CKD and Cardiovascular Disease: Moving from Hades to Athena

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Disclosures and perspectives

- Consultant Nephrologist and Medical Examiner
- Chair South East Clinical Senate, NHS England
- Grant support from National Institute of Health Research
- Guideline nerd

Talk Outline

- Hades and Athena
- 20 years ago – what did we talk about then?
- CKD - a global problem
- KDIGO evolution
- Data, population risk and individual risk
- Holistic treatment
- Pillar therapy
- A note of realism

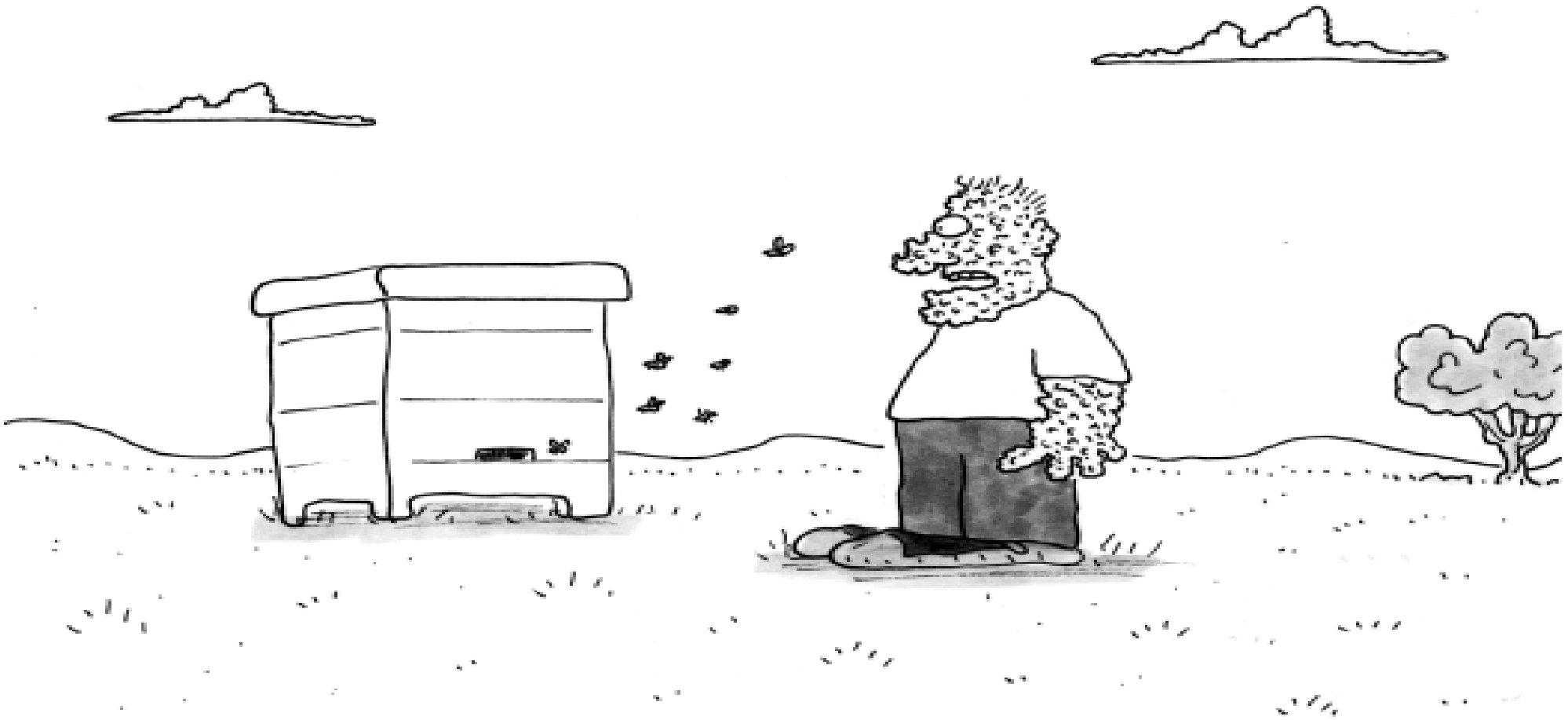
HADES

- Ruler of the Underworld
- Son of Cronus
- Brother of Zeus and Poseidon
- Stern and pitiless, unmoved by prayer or sacrifice

ATHENA

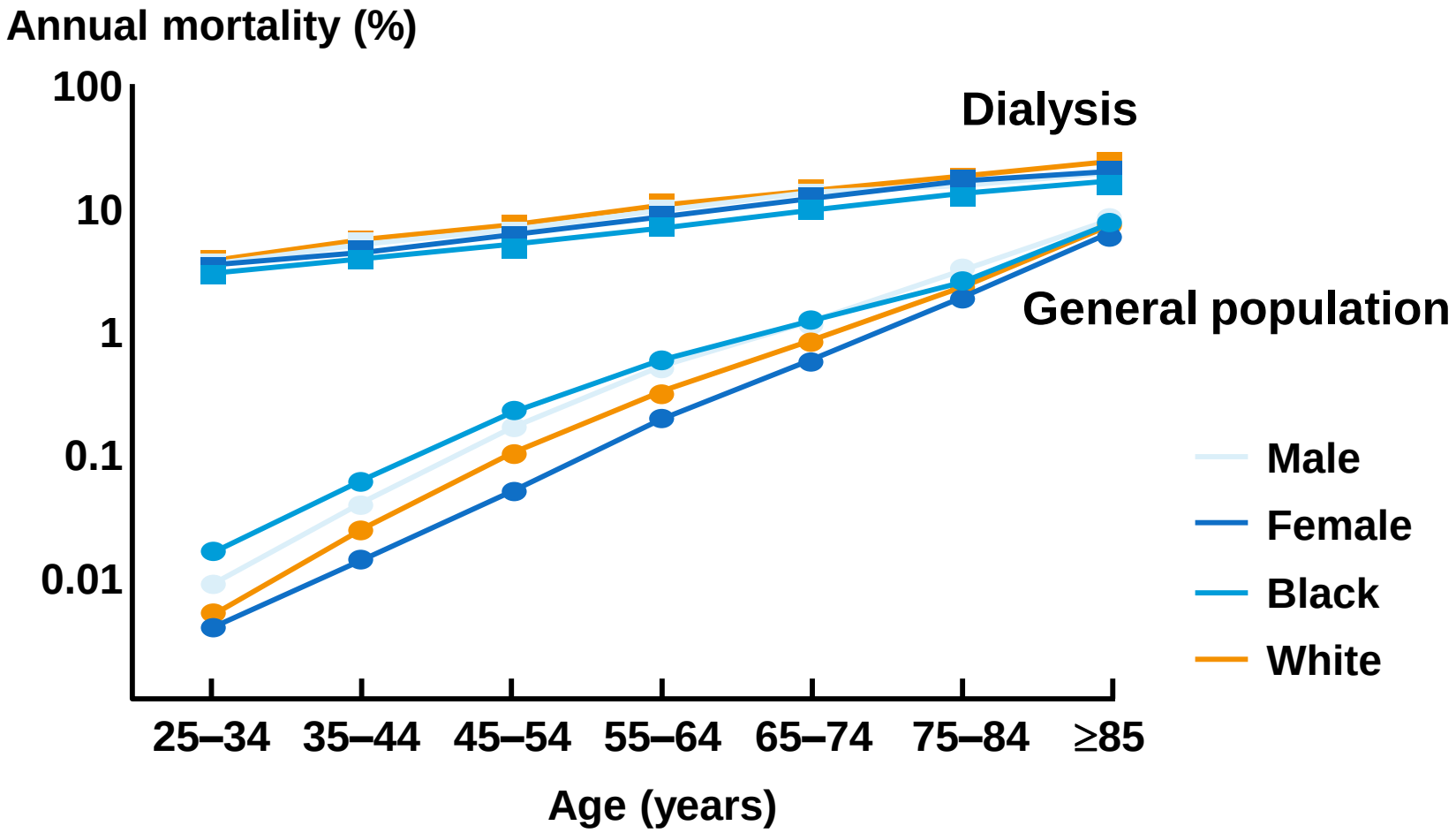
- Daughter of Zeus
- Goddess of war *but also*
- Goddess of good counsel, of prudent restraint and practical insight

What About Outcomes?



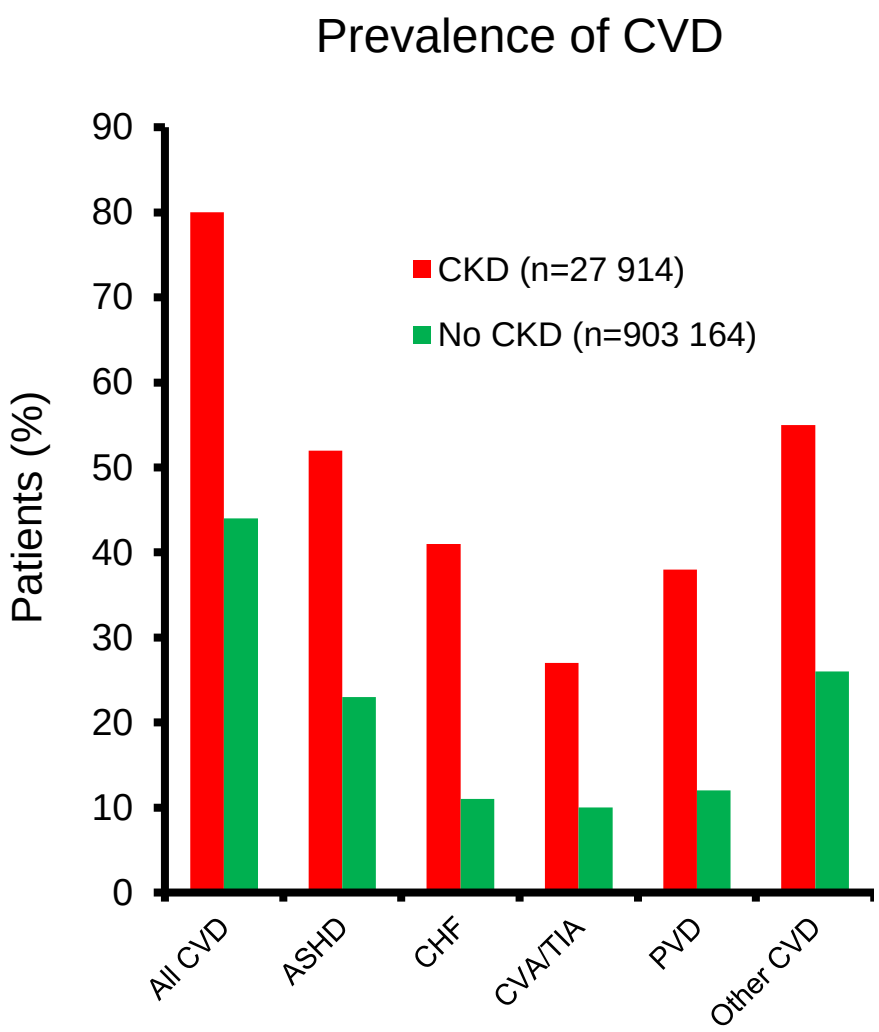
“You had your fun, didn’t you? Well, I’ve got news for you. You’re all going to die now. So there.”

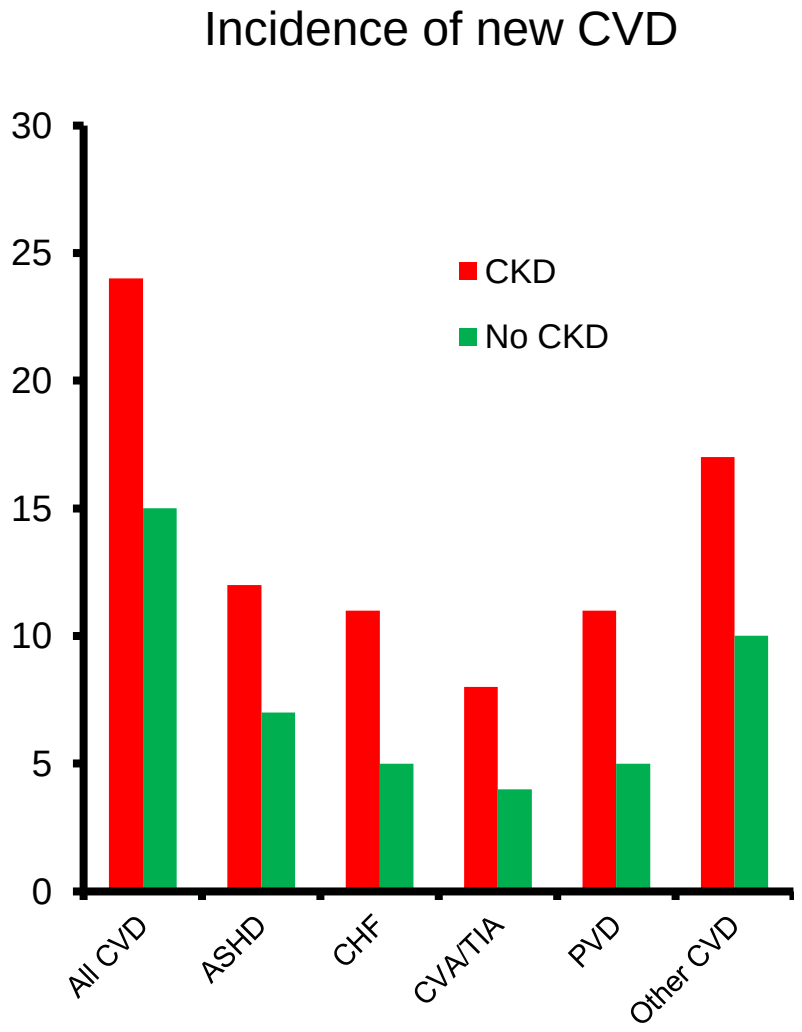
CVD Mortality in the Dialysis Population (USRDS)



Foley RN, AJKD 1998;32:S112-9

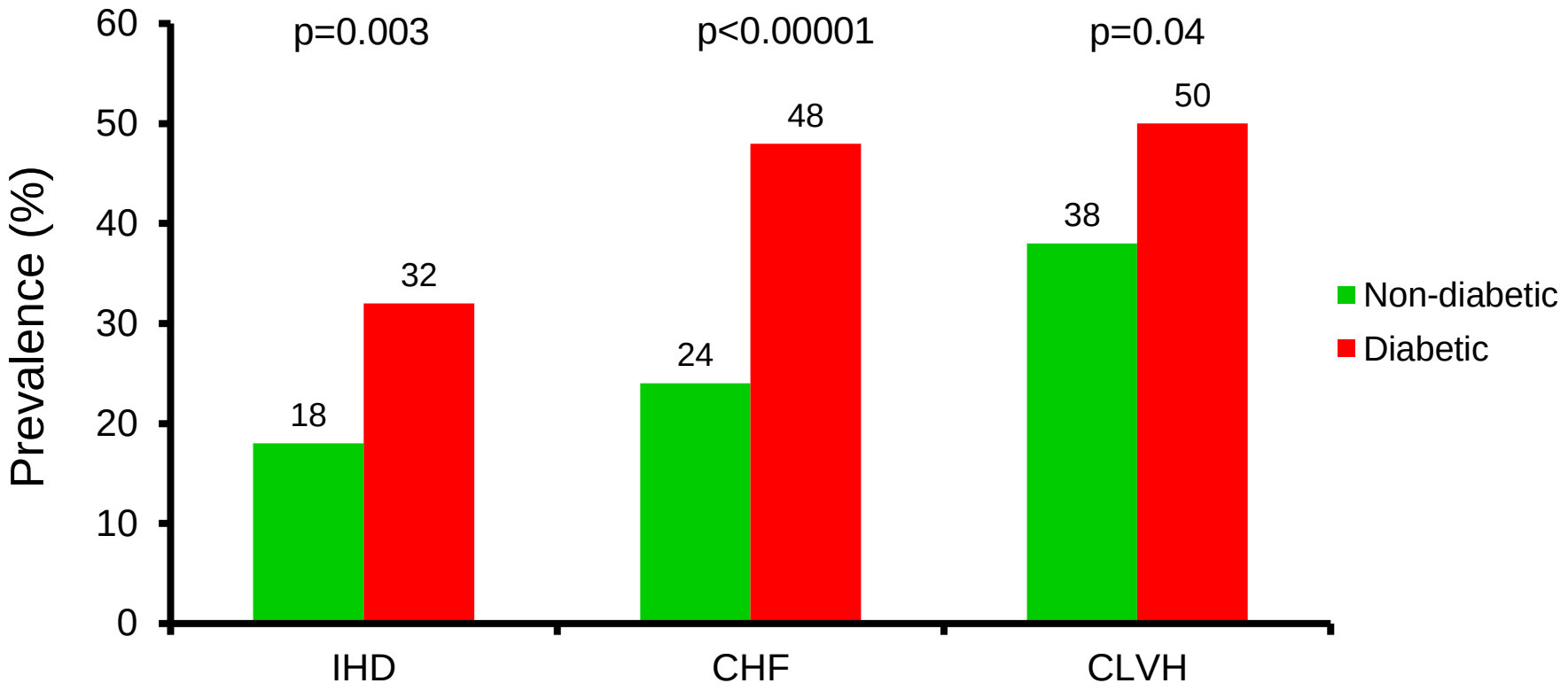
CVD is More Common in CKD





Collins et al KI 2003;64(S87):S24-S31

Prevalence of CVD Higher in DKD versus non-DKD



IHD, ischaemic heart disease; CHF, chronic heart failure;
CLVH, concentric left ventricular hypertrophy

Foley RN et al Diabetologia 1997; 40: 1307-1312

Incidence and Outcomes of Diagnosed CKD

- Retrospective cohort study, 5.5 year follow up
- 4228 cases SCr ≥ 150 μmol/L 1992-1994
  - 1076 chronic disease
  - 1324 acute disease
  - 1828 unknown
- Overall CKD incidence 1701 pmp/yr
  - Median age 77, M:F 1.6
  - 1071 pmp/yr age <80

Drey et al, AJKD 2003;42:677-684

Incidence and Outcomes of Diagnosed CKD

- 39/1076 (4%) progressed to receive RRT
- 741/1076 (69%) died during follow up
- Median survival 35 months
  - SMR 36x normal in 16-49 age group
  - SMR 12x normal in 16-49 age group
  - SMR 2x normal in those 65+
- **46% of deaths were cardiovascular**

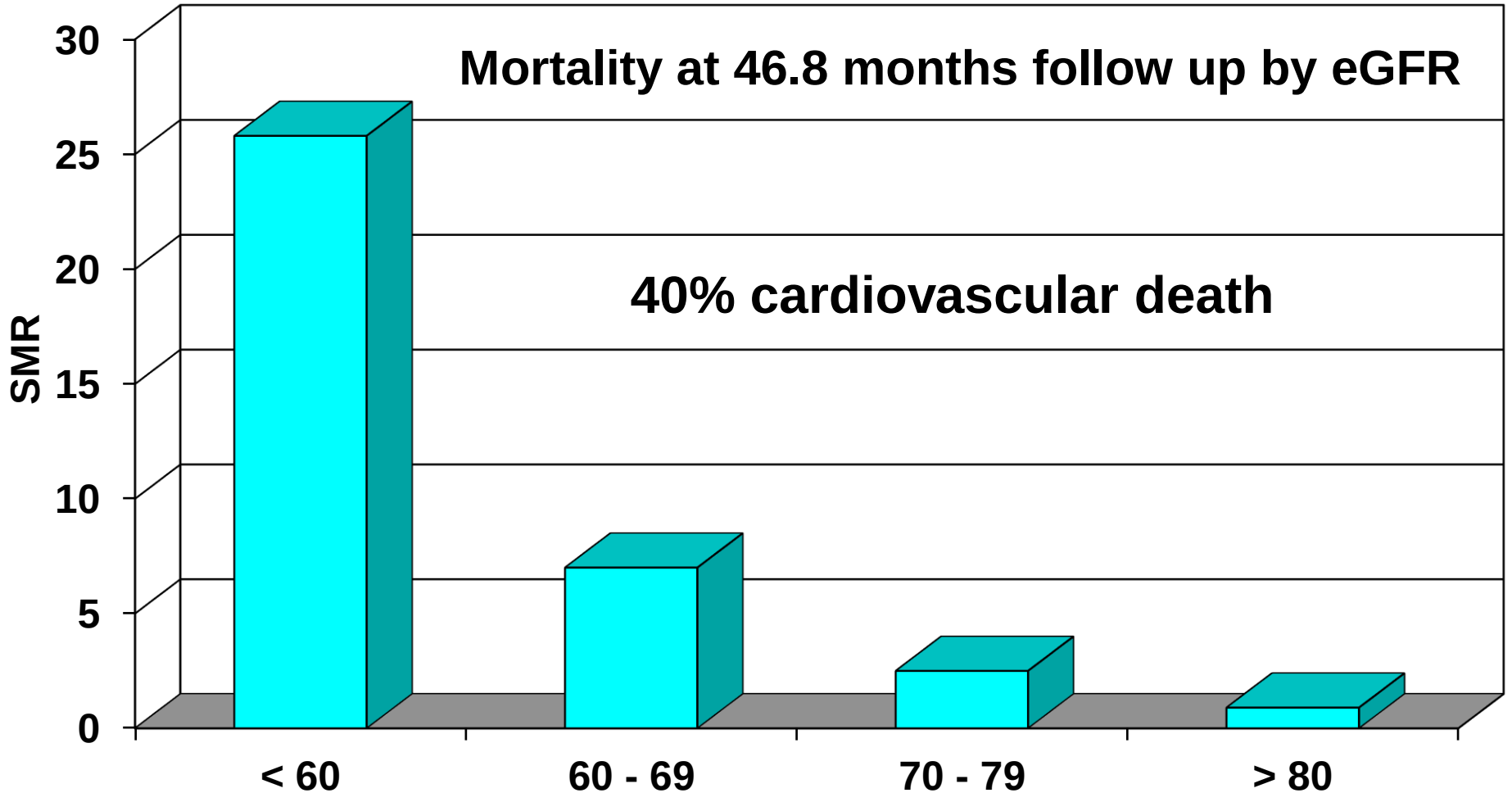
Drey et al, AJKD 2003;42:677-684

Unreferred Chronic Kidney Disease

- East Kent – population 688,193, 51.4% female, 558,665 aged 15+
- Small ethnic minority but 13.8% aged over 70 compared with UK average of 11.5%
- Lab database screened prospectively for patients fulfilling US NIH referral criteria (SCr >180 in men >135 in women)
- Overall prevalence 5554 pmp, 85% unknown to nephrology
- Median age unreferred 83 vs. 70 years in those known
- eGFR 23.4 mL/min/1.73m^2 unreferred vs. 28.5 in those known

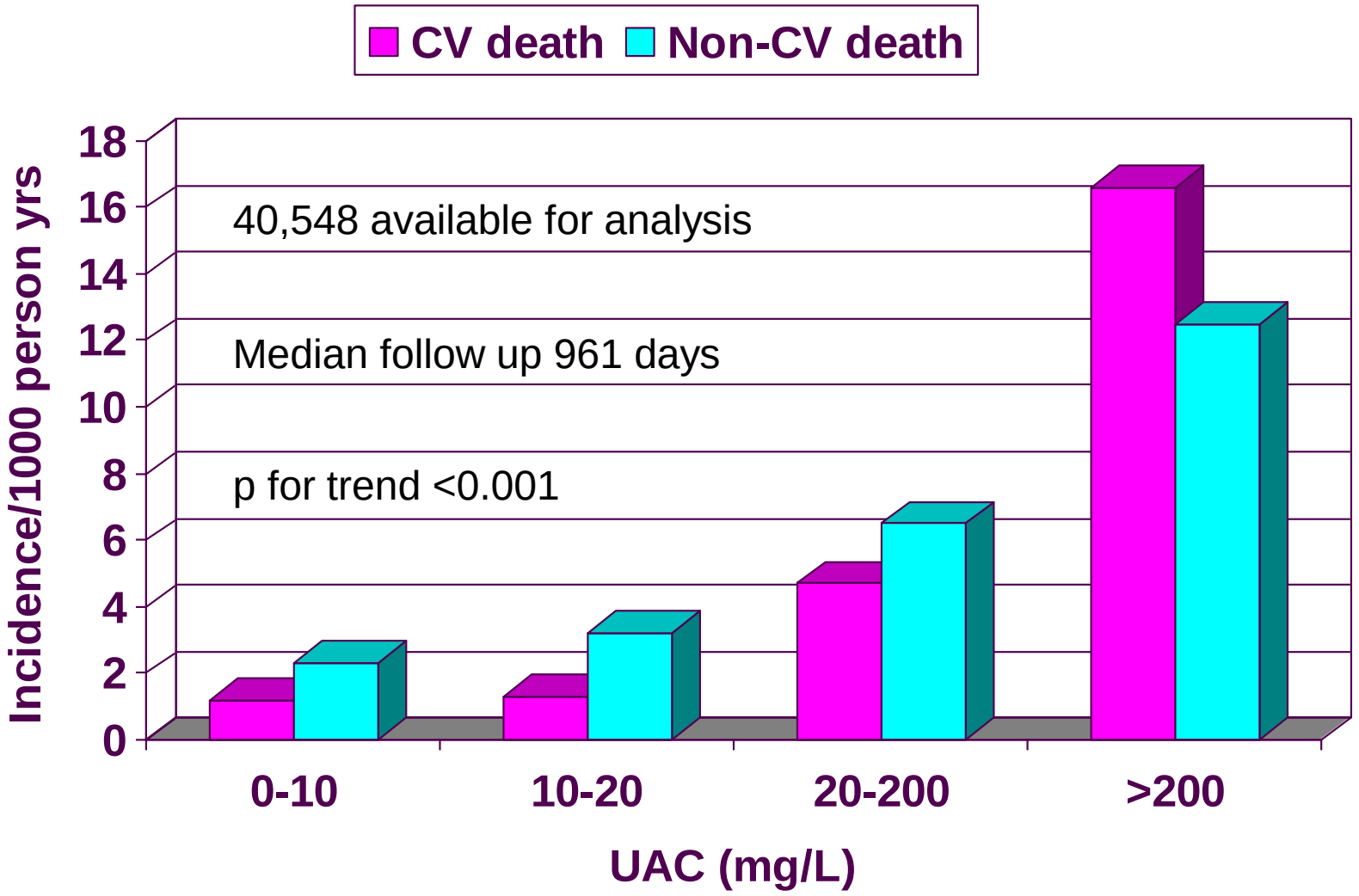
John et al AJKD 2004;43:825-835

UNREFERRED CHRONIC KIDNEY DISEASE



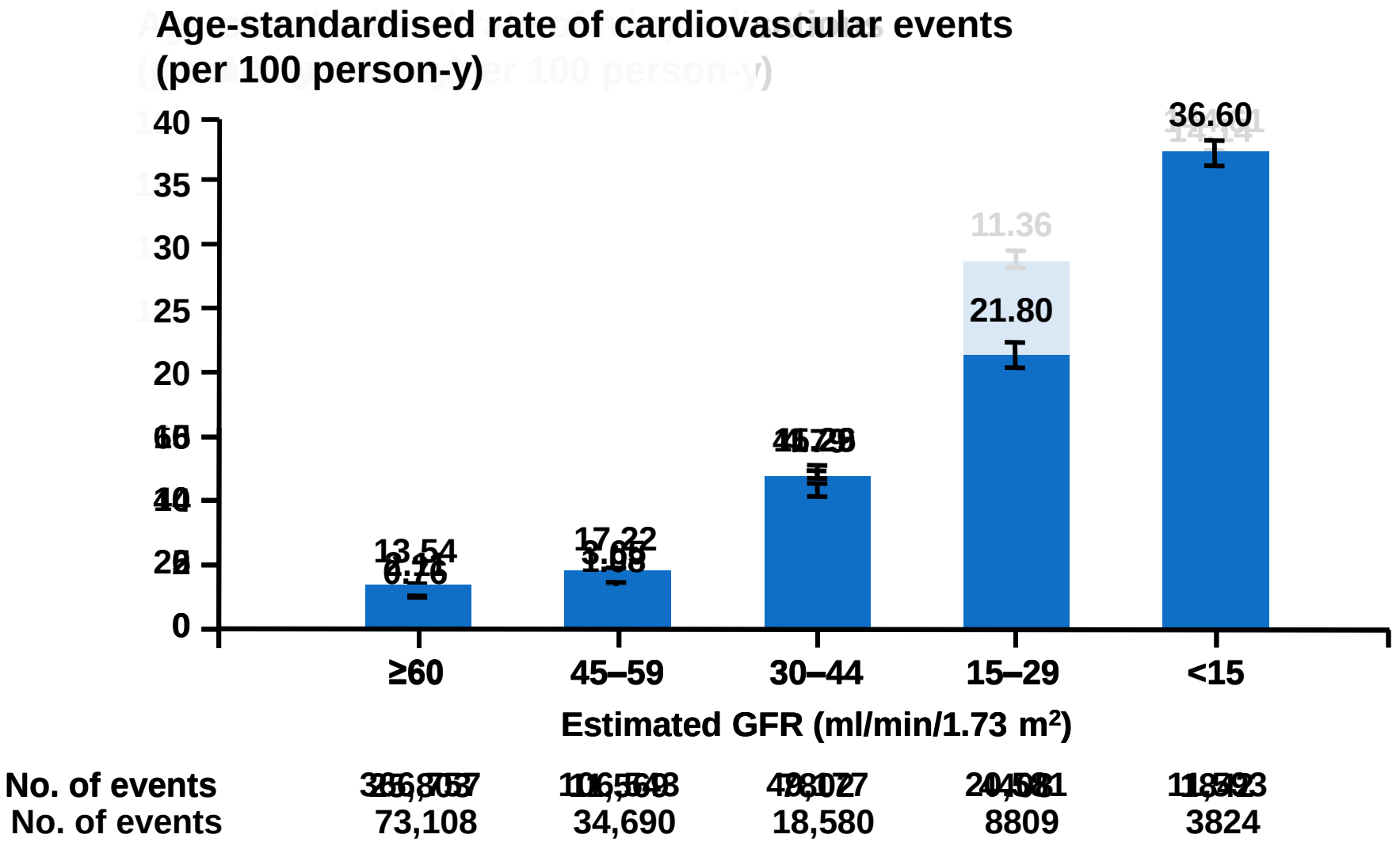
John et al AJKD 2004;43:825-835

ALBUMINURIA AND OUTCOMES: PREVEND STUDY



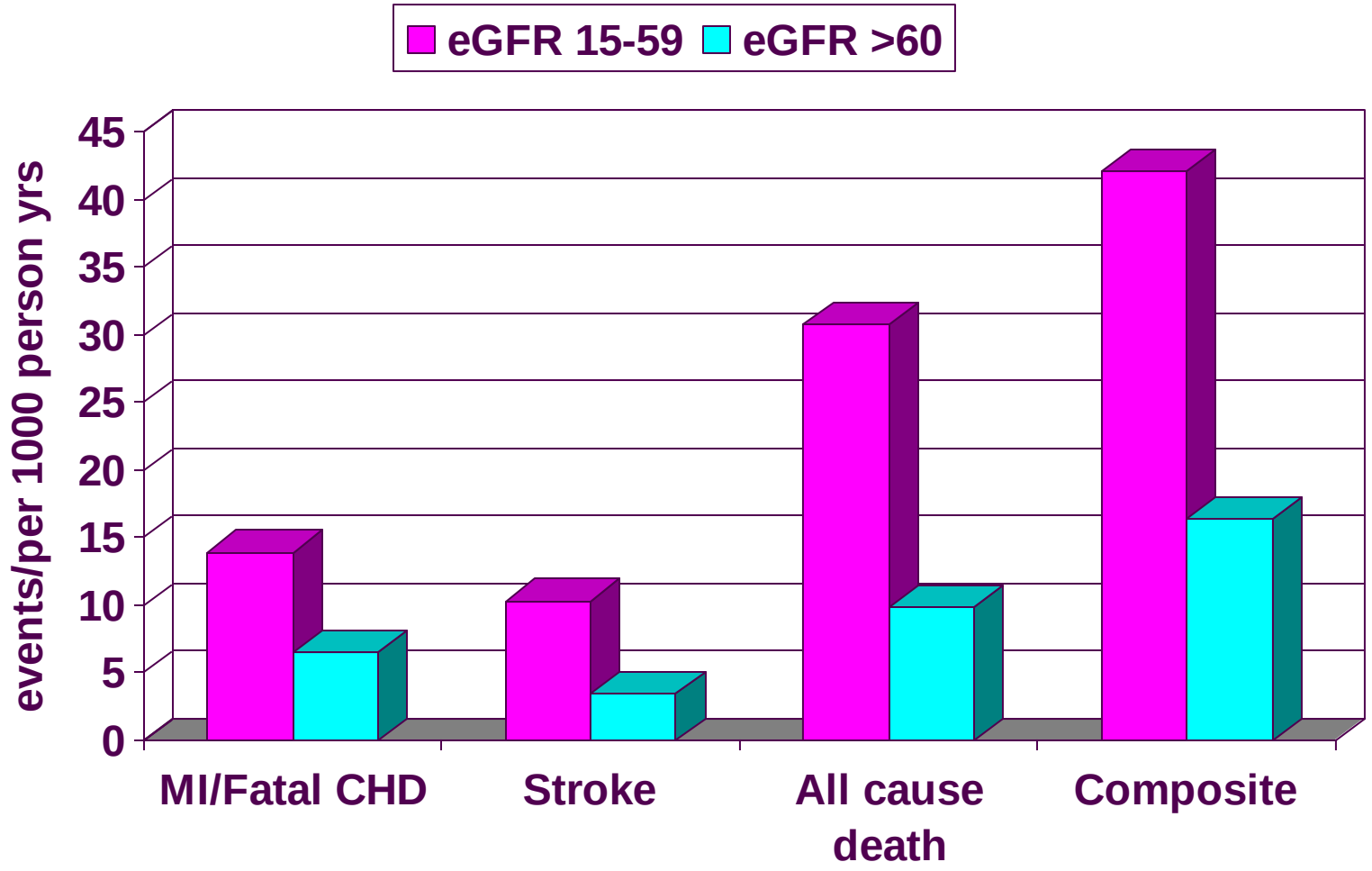
Hillege et al, Circulation 2002;106:1777-1782

CKD In a Managed Healthcare Organisation



Go et al NEJM 2004

Cardiovascular Outcomes by Level of GFR:
Pooled Data From ARIC, CHS, FSH, FSH Offspring



19% increased risk of MI/fatal CHD/stroke

36% increased risk of all cause mortality

Weiner et al, J Am Soc Nephrol 2004;15:1307-1315

Risk Factors for CKD, Progression, CVD and Death

	Importance for different outcomes		
Outcome	CKD stage	CKD diagnosis	Proteinuria
Complications	+++	+	+
10 yr CVD risk/mortality	+++	+	+++
10 yr risk of kidney failure	+++	++	+
Rate of GFR decline	+	+++	++

Levey et al, Kidney Int 2005;67:2089-2100

What Determines Outcomes?

Traditional

- Older age
- Male gender
- ↑ BP and LVH
- ↑ LDL-C ↓ HDL-C
- Diabetes
- Smoking
- Inactivity
- Menopause
- CKD diagnosis
- Family history

Non-modifiable

– Older age

– Male gender

– CKD diagnosis

– Menopause

– Family history

Modifiable

CKD related

- Albuminuria / proteinuria
- ↓ GFR
- RAS activity
- ECFV overload
- Ca/PO4 abnormalities
- Anaemia
- MIA syndrome/ ↑CRP
- Oxidative stress
- ↑ homocysteine
- Lipoprotein a
- Thrombogenic factors

– Blood pressure

– Diabetes

– Smoking

– Inactivity

– Protein leak

– Anaemia

– Cholesterol

– Loss of GFR

– Fluid overload

– Kidney bone disease

Key Aspects of Management

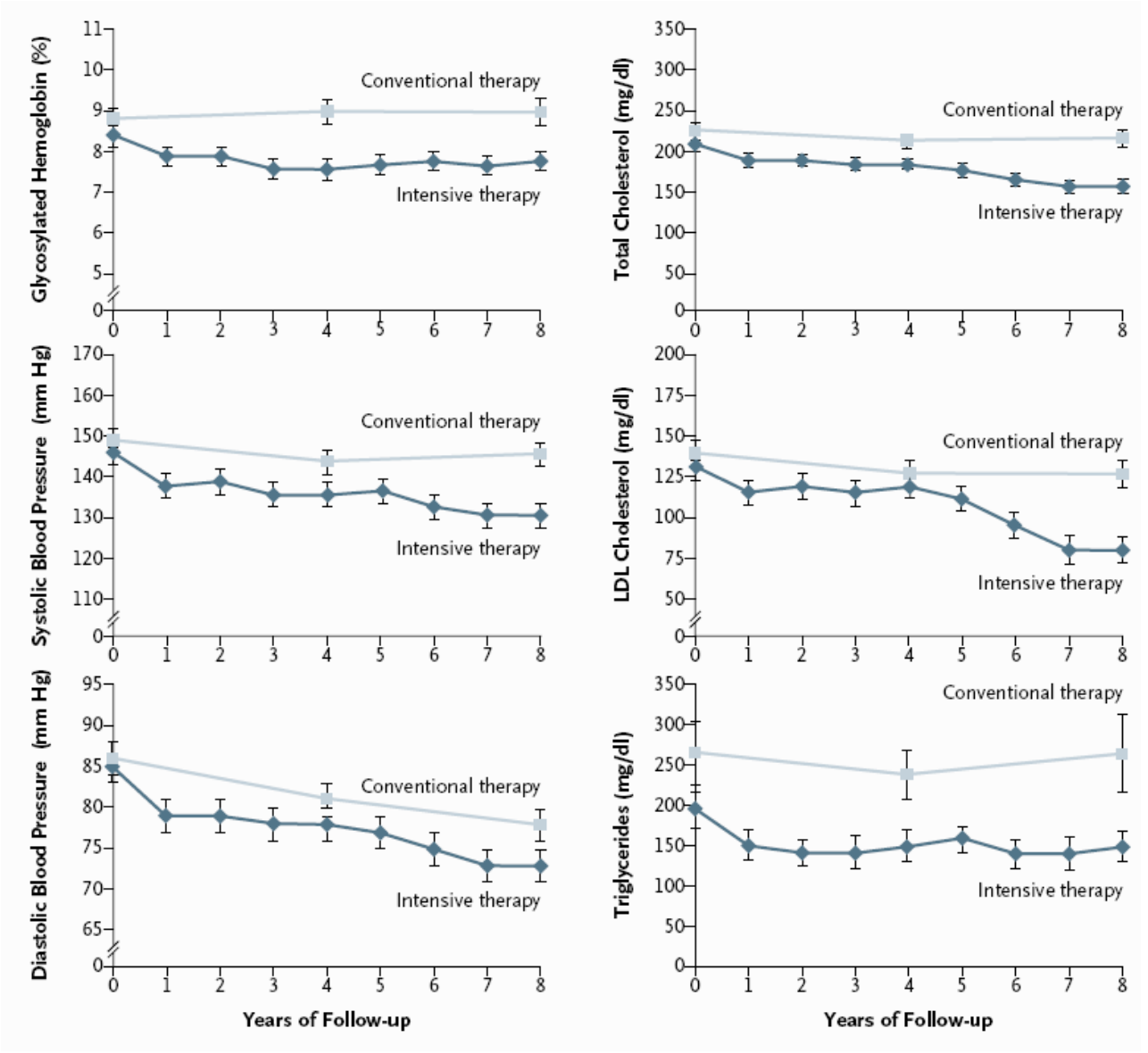
"I've always been a high achiever, always striving for bigger, faster, greater … and now suddenly I'm expected to settle for *lower* blood pressure and *less* cholesterol?!"

STENO-2 STUDY

8 year study, n = 160 randomised to intensive versus conventional goals

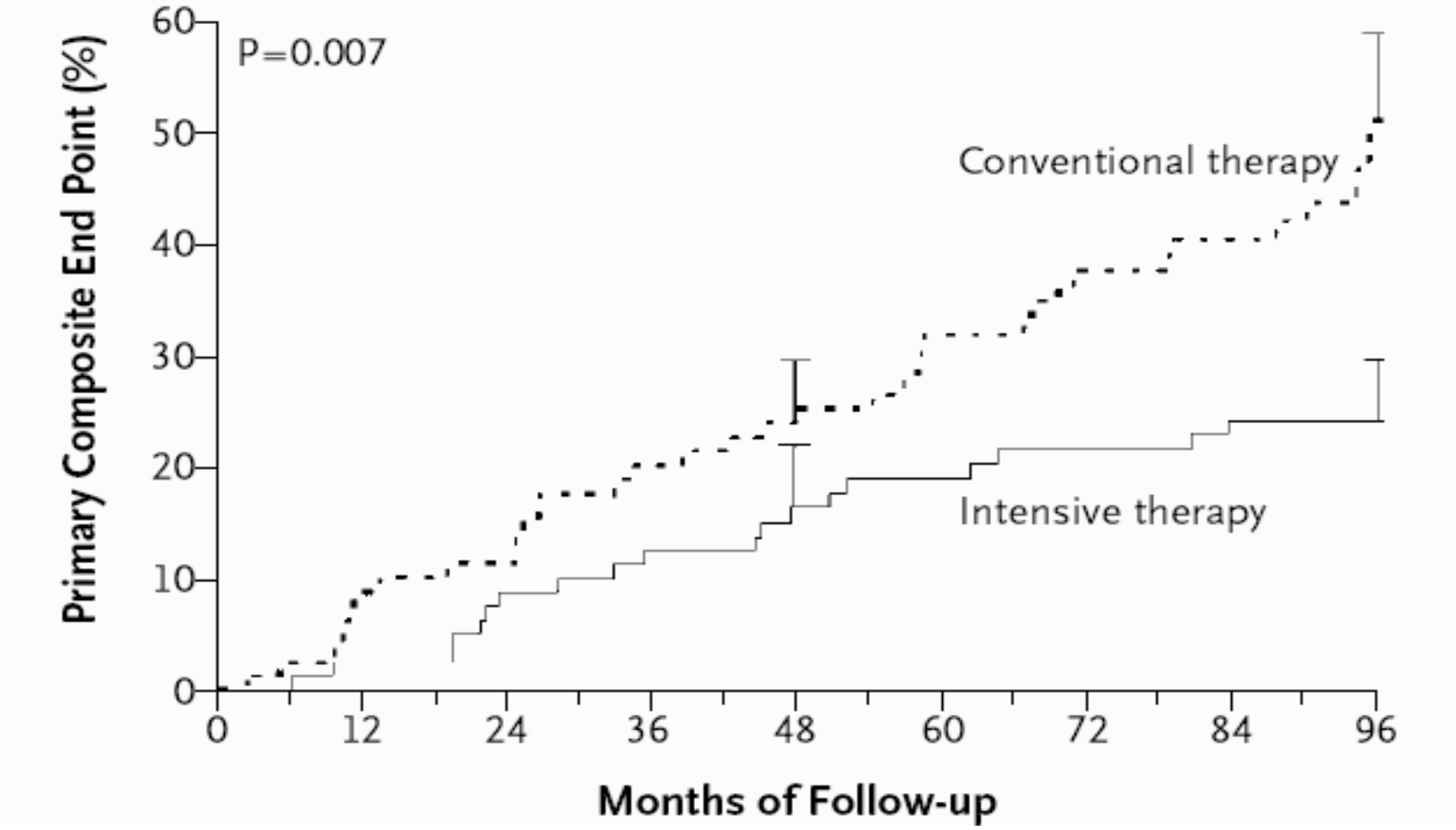
Intensive Goals

- SBP <130 mmHg
- DBP <80 mmHg
- HbA1C <6.5%
- TC <175 mg/dL
- TGs < 150 mg/dL
- ACEI/ARB
- Aspirin



Gaede et al, NEJM 2003;348:383-393

STENO-2 STUDY



Composite end point of CVD death, nonfatal MI, nonfatal stroke, revascularization, and amputation

HR for CVD risk 0.47 (0.24-0.73 95% CI)

Gaede et al, NEJM 2003;348:383-393

Modifiable Risk Factors - Reality

304 patients referred to 4 Canadian centres

Mean GFR 31 mL/min

CVD 39%, DM 38%, dyslipidaemia 43%, smokers 27%, hypertension 80%

BP > 140/90	35%
ACEI/ARB	65%
Aspirin	27%
Statin	18%

1724 patients with MI on coronary care registry in Detroit

GFR < 46 mL/min

Aspirin	28%
Beta blocker	19%
CCB	32%
ACEI/ARB	25%

Tonelli M, AJKD 2001;37:484-489 and Beattie JN, AJKD 2001;37:1191-1200

COMMUNITY TREATMENT OF CKD, UK 2003

Representative UK Population Study, n = 130,262 adults (38,262 with SCr, mean age 58.1 yrs)

Hypertension and GFR < 60 mL/min/1.73m^2, n = 8839	
Use of ACEi/ARB	38.7%
BP <150/80	54.9%
BP < 140/85	22.4%
BP <130/80	12.6%
CVD and GFR < 60 mL/min/1.73m^2, n = 3691	
Use of ACEi/ARB	41.1%
Anti-platelet agents	51.4%
Lipid lowering agents	50.7%

Diabetes and GFR < 60 mL/min/1.73m^2, n = 1568	
Use of ACEi/ARB	44.0%
Anti-platelet agents	39.6%
Lipid lowering agents	60.1%
Hb A1C <7.5%	59.1%
Hypertension on treatment	83.7%
BP <130/80 on treatment	21.0%

Stevens et al, Kidney Int 2007;72:90-99

Epidemiology of chronic kidney disease: an update 2022

kidney INTERNATIONAL supplements

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Extremely common

843,6 Million in 2017

Approximately **1 in 10**

Increasing death rate

+41.5% 1990 to 2017

Large burden in low- and middle-income countries

Among the **top 10 causes** of death in Singapore, Greece, and Israel

Kovesdy, 2022

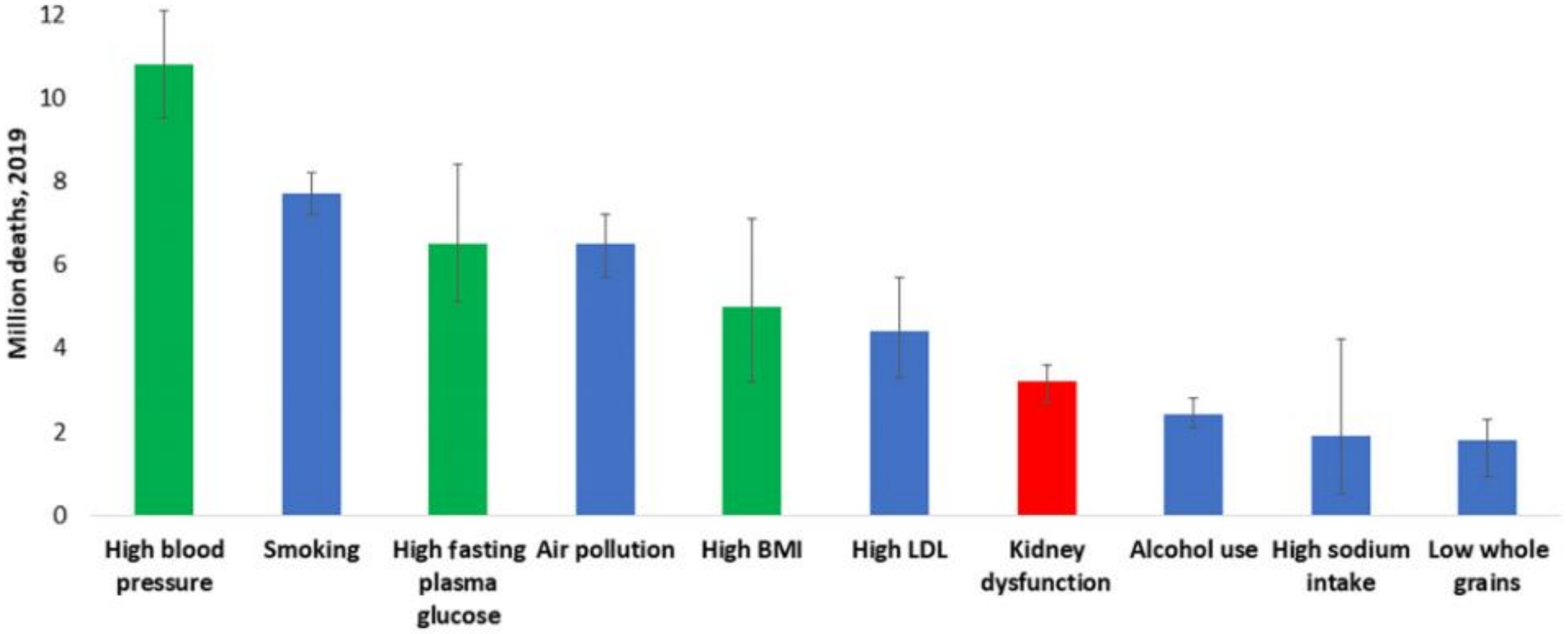
Kidney International Supplements (2022) 12, 7–11

CONCLUSION

Chronic kidney disease (CKD) occurs frequently and has devastating consequences. This should prompt major efforts to develop preventative and therapeutic measures that are effective. The aim of these measures should be lowering the incidence of CKD and slowing its progression.

KDIGO KIDNEY DISEASE · IMPROVING GLOBAL OUTCOMES

All Ages, Top 10 Global Risk Factors for Death, 2019



Luyckx VA et al. Kidney Int 2024;105:406-417

KDIGO CKD 2024 Guideline Evolution

Definition and Classification

CGA Staging; growing emphasis on prognosis and risk

2002
- KDOQI

2012
- KDIGO CKD
- KDIGO Anaemia

2013
- KDIGO Lipids

2017
- KDIGO CKD-MBD

2021
- KDIGO BP
- KDIGO Glomerular Diseases

2022
- KDIGO Hepatitis C
- KDIGO Diabetes

2024
- KDIGO Vasculitis
- KDIGO Lupus
- KDIGO CKD

Tailored therapies

New tools, better understanding of evaluation and risk, generic therapies

CKD-PC Consortia Data

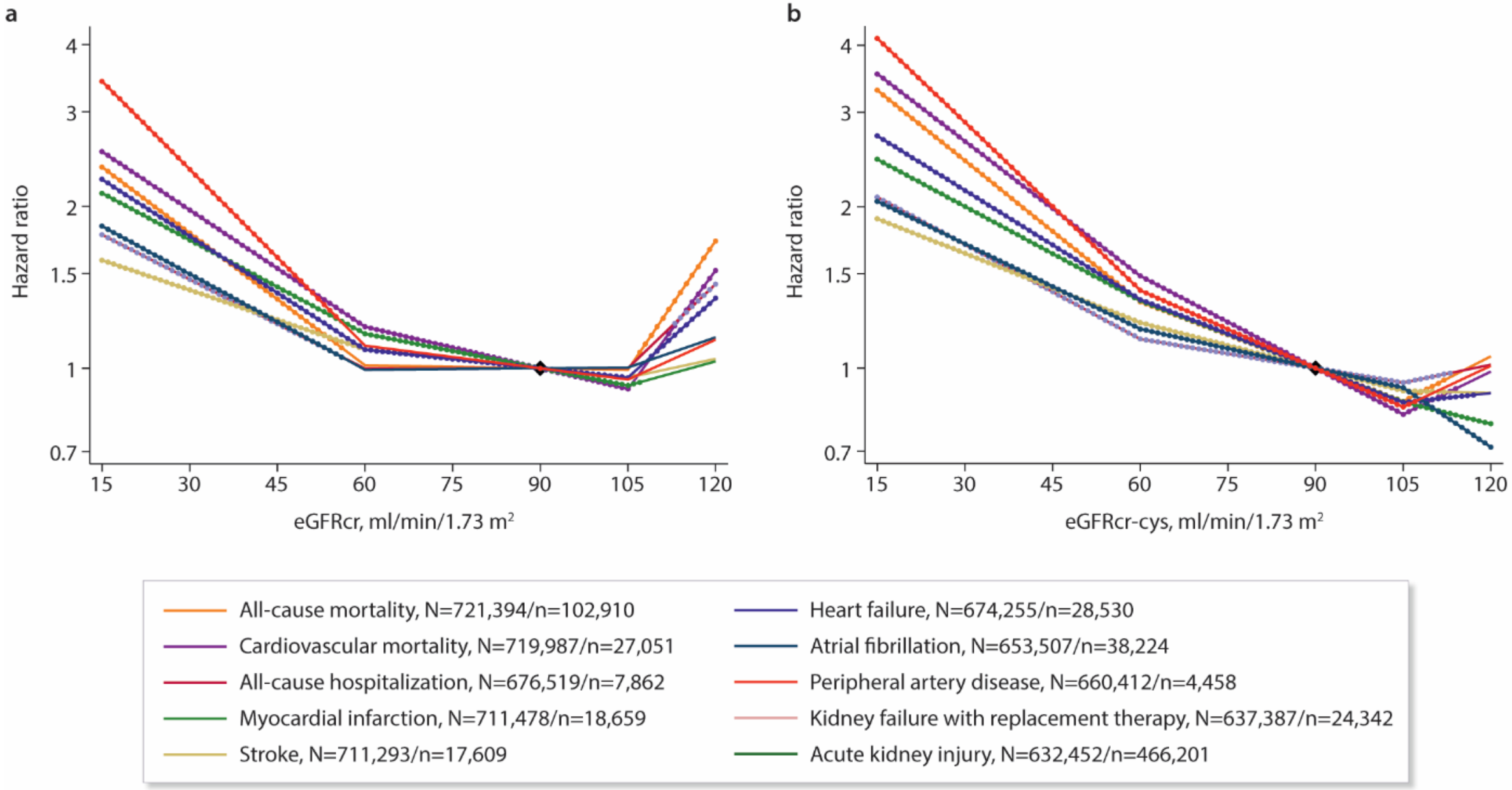
- Categorical meta-analysis of large multinational population studies in the CKD prognosis consortium
- Population base roughly 27.5 million people
  - eGFRcr and ACR (roughly a third of the cohort), subset 720,736 with eGFRcr-cys
- 10 outcomes, 6 cardiovascular, 2 kidney specific, 2 general
- Specific questions of interest relate to eGFR G3a without albuminuria and age
- Analyses repeated using eGFRcr-cys

Grams M et al. JAMA 2023;330:1266-1277

Overall	Urine albumin-creatinine ratio, mg/g					Urine albumin-creatinine ratio, mg/g				
eGFRcr	<10	10–29	30–299	300–999	1000+	<10	10–29	30–299	300–999	1000+
	All-cause mortality: 82 cohorts Participants=26,444,384; events=2,604,028					Myocardial infarction: 64 cohorts Participants=22,838,356; events=451,063				
105+	1.6	2.2	2.9	4.3	5.8	1.1	1.4	2.0	2.7	3.8
90–104	ref	1.3	1.8	2.6	3.1	ref	1.3	1.6	2.2	3.2
60–89	1.0	1.3	1.7	2.2	2.8	1.1	1.3	1.6	2.2	3.1
45–59	1.3	1.6	2.0	2.4	3.1	1.4	1.7	2.0	2.8	3.7
30–44	1.8	2.0	2.5	3.2	3.9	1.9	2.0	2.4	3.2	4.3
15–29	2.8	2.8	3.3	4.1	5.6	2.7	3.1	3.1	4.2	5.1
<15	4.6	5.0	5.3	6.0	7.0	4.6	5.6	4.8	6.0	6.0
	Cardiovascular mortality: 76 cohorts Participants=26,022,346; events=776,441					Stroke: 68 cohorts Participants=24,746,436; events=461,785				
105+	1.4	2.0	3.0	4.1	5.4	1.2	1.6	2.2	3.1	4.3
90–104	ref	1.3	1.9	2.7	3.6	ref	1.3	1.6	2.4	3.1
60–89	1.0	1.4	1.7	2.4	3.2	1.1	1.3	1.7	2.2	3.0
45–59	1.4	1.7	2.2	2.8	3.8	1.4	1.6	1.9	2.3	2.9
30–44	2.0	2.3	2.8	3.7	4.6	1.6	1.7	2.0	2.4	3.0
15–29	3.2	3.1	3.5	5.0	6.5	1.8	2.1	2.1	2.7	3.0
<15	6.1	6.4	6.4	7.3	8.2	3.2	2.8	2.9	3.2	3.8
	Kidney failure with replacement therapy: 57 cohorts Participants=25,466,956; events=158,846					Heart failure: 61 cohorts Participants=24,603,016; events=1,132,443				
105+	0.5	1.2	2.9	7.7	25	1.2	1.7	2.7	4.2	6.9
90–104	ref	1.8	4.3	12	43	ref	1.3	2.0	2.8	4.2
60–89	2.3	4.9	10	27	85	1.1	1.4	1.9	2.7	4.2
45–59	13	19	37	89	236	1.6	1.8	2.4	3.4	5.0
30–44	50	58	115	240	463	2.2	2.5	3.1	4.2	6.5
15–29	283	301	443	796	1253	3.6	3.5	4.1	5.8	8.1
<15	770	1040	1618	2297	2547	5.1	5.7	5.8	7.9	9.9
	Acute kidney injury: 49 cohorts Participants=23,914,614; events=1,408,929					Atrial fibrillation: 50 cohorts Participants=22,886,642; events=1,068,701				
105+	1.0	1.6	2.4	3.7	5.5	1.1	1.3	1.7	2.4	3.5
90–104	ref	1.4	2.1	3.2	5.0	ref	1.2	1.5	1.9	2.3
60–89	1.6	2.2	3.1	4.3	6.7	1.0	1.2	1.4	1.7	2.2
45–59	3.5	4.0	5.1	6.9	9.0	1.2	1.3	1.5	1.8	2.4
30–44	5.6	5.9	6.8	8.6	11	1.4	1.5	1.7	2.0	2.4
15–29	8.3	8.0	8.5	9.9	10	1.9	1.8	2.0	2.6	3.0
<15	8.5	11	7.9	5.5	5.7	2.6	2.5	3.1	3.6	4.2
	Hospitalization: 49 cohorts Participants=25,426,722; events=8,398,637					Peripheral artery disease: 54 cohorts Participants=24,830,794; events=378,924				
105+	1.4	1.7	2.1	2.1	2.3	0.9	1.4	1.9	2.8	5.0
90–104	ref	1.1	1.3	1.5	1.7	ref	1.3	1.9	2.8	4.3
60–89	1.0	1.1	1.3	1.5	1.8	1.0	1.3	1.8	2.5	3.8
45–59	1.3	1.3	1.5	1.7	2.1	1.5	1.7	2.1	2.9	4.2
30–44	1.5	1.5	1.6	1.9	2.3	2.0	1.9	2.5	3.6	5.0
15–29	1.8	1.8	1.9	2.4	2.8	3.3	3.3	3.8	5.7	8.1
<15	2.7	2.8	3.0	3.2	3.8	9.1	9.0	9.6	13	14

	Urine albumin-creatinine ratio, mg/g				Urine albumin-creatinine ratio, mg/g			
eGFRcr-cys	<10	10–29	30–299	300+	<10	10–29	30–299	300+
	All-cause mortality: 11 cohorts Participants=692,802; events=97,006				Myocardial infarction: 10 cohorts Participants=649,365; events=17,926			
105+	1	1.3	1.6	2.5	0.9	1.2	1.4	2.8
90–104	ref	1.3	1.5	2	ref	1.2	1.4	1.8
60–89	1.2	1.5	1.9	2.5	1.2	1.4	1.5	1.9
45–59	1.7	2.2	2.5	3.3	1.6	1.9	2.3	3.3
30–44	2.3	2.6	3.4	4.4	2.1	2.6	3.1	3.3
<30	3.6	4	5.5	7.1	5.1	3	4.9	5
	Cardiovascular mortality: 11 cohorts Participants=692,322, events=25,322				Stroke: 9 cohorts Participants=662,605; events=16,909			
105+	1	1.4	1.8	4.1	1	1.2	1.6	2.5
90–104	ref	1.5	1.6	2.9	ref	1.2	1.5	2.3
60–89	1.2	1.7	2.3	3.4	1.2	1.4	1.8	2.5
45–59	1.9	2.7	3.2	4.6	1.6	1.7	2.1	2.7
30–44	2.5	3.5	4.5	5.9	1.7	2	2.3	2.6
<30	5.8	5	6.1	8.7	1.9	2.3	2.8	4.4
	Kidney failure with replacement therapy: 5 cohorts Participants=630,370; events=4,306				Heart failure: 9 cohorts Participants=641,298; events=27,406			
105+	0.6	0.8	2.3	10	0.9	1.2	1.7	3.7
90–104	ref	1.5	4.5	11	ref	1.3	1.4	2.5
60–89	1.9	3.7	8.3	31	1.2	1.6	1.9	3
45–59	5.8	13	25	73	1.5	2.2	3	4.1
30–44	20	23	78	191	2.5	2.9	4.1	5.7
<30	111	261	343	580	5.3	4.8	6.5	7.7
	Acute kidney injury: 5 cohorts Participants=630,370; events=24,062				Atrial fibrillation: 5 cohorts Participants=607,102; events=37,278			
105+	0.8	1	1.4	3.5	0.9	1	1.1	1.9
90–104	ref	1.3	1.7	2.8	ref	1.2	1.4	2.2
60–89	1.6	2.5	2.9	5.3	1.1	1.3	1.5	2
45–59	3.9	4.7	5.5	7.5	1.3	1.6	1.8	2.2
30–44	5.8	7	8.4	10	1.6	2	2.2	2.5
<30	11	12	12	21	2	2	2.7	4.4
	Hospitalization: 3 cohorts Participants=630,489; events=464,894				Peripheral artery disease: 6 cohorts Participants=642,624; events=3,943			
105+	1	1.1	1.1	1.6	0.9	1.9	1.8	2.9
90–104	ref	1.1	1.3	1.4	ref	1.5	2	3.2
60–89	1.1	1.2	1.3	1.6	1.3	1.8	2.1	3.9
45–59	1.3	1.4	1.5	1.7	2.5	3.7	3.3	4
30–44	1.5	1.5	1.6	2.1	4	3.7	4.5	6.9
<30	1.8	2	2.1	3	7.8	4.5	9	12

Grams M et al. JAMA 2023;330:1266-1277



Grams M et al. JAMA 2023;330:1266-1277

Heatmaps evaluated by age using eGFRcr-cys

Relative risks much more similar by age when using eGFRcr-cys

G3a associated with significant risk in every outcome (both optimal ACR <10; and high normal ACR 10-29)

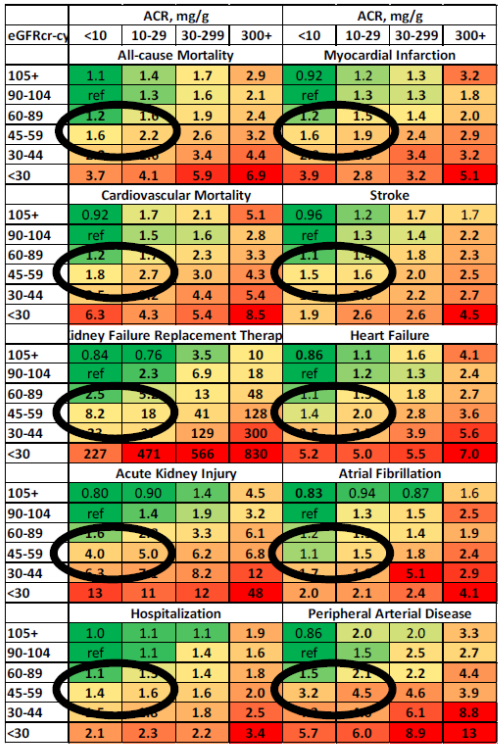
Age <65	ACR, mg/g				ACR, mg/g			
eGFRcr-cys	<10	10–29	30–299	300+	<10	10–29	30–299	300+
	All-cause mortality				Myocardial infarction			
105+	0.99	1.2	1.5	2.4	0.93	1.0	1.1	2.6
90–104	ref	1.3	1.5	2.5	ref	1.2	1.3	1.9
60–89	1.2	1.6	2.0	2.9	1.3	1.4	1.6	2.1
45–59	2.1	2.7	2.9	4.5	1.8	2.6	3.1	3.5
30–44	2.7	3.8	4.2	5.6	1.9	2.3	3.0	3.9
<30	5.2	4.0	7.1	8.6	4.1	3.6	4.7	5.8
	Cardiovascular mortality				Stroke			
105+	0.95	1.4	1.7	4	0.96	1.2	1.6	2.7
90–104	ref	1.6	1.8	3.5	ref	1.2	1.5	2.2
60–89	1.3	1.7	2.3	3.9	1.2	1.4	1.7	2.6
45–59	2.5	4.0	4.6	6.0	1.9	2.0	2.5	3.8
30–44	3.1	6.6	5.3	7.1	2.6	3.7	3.5	3.5
<30	6.0	5.5	9.4	12	2.6	2.9	5.1	5.1
	Kidney failure replacement therapy				Heart failure			
105+	0.57	0.77	2.3	12	0.86	1.1	1.7	3.4
90–104	ref	1.4	3.9	11	ref	1.3	1.5	3.0
60–89	1.9	3.7	8.3	33	1.2	1.7	2.1	3.6
45–59	7.0	16	28	100	1.7	3.3	3.4	5.3
30–44	22	34	109	210	3.5	4.3	6.8	5.7
<30	335	267	419	625	7.5	6.3	9.7	8.9
	Acute kidney injury				Atrial fibrillation			
105+	0.75	1.0	1.4	3.4	0.93	1.0	1.3	1.9
90–104	ref	1.2	1.8	2.6	ref	1.2	1.4	2.3
60–89	1.6	2.7	2.9	5.8	1.1	1.3	1.5	1.8
45–59	4.2	6.0	5.6	7.6	1.5	2.0	2.1	2.6
30–44	5.7	9.4	9.8	9.4	1.8	2.4	3.0	2.8
<30	15	14	14	13	3.7	2.9	4.3	5.4
	Hospitalization				Peripheral artery disease			
105+	1.0	1.1	1.1	1.5	0.93	1.9	1.5	2.6
90–104	ref	1.1	1.2	1.3	ref	1.8	2.1	3.9
60–89	1.1	1.2	1.3	1.6	1.2	2.1	2.2	5.4
45–59	1.3	1.7	1.5	2.0	3.2	7.3	3.4	8.4
30–44	1.5	1.8	1.6	2.1	6.5	9.1	6.6	13
<30	2.1	2.4	2.4	3.5	1.4	7.6	18	16

Age 65+	ACR, mg/g				ACR, mg/g			
eGFRcr-cys	<10	10–29	30–299	300+	<10	10–29	30–299	300+
	All-cause mortality				Myocardial infarction			
105+	1.2	1.4	1.9	3.5	0.97	1.4	2.0	19
90–104	ref	1.2	1.4	2.0	ref	1.2	1.1	1.9
60–89	1.2	1.5	1.8	2.3	1.1	1.4	1.5	1.9
45–59	1.6	2.0	2.4	2.9	1.6	1.9	2.3	3.4
30–44	2.0	2.4	3.2	4.1	2.1	2.6	3.1	3.8
<30	3.4	4.1	5.1	6.5	4.9	3.0	5.1	5.0
	Cardiovascular mortality				Stroke			
105+	1.1	1.5	2.0	12	1.2	1.3	1.5	3.3
90–104	ref	1.4	1.4	3.4	ref	1.3	1.3	2.8
60–89	1.2	1.7	2.2	3.1	1.1	1.4	1.8	2.5
45–59	1.7	2.4	3.0	4.3	1.5	1.7	2.0	2.3
30–44	2.4	3.1	4.5	5.8	1.5	2.0	2.1	2.3
<30	5.7	5.2	5.1	7.8	1.7	2.0	2.4	4.8
	Kidney failure replacement therapy				Heart failure			
105+	2.0	1.0	2.1		0.99	1.5	1.7	7.0
90–104	ref	1.9	4.7	10	ref	1.3	1.5	2.2
60–89	1.4	2.6	6.2	19	1.2	1.5	2.0	3.2
45–59	3.7	7.9	16	42	1.6	2.0	2.9	4.1
30–44	14	14	46	137	2.3	2.9	3.5	6.1
<30	87	364	241	406	4.4	4.1	5.5	7.2
	Acute kidney injury				Atrial fibrillation			
105+	0.91	1.1	1.3	1.9	0.95	1.1	1.0	3.7
90–104	ref	1.3	1.4	3.9	ref	1.2	1.3	2.4
60–89	1.5	2.1	2.7	4.7	1.1	1.2	1.5	2.0
45–59	3.6	4.3	5.1	7.3	1.2	1.4	1.7	1.9
30–44	5.7	5.9	7.2	9.8	1.5	1.8	2.0	2.2
<30	10	11	11	22	1.8	1.8	2.2	3.2
	Hospitalization				Peripheral artery disease			
105+	1.0	1.1	1.2	2.2	1.1	2.3	2.9	4.9
90–104	ref	1.1	1.3	1.4	ref	1.3	2.0	4.8
60–89	1.1	1.2	1.3	1.5	1.3	1.6	2.0	3.2
45–59	1.2	1.2	1.4	1.6	2.0	2.8	3.1	3.1
30–44	1.5	1.4	1.6	2.0	3.5	2.8	3.8	5.9
<30	1.9	1.9	2.0	2.6	8.4	4.1	5.9	10

Grams M et al. JAMA 2023;330:1266-1277

Is there still a risk at G3a, Without Albuminuria?

Risks of subsequent adverse outcomes within CKD category G3a compared to eGFR 90-105 mL/min/1.73m^2 for ACR <10 mg/g, ACR 10-29 mg/g and missing ACR by eGFRcr-cys

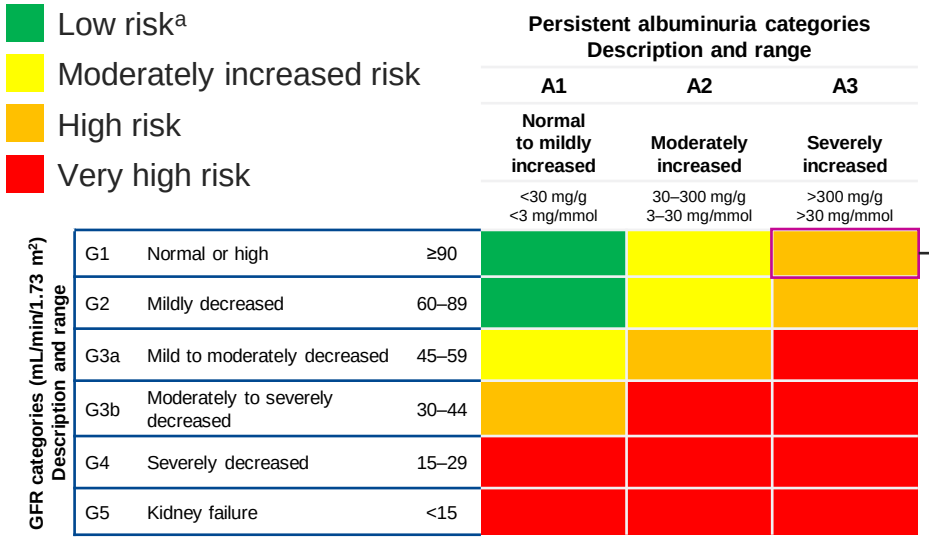


eGFRcr-cy	ACR, mg/g <10	10-29	30-299	300+	ACR, mg/g <10	10-29	30-299	300+
	All-cause Mortality				Myocardial Infarction			
105+	1.1	1.4	1.7	2.9	0.92	1.2	1.3	3.2
90-104	ref	1.3	1.6	2.1	ref	1.3	1.3	1.8
60-89	1.2	1.6	1.9	2.4	1.2	1.5	1.4	2.0
45-59	1.6	2.2	2.6	3.2	1.6	1.9	2.4	2.9
30-44			3.4	4.4			3.4	3.2
<30	3.7	4.1	5.9	6.9	3.9	2.8	3.2	5.1
	Cardiovascular Mortality				Stroke			
105+	0.92	1.7	2.1	5.1	0.96	1.2	1.7	1.7
90-104	ref	1.5	1.6	2.8	ref	1.3	1.4	2.2
60-89	1.2	1.7	2.3	3.3	1.1	1.4	1.8	2.3
45-59	1.8	2.7	3.0	4.3	1.5	1.6	2.0	2.5
30-44			4.4	5.4			2.2	2.7
<30	6.3	4.3	5.4	8.5	1.9	2.6	2.6	4.5
	idney Failure Replacement Therap				Heart Failure			
105+	0.84	0.76	3.5	10	0.86	1.1	1.6	4.1
90-104	ref	2.3	6.9	18	ref	1.2	1.3	2.4
60-89	2.5		13	48	1.1		1.8	2.7
45-59	8.2	18	41	128	1.4	2.0	2.8	3.6
30-44			129	300			3.9	5.6
<30	227	471	566	830	5.2	5.0	5.5	7.0
	Acute Kidney Injury				Atrial Fibrillation			
105+	0.80	0.90	1.4	4.5	0.83	0.94	0.87	1.6
90-104	ref	1.4	1.9	3.2	ref	1.3	1.5	2.5
60-89	1.6		3.3	6.1	1.2		1.4	1.9
45-59	4.0	5.0	6.2	6.8	1.1	1.5	1.8	2.4
30-44			8.2	12			5.1	2.9
<30	13	11	12	48	2.0	2.1	2.4	4.1
	Hospitalization				Peripheral Arterial Disease			
105+	1.0	1.1	1.1	1.9	0.86	2.0	2.0	3.3
90-104	ref	1.1	1.4	1.6	ref	1.5	2.5	2.7
60-89	1.1		1.4	1.8	1.5		2.2	4.4
45-59	1.4	1.6	1.6	2.0	3.2	4.5	4.6	3.9
30-44			1.8	2.5			6.1	8.8
<30	2.1	2.3	2.2	3.4	5.7	6.0	8.9	13

Hazard Ratio (95% CI)	eGFRcr-cys 45-59 and ACR<10	eGFRcr-cys 45-59 and ACR 10-29
All-cause mortality	1.67 (1.51, 1.85)	2.18 (2.04, 2.34)
Cardiovascular mortality	1.78 (1.58, 2.00)	2.65 (2.31, 3.04)
Kidney failure with replacement therapy	5.77 (2.35, 14.15)	12.50 (5.38, 29.05)
Acute kidney injury	3.94 (3.50, 4.42)	4.65 (4.14, 5.23)
Hospitalization	1.38 (1.18, 1.61)	1.56 (1.48, 1.66)
Coronary heart disease	1.63 (1.33, 1.99)	1.91 (1.58, 2.30)
Stroke	1.58 (1.34, 1.86)	1.65 (1.42, 1.92)
Heart failure	1.53 (1.12, 2.10)	2.20 (1.75, 2.77)
Atrial fibrillation	1.27 (1.03, 1.56)	1.61 (1.38, 1.88)
Peripheral artery disease	2.94 (2.16, 4.00)	4.02 (3.01, 5.37)

All p values <0.001

Transitioning to Risk Prediction



CKD staging heatmaps reflect **relative risk** of adverse outcomes at a **population level**

To calculate **absolute risk** of adverse outcomes on an **individual level, risk prediction** equations are required

Individual risk for each outcome is influenced by:

- Underlying etiology of CKD
- Demographic characteristics
- Comorbid conditions
- Lifestyle
- Socioeconomic status
- Nutrition
- Intercurrent events

KDIGO 2024 guidelines recommend the use of an **externally validated risk equation** to estimate the **absolute risk of kidney failure** and **advise using CVD risk prediction to guide therapy**

Using Risk Evaluation to Aid Decision Making

CKD-PC Risk Models

Chronic Kidney Disease Prognosis Consortium (CKD-PC) is a research group composed of investigators representing cohorts from around the world. For more information, please visit our website, www.ckdpc.org. Below are some of the models we have developed.

The Kidney Failure Risk Equation

This model gives the 2 and 5 year risk of kidney failure in patients with Chronic Kidney Disease stage 3 to 5 (eGFR <60 mL/min/1.73m²).

Tangri N, Grams ME, Levey AS, Coresh J, Appel LJ, Astor BC et al. Multinational Assessment of Accuracy of Equations for Predicting Risk of Kidney Failure. A Meta-analysis. JAMA. 2016;315(2):164-174

Continue to model »

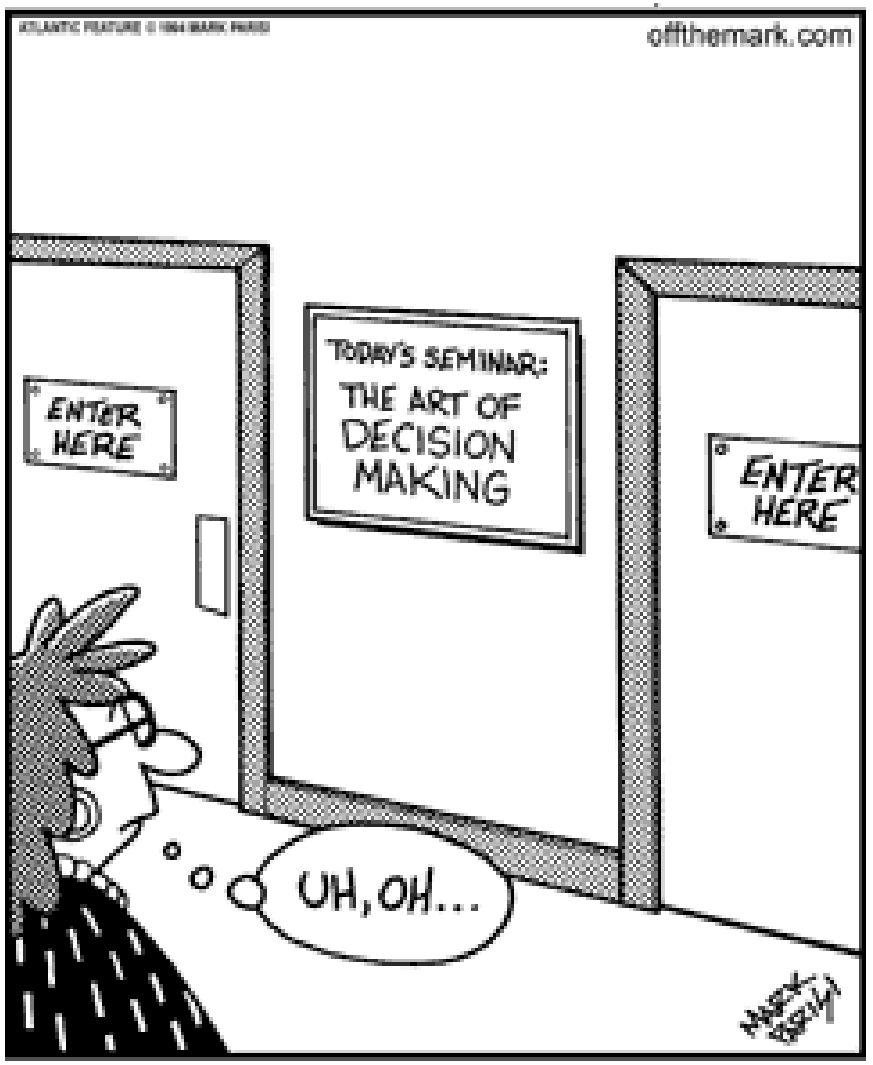
Timing of Clinical Outcomes in CKD with Severely Decreased GFR

This model gives the risk of various clinical outcomes and their timing in patients with Chronic Kidney Disease Stage G4 (eGFR <30 mL/min/1.73m²).

Grams ME, Sang Y, Ballew SH, Carrero JJ, Djurdjev O, Heerspink HJL et al. Predicting timing of clinical outcomes in patients with chronic kidney disease and severely decreased glomerular filtration rate. Kidney Int 2018; 93:1442-1451

Continue to model »

ESRD Risk Tool for Kidney Donor Candidates



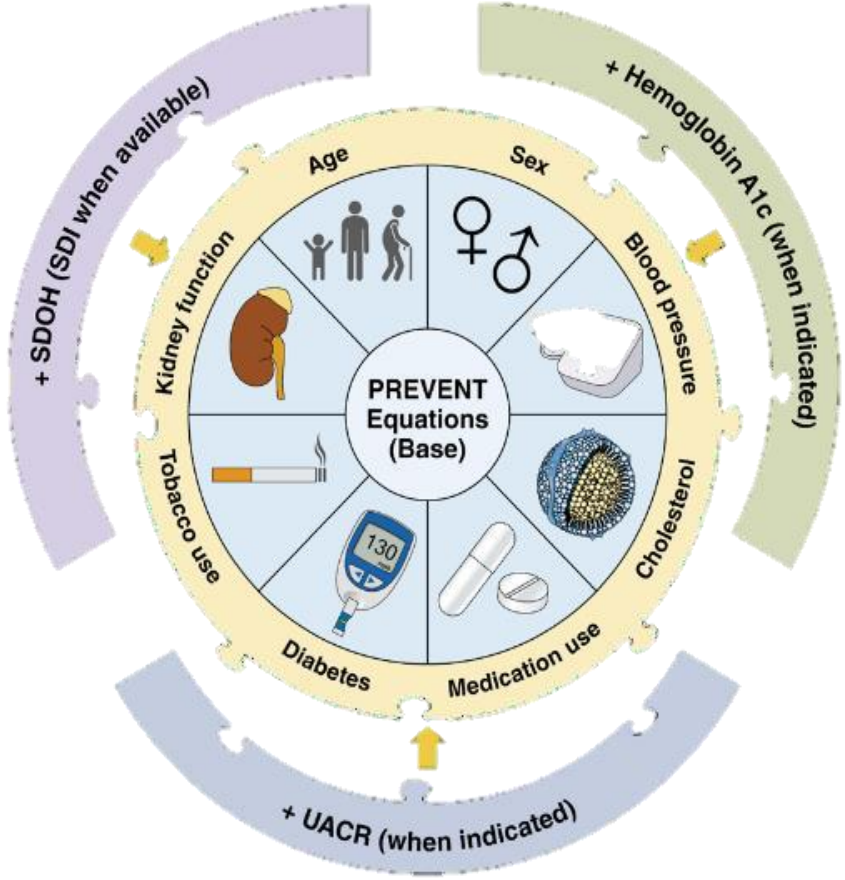
Prediction Equations for CVD With CKD

- SCORE 2-OP (Europe) predicts myocardial infarction, stroke and CVD mortality
- Pooled Cohort Equation (US) predicts atherosclerotic cardiovascular disease (coronary heart disease and stroke)
- QRisk3 (UK) predicts risk of coronary artery disease and stroke

Limitations of all 3 include exclusion of heart failure, use of older data and limited geography.

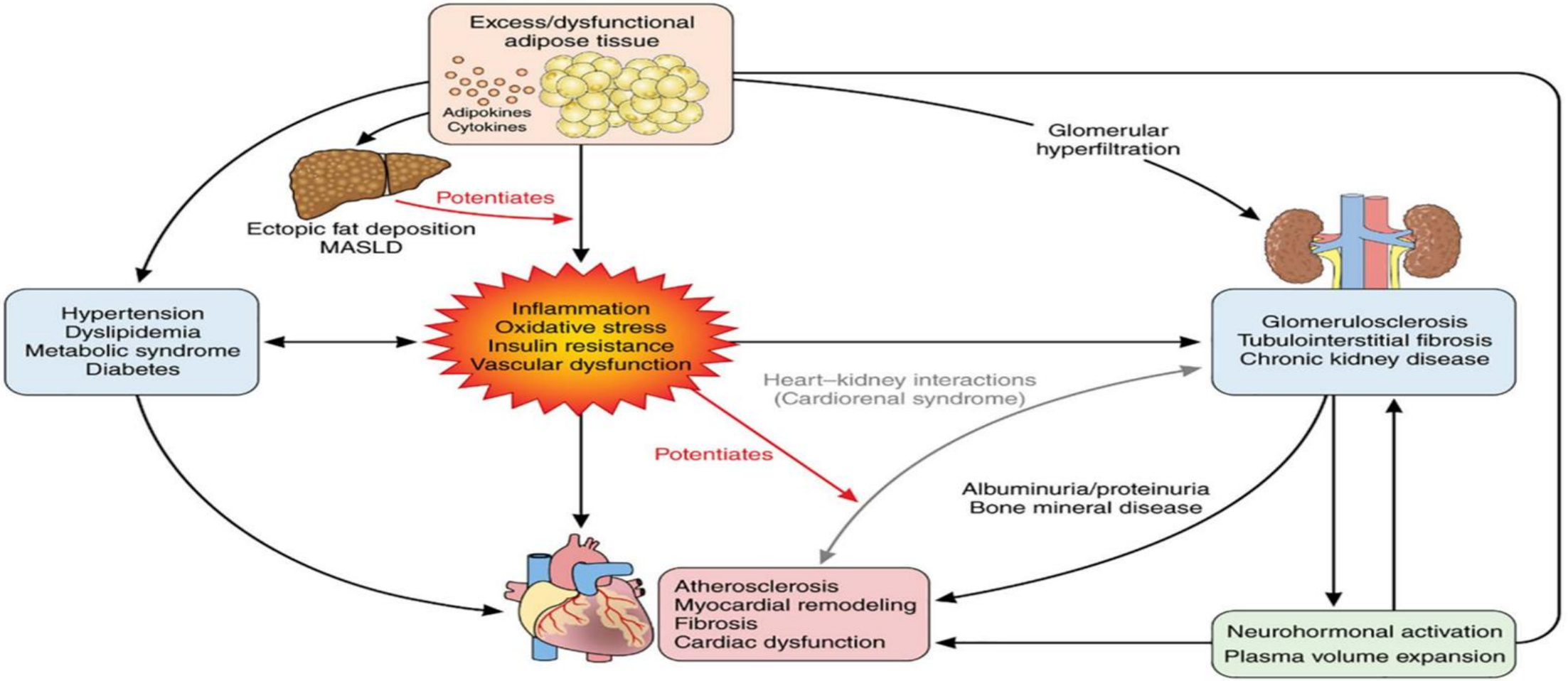
POTENTIAL ADVANTAGES OF PREVENT™

- Large contemporary data from EMR
- Addition of CHF
- Inclusion of GFR and ACR
- Inclusion of social deprivation index
- Lower age cut off for risk prediction and extended long term estimates
- Optional models for Cardiovascular-Kidney-Metabolic indicators



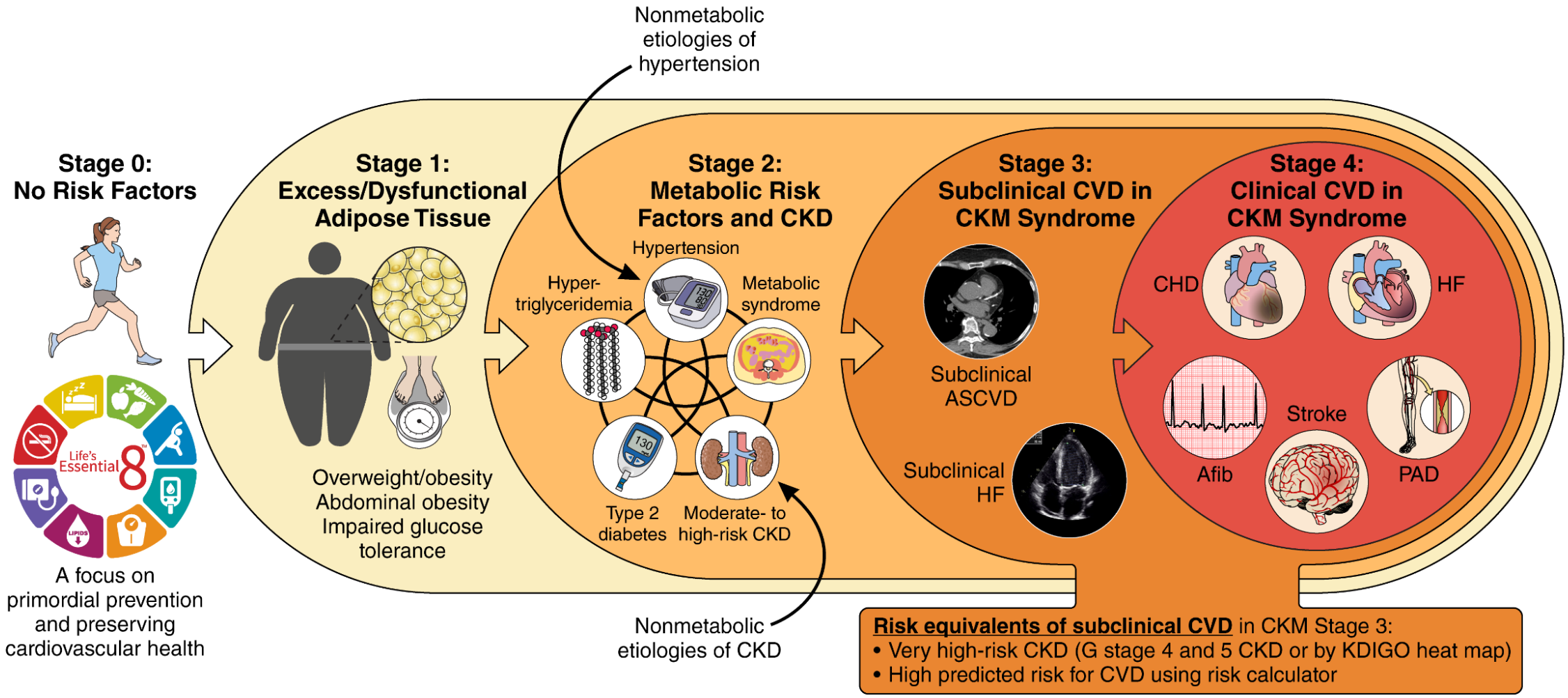
Khan S et al. Circulation 2024 (6):430-449

CARDIOVASCULAR-KIDNEY-METABOLIC SYNDROME



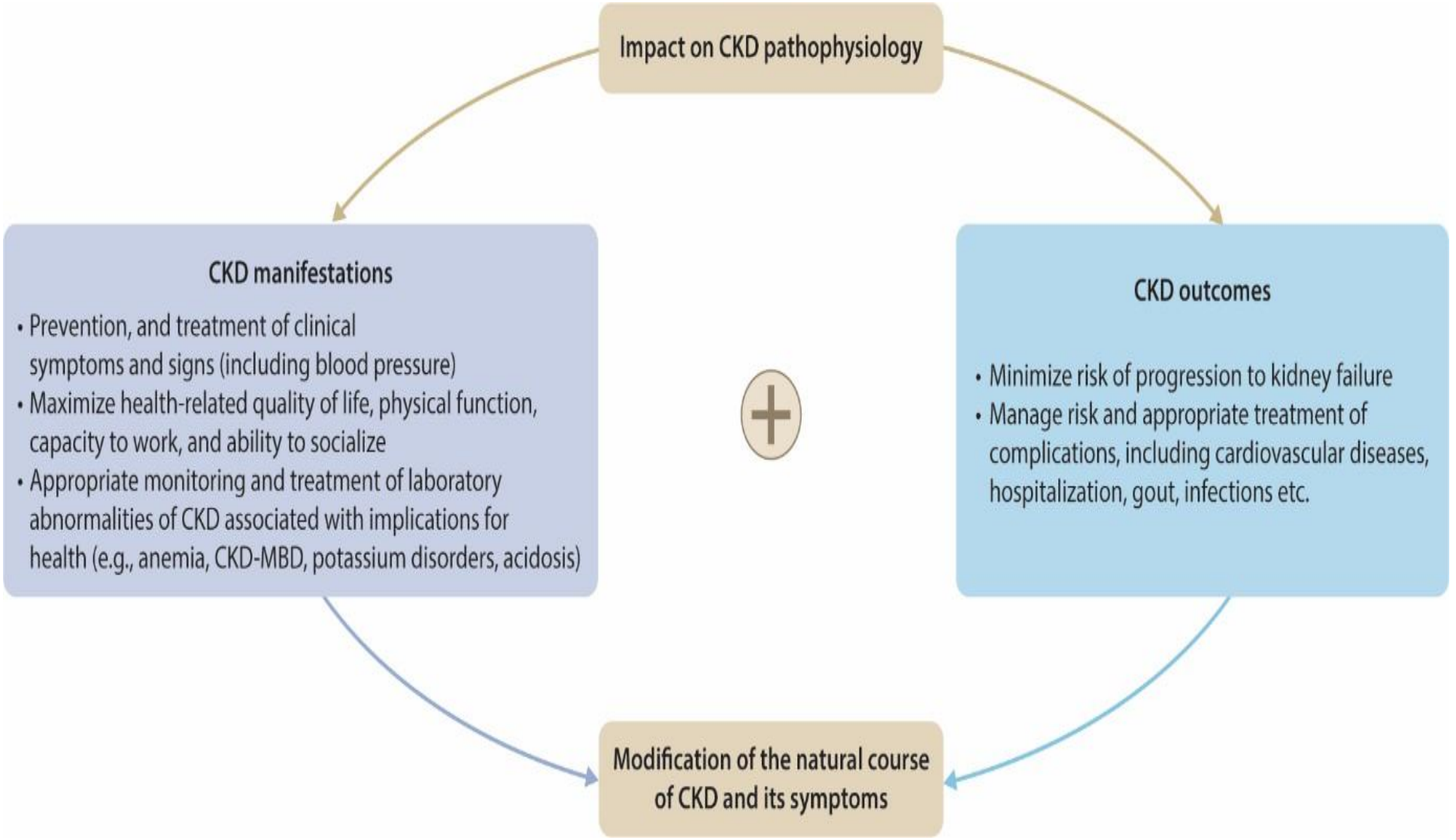
Ndumele et al. Circulation 2023;148:1636-1664

CKM Staging – Guide to Risk Management?

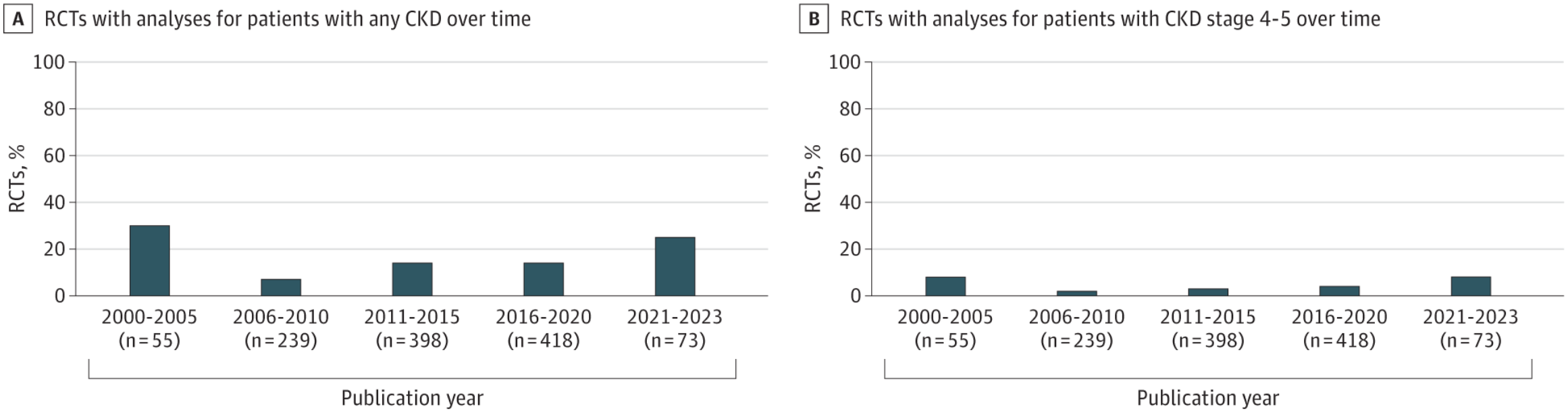


Ndumele et al. Circulation 2023;148:1636-1664

Practice point: Treat people with CKD with a comprehensive treatment strategy to reduce risks of progression of CKD and its associated complications



CKD Representation in CVD Medication Trials

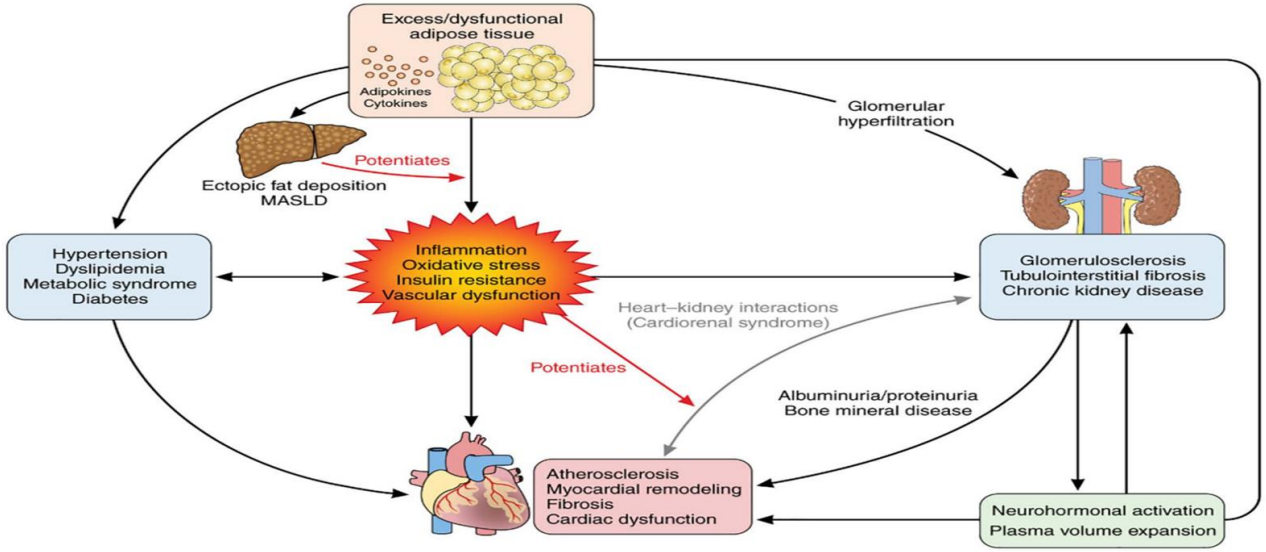


- 1194 RCTs involving 2 207 677 participants
- Since 2000, *exclusion* of patient with CKD increased from 66%to 79%
- Only 158 RCTs (13%) reported results for patients with CKD separately and only 23 (2%) for CKD stage 4 and 5
- Mean (SD) eGFR in RCTs with CKD subgroup analyses was 71 (±12) mL/min/1.73m^2

Colombijn J et al. JAMA Netw Open. 2024;7(3):e240427

Rearranging Risk Factors and modifiers for CKD and CVD to Align With Complementary Mechanisms

- Modulating inflammation and fibrosis
- Addressing haemodynamic factors (BP, GFR, RBF)
- Addressing metabolic factors



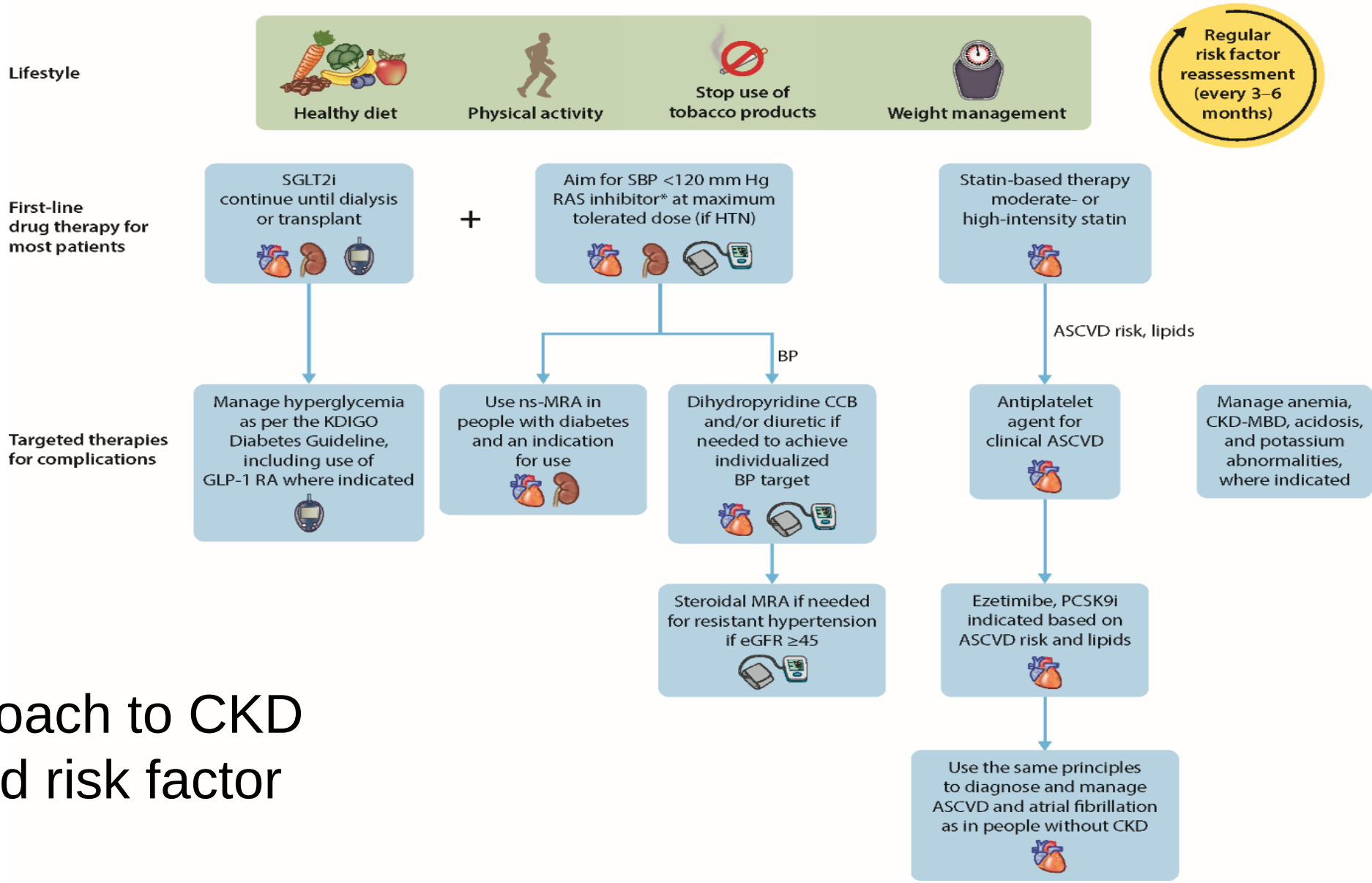
Candidates proven to have reno-protective and cardio-protective effects

- ACEi, ARBs, ns-MRA
- SGLT2i
- Metformin, GLP-1 receptor agonists

Under investigation in trials

- Aldosterone synthase inhibitors, Endothelin receptor antagonists

Holistic approach to CKD treatment and risk factor modification



DIET

Plant-based foods

Absorption rate
50%–60%

Plant-based foods may have low absorption rate, net alkalizing effect, and carbohydrate content encourages K^+ shifts into intracellular space, minimizing impacts on serum K^+

Animal-based foods

Absorption rate
70%–90%

Animal-based protein has higher absorption and net acid effect results in higher amounts of K^+ remaining in serum

Processed foods

Absorption rate
90%

Potassium salts (often found in processed foods) absorption rate has been reported to be 90%

Practice Point: Advise people with CKD to adopt healthy and diverse diets with a higher consumption of plant-based foods compared to animal-based foods and a lower consumption of ultraprocessed foods

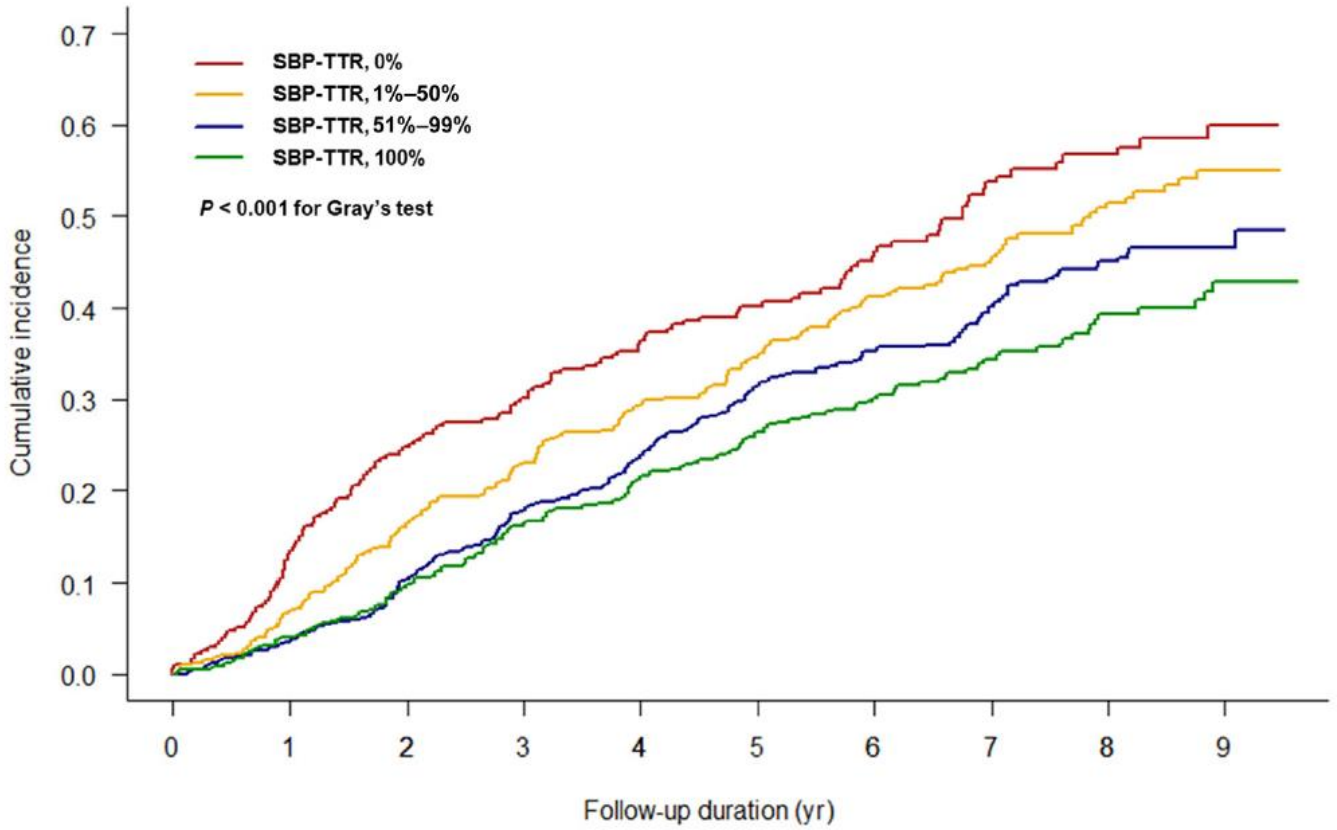
Beneficial effects on acidosis, hyperkalaemia, hyperphosphataemia and reduced risk of protein energy wasting

Blood Pressure Control

Recommendation: We suggest that adults with high BP and CKD be treated with a target systolic blood pressure (SBP) of <120 mm Hg, when tolerated, using standardized office BP measurement (2B).

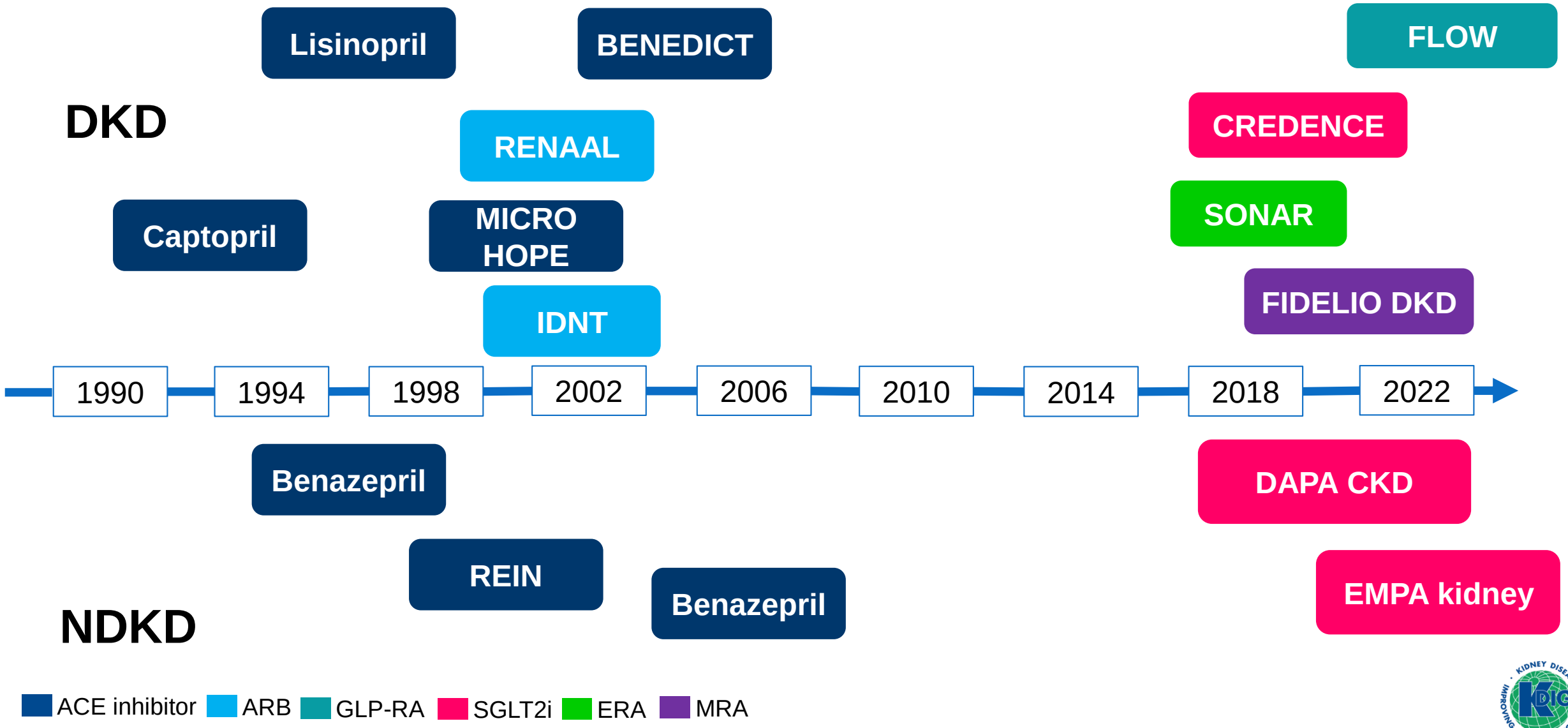
Practice Point: Consider less intensive BP-lowering therapy in people with frailty, high risk of falls and fractures, very limited life expectancy, or symptomatic postural hypotension.

Cumulative incidence of CKD progression by time spent in target SBP range



Park CH et al. KNOW-CKD Kidney Int 2024;105;835-843

Disease Modifying Medication Trials

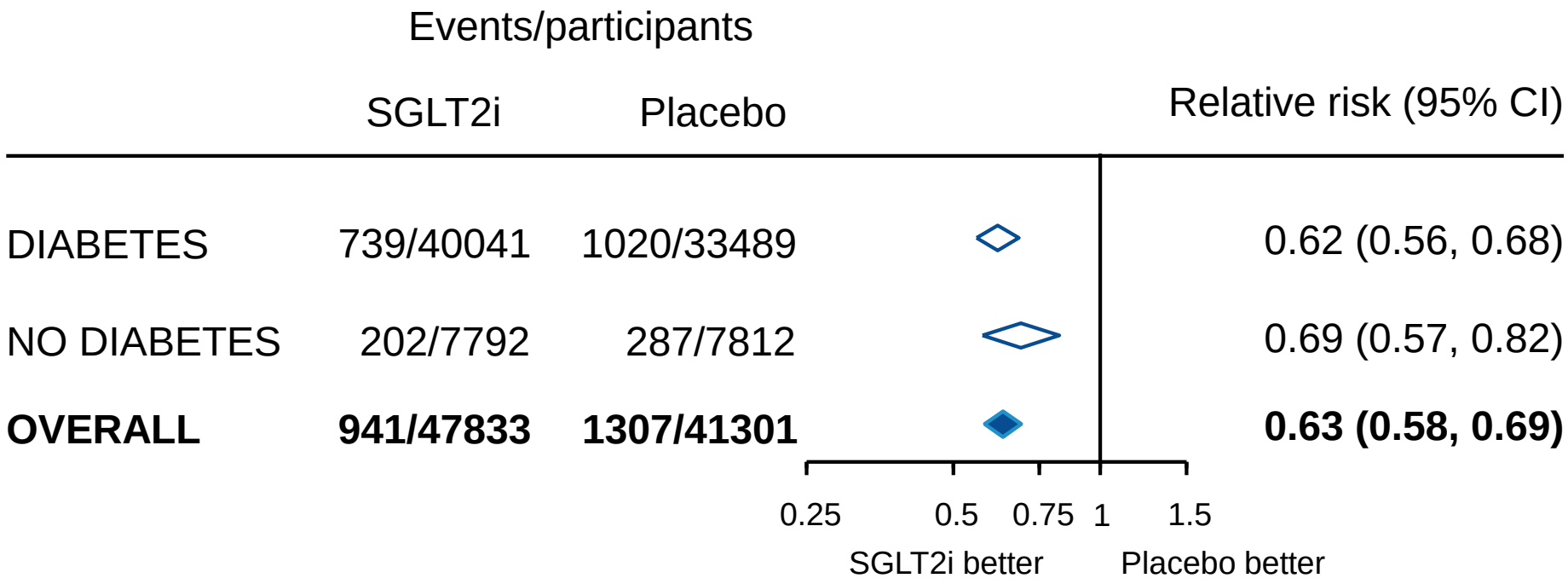


SGLT2 INHIBITORS IN CKD – LANCET METANALYSIS

Population	Trials	Mean eGFR, ml/min/1.73m^2 (range)	Median follow-up, years (range)	Number (%) without diabetes	Total participants
Type 2 diabetes & high CV risk	4	74-85	3.0-4.2	0 (0%)	42,568
Heart failure	5	50-66	1.3-2.6	10,985 (50%)	21,947
CKD	4	37-56	0.8-2.2	4968 (19%)	25,898
TOTAL	**13**			**15,953 (18%)**	**90,413**

SMART-C, Lancet. 2022;400:1788–1801

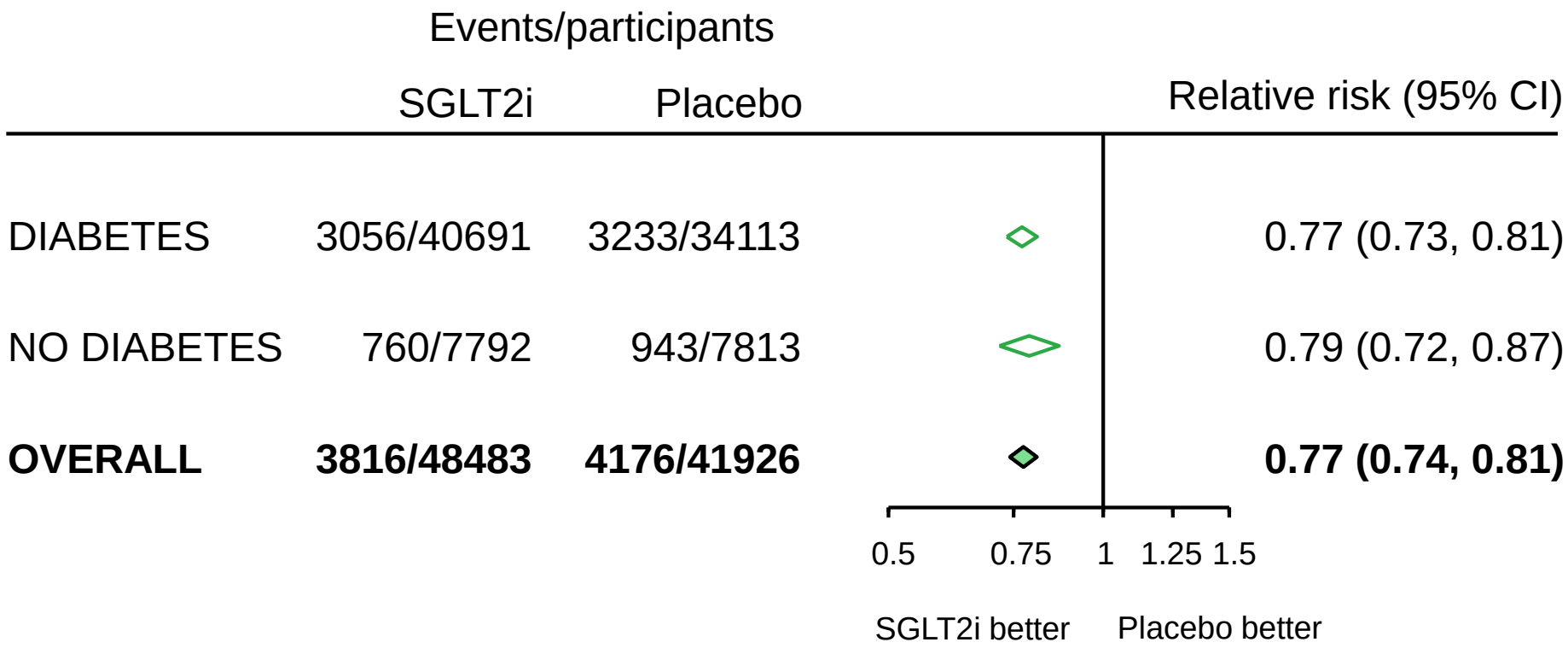
KIDNEY DISEASE PROGRESSION



Recommendation: We recommend treating patients with type 2 diabetes (T2D), CKD, and an eGFR ≥20 ml/min per 1.73 m^2 with an SGLT2i (1A)

Recommendation: We suggest treating adults with eGFR 20 to 45 ml/min per 1.73 m^2 with urine ACR <200 mg/g (<20 mg/mmol) with an SGLT2i (2B).

CV Death or Hospitalisation for Heart Failure



Recommendation: We recommend treating adults with CKD with an SGLT2i for the following (1A):

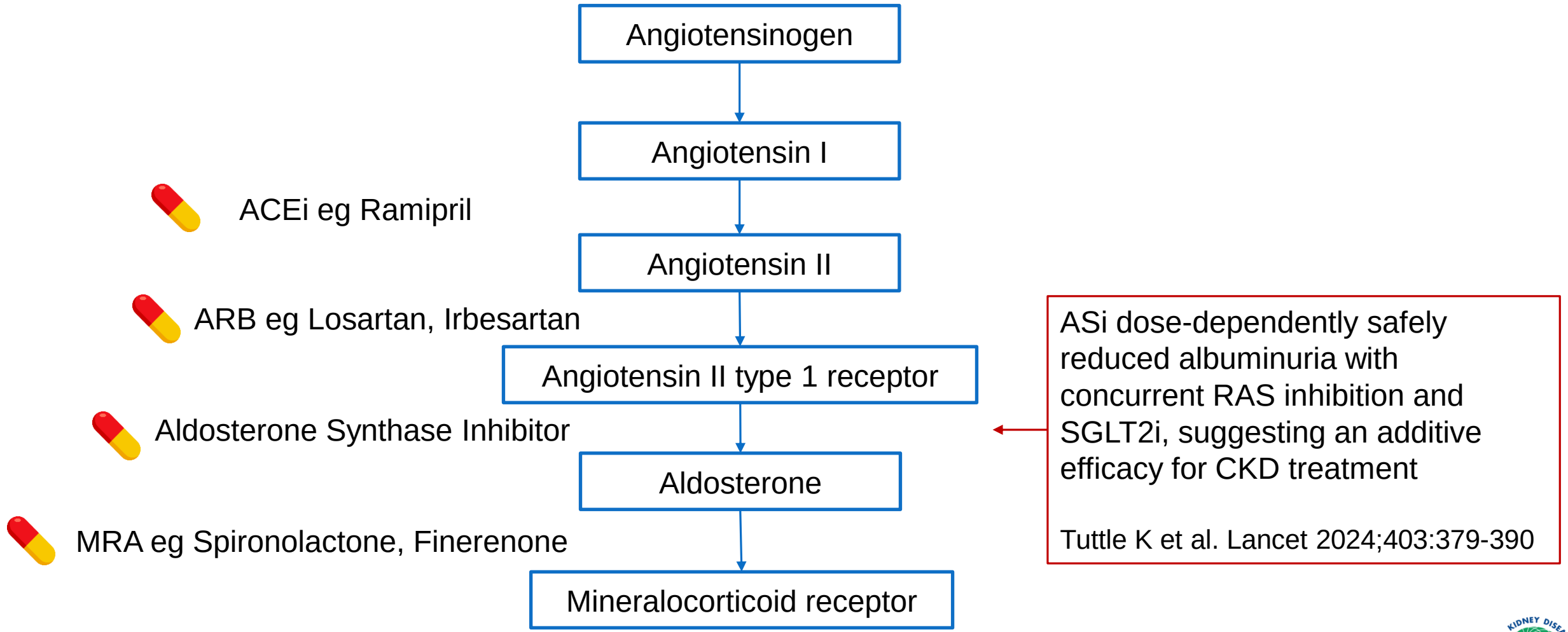
- eGFR ≥20 ml/min per 1.73 m^2 with urine ACR ≥200 mg/g (≥20 mg/mmol), or
- heart failure, irrespective of level of albuminuria

FINERENONE AND CVD AND CKD OUTCOMES IN DKD

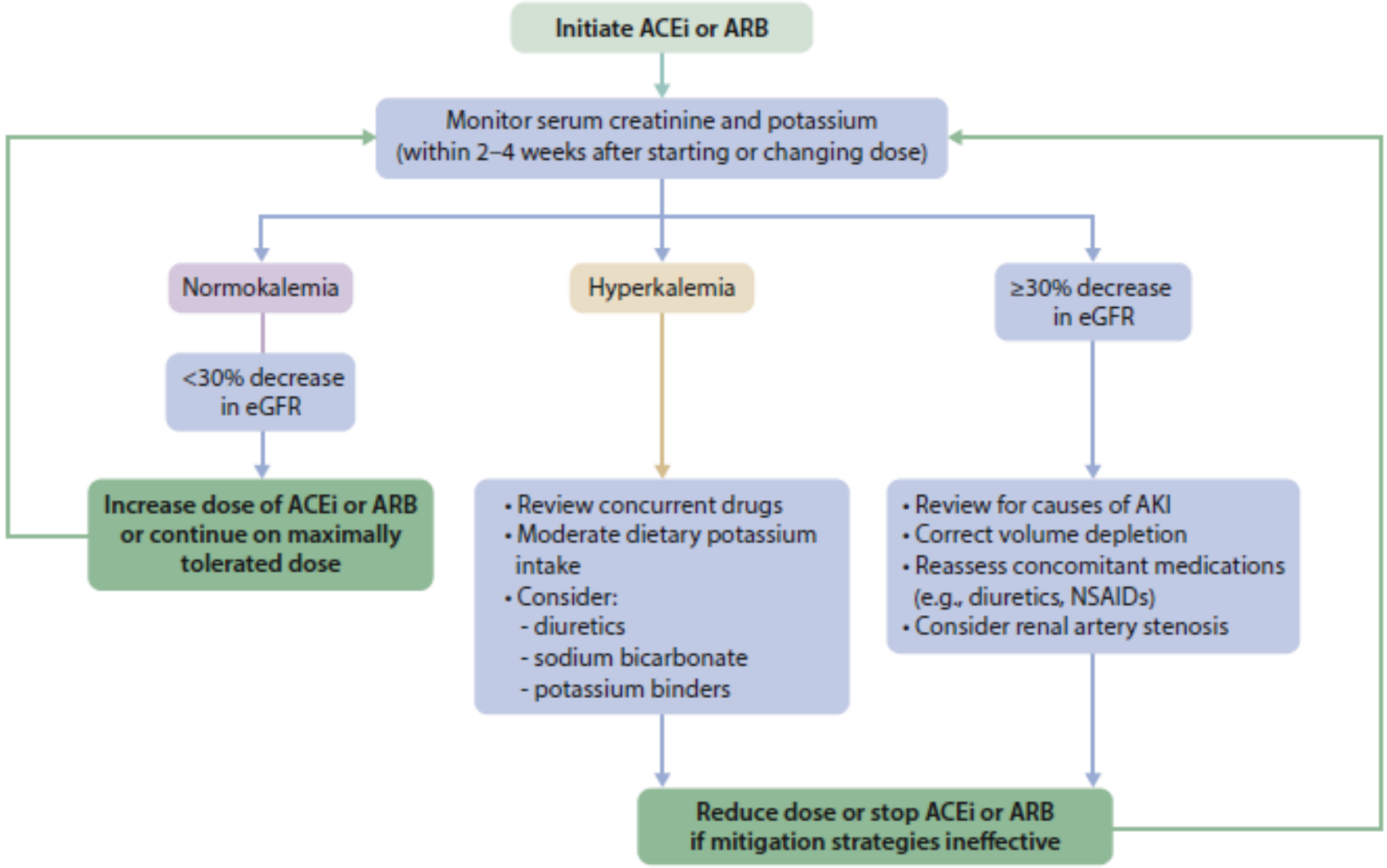
	FIDELIO-DKD	FIGARO-DKD
Patients	Predominantly stage 3–4 CKD with severely increased albuminuria	Predominantly stage 1–2 CKD with moderately or severely increased albuminuria
Primary endpoint	↓ CKD progression by 18% (HR=0.82; CI 0.73–0.93)	↓ CV mortality and morbidity by 13% (HR=0.87; 95% CI 0.76–0.98)
Secondary endpoint	↓ CV mortality and morbidity by 14% (HR=0.86; CI 0.75–0.99)	↓ CKD progression by 13% (non-statistically significant) (HR=0.87; 95% CI 0.76–1.01)
Safety	Both trials showed that finerenone was generally well tolerated and that the increased incidence of hyperkalemia had a minimal clinical impact in the studies	

Bakris GL, et al. NEJM 2020;383:2219–2229 and Pitt B et al. NEJM 2021 Dec 9;385(24):2252-2263

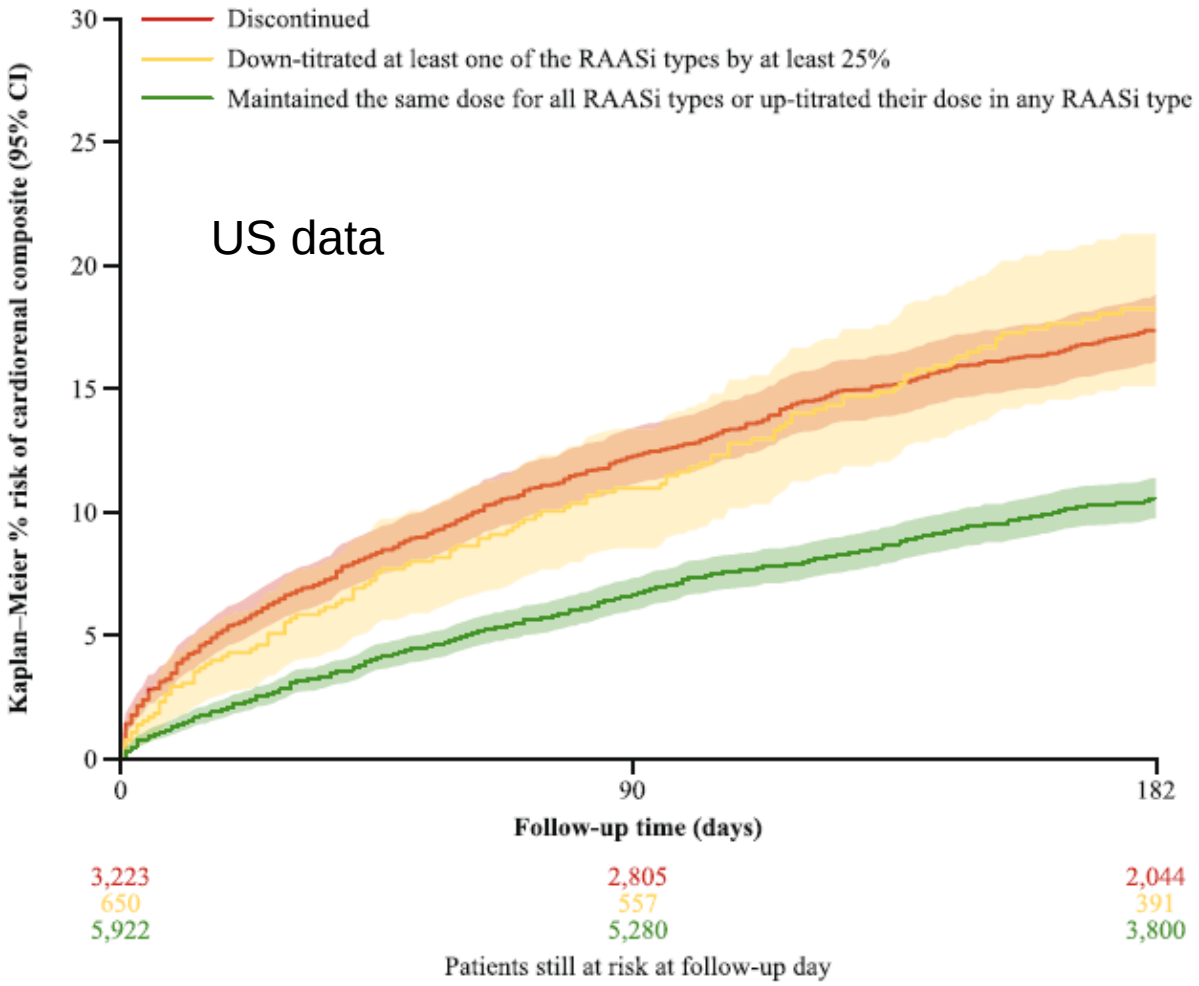
Renin-Angiotensin-Aldosterone System

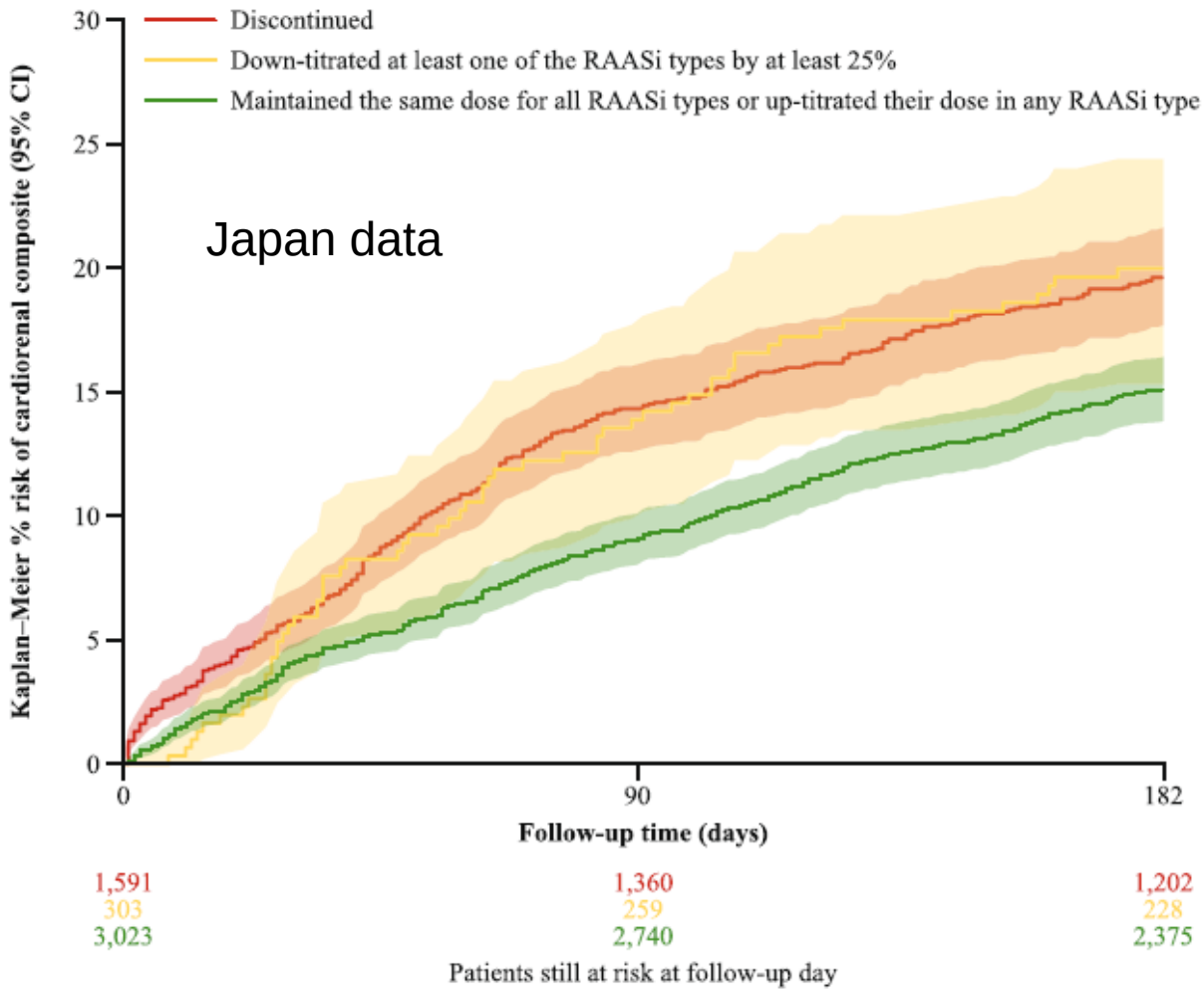


Monitoring haemodynamically active medications



Impact of Suboptimal RAASi Therapy

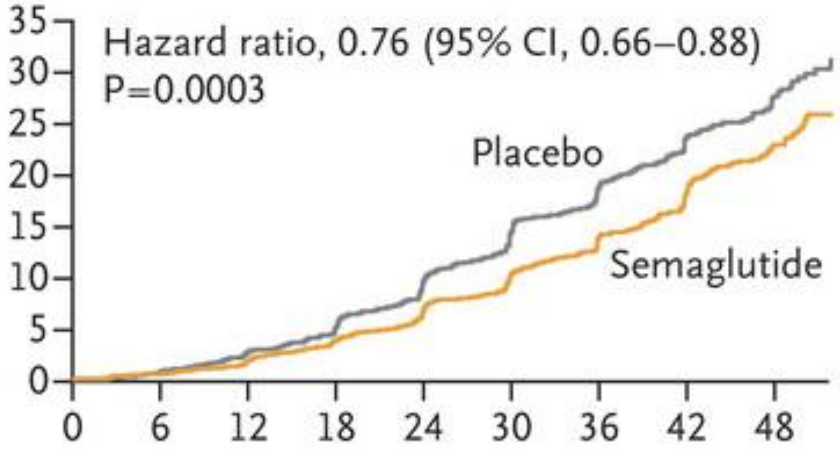




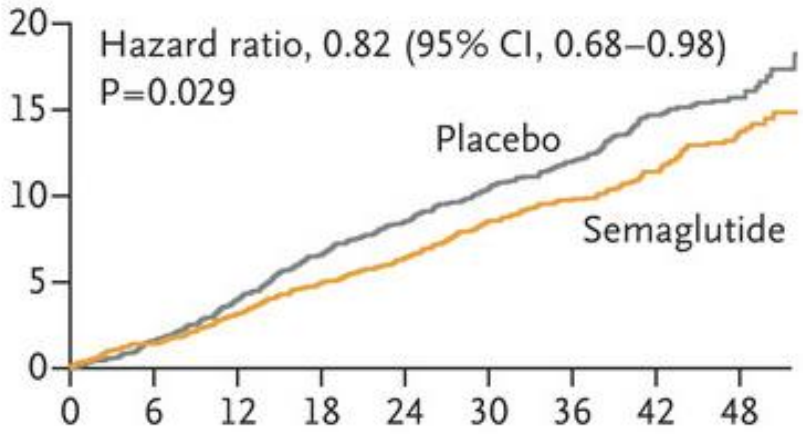
Kanda E et al. BMC Nephrology 2023:24:18

SEMAGLUTIDE IN DIABETIC KIDNEY DISEASE

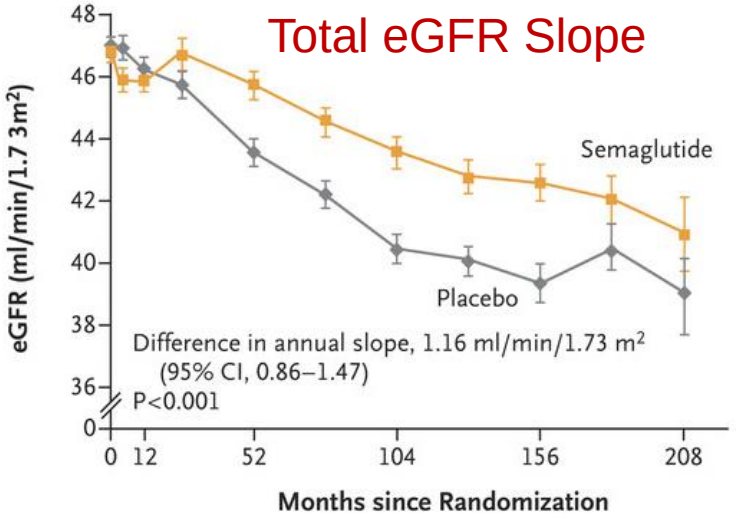
First Major Kidney Disease Event



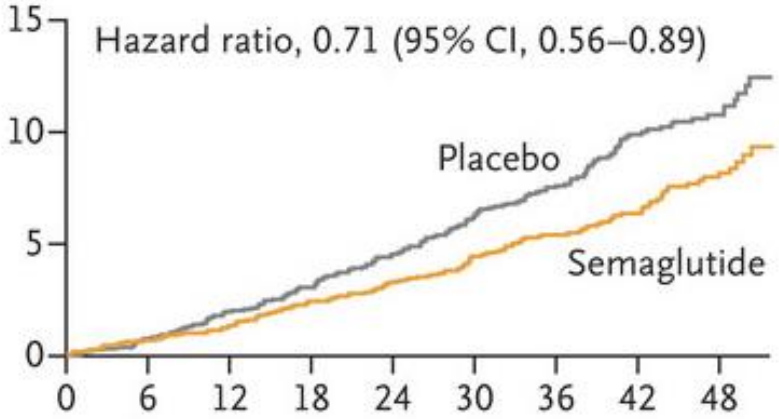
First Major CVD Event



Total eGFR Slope



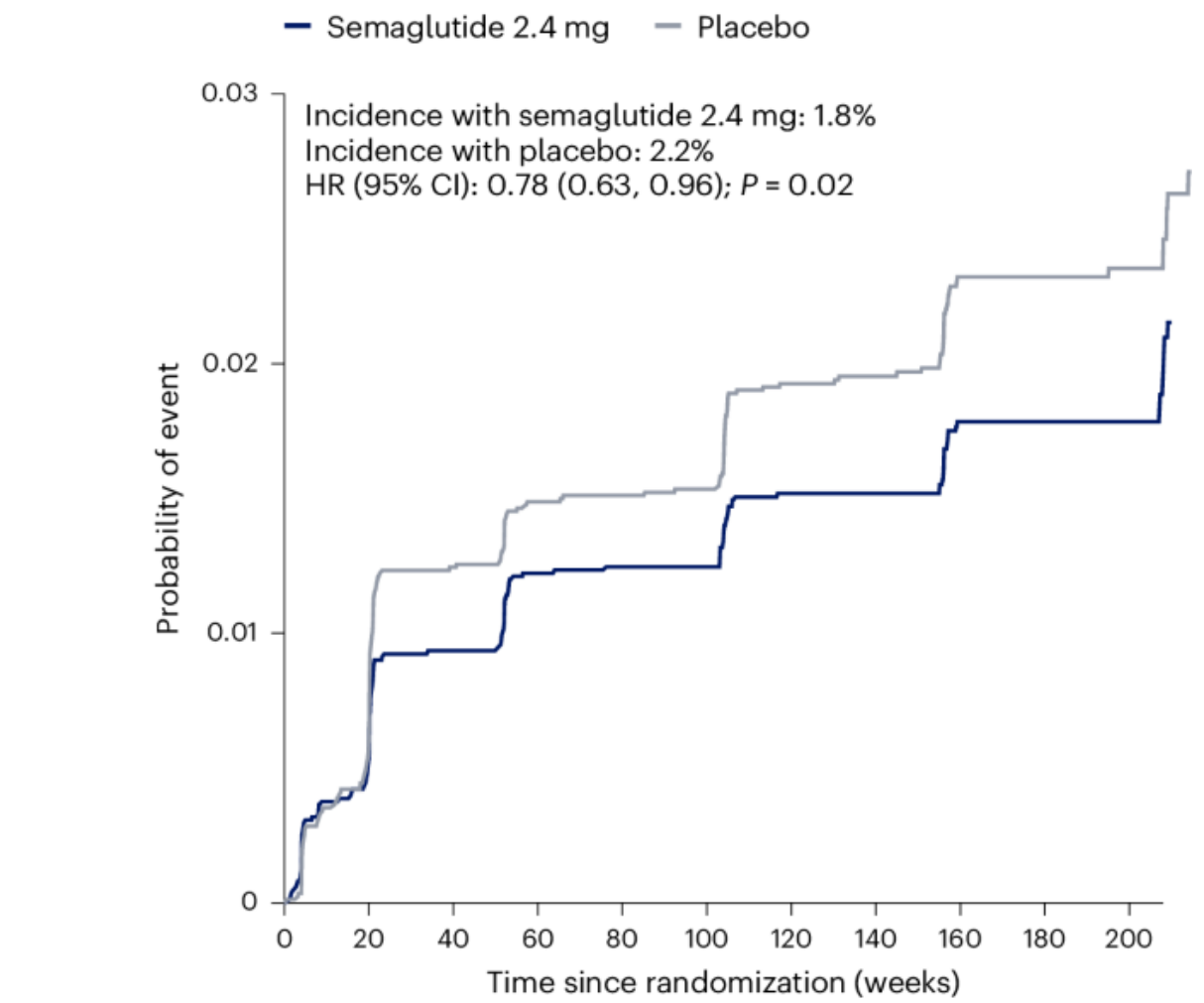
CVD Death



Perkovic et al. NEJM May 2024 online

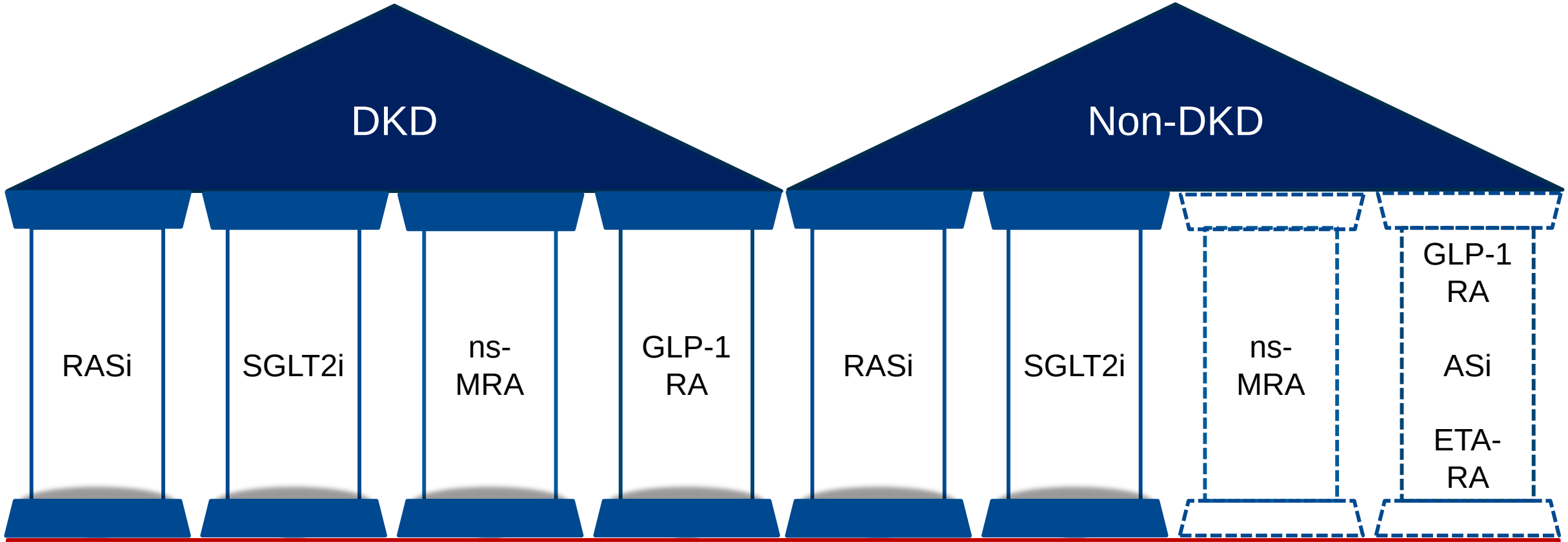
SELECT TRIAL: CKD OUTCOMES

- Overweight/obese patients with CVD without diabetes, n = 17,604, c. 20% CKD
- Randomised to 2.4 mg Semaglutide or placebo, median follow up 182 weeks
- Composite kidney end point (CKD death, KRT, CKD 5, ≥50% reduction in eGFR or macroalbuminuria)
- HR for Semaglutide treatment 0.78 (95% CI 0.63-0.96)
- Suggests a benefit of semaglutide on kidney outcomes in overweight/obese individuals, without diabetes



Colhoun HM et al. Nature Med Online May 2024.

Pillars of Therapy



Lifestyle modifications: absence of tobacco, diet, healthy weight, physical activity
Glycaemic control, sodium intake, lipid management and blood pressure control

Rationale for Combination Therapy

- Estimated lifetime CVD, CKD and mortality benefits from SGLT2i, GLP-1 RA and ns-MRA in DKD vs. RAS blockade using trial data from CANVAS, CREDENCE, FIDELIO, FIGARO and 8 GLP-1RA trials
- Reduction in MACE HR 0.65 (95% CI 0.55-0.76); risk reduction 4.4% over 3 years, NNT 23

Projected event free survival gain combination vs. conventional therapy, Years (95% CI)			
MACE event free survival	3.2 (2.1 – 4.3)	Cardiovascular death	2.2 (1.2 – 3.0)
Survival free from hospitalised CHF	3.2 (2.4 – 4.0)	All cause death	2.4 (1.4 – 3.4)
CKD progression	5.5 (4.0-6.7)		

Neuen BL et al. Circulation 2024;149:450-462

Approaches to Implementing Pillar Therapy

- **Traditional approach**
  Sequential implementation with reassessment every 3-6 months
  Does not prioritise high risk and may promote low adherence

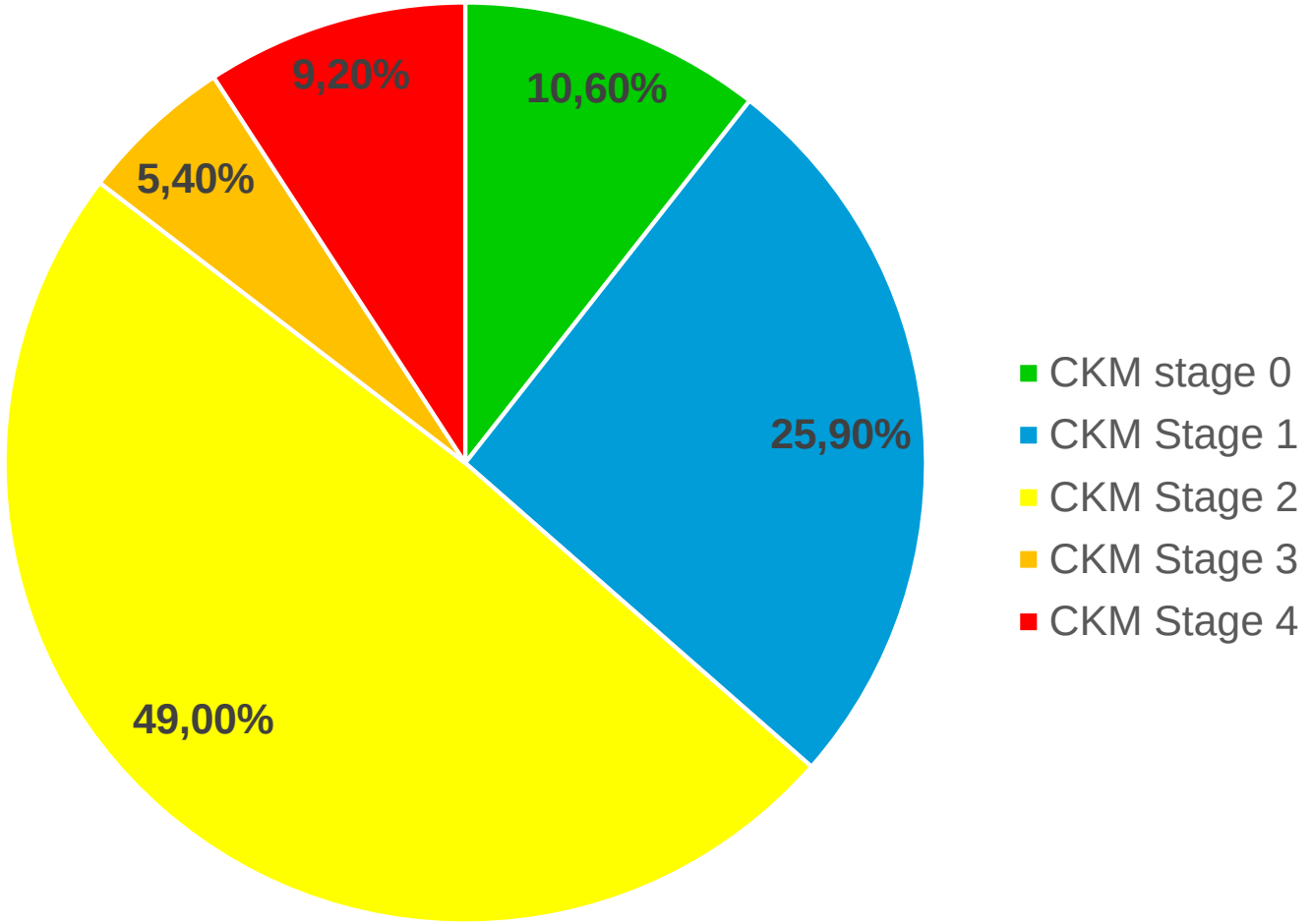
- **Rapid sequence**
  Assumes all are at equal risk, cost-effectiveness and safety untested

- **Accelerated risk-based approach**
  High risk prioritised using validated risk scores, matches treatment to risk

"It's a mood elevator. Each capsule contains 10mg of 'zippity' and 5mg of 'do-da'."

US Adult CKM Population Prevalence

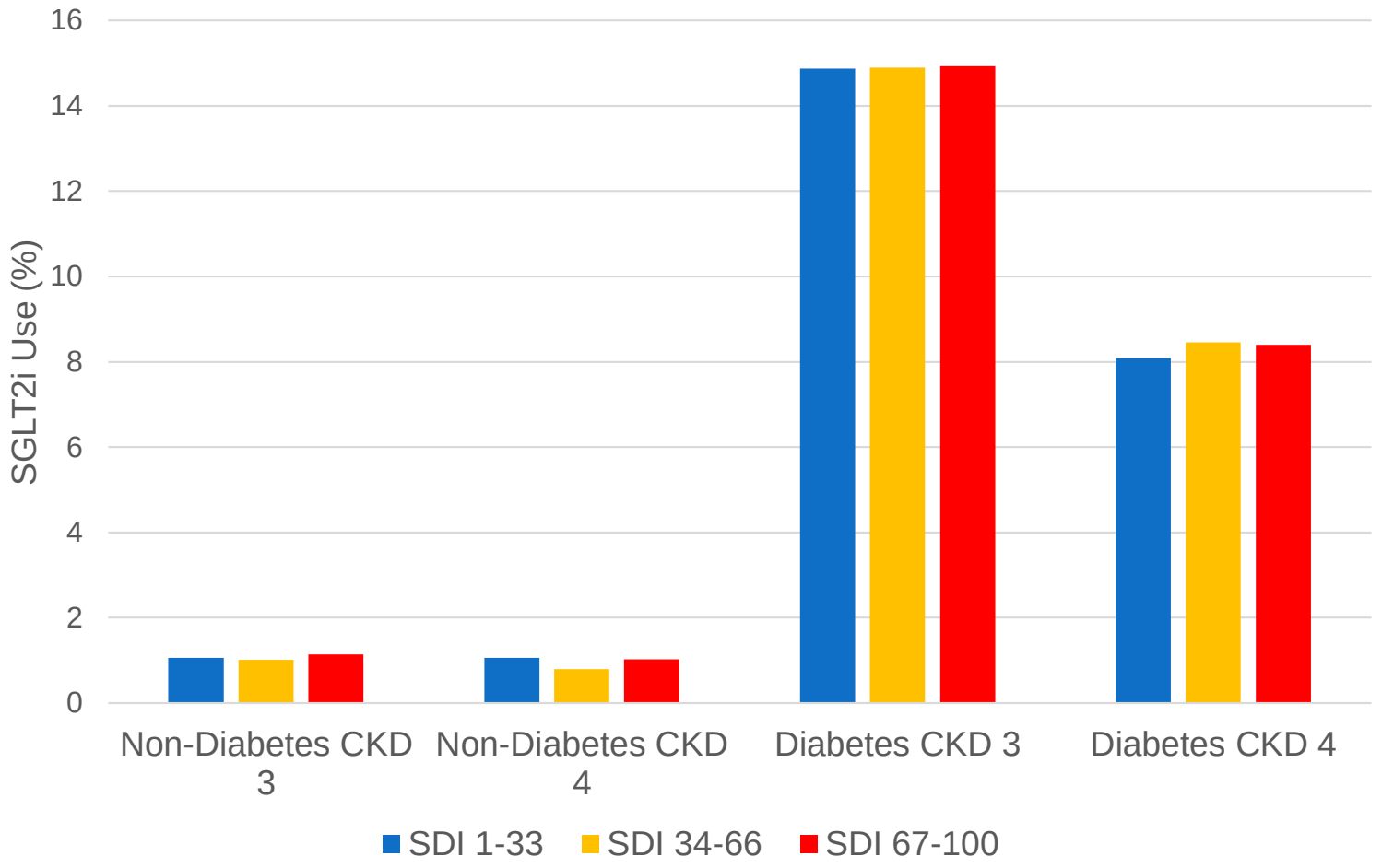
- 10,762 adults from NHANES
- Mean (SD) age 47.3 (17.0)
- 51.8% female, 64.4% white
- Adults 65+ more likely to have advanced stages
- *But* only 18.2% of adults aged 20-44 had stage 0



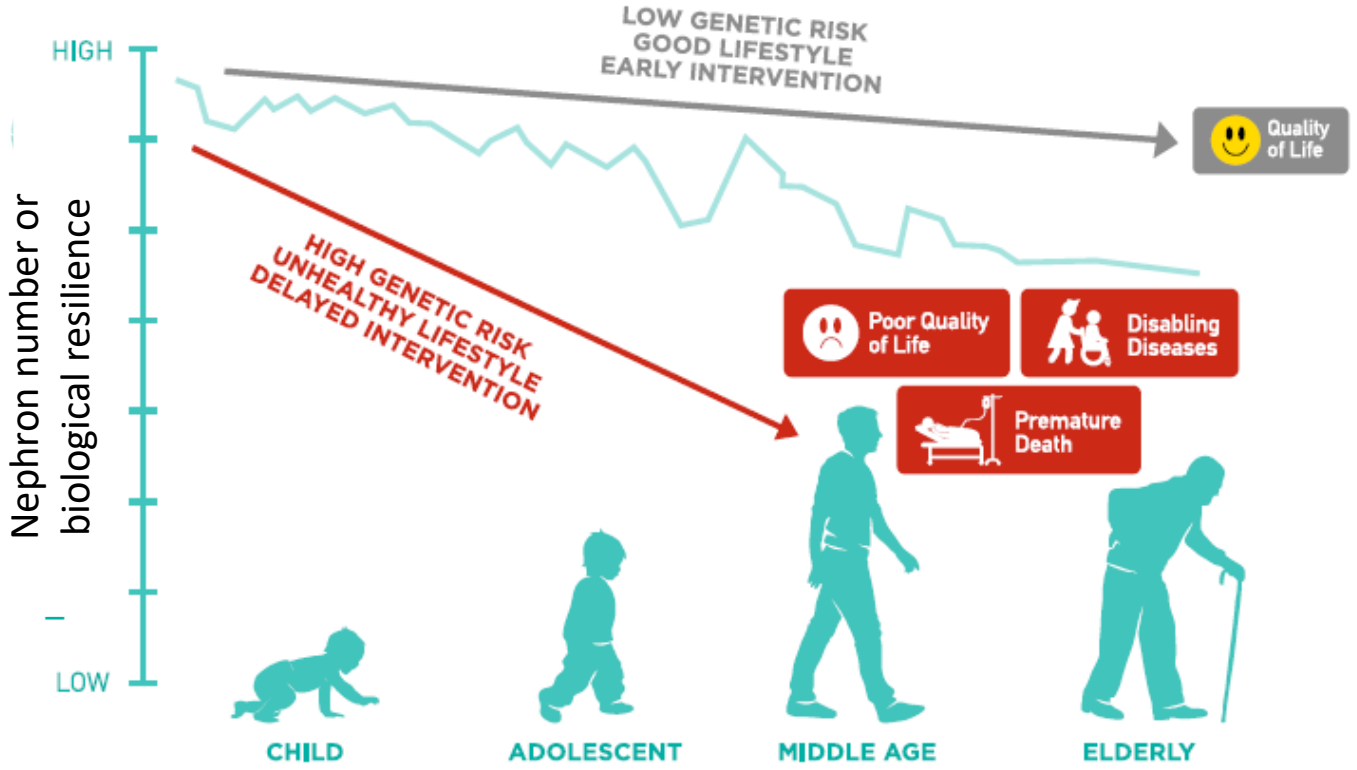
Aggarwal R et al. JAMA 2024;331:1858-1860

Pillar Prescription in Stage 3 & 4 CKD & DM

SDI 1-33	SDI 34-66	SDI 67-100
ACEi/ARB use, stage 3 Non-DKD (%)		
50.0	53.01	55.53
ACEi/ARB use, stage 4 Non-DKD (%)		
45.62	45.61	47.1
ACEi/ARB use, stage 3 DKD (%)		
68.88	69.86	71.89
ACEi/ARB use, stage 4 DKD (%)		
61.7	59	57.91



Source: 2023 USRD Annual Data Report

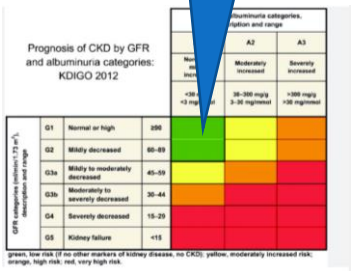


- ✓ Genetics
- ✓ Family history
- ✓ Intra uterine exposure
- ✓ Gestational diabetes
- ✓ Extremes of birth weight
- ✓ Socioeconomic status
- ✓ Education
- ✓ Occupation
- ✓ Environmental exposure
- ✓ Intercurrent illness / AKI
- ✓ Exposure to drugs/toxins
- ✓ Lifestyles (e.g. nutrition, exercise, tobacco, sleep, stress)
- ✓ Risk factors (BP/BW/A1c/lipids)

This is where my kidneys belong (G1A1)

Favorable Outcome

- Maintain kidney function
- Improve kidney function



Early intervention

- Lifestyle changes
- Drugs (metformin, RASi, statin, SGLT2i, GLP1RA, nsMRA….)

Early detection

- Urinalysis (RBC, proteins..)
- eGFR
- ACR
- biomarkers

Adapted from Xie F, Chan J and Ma R JDI 2018;9:998-1015

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