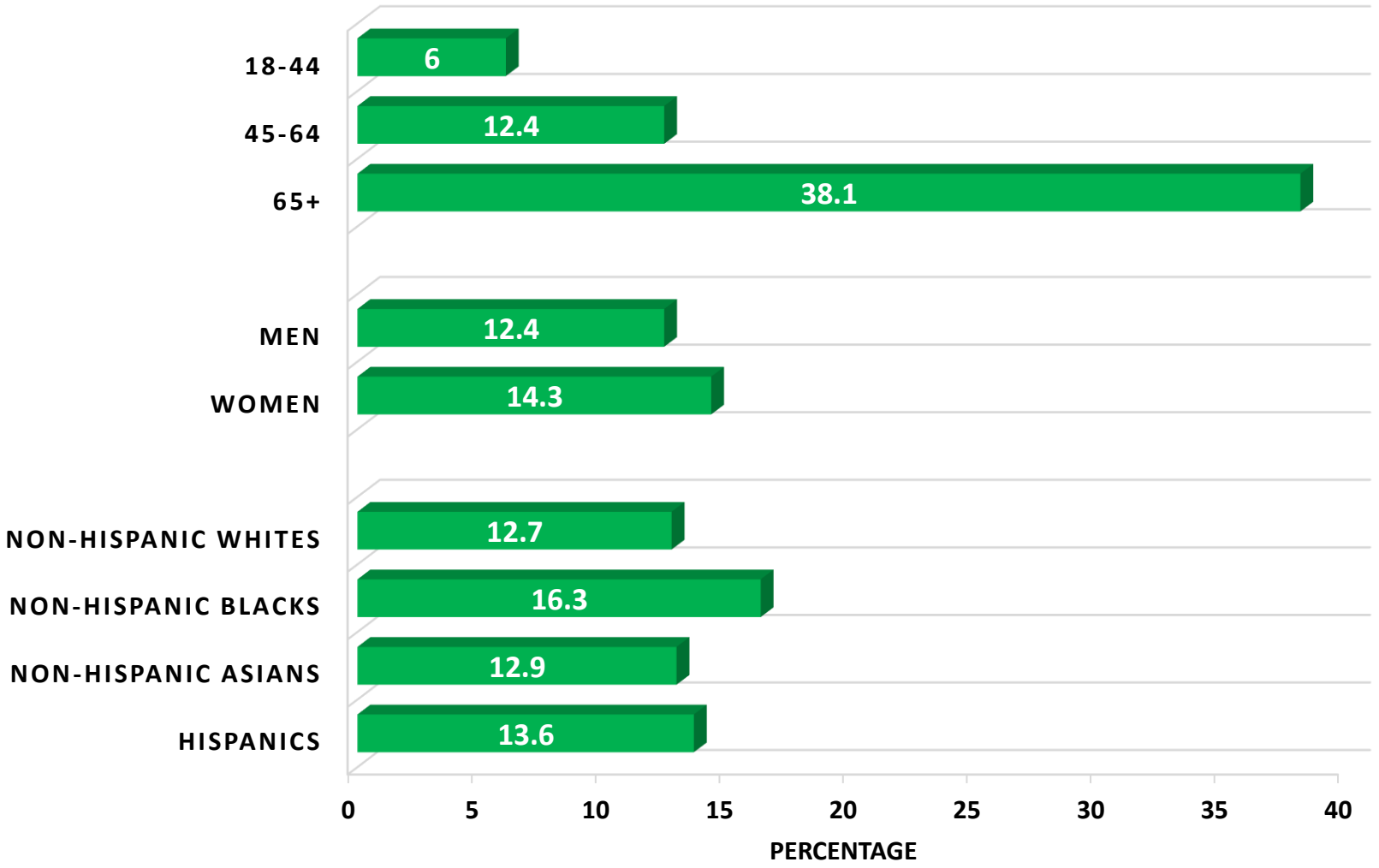
Fast Stats

- More than 1 in 7, that is 15% of US adults or 37 million people, are estimated to have CKD
- As many as 9 in 10 adults with CKD ***do not know*** they have CKD
- About 2 in 5 adults with severe CKD ***do not know*** they have CKD



https://www.cdc.gov/kidneydisease/publications-resources/ckd-national-facts.html

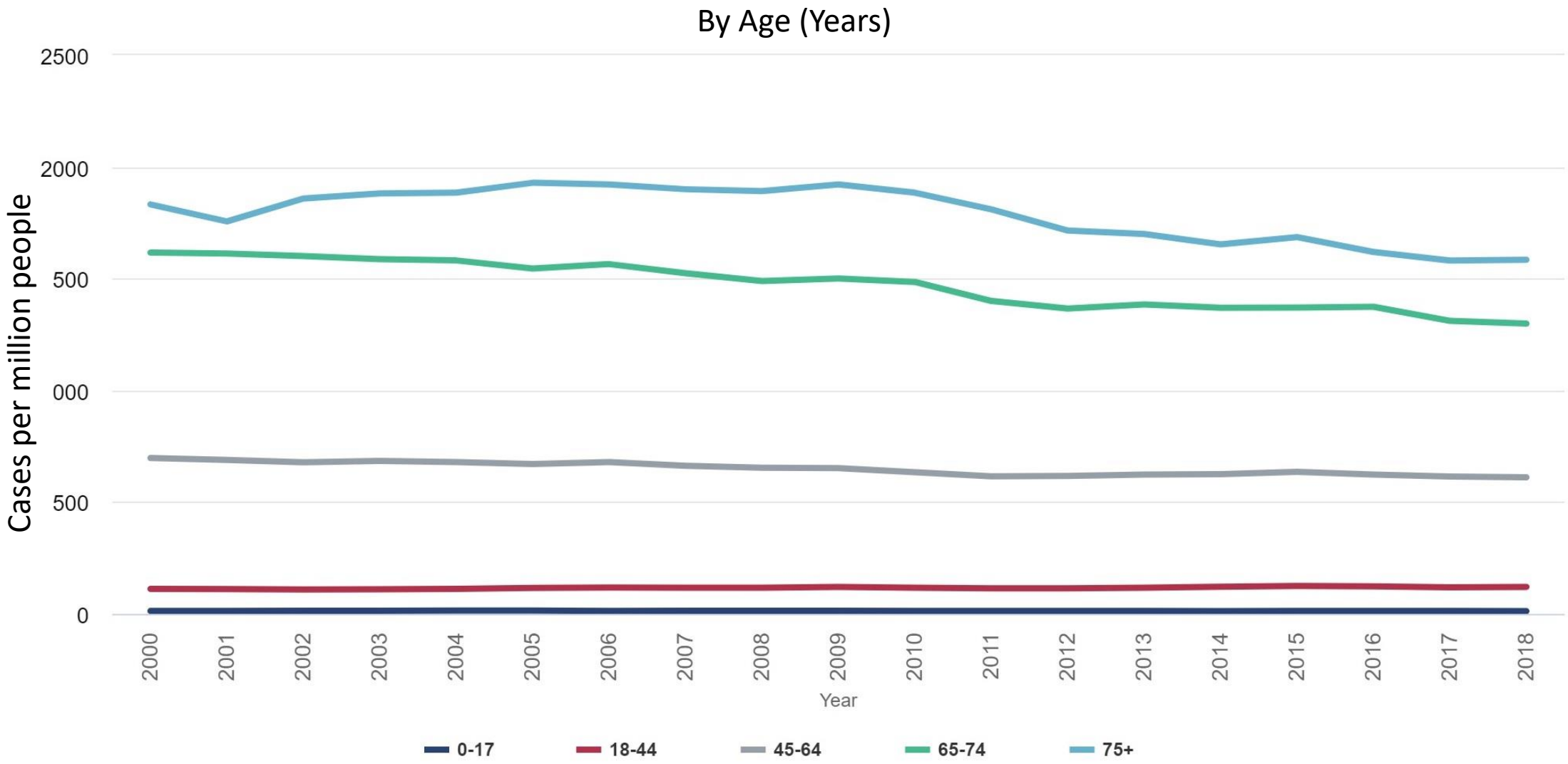
Percentage of US Adults Aged 18 Years of Older with CKD*



*CKD stages 1-4 using data from the 2015-2018 National Health and Nutrition Examination Survey and the CKD Epidemiology Collaboration (CKD-EPI) equation

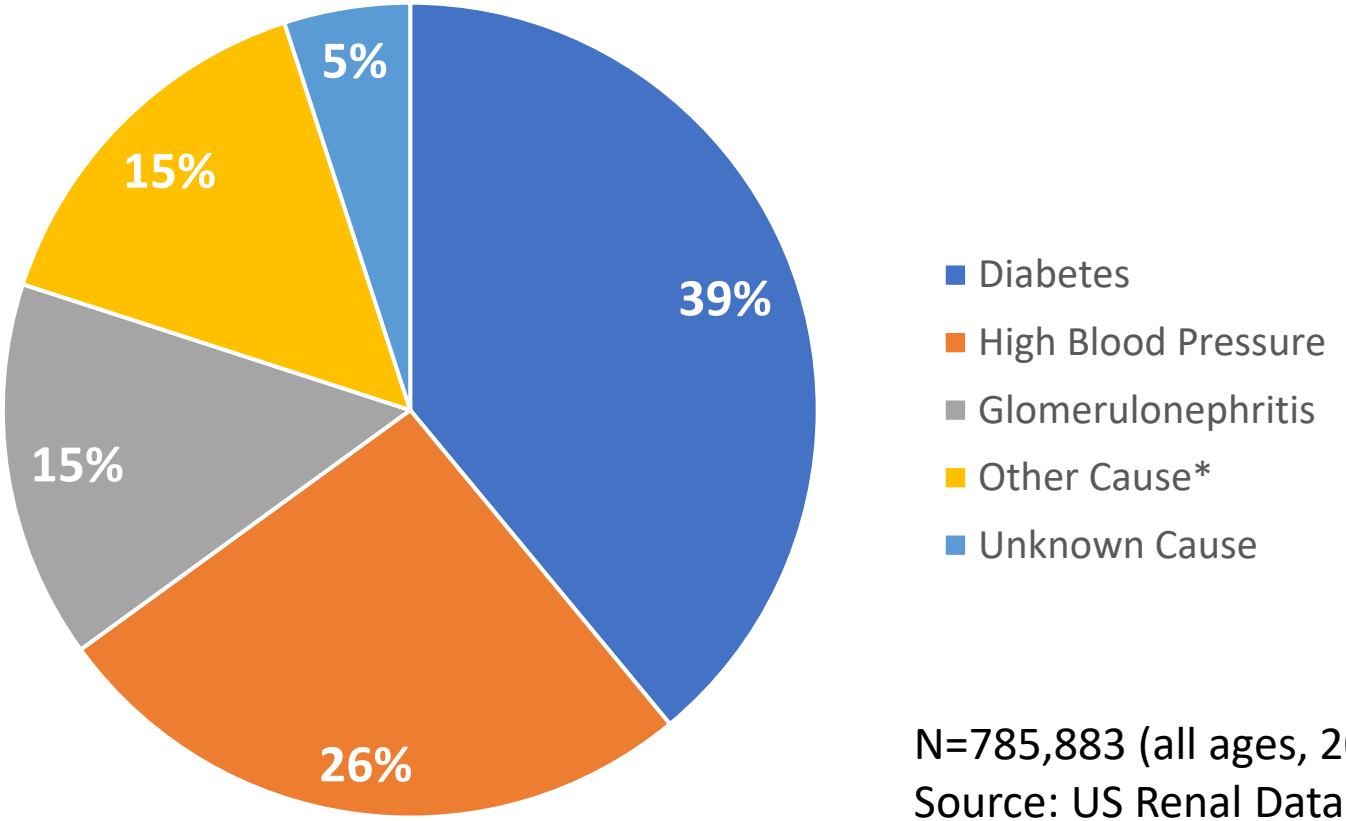
https://www.cdc.gov/kidneydisease/publications-resources/ckd-national-facts.html

Adjusted ESRD Incidence by Age, 2000-2018



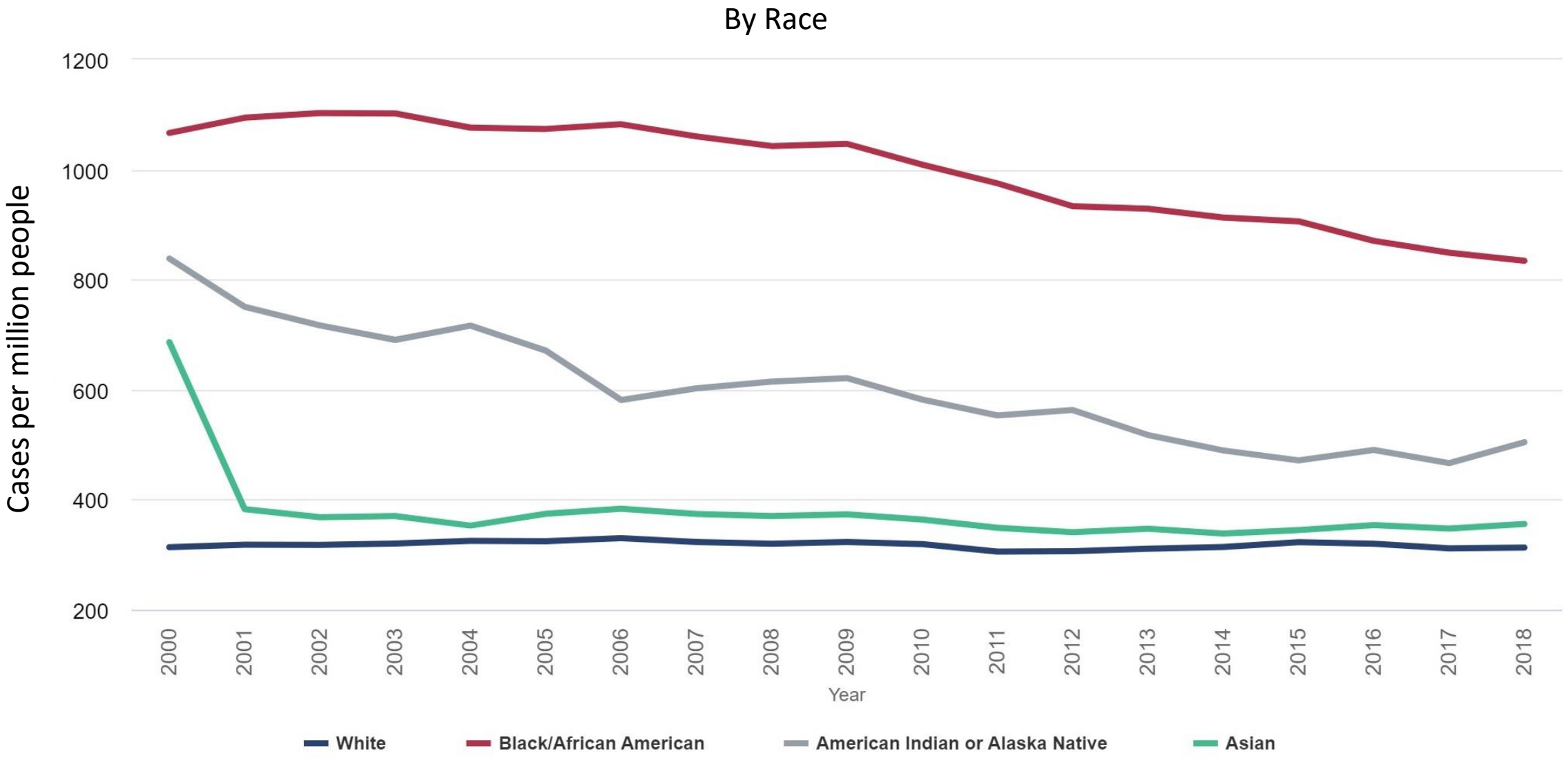
Data Source: USRDS: 2020 Annual Data Report (https://adr.usrds.org/2020/end-stage-renal-disease/1-incidence-prevalence-patient-characteristics-and-treatment-modalities)

Reported Causes of End-Stage Renal Disease in the United States



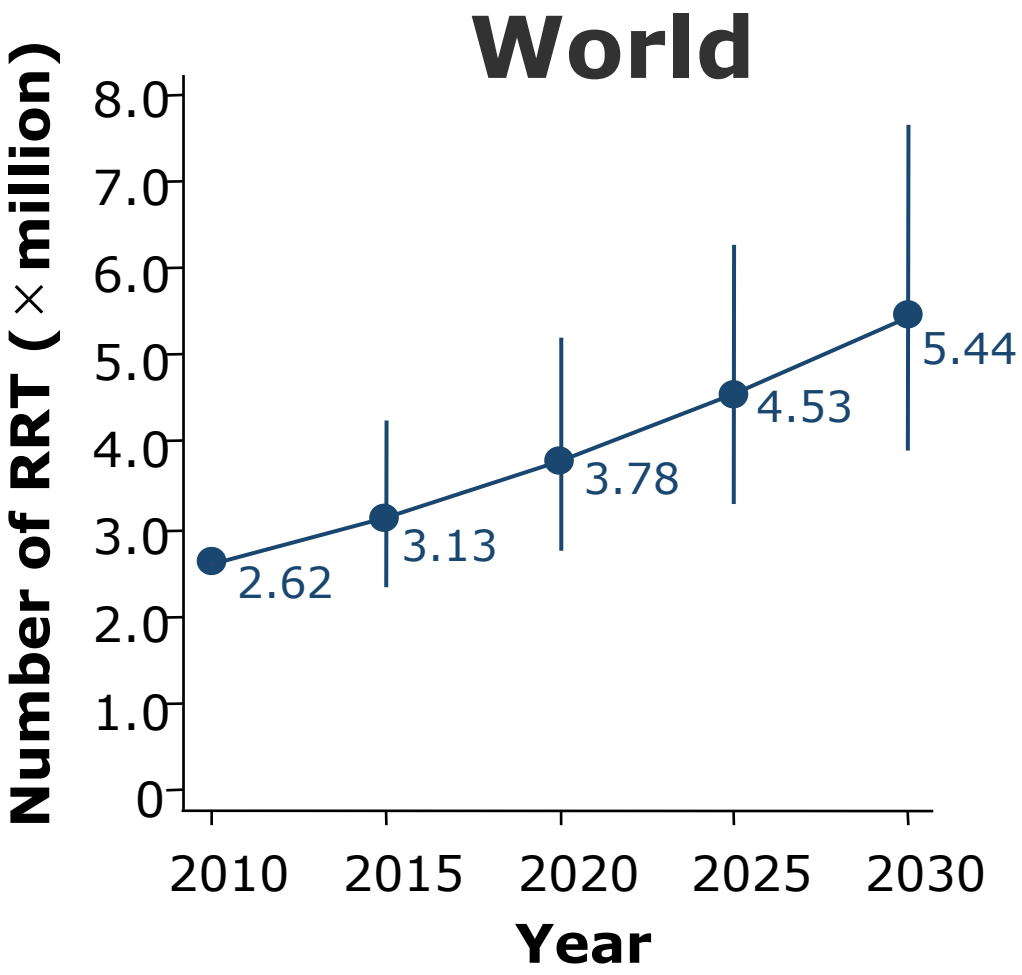
N=785,883 (all ages, 2018)
Source: US Renal Data System
*Includes polycystic kidney disease, among other causes.

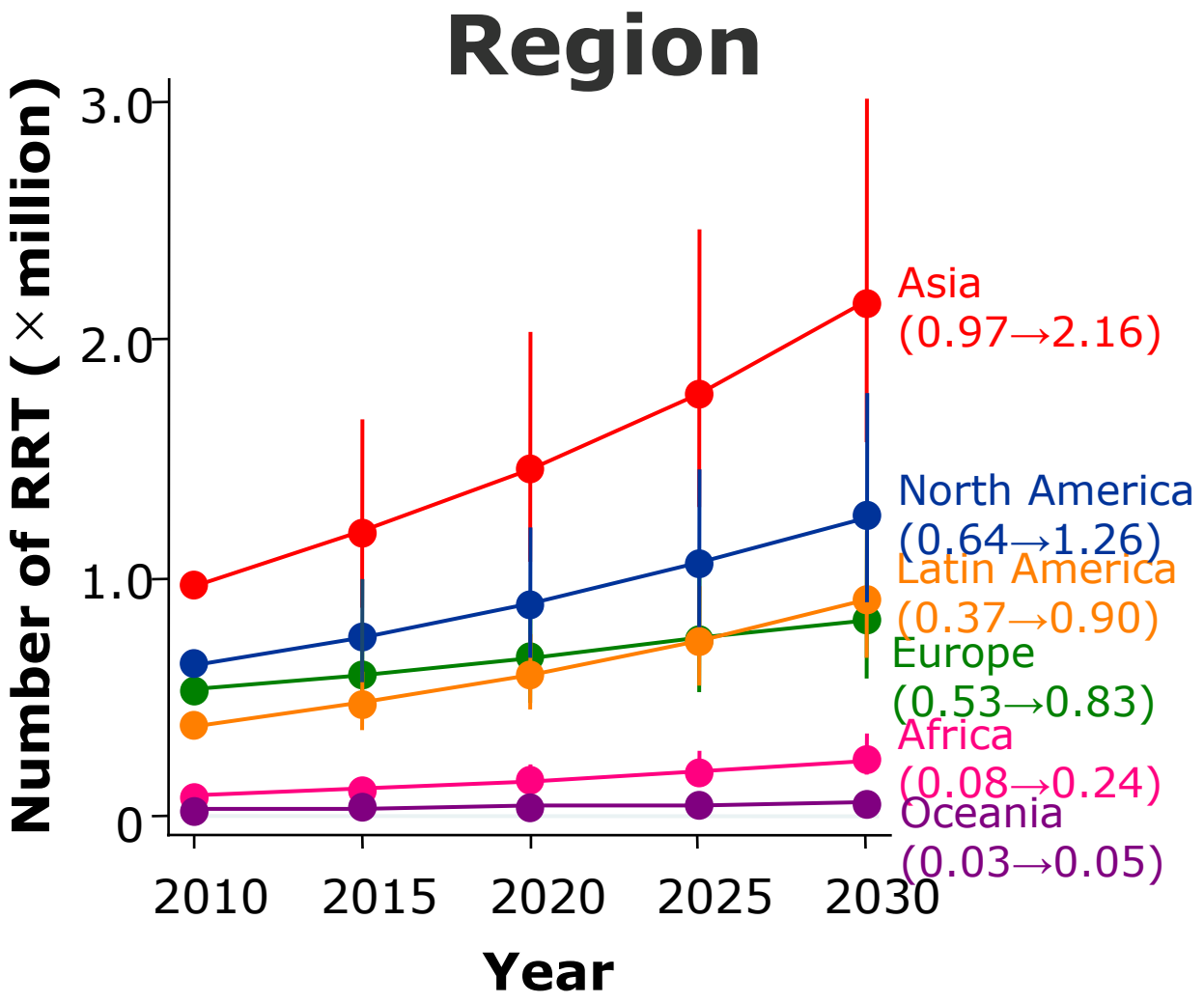
Adjusted ESRD Incidence by Race, 2000-2018



Data Source: USRDS: 2020 Annual Data Report (https://adr.usrds.org/2020/end-stage-renal-disease/1-incidence-prevalence-patient-characteristics-and-treatment-modalities)

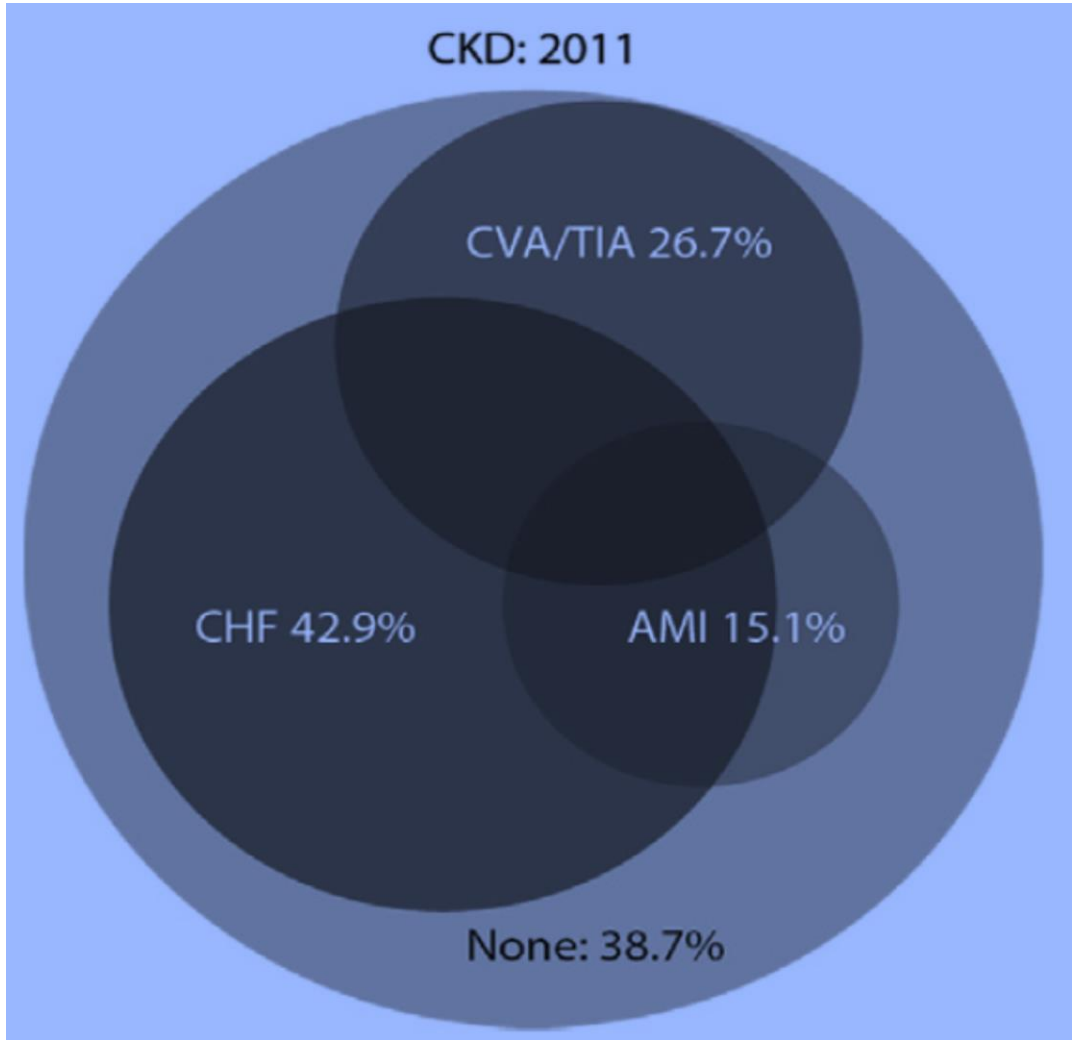
Number of People Receiving Renal Replacement Therapy Is Projected to Double

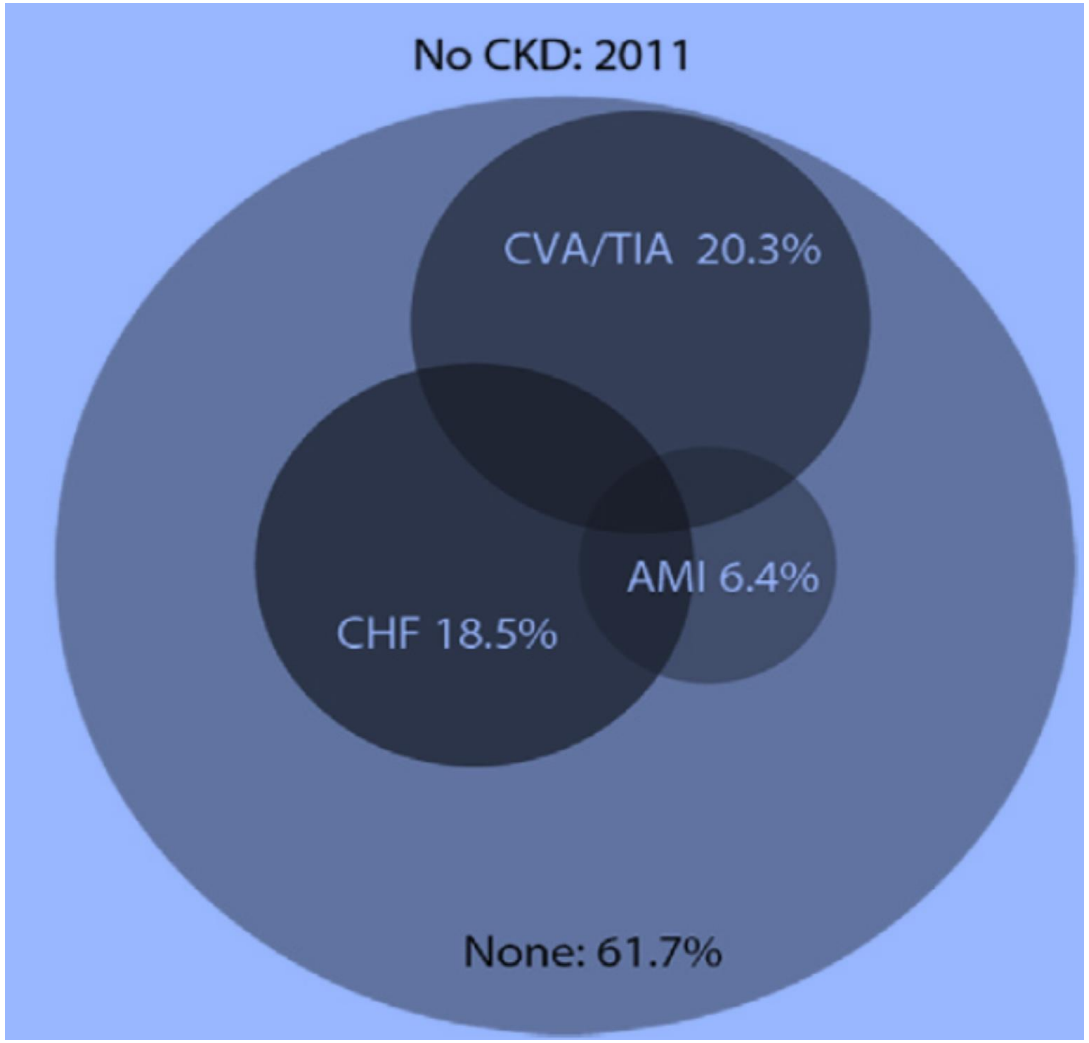




Liyanage T, et al. Lancet. 2015;385(9981):1975-1982.

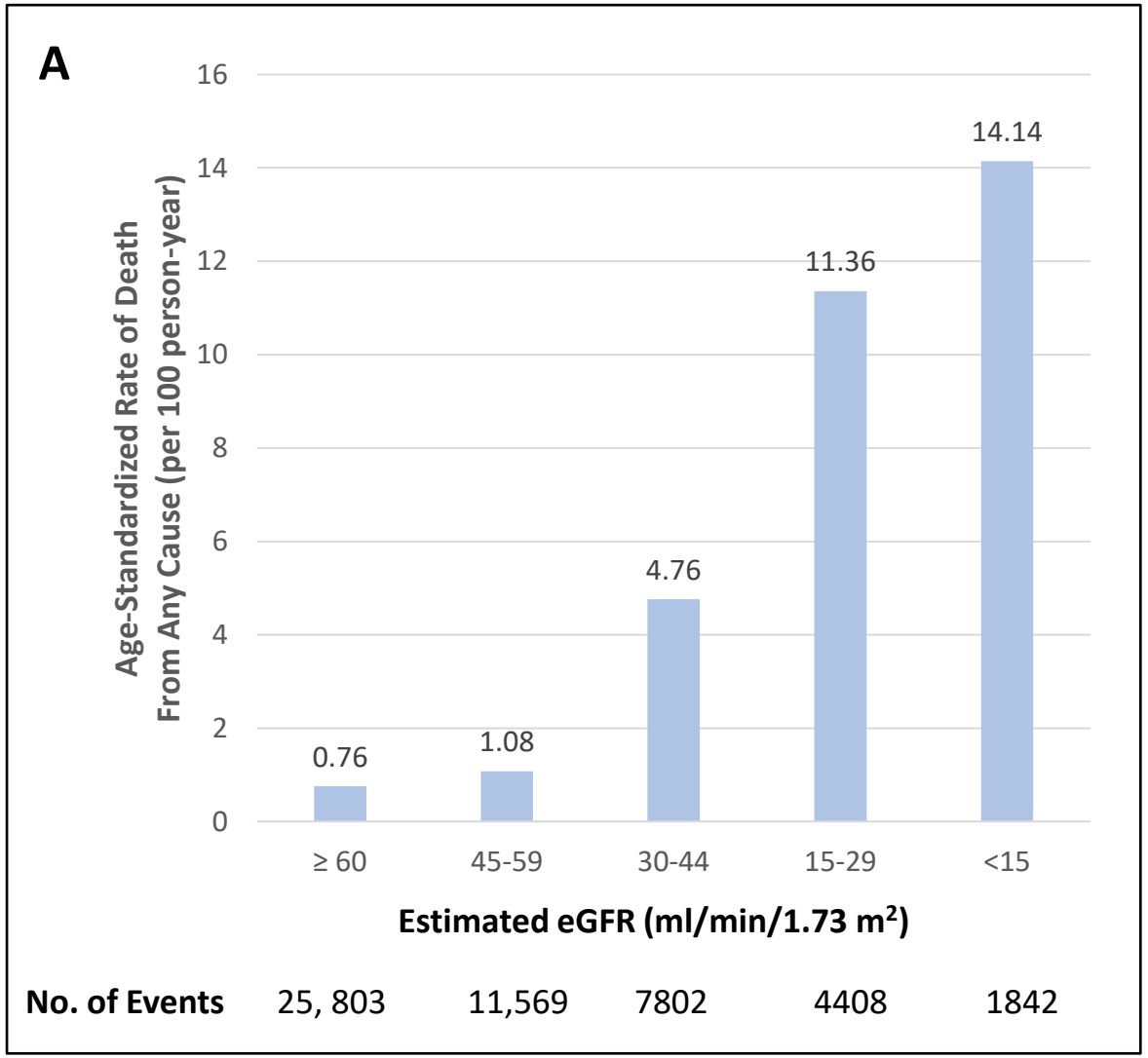
Cardiovascular Disease in Patients With or Without Chronic Kidney Disease

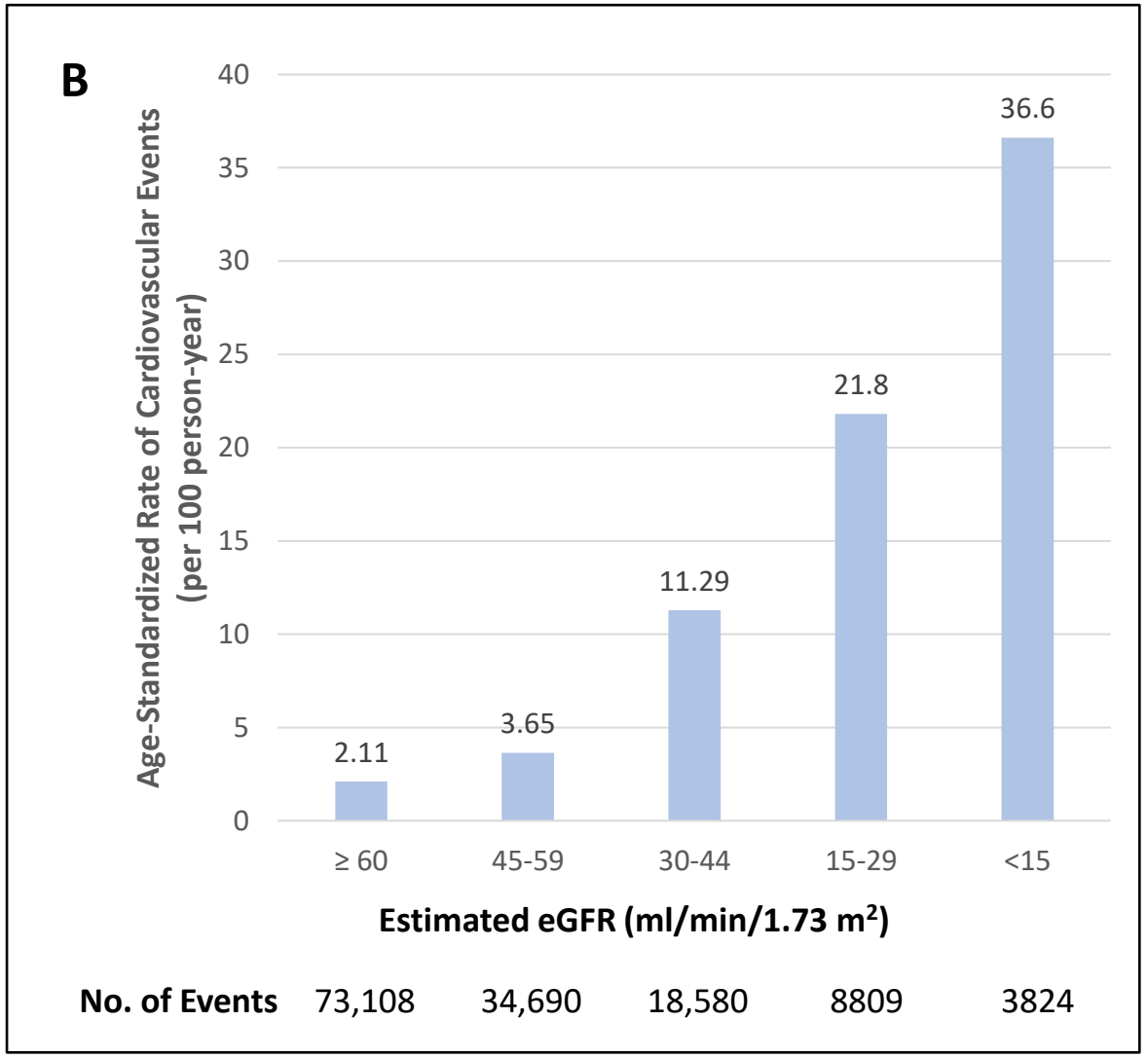




House AA Am J Kidney Dis 2018;72:284

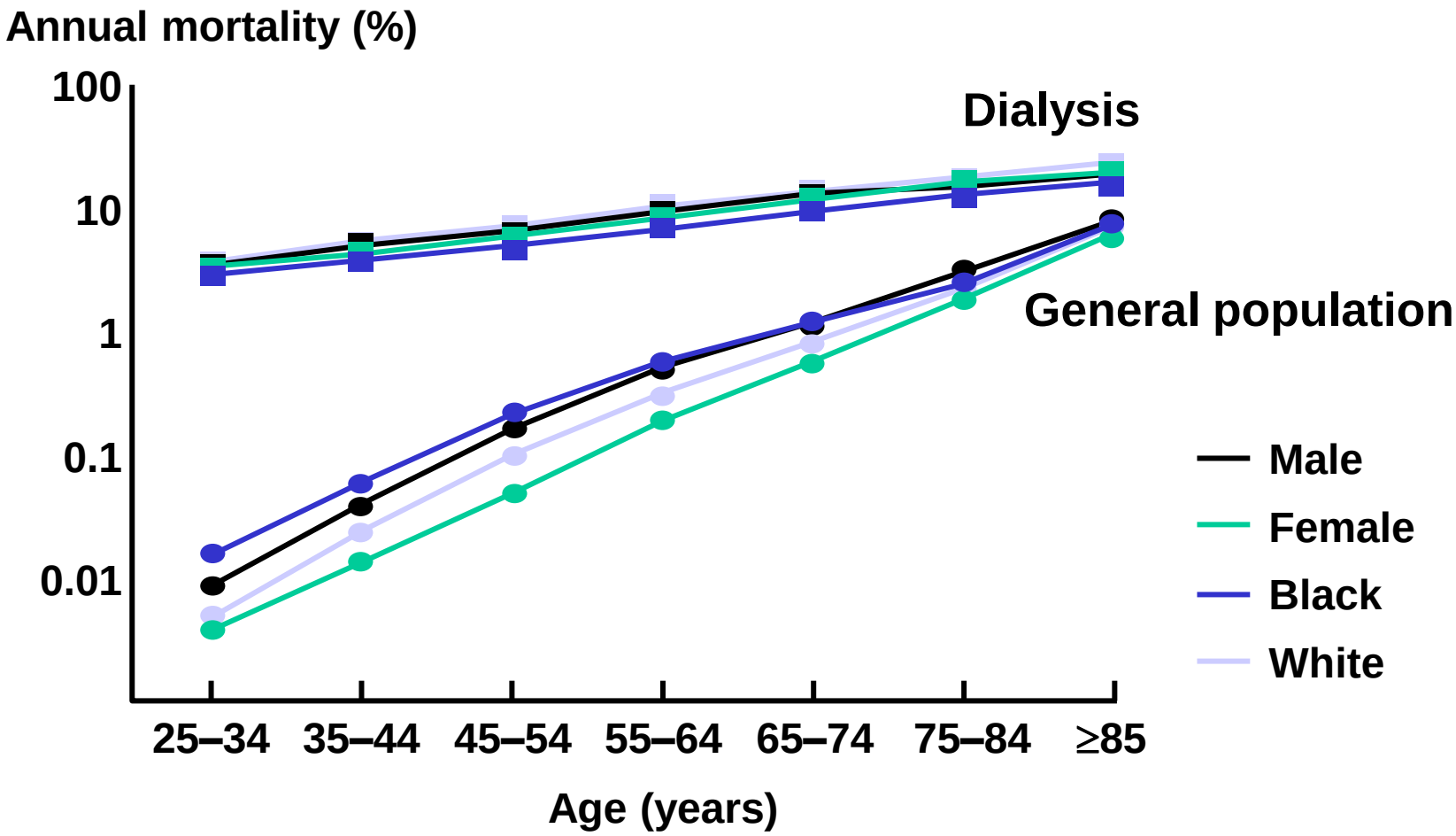
Age-Standardized Rates of Death from Any Cause (Panel A) and Cardiovascular Events (Panel B), According to the Estimated GFR among 1,120,295 Ambulatory Adults





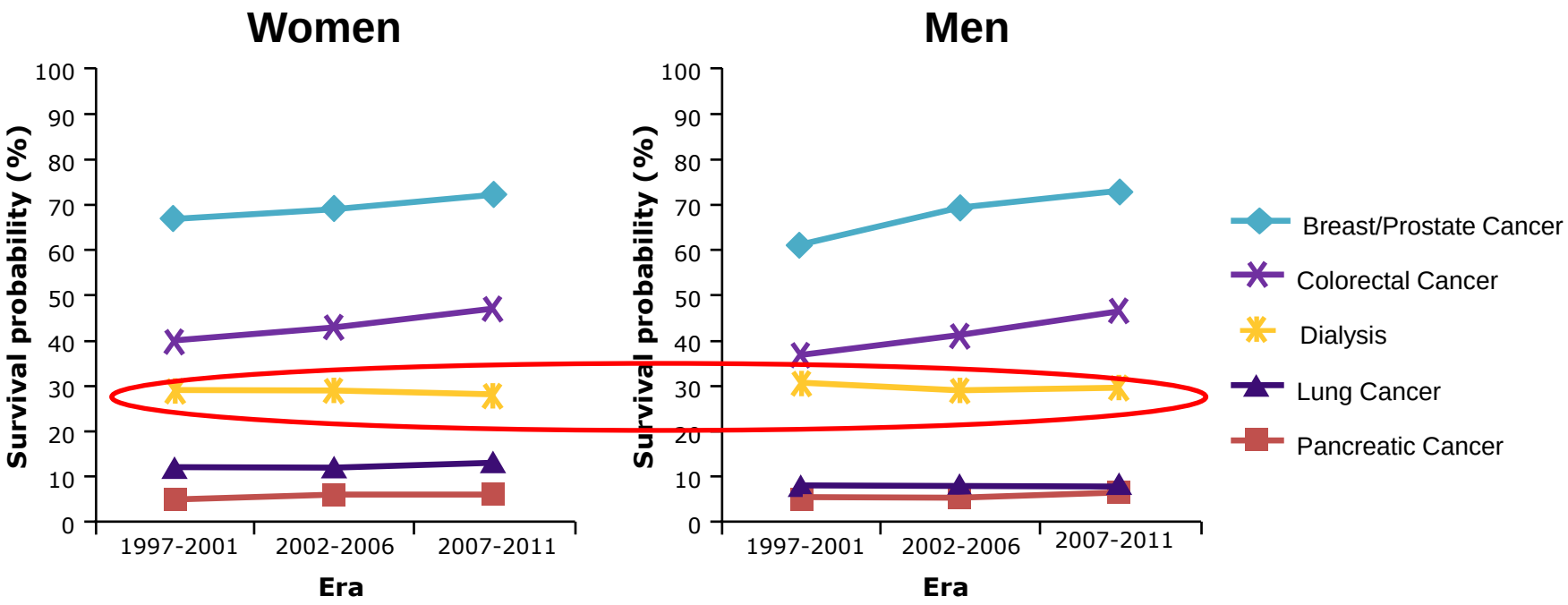
Go, A, et al. NEJM 2003;351: 1296-1305

Cardiovascular Mortality in the General Population and in ESRD Treated by Dialysis



Sarnak, MJ et al. Hypertension 2003;42: 1050-1065

Dialysis Survival is Shorter than Common Cancers

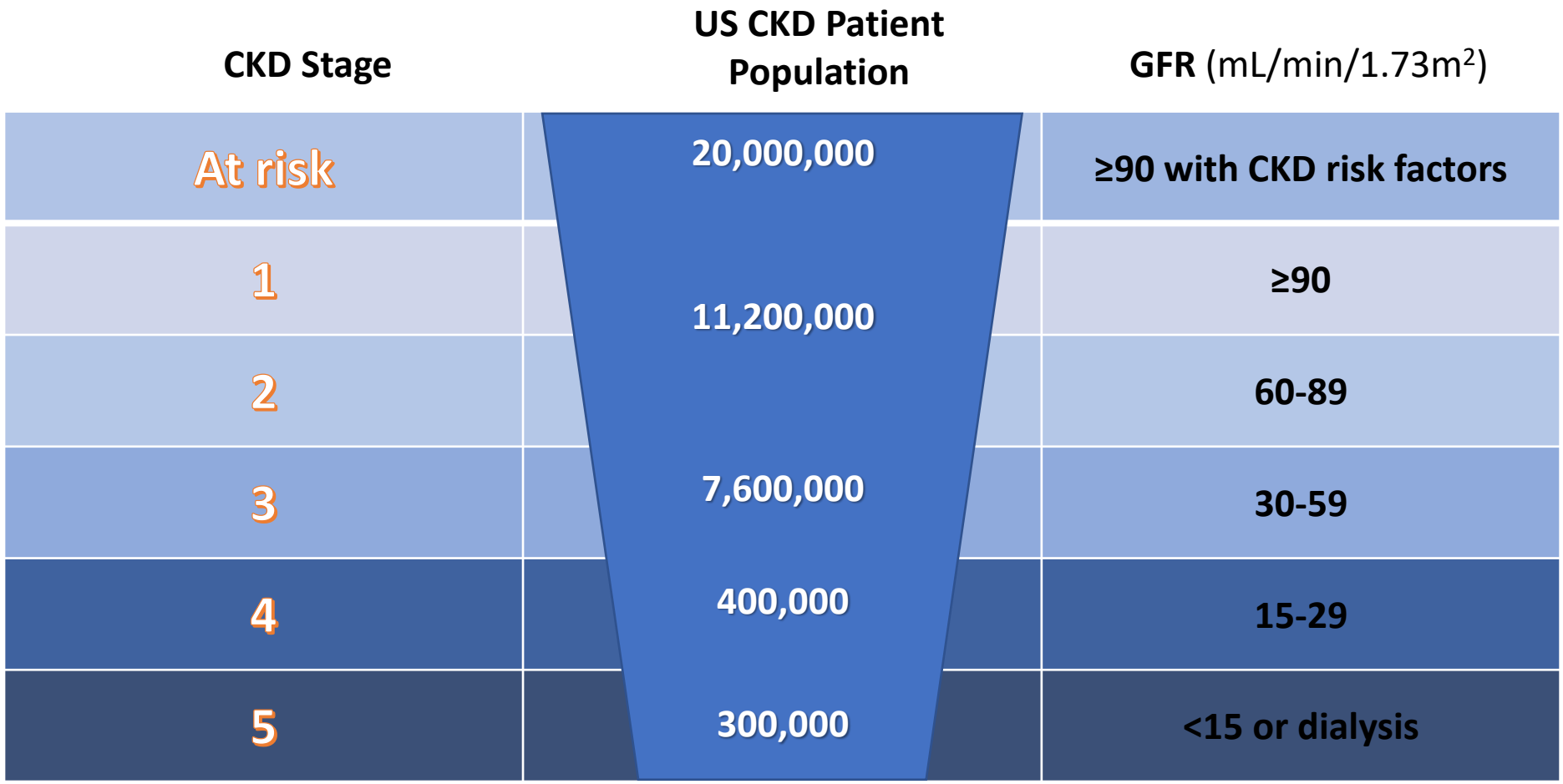


Unadjusted 10-year survival for all-cause mortality in Canada

n = 33,500 incident dialysis patients; 532,452 incident cancer patients

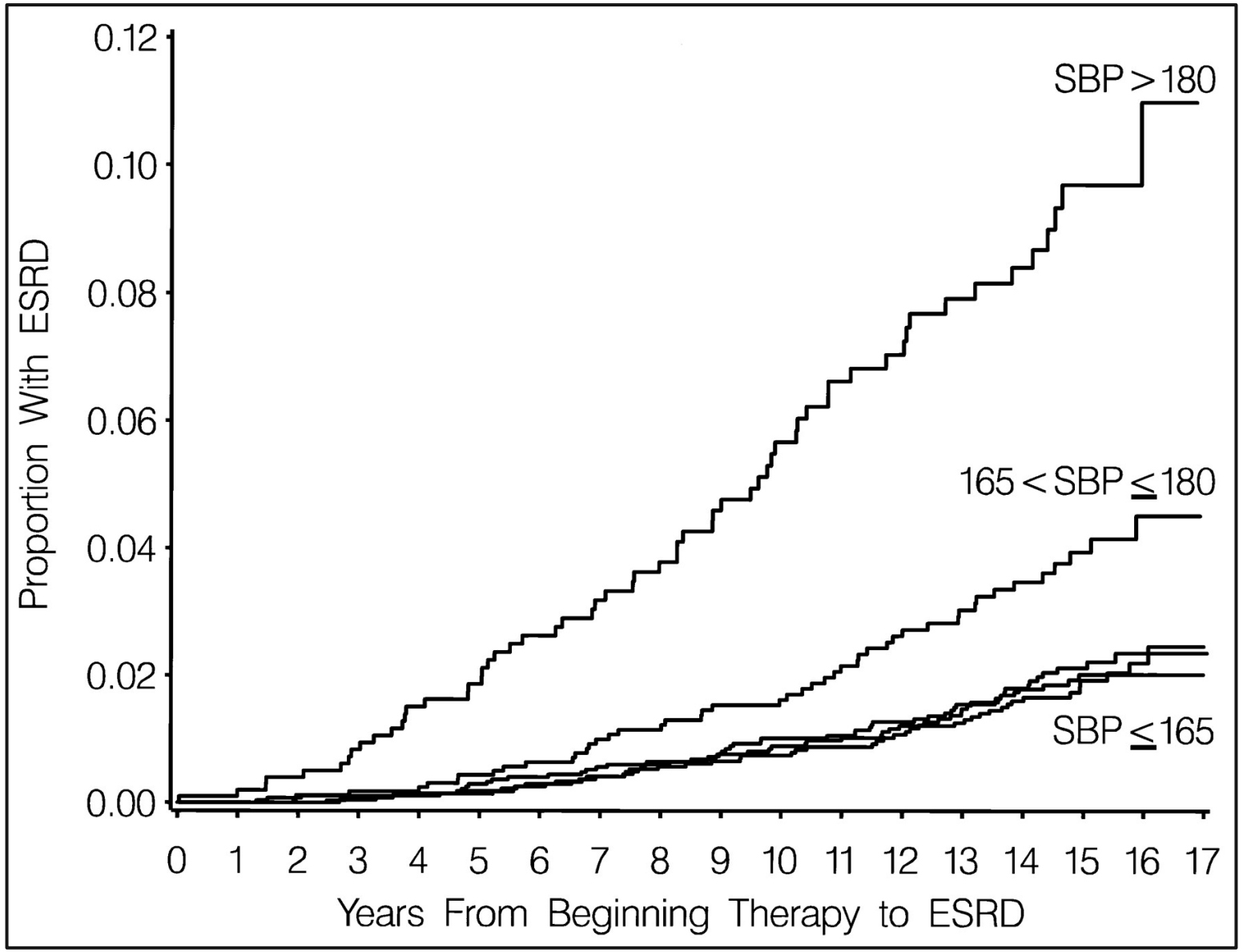
Naylor KL, et al. Am J Kidney Dis. 2019; 73(6):765-776

CKD is Highly Prevalent in the General Population



Adapted from the National Kidney Foundation, 2002

17 Year Follow-Up from VA Hypertension Clinics on ESRD



H. M. Perry, Jr., et.al *Hypertension* 25 (4 Pt 1):587-594, 1995.

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Stages of CKD and Associated Risks

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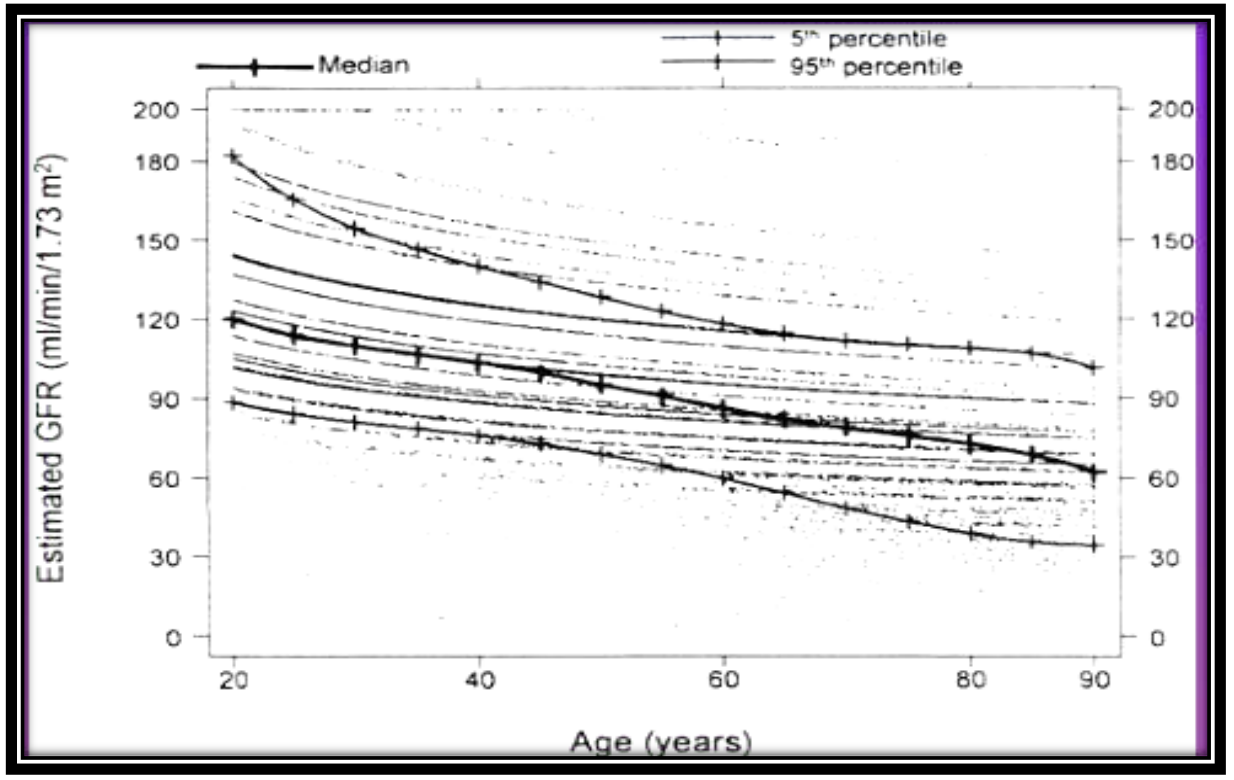
What are normal GFR values for adults?
NHANES III

Age (Years)	Average GFR
20-29	116 mL/min/1.73 m^2
30-39	107 mL/min/1.73 m^2
40-49	99 mL/min/1.73 m^2
50-59	93 mL/min/1.73 m^2
60-69	85 mL/min/1.73 m^2
70+	75 mL/min/1.73 m^2



In patients >70 an eGFR b/w 60 and 90 could be normal

Coresh AJKD 41(1) 1-12 NHANES III.

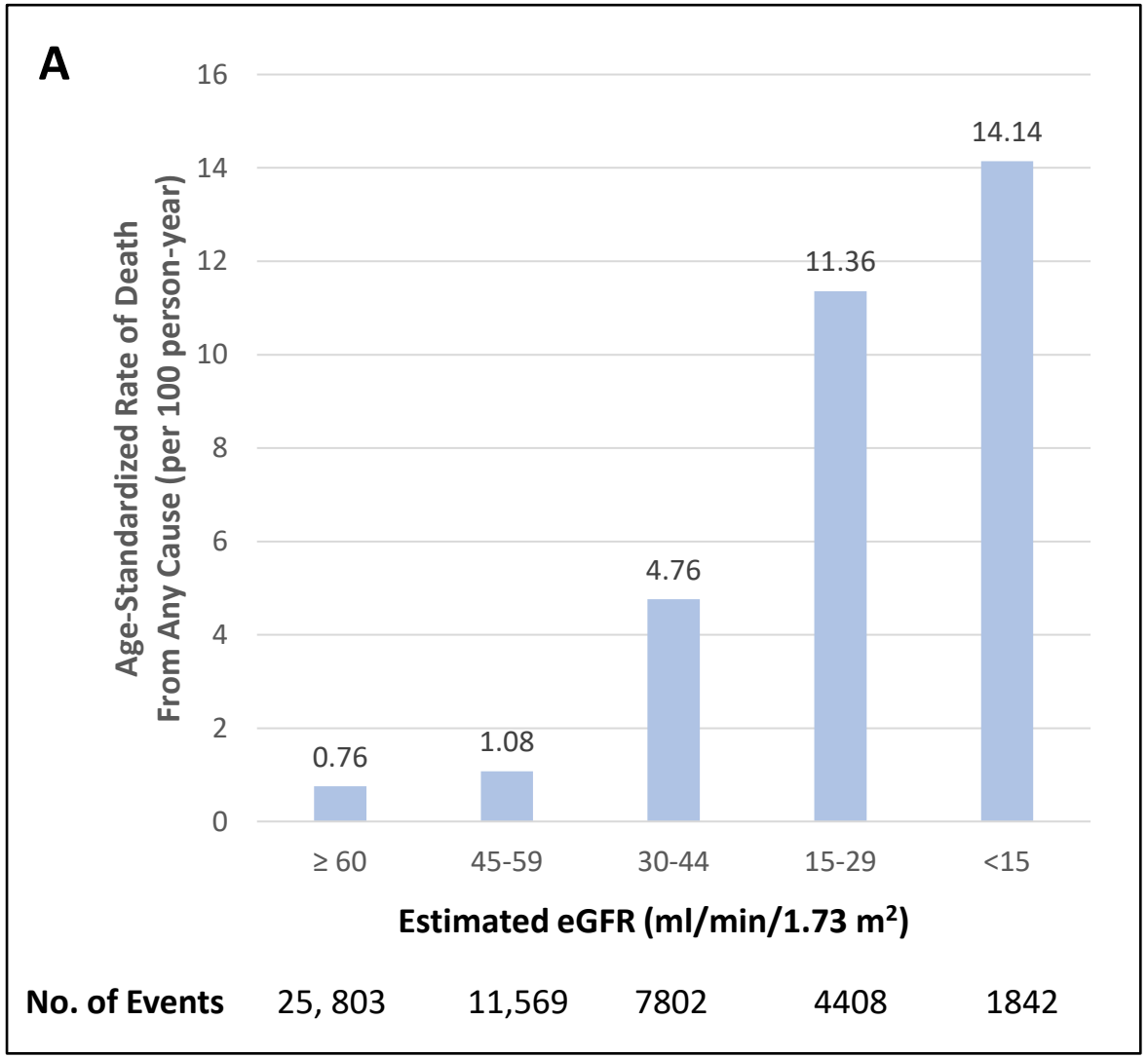
Composite Ranking for Relative Risks by glomerular filtration rate (GFR) and Albuminuria (Kidney Disease: Improving Global Outcomes (KDIGO) 2009

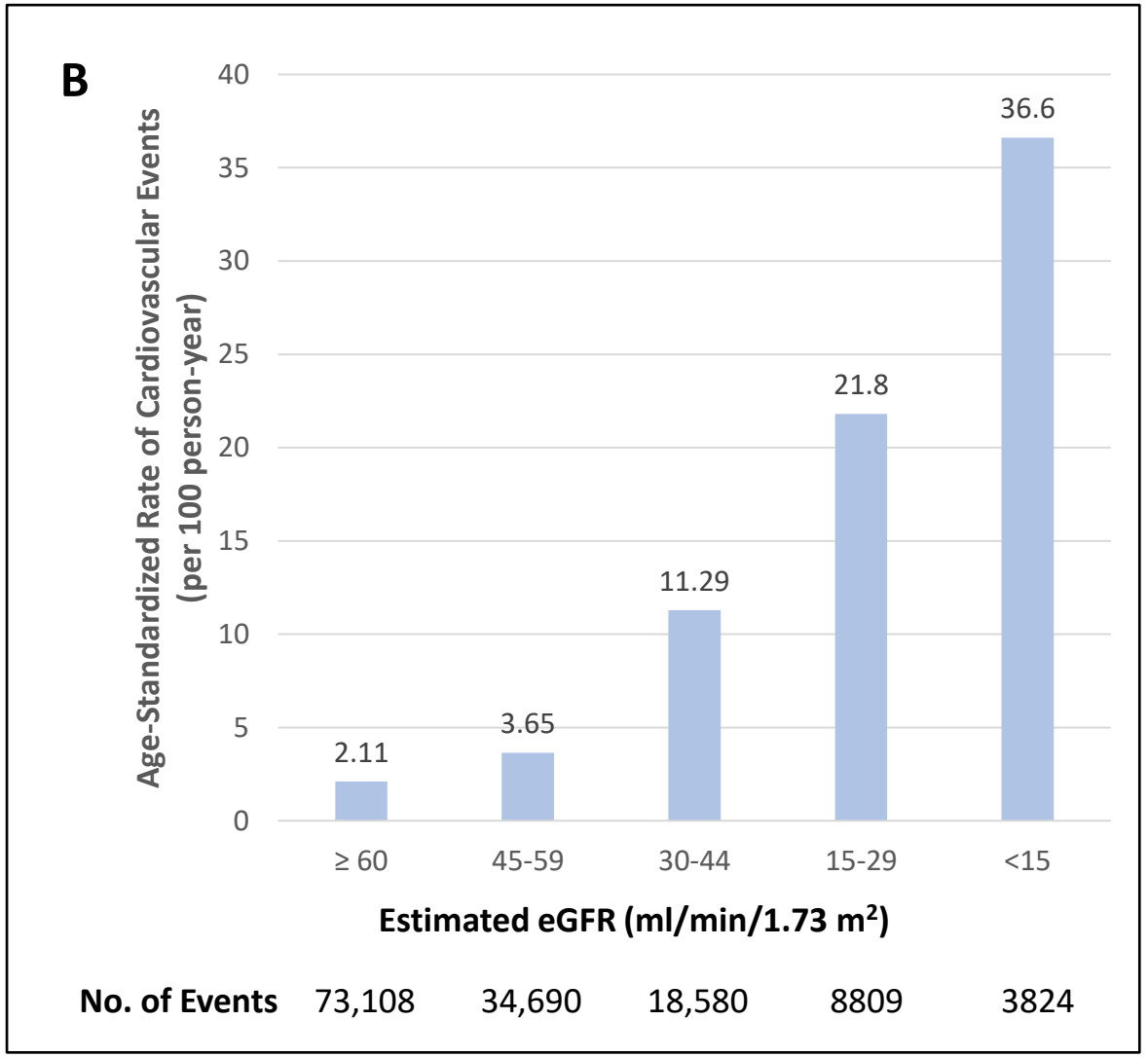
Composite ranking for relative risks by GFR and albuminuria (KDIGO 2009

GFR stages, description and range (ml/min per 1.73m$^{2)}$				Albuminuria stages, description and range (mg/g)				
				A1		A2	A3	
				Optimal and high-normal		High	Very high and nephrotic	
				<10	10-29	30-299	300-1999	≥2000
	G1	High and optimal	>105					
			90-104					
	G2	Mild	75-89					
			60-74					
	G3a	Mild-moderate	45-59					
	G3b	Moderate -severe	30-44					
	G4	Severe	15-29					
	G5	Kidney failure	<15					

Levey AS et.al. Kidney Int 2010; doi: 10.1038/ki.2010.483

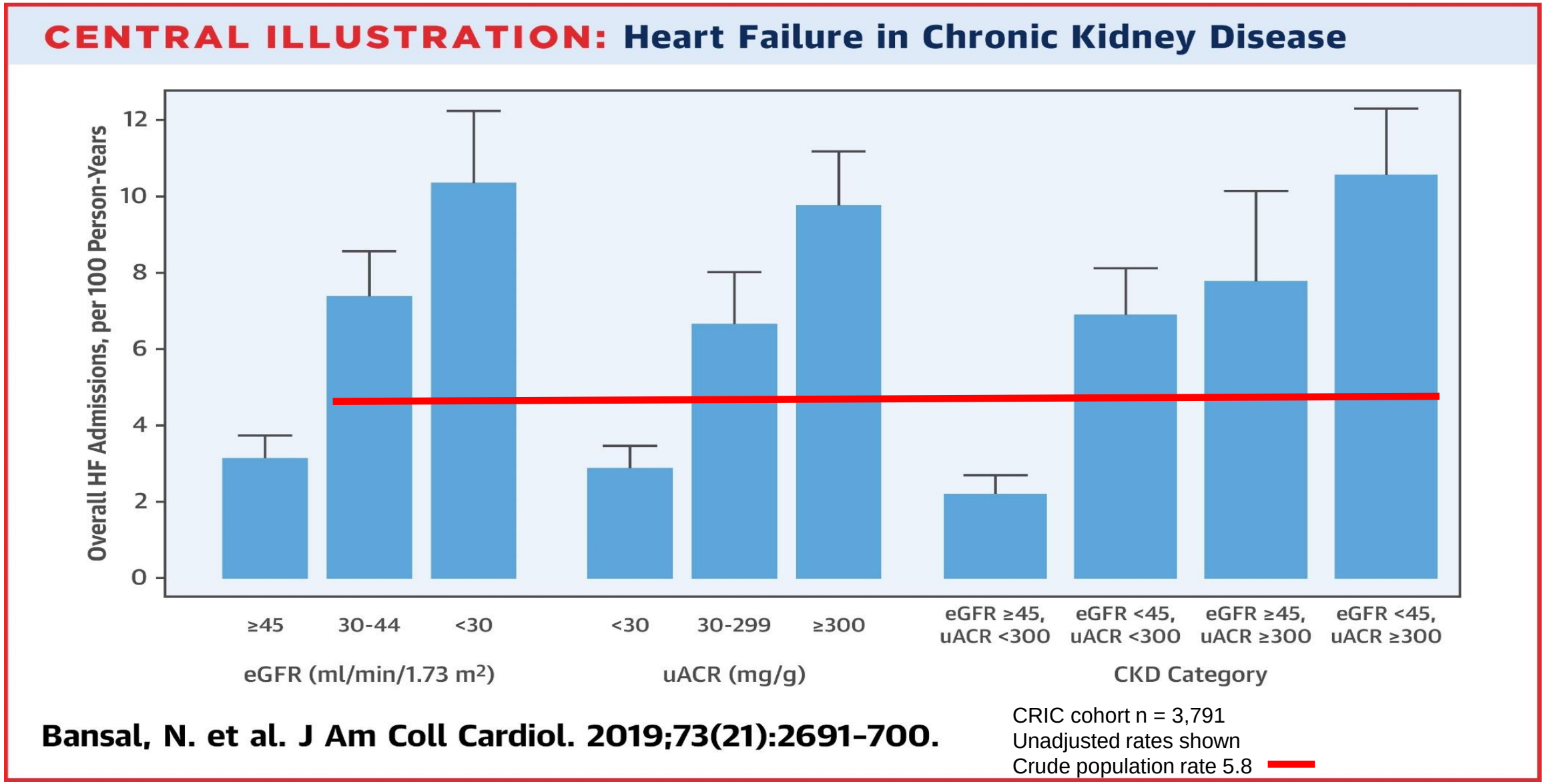
Age-Standardized Rates of Death from Any Cause (Panel A) and Cardiovascular Events (Panel B), According to the Estimated GFR among 1,120,295 Ambulatory Adults





Go, A, et al. NEJM 2003;351: 1296-1305

Heart Failure by eGFR and uACR



Management of Modifiable Risk Factors & Complications of CKD

- Hypertension
- Diabetes Mellitus
- Dyslipidemia
- CKD Metabolic acidosis

} Impacts CKD progression & morbidity

- CKD Anemia (Stage 4-5)
- CKD Bone and Mineral Disorder (Stage4-5)

} Impacts morbidity

Classification of CKD

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/1.73m^2) Description and range	G1	Normal or high	≥90	1 if CDK	Treat 1	Refer* 2
	G2	Mildly decreased	60-89	1 if CDK	Treat 1	Refer* 2
	G3a	Mildly to moderately decreased	45-59	Treat 1	Treat 2	Refer 3
	G3b	Moderately to severely decreased	30-44	Treat 2	Treat 3	Refer 3
	G4	Severely decreased	15-29	Refer* 3	Refer* 3	Refer 4+
	G5	Kidney failure	<15	Refer 4+	Refer 4+	Refer 4+

Levy AS, et al. American Journal of Kidney Diseases 2013;61.5: 686-688

Observational Studies of Early versus Late Nephrology Consultation

Variable	Early referral Mean (SD)	Late referral mean (SD)	P value
Overall mortality %	11 (3)	23 (4)	<0.0001
1-year mortality %	13 (4)	29 (5)	0.028
Hospital stay, days	13.5 (2.2)	25.3 (3.8)	0.0007
KRT serum albumin (mg/dL)	3.62 (0.05)	3.40 (0.03)	0.001
KRT hematocrit %	30.54 (0.18)	29.71 (0.10)	0.013

Chan M, et al. *Am J Med*. 2007;120:1063-1070.
KDIGO CKD Work Group. *Kidney Int Suppls*. 2013;3:1-150.

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Screening, Diagnosis, and Prediction of CKD Progression

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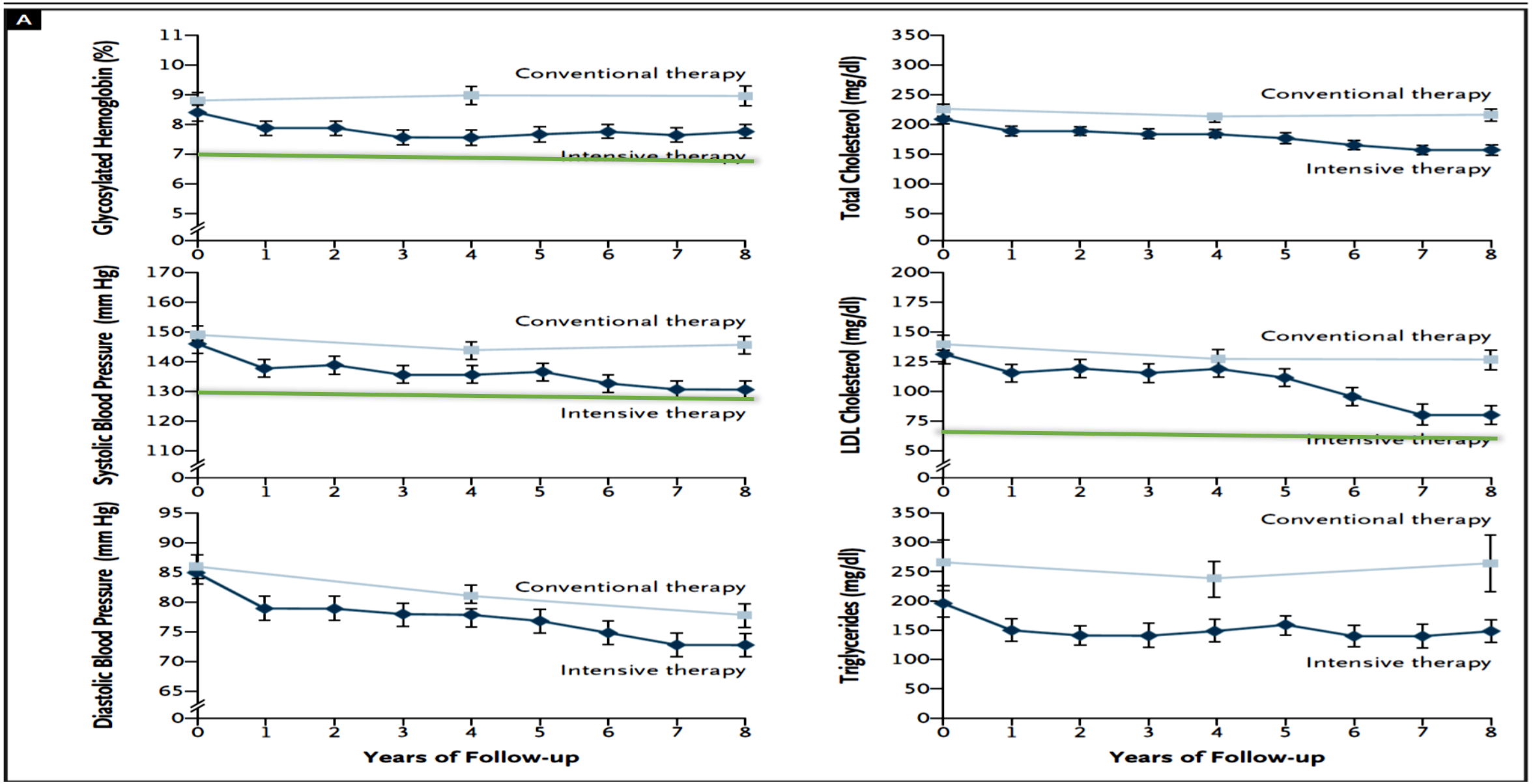
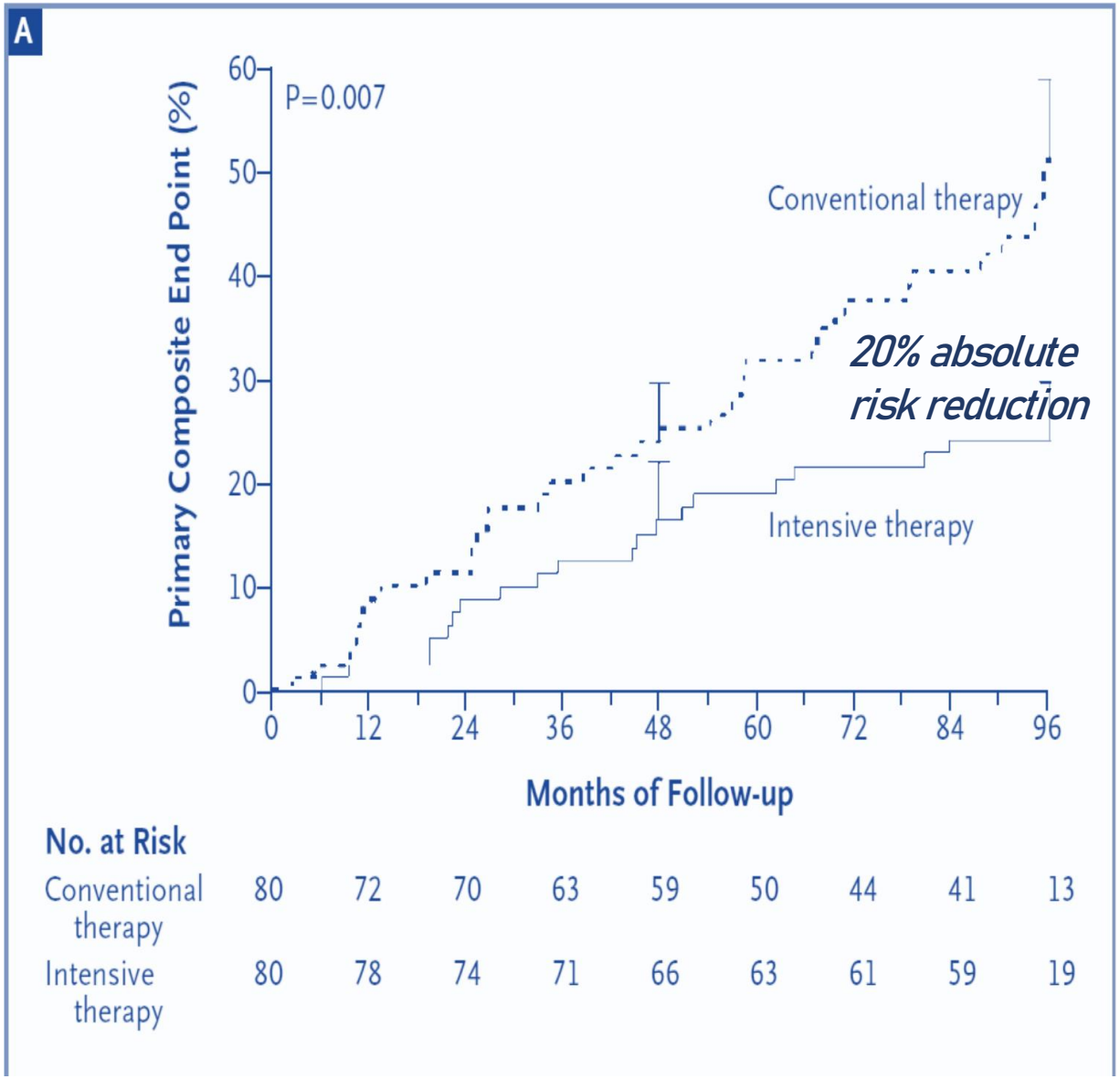
What Can YOU do to MARKEDLY slow CKD progression at Stage 2 CKD??

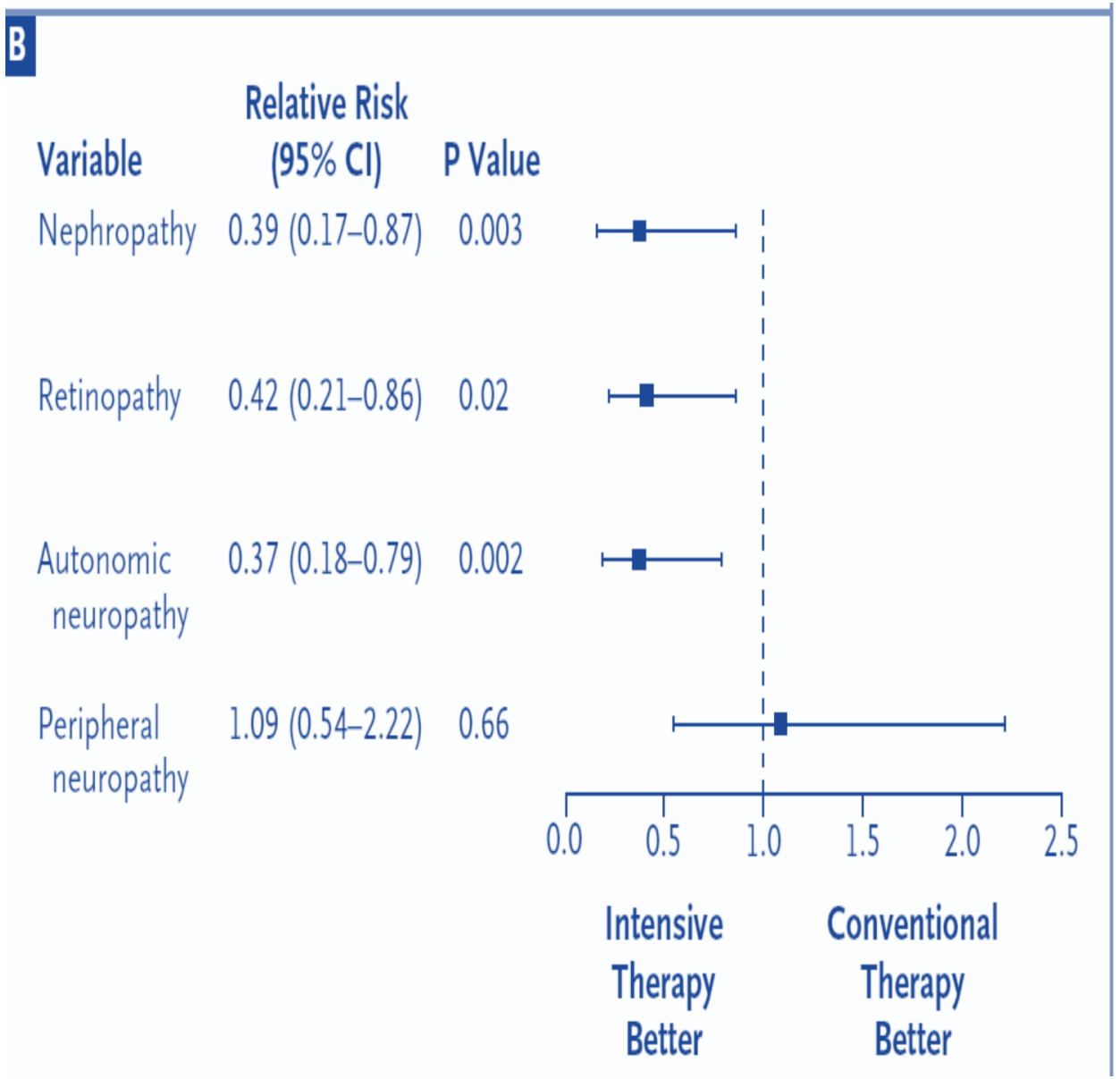
Changes in Selected Risk Factors in the Intensive-Therapy Group and the Conventional-Therapy Group during Follow-up



Gaede P, et.al. N. Engl J Med. 2003;348:383-93.

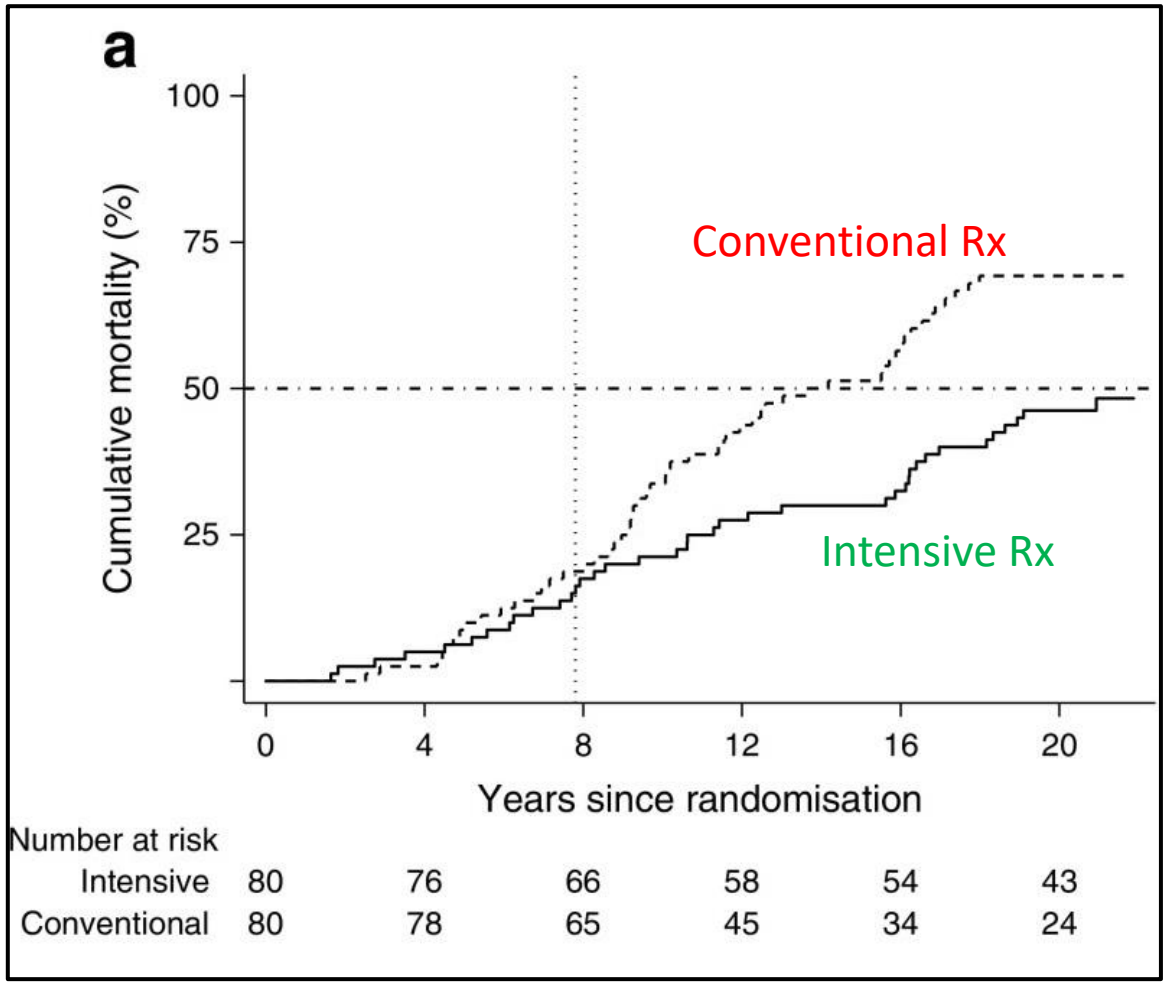
Kaplan–Meier Estimates of the Composite End Point of Death from Cardiovascular Causes, (A) and Relative Risk of Progression of Nephropathy, Retinopathy, and Autonomic and Peripheral Neuropathy (B)

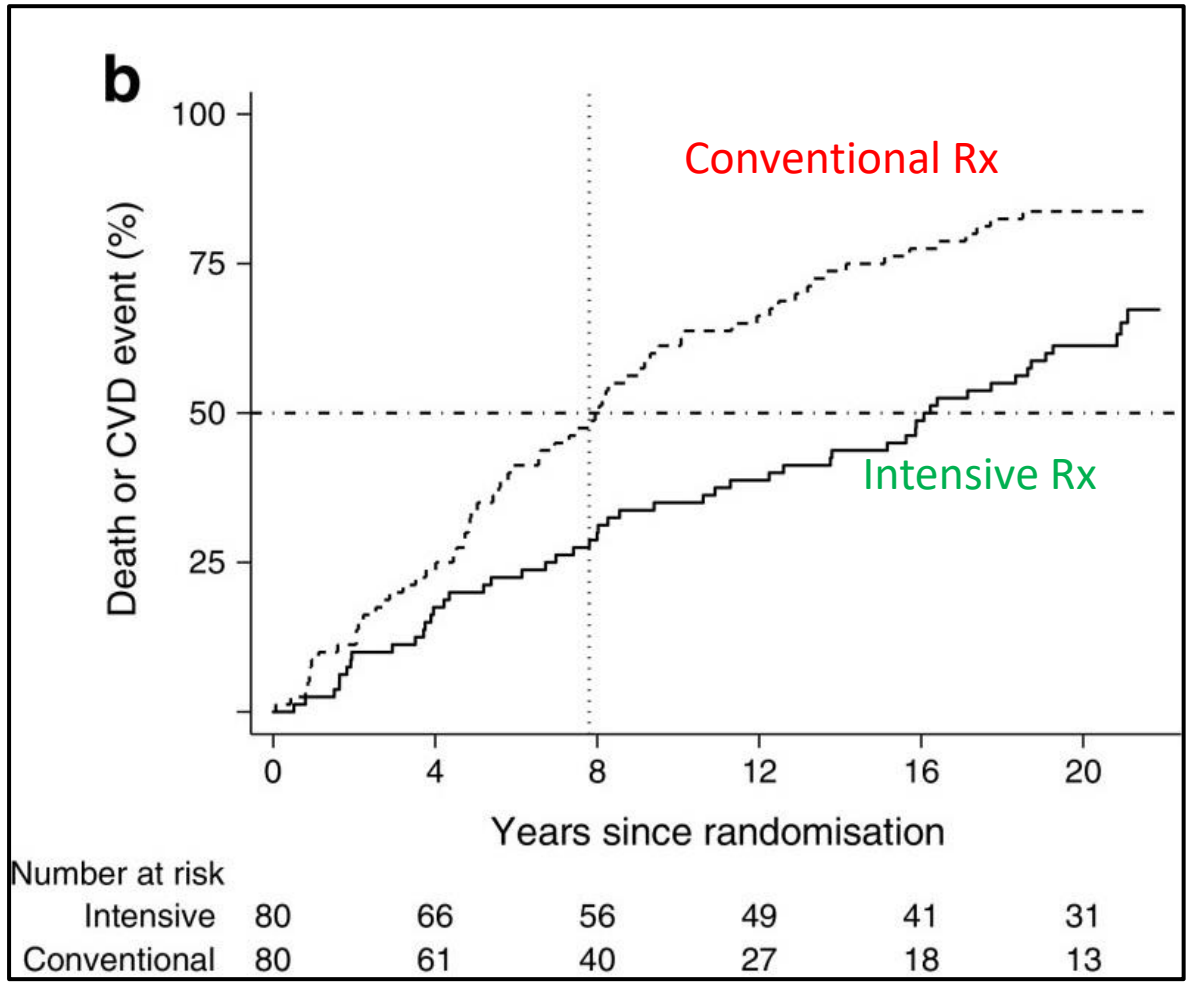




Gaede P, et.al. N. *Engl J Med. 2003;348:383-93.*

Cumulative mortality (a) and cumulative incidence of the composite CV or death endpoint (b)





Gaede P et.al. Diabetologia 2016;59:2298–2307

What is the Role of Albuminuria for Staging and Treatment?

- Must be included or staging will be incorrect at least 50% of the time.

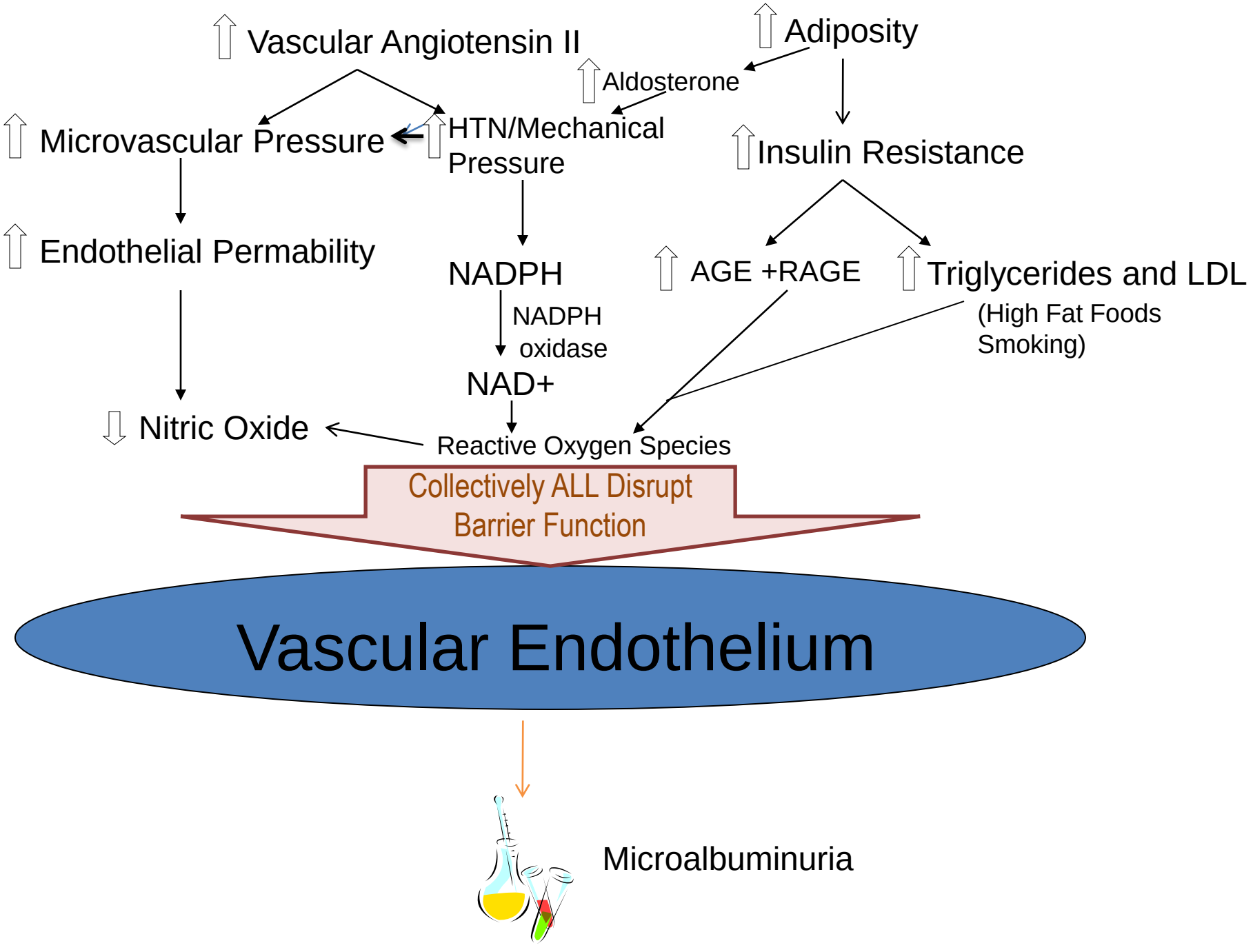
- Helps identify people at risk who may have a reasonable GFR-case to come.

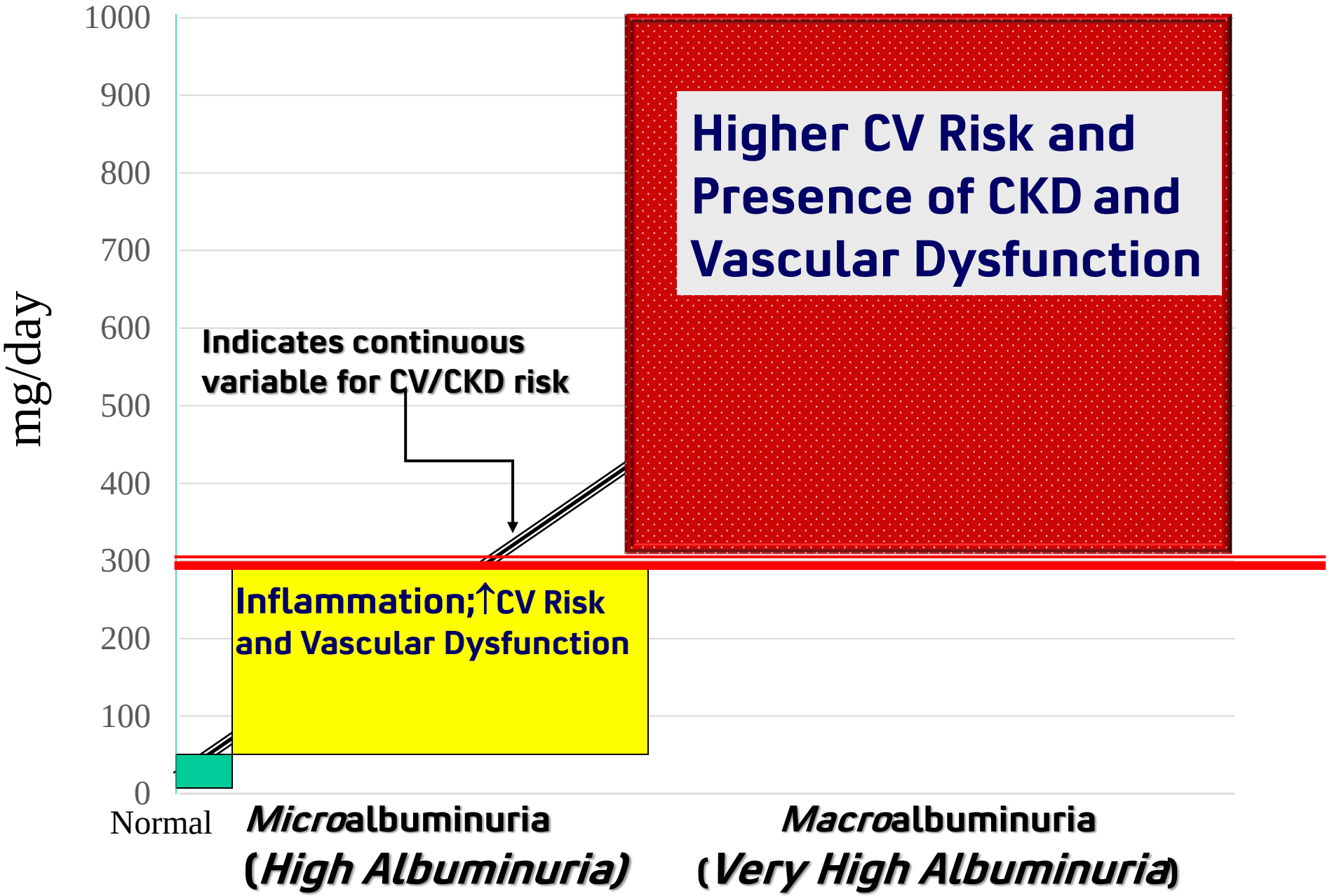
Who to Screen?

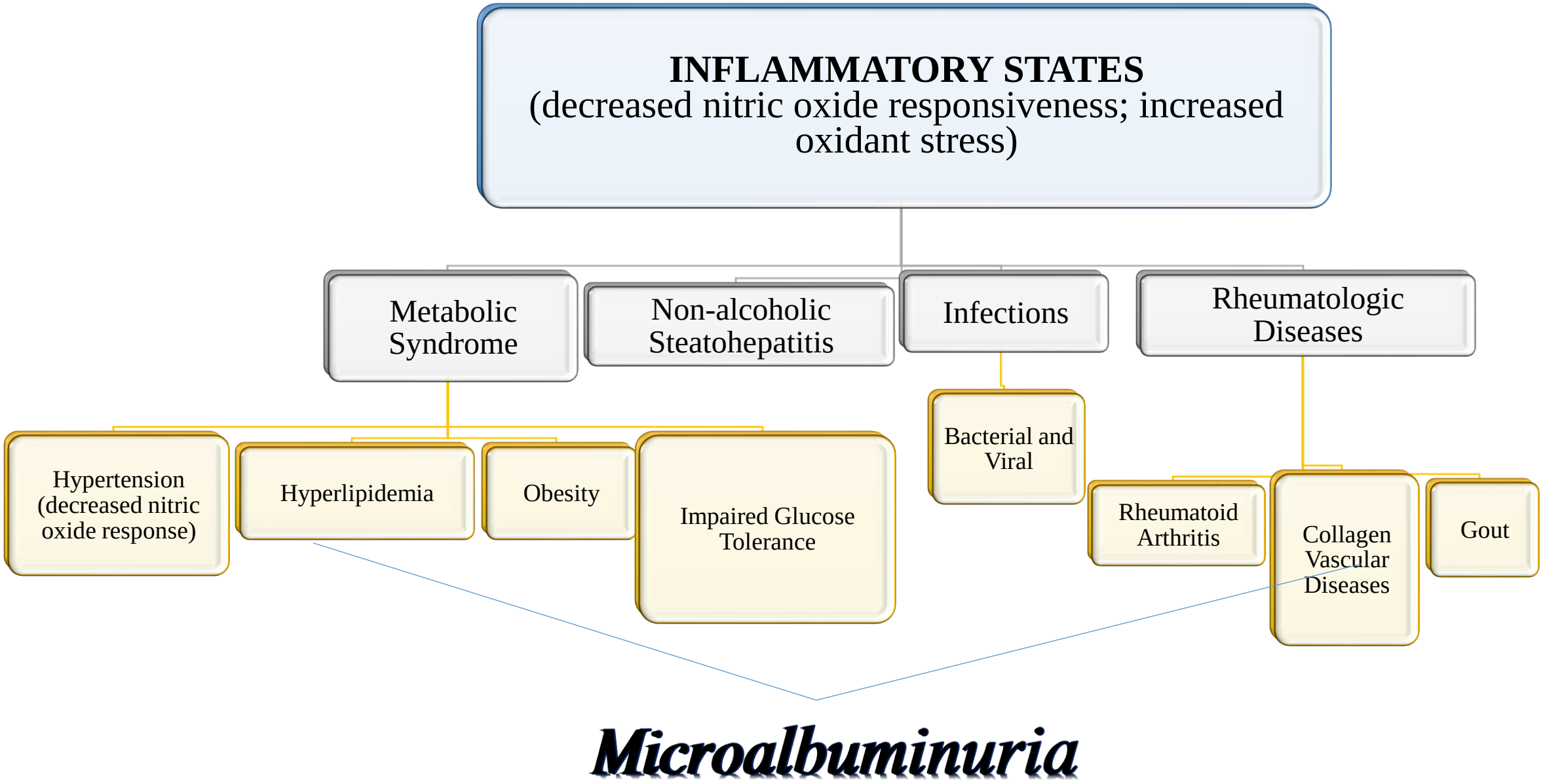
- Those with diabetes it is MANDATED per guidelines that you check it annually if not more frequently if treating
- Those with hypertension it is suggested it be checked every 2-3 years
- In those without diabetes or hypertension that have a reduced GFR <60 ml/min/1.73m^2 it is suggested to check as a screen.

How Should you Check it?

- First morning void is best when fasting. If elevated should be repeated within the week to ensure elevated. (many things can give false positive increases. Also, drugs like NSAIDs can give false negative results as they decrease albuminuria).
- If patient has a fever or other non-renal inflammatory condition like a flare of Rheumatoid arthritis should wait until flare is resolved.
- If you check it and the patient has moderately increased albuminuria (microalbuminuria) then what.


Vascular Angiotensin II
Adiposity
Aldosterone
Microvascular Pressure
HTN/Mechanical Pressure
Insulin Resistance
Endothelial Permability
NADPH
AGE +RAGE
Triglycerides and LDL
(High Fat Foods Smoking)
NADPH oxidase
NAD+
Nitric Oxide
Reactive Oxygen Species
Collectively ALL Disrupt Barrier Function
Vascular Endothelium
Microalbuminuria

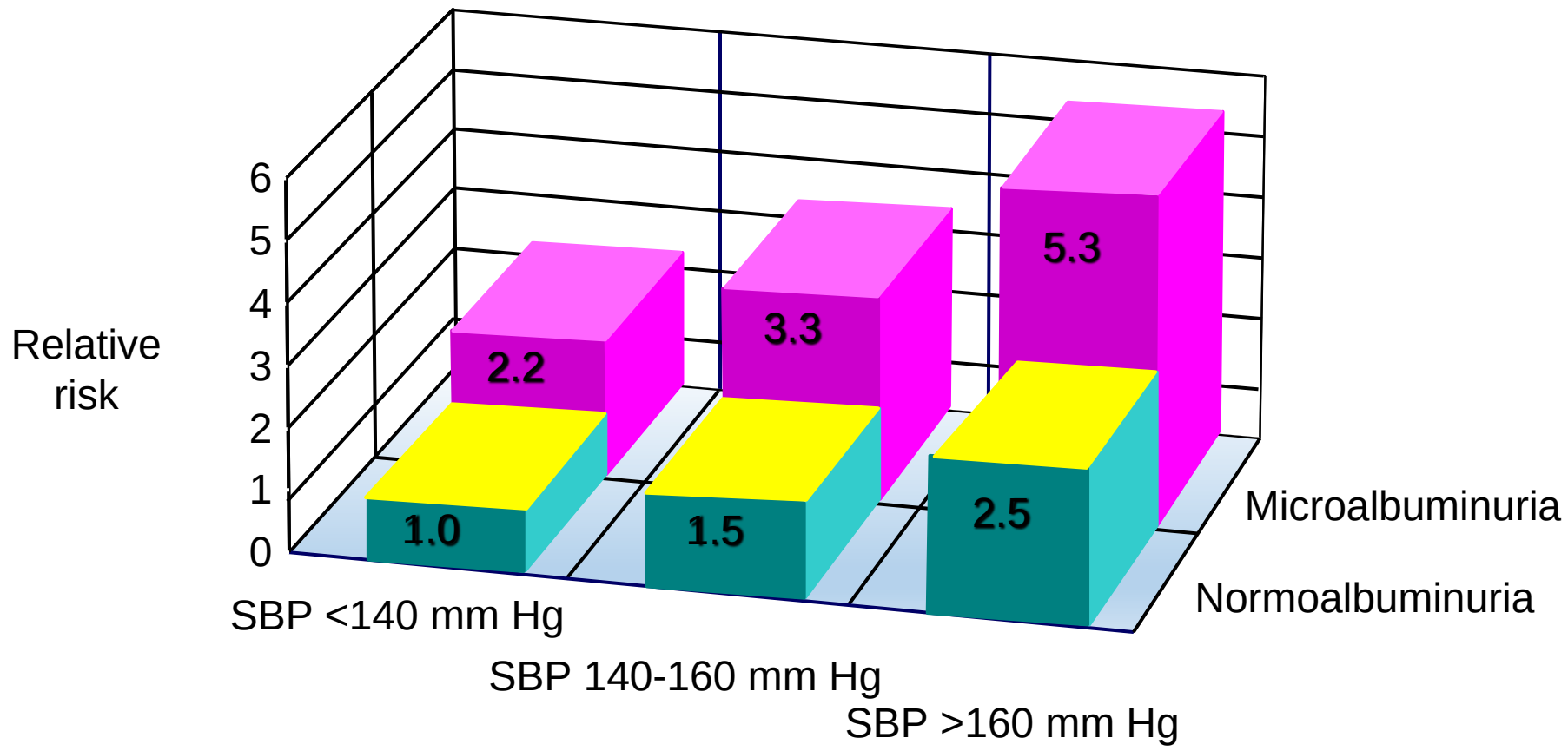

1000
900
800
700
600
500
400
300
200
100
0
mg/day
Higher CV Risk and Presence of CKD and Vascular Dysfunction
Indicates continuous variable for CV/CKD risk
Inflammation;↑CV Risk and Vascular Dysfunction
Normal
Microalbuminuria (High Albuminuria)
Macroalbuminuria (Very High Albuminuria)



Bakris G and Molitch M -Diabetes Care-2014;37(3): 867-875

Ischemic Heart Disease

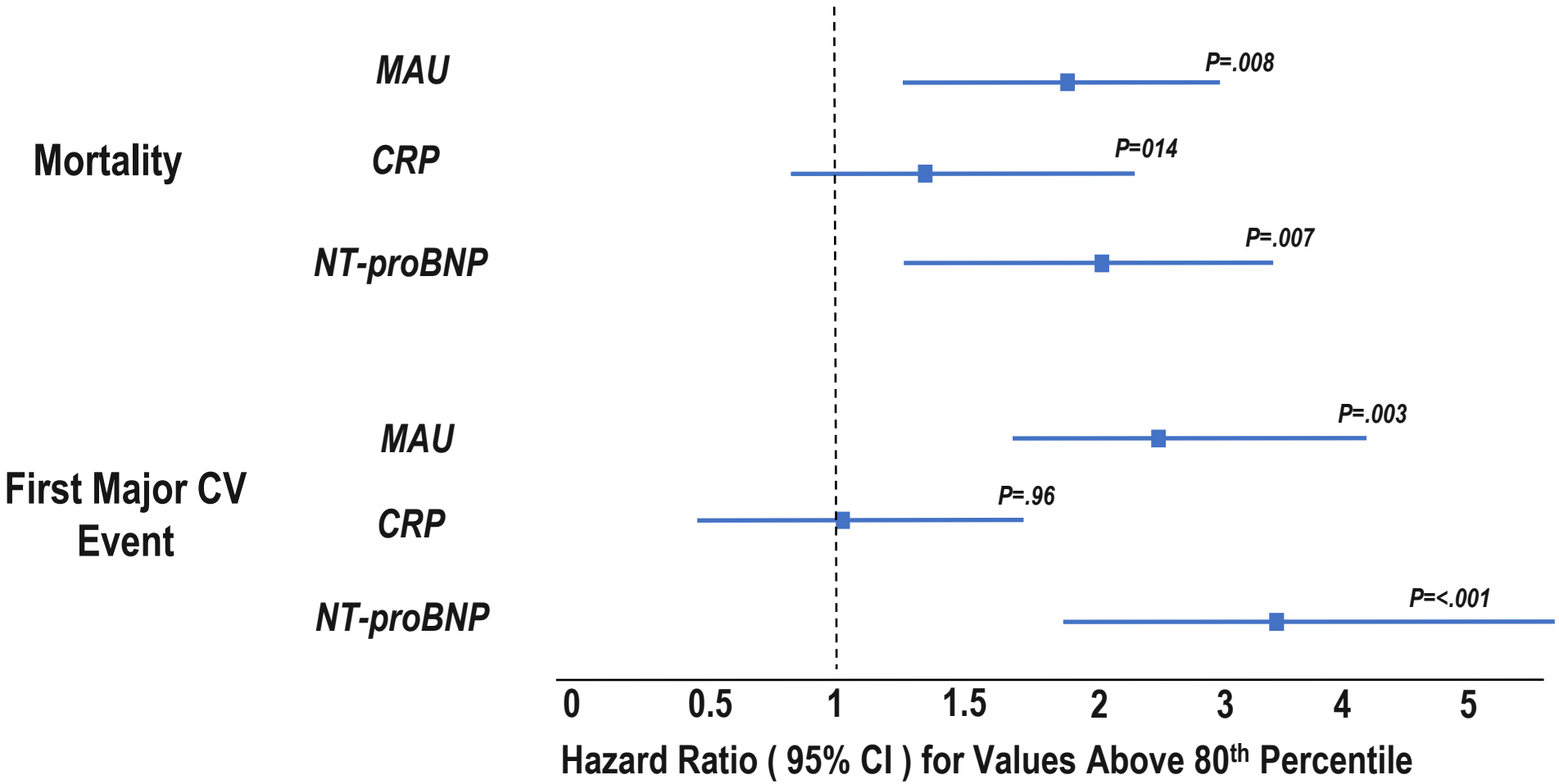
Relationship Between Microalbuminuria and BP



N=2085; 10-yr follow-up.

Borch-Johnsen K et al. Arterioscler Thromb Vasc Biol. 1999;19:1992-1997.

Use of MAU, CRP, and BNP as Predictors of Mortality and CV Events

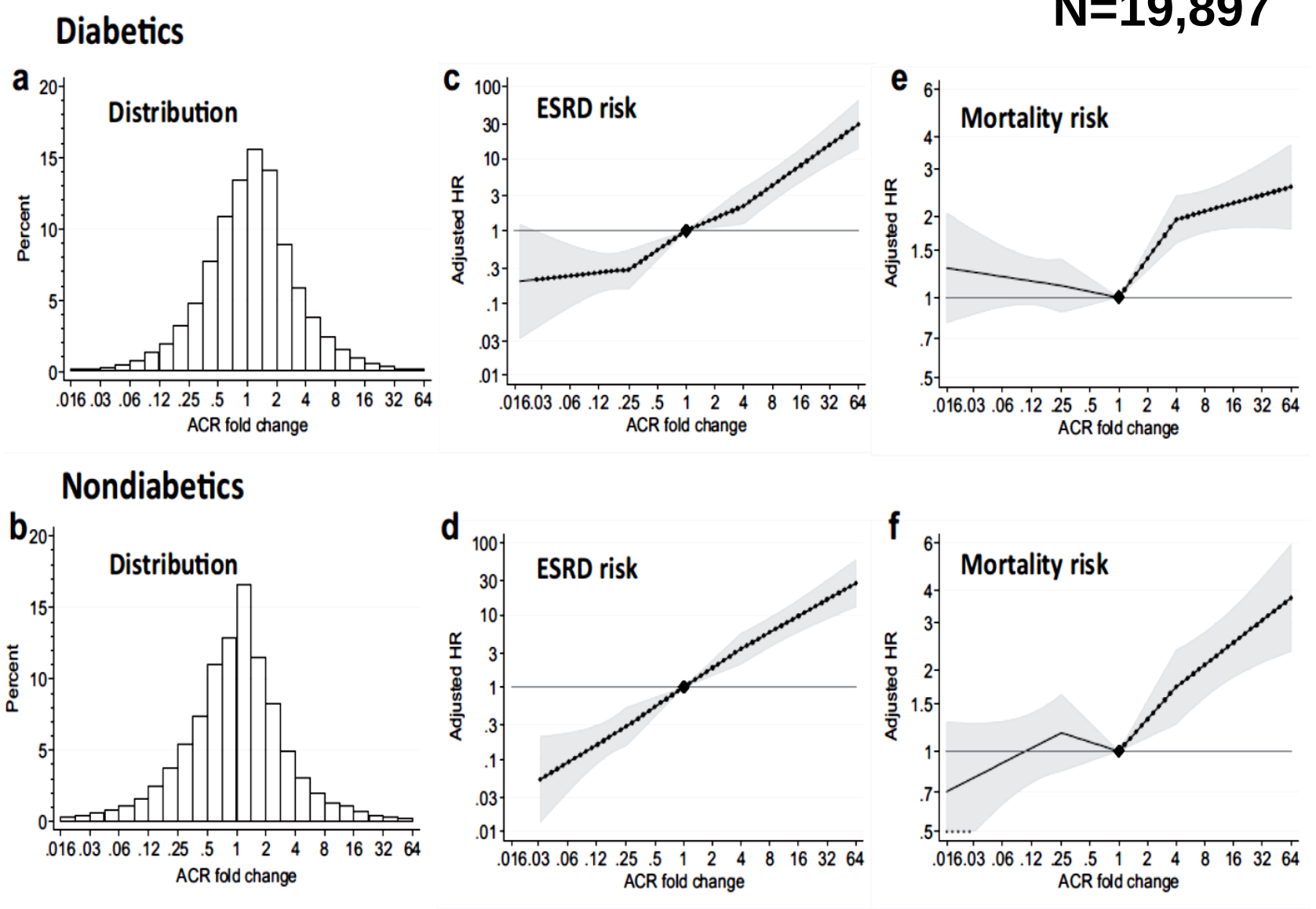


Adjusted for age, sex, smoking, DM, HTN, Afib, LVEF<50%, LVH, total cholesterol, serum creatinine. Mortality analysis based on 91 deaths, and CV event data based on 63 events due to missing covariates. The 80th percentile corresponds to values more than 5.85 pg/mL for NT-proBNP, 5.76 mg/L for CRP, and 18.4 mg/g for MAU.

Kistorp K, et al. JAMA. 2005;293:1609-1616.

Distribution of 2-year albumin-to-creatinine ratio (ACR) fold changes

N=19,897



Carrero JJ et.al. Kidney Int 2017;91:244-251

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Treatment of CKD, Stages 1-4

George Bakris, MD
Professor of Medicine
University of Chicago Medicine

What if you have >300-then you have HIGH CV Risk and Clear evidence of CKD?

Prevalence of CKD in the US population by eGFR and albuminuria stages

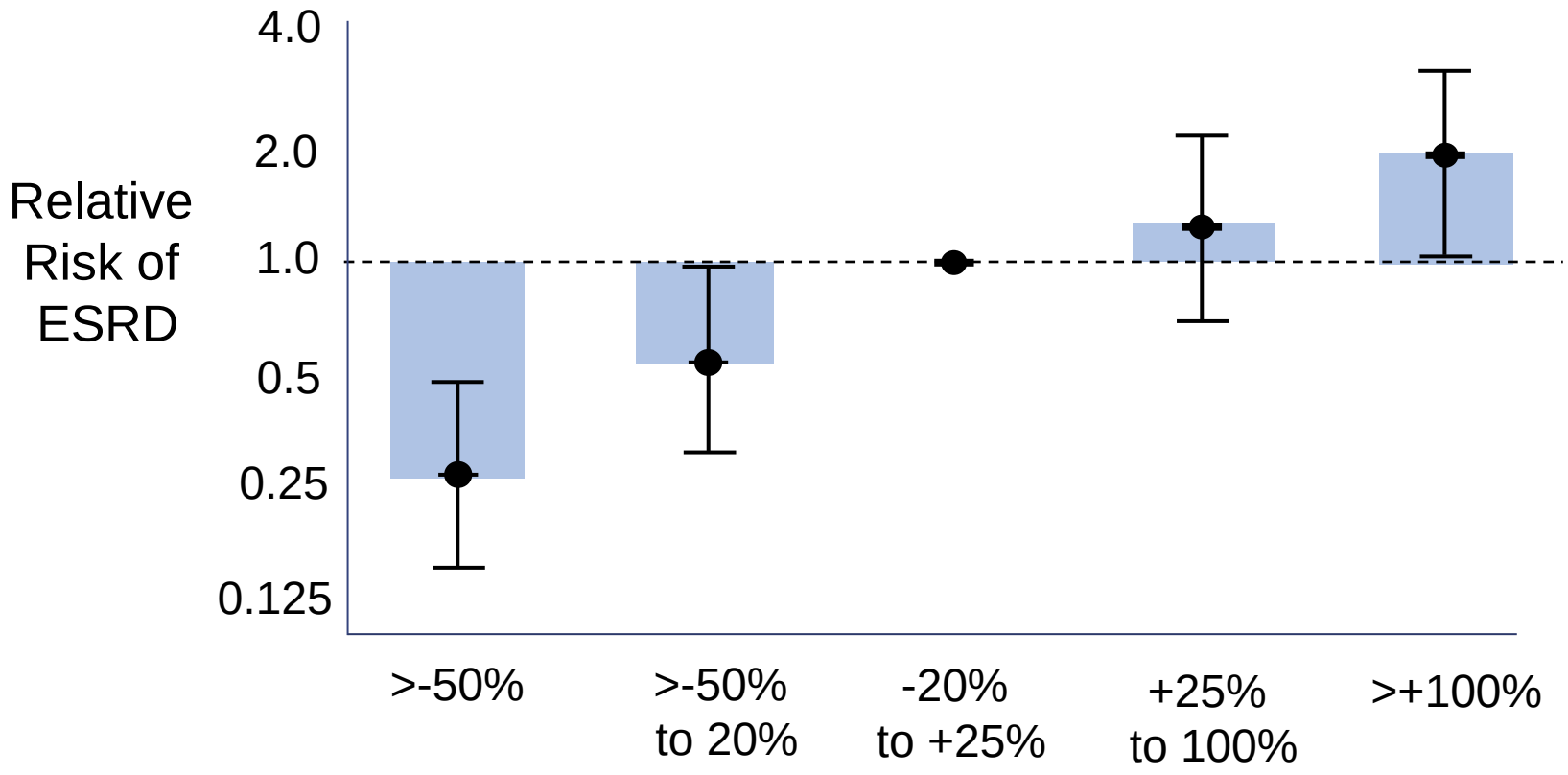
- Percentage of US population by eGFR and albuminuria category (KDIGO 2009 and NHANES III (1988 – 1994)
- Combined stages G3-G5 and A2-A3 account for 13.9% of the population
- Stages G3-G5 and A2-A3 account for 6.7% and 9.1% of the population, resp.

eGFR stages, description, and range (ml/min/1.73m²)				Albuminuria stages, description, and range (mg/g) [by UACR]				
				A1		A2	A3	All
				Optimal and high-optimal		High	Very high	
				<10	10-29	30-299	>300	
	G1	Increased and optimal	>105	23.6	5.7	1.9	0.1	31.4
			90-104	20	4.7	1.7	0.3	26.7
	G2	Mild	75-89	17.3	4.1	1.6	0.2	23
			60-74	8.2	2.7	1.3	0.1	12.2
	G3a	Mild-moderate	45-59	2.5	1.1	0.8	0.2	4.7
	G3b	Moderate-severe	30-44	0.6	0.4	0.4	0.2	1.5
	G4	Severe	15-29	0.1	0.1	0.1	0.1	0.4
	G5	ESRD	<15	0	0	0	0.1	0.1
	All			72.2	18.8	7.8	1.3	100

Levey AS, Coresh J. Lancet. 2012;379(9811):165-180.

What Do you do if you have Albuminuria and Why?

Six Month Change in Proteinuria from Baseline Predicts Outcome of Kidney Disease: Results from the AASK trial

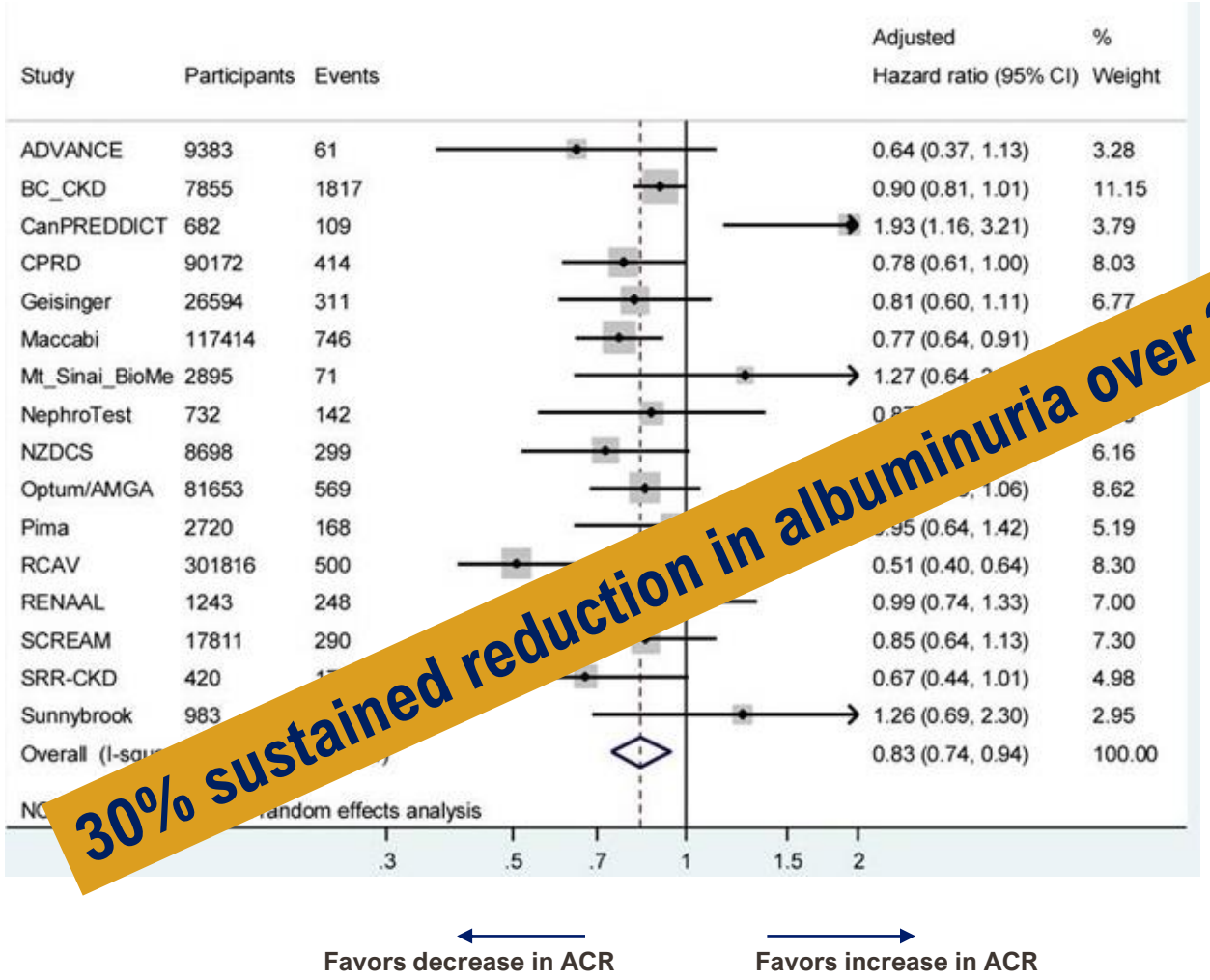


Lea J et.al. Arch Intern Med. 2005;165:947

Forest plot of individual study and meta-analyzed estimates of adjusted HR for ESKD associated with 2-year change in ACR

30% sustained reduction in albuminuria over 2 years is a valid surrogate for slowed CKD

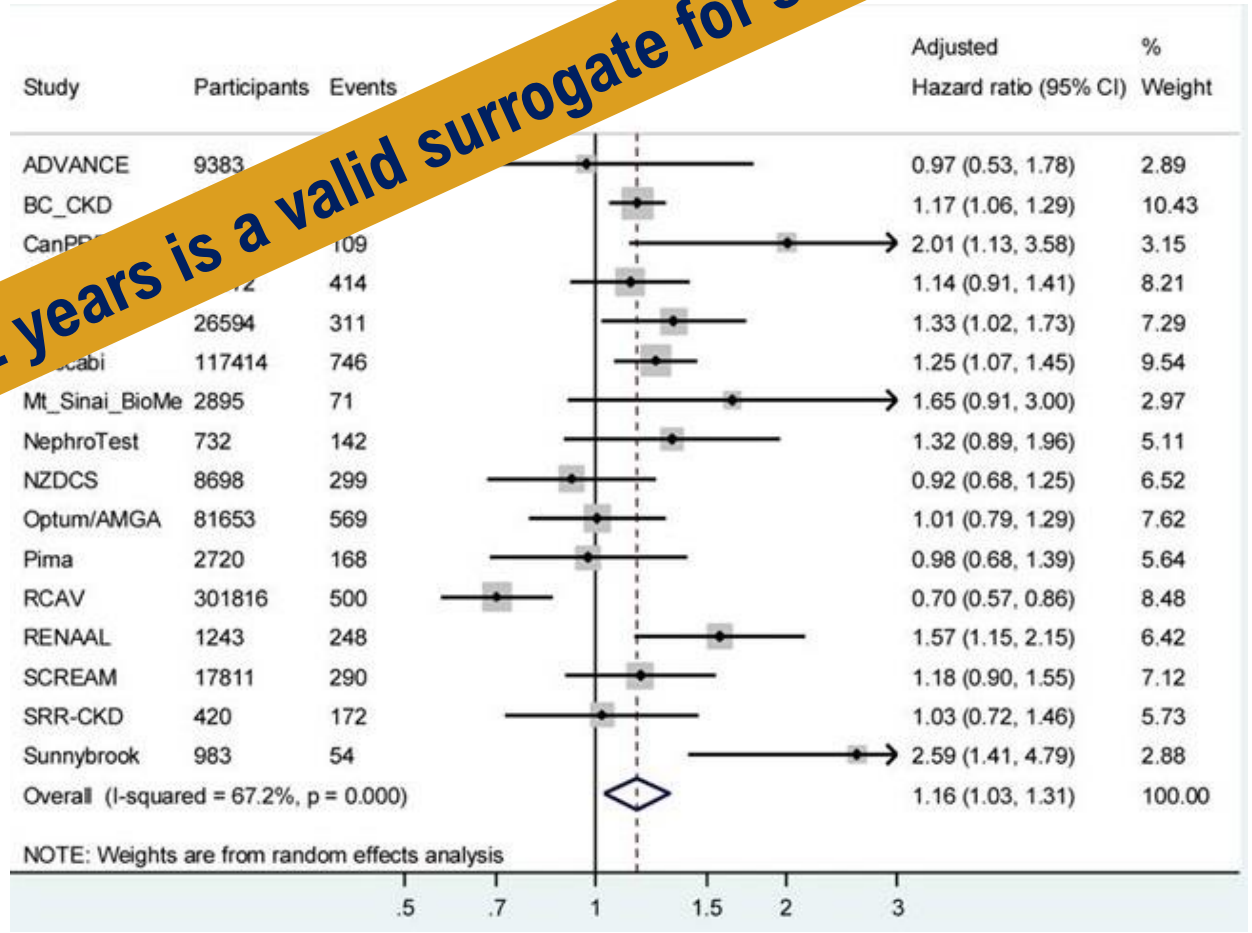
A 30% decrease in ACR



Favors decrease in ACR

Favors increase in ACR

B 43% decrease in ACR

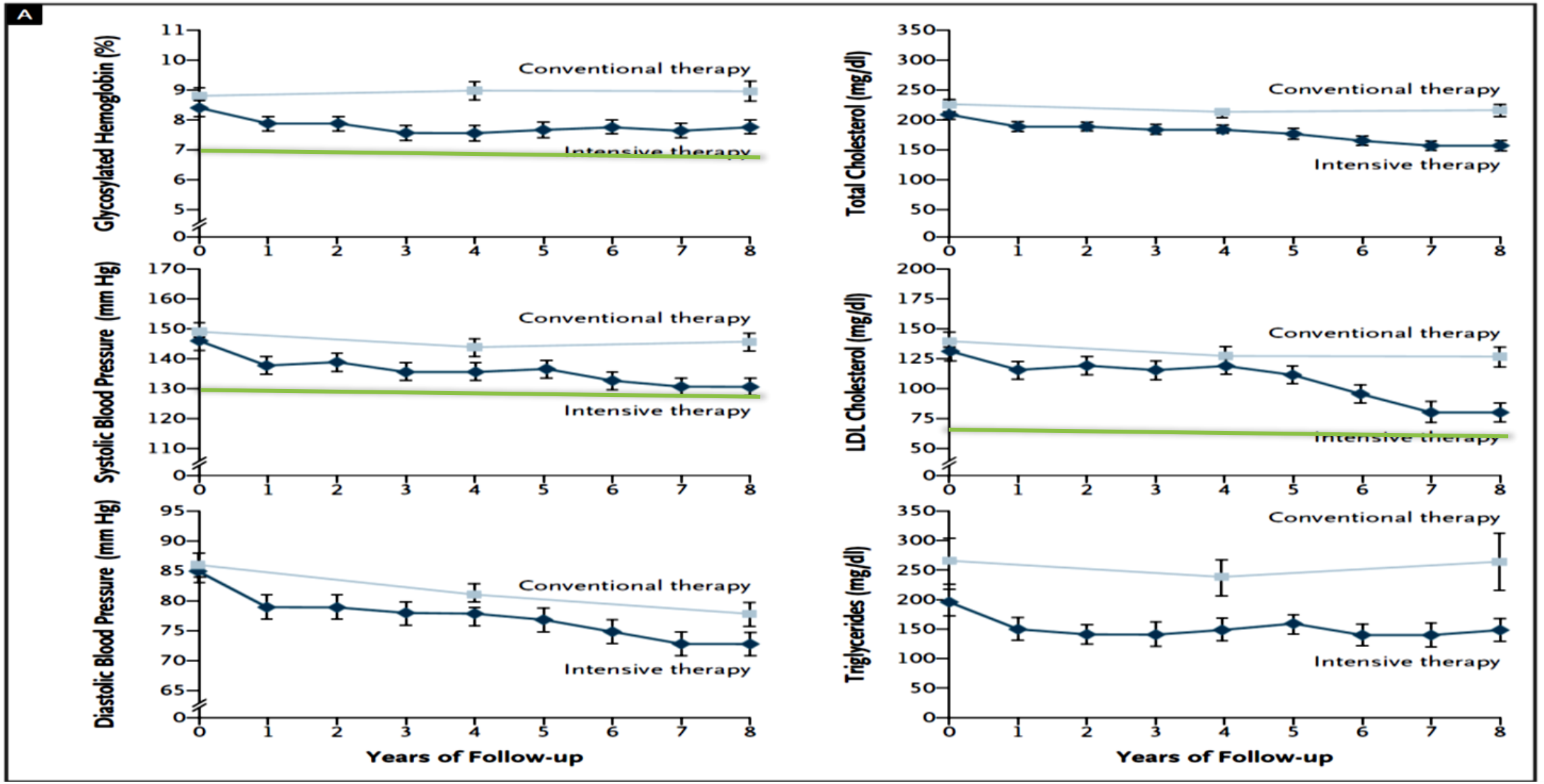


Favors decrease in ACR

Favors increase in ACR

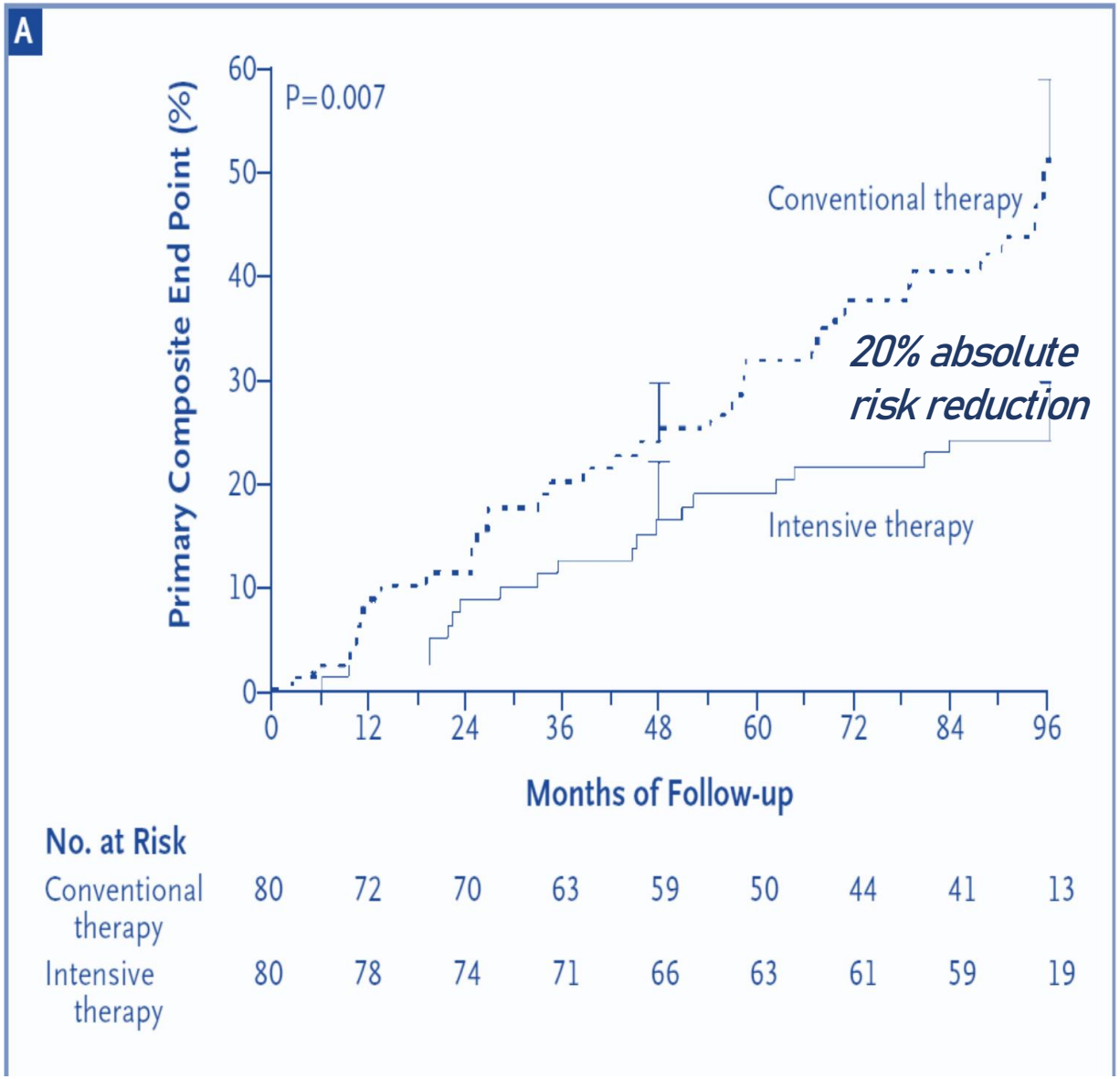
Coresh J et.al Lancet Diabetes Endocrinol 2019; 7: 115–27

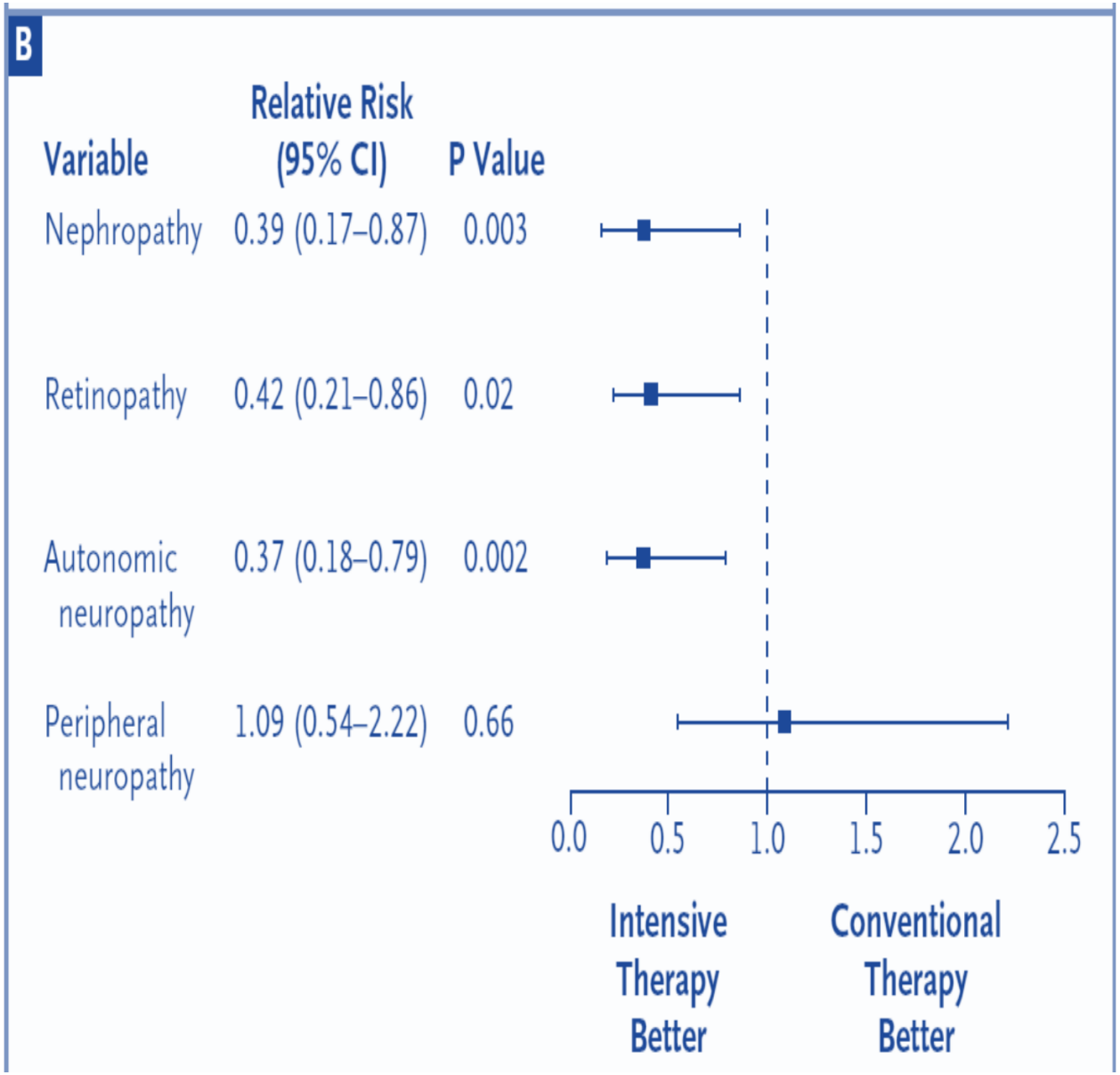
Changes in Selected Risk Factors in the Intensive-Therapy Group and the Conventional-Therapy Group during Follow-up



Gaede P, et.al. N. Engl J Med. 2003;348:383-93.

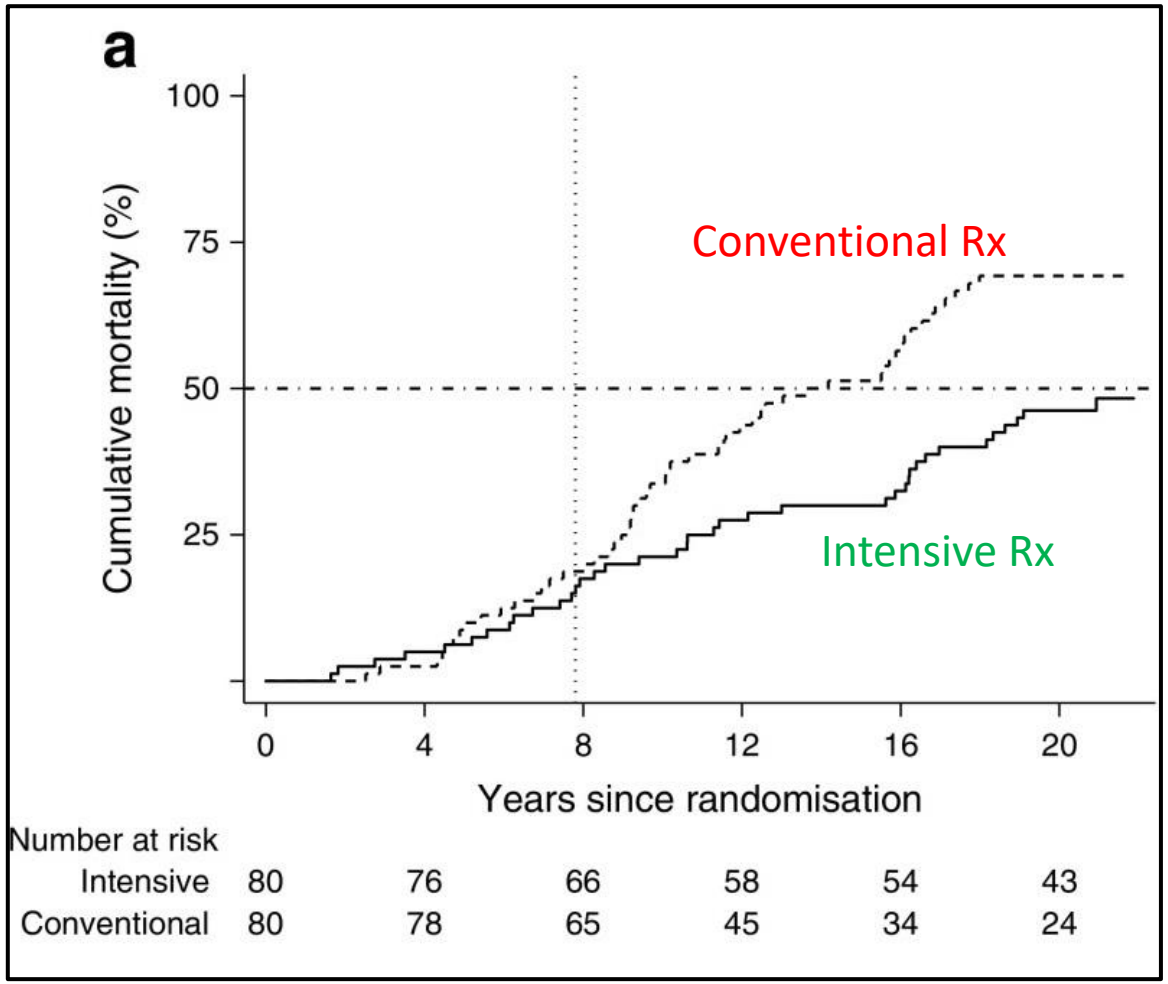
Kaplan–Meier Estimates of the Composite End Point of Death from Cardiovascular Causes, (A) and Relative Risk of Progression of Nephropathy, Retinopathy, and Autonomic and Peripheral Neuropathy (B)

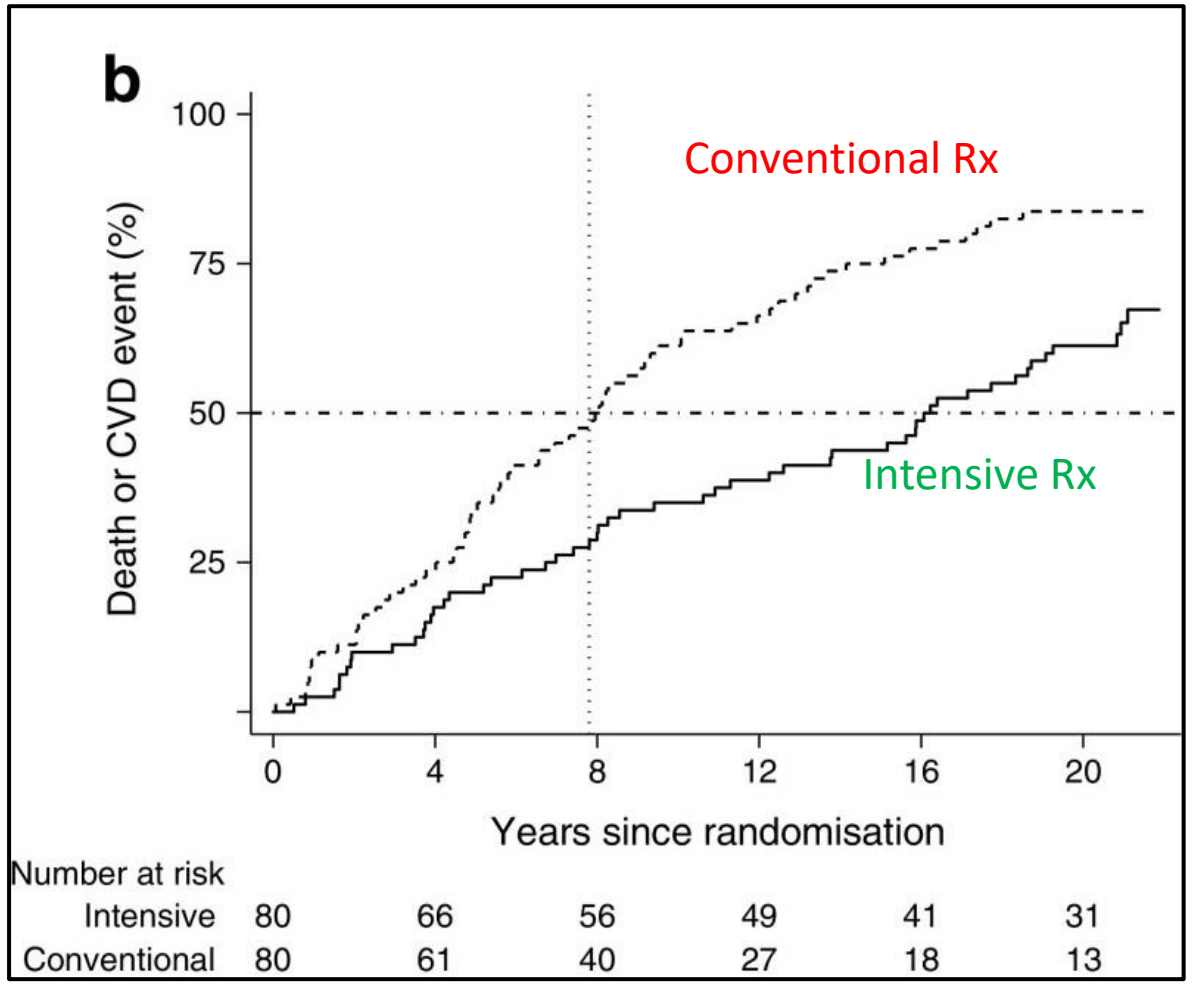




Gaede P, et.al. N. *Engl J Med. 2003;348:383-93.*

Cumulative mortality (a) and cumulative incidence of the composite CV or death endpoint (b)





Gaede P et.al. Diabetologia 2016;59:2298–2307

Pharmacological Agents that Reduce albuminuria and Have an FDA Indication for Slowing Nephropathy and/or CV Risk Reduction

- **Maximally dosed RAS blockers-ACEi or ARBs**
- **SGLT2 inhibitors**
- **NS-MRA finerenone**

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Case of Diabetic Nephropathy with a Missed Opportunity

George Bakris, MD
Professor of Medicine
University of Chicago Medicine

The Story of a Celebrity

- 45 yr HM with Diabetes for 10 yrs, “reasonably well controlled”
- PMH:
  - Hypertension for 7 yrs. well controlled
  - BMI of 30
  - Dyslipidemia
- Fam Hx: Diabetes;
- Soc Hx: Sedentary; non-smoker; Comedian
- Exam
  - 139/85 – Mild Obesity, rest fairly normal
- Labs
  - BUN 28, Creatinine 1.8, Urine protein (dipstick) 2+

MDRD GFR

- Diabetic, Hypertension, Metabolic Syndrome X
- Stage 3b CKD
- GFR = 44 ml/min/1.73 m^2 ; albuminuria 1gram/day

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/1.73m^2) Description and range	G1	Normal or high	≥90	1 if CDK	Treat 1	Refer* 2
	G2	Mildly decreased	60-89	1 if CDK	Treat 1	Refer* 2
	G3a	Mildly to moderately decreased	45-59	Treat 1	Treat 2	Refer 3
	G3b	Moderately to severely decreased	30-44	Treat 2	Treat 3	Refer 3
	G4	Severely decreased	15-29	Refer* 3	Refer* 3	Refer 4+
	G5	Kidney failure	<15	Refer 4+	Refer 4+	Refer 4+

Mr. George Lopez