Much ado about nothing?

CKD

- what it is and what it isn’t

Chronic Kidney Disease

- We will try to define what this phrase means – and what it does not mean
- And where it comes from and why we see it now
- And in doing so we will discuss renal function and how it is measured
- We will cover why we should be concerned about CKD but why we should not over-react

CKD – the phrase

- A misnomer
  - it is not a single disease entity
- It would be better thought of as
  - *Chronic Kidney Dysfunction* or
  - *Chronic Kidney Disorder*
- So be aware that the disease that is causing this dysfunction may not yet have been diagnosed

So where did “CKD” come from?

- 1997 - US National Kidney Foundation
  - USNKF Dialysis Outcome Quality Initiative Guidelines
  - Aimed to improve treatment of people with ESRD
- 2000 – US National Kidney Foundation
  - Kidney Disease Outcome Quality Initiative Guidelines
  - Aimed to improve the diagnosis and treatment of people with earlier stages of renal disease

USNKF - Kidney Disease Outcome Quality Initiative Guidelines

- Defined laboratory methods for laboratory evaluation of kidney disease
- Stratified the risk of adverse outcome versus level of kidney function
- Standardised the definition of the stages of Chronic Kidney Disease…….

CKD – the definitions

- Either - the presence of markers of kidney damage for ≥ 3 months (BP, proteinuria, haematuria, imaging, genetic risk) with or without eGFR reduction

- Or - the presence of a GFR < 60 for ≥ 3 months, with or without other signs of kidney damage

- Five stages defined as…….

Table 10. Stages of Chronic Kidney Disease

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or ↑ GFR	≥90
2	Kidney damage with mild ↓ GFR	60–89
3	Moderate ↓ GFR	30–59
4	Severe ↓ GFR	15–29
5	Kidney failure	<15 (or dialysis)

The new GP Contract

- Commenced in April 2004
- Pay geared not so much to number of patients and individual items of treatment but more to…..
- Performance, measured by the *Quality and Outcomes Framework* (QOF)

QOF payments

- Intended to incentivise performance and quality measured against 146 indicators
- In four different domains – clinical, organisational, patient experience and additional services.
- Points are earned for these indicators – eg percentage of patients with their smoking status recorded, or for the number of diabetics whose last BP was below 140/80
- And points convert to income

QOF payments

- In April 2006, CKD added to the Clinical Domain
- Points for keeping a register of patients with CKD3 or worse
- eGFR's and "CKD" start to appear in GPR's
- Puzzlement and confusion start to appear on underwriters' faces

So, a CKD Register

- Why?

"The compilation of a register of people with CKD will enable appropriate advice, treatment and support for the patient to preserve kidney function and to reduce the risk of cardiovascular disease".

QOF - CKD

- **And then in April 2008**
  - Points for CKD register patients with BP recorded
  - Points for those whose BP is <140/85 and…….
  - Points for CKD register patients with hypertension and proteinuria who are on ACEI or ARB medication
- **Why?**
  - Lower BP associated with slower deterioration in GFR
  - ACEIs and ARBs better than other anti-hypertensives at slowing deterioration in kidney function especially where there is significant proteinuria.

CKD 3 to 5 - defined by eGFR

- So what is eGFR?
- *Estimated* GFR is but one of the measures of a kidney's function
- So what are the kidney's functions?

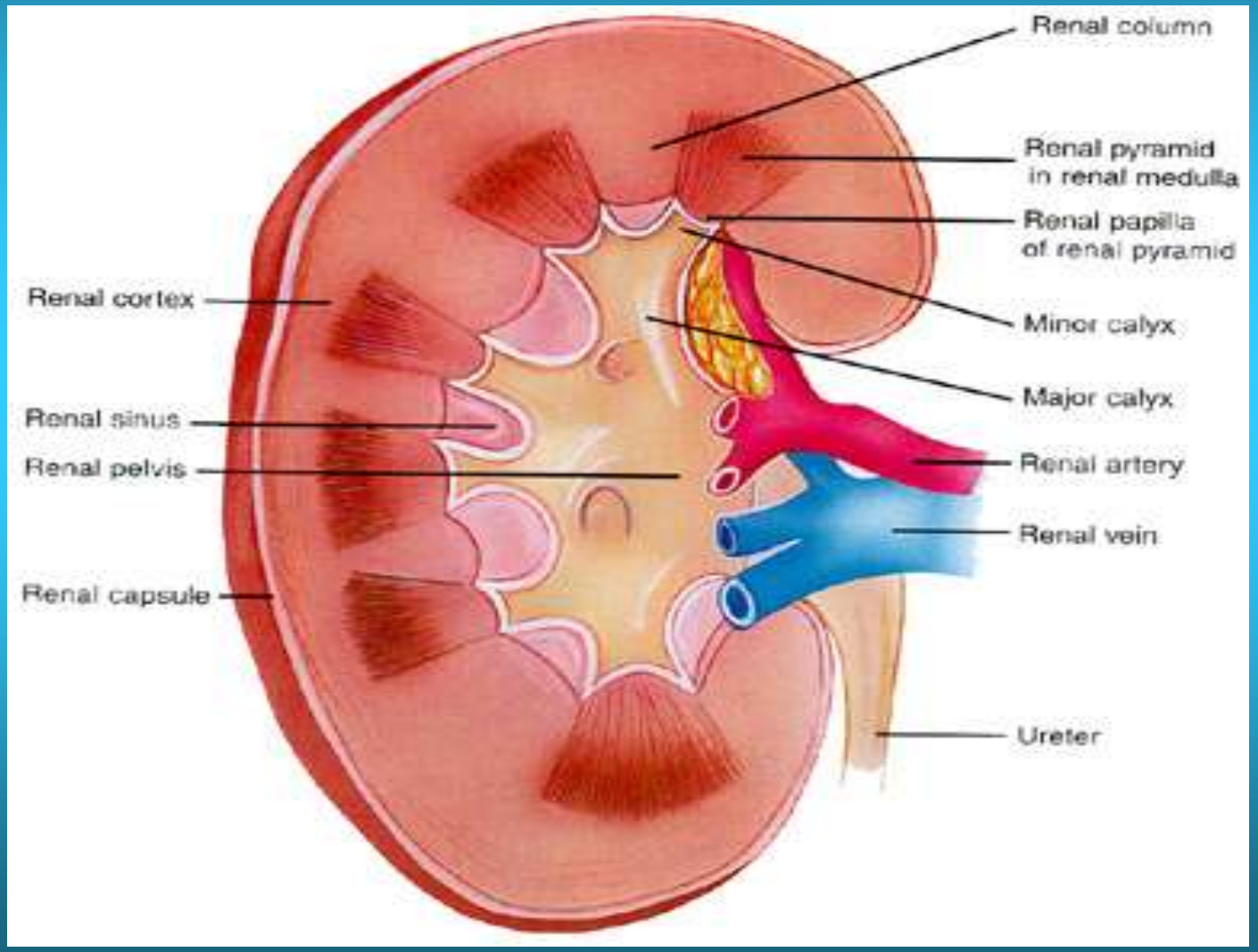
Kidneys…….

- Remove toxic waste products - ‘clearance’
- Remove excess water and salts
- Control blood pressure by producing Renin
- Control Hb level by producing Erythropoietin (“Epo”)
- Control calcium, phosphate and bone strength by metabolising Vitamin D
- Maintain acid balance
- Maintain water balance

So how do we measure renal function?

- By measuring the clearance of waste, the glomerular filtration rate
- By measuring the effectiveness of the filter – proteinuria
- By measuring BP
- By measuring sodium and potassium
- By measuring Hb
- By measuring Calcium, Phosphate
- Indirectly, by imaging – IVP, USS etc

The kidney

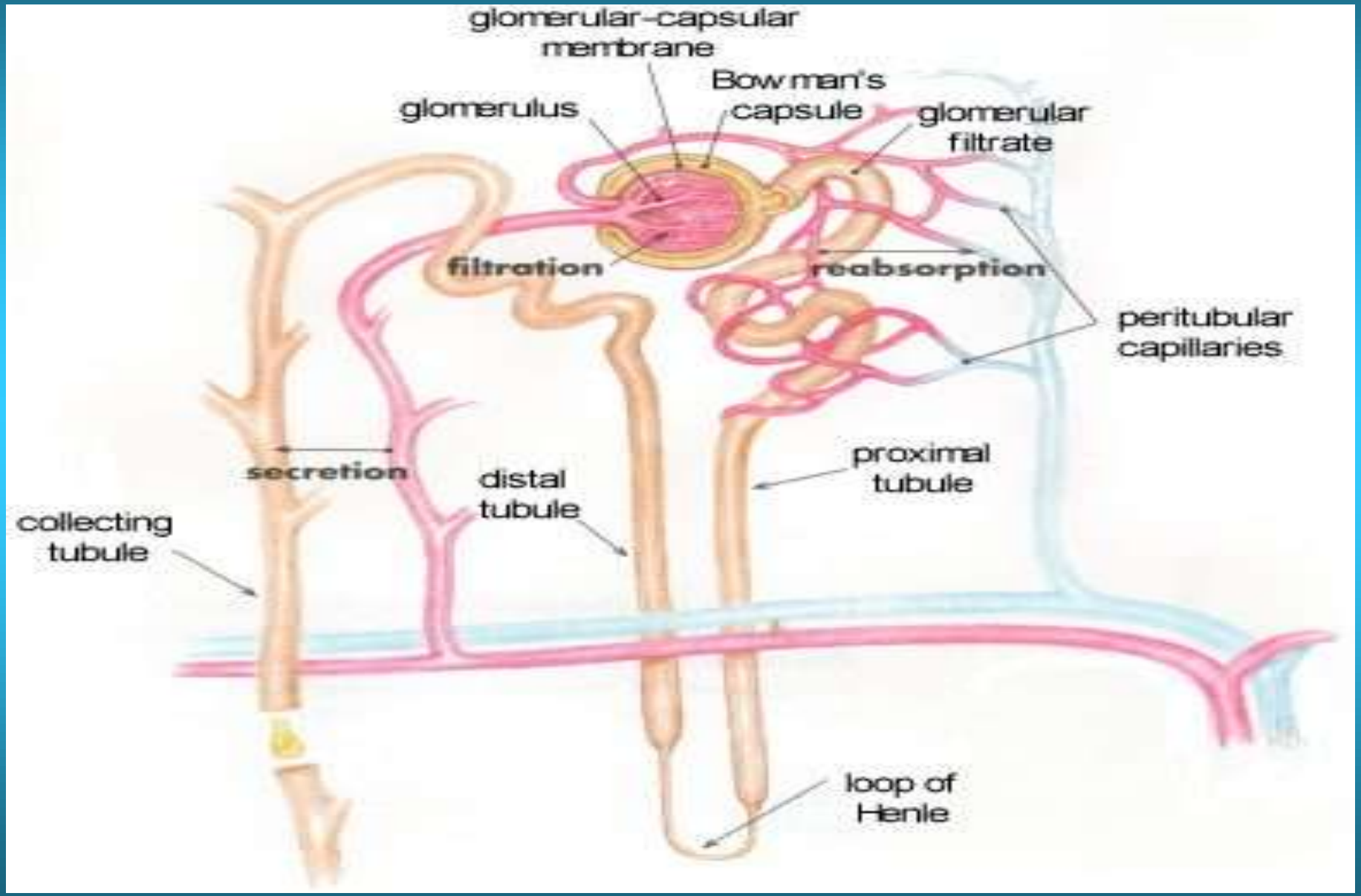

Renal column
Renal pyramid in renal medulla
Renal papilla of renal pyramid
Minor calyx
Major calyx
Renal artery
Renal vein
Ureter
Renal cortex
Renal sinus
Renal pelvis
Renal capsule

Filtration…….

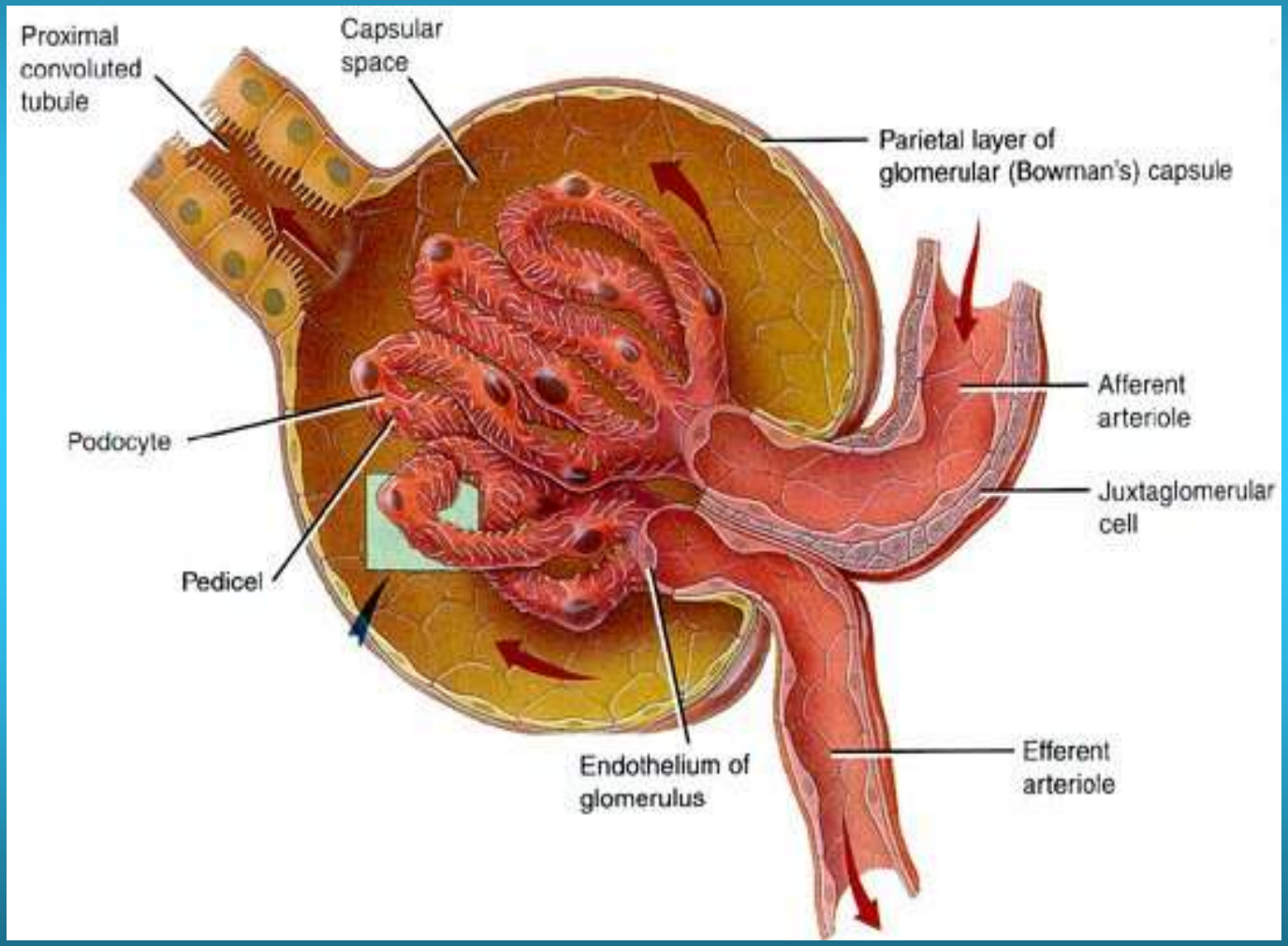
- The kidneys filter approximately 100mls/min, or 150 litres per day (the GFR).

- 99mls is reabsorbed in the nephron, so that only about 1ml/min finally passes into urine

The Nephron – glomerulus and renal tubule



The glomerulus – the filter



GFR – the measure of filtration

- **The GFR** - is a reflection of number of functioning nephrons and glomeruli and so a reflection of overall kidney function
- **Creatinine Clearance** - is a *measurement* of glomerular filtration rate
- **eGFR** - is an *estimate* of glomerular filtration rate
- **Creatinine** - is a *guide* to glomerular filtration rate

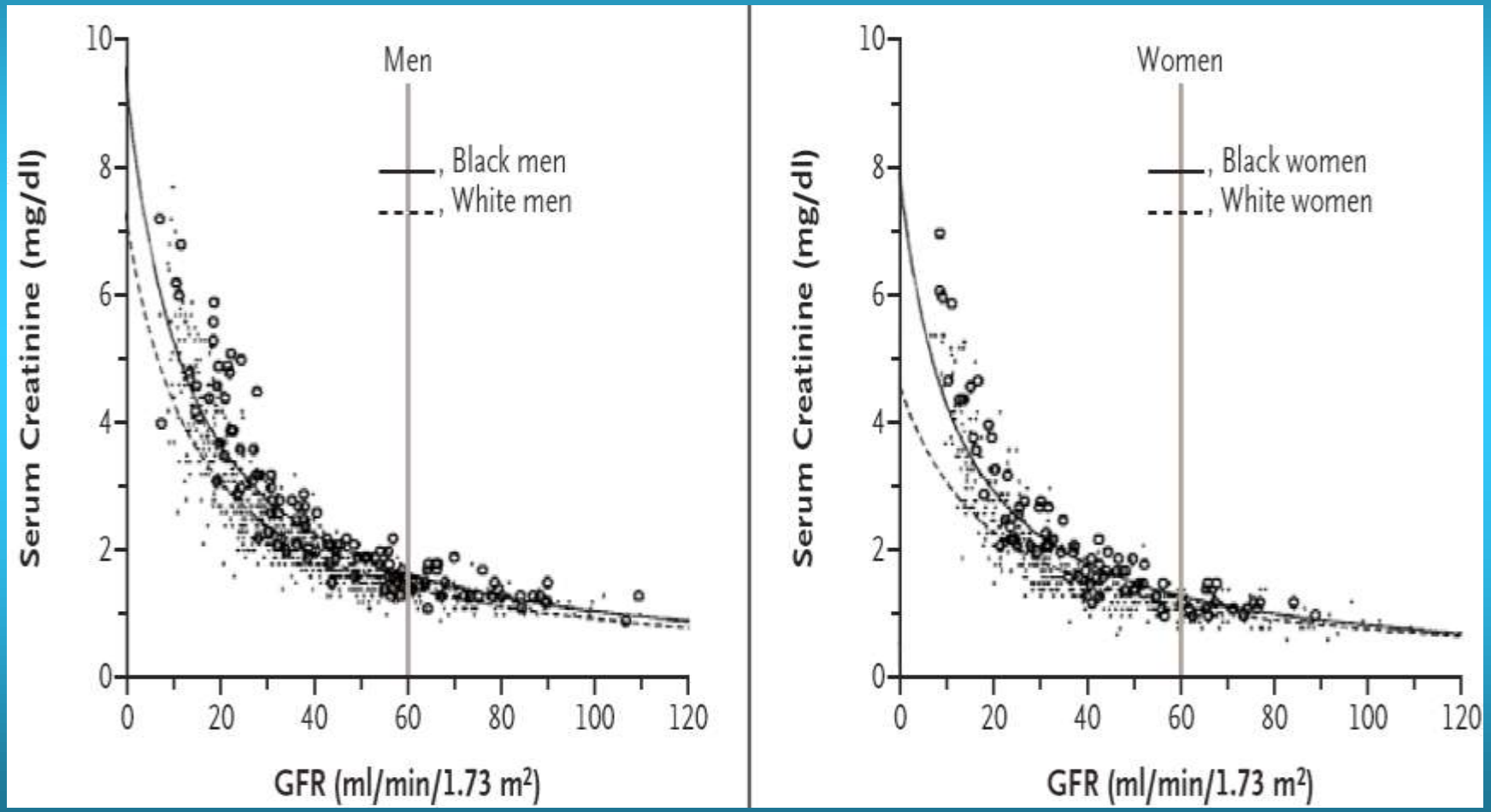
Measurement of Filtration ……

- Urea
  - a break down product of protein
  - affected by protein intake, fluid intake, diuretics and muscle breakdown in illness
- Creatinine
  - a metabolic by-product of muscle metabolism
  - affected by meat intake, muscle mass
  - age of sample

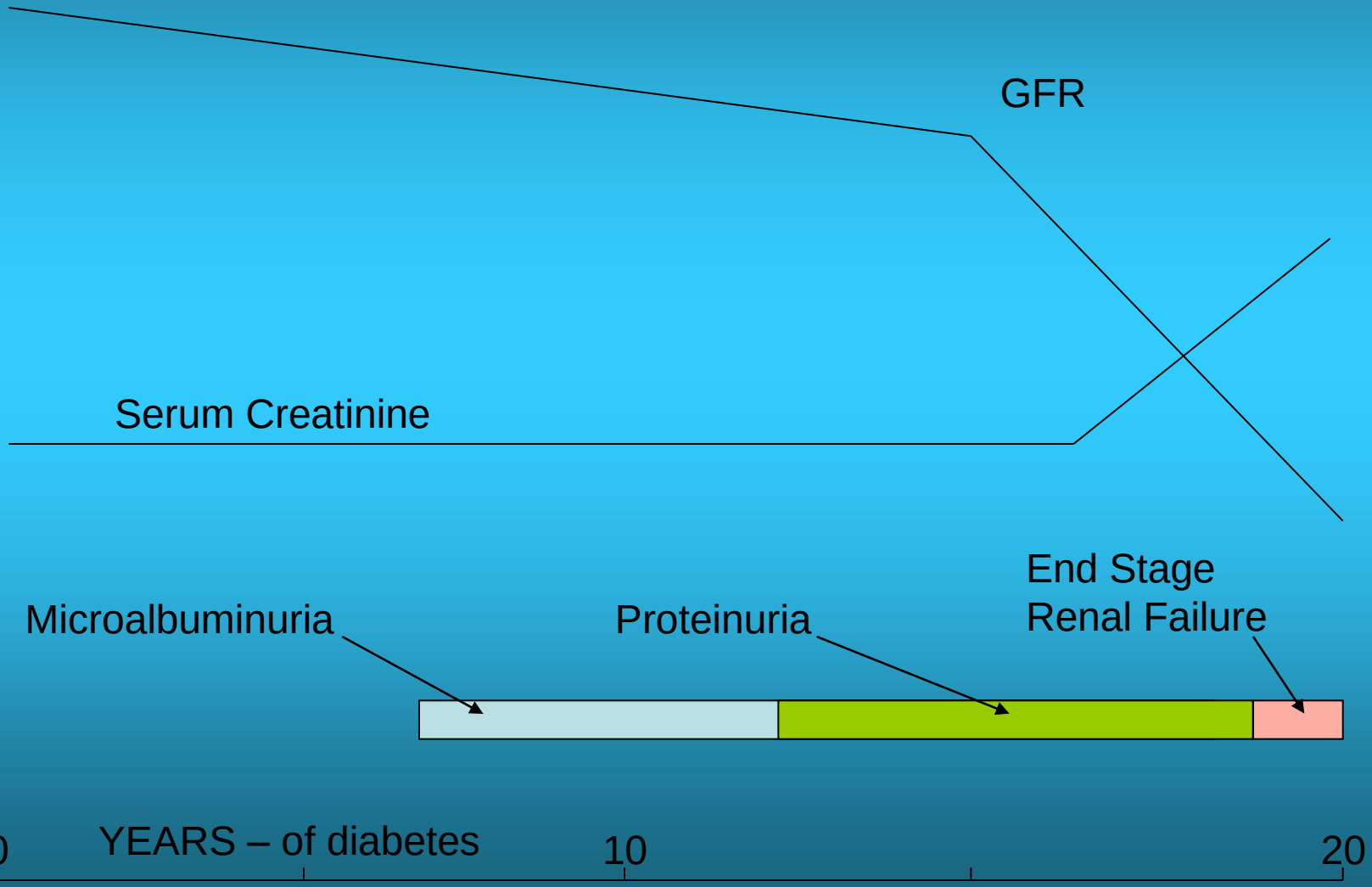
Creatinine measurement

- probably the most widely used guide to glomerular filtration rate
- easy and inexpensive to measure
- BUT very insensitive to even substantial declines in renal function
  - *glomerular filtration rate may be reduced by up to 50% before serum creatinine becomes elevated*

Relationship of GFR to creatinine



Relationship of creatinine, proteinuria and GFR



Factors affecting creatinine levels

Factor	Effect on Serum Creatinine
Aging	Decreased
Female sex	Decreased
Race or ethnic group†	
Black	Increased
Hispanic	Decreased
Asian	Decreased
Body habitus	
Muscular	Increased
Amputation	Decreased
Obesity	No change
Chronic illness	
Malnutrition, inflammation, deconditioning (e.g., cancer, severe cardiovascular disease, hospitalized patients)	Decreased
Neuromuscular diseases	Decreased
Diet	
Vegetarian diet	Decreased
Ingestion of cooked meat	Increased

Creatinine affected by build

Normal renal function
Creat 60

Normal renal function
Creat 120

So with all these factors affecting creatinine levels…….

Forget the idea of a normal range

Kidney disease?

Creatinine normal range 60-110

- Male age 20 – creatinine 140, nil else
- eGFR is over 60 so normal.

- Female age 60 – creatinine 90
- eGFR is LESS than 60 = CKD3!

And remember….

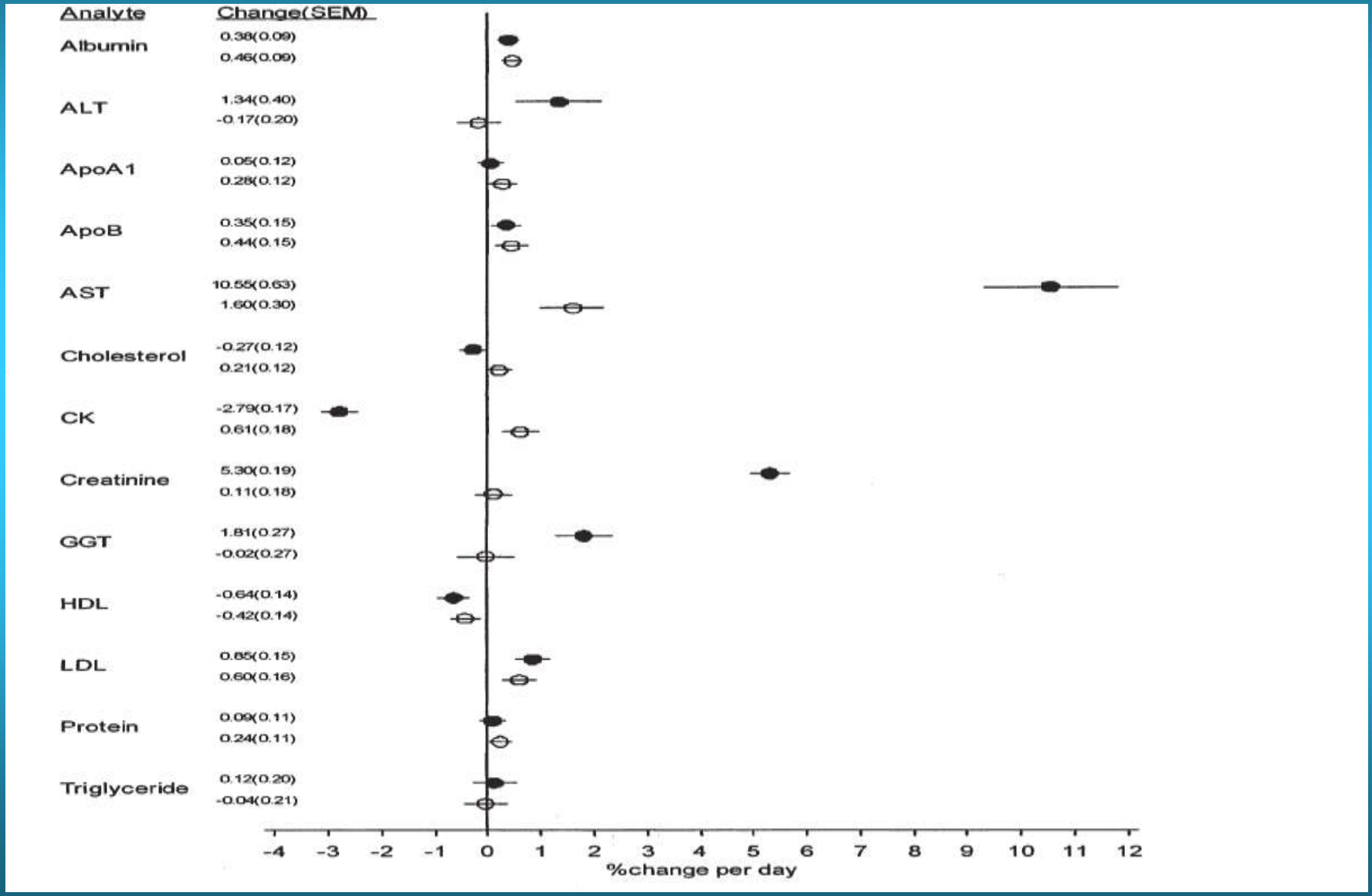
Creatinine level affected by TIME to analysis

Creatinine increases by approximately 5% per day of delay.

But not just creatinine……

% change after delayed testing

International Journal of Epidemiology 2003;**32**:125–130



How do we make the creatinine level more sensitive?

- Use it to calculate the Creatinine Clearance

- Use it to calculate the eGFR
  - by correcting for age, gender and weight
    - the Cockcroft Gault method
  - by correcting for age, gender and ethnicity
    - the MDRD method

eGFR calculation – the Cockroft Gault method

Cockcroft-Gault Calculator (with SI Units)

Plasma creatinine
mg/dL / umol/L

Weight
kilograms / pounds

Gender ☐ Male ☐ Female

Age

Creatinine Clearance

Cockcroft D, Gault MD. Nephron, 16:31-41, 1976

But the UK and USA use the MDRD calculator……

Using the four-variable MDRD, the eGFR (mL/min/1.73 m2) =

175 x [serum creatinine (umol/L) x 0.011312] -1.154 x

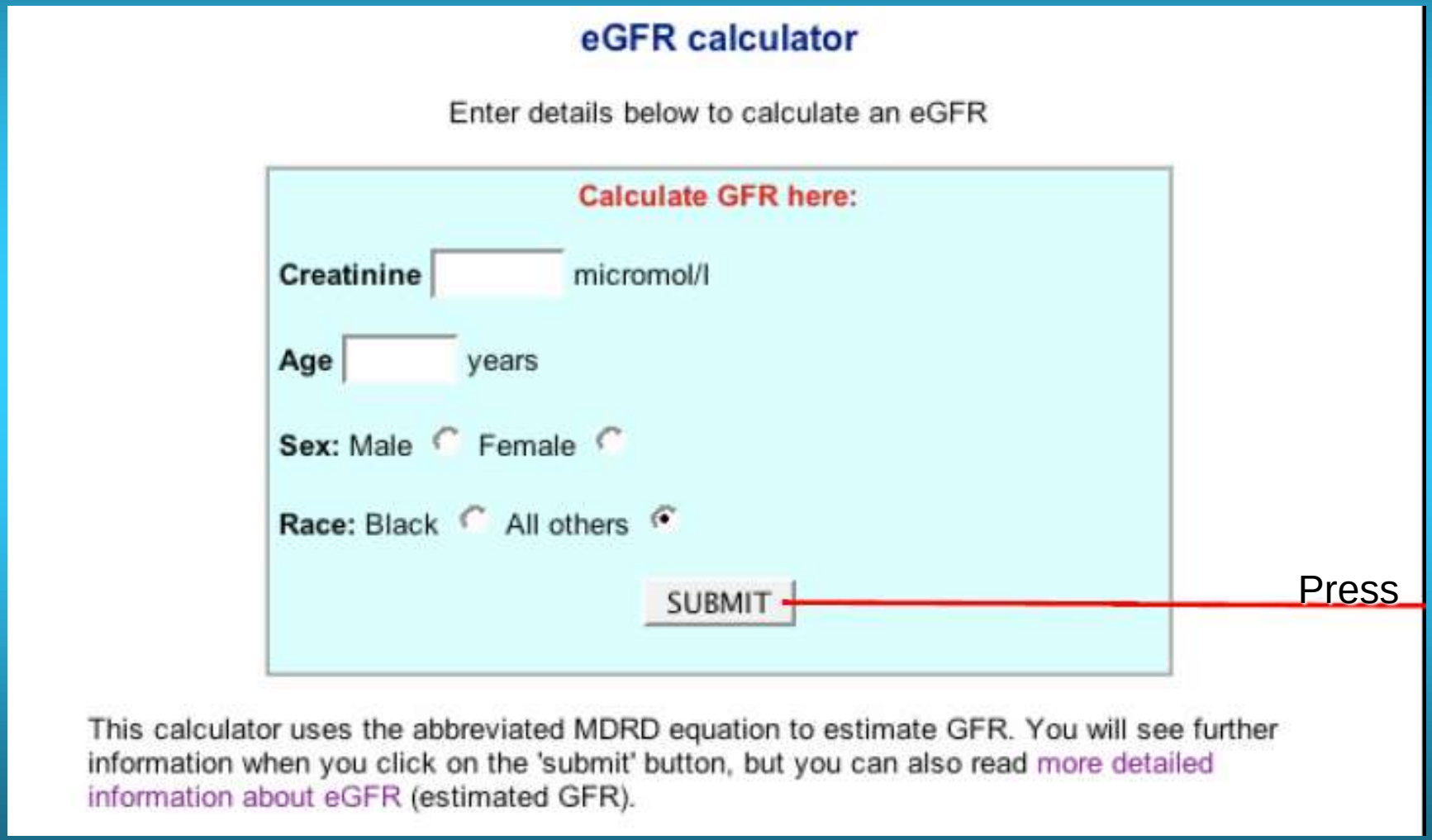
[age] - 0.203 x

[1.212 if black] x

[0.742 if female]

Got that?!

Online eGFR calculator



Estimated GFR problems

- **Accuracy** - even for the MDRD equation, which is the best there is, the confidence limits are wide. 90% of values are within 30% of the true value; 98% within 50%
- **Extremes** - none of the methods for estimating GFR are likely to be accurate in extreme examples of low muscle mass, or other unusual circumstances
- **Stability** - for all methods, creatinine must not be changing quickly
- **Systematic errors** - MDRD is better at low than at near normal GFRs
- **Age** - the MDRD should not be used in children.

So what is CKD?

- Chronic Kidney Disease
  - ***not so much a diagnosis; more a marker of the possibility or probability of an underlying chronic renal disorder***
- Developed by the National Kidney Foundation in the USA in 2000
- Now an internationally accepted standard
- Came to the forefront in the UK when incorporated in GP Quality Points framework in 2004

Prevalence levels of CKD

Stage	GFR (ml/min)	Number	Pop. prevalence
1	≥ 90	8,745	
2	60-89	25,323	
3	30-59	6884	4.2%
4	15-29	280	0.17%
5	<15	64	0.04%

Stevens et al, EDTA-ERA Lisbon 2004

eGFR – UK prevalence and guidelines

Stage	Description	GFR (mL/min/1.73m^2)	Pop'n prevalence (%)	Recommended Testing Frequency
1* remember these have to have urinary abnormalities to be classified as CKD	Kidney damage with normal or increased GFR	≥90	**3.3**	12 monthly testing, aspirin, statin, & BP control
2* remember these have to have urinary abnormalities to be classified as CKD	Kidney damage and mildly decreased GFR	60-89	**3.0**	12 monthly testing, aspirin, statin, & BP control
3	Moderately decreased GFR	30-59	**4.3**	6 Monthly testing, aspirin, statin, & BP control
4	Severely reduced GFR	15-29	**0.2**	3 Monthly testing, referral to hospital
5	Kidney failure (established renal failure)	<15	**0.2**	3 Monthly testing

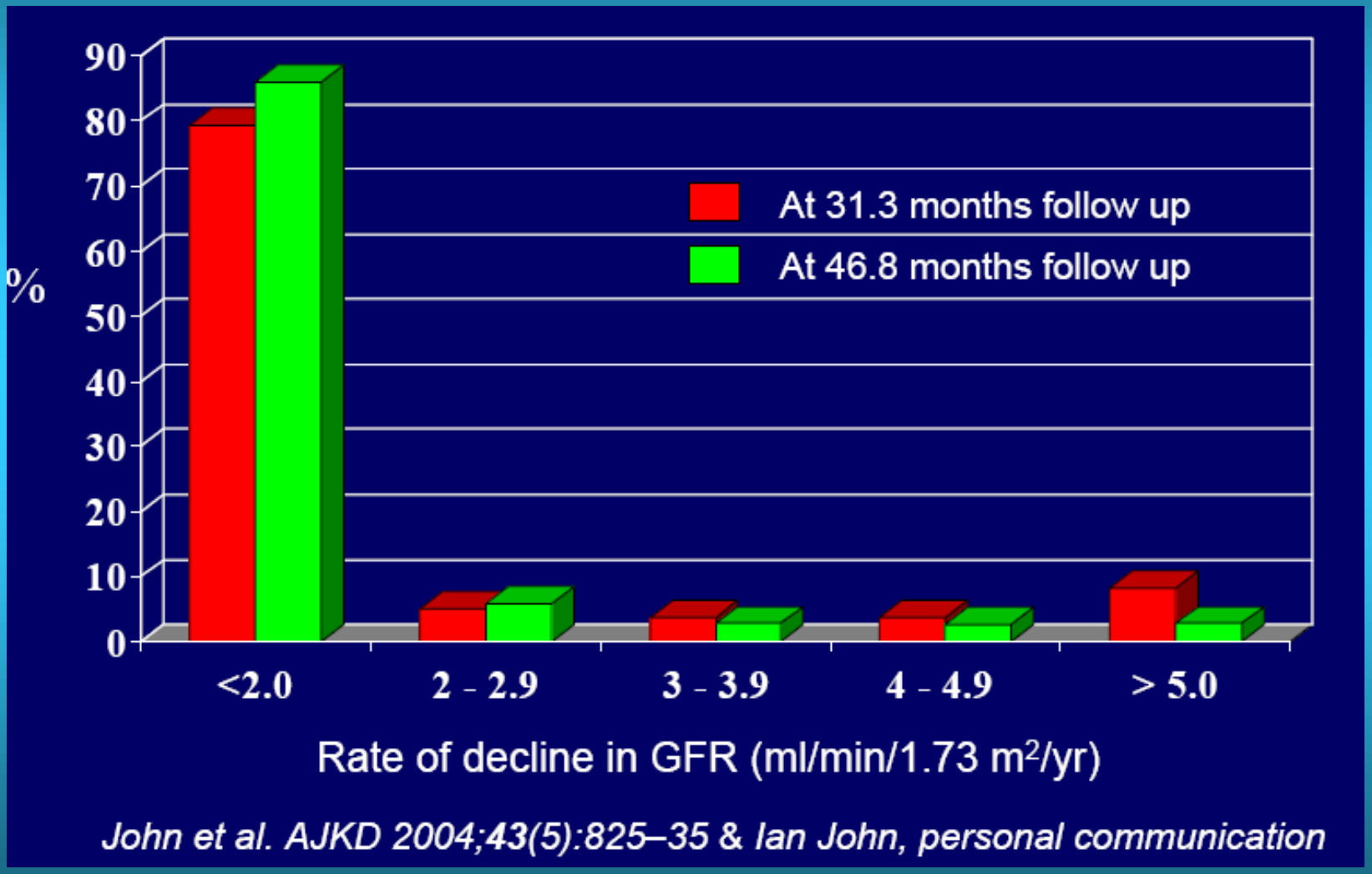
So why do we worry?

- Future renal failure
  - less important
- A marker for other risks
  - the main reason for concern

Impaired eGFR

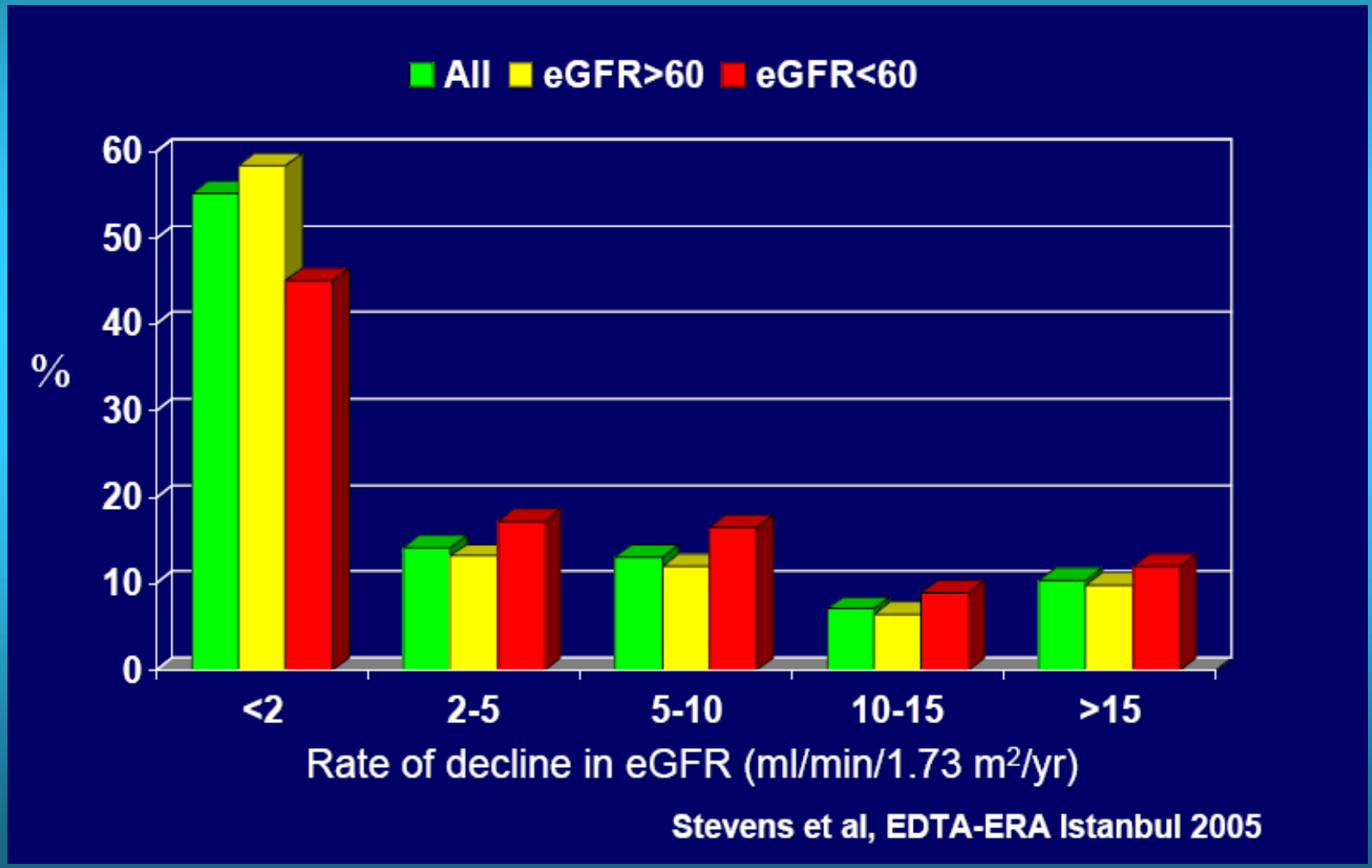
- Up to 10% population have reduced renal function
- Most are elderly and will not develop renal failure
- Dialysis usually starts when GFR <10 mls/min/1.73m^2

Rate decline of eGFR



*John et al. AJKD 2004;**43**(5):825–35 & Ian John, personal communication*

Reduction of eGFR related to starting position



Deterioration of eGFR

Most people 1-2 mls/min… per year

4-5 mls/min….year - RED FLAG

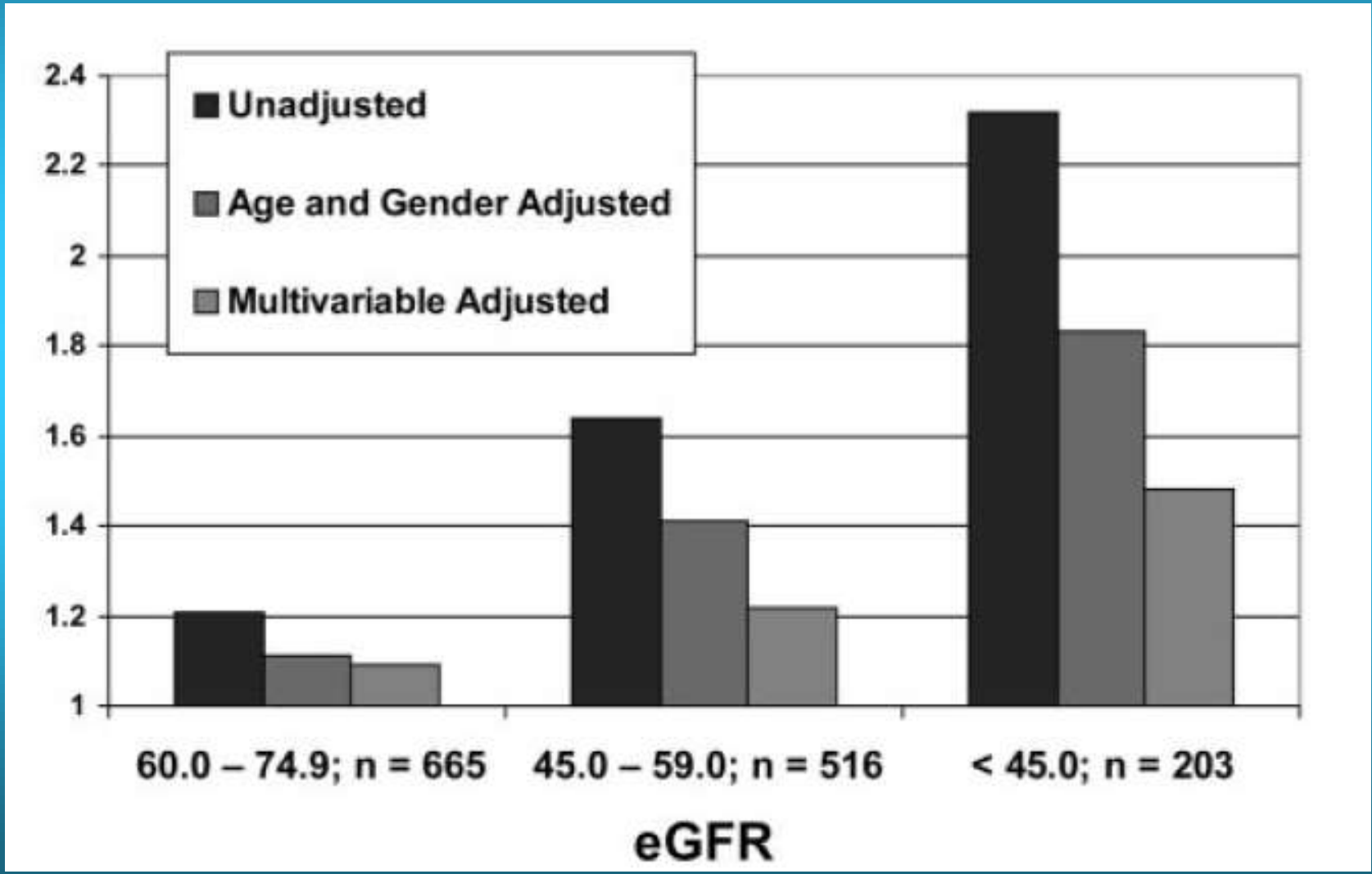
For renal failure

BUT.....

eGFR is also a marker for Vascular Risk

Yes another!

CV risk with eGFR



US study 1

Go et al reported on 1.1 million ambulatory adults in a US healthcare system.

eGFR	Risk Death	CV event	Hospitalisation
45-59	1.2	1.4	1.1
30-44	1.8	2	1.5
15-29	3.2	2.8	2.1
<15	5.9	3.4	3.1

Relative to those with an eGFR of >60 mls/min/1.73m2

Go et al 2

eGFR mls/min/1.73m^2	Age standardised rates for cardiovascular events per 100 person years
>60	2.11
45-59	3.56
30-44	11.29
15-29	21.80
<15	36.6

A cardiovascular event was defined as hospitalization for coronary heart disease, heart failure, ischemic stroke, and peripheral arterial disease

The Veterans Administration

O’Hare - 2.5 million people aged 18-100

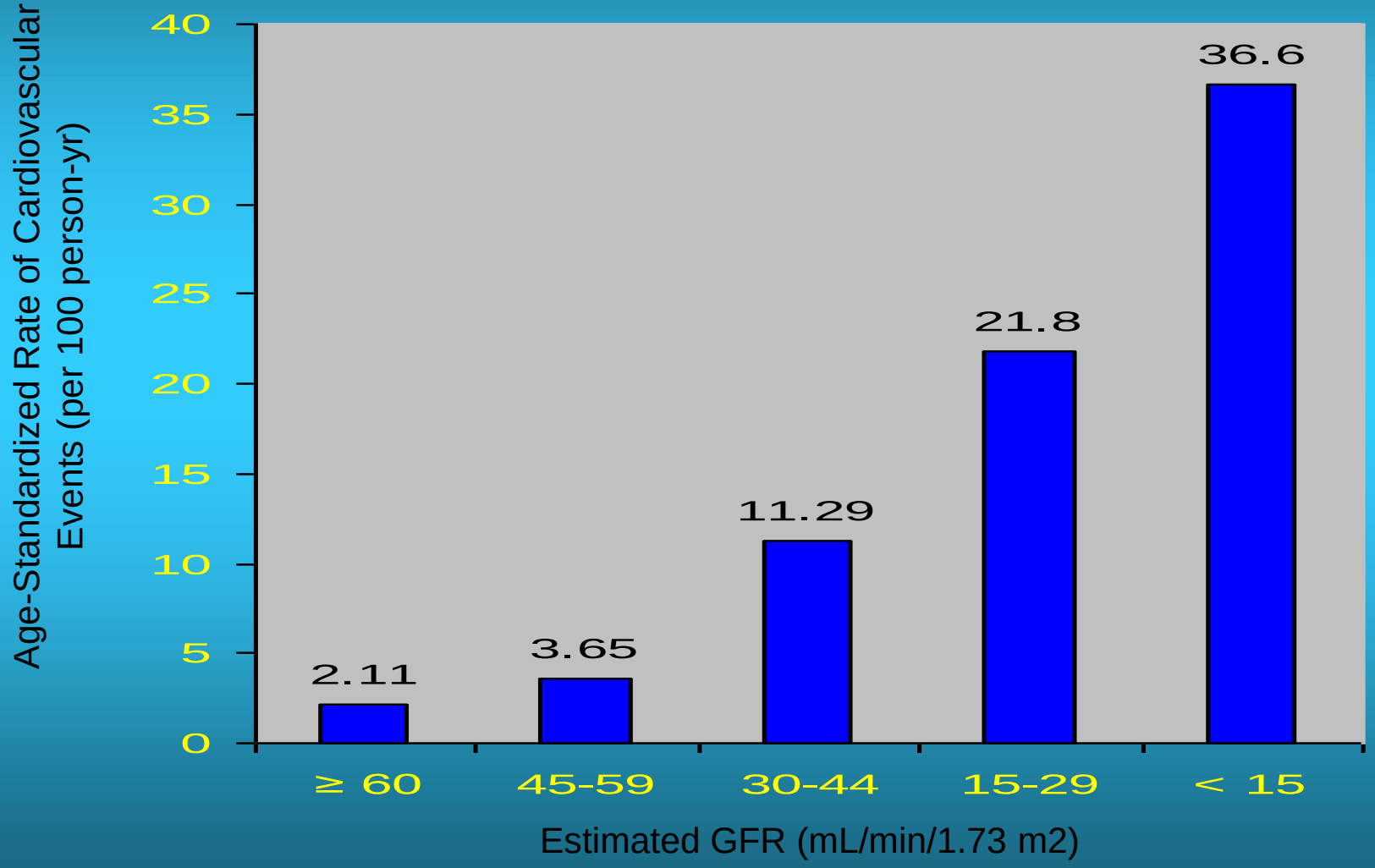
- a single measurement of reduced eGFR was associated with increased mortality for any cause.
- relative risk was higher with greater reduction in eGFR and at younger ages.

West of Ireland study

1600 patients with CV disease

For every 10 ml decrement in estimated GFR there was a corresponding 20% increase in hazard of the cardiovascular composite endpoint and a 33% increase in hazard of death from any cause.

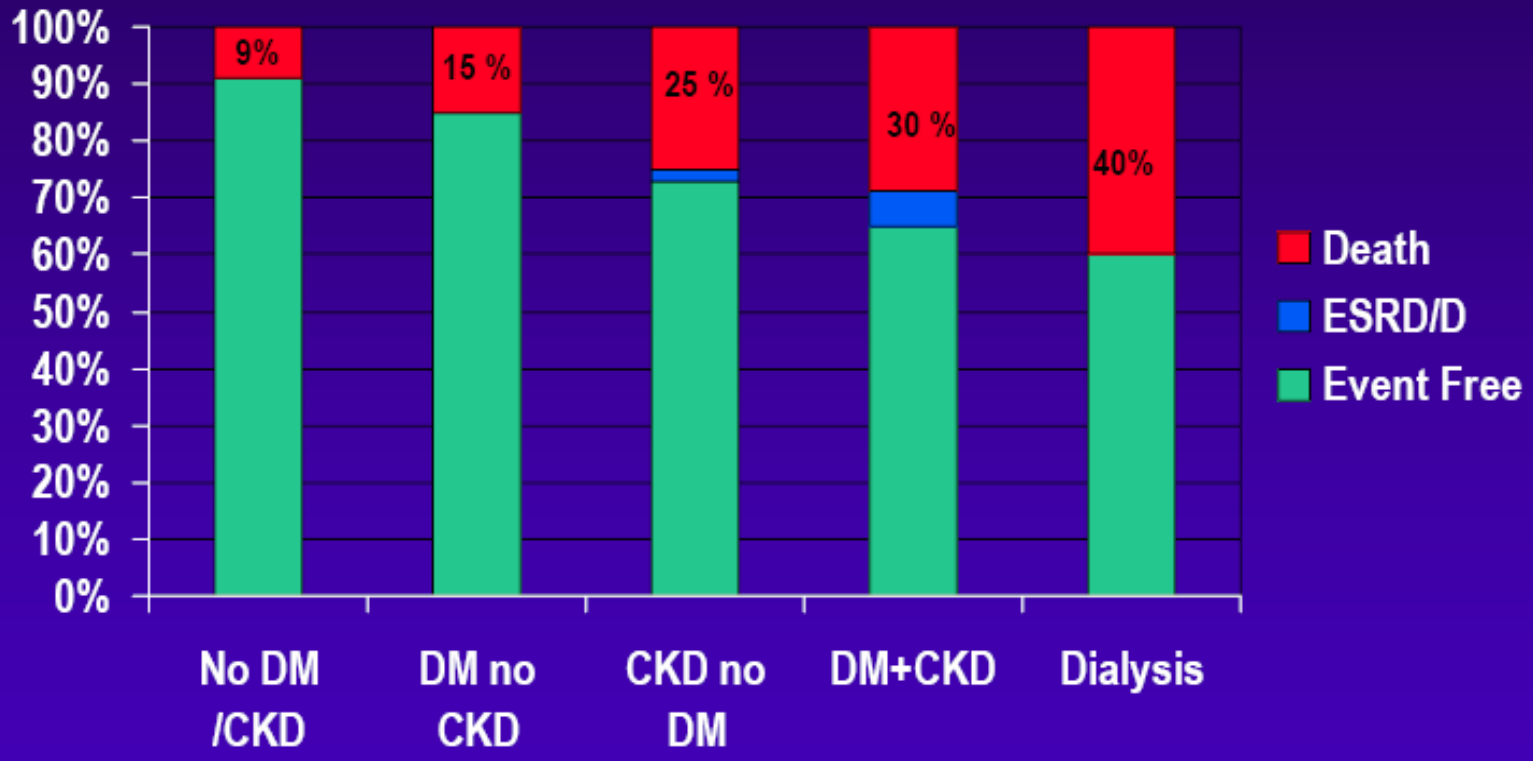
CKD Predicts CVD



And more.....

- SNHNES survey
  - Those with eGFR <70 had 68% extra risk of death, 57% extra risk of CV death compared with those with eGFR >90
- Arteriosclerosis Risk in Communities Study
  - eGFR of 15-59 had 38% extra CV risk compared with those with eGFR >90

Patients with CKD are more likely to die than go onto dialysis



Adapted from Collins, Adv Studies in Med, (3C) 2003, Medicare Cohort 1998-99

So, CKD is not a disease but a significant Cardio-Vascular Risk Factor.

So why ?

- Reduced eGFR is associated with.....
  - Increased inflammatory markers
  - Abnormal Lipoproteins
  - Increased homocysteine
  - Increased coagulability
  - Anaemia
  - LVH
  - Arterial calcification
  - Arterial stiffness
- But no-one really knows

A few tips……

If there is a diagnosed kidney disease, rate for that first

Then consider the impact of the eGFR on CV risk.

If you have one renal abnormality, look for others

If you have one significant CV risk factor, look for others

- so if there is hypertension, check for cholesterol, smoking etc, but also eGFR, urinalysis etc
- consider client's age and SA to help decide whether to obtain missing info
- risk of significant underlying kidney disease more likely in young with eGFR <60 but impact of low eGFR on CV risk is also higher

Don’t be influenced by normal ranges for creatinine

- be very ready to use the eGFR calculator esp if lowish BMI, older, female.
- ***don’t get mugged by the little old lady!***

A few more tips……

- If you have several creatinines with no clear trend, take the average
- If you are given the eGFR by the GP, use that

Summary

- CKD is important
- Not simply an indicator of possible renal disease
- So especially in older people do not get hung up on the fear of renal failure
- Instead remember……..

CKD

is an important marker for increased risk of Cardiovascular Disease

Thank you

Grading of urinary protein concentration

- Life Guide now contains several versions
  - under Chronic Interstitial Nephritis

    "Mild: 1+ (21 - 65 mg/dl; 31 - 99 mg/mmol Cr; 301 - 999 mg/g Cr)"
  - under Chronic Glomerulonephritis

    "2+ (≥ 135mg/dl or 2g/24hrs)"
  - under Proteinuria

    this is the most comprehensive guide to grading the degree of proteinuria

Urinary protein concentration and approximate equivalents and clinical correlates

	Dipstick reading	Urine protein: creatinine ratio, mg/mmol (urine protein mg/L)	Urine total protein excretion, mg/24 h (g/24 h)	Urinary albumin: creatinine ratio, mg/mmol	Urinary albumin excretion, µg/min (mg/24 h)
Normal	Negative	<15 (<100)	<150 (<0.150)	<2.5 (males), <3.5 (females)	<20 (<30)
Microalbuminuria	Negative	<15 (<100)	<150 (<0.150)	≥2.5–30 (males),	20–200
'Trace' protein	Trace	15–44 (100–299)	150–449 (0.150–0.449)	≥3.5–30 (females)	(30–300)
Clinical proteinuria ('macro-albuminuria')	1+	45–149 (300–999)	450–1499 (0.450–1.499)	>30	>200 (>300)
	2+	150–449 (1000-2999)	1500–4499 (1.500–4.499)		
Nephrotic range proteinuria	3+	≥450 (3000)	≥4500 (4.500)		