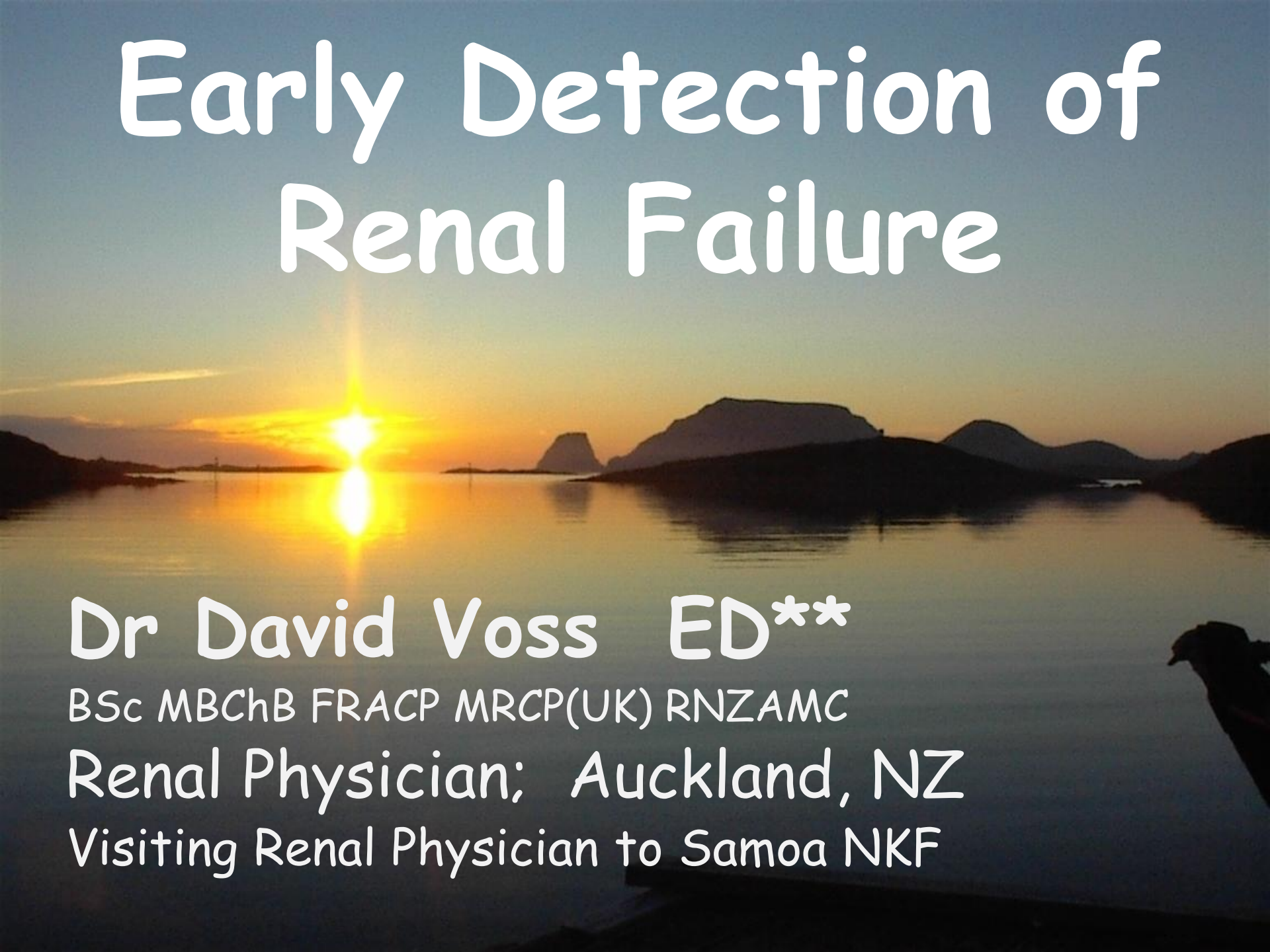
Early Detection of Renal Failure



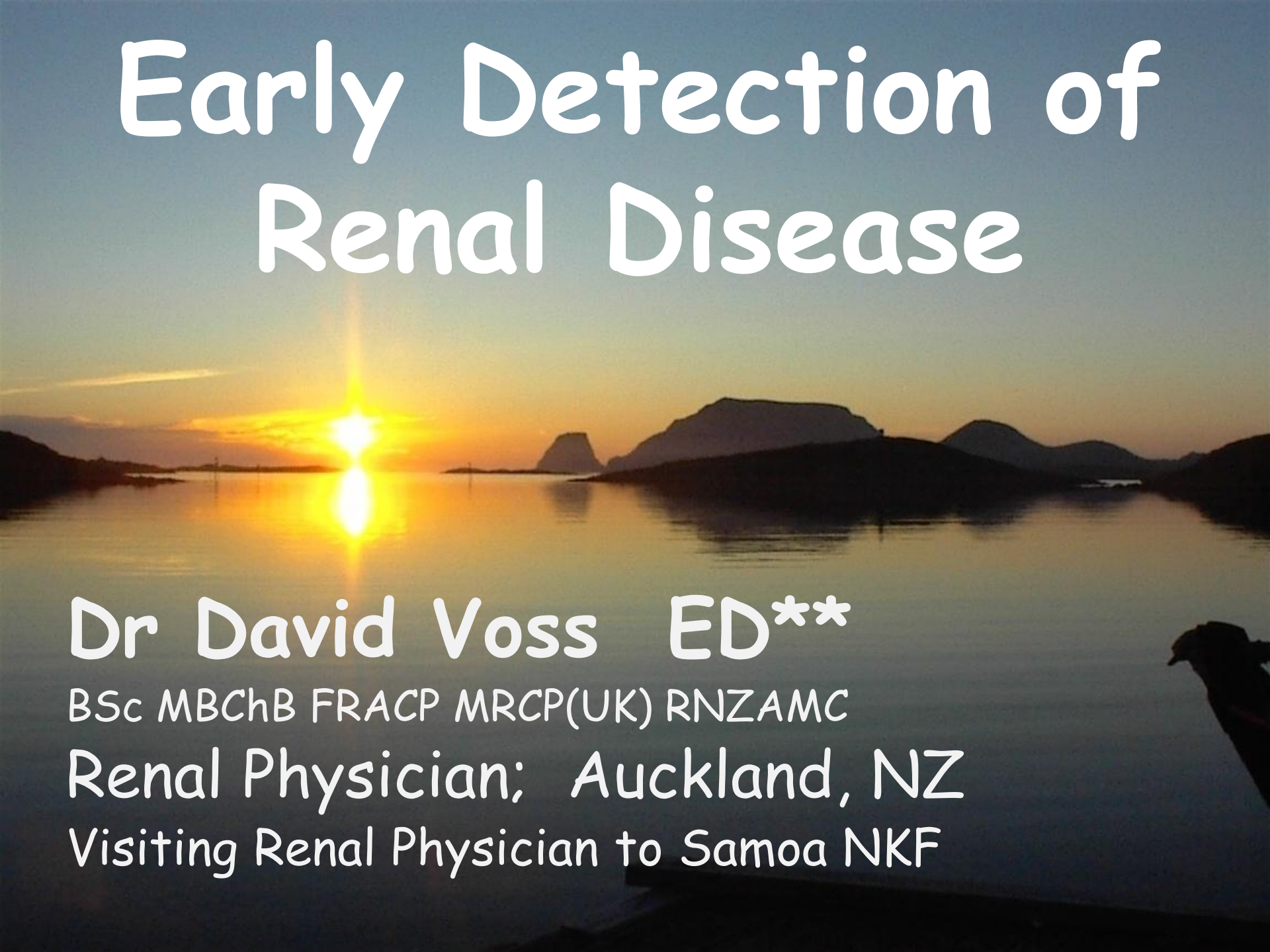
Dr David Voss ED**

BSc MBChB FRACP MRCP(UK) RNZAMC

Renal Physician; Auckland, NZ

Visiting Renal Physician to Samoa NKF

Early Detection of Renal Disease



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Summary

- Early detection
  - Essentially to avoid progression
  - “cost effective”
- Screening for renal involvement/disease
  - History, medications (illicit, OTCs), BP
  - Renal function: electrolytes; urea; creatinine; eGFR
  - MSU: proteinuria; WBC, RBC
    - Casts, specific gravity
  - Quantify proteinuria
    - ACR or PCR

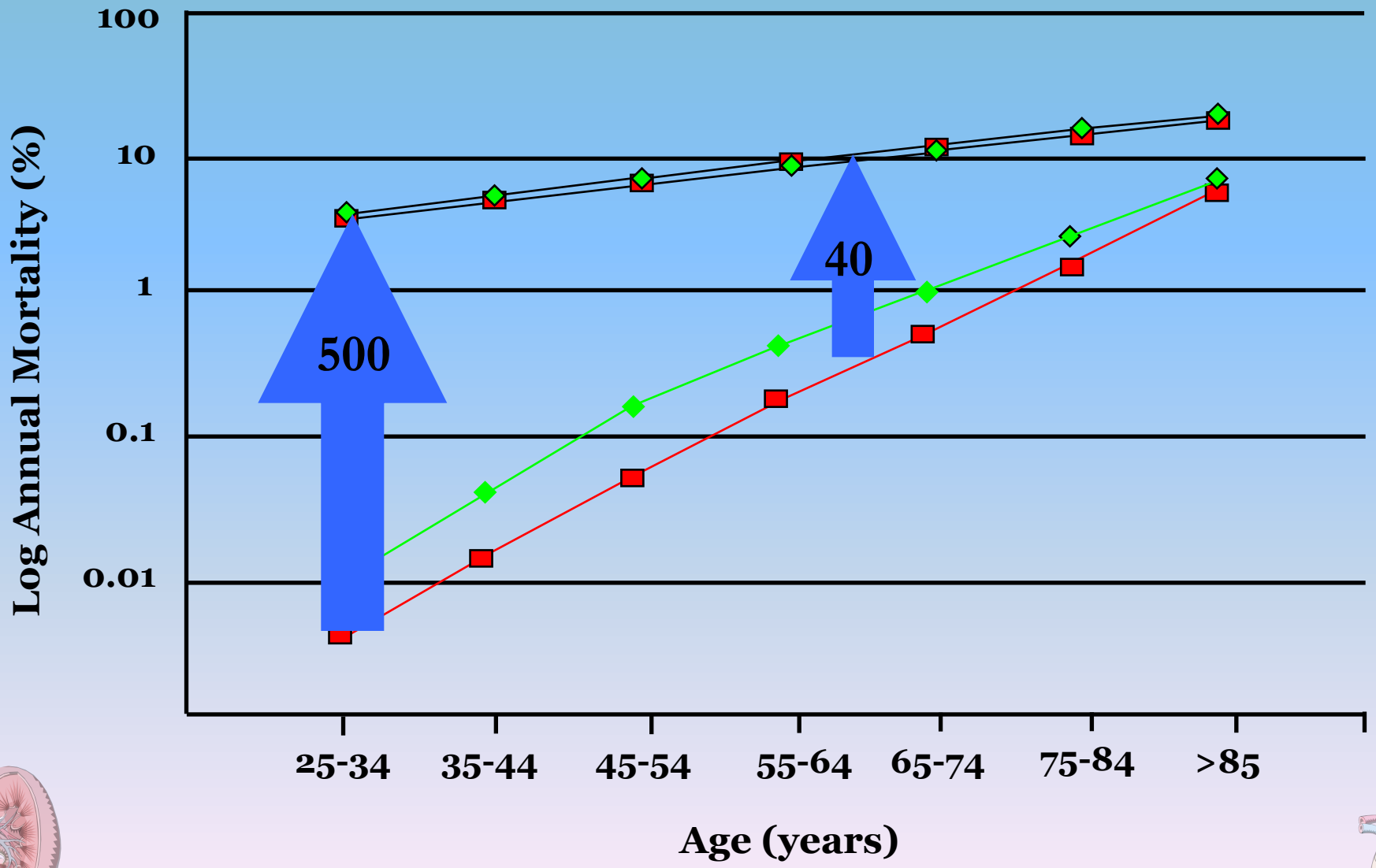
Summary

- Goal BP
  - <160/90mmHg in non-renal disease
  - 130/80 in CKD and proteinuria
  - ?140/80 in CKD
  - 125/75 in DM with DN (CKD and proteinuria)
- Minimise proteinuria
  - ACEi; ARB
  - non-dihydropyridine CCB
  - spironolactone
- Avoid nephrotoxins

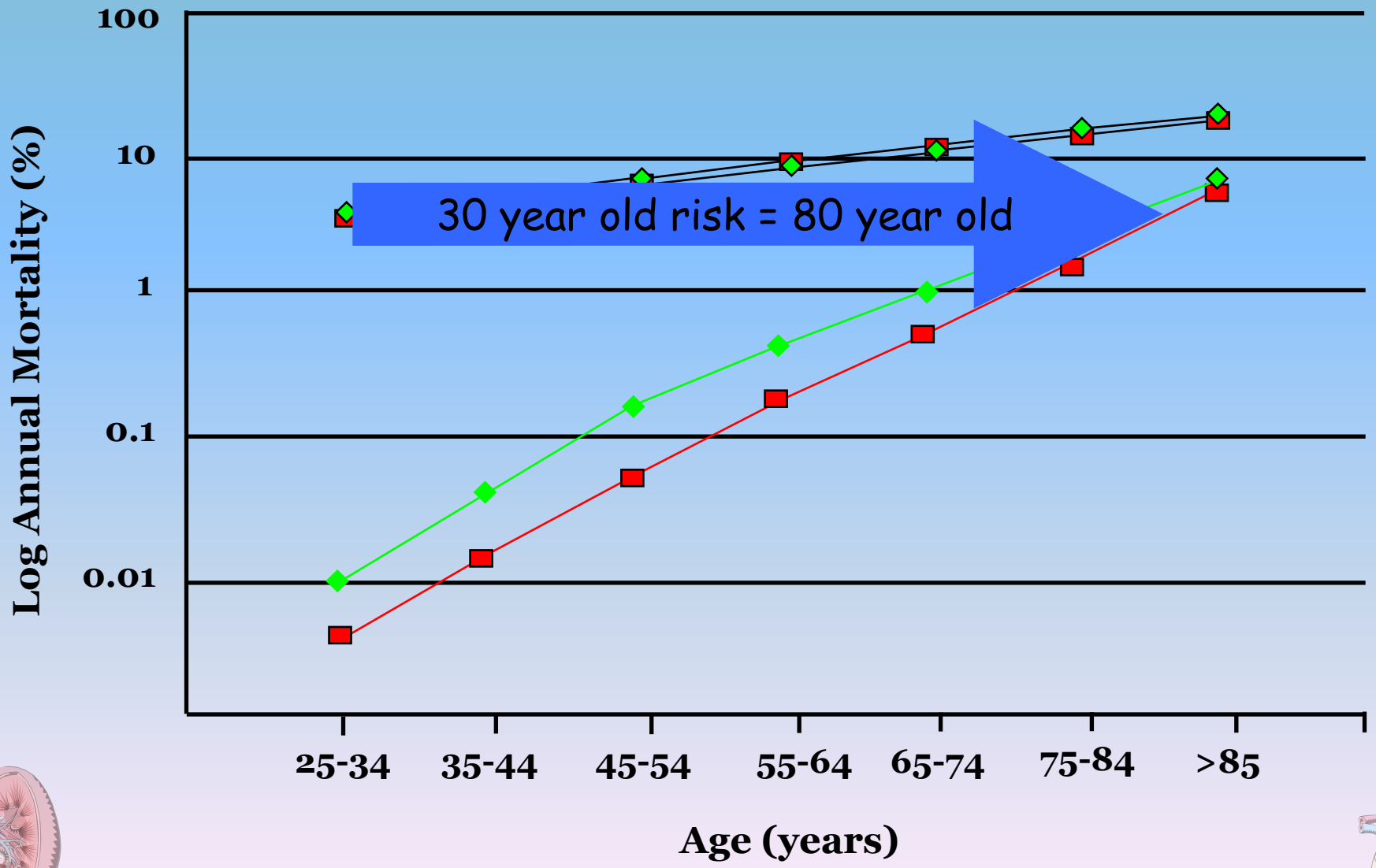
CKD categories

- CKD1 – eGFR > 90ml/min/1.73m² BSA
- CKD2 – eGFR 60-89ml/min/1.73m² BSA
- CKD3 – eGFR 30-59ml/min/1.73m² BSA
  - CKD3A = 45-59
  - CKD3B = 30-45
- CKD4 – eGFR 15-29ml/min/1.73m² BSA
- CKD5 – eGFR <15ml/min/1.73m² BSA
- NOT ALONE:
  - Presence of other potential renal issues

Heart Disease in Haemodialysis Patients



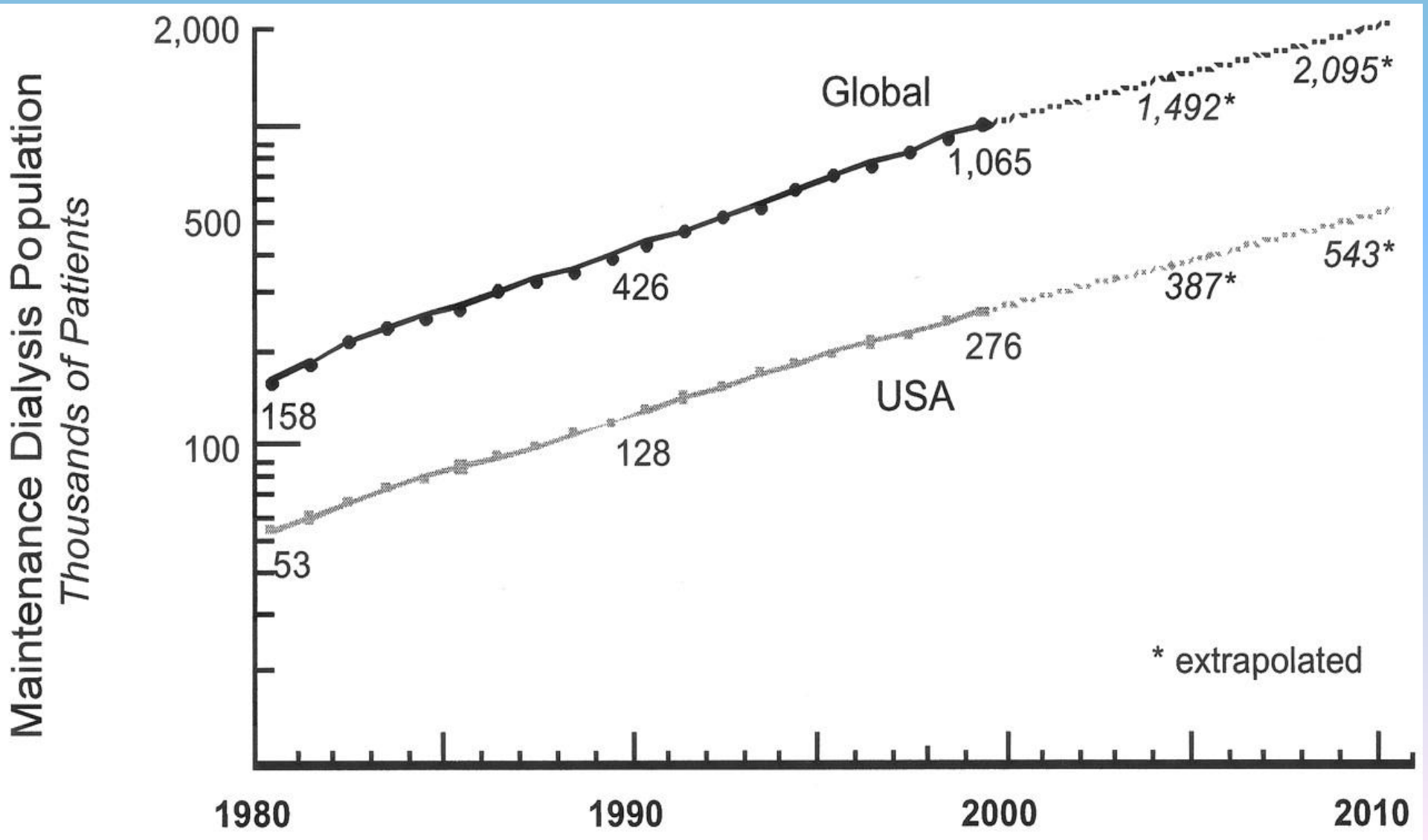
Heart Disease in Haemodialysis Patients



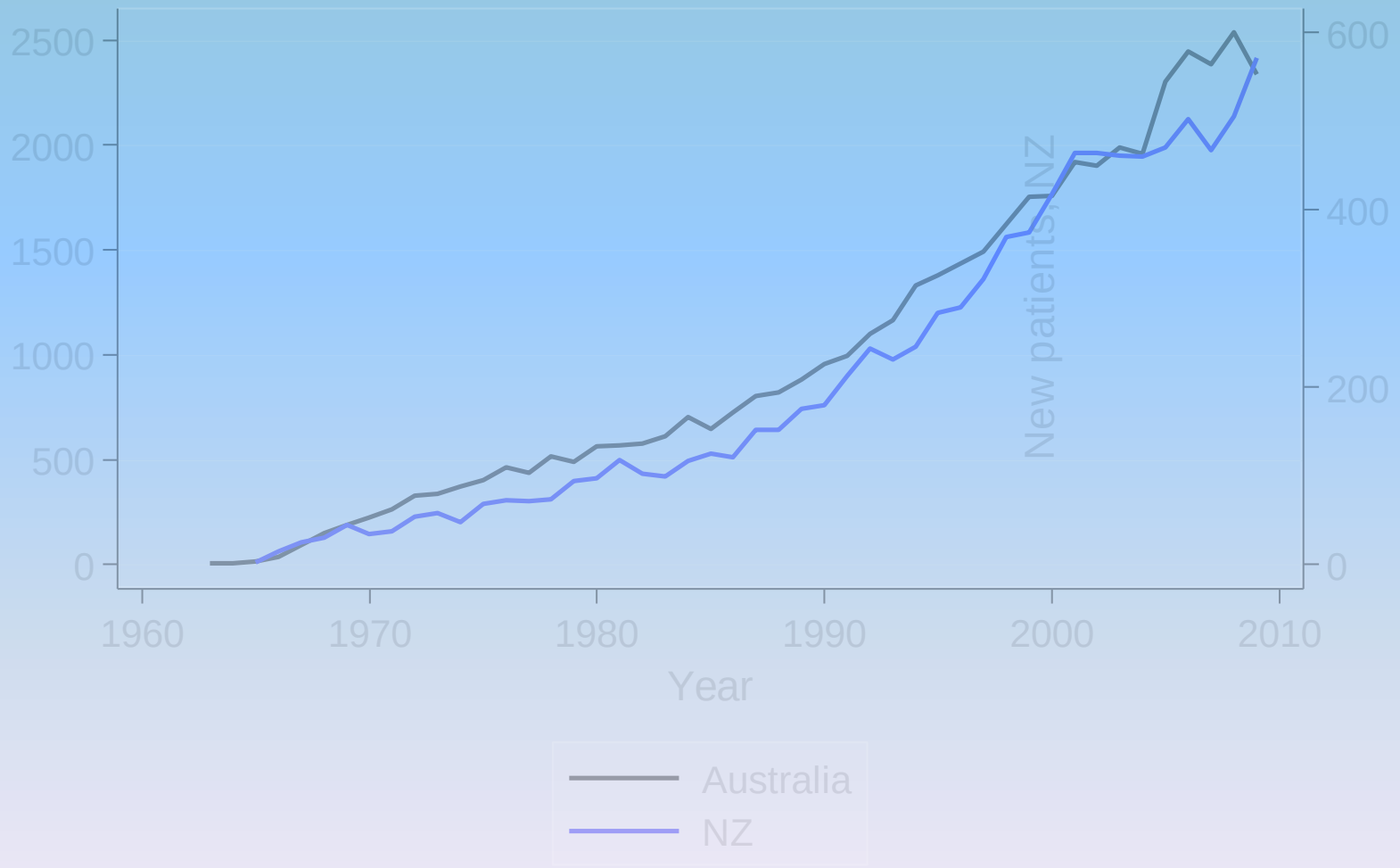
Protective Potential

- Decline in GFR
  - Hypertension control
  - Minimisation of proteinuria
  - Avoidance of nephrotoxins
  - Other renal damage – trauma, stones, ?pyelonephritis
- Monitor for renal dysfunction
  - depends upon expected rate of progression

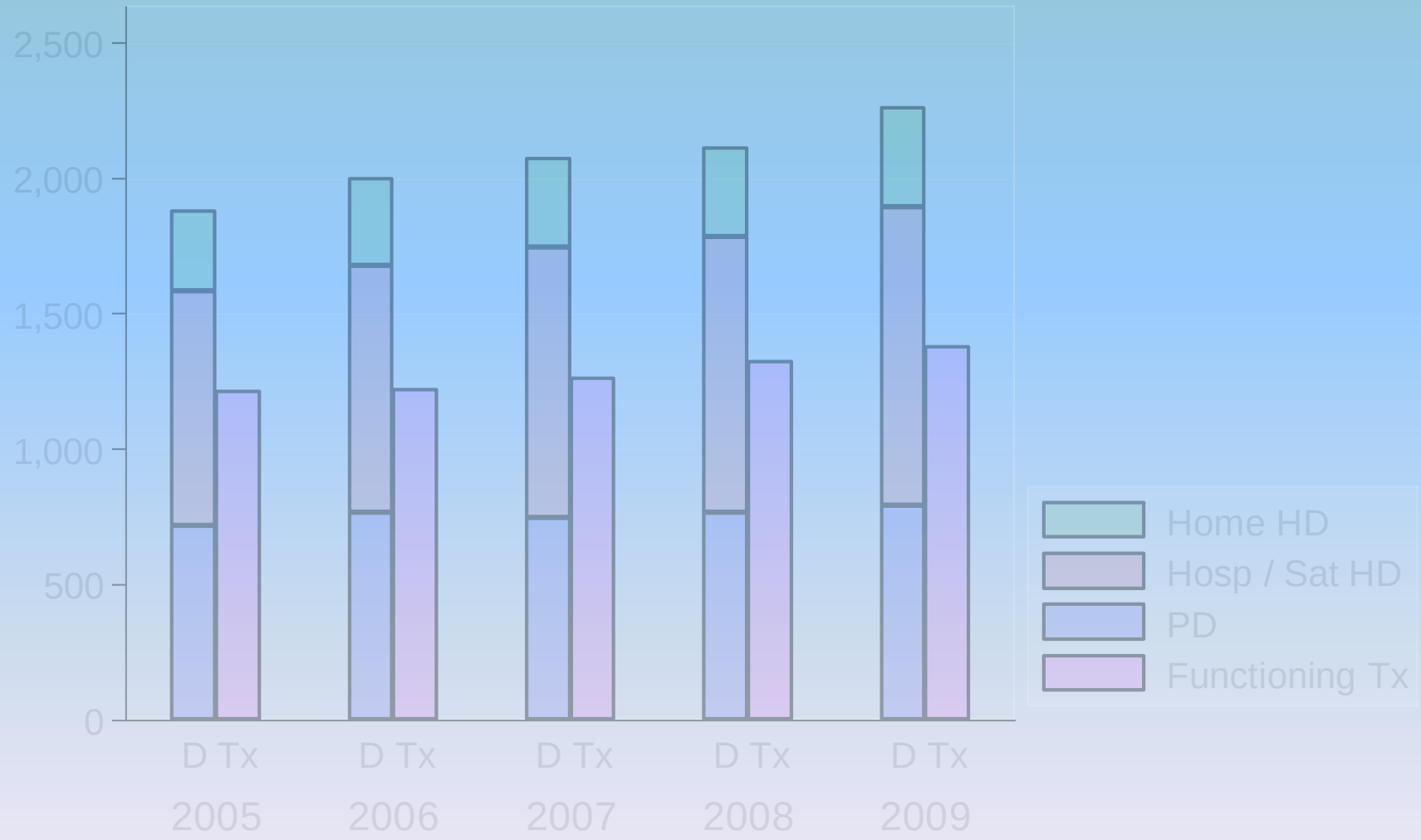
Dialysis numbers growth



New Patients
Australia and New Zealand



Prevalent Dialysis and Transplant New Zealand (at 31 December)



Prevent what?

- Renal failure - ESRF
- Partial renal damage - CKD
  - How bad is temporary damage?
- Avoid complications of renal failure
  - Pharmaceuticals dose adjustments
  - Acid-base; anaemia; cardiovascular; endocrine; nutrition; neurological; musculoskeletal…

Cardiovascular risk

CKD / CAD and death rates

- Medicare (US) – 2 year follow-up (*n*=1,000,000)
  - 22,000 CKD without DM
    - 1.6% required RRT
    - 17.7% died
    - 30.7% had heart failure
  - 16,000 CKD + DM
    - 3.4% required RRT
    - 19.9% died
    - 52.5% had heart failure

CKD / CAD and death rates

- Longitudinal follow-up of 30,000 patients with eGFR < 90ml/min/1.73m² BSA (= CKD2-5); followed for 5 years….risk of RRT and death:
  - CKD 2 1.1% 19.5%
  - CKD 3 1.3% 24.3%
  - CKD 4 19.9% 45.7%
- Those who died had more of:
  - Coronary artery disease; heart failure; diabetes mellitus; anaemia

CKD / CAD and death rates

- 12,000 older patients with DM:
  - 48% had DN (defined as CKD 3-5; or proteinuria)
  - @ 3 years mortality rates:
    - Normal RF 5%
    - CKD 2 6%
    - CKD 3 10%
    - CKD 4 20%
    - CKD5 30%
  - *Cf.* need for RRT <1% (CKD2); 14% (CKD4)

CKD / CAD and death rates

- Nat Health and Nutrition Examination Survey cardiovascular death rate:
  - eGFR > 90 4.1 deaths per 1000 person-year
    - (CKD1)
  - eGFR 70-89 8.6 deaths per 1000 person-year
  - eGFR <70 20.5 deaths per 1000 person-year
    - (CKD2)

CKD / CAD and death rates

- CKD is a risk factor for IHD
  - Risk of cardiac death > 10 fold
  - Risk of heart failure > 20 fold
  - Death rate increases with severity of CKD
    - 2-18 fold (mortality at better renal function)
      - CKD 2 (1:7-17.7); CKD4 (1:2.1-2.3)

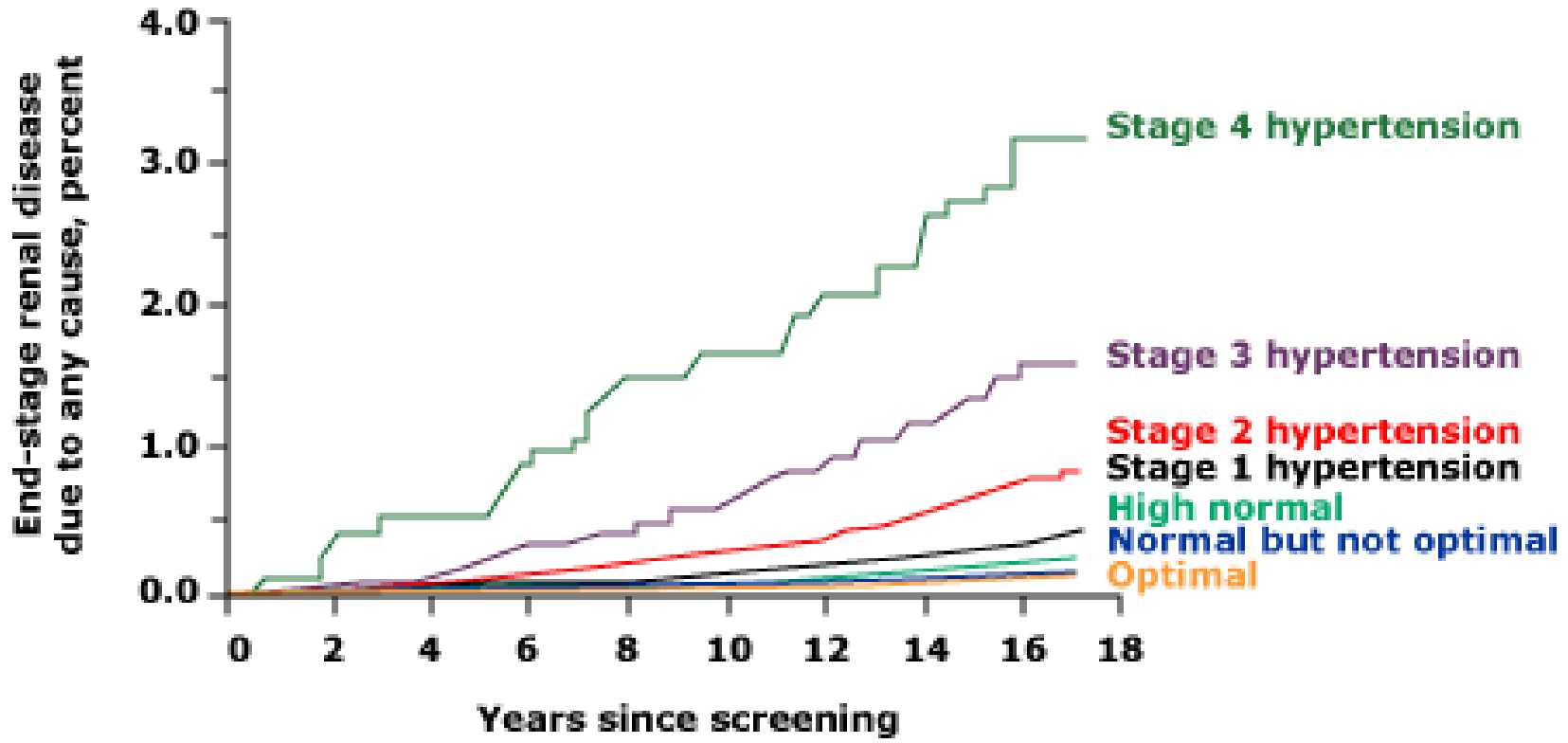
- More likely to die from CVD than end up with RRT
- Risk of IHD is higher in CKD

Overall cardiac risk - summary

- Absolute risk of CV events in CKD alone is about half that of patients with pre-existing heart disease and **without** CKD
- Risk increases with progressive CKD and/or proteinuria
  - Pragmatically CKD is eGFR < 60ml/min/1.73m^2
  - And proteinuria >1g/24 hours
    - ~PCR 80-100 or ACR 50-60mg/mmol (g/mol)

Hypertension

Risk of ESRD and hypertension



Hypertension in CKD

- Causes/factors
  - Reduced sodium clearance
  - Increased renin-angiotensin system activity
  - 2º hyperparathyroidism -> hypercalcaemia -> vasoconstriction
  - Increased sympathetic activity
  - Low erythropoietin levels
  - Higher central pulse pressure, “stiff vessels”; and isolated systolic hypertension

Hypertension in CKD

- Goal of 130/80mmHg or below
  - Requires 3 or more drugs
  - Include:
    - ACE and/or ARB
      - In combination hyperkalaemia is limiting factor
    - Diuretic – loop +/- chlorthalidone
      - In combination with Na^+ restriction diet (<100mmol)
    - CCB – diltiazem or verapamil
      - Not dihydropyridines by choice - but are OK to use
    - 4^{th} agent…spironolactone (K^+)

Hypertension

- Non-diabetics with CKD with proteinuria (>500mg/24 hrs; ~ PCR 30-50)
  - Goal BP is < 130/80mmHg reduces progression of CKD and maybe mortality
- Non-proteinuric patients
  - JURY STILL OUT (no evidence yet)
    - ?<140/90; or ?130/80 (maybe the later since CKD is a CVD risk factor)

Hypertension in CKD

- Diabetes mellitus
  - With proteinuria (and therefore assume DN)
  - Goal BP <125/75mmHg

Proteinuria

Proteinuria

- Meta-analysis of general population cohort: *n*=105,872 (ACR) , plus *n*=1,128,310 (dipstick proteinuria); mean follow-up of 7.9 years (*cf*. a group with mean eGFR of 95)
  - Hazard ratios for all cause mortality
    - eGFR 60 1.18 (CI 1.05-1.32)
    - eGFR 45 1.57 (CI 1.39-1.78)
    - eGFR 15 3.14 (CI 2.30-4.13)

Other proteinuria evidence

- Presence of proteinuria alone -> RR of cardiovascular event = 1.3
- Nat Health and Nutrition Examination Survey cardiovascular death rate (unadjusted):
  - Proteinuria <30 6.2 deaths / 1000 person-yr
  - Proteinuria 30-299 17.9 deaths / 1000 person-yr
  - Proteinuria >300 37.2 deaths / 1000 person-yr
- When adjusted:
  - Relative hazard 1.57 (30-299 cf. <30 cohort)
  - Relative hazard 1.8 (>300 cf. <30 cohort)

Microalbuminuria

- Associated with LV dysfunction; stroke; MI
- Doubles mortality in DM
  - Especially in type I DM
- Indicator of inflammation
  - Within renal tissue
  - Endothelium

Dietary salt and proteinuria?

- Anti-proteinuria effects of ACE reduced with high salt diet in NON-DIABETICS
- Therefore in the non-diabetic with proteinuria
  - With good BP (systolic < 130mmHg)
  - Should have sodium restricted diet
    - 24 hour urine Na < 100mmol.

So what do we do in clinical practice?

Osler Principles to Renal Medicine

- Look
  - Skin
    - Rashes
    - Vasculitis
    - CT diseases
  - Anaemia
  - Fundi
  - Oedema

Osler Principles to Renal Medicine

- Feel
  - Pulses
    - asymmetry
  - Cardiac
    - Apex
    - Thrust/heave
  - Oedema; ascites
  - Bladder
  - Prostate

Osler Principles to Renal Medicine

- Listen
  - BP
    - Lying and standing
    - Both arms
  - Murmurs
  - Bruits

Osler Principles to Renal Medicine

- Smell
  - Foetor breath
    - Ammonia
  - Acidosis
  - Urine (incontinence)
- Taste

Investigation internal medicine

- Asymptomatic
  - Down to your last 10% of renal function before symptoms
  - Renal disease symptoms are NON specific
- Laboratory testing
  - Blood
  - MSU
  - Proteinuria - PCR vs ACR
- Radiology testing
  - USS

Kidney Disease – AKI model

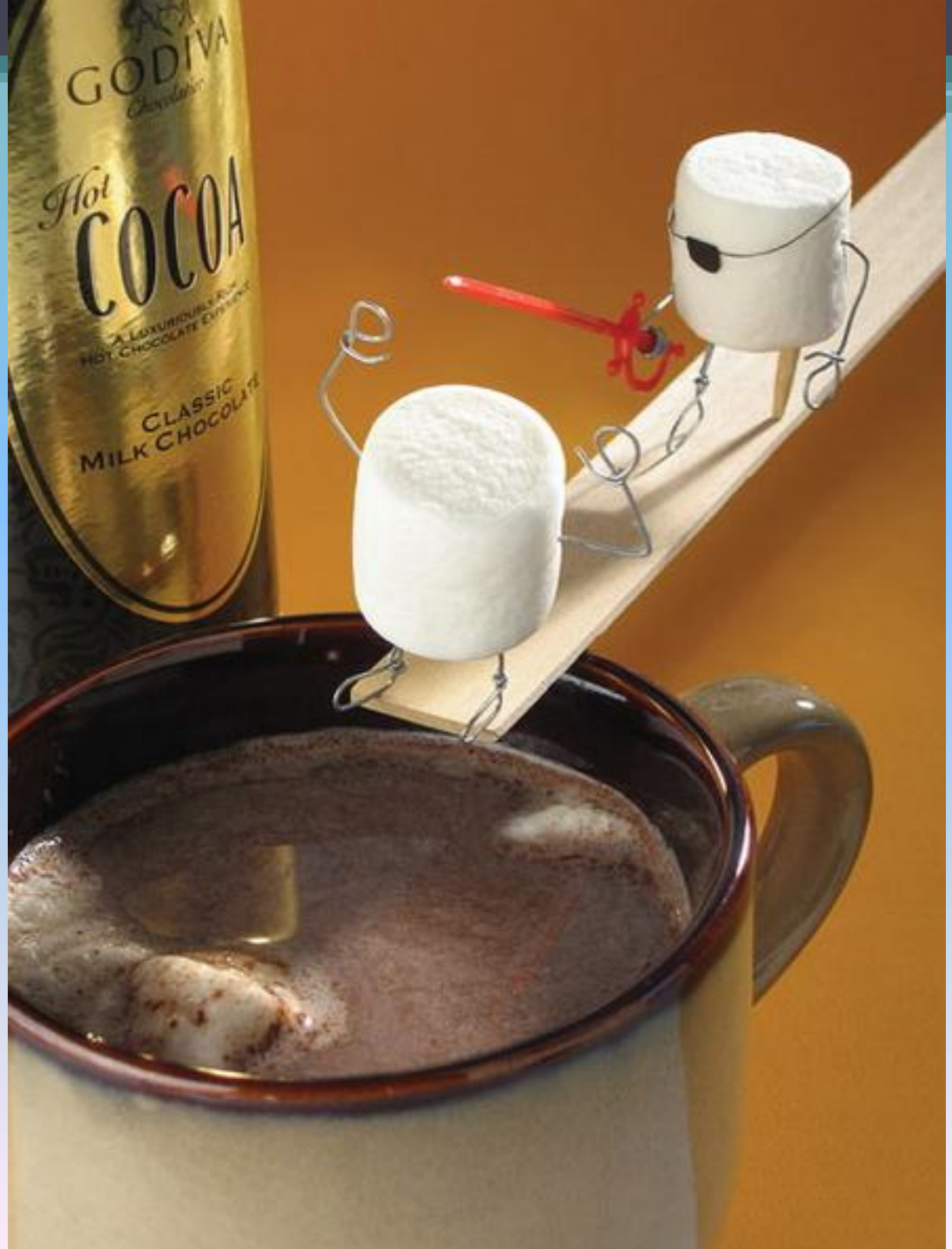
- Pre-renal
  - BP, vascular/PVD, vasculitis
- Post-renal
  - Obstruction
  - USS
  - Rarely functional – DTPA
- Renal
  - Everything else
  - Laboratory and radiology investigation

Monitoring

- How often?
  - Depends upon progression rates (annual)
    - DM2 – 10-12ml/min/1.73m² BSA
      - 3 monthly diabetes care programme
    - Gn – 1-2ml/min/1.73m² BSA
    - Body rot – 0.5-1ml/min/1.73m² BSA

Nephrotoxins

- PPI
  - Class effect
- NSAIDs
  - COX-2 is no different


GODIVA
Hot
COCOA
A LUXURIOUSLY RICH
HOT CHOCOLATE EXPERIENCE
CLASSIC
MILK CHOCOLATE

Summary

- Early detection
  - Essentially to avoid progression
- Screening for renal involvement/disease
  - History, medications (illicit, OTCs), BP
  - Renal function: electrolytes; urea; creatinine; eGFR
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  - non-dihydropyridine CCB
  - spironolactone
- Avoid nephrotoxins

Nephrotoxins

Nephrotoxins

- Present as….

- Interstitial nephritis picture
  - Sterile pyuria
- May have proteinuria
- May have impaired renal function
  - Acutely or chronically

Avoiding Nephrotoxins

- Common toxins
  - Lithium.
  - Some chemotherapeutic agents.
  - NSAIDs; COX-2 inhibitors
  - Allopurinol.
  - H_2 / proton pump blockers – omeprazole, pantoprazole, lansoprazole, etc.
  - OTC/herbals.
  - Fibrates.
  - Quinolone antibiotics (uncommon)

Nephrotoxins

- Chinese herbals:
  - Aristolochic acid (Guan Xin Su He)
  - NSAID (Sang Ju Gan Mao Pian)
  - NSAID (Yen Qiao Jie Du Pian)
  - NSAID (tung Shueh pills)
  - Others: Guan Mu Tong; Dahuong Qingwei, Daochi, Fenqing Wulin, Longdon Xiegan pills; Xiaoer Jindan tablets.

Nephrotoxins

- Glycyrrhiza
  - Fanconi syndrome
- Noni juice
  - Hyperkalaemia and diuretic
- Cat' claw (*Uncaria tomentosa*)
  - AKI
- *Taxus celebica*
  - AKI, haemolysis

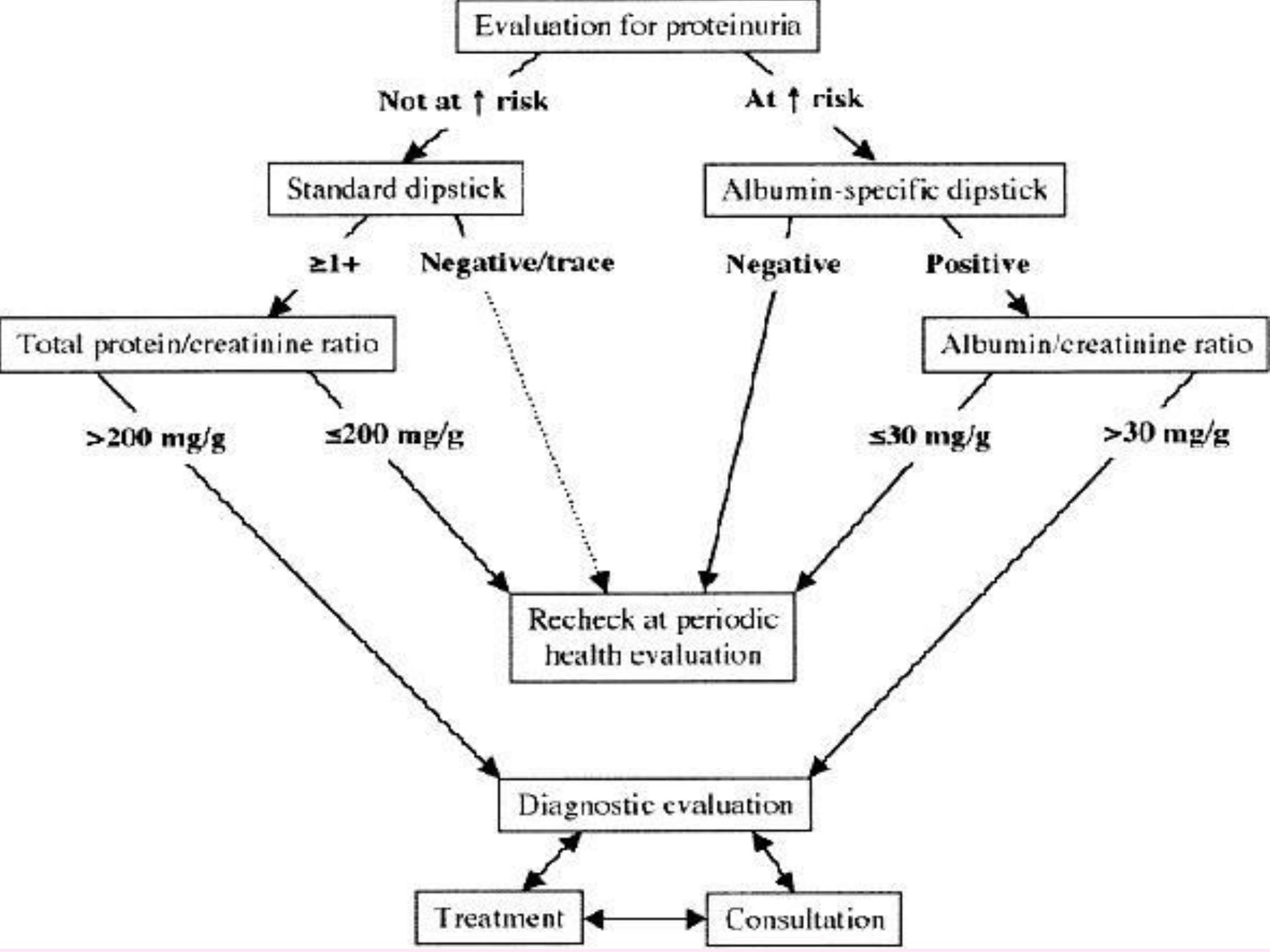
Nephrotoxins

- Salicin
  - Willow bark
- Sorrel (*Rumex acetosa*)
  - Oxalosis, kidney stones
- Essiac (*Ulvis spp*)
  - Oxalosis, kidney stones
- Peppermint oil
  - Interstitial nephritis
- St John's wort
  - Interstitial nephritis

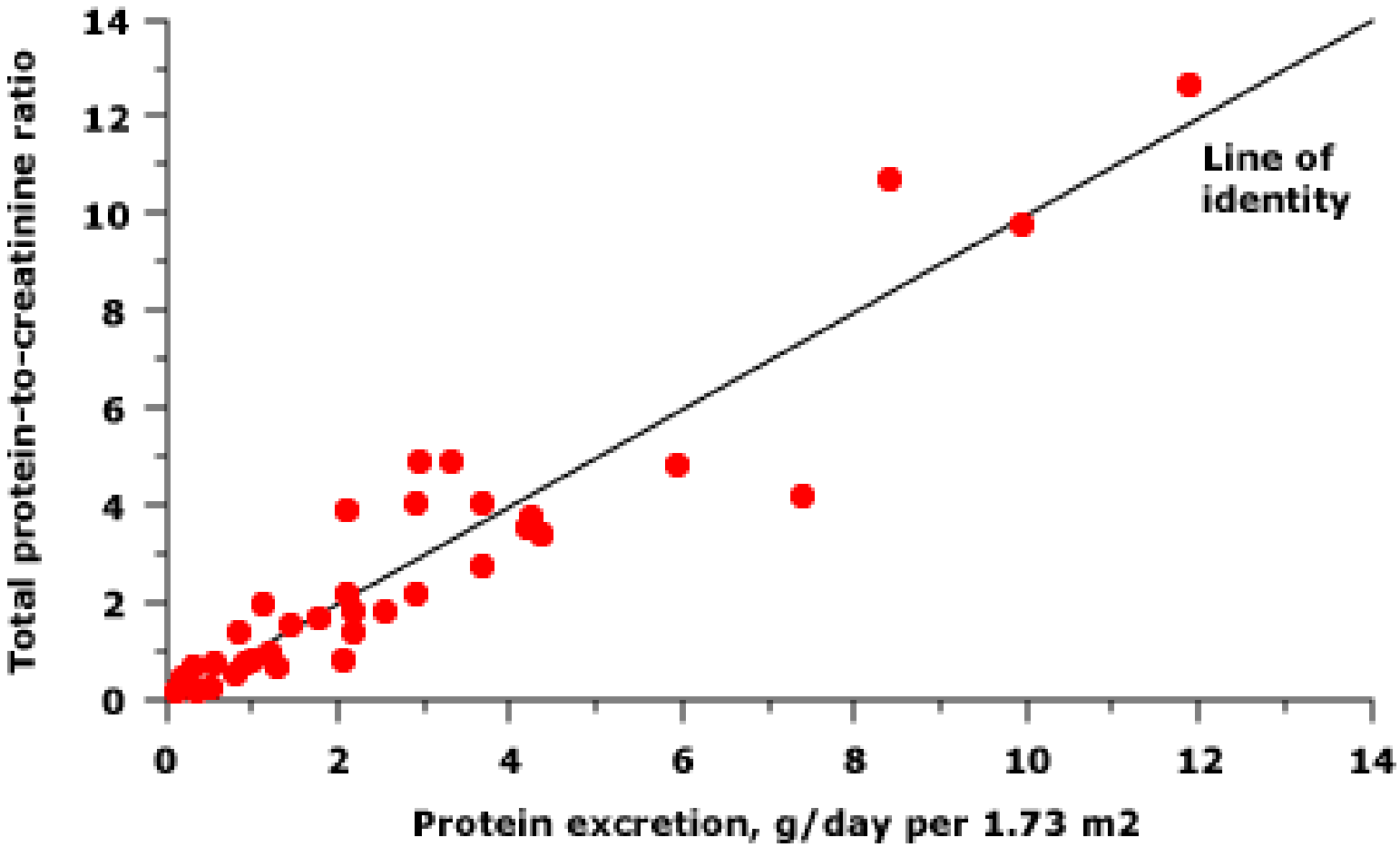
Nephrotoxins

Toxic agent	Effect
Aristocochic acid	“herbal nephropathy” (IN and CKD)
Cat’s claw	Hypertension; AKI
Ephedra	Hypertension
Noni juice	hyperkalaemia
Peppermint oil	Interstitial nephritis (IN)
St John’s Wort	Interstitial nephritis (IN)
Yohimbine	Progressive CKD

Proteinuria


Evaluation for proteinuria
Not at ↑ risk
At ↑ risk
Standard dipstick
Albumin-specific dipstick
≥1+
Negative/trace
Negative
Positive
Total protein/creatinine ratio
Albumin/creatinine ratio
>200 mg/g
≤200 mg/g
≤30 mg/g
>30 mg/g
Recheck at periodic health evaluation
Diagnostic evaluation
Treatment
Consultation

Proteinuria measurement

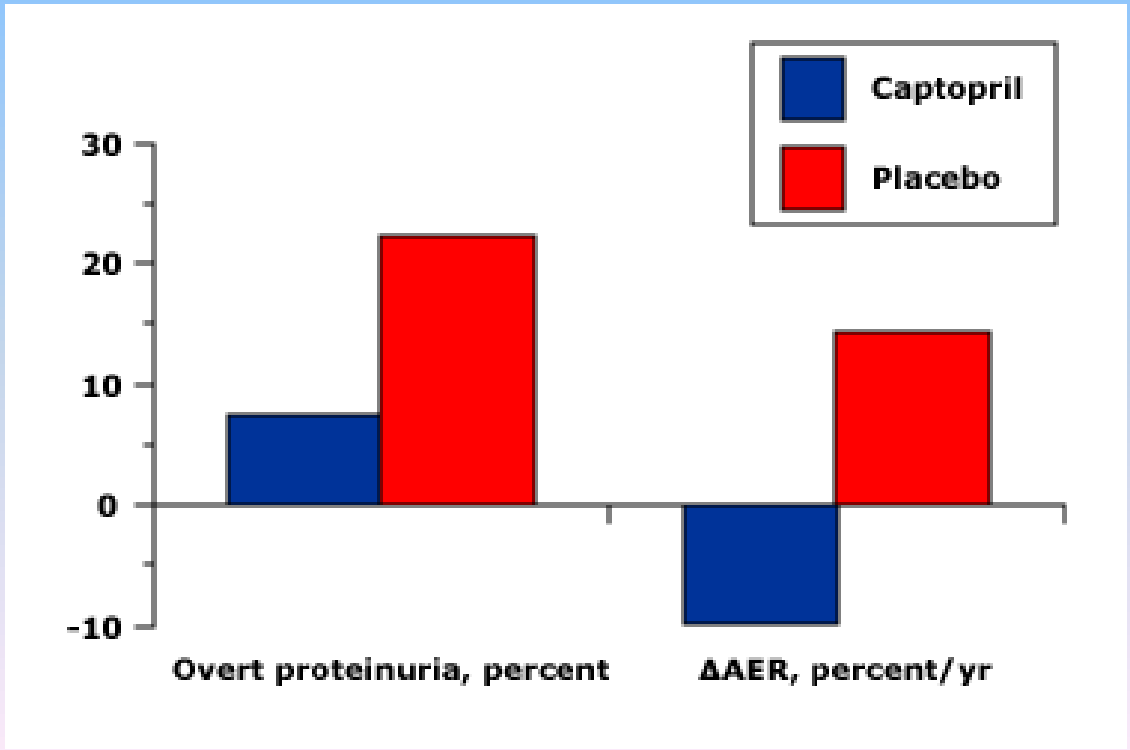


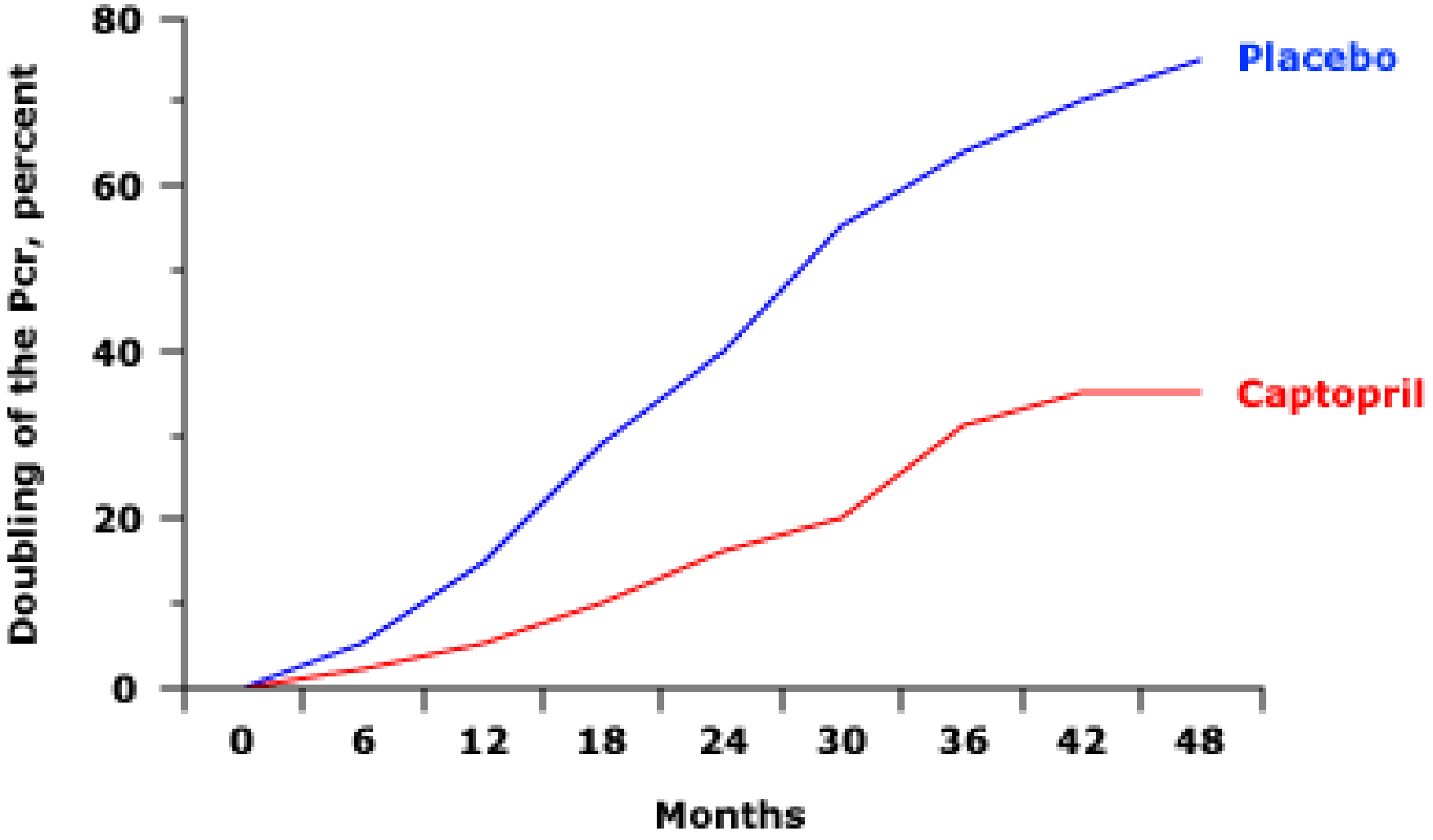
Proteinuria measurement

ACR (mg/L)	24 hour proteinuria	PCR (mg/L)
30	1	60
100	3	200
225	6	400
350	10	600

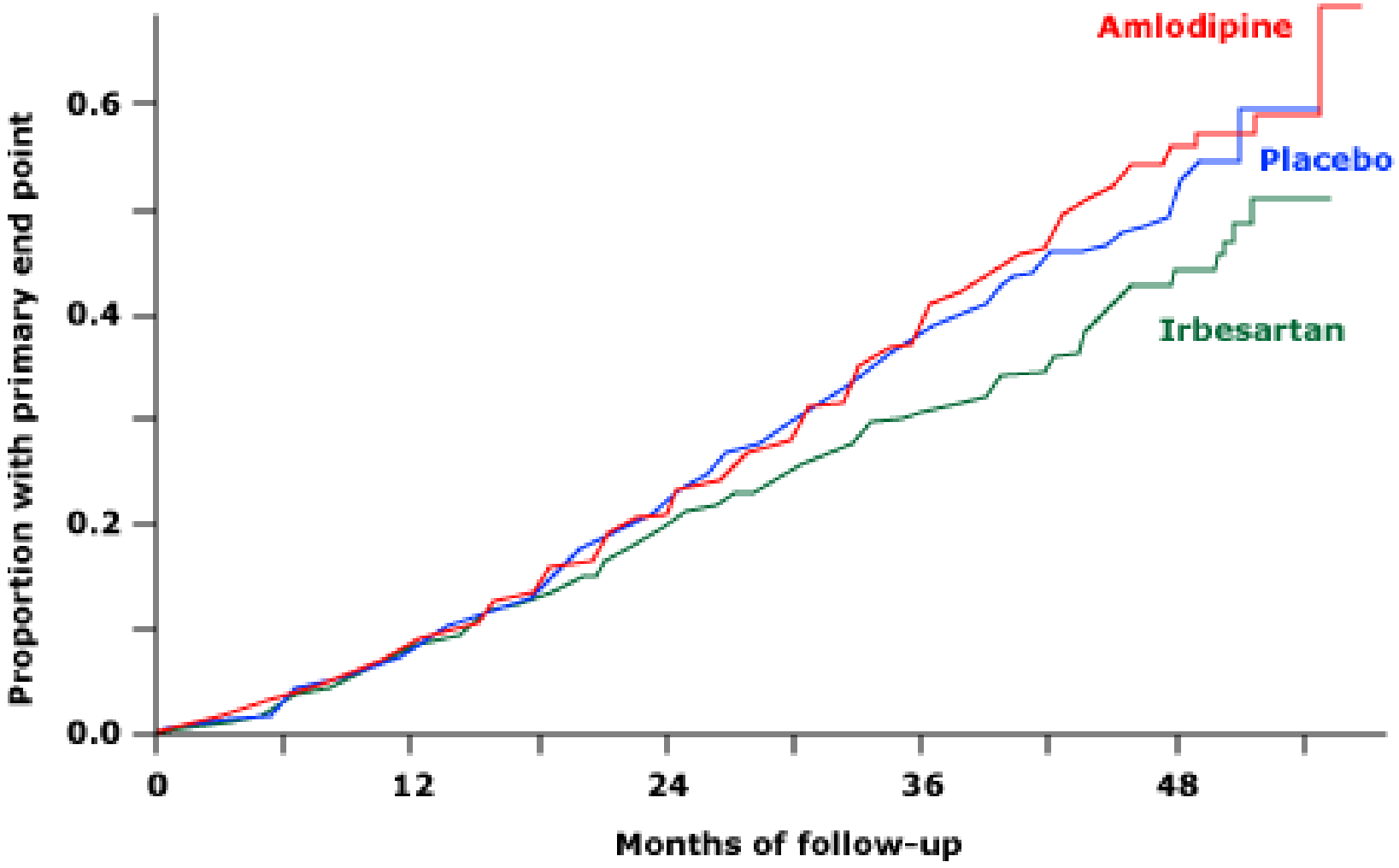
Proteinuria reduction

- Most of the evidence is in ACEs (type 1 DM) and in ARBs (type 2 DM)




Doubling of the Pcr, percent
80
60
40
20
0
0
6
12
18
24
30
36
42
48
Months
Placebo
Captopril

DN2 – Irbesartan (and RENAAL)



What about ACEi **AND** ARB?

- Together in BOTH type 1 and 2 DN
- ACE + ARB reduces proteinuria
- BUT
  - No evidence that combination is better than monotherapy in progression of CKD
- AND adverse events (ONTARGET trial)
  - Hyperkalaemia
  - Decline in eGFR/renal function
    - Accept rise up to 30% from baseline serum creatinine

More on proteinuria

- Aldosterone antagonists
  - 34% reduction cf. placebo in proteinuria
  - (cf. losartan – 17% reduction)
  - BUT Ace + ARB +aldo antag -> +++$[K^+]_s$
- Diltiazem and verapamil (in diabetics only)
  - Verapamil + ACE at non-max doses had similar effect, with less side effects (hyperkalaemia) in DN of DM-2.

Lipids and kidneys

Lipids and kidney disease

- Reduce cardiac disease in ***absence*** of CKD
- SHARP
  - Lipid lowering in CKD (not on RRT) reduced CV events, BUT NOT overall mortality
- Statins have a pleiotropic effect
  - May reduce progression of CKD
- No trials that tell us the goal cholesterol
  - Trials that look at statin dose
    - CV risk falls with LDL reduction
  - Trials that document dyslipidaemia lowering

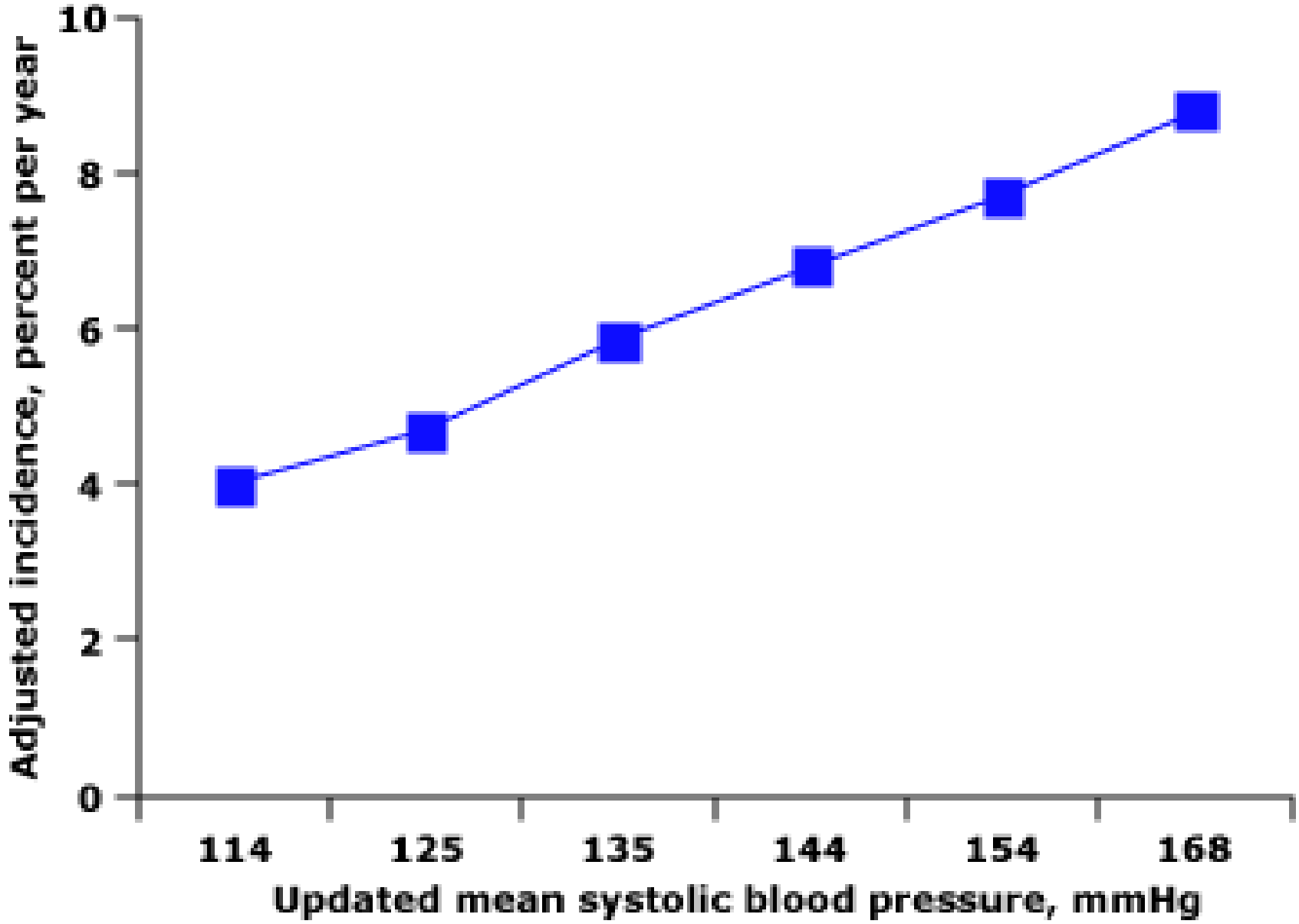
Aspirin in CKD

- HOT trial
  - Reduction in CV events in CKD3A
  - Increased risk of bleeding in some CKD groups
    - CV benefit out-weighed this bleeding risk
    - Overall risk ~ 2.5% per person-year (*n*=255 HD*)
- DOPPS
  - Reduced stroke
  - Increased risk of CV events (MI)
    - But wise variety of use:
    - Japan (8%) cf. 41% (ANZ)

*HD = haemodialysis

Other factors in delaying CKD progression

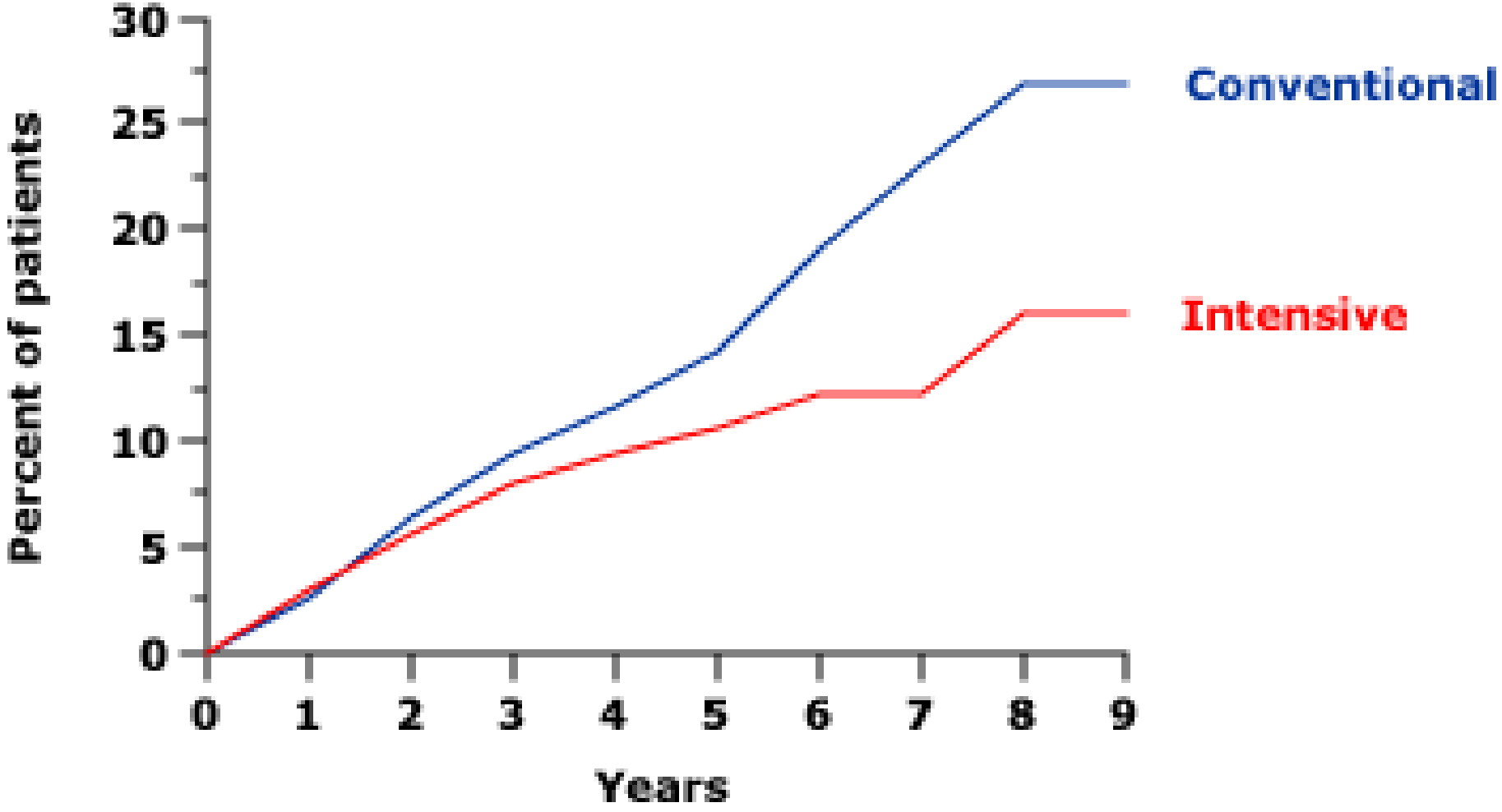
- Smoking cessation
- Maintenance of IBW
- Active lifestyle
- Other possibilities:
  - Correction of anaemia
  - Reduction of oxidative stress
  - Ca-P product
  - Systemic inflammation reduction


Adjusted incidence, percent per year
10
8
6
4
2
0
114
125
135
144
154
168
Updated mean systolic blood pressure, mmHg

Diabetes control and progression of renal disease

Glycaemic control

- Type 1 DM
  - Good control of blood glucose levels…
    - Partly reverses the hyperfiltration and glomerular hypertrophy
    - Delays development of albuminuria
    - Regress/completely reverse albuminuria
      - May take 2 years of normal glucose levels
    - Following pancreas transplant (PAK)
      - Prevents recurrent DN in renal allograft


Percent of patients
30
25
20
15
10
5
0
0
1
2
3
4
5
6
7
8
9
Years
Conventional
Intensive

Glycaemic control

- Type 2 DM
  - Good control of blood glucose levels…
    - Delays development of albuminuria

Salt and hypertension

Case 1

- 58 male
  - BP sub-optimal control
    - 130/85 – 160/110; ?recurrence of RAS
  - eGFR 58ml/min/1.73m2 (creat 118 µmol/L)
- Kidney stones (2x in 10 years)
- R renal a stenosis
  - 5 years prior, check 12/12 later – OK
- Gout
- Accountant; rarely etOH; non-smoker

Case 1

- Medications:
  - Allopurinol 100mg
  - Colchicine prn (rarely)
  - Accupril 10mg bd
  - Hyzaar 50/12.5 mane
  - Atenolol 50mg daily
  - Cartia 1 daily

Case 1

- Examination
  - Thin, well-looking
  - 146/76 lying; 140/74 standing
  - PR 60/min
  - Good peripheral pulses
  - No abdominal bruit
  - Feel L kidney, not right
  - No other abnormality

Case 1

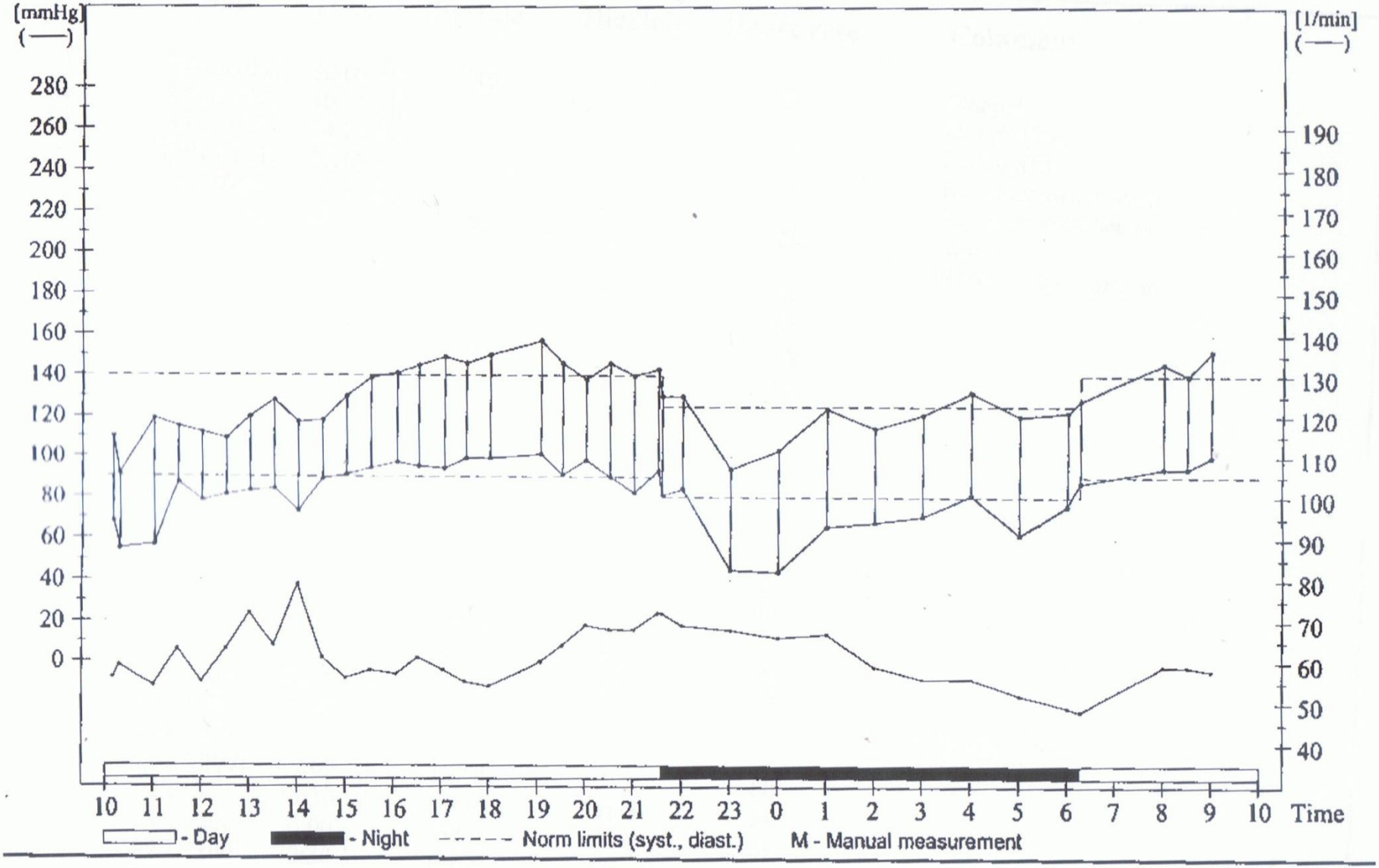
- Plan:
  - Hypertension
    - 24 hour BP monitor
    - Goal <130/80
    - Home monitoring
  - Gout
    - Stop thiazide of Hyzaar – Cozaar
    - Aim for uric acid <0.36mmol/L
  - eGFR
    - Renal tract USS; myeloma screen

Case 1

- Progress:
  - USS normal
  - BP 150-159/96-97; 146/93 average at home
  - 361mmol Na+/24 hours
    - Dietitian
    - Breakfast cereal, breads, Vegemite®,
  - Review
    - 5 months: 62mmol Na+/24 hours

Profile

Measurement row 1 (MG)
Begin: 09/13/01, 10:09
End : 09/14/01, 09:00



Remarks:

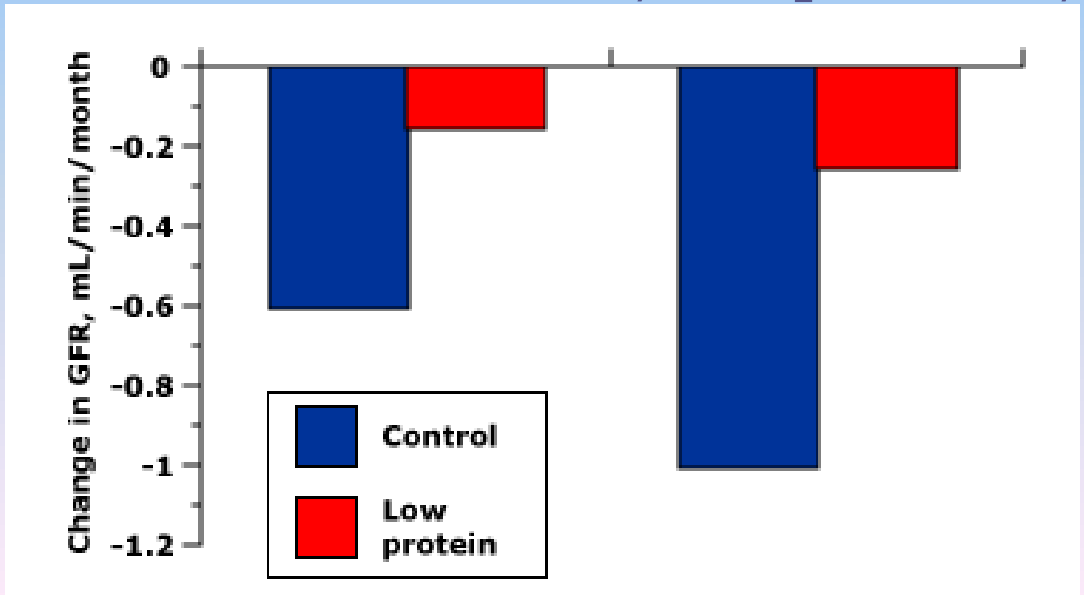
Dietary salt and proteinuria?

- Anti-proteinuria effects of ACE reduced with high salt diet in NON-DIABETICS
- Therefore in the non-diabetic with proteinuria
  - With good BP (systolic < 130mmHg)
  - Should have sodium restricted diet
    - 24 hour urine Na < 100mmol.

Protein restriction

Dietary protein restriction

- DM – type 1
  - 2 small trials (*n*=54 in total)
  - Diet protein and phosphate restriction
    - Decline in GFR from 12ml/min pa to 3ml/min pa



Dietary protein restriction

- BUT larger studies have shown no benefit on progression of CKD (in DM)
  - Better BP and proteinuria control

- NON-DM dietary protein restrition
  - Low protein diet results in more CHO and fat
  - Malnutrition
    - Especially PEM
      - Results in greater mortality

Uric acid

Hyperuricaemia

- Association of hyperuricaemia and:
  - CHD and mortality
- Cause, association, surrogate or effect?
  - Increased risk of hypertension
  - ?oxidative stress
  - Marker for hypertension; abnormal lipids; DM
- Or is hyperuricaemia a marker of CKD?

Calcification of arterial tree

Arterial calcification

- In meta-analysis of 17 studies (n>15,000)
- "Arterial stiffness" (aortic pulse wave)
  - pulse wave velocity between carotid and femoral
- When comparing APW (aortic pulse wave)
  - RR of any coronary event 2.26
  - RR of CV mortality 2.02
  - RR of all-cause mortality 1.90
- CKD
  - Calcium phosphate abnormalities
  - Hyperparathyroidism
  - Calcium phosphate binders

Arterial calcification

- HMO study (n=139,849)
  - Follow-up mean of 28 years
  - Aortic calcification on CXR
  - RR of CAD (men) 1.27
  - RR of CAD (women) 1.22
  - RR of stroke (women) 1.46
- Framingham study (*n*=2,515)
  - Follow-up 22 years
  - Increased risk of aortic calcification -> death

Arterial calcification

- Large long-duration observational studies have shown calcification of aorta is associated with increased risk of CVD death.

Arterial calcification

- CKD
  - Calcium - phosphate abnormalities
  - Hyperparathyroidism
  - Calcium-based phosphate binders
- More recent techniques of CT of coronary vessel calcification in CKD patients similarly associated with increased death rate
  - Is *only* an association
  - What will happen with intervention and calcium load reduction?

Hyperphosphataemia

Hyperphosphataemia of CKD

- Framingham Study subgroup (*n*=3,368), mean age 44 years.
  - Hyperphosphataemia associated with increased risk of CAD
    - RR 1.55 (high vs. low serum phosphate)

Nephrotoxins

Nephrotoxins

- Present as….

- Interstitial nephritis picture
  - Sterile pyuria
- May have proteinuria
- May have impaired renal function
  - Acutely or chronically

Avoiding Nephrotoxins

- Common toxins
  - Lithium.
  - Some chemotherapeutic agents.
  - NSAIDs; COX-2 inhibitors
  - Allopurinol.
  - H_2 / proton pump blockers – omeprazole, pantoprazole, lansoprazole, etc.
  - OTC/herbals.
  - Fibrates.
  - Quinolone antibiotics (uncommon)

Nephrotoxins

- Chinese herbals:
  - Aristolochic acid (Guan Xin Su He)
  - NSAID (Sang Ju Gan Mao Pian)
  - NSAID (Yen Qiao Jie Du Pian)
  - NSAID (tung Shueh pills)
  - Others: Guan Mu Tong; Dahuong Qingwei, Daochi, Fenqing Wulin, Longdon Xiegan pills; Xiaoer Jindan tablets.

Nephrotoxins

- Glycyrrhiza
  - Fanconi syndrome
- Noni juice
  - Hyperkalaemia and diuretic
- Cat' claw (*Uncaria tomentosa*)
  - AKI
- *Taxus celebica*
  - AKI, haemolysis

Nephrotoxins

- Salicin
  - Willow bark
- Sorrel (*Rumex acetosa*)
  - Oxalosis, kidney stones
- Essiac (*Ulvis spp*)
  - Oxalosis, kidney stones
- Peppermint oil
  - Interstitial nephritis
- St John's wort
  - Interstitial nephritis

Nephrotoxins

Toxic agent	Effect
Aristocochic acid	“herbal nephropathy” (IN and CKD)
Cat’s claw	Hypertension; AKI
Ephedra	Hypertension
Noni juice	hyperkalaemia
Peppermint oil	Interstitial nephritis (IN)
St John’s Wort	Interstitial nephritis (IN)
Yohimbine	Progressive CKD