Cardiovascular complications in Chronic Kidney Disease

- **Hopes and Challenges**

Nihil Chitalia
Consultant Nephrologist
Epsom and St. Heliers' University Hospital NHS trust

CV complications in CKD

- Magnitude
- Mechanisms
- Evidence base
- Conclusion

Case Presentation

Mrs. Kamalben Patel, 42 year female, no DM

- Creatinine 250µmol/L, Haemoglobin 10.5 g/dL
- Non smoker, BMI 29, BP 145/85, Cholesterol 5.2 mmol/L, CRP 5.3
- Urinary Protein:creatinine ratio 100 mg/mmol

Medications: aspirin 75, amlodipine 10 mg, ramipril 5 mg

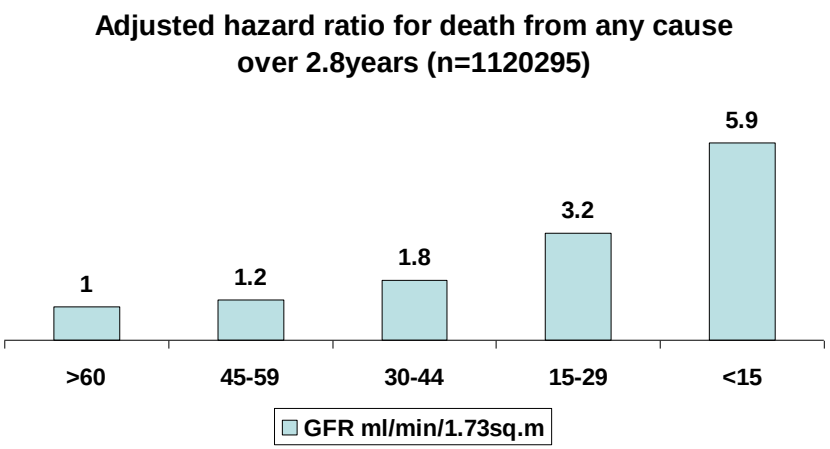
- At present her eGFR is 16 ml/min/1.73m^2

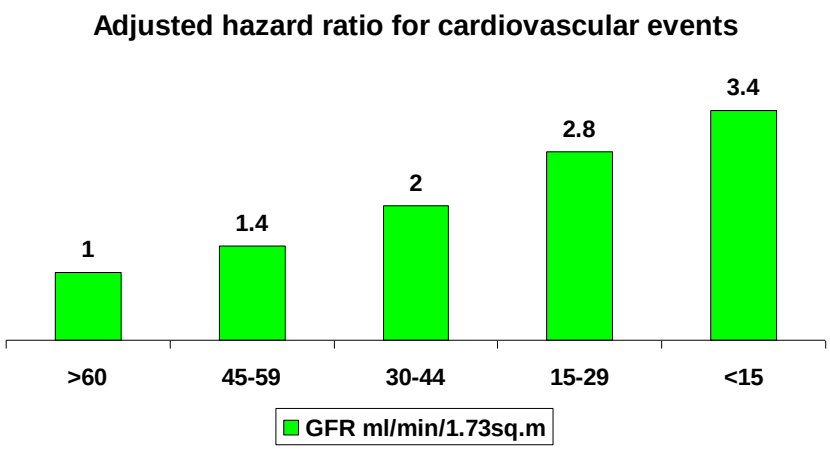
- She presents to A&E with chest pain; ECG T inv V4-V6; trop I 65
  - What is the cause?

NSTEMI

Magnitude of CV disease in CKD

Mortality and CV events in CKD



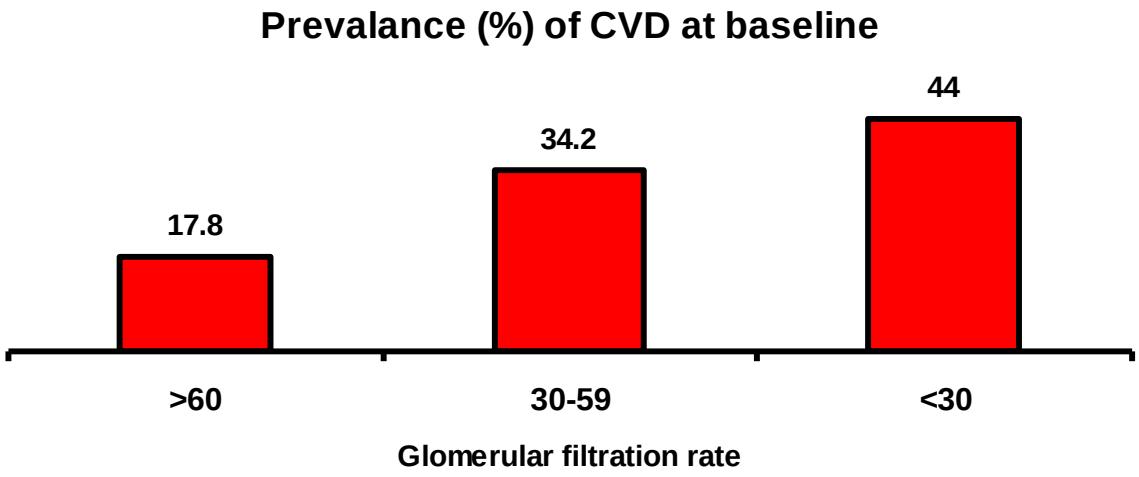


eGFR ml/min	Risk of CV death *
45-59	40%
30-44	100%
15-29	180%
<15	240%

*Ref group: >60ml/min

Go NEJM 2004;351;1296

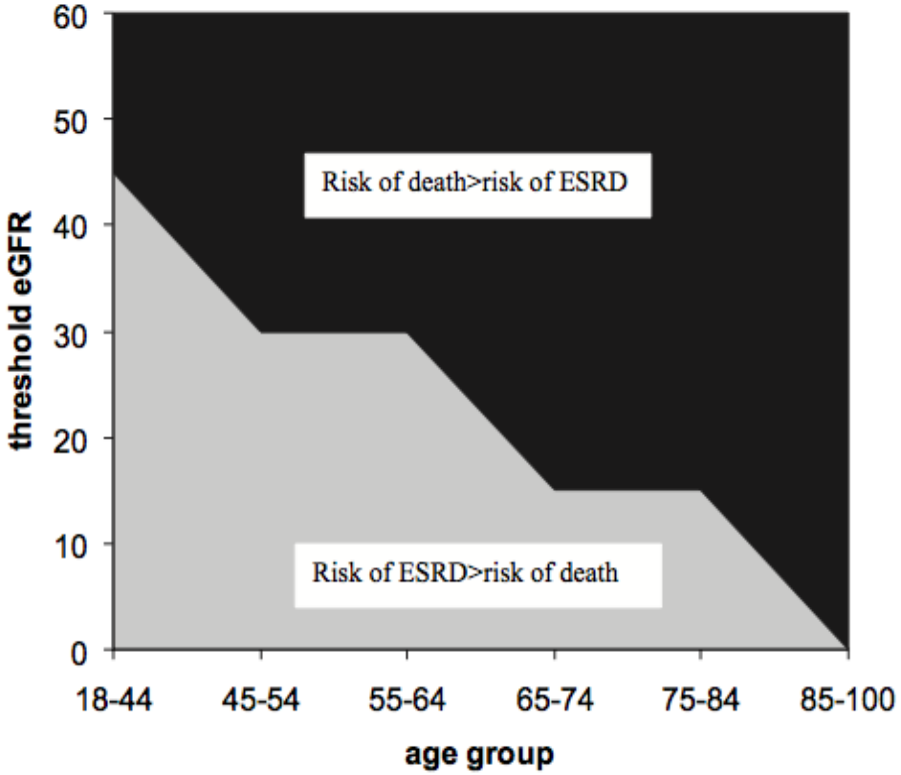
Prevalence of CVD in CKD



Not just higher incidence but also higher prevalence of CVD in CKD

Banerjee Int J Urol Nephrol 2009

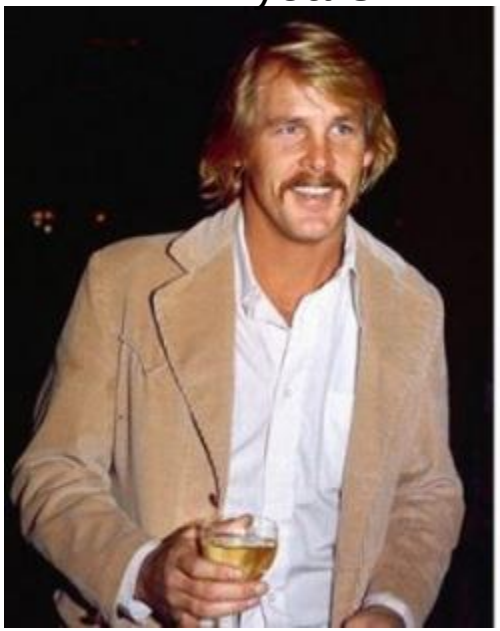
Risk of Death vs. ESRD



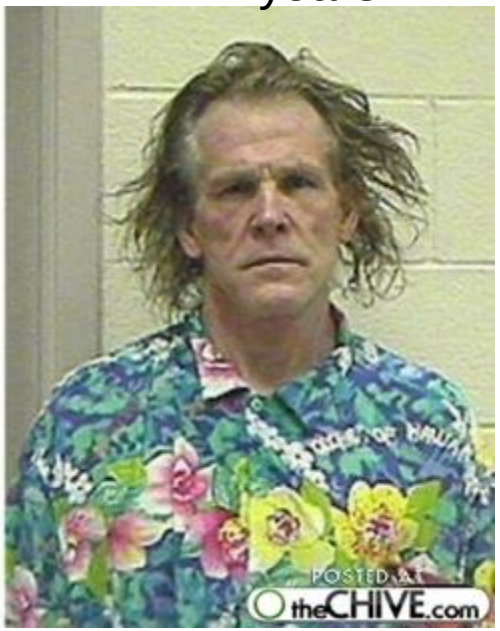
O'Hare et al, JASN 2007

Young vs. old

27 years



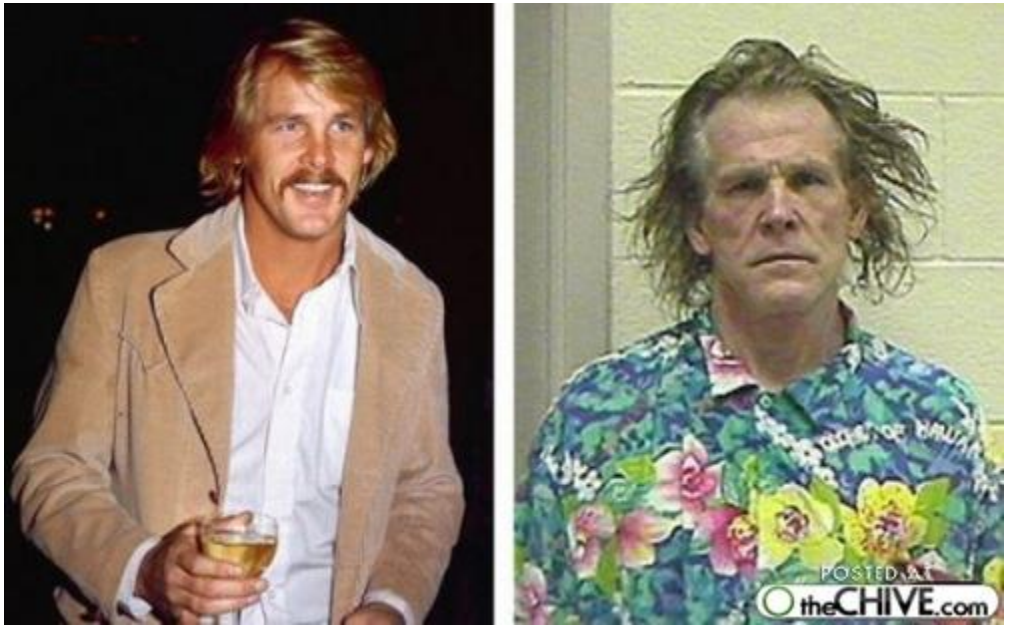
77 years



Both on dialysis

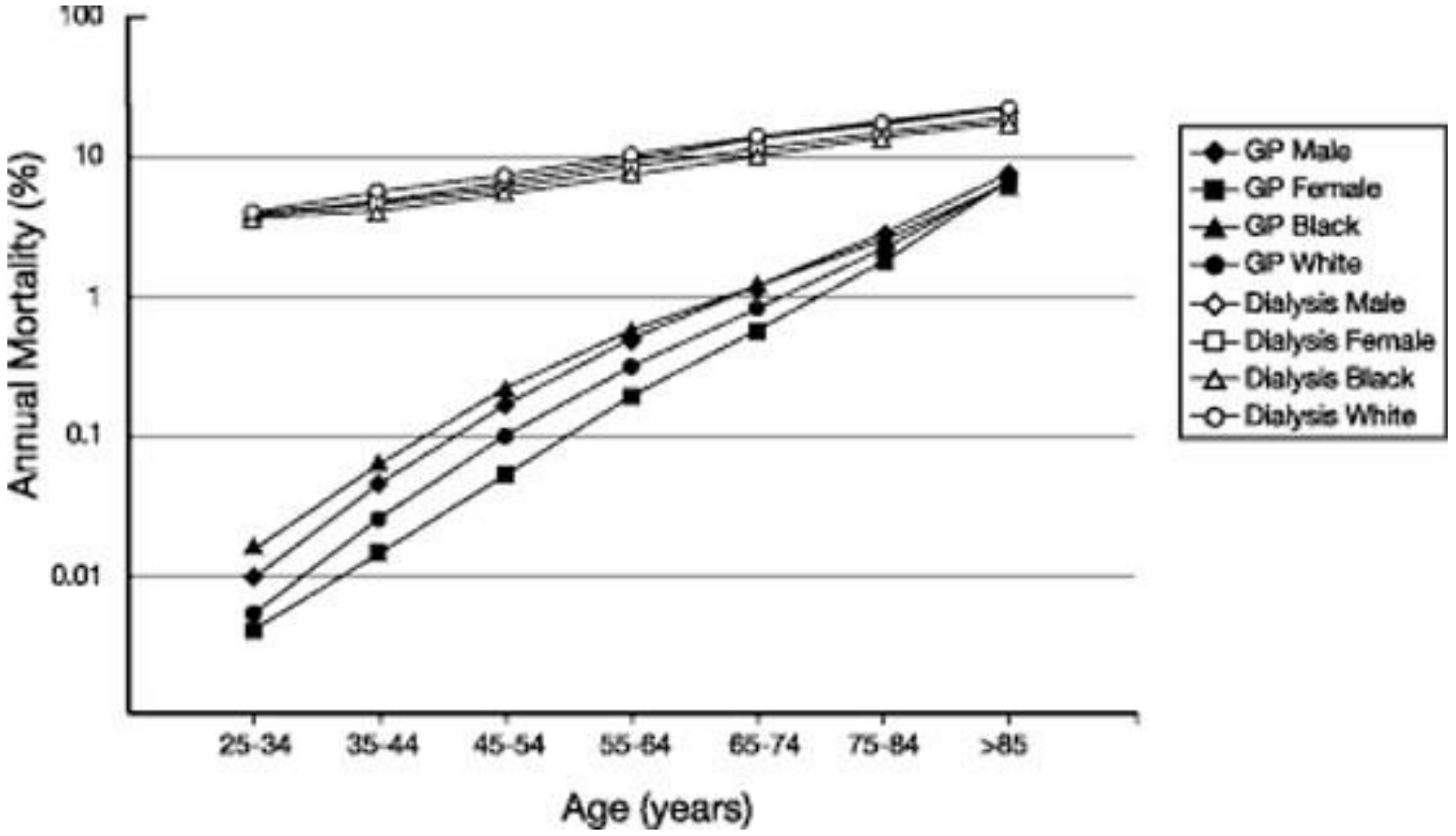
who is more likely to die compared to somebody of similar age but no CKD?

Young vs. old



More at risk compared to non CKD of same age

CVD mortality is high on Dialysis



CVD mortality in dialysis patients (USRDS) compared to the general population (NCHS)

Foley et. al., 1998 Am J Kid Disease 32

Case Presentation

- 68 year male on HD for 3 years
- Attended regular dialysis session in the evening
- Found dead the following day

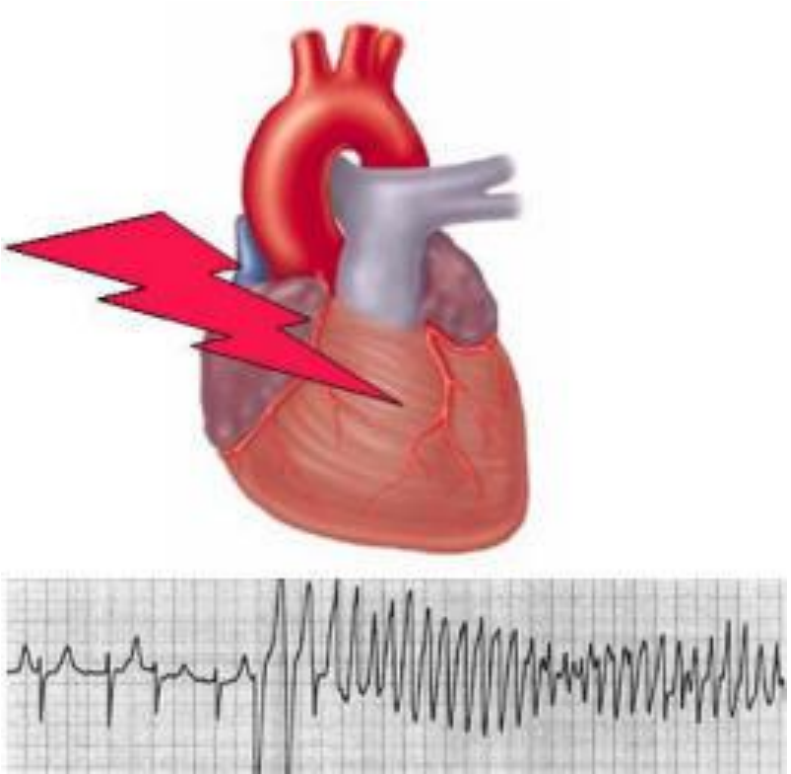
Cause of death?

1. MI
2. Brain haemorrage
3. Pulmonary embolism
4. Sudden cardiac death

Cardiovascular mortality in HD

USRDS: >50% of all deaths are cardiovascular

- 20% of all CV deaths are due to MI
- **65% of all CV deaths are due to arrhythmias**



Rocco et al AJKD 2002;39:146

Frequency of cardiac arrests increases with time on HD

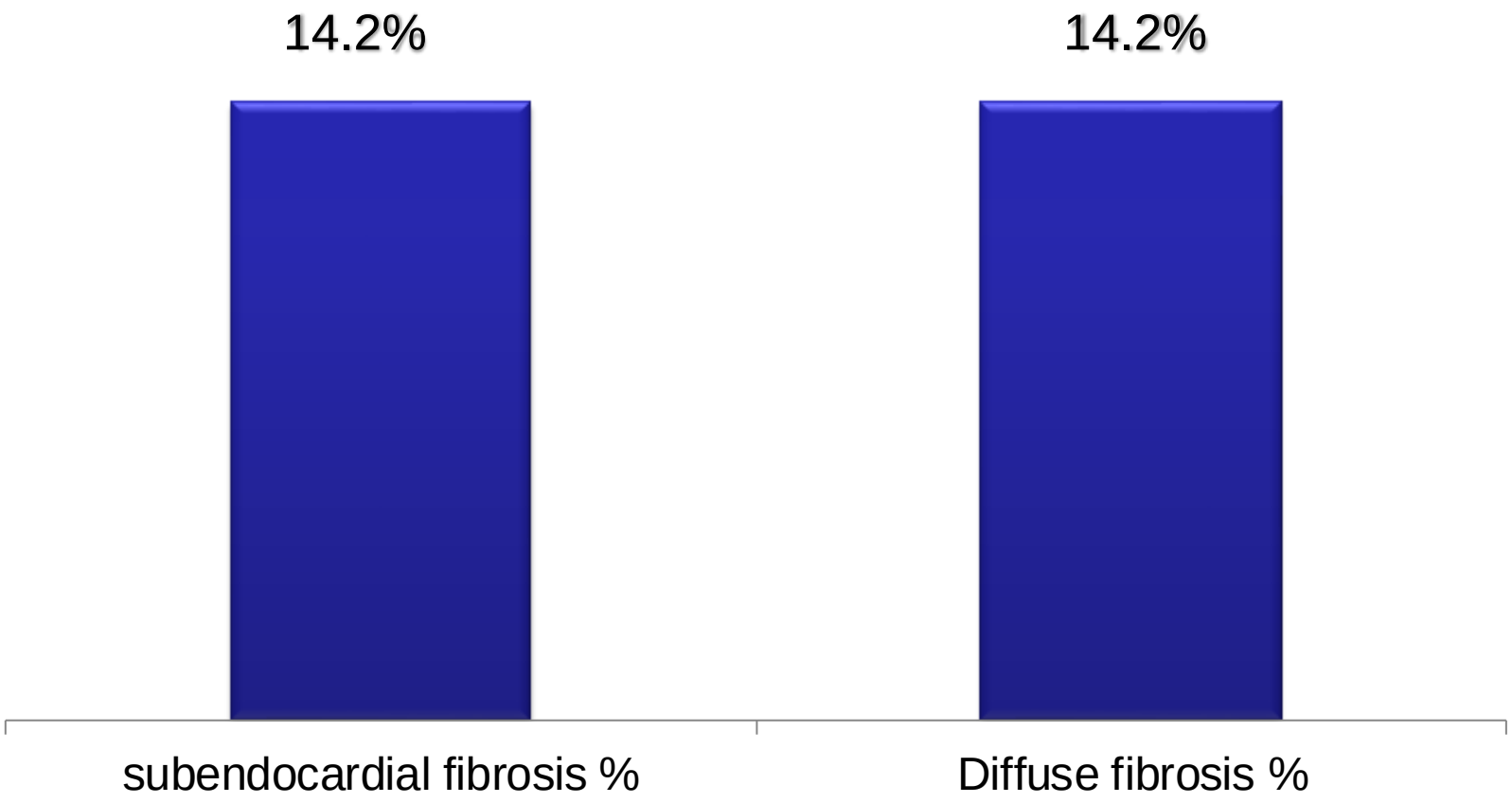
Events per 1000 patient years

	1st year	4th Year
DM	110	208
Non DM	70	131

- 1.6x higher in DM
- 2 x higher in 4th year vs. 1st year

Herzog CA KI 2003; 84:S197

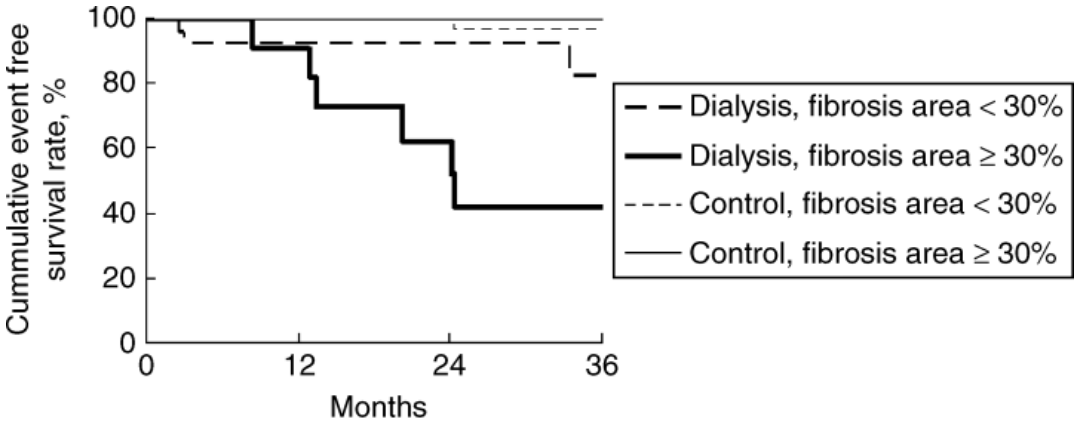
Cardiac Fibrosis in ESRD patients



134 HD patients studies with Cardiac MR

- Mark PB, Kid Int 2006

Cardiac fibrosis a strong predictor of death in ESRD



Patients at risk				
Dialysis group				
Fibrosis <30%	28	17	14	8
Fibrosis ≥30%	12	10	6	2
Control group				
Fibrosis <30%	40	33	29	23
Fibrosis ≥30%	10	9	5	4

40 HD patients with DCM. No CAD

vs.

50 nonHD patients with DCM

Aoki; KI (2005) 67:333

Case Presentation

Mrs. Kamalben Patel, 42 year female, no DM

- Creatinine 250µmol/L, Haemoglobin 10.5 g/dL
- Non smoker, BMI 29, BP 145/85, Cholesterol 5.2 mmol/L, CRP 5.3
- Urinary Protein:creatinine ratio 100 mg/mmol

Medications: aspirin 75, amlodipine 10 mg, ramipril 5 mg

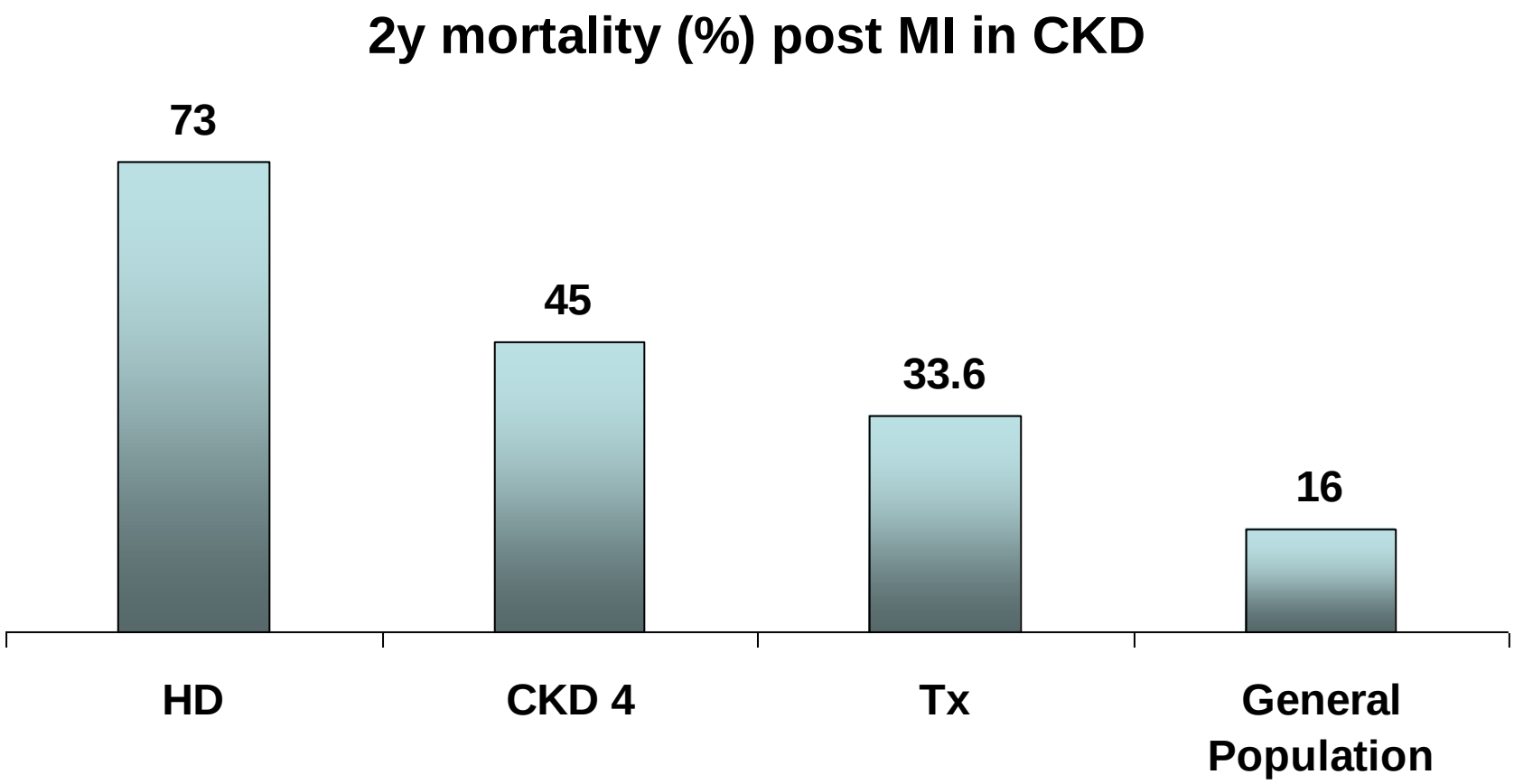
- At present her eGFR is 16 ml/min/1.73m^2

- She presents to A&E with chest pain; ECG T inv V4-V6; trop 1.2

  – What is the cause?
  – What is her prognosis?

NSTEMI

Mortality post MI



Herzog AJKD 2000;36 145
Herzog NEJM 1998;339 799

Gottlieb NEJM 339: 489

Risk factor inverventions….

Case Presentation

Mrs. Kamalben Patel, 42 year female, no DM

- Creatinine 250µmol/L, Haemoglobin 10.5 g/dL
- Non smoker, BMI 29, BP 145/85, Cholesterol 5.2 mmol/L, CRP 5.3
- Urinary Protein:creatinine ratio 100 mg/mmol

Medications: aspirin 75, amlodipine 10 mg, ramipril 5 mg

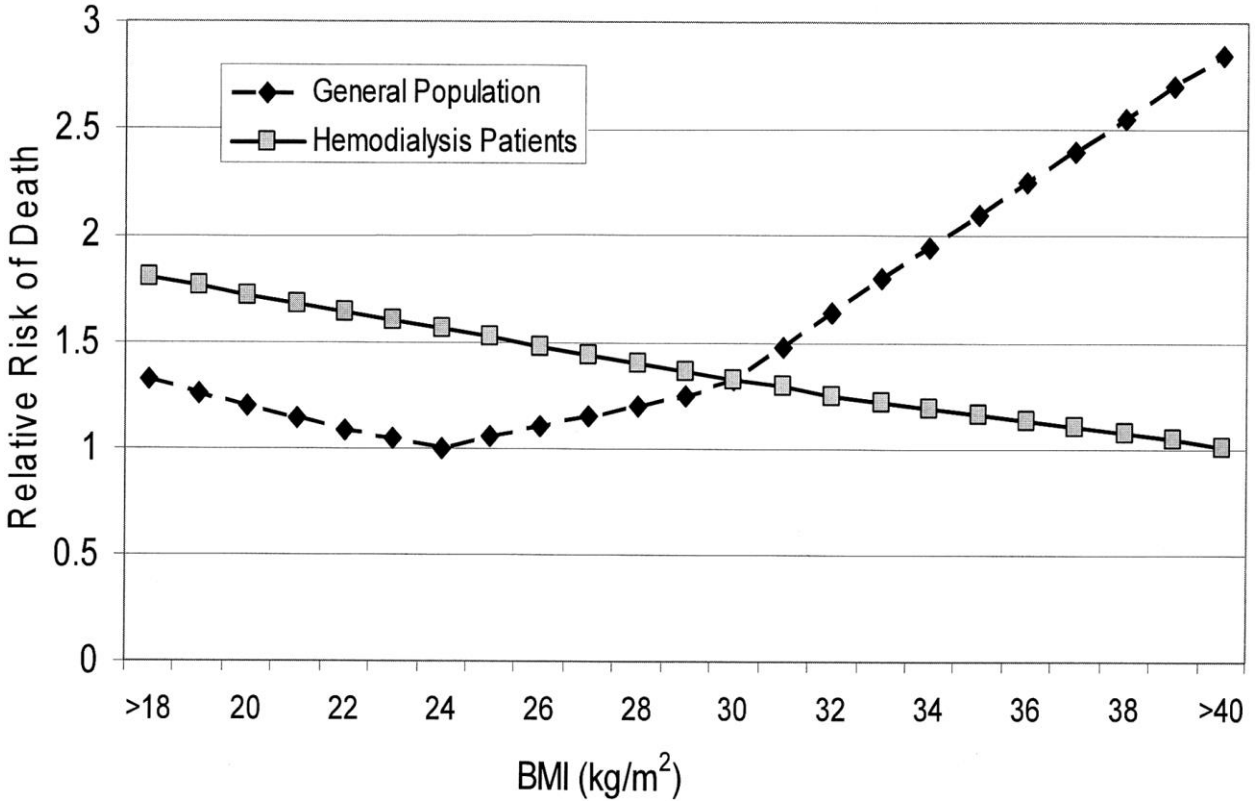
- At present her eGFR is 16 ml/min/1.73m^2

- She presents to A&E with chest pain; ECG T inv V4-V6; trop 1.2

  – What is the cause?
  – What is her prognosis?

NSTEMI

Obesity and CV death in ESRD



Inverse epidemiology in ESRD patients, not so in predialysis CKD

Kalantar-Zadeh K 2005

Case Presentation

Mrs. Kamalben Patel, 42 year female, no DM

- Creatinine 250µmol/L, Haemoglobin 10.5 g/dL
- Non smoker, BMI 23, BP 145/85, Cholesterol 5.2 mmol/L, CRP 5.3
- **Urinary Protein:creatinine ratio 100mg/mmol**

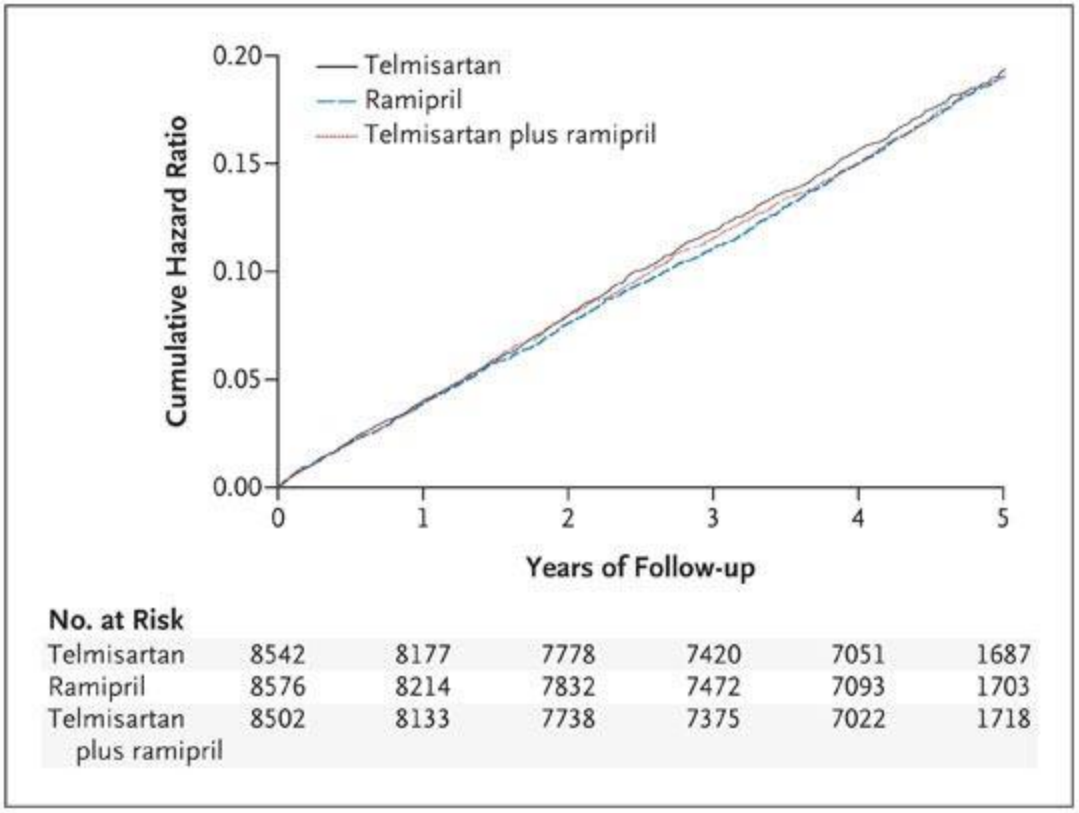
Medications: aspirin 75, amlodipine 10 mg, **ramipril 10 mg**

- At present her eGFR is 16 ml/min/1.73m^2

- She presents to A&E with chest pain; ECG T inv V4-V6; trop 1.2

NSTEMI

Dual Therapy ACE- & A II RB ?



No. at Risk						
Telmisartan	8542	8177	7778	7420	7051	1687
Ramipril	8576	8214	7832	7472	7093	1703
Telmisartan plus ramipril	8502	8133	7738	7375	7022	1718

Telmisartan 80mg vs. Ramipril 10mg *vs*. Temisartan 80+ Ramipril 10

ONTARGET study NEJM 2008

Dual Therapy ACE- & A II RB

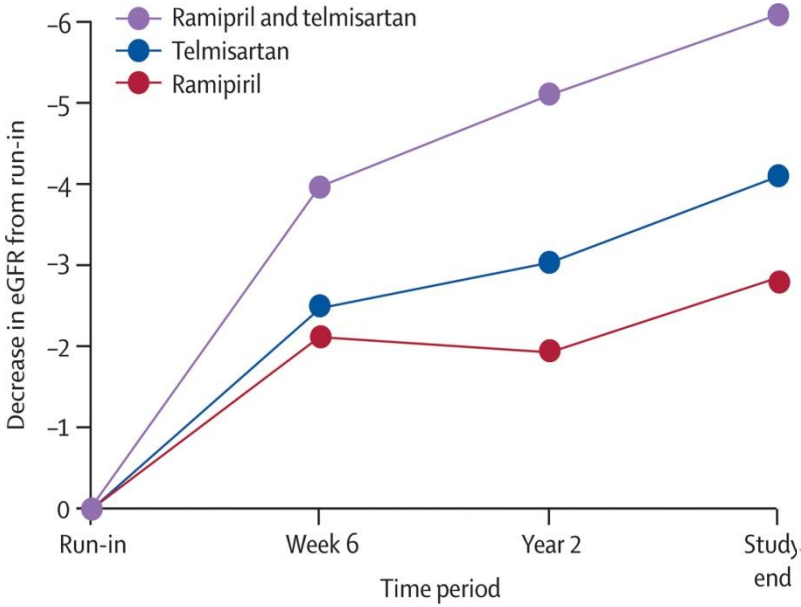
Change in BP in the 3 treatment groups

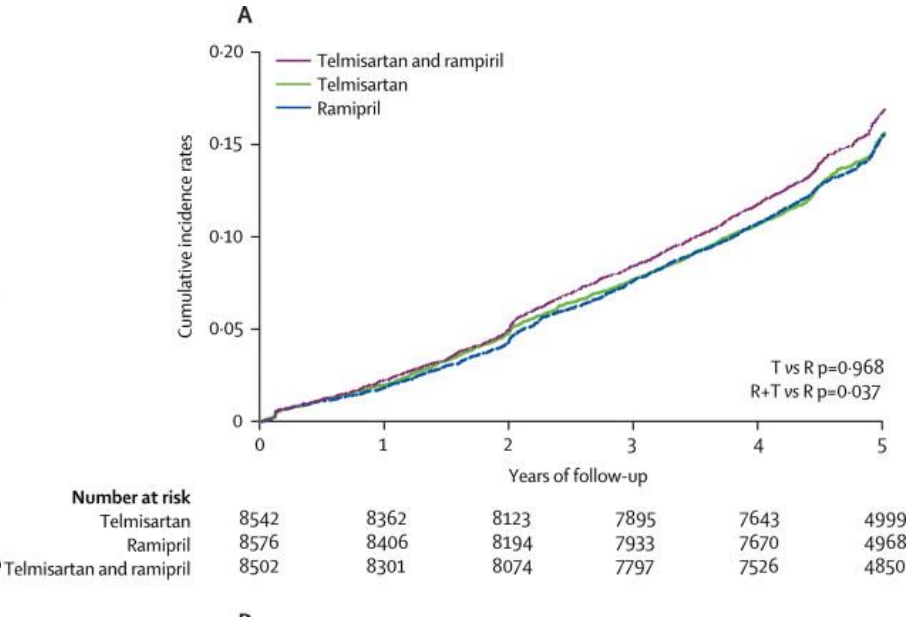
Change in BP	Ramipril	Telmisartan	Combination
Systolic *mmHg*	-6	-6.9	-6.4
Diastolic *mmHg*	-4.6	-5.2	-6.0

Higher Hypotension, syncope and diarrhoea in combination therapy group

ONTARGET study NEJM 2008

Dual therapy with ACE- & A II RB





Dual therapy is associated 24% higher risk of adverse worse renal outcomes (Doubling of creatinine or initiation of dialysis)

Mann JF, Lancet 2008

Case Presentation

Mrs. Kamalben Patel, 42 year female CRF, no DM, first presentation

- Creatinine 250µmol/L, Haemoglobin 10.5 g/dL
- Non smoker, BMI 23, BP 145/85, **Cholesterol 5.2 mmol/L,** CRP 5.3
- Urinary Protein:creatinine ratio 100 mg/mmol

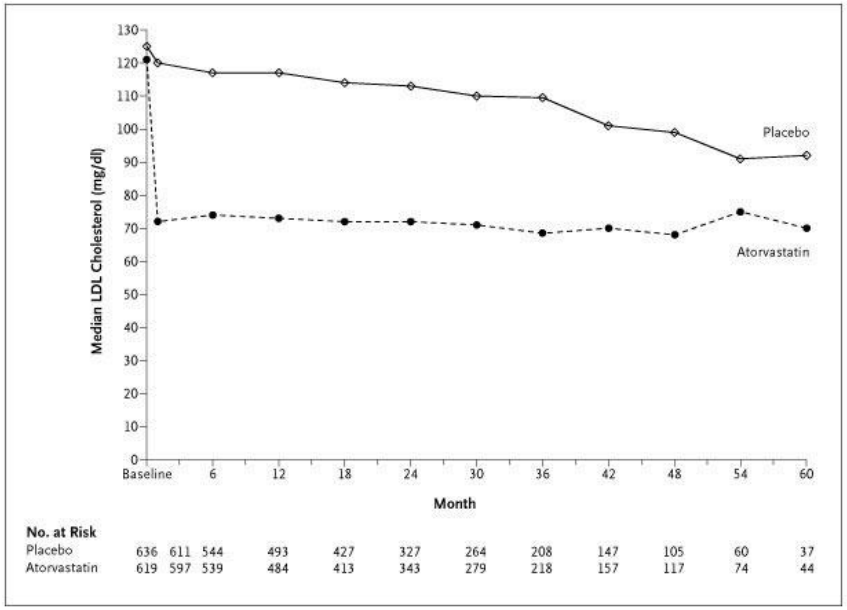
Medications: aspirin 75, amlodipine 10 mg, ramipril 10 mg

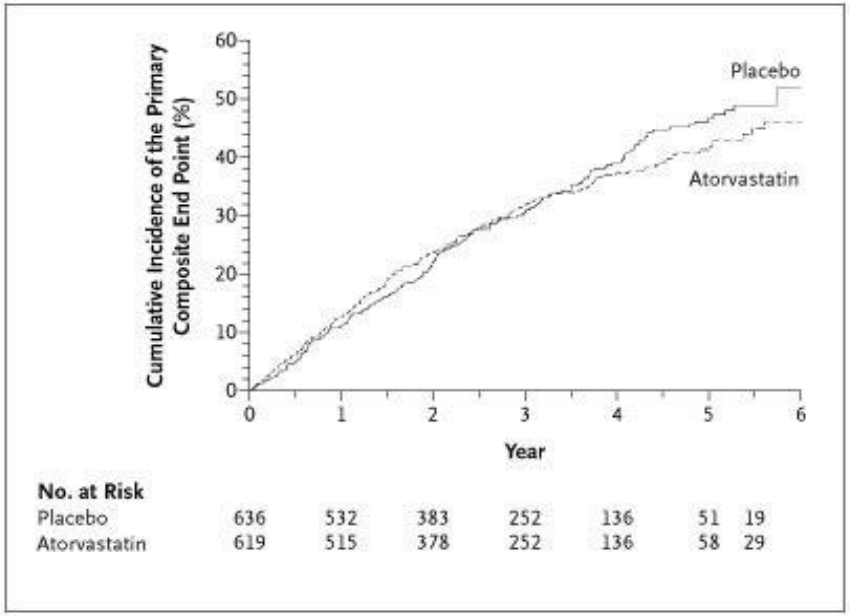
- At present her eGFR is 16 ml/min/1.73m^2

- She presents to A&E with chest pain; ECG T inv V4-V6; trop 1.2

NSTEMI

Lipids and CV risk in ESRD

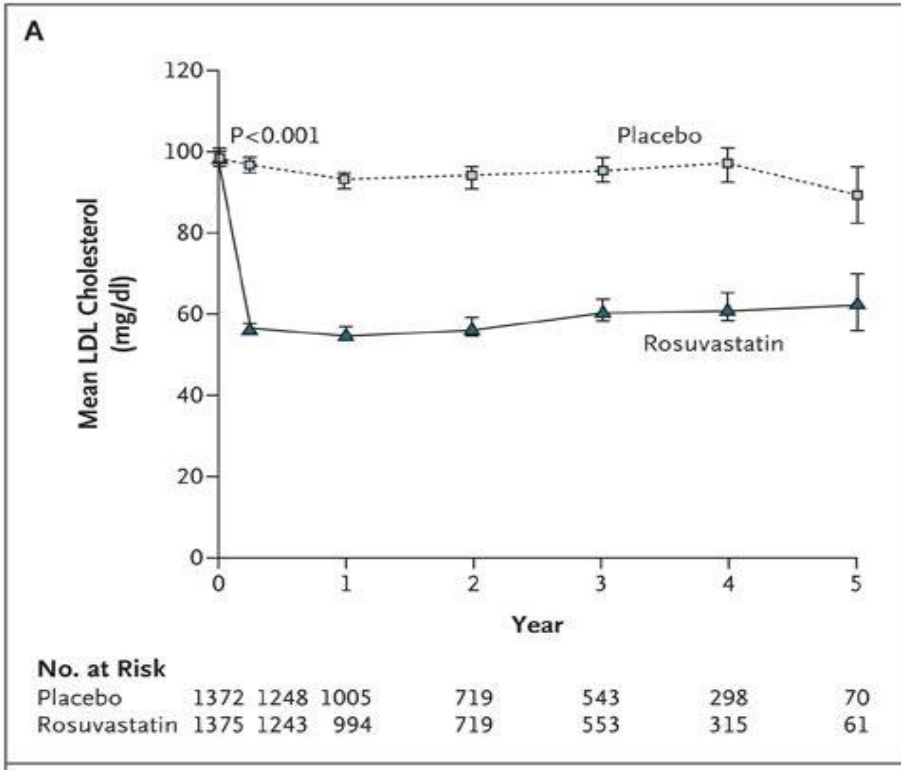


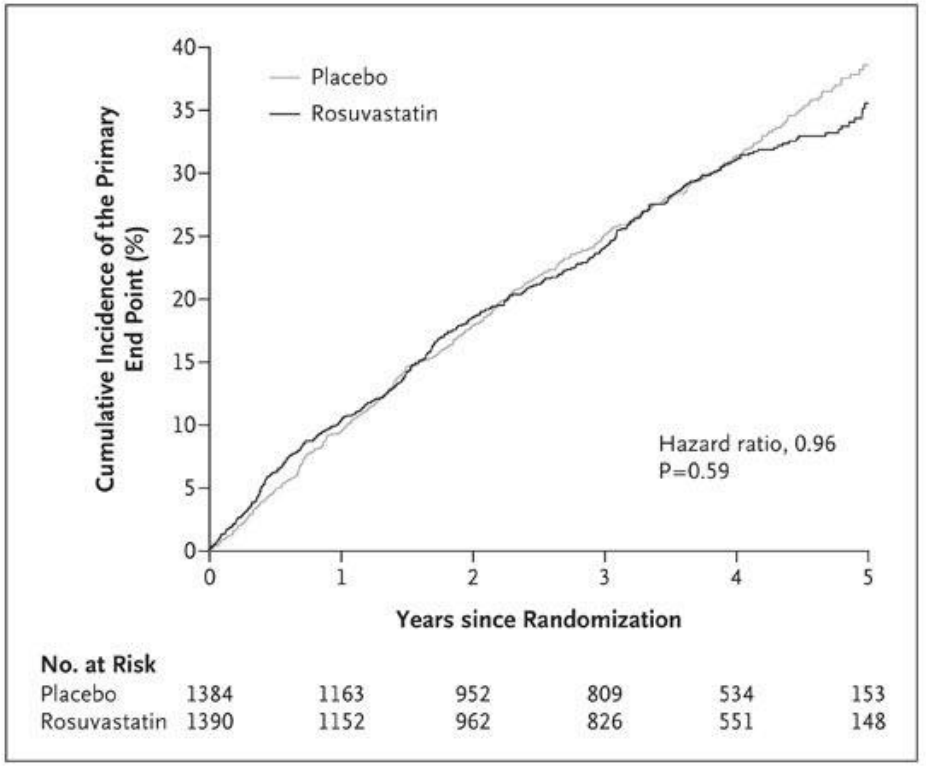


1255 type II DM HD patients
20 mg Atorvastatin vs. Placebo
LDL>2.1 mmol/L
4 year F/U

4D Study NEJM 2005

Lipids and CV risk in ESRD





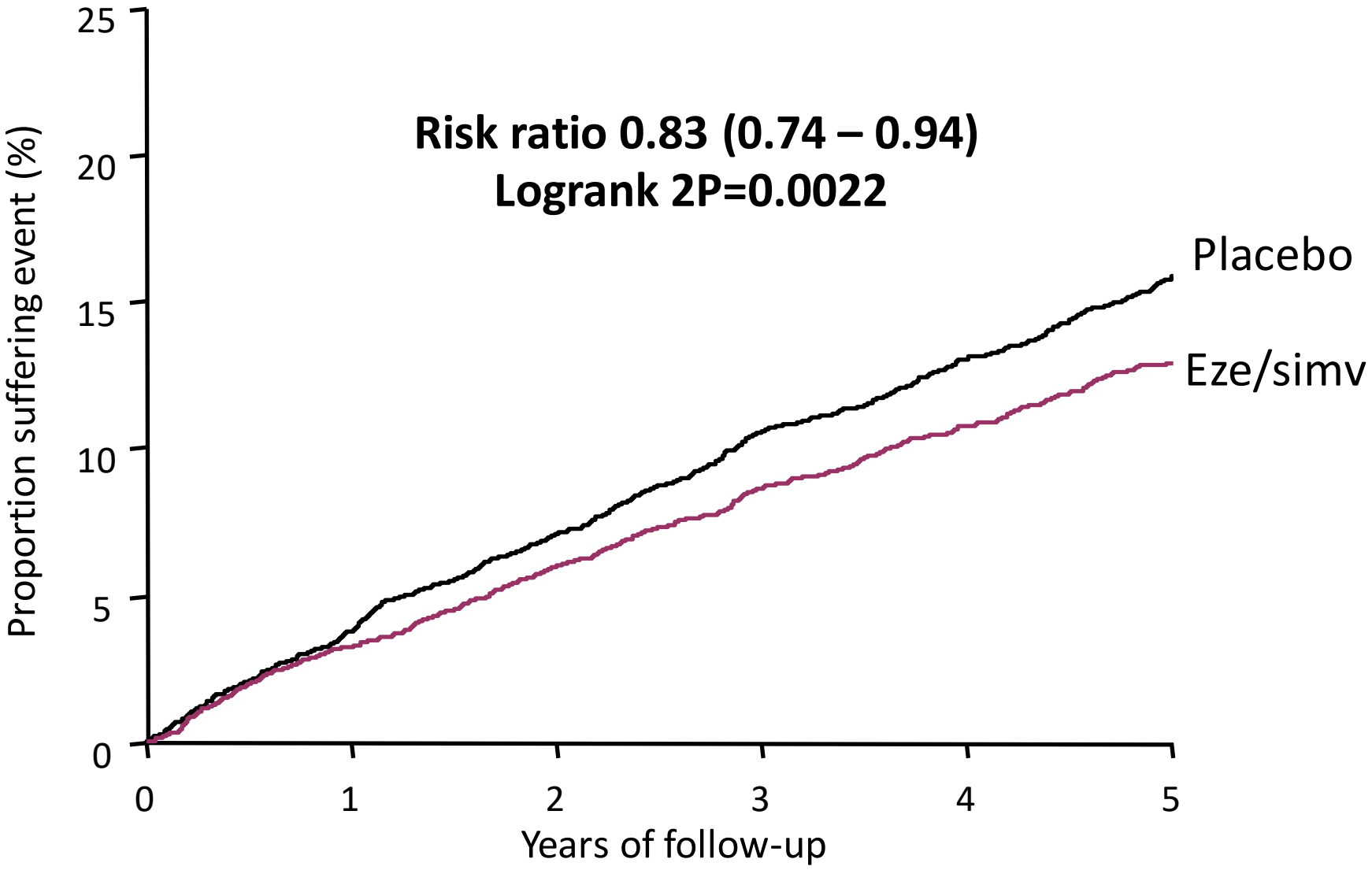
2766 HD patients
10 mg Rosuvastatin vs. Placebo
5 years f/u
28% DM

AURORA study, NEJM 2009

Lipids and CV risk in CKD

- 9000 CKD patients (6000 predialysis CKD; 3000 ESRD patients)
- 20 mg Simvastatin + 10 mg Ezetimibe *vs*. Placebo

SHARP: Major Atherosclerotic Events



Case Presentation

Mrs. Kamalben Patel, 42 year female CRF, no DM, first presentation

- Creatinine 250µmol/L, Haemoglobin 10.5 g/dL
- Non smoker, BMI 23, BP 145/85, Cholesterol 5.2 mmol/L, **CRP 5.3**
- Urinary Protein:creatinine ratio 50 mg/mmol

Medications: aspirin 75, amlodipine 10 mg, ramipril 10 mg

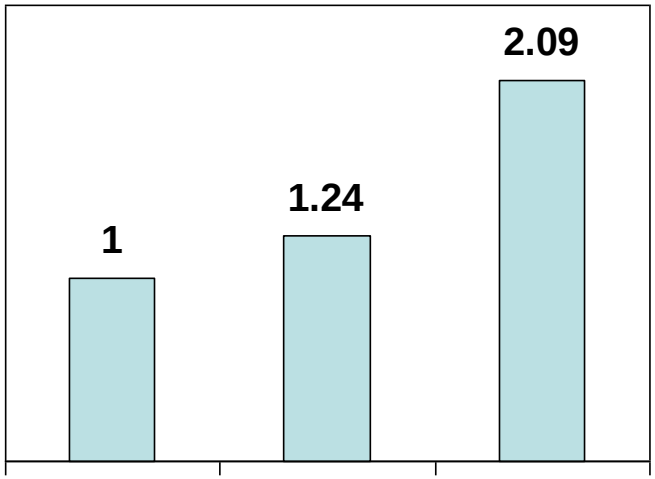
- At present her eGFR is 16 ml/min/1.73m^2

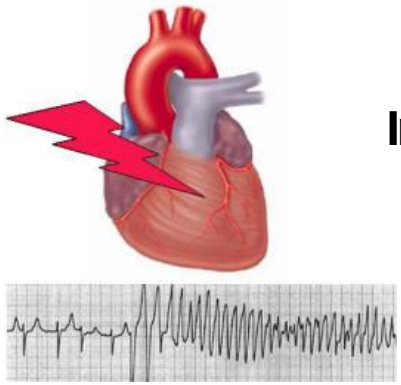
- She presents to A&E with chest pain; ECG T inv V4-V6; trop 1.2

NSTEMI

Inflammation as risk factor

CRP and SCD in 1041 HD patients





Increasing sudden cardiac deaths with rising CRP

Parekh KI 2008 74;1335

Case Presentation

Mrs. Kamalben Patel, 42 year female CRF, no DM, first presentation

- Creatinine 250µmol/L, Haemoglobin 10.5 g/dL
- Non smoker, BMI 23, **BP 145/85**, Cholesterol 5.2 mmol/L, CRP 5.3
- Urinary Protein:creatinine ratio 50 mg/mmol

Medications: aspirin 75, amlodipine 10 mg, ramipril 10 mg

- At present her eGFR is 16 ml/min/1.73m^2

- She presents to A&E with chest pain; ECG T inv V4-V6; trop 1.2

NSTEMI

PROTOCOL FOR BLOOD PRESSURE CONTROL IN RENAL FAILURE PATIENTS

Target <130/80 mm Hg

With all steps	Salt restriction < 100 mmol/day (< 6g NaCl or <2.4 g Na^+/day), Exercise 30 mins/daily, Stop smoking
Step 1	Ramipril 5 mg od or Irbesartan 150 mg od
Step 2	Frusemide 40 od-bd
Step 3	Ramipril 10 mg od or Irbesartan 300 mg od
Step 4	Amlodipine 5 mg od or Nifedipine LA 30 mg od
Step 5	Amlodipine 10 mg od or Nifedipine LA 90 mg od
Step 6	Doxazocin XL 4 mg od or Metoprolol 50 mg bd
Step 7	Doxazocin XL 8 mg od or Metoprolol 100 mg bd
Step 8	Moxonidine/Hydralazine/Minoxidil

- On average a patient may need **three** antihypertensives
- Move to the next step if one step is not tolerated

Case Presentation

Mrs. Kamalben Patel, 42 year female CRF, no DM, first presentation

- Creatinine 250µmol/L, Haemoglobin 10.5 g/dL
- Non smoker, BMI 23, BP 145/85, Cholesterol 5.2 mmol/L, CRP 5.3
- Urinary Protein:creatinine ratio 50 mg/mmol
- **Calcium 2.5mmol/L, Phos 2.2mmol/L, PTH 200**

Medications: aspirin 75, amlodipine 10 mg, ramipril 10 mg

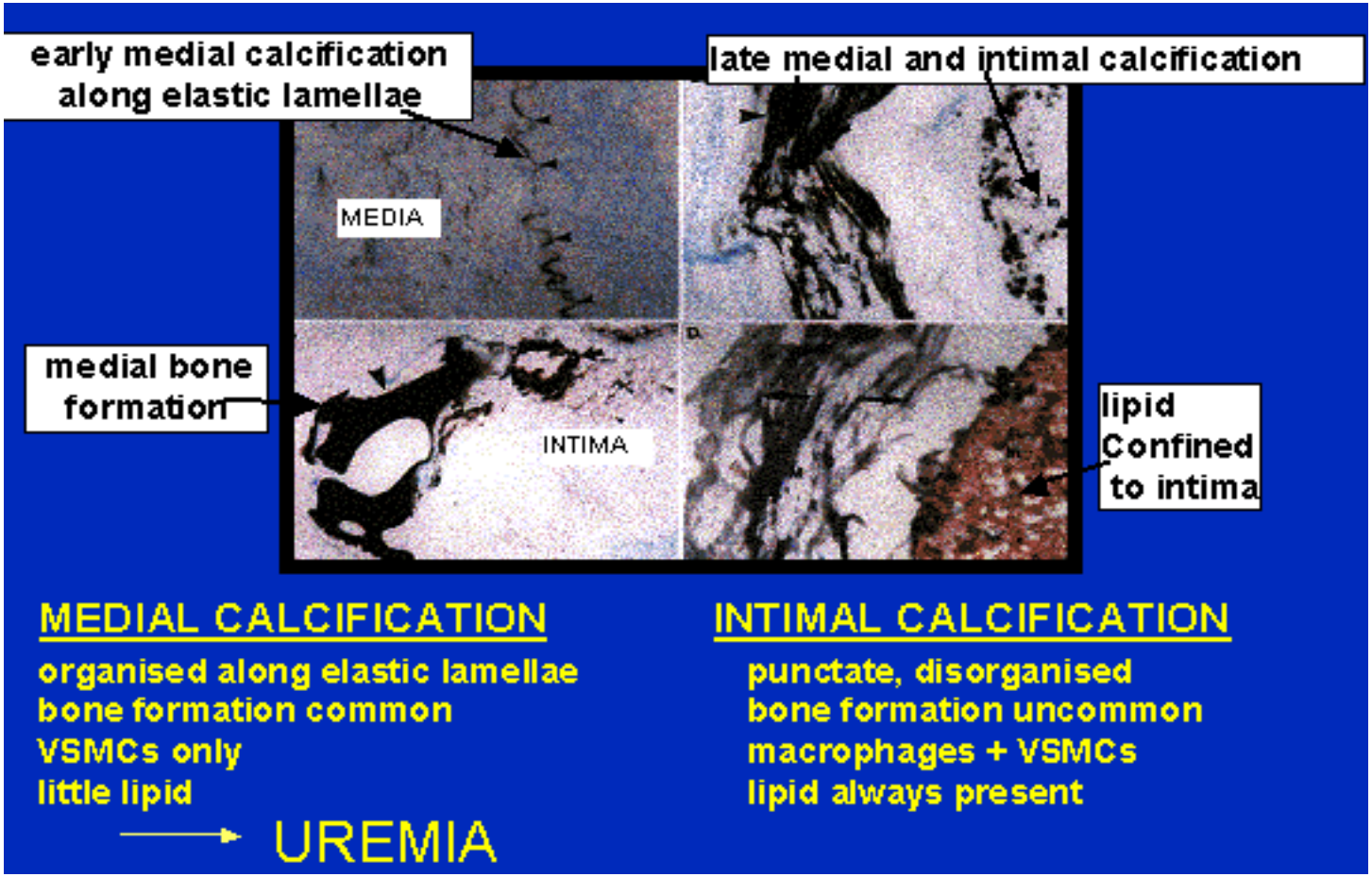
- At present her eGFR is 16 ml/min/1.73m^2

- She presents to A&E with chest pain; ECG T inv V4-V6; trop 1.2

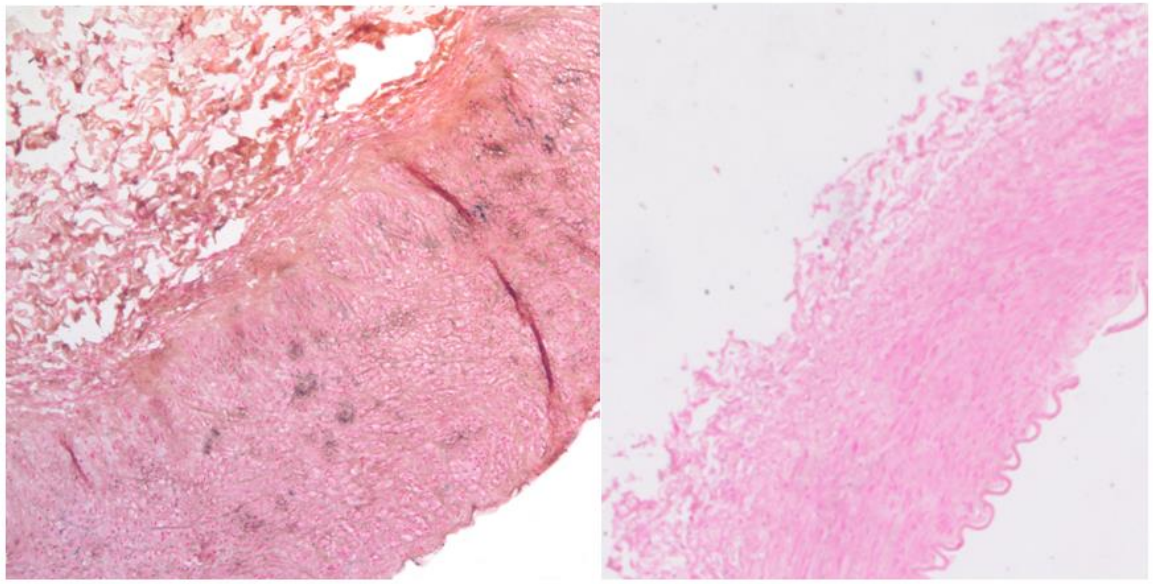
NSTEMI

Vascular pathology in ESRD

Vascular calcification in CKD



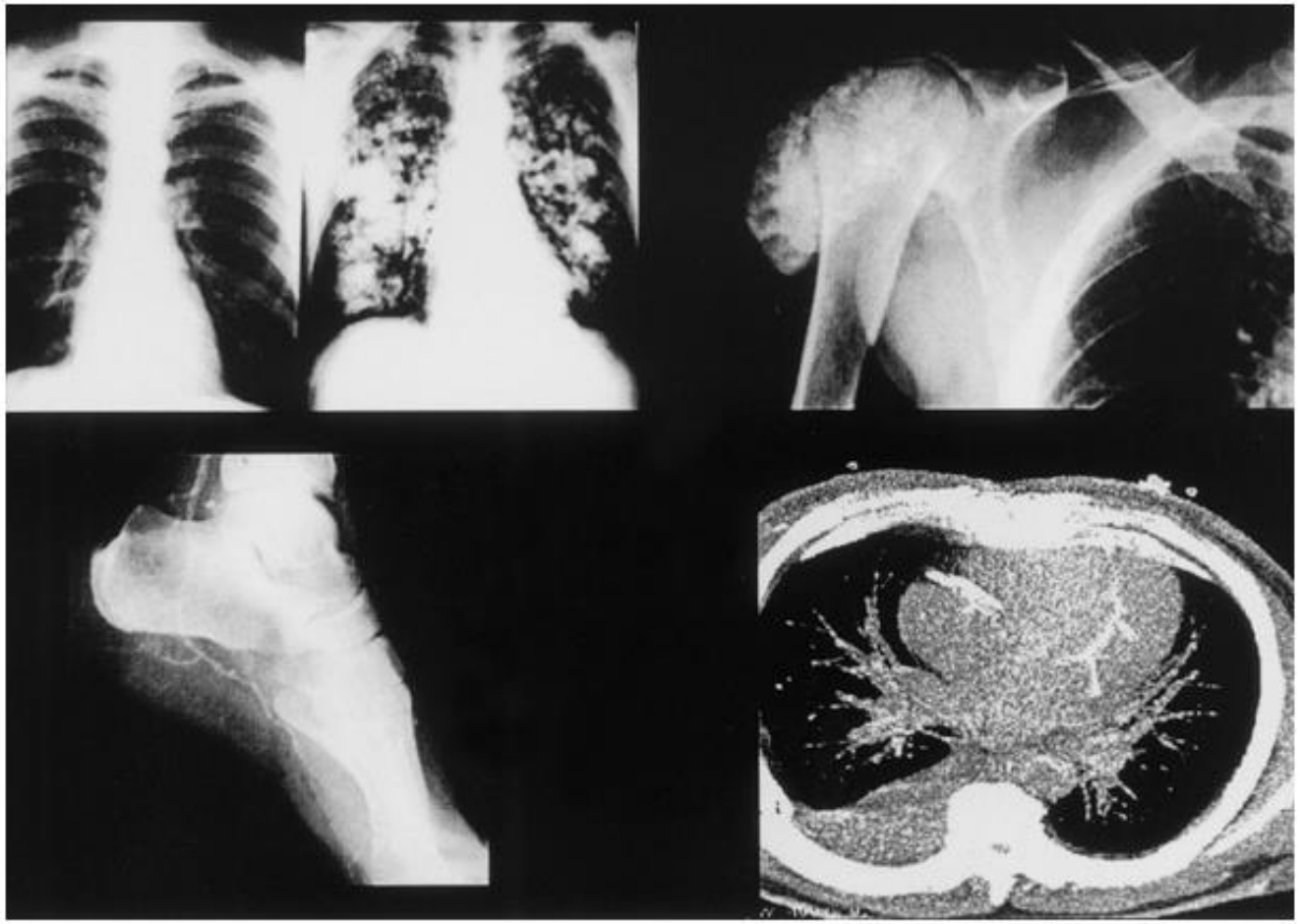
Medial calcification in CKD patients



Von Kossa Stain

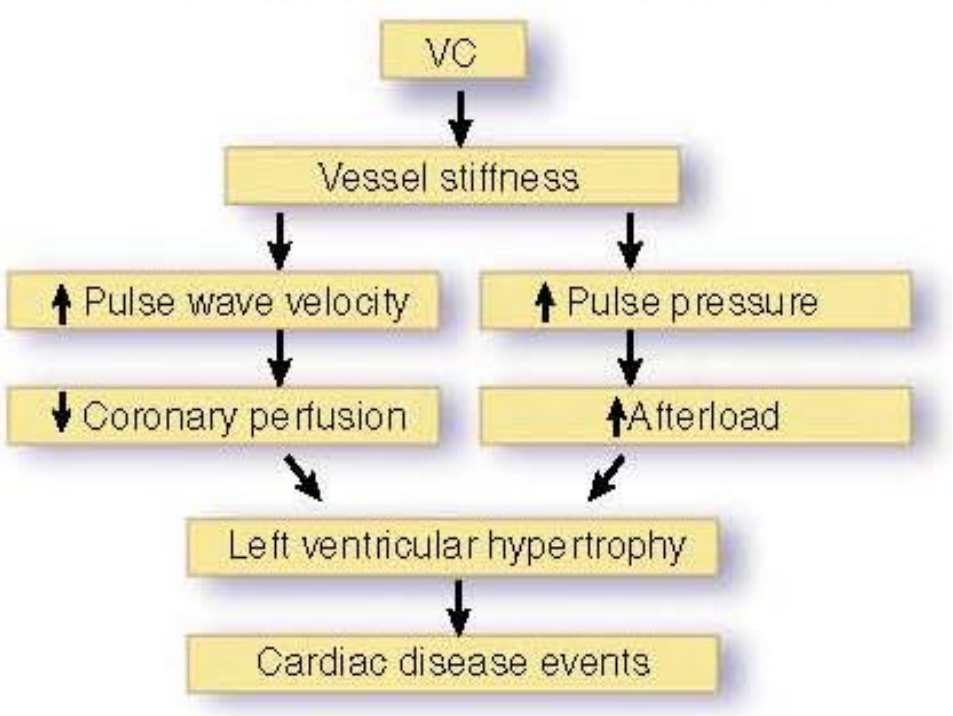
N Chitalia, et al. Accepted for Publication in Seminars in Dialysis

Extraskeletal manifestation of renal bone disease



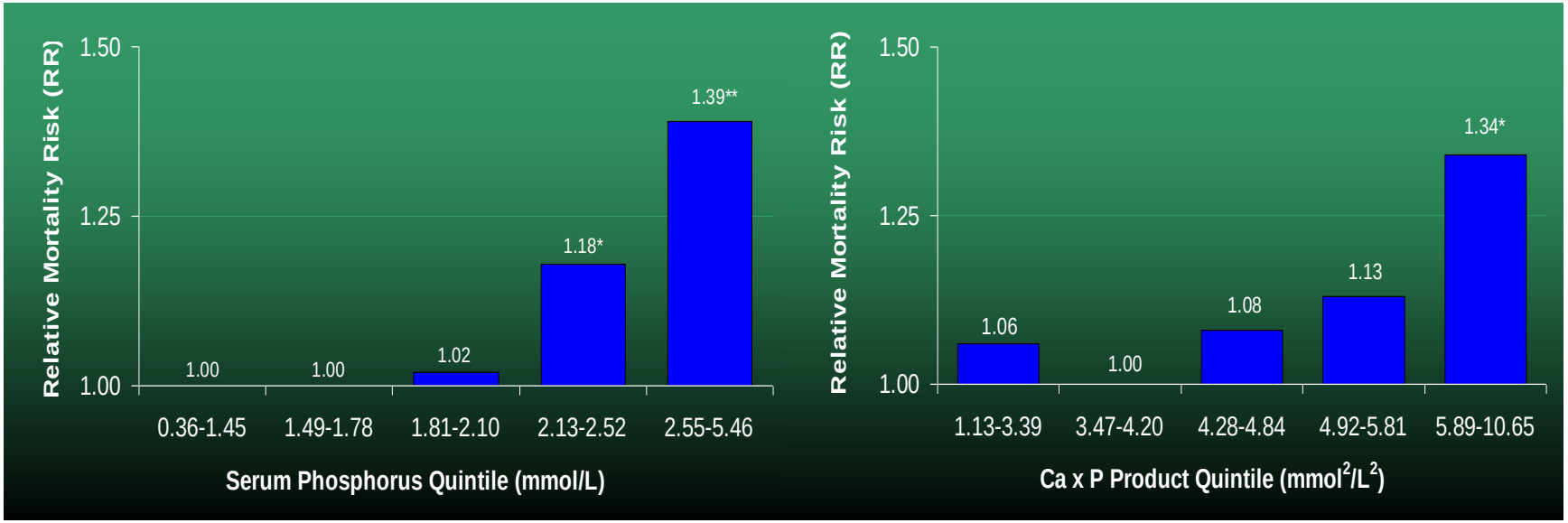
Brenner & Rector's. *The Kidney*. Seventh Edition 2004

CV effects of medial calcification/Arteriosclerosis



Keith A, Hruska et al. *Kidney International. 74(2):148-57, 2008 Jul*

Effects of Hyperphosphatemia and elevated Ca x P product on mortality in CKD



P=0.03 ***P*<0.0001 (N=6407)

Block GA, et al. *Am J Kidney Dis.* 1998;31:607-617

NKF-K/DOQI bone metabolism guidelines

Parameter	Target range
iPTH	**150–300 pg/mL 16.5–33.0 pmol/L**
Ca x P	**< 4.51 $mmol^2/L^2$**
Phosphorus	**1.10–1.78 mmol/L**
'Corrected' calcium	**2.10–2.37 mmol/L**

Aluminium level <2.2 mmol/l (60mg/l) (ferritin >100) – RA standards 2002

Calcium dosage Less than 1500mg elemental calcium

Eknoyan G *et al. Am J Kidney Dis* 2003;42(Suppl 3):1–201

Case Presentation

Mrs. Kamalben Patel, 42 year female CRF, no DM, first presentation

- Creatinine 250µmol/L, **Haemoglobin 10.5 g/dL**
- Non smoker, BMI 23, BP 145/85, Cholesterol 5.2 mmol/L, CRP 5.3
- Urinary Protein:creatinine ratio 50 mg/mmol
- Calcium 2.5mmol/L, Phos 2.2mmol/L, PTH 200

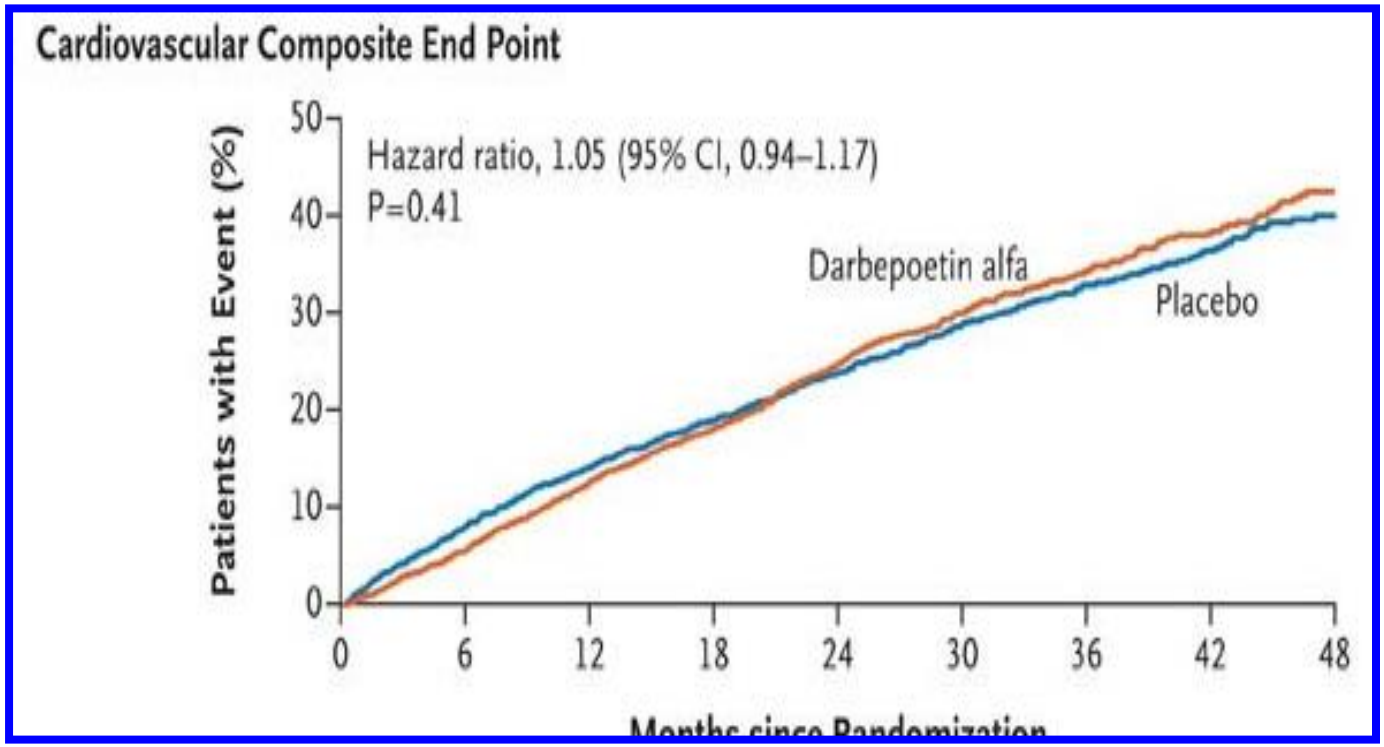
Medications: aspirin 75, amlodipine 10 mg, ramipril 10 mg

- At present her eGFR is 16 ml/min/1.73m^2

- She presents to A&E with chest pain; ECG T inv V4-V6; trop 1.2

NSTEMI

Anaemia correction



4038 diabetics CKD patients followed for 4 y
EPO group to achieve Hb 13 g%

Pfeffer NEJM 2009 361 2019

Case Presentation

Mrs. Kamalben Patel, 42 year female CRF, no DM, first presentation

- Creatinine 250µmol/L, Haemoglobin 10.5 g/dL
- Non smoker, BMI 23, BP 145/85, Cholesterol 5.2 mmol/L, CRP 5.3
- Urinary Protein:creatinine ratio 50 mg/mmol
- Calcium 2.5mmol/L, Phos 2.2mmol/L, PTH 200

Medications: aspirin 75, amlodipine 10 mg, ramipril 10 mg

- At present her eGFR is 16 ml/min/1.73m^2

- She presents to A&E with chest pain; ECG T inv V4-V6; trop 1.2

- **Does coronary intervention help?** NSTEMI

Benefits of coronary PCI in HD

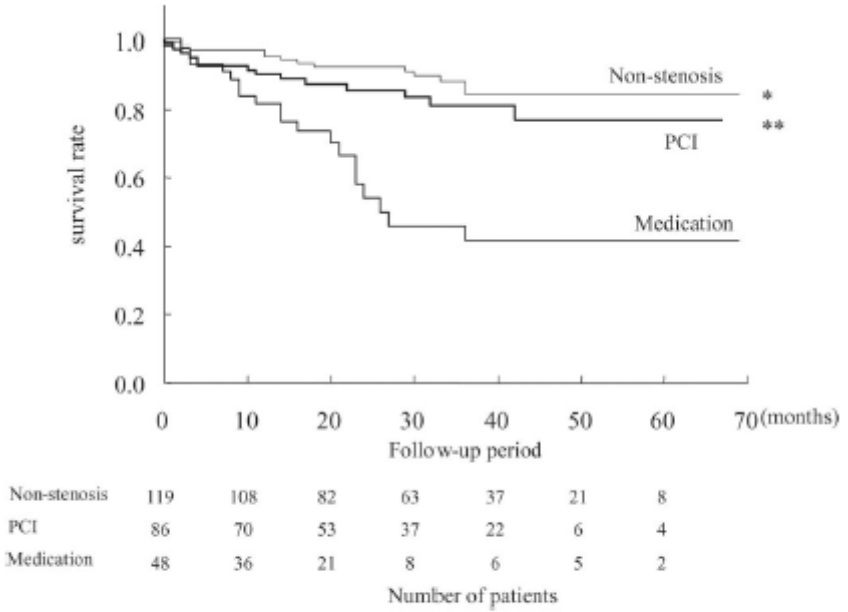


Figure 2. Kaplan-Meier analysis of cardiac survival among the three groups after coronary angiogram. $*P < 0.0001$ *versus* medication; $**P = 0.0006$ *versus* medication.

259 patients followed for 5 years

Yasuda JASN 2006 17 2322

CABG vs PCI in ESRD

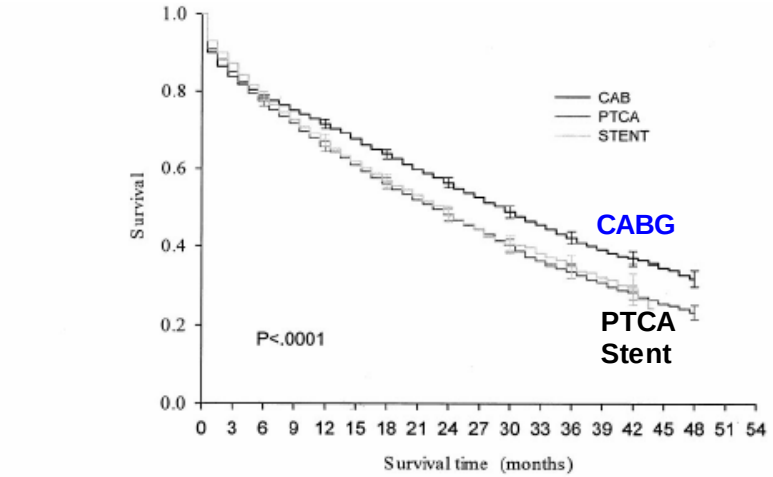


Figure 1. Estimated all-cause survival of dialysis patients after CABG, PTCA, and stenting. Bars indicate SEMs.

15700 patients followed for 4 years USRDS

Herzog Circulation 2002 106 2207


SPEED LIMIT 40
ONE WAY
ONE WAY
ONE WAY
ONE WAY
ONE WAY
ONE WAY
ONE WAY
http://go.to/funpic

So what did I say…..

- CKD is a CVD risk – graded relationship but all stages
- Risk factors of CVD in CKD – traditional and non traditional
- SCD commonest cause of CV mortality in ESRD
- Treatment of hypercholesterolemia probably beneficial in predialysis CKD, but no evidence in ESRD (for primary prevention)
- Phosphate control is important in CKD to prevent CV mortality
- Coronary revascularisation beneficial