Primary Care Cardiovascular Society

Driving primary care to deliver the best in cardiovascular health

Chronic kidney disease: the hidden public health emergency

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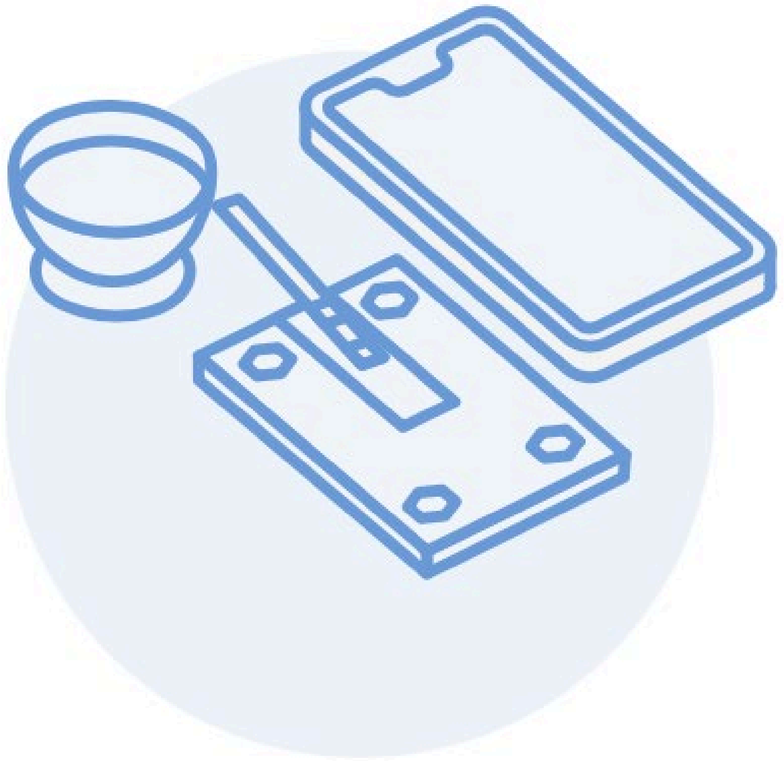
Best practice, Birmingham, Oct 2022

Declarations:

AstraZeneca
Novartis
Bayer
Medtronic
Omron



Today's talk:

CKD as a risk factor for CVD

The importance of ACR testing [Prev/Sev/Risk]

How to improve outcomes for your patients

Progression of CKD by GFR and Albuminuria Categories				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/mol	≥300 mg/g ≥30 mg/mmol
GFR categories (ml/min/1.73m²) Description and range	G1	Normal to high	≥90			
	G2	Mildly decreased	60-90			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	15			

Green: low risk (if no other markers of kidney diseases, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk

Reflection:

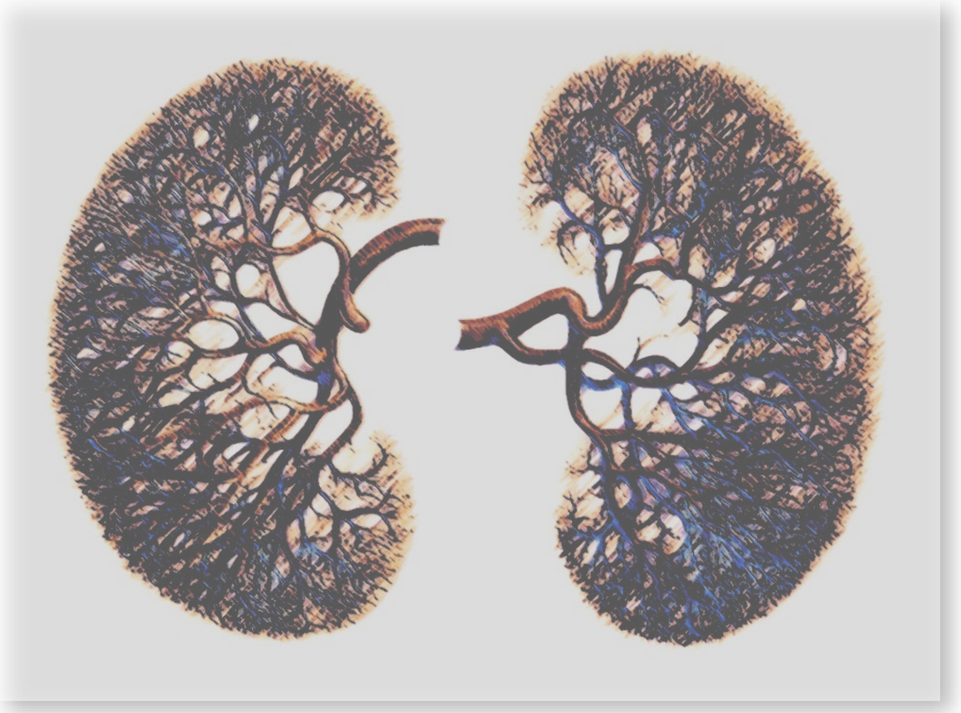
- Have we forgotten about the importance of Chronic Kidney Disease (CKD) as a risk factor for CVD?
- Do we understand the importance of albumin-to-creatinine ratio (ACR) testing?
- What are we doing to improve outcomes for our patients?

What is Chronic Kidney Disease?

"The presence of kidney damage, mainly albuminuria

and/or

decreased kidney function (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m2) for at least 3 months"



Ref: Levey and Coresh, 2012

Diagnosing and Classifying CKD [NICE, CKD 2021]:

Requires **both** blood testing [eGFR] and urine testing [ACR] to investigate patients for CKD

Key:

- Low risk
- Medium risk
- High risk
- Very high risk

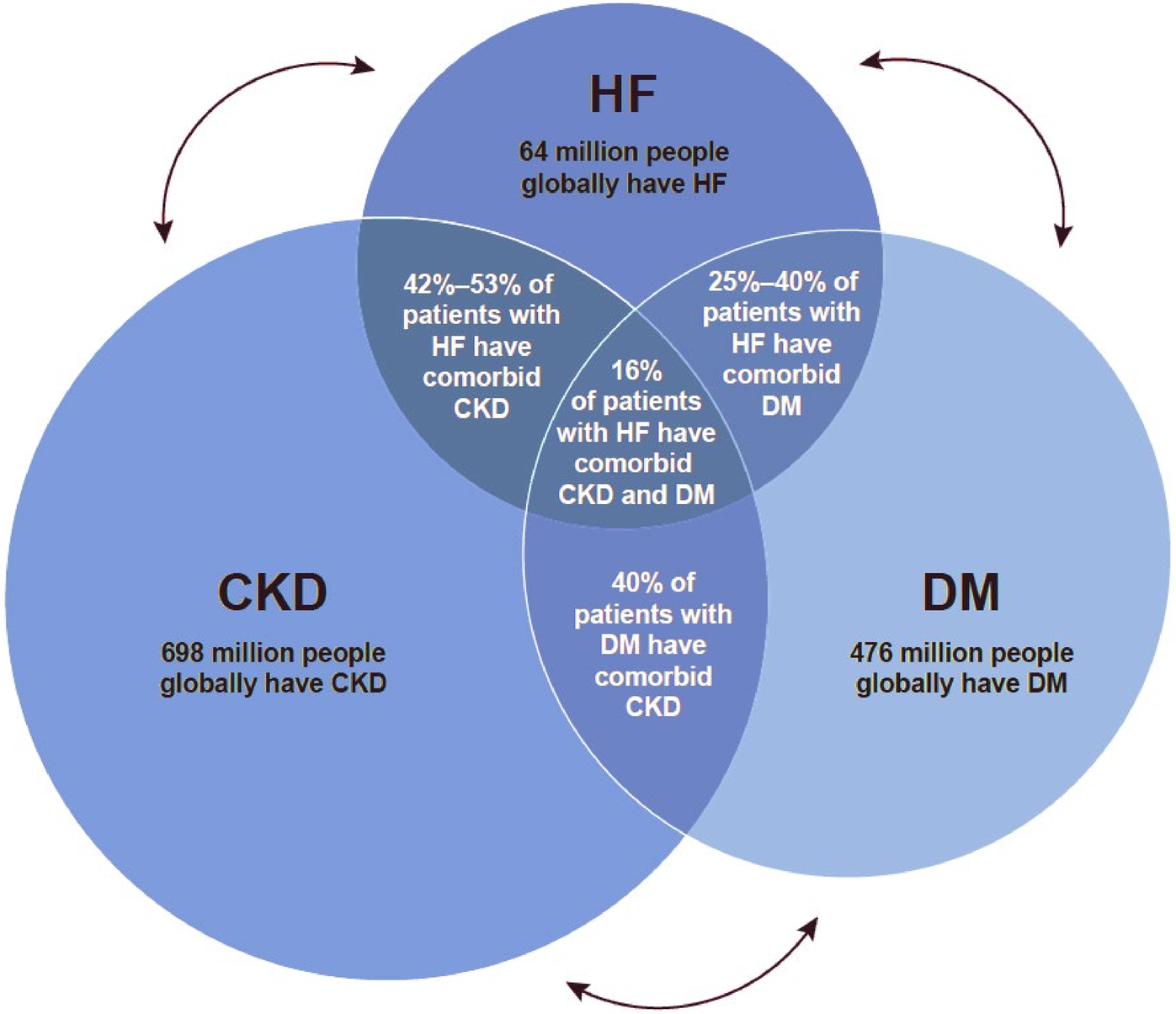
Who should be tested for CKD?

NICE NG203, CKD

1.1.21: Offer testing for CKD using eGFR and ACR to adults with any of the following risk factors:

- diabetes
- hypertension
- previous episode of acute kidney injury
- cardiovascular disease
- structural renal tract disease inc. stones, prostate disease
- gout
- multisystem diseases – e.g. SLE
- family history of end-stage renal disease (GFR category G5) or hereditary kidney disease

Heart Failure in Patients with Diabetes and Chronic Kidney Disease: Challenges and Opportunities



Review Article

Cardiorenal Med 2022;12:1–10
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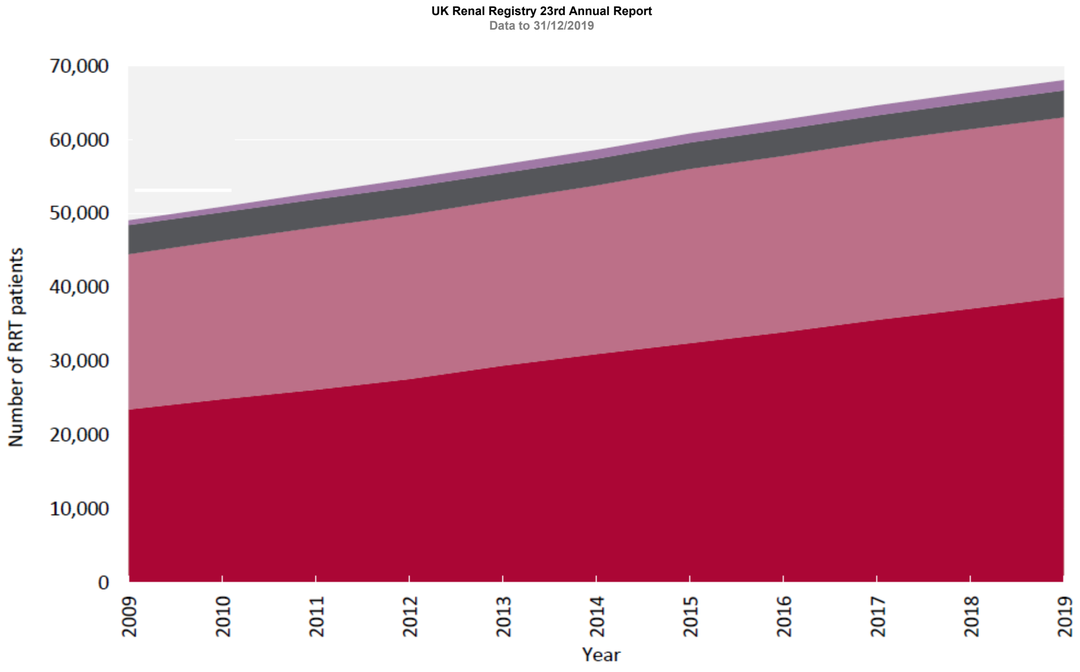
CKD Epidemic:

- Global prevalence of CKD has risen by 87% between 1990–2016
- Estimated further increase of 17% in prevalence of CKD by 2030
- 3rd fastest growing cause of death
- 5th ranked cause of death by 2040
- UK: 2020 (3.63 million) 2030 (4.38 million) (Xie et al., 2018)
- 34% of CKD cases are undiagnosed
- Higher rates of CKD in under-served comm
- South Asians with diabetes 10x more likely to get kidney failure than Caucasians with diabetes

Renal replacement therapy vs time



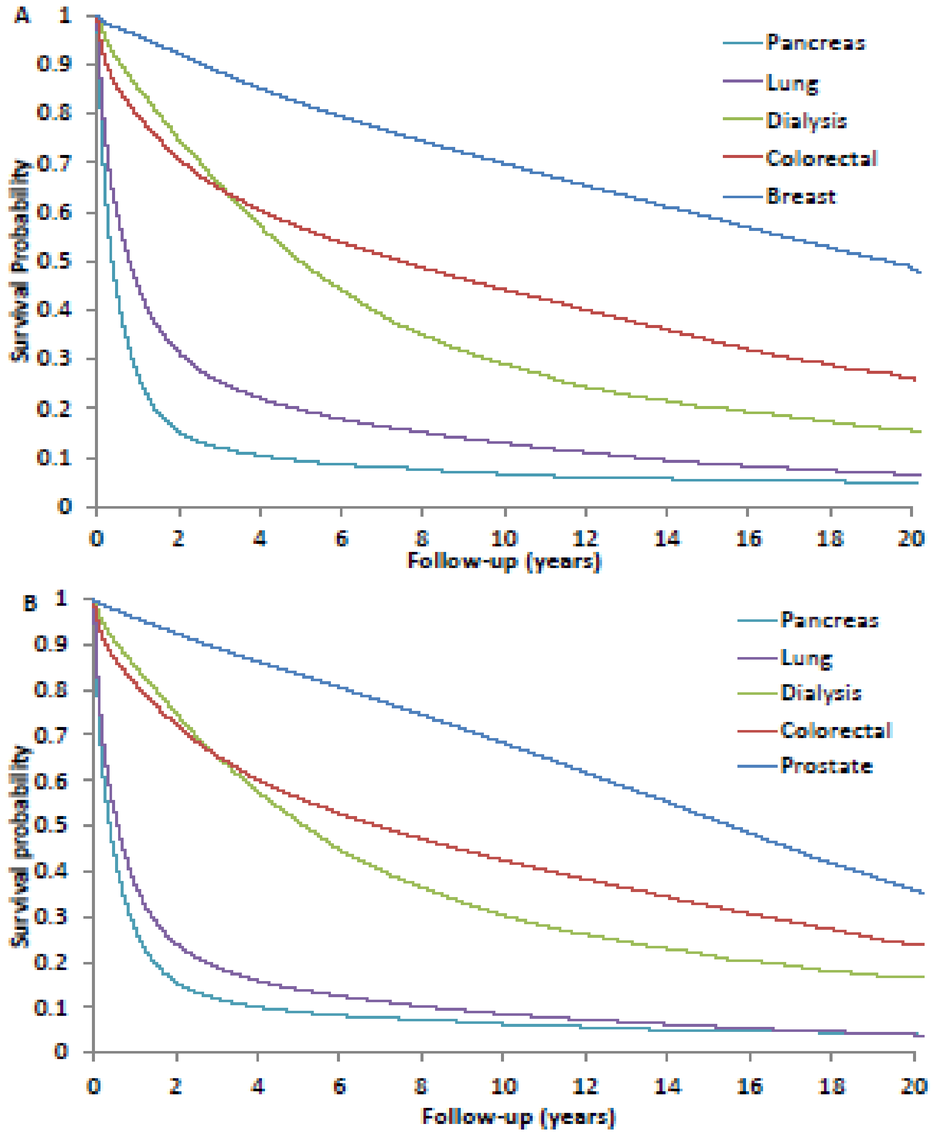
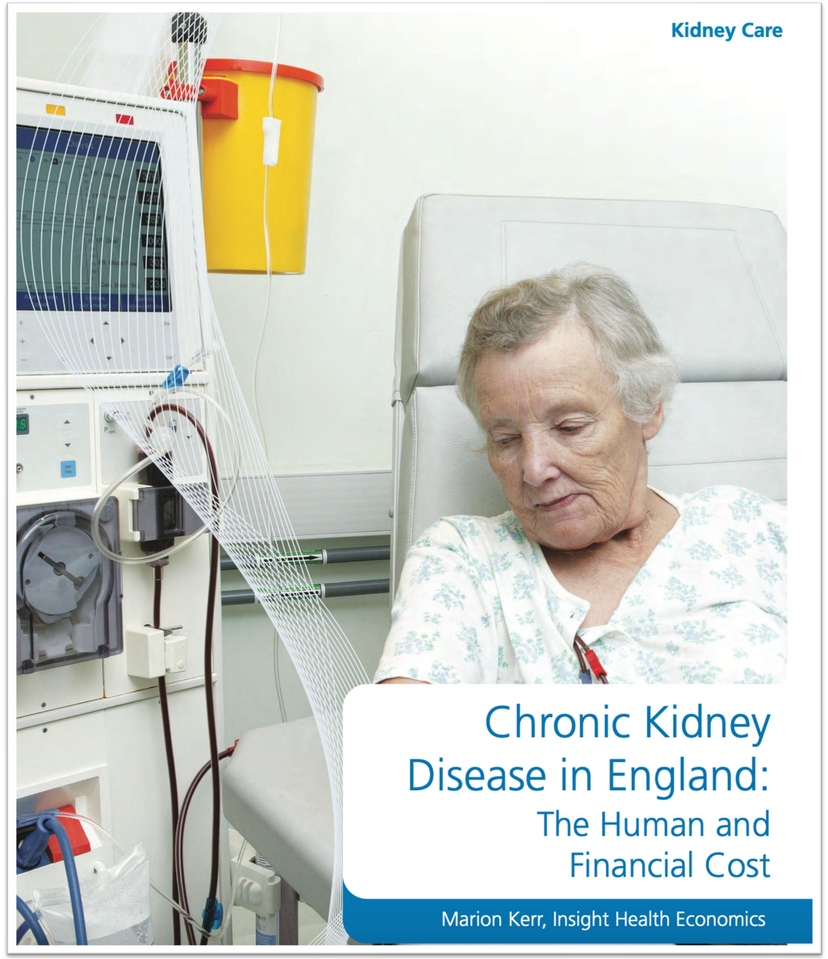


Figure 1. Survival probabilities for all-cause mortality in (A) female maintenance dialysis patients and patients with cancer (log-rank $P < 0.001$) and (B) male maintenance dialysis patients and patients with cancer (log-rank $P < 0.001$).

End Stage Kidney Disease has worse survival rates than colorectal, prostate and breast cancer

Naylor et al AJKD 2019 doi: 10.1053/j.ajkd.2018.12.011

Health Economics of CKD:



- **NHS England spent an estimated £1.45 billion on CKD in 2009–10:** equivalent to £1 in every £77 of NHS expenditure. This spending estimate covers both treatment directly associated with CKD (renal care and prescribing to prevent disease progression), and also treatment for excess non-renal problems such as strokes, heart attacks and infections in people with CKD.

- **There were an estimated 7,000 extra strokes and 12,000 extra myocardial infarctions in people with CKD in 2009–2010**, relative to the expected number in people of the same age and sex without CKD. The cost to the NHS of health care related to these strokes and MIs is estimated at £174–178 million.

- **People with CKD have longer hospital stays** than people of the same age without the condition, even when they go into hospital for treatments unrelated to CKD. We estimate that the average length of stay is 35% longer for people with CKD, and that the cost to the NHS of excess hospital bed days for patients with CKD was £46 million in 2009–10.

The association of CKD with Cardiovascular Disease

CVD prevention is a national priority

"Cardiovascular disease causes a quarter of all deaths in the UK and is the largest cause of premature mortality in deprived areas. This is the single biggest area where the NHS can save lives over the next 10 years."

Ambition: To Prevent 150,000 strokes, heart attacks and cases of dementia in 10 years

NICE National Institute for Health and Care Excellence

NICEimpact cardiovascular disease prevention

1.2 million people with CKD are undiagnosed [=undiagnosed + uncoded].

Effective coding and management of CKD can reduce emergency admission to hospital.

Primary care is responsible for a number of key interventions in early-stage CKD.

Many of those with CKD have poor blood pressure control and poor proteinuria control

CKD is recognised in 'Six-High-Risk Conditions for Cardiovascular Disease' by $CVD_{PREVENT}$

CVDPREVENT

1. Atrial fibrillation (AF)
2. Hypertension
3. Familial hypercholesterolemia (FH)
4. Chronic kidney disease (CKD)
5. Non-diabetic hyperglycemia (NDH)
6. Type 1 or 2 diabetes mellitus

For every 100 patients with moderate to severe CKD:

7

events of acute kidney injury per year

6

cardiovascular events per year

38

unplanned hospital admissions per year

2 ICU

admissions to the Intensive Care Unit per year

7

deaths per year

National CKDAudit

A quality improvement programme for chronic kidney disease

https://www.lshtm.ac.uk/media/10136

CKD is associated with unplanned admissions

Findings for every
100 Patients

With CKD **Stage 3:**
36 unplanned admissions annually

With CKD **Stage 4:**
75 unplanned admissions annually

Classification of chronic kidney disease using GFR and ACR categories

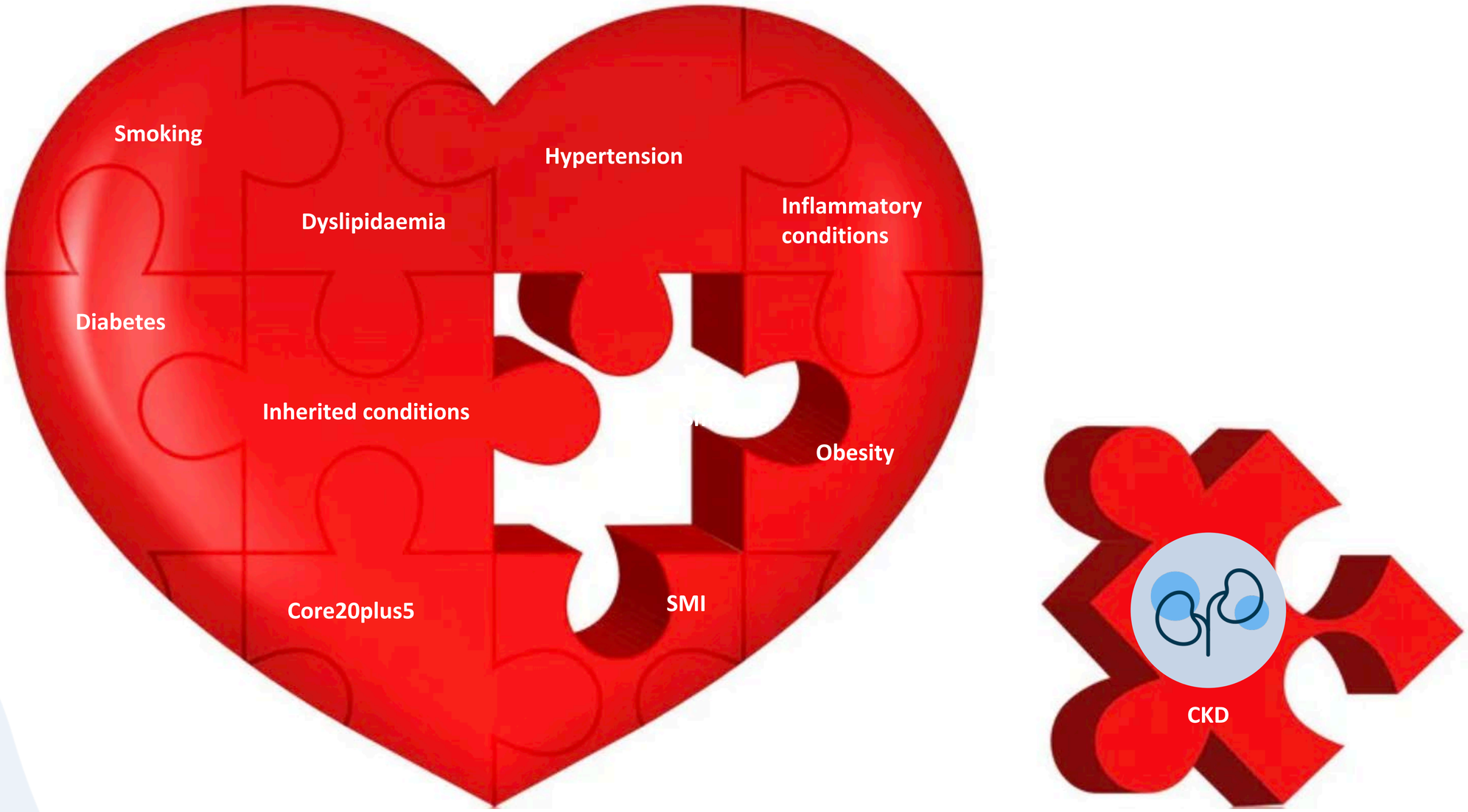
GFR and ACR categories and risk of adverse outcomes			ACR categories (mg/mmol), description and range		
			<3 Normal to mildly increased	3–30 Moderately increased	>30 Severely increased
			A1	A2	A3
GFR categories (ml/min/1.73m²), description and range	≥90 Normal and high	G1	No CKD in the absence of markers of kidney damage		
	60–89 Mild reduction related to normal range for a young adult	G2			
	45–59 Mild–moderate reduction	G3a[1]			
	30–44 Moderate–severe reduction	G3b			
	15–29 Severe reduction	G4			
	<15 Kidney failure	G5			

Increasing risk

Increasing risk

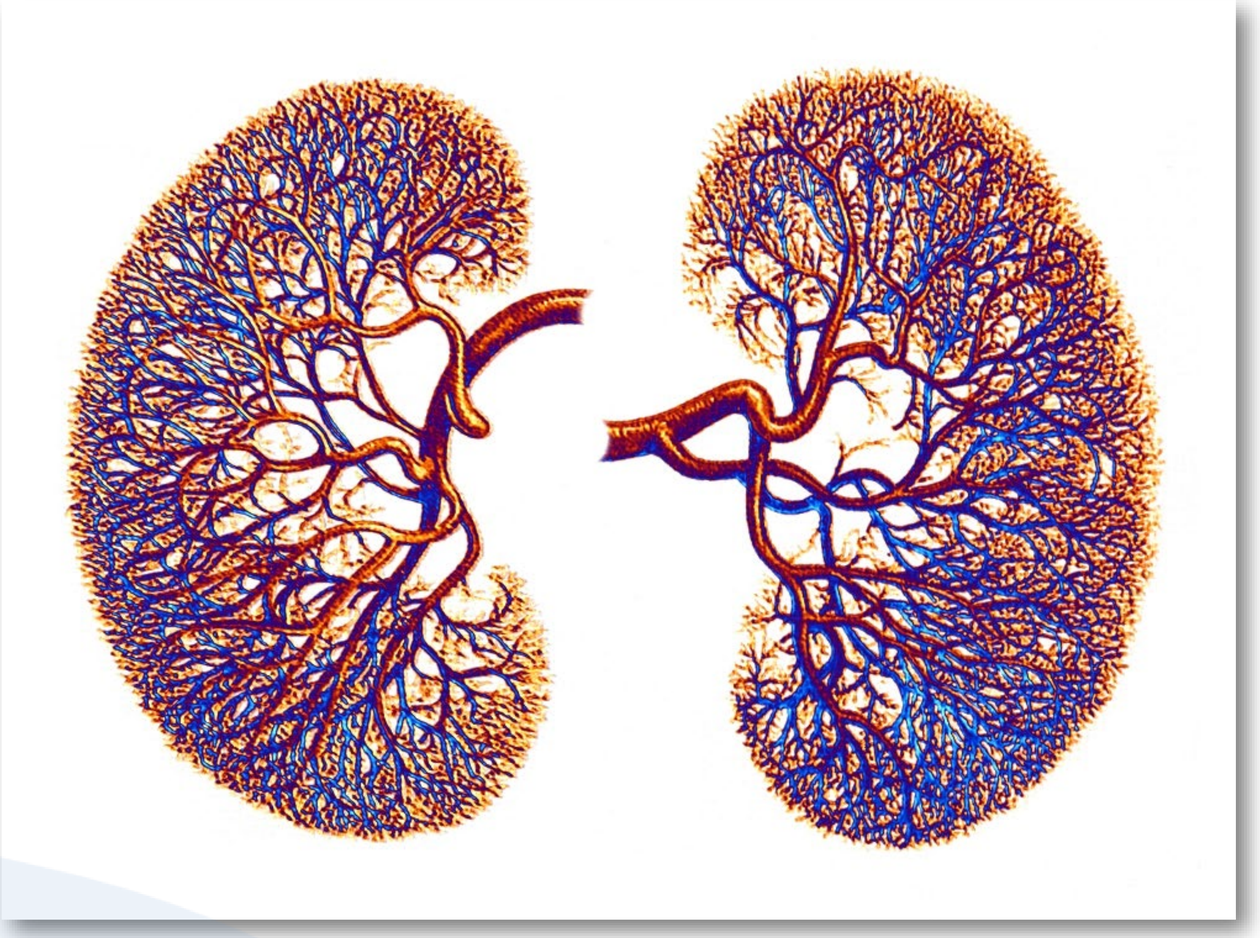
National Chronic Kidney Disease Audit // National Report: Part 2 December 2017. https://www.lshtm.ac.uk/media/9951..

CKD is an under-recognised risk factor



Kidney vasculature is a lens into the body's cardiovascular health:

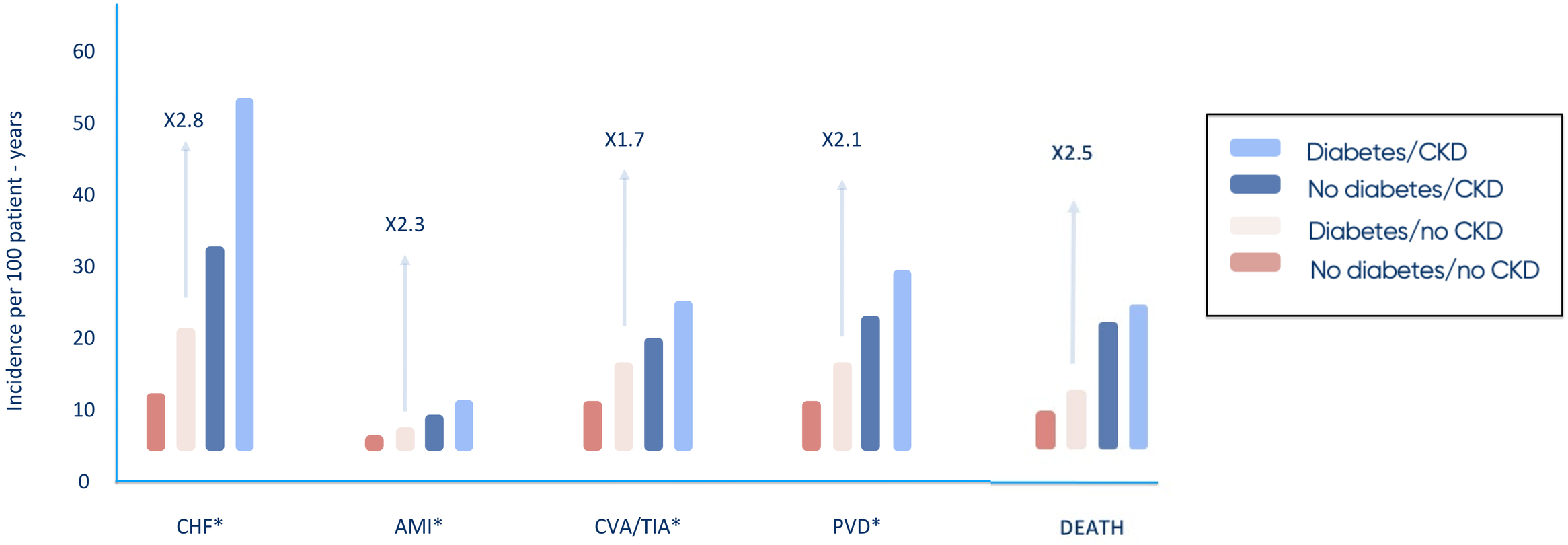
- Approximately 10 km of capillaries in both kidneys
- 180L plasma filtered by kidneys in 24 hours
- 20-25% cardiac output
- CKD is a cardiovascular risk state
- Patients with CKD are 20x more likely to die from CVD than renal failure
- **CKD must be considered one of the strongest risk factors for the development of CVD***



*Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, McAlister F, Garg AX. Chronic kidney disease and mortality risk: a systematic review. J Am Soc Nephrol. 2006;17:2034–2047

CKD is a ‘stronger’ risk factor for ALL cardiovascular events than diabetes:

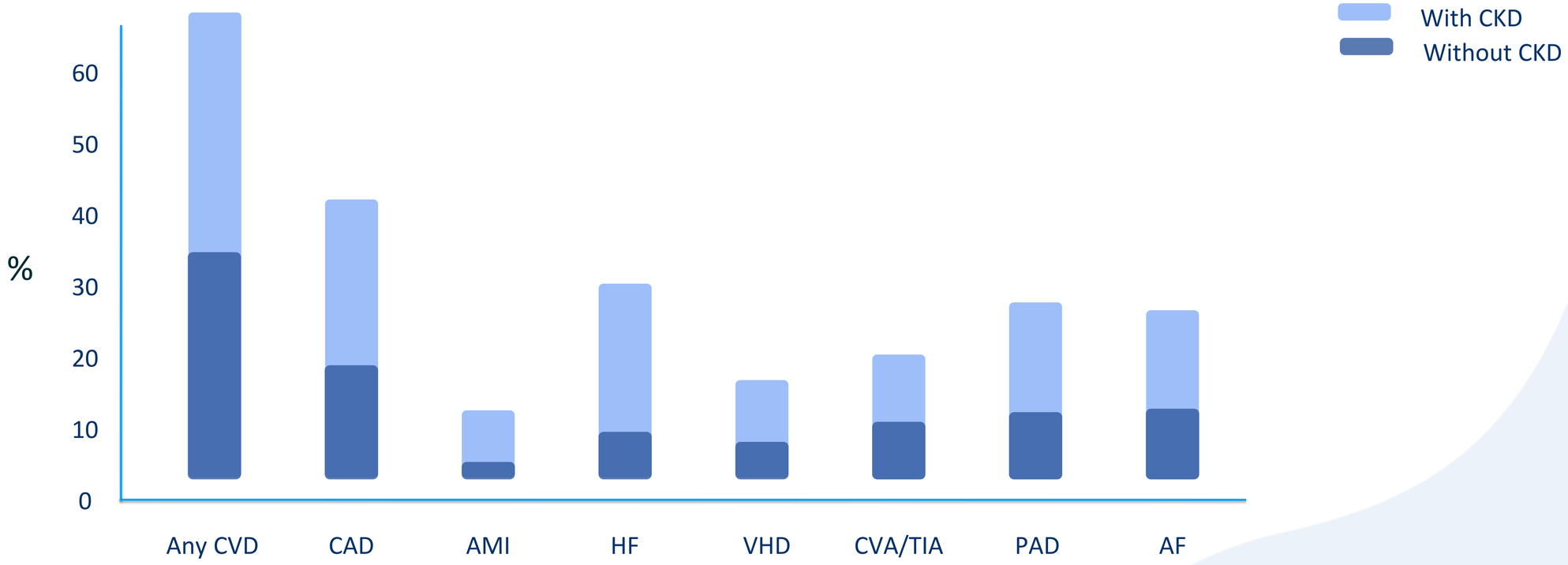
Foley RN, et.al.Am. Soc. Nephrol. 2005.



CHF - congestive heart failure; AMI - acute myocardial infarction; CVA/TIA - cerebrovascular accident/transient ischemic attack; PVD - peripheral vascular disease; ASVD - atherosclerotic vascular disease. *ASVD was defined as the first occurrence of AMI, CVD/TIA, or PVD.

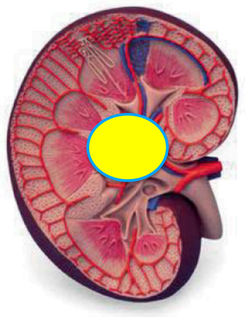
All forms of CVD are more likely to have CKD, than not. These people have worse outcomes

Prevalence of common cardiovascular diseases in patients with or without CKD in United States (2015)



Reference: Provenzano et al 2019

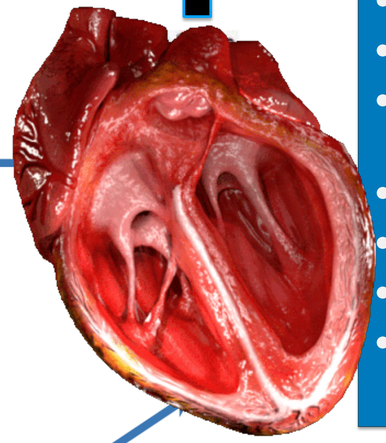
Cardiorenal syndromes



Stage 1–2
- Comorbidities: DM, smoking, HP, obesity, dyslipidemia
- Genotype
- Chronic inflammation

Stage 3–5
- Comorbidities
- Anemia
- Uremic toxin
- Malnutrition
- Calcio-phosphorus abnormalities
- Neurohormonal activation (sympathetic overactivity, activation of RAAS)
- Oxidative stress
- Endothelial dysfunction, LV hyper-trophy, ischemic intolerance

Stage 5 with dialysis
- Increased inflammation
- Blood-membrane interaction
- Blood-catheter interaction
- Dialysate contaminant, endotoxin, catheter infection
- Hemodynamic stress



- Hypertension
- Valve disease
- Heart failure, LVH, cardiomyopathy, myocardial fibrosis
- AF
- CAD
- Stroke
- Sudden cardiac death – fatal arrhythmias [2/3 advanced CKD -59X popn adjusted risk]

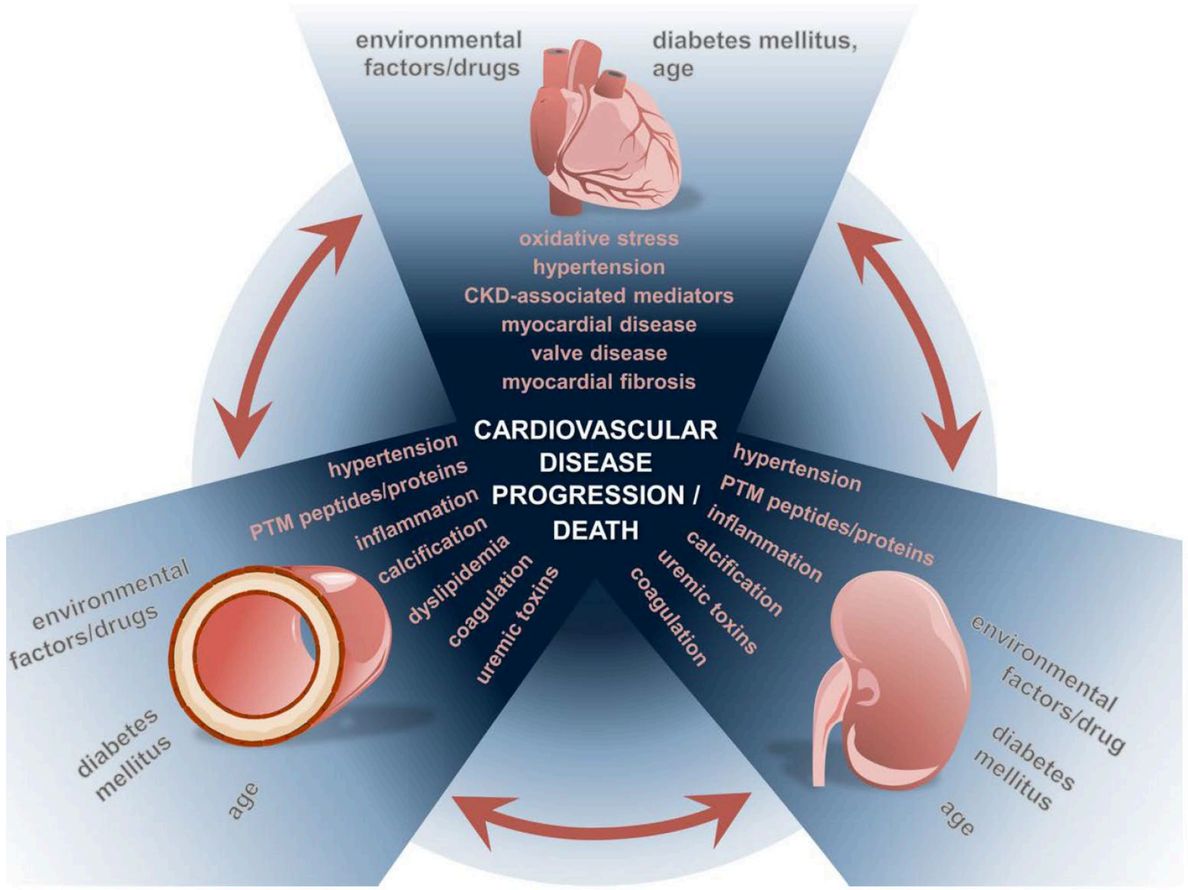
CRS type 1	Acute worsening of heart function causing acute kidney injury and/or dysfunction
CRS type 2	Chronic abnormalities in cardiac function leading to progressive CKD
CRS type 3	Sudden worsening of renal function causing acute cardiac injury and/or dysfunction
CRS type 4	Condition of primary CKD leading to a reduction in cardiac function (ventricular hypertrophy, diastolic dysfunction) and/or increased risk of cardiovascular events
CRS type 5	Systemic disorders (e.g. sepsis) that concurrently induce cardiac and kidney injury and/or dysfunction

Clementi et al.: Cardiorenal Syndrome Type 4: A Review
Cardiorenal Med 2013;3:63–70

Why does CKD cause cardiovascular complications?

CKD increases CVD for the following reasons:

- Traditional CAD risk factors also damage the kidney e.g. smoking, dyslipidaemia, HTN, diabetes etc
- Activation of Renin – Aldosterone System
- Arterial stiffening
- Instability of atherosclerotic plaque in uraemia
- Renal anaemia
- Cardiac remodelling inc. LVH (30-80%) and fibrosis
- Marked accelerated vascular (45x) and valve calcification esp. aortic (40% CKD3, almost all CKD5)
- Chronic inflammation – endothelial dysfunction and NO production.



Circulation. 2021;143:1157–1172

What is Chronic Kidney Disease?

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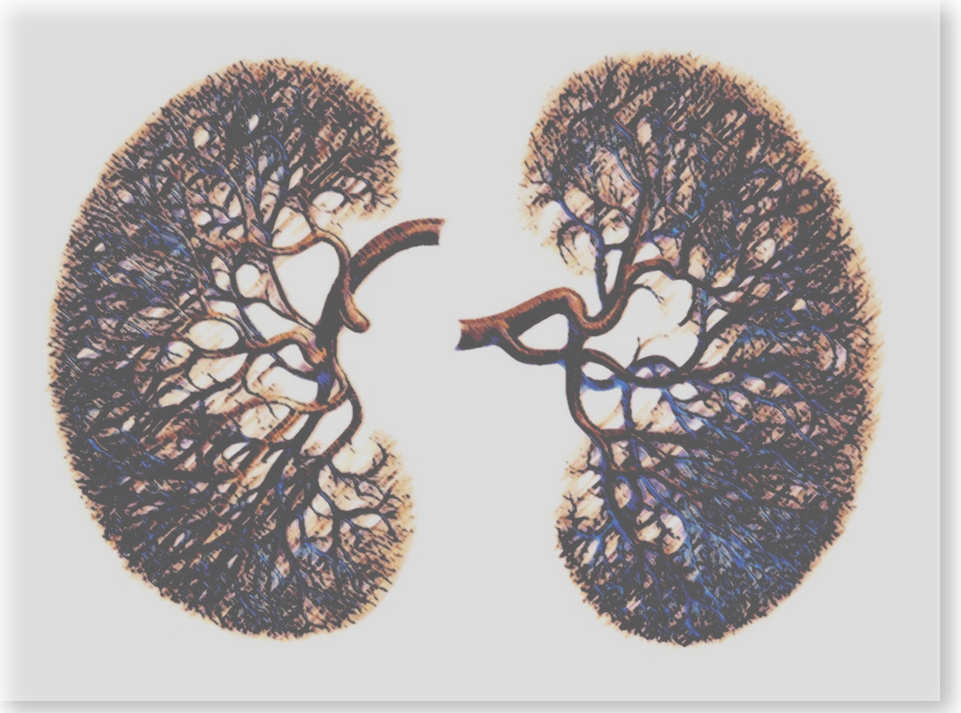
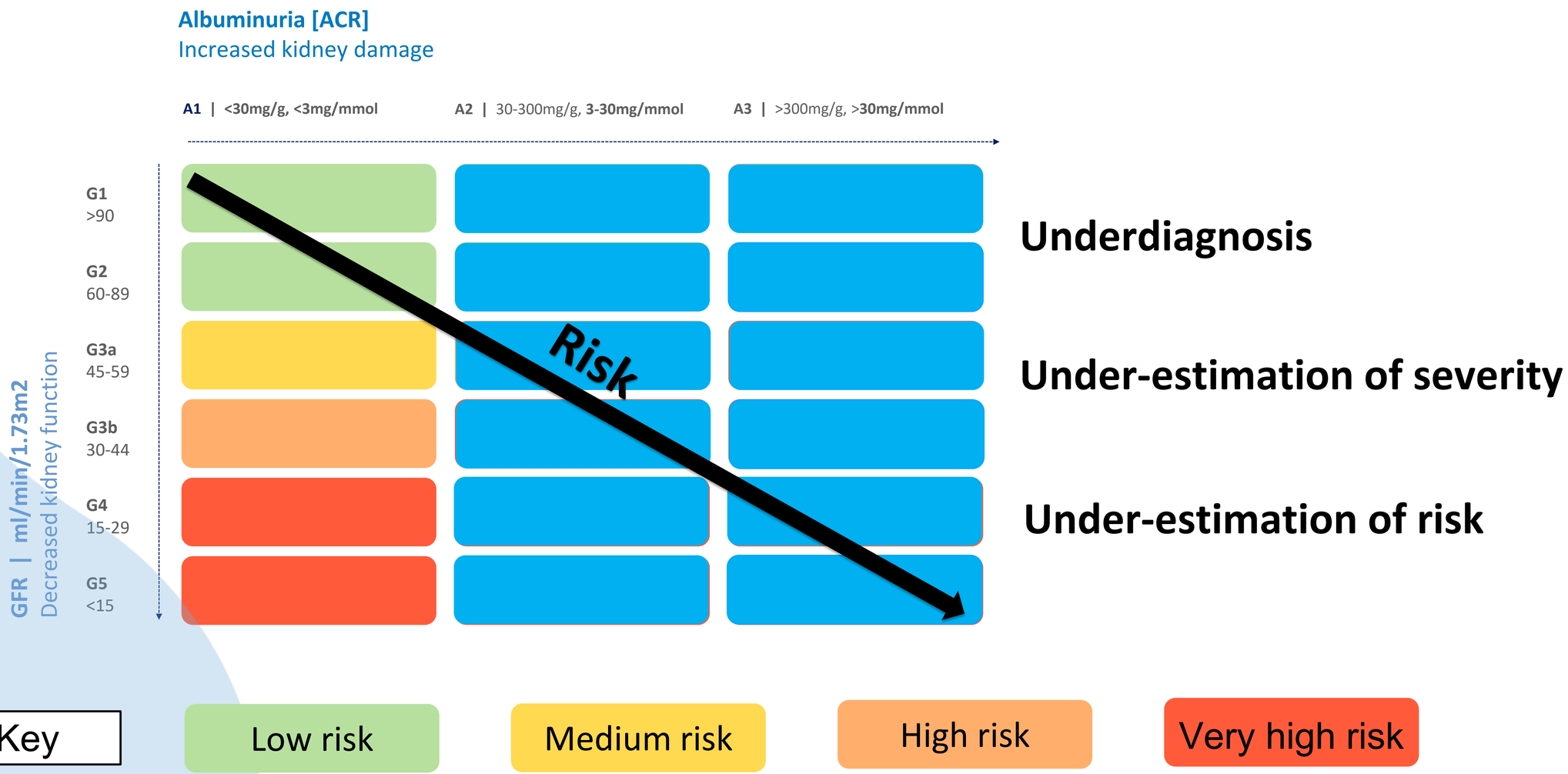


Ref: Levey and Coresh, 2012

What happens if we don't check the urine for albuminuria?



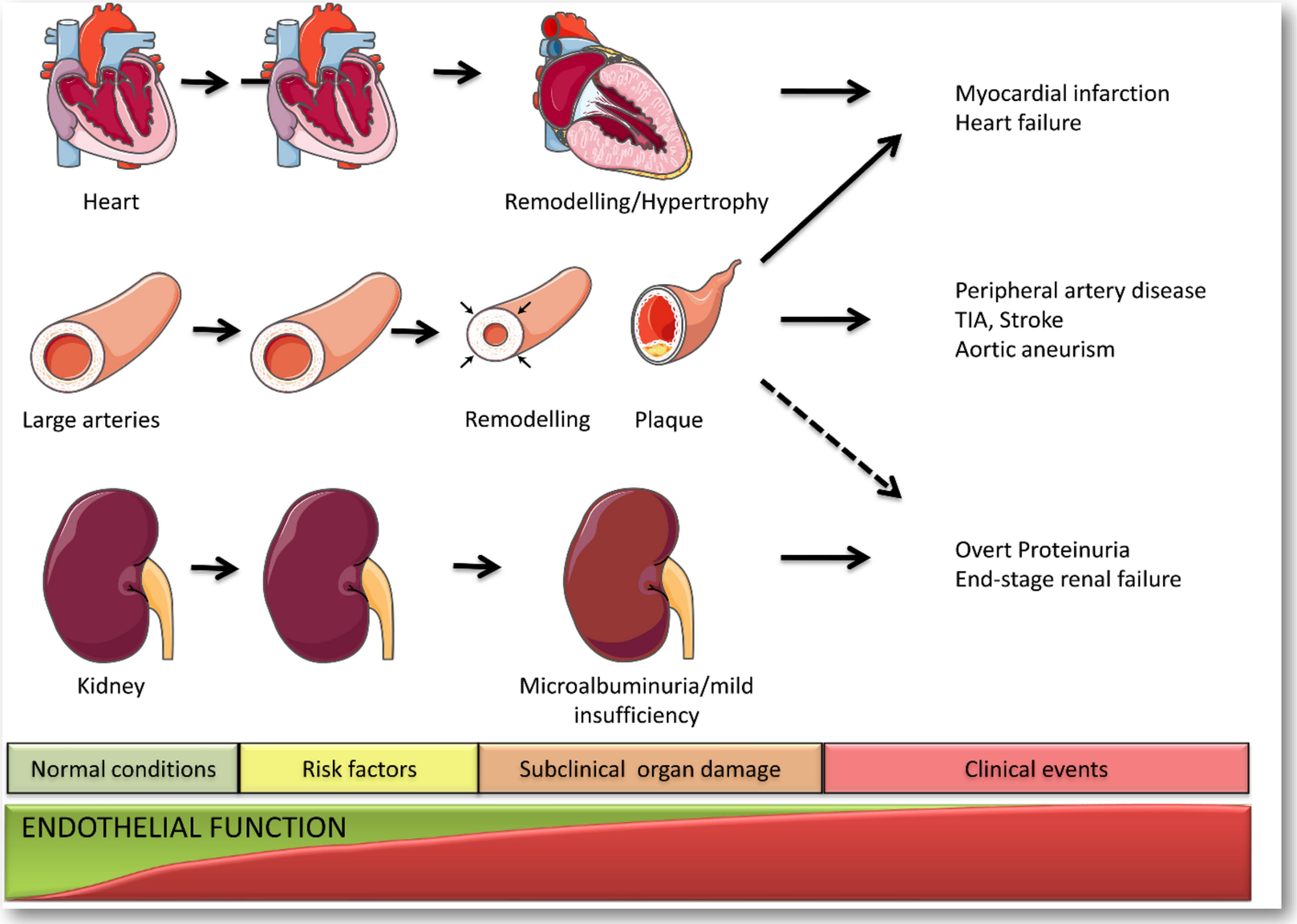
CVDprevent data: B’ham

CVDP004CKD: Percentage of patients aged 18 and over with GP recorded CKD (G3a to G5), with a record of a urine albumin:creatinine ratio (or protein:creatinine ratio) test in the preceding 12 months

23.56%

Area value

Albuminuria is an early marker of cardiovascular disease



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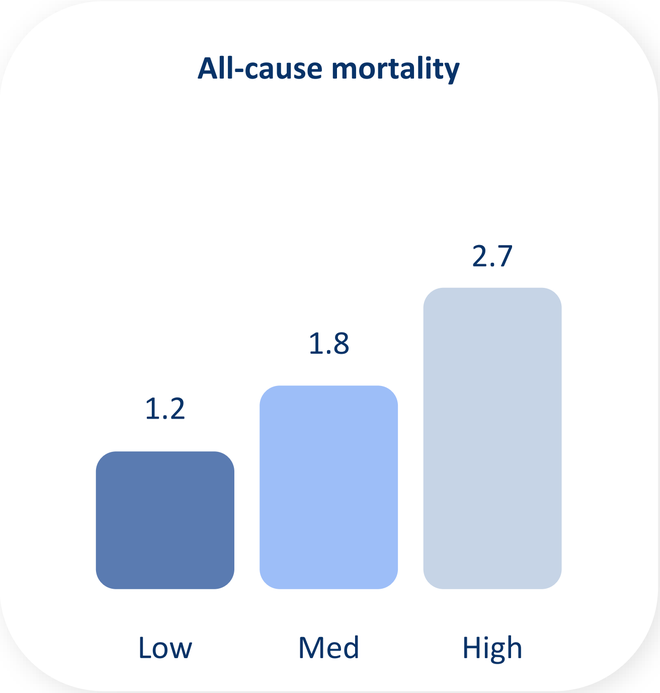
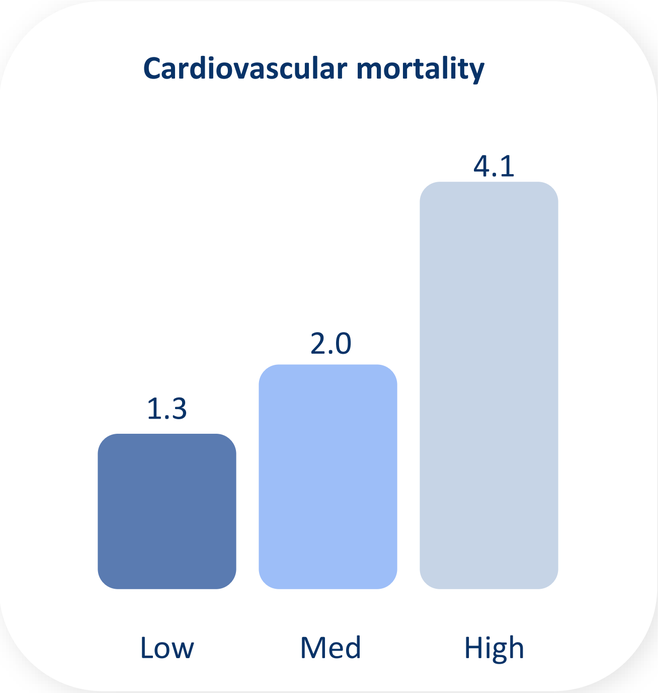
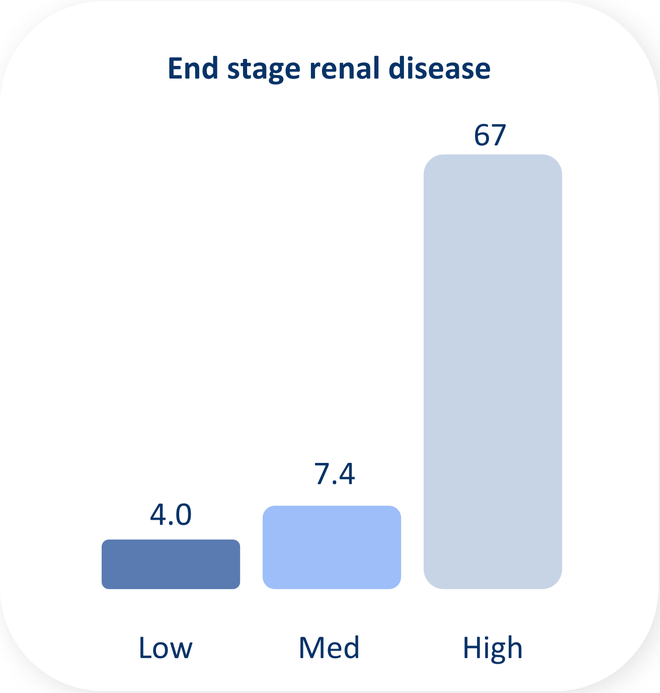
CVD Academy
Driving primary care to deliver the best in cardiovascular health

Albuminuria is a strong independent risk predictor for End-Stage Renal Disease (ESRD), CVD and death

Adjusted Hazard Ratio for cohort with eGFR stage 3, by ACR level





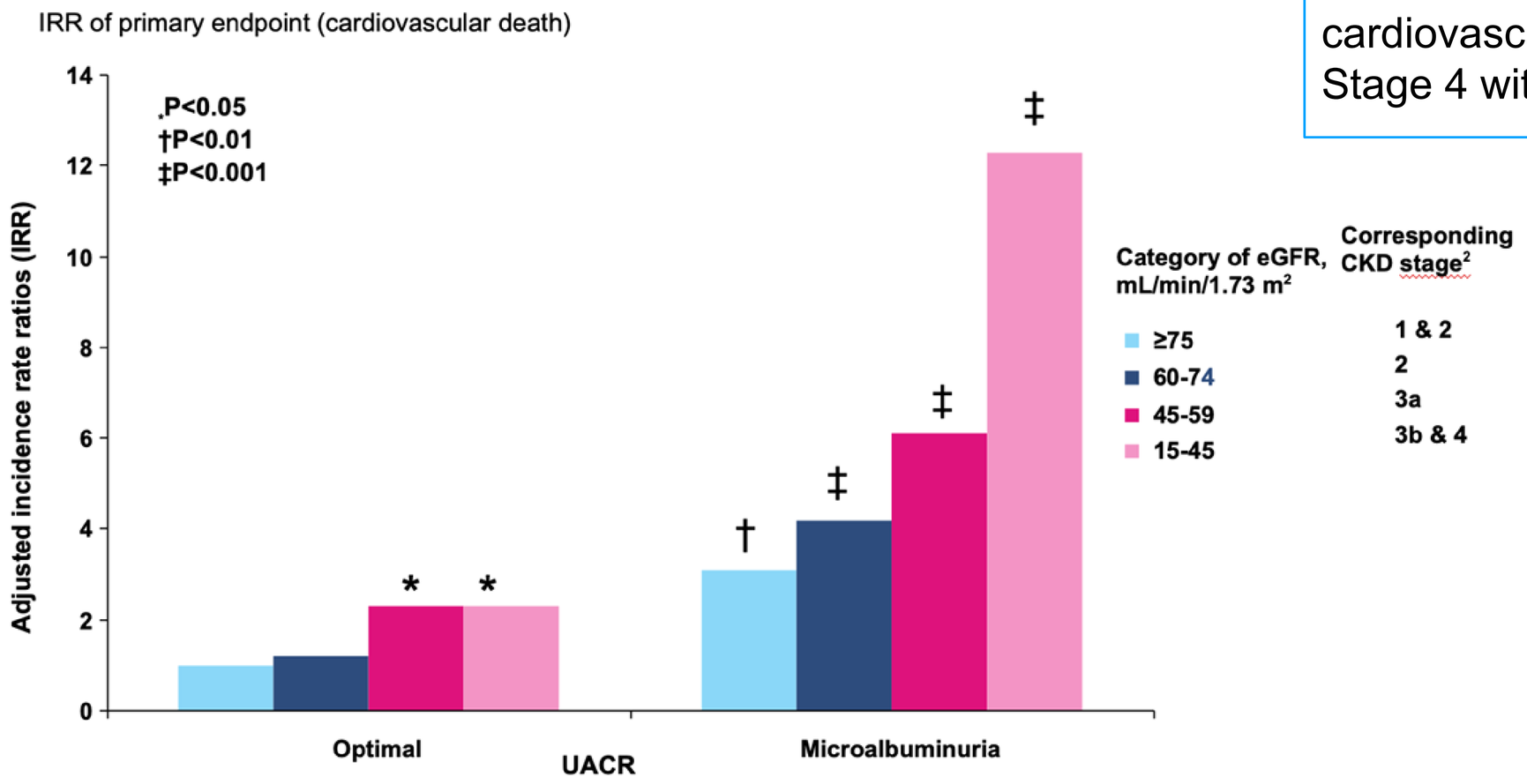


Definitions: Low is ACR <3mg/mmol, Med is ACR 3-30mg/mmol, High is ACR > 30 mg/mmol

Reference: Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int 2010; 80:17

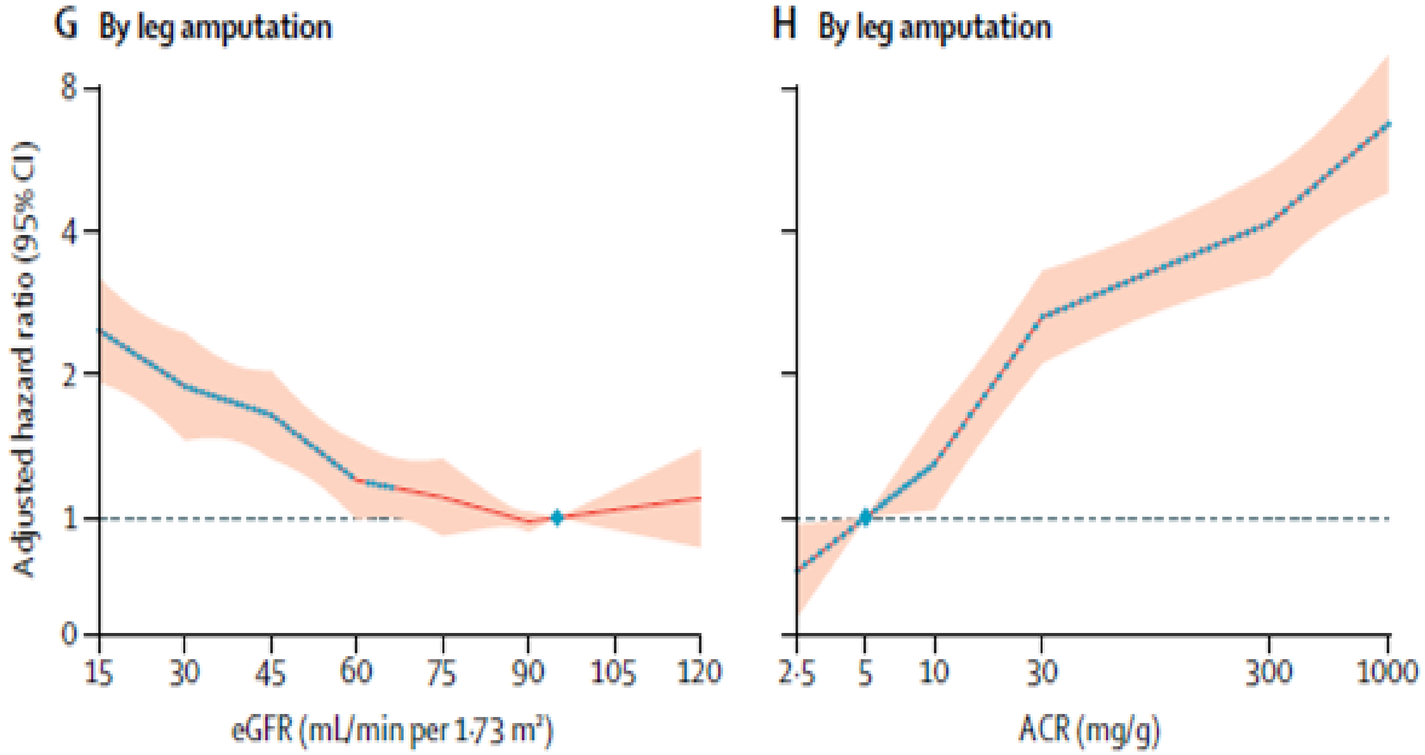
Risk is intensified with microalbuminuria

Microalbuminuria with eGFR >75 mls/min/1.73m^2 is associated with higher risk of cardiovascular death than CKD Stage 4 without albuminuria



1. Adapted from Hallan et al. *Archives Internal Medicine* 2007 167;22;2490-2496
2. NICE Management of CKD: *NICE*

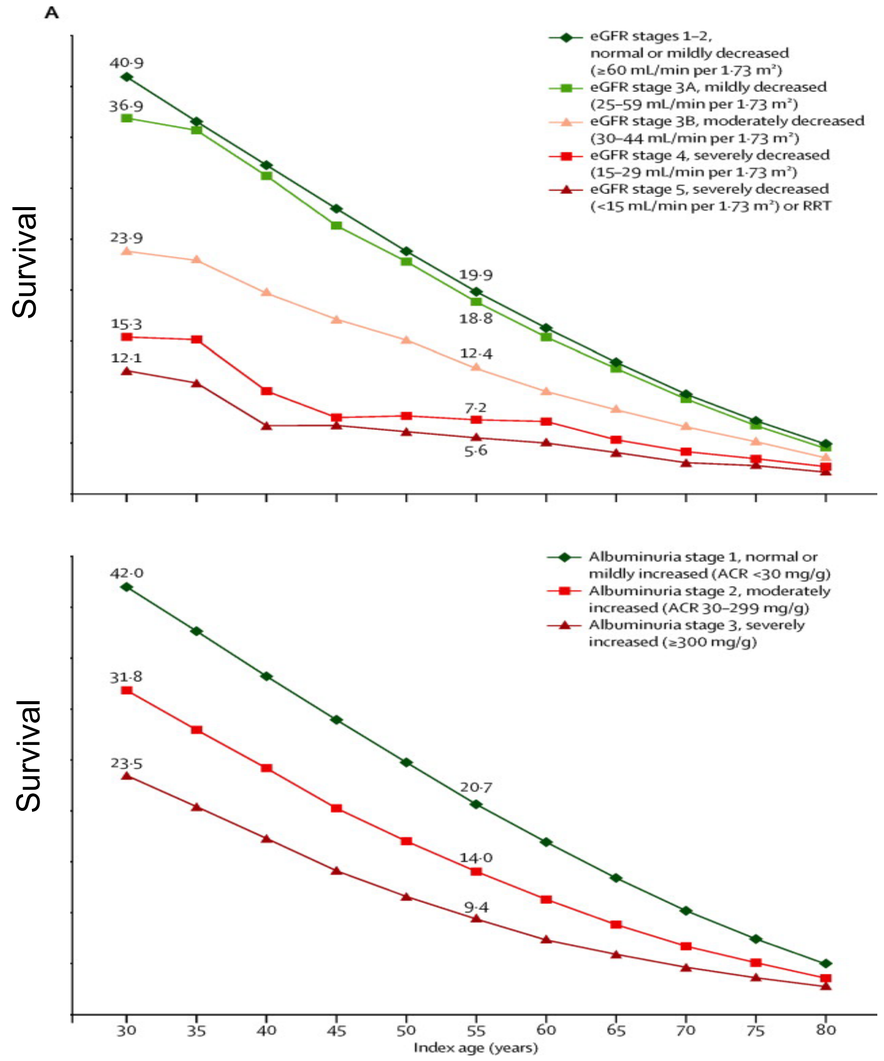
Risk of leg amputation in Diabetic Kidney Disease

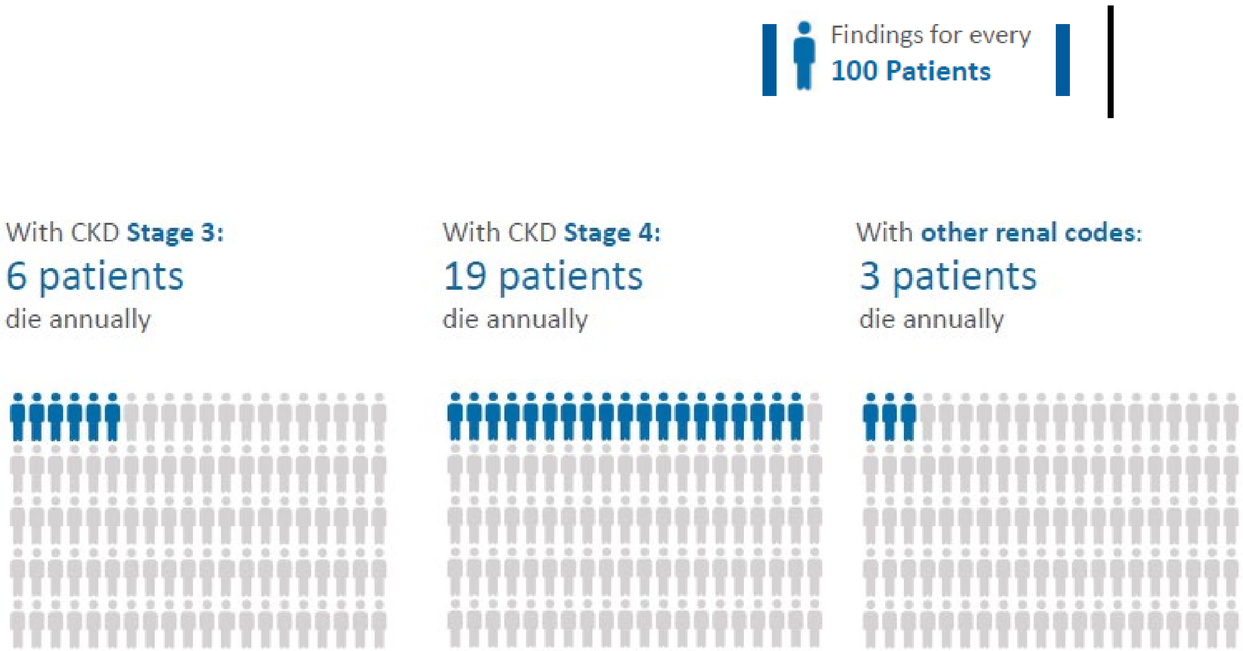


Amputation risk is significantly higher with declining eGFR, and rising albuminuria.

Matsushita K. et al. Lancet Diab Endo. 2017, 15.

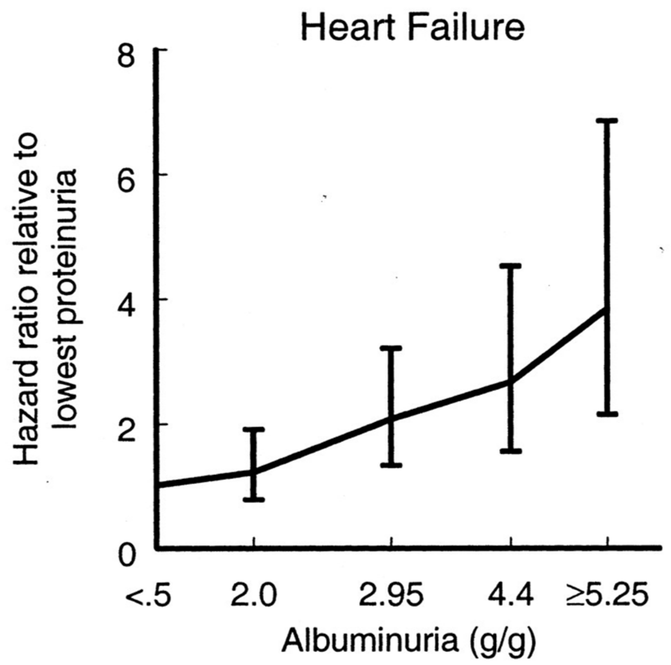
Low eGFR and raised ACR are independently associated with reduced life expectancy, even at early stages



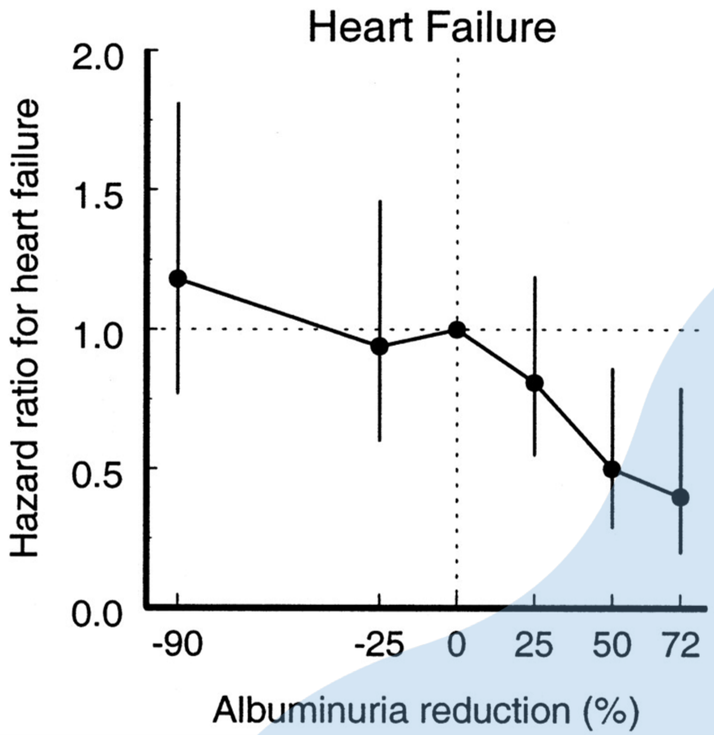


National Chronic Kidney Disease Audit // National Report: Part 2 December 2017. https://www.lshtm.ac.uk/media/9951.

Heart Failure and its link to Albuminuria



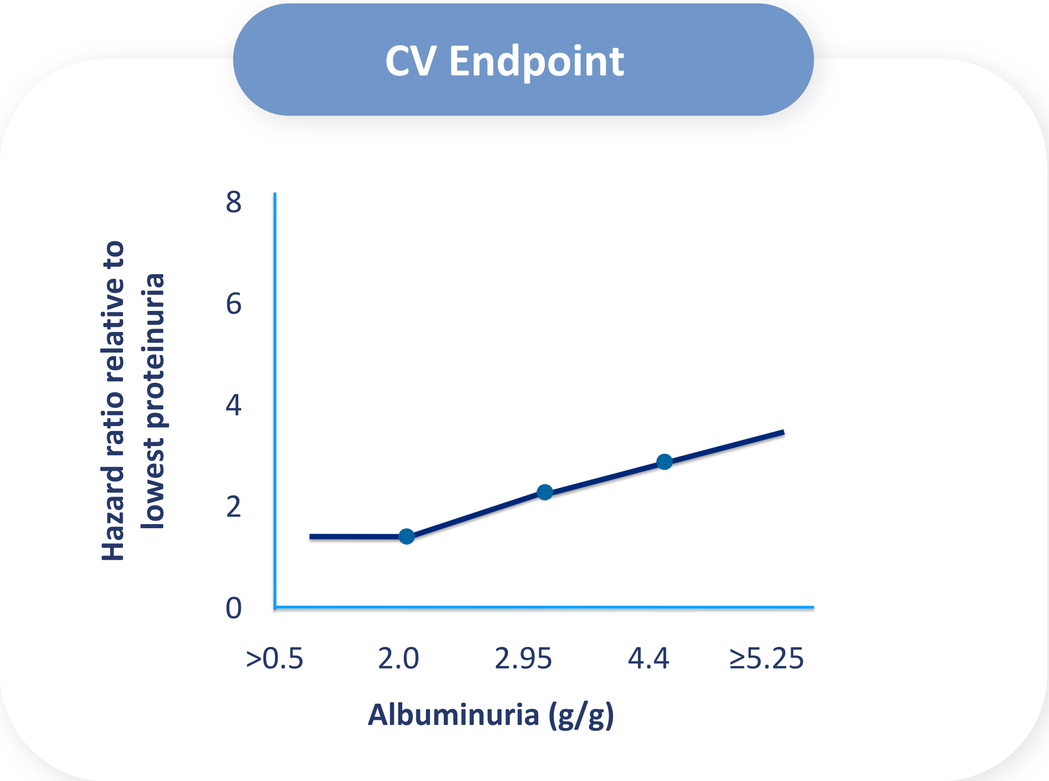
Risk of Heart Failure is higher with high baseline Albuminuria

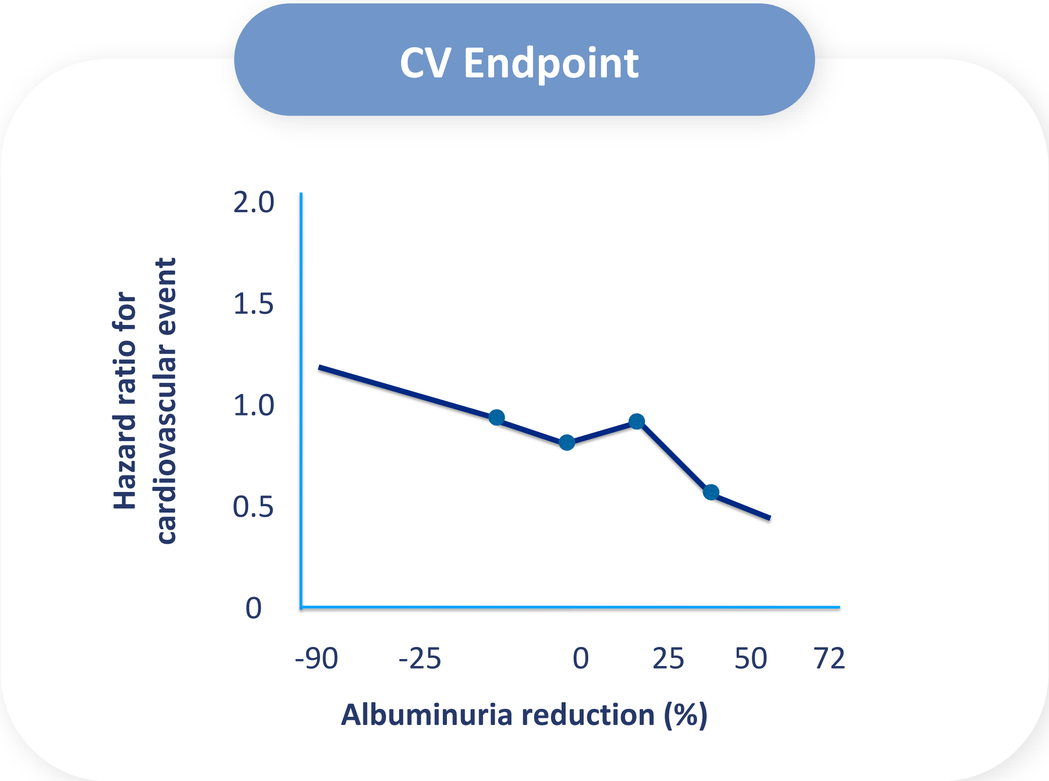


Risk of Heart Failure is significantly reduced at six months with Albuminuria reduction

Zeeue D. et al. Circulation , 2004 Vol 110
(Posthoc analysis of RENAAL trial)

Cardiovascular events are more common with albuminuria and less likely to occur if albuminuria is reduced





Ref : Post hoc analysis of ‘RENAAL’ trial (1513 patients with diabetic nephropathy – Losartan v placebo) de Zeeuw et al Circulation 2004

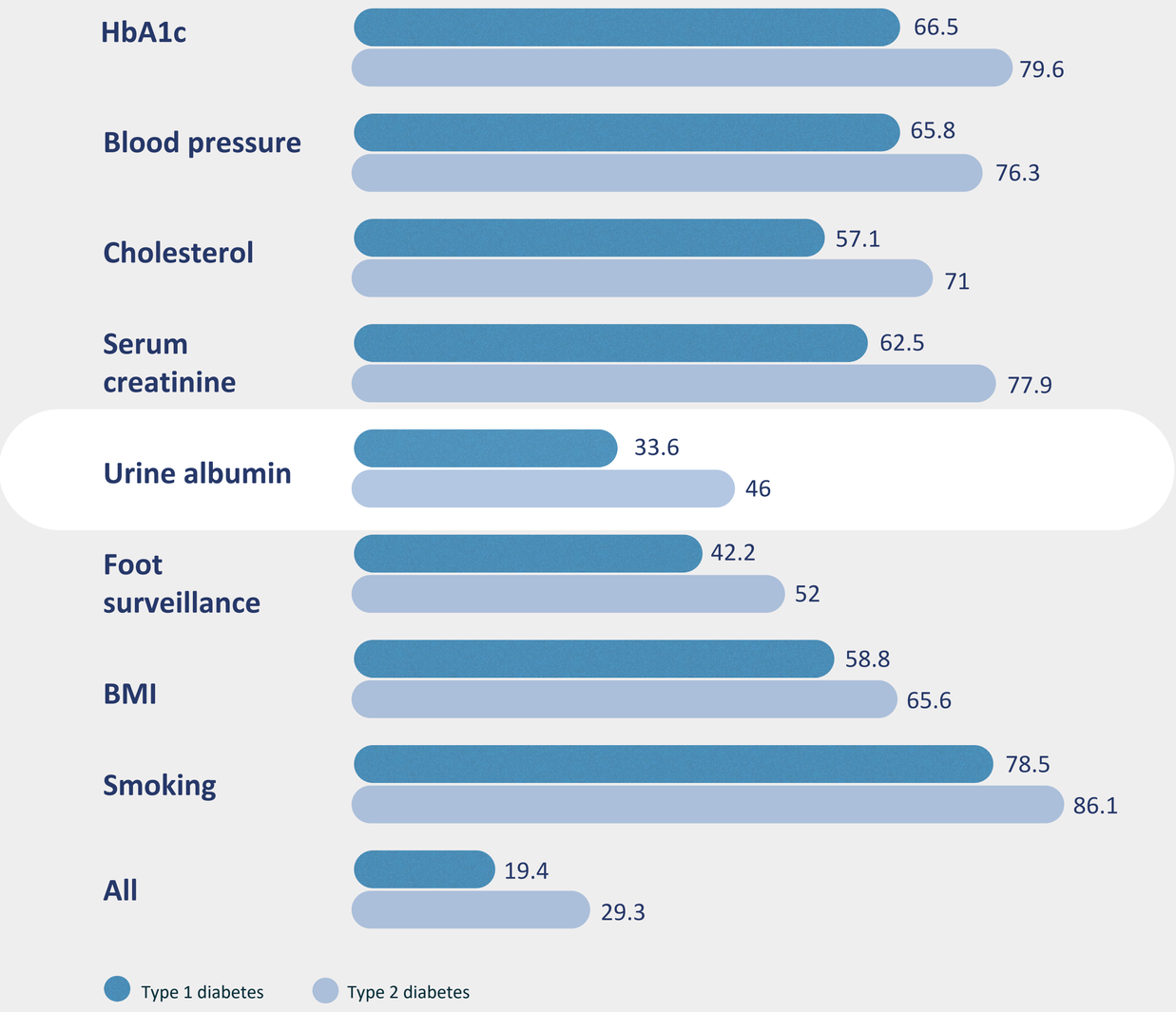
Summary

1. CKD is a strong predictor of adverse cardiovascular outcomes
2. CKD is a greater risk factor for CVD than diabetes
3. Testing for eGFR alone is not enough – albuminuria is strong independent predictor of CVD and renal failure
4. Failure to test for albuminuria underestimates prevalence, severity of CKD and risk
5. Treatment of albuminuria significantly improves outcomes
6. Coding patients with CKD can reduce admissions and death
7. It is important to look for CKD in at risk patients [NICE]

Why is ACR testing adherence so poor?

Clear guidance, but low compliance

National uptake of ACR testing compared with other care processes for people with diabetes.



Why don’t patients complete their test?

Clinician factors

- Do we take the test seriously enough?
- Do we check to see its been done at reviews?
- Contractual levers
- Workload

Patient factors

- How easy is it to get a test done?
- How much do they really know about it?

Identification and management in primary care

Identification

- CKD coding
- Case finding for unidentified CKD using eGFR and ACR
- Inequalities

Management

- Education – Cardiovascular health / lifestyle / modifiable risk-factors

Medical Optimisation

- Maximum Renin Angiotensinogen Aldosterone inhibition
- Sodium Glucose Transporter-2 inhibitor
- Blood Pressure Optimisation
- Statins

Why should we code for CKD?

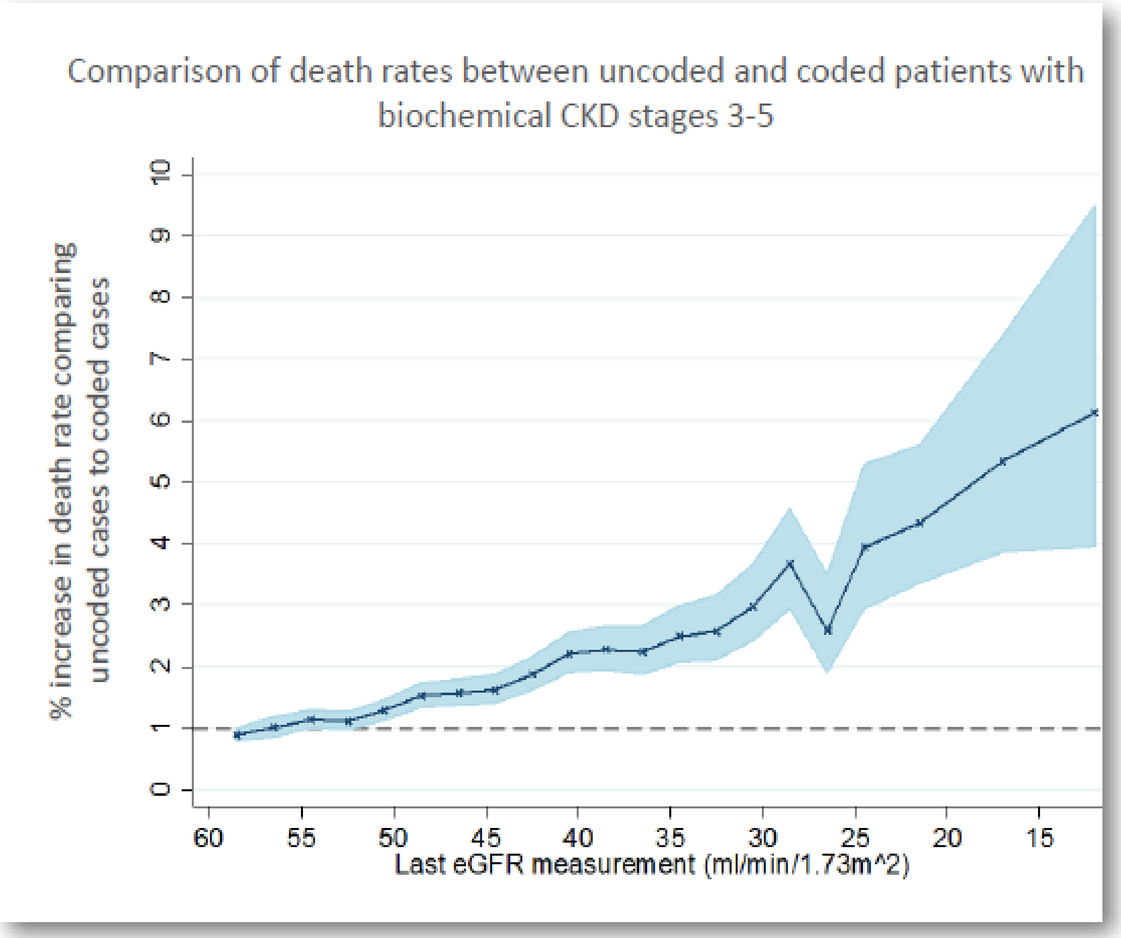
Significant number of patients uncoded

CQC may look at coding as a quality marker

Uncoded patients with CKD have worse outcomes than coded patients (CKD audit, 2017)

- x2 mortality
- higher admissions

Coding facilitates audit of care through $CKD_{PREVENT}$ e.g. Proportion of patients with CKD Stage 3-5 prescribed lipid lowering therapy



CVD risk management in patients with CKD should be initiated early

- Code patient's CKD status on medical record
- Full cardiovascular risk assessment including relevant history: smoking status, physical examination (inc. weight), labs and QRISK etc
- Discuss/offer lifestyle measures for control of modifiable risk factors e.g. referral to local weight loss pathway, smoking cessation etc
- Uptitrate to maximum tolerated dose of ACEi or ARB. Consider addition of SGLT2i inline with local pathways
- Avoid NSAIDs and other nephrotoxic medications
- Aim for BP <140/90 unless ACR >70 mg/mmol, whereby aim BP <130/80
- Consider antiplatelet and lipid lowering therapy as indicated by cardiovascular risk[3]
- Consider referral to secondary care as per NICE guidance and local pathways

+optimise secondary prevention – e.g. HF

Evidence for SGLT2i on CVD and Renal outcomes in Patients with and without Diabetic Kidney Disease

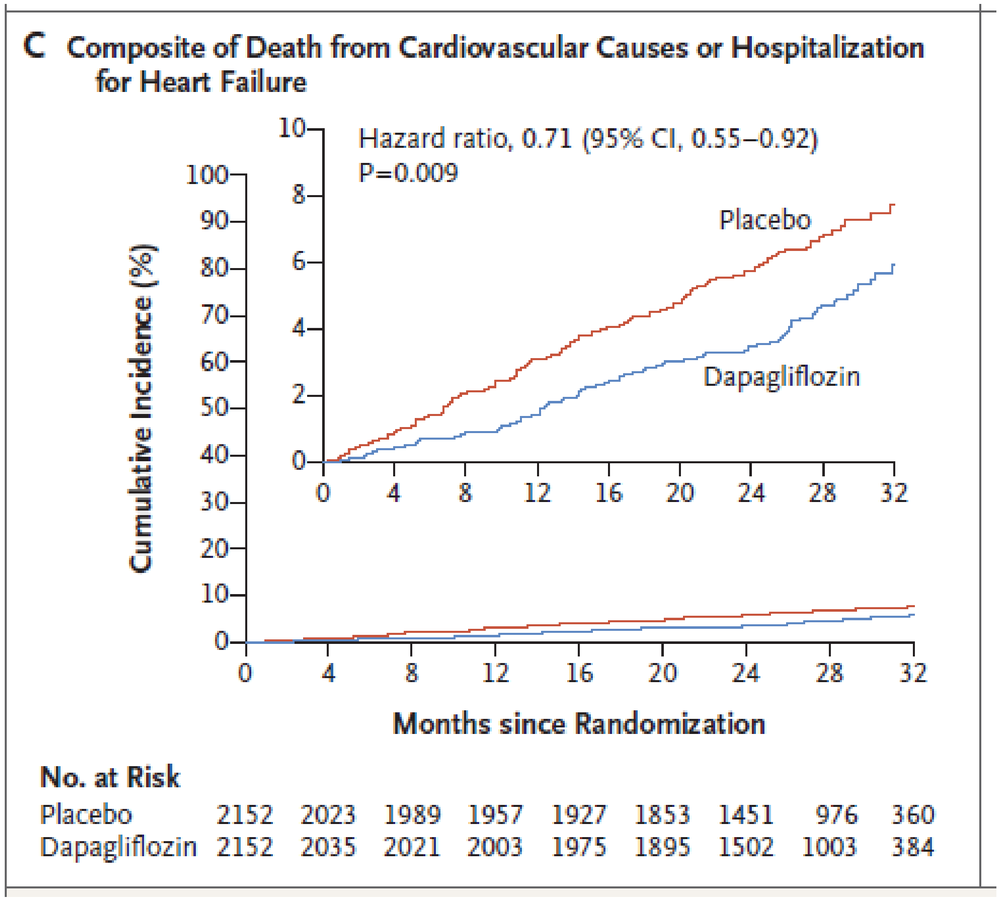
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J.L. Heerspink, Ph.D., Bergur V. Stefánsson, M.D., Ricardo Correa-Rotter, M.D., Glenn M. Chertow, M.D., Tom Greene, Ph.D., Fan-Fan Hou, M.D., Johannes F.E. Mann, M.D., John J.V. McMurray, M.D., Magnus Lindberg, M.Sc., Peter Rossing, M.D., C. David Sjöström, M.D., Roberto D. Toto, M.D., Anna-Maria Langkilde, M.D., and David C. Wheeler, M.D., for the DAPA-CKD Trial Committees and Investigators*

Primary Composite Outcome = GFR decline >5-%, ESKD, Death from renal or cardiovascular cause



Dapagliflozin for treating chronic kidney disease

Technology appraisal guidance [TA775] Published: 09 March 2022

Download guidance (PDF)

Guidance

Next

1 Recommendations

1.1 Dapagliflozin is recommended as an option for treating chronic kidney disease (CKD) in adults. It is recommended only if:

- it is an add-on to optimised standard care including the highest tolerated licensed dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs), unless these are contraindicated, and
- people have an estimated glomerular filtration rate (eGFR) of 25 ml/min/1.73 m^2 to 75 ml/min/1.73 m^2 at the start of treatment and:
  - have type 2 diabetes or
  - have a urine albumin-to-creatinine ratio (uACR) of 22.6 mg/mmol or more.

RESEARCH SUMMARY

Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes

Pitt B et al. DOI: 10.1056/NEJMoa2110956

CLINICAL PROBLEM

Finerenone, a selective nonsteroidal mineralocorticoid receptor antagonist, improves cardiorenal outcomes in patients with stage 3 or 4 chronic kidney disease (CKD) with severely elevated albuminuria and type 2 diabetes. Whether finerenone is beneficial in patients with diabetes and less-advanced CKD is unclear.

CLINICAL TRIAL

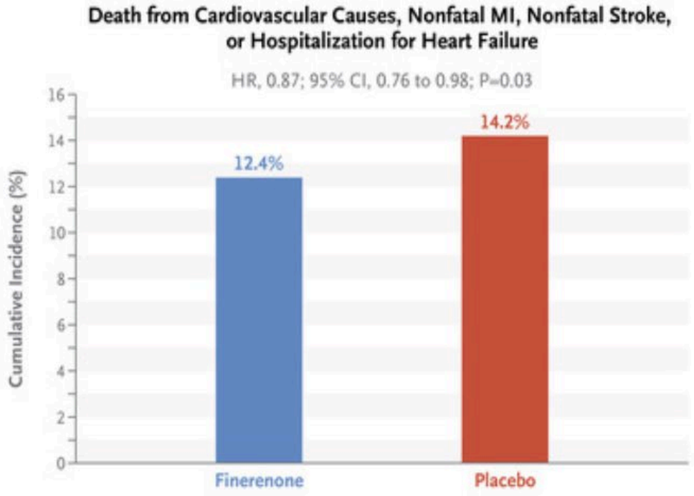
Design: A phase 3, multicenter, randomized, placebo-controlled trial examined the efficacy and safety of finerenone in adults with type 2 diabetes and a range of CKD stages.

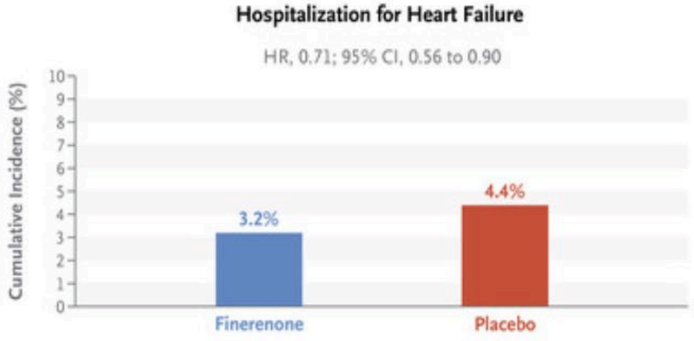
Intervention: 7437 patients with diabetes and CKD treated with a maximum-dose renin–angiotensin system inhibitor were assigned to receive oral finerenone or placebo. Eligible patients had persistent, moderately elevated albuminuria plus an estimated glomerular filtration rate (eGFR) of 25 to 90 ml per minute per 1.73 m^2 (stage 2 to 4 CKD) or persistent, severely elevated albuminuria plus an eGFR of at least 60 ml per minute per 1.73 m^2 (stage 1 or 2 CKD). The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure.

RESULTS

Efficacy: During a median 3.4 years of follow-up, the incidence of primary outcome events was lower with finerenone than with placebo, a difference driven mainly by a lower incidence of hospitalization with finerenone.

Safety: The incidence of serious adverse events was similar in the two groups. Hyperkalemia occurred more often with finerenone but did not result in any deaths and rarely resulted in treatment discontinuation.





Quality improvement ideas in CKD

Population health

- Code patients with CKD
- Actively look for patients at risk of having CKD using eGFR and ACR
- Ensure patients with CKD are auscultated for valve disease
- Have a high index of suspicion for heart failure

Management

- Ensure patients with CKD esp with albuminuria are optimised
- Optimise CVD risk at an early stage
- Optimise secondary prevention

Summary slide 2

1. CKD is a stronger predictor of CVD outcomes than diabetes
2. CKD is under coded and under diagnosed primary care. This increases risk of admission/death.
3. It is important to look for CKD in at risk patients [NICE] by checking both eGFR and ACR
4. Albuminuria is a strong independent risk factor for CVD
5. Treatment of CKD improves outcomes - by looking at the underlying cause, lifestyle factors, and optimising with ACEi/ARBs, SGLT2i, statins and BP control

Q&A