Predictors of cardiovascular disease in the renal patient

Dr Shabbir Moochhala

Royal Free Hospital, London

Cause of death in prevalent RRT patients by cohort year
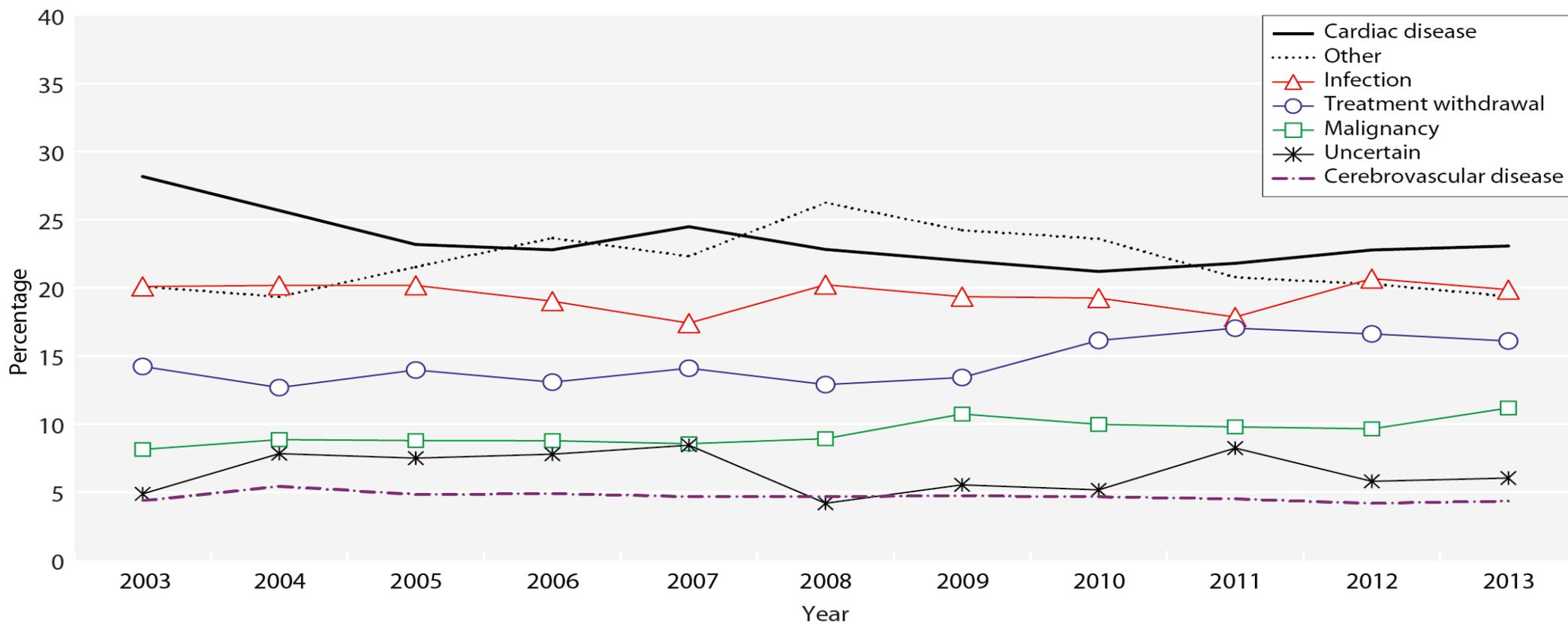
UK Renal Registry 18th Annual Report

ACCELERATED ATHEROSCLEROSIS IN PROLONGED MAINTENANCE HEMODIALYSIS

ARMANDO LINDNER, M.D., BERNARD CHARRA, M.D., DONALD J. SHERRARD, M.D., AND
BELDING H. SCRIBNER, M.D.

Abstract The survival experience of 39 patients receiving long-term regular hemodialysis in Seattle since 1960 was studied with particular reference to mortality and morbidity from arteriosclerotic cardiovascular complications. Mean age ($\pm$ 1 S.D.) was 37.0 $\pm$ 9.5 years for the group at the start of dialysis. Mean duration of treatment was 6.5 years (range, one to 13). Overall mortality was 56.4 per cent at the end of the 13-year follow-up period, and 14 of 23 deaths could be attributed to arteriosclerotic complications: myocardial infarction was responsible for eight, strokes for three, and refractory congestive heart failure for three deaths.

The incidence of these complications was many times higher than for normal and hypertensive groups of comparable age, and similar to rates found in Type 2 hyperlipoproteinemia. These results indicate that accelerated atherosclerosis is a major risk to long-term survivors on maintenance hemodialysis. (N Engl J Med 290:697-701, 1974)

"Overall, mortality was 56.4% at the end of the 13-year follow-up period.."
"14 of 23 deaths could be attributed to atherosclerotic complications".

Cause of Death in Patients with Reduced Kidney Function

Stephanie Thompson,* Matthew James,[†] Natasha Wiebe,* Brenda Hemmelgarn,[†]
Braden Manns,[†] Scott Klarenbach,* and Marcello Tonelli[†]
for the Alberta Kidney Disease Network

*Division of Nephrology, University of Alberta, Edmonton, Alberta, Canada; and [†]Division of Nephrology, University of Calgary, Foothills Medical Centre, Calgary, Alberta, Canada
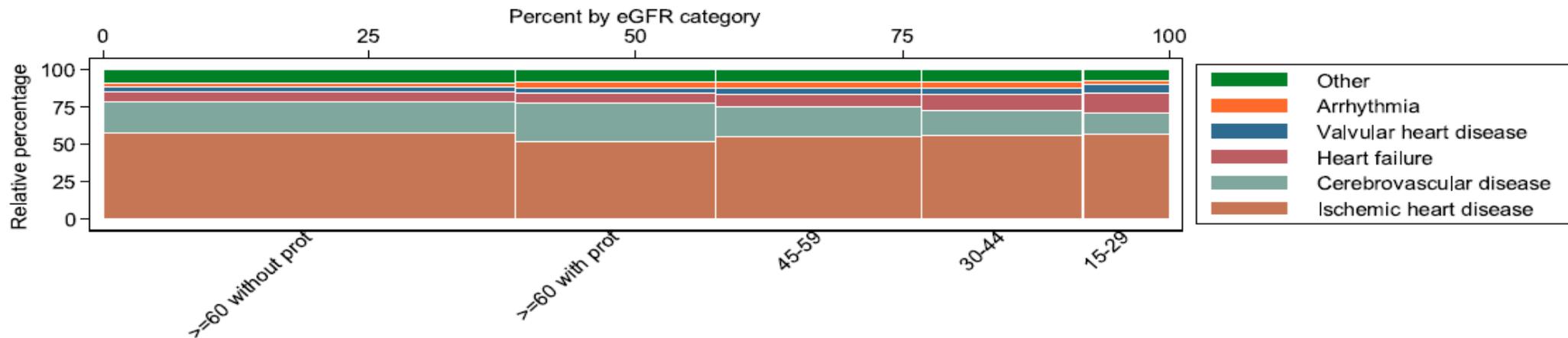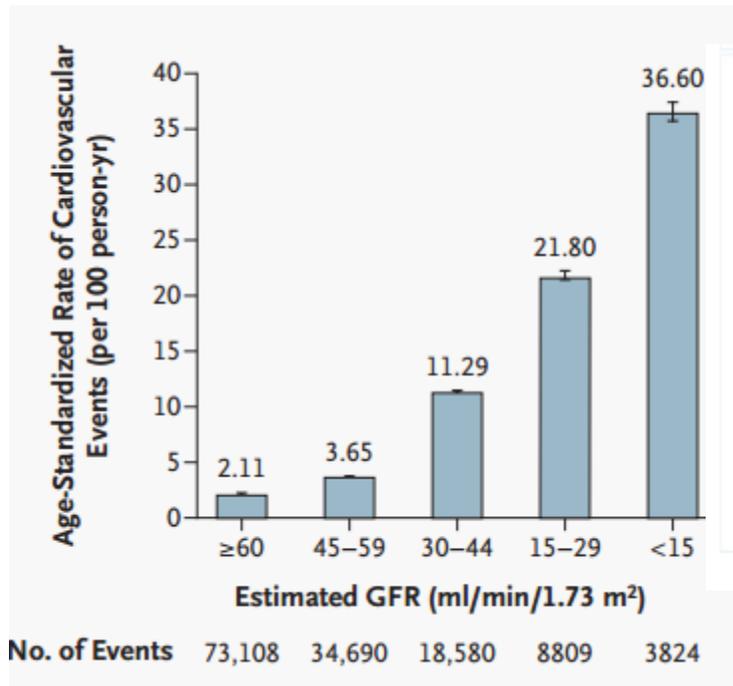
Cardiovascular deaths

Predictors of cardiovascular disease in the renal patient

- What can we use to predict cardiovascular outcomes in CKD patients?
- Does the pathophysiology guide us?
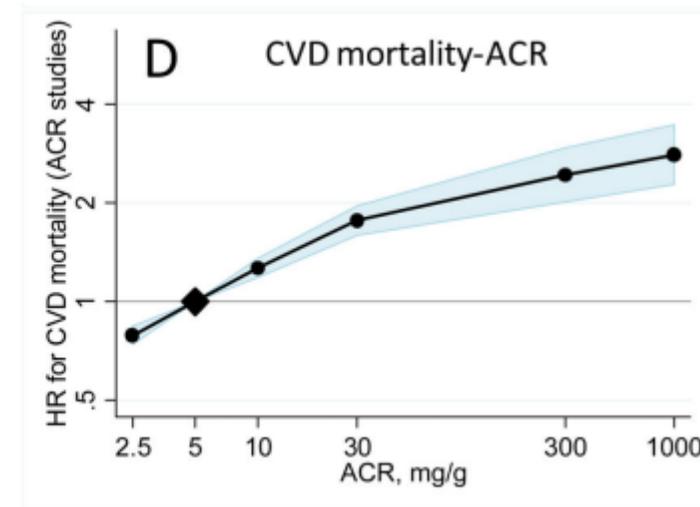- What can we do to reduce cardiovascular risk?

What can we use to predict cardiovascular outcomes in CKD patients?

Albuminuria is independently associated with cardiovascular mortality ... and so is eGFR

| No. of Events | 73,108 | 34,690 | 18,580 | 8809 | 3824 |

Rates of cardiovascular events for each CKD stage in 1,120,295 adults

Go et al 2004 NEJM

Association between cardiovascular mortality and (B) eGFR (D)ACR. Hazard ratios were adjusted for each other, age, sex, ethnicity, CVD history, blood pressure, diabetes, smoking.

Matsushita et al, Lancet 2010

Cardiovascular mortality prediction in CKD patients

	ACR <1	ACR 1-3	ACR 3-29	ACR ≥30
eGFR >105				
eGFR 90-105	Ref			
eGFR 75-90				
eGFR 60-75				
eGFR 45-60				
eGFR 30-45				
eGFR 15-30				

ACR in mg/mmol
eGFR in ml/min/1.75m²

Levey AS et al, Kidney Inter 2011;80-17-28

# Cardiovascular mortality prediction in CKD patients

	ACR <1	ACR 1-3	ACR 3-30	ACR ≥30
eGFR >105	0.9	1.3	2.3	2.1
eGFR 90-105	Ref	1.5	1.7	3.7
eGFR 75-90	1.0	1.3	1.6	3.7
eGFR 60-75	1.1	1.4	2.0	4.1
eGFR 45-60	1.5	2.2	2.8	4.3
eGFR 30-45	2.2	2.7	3.4	5.2
eGFR 15-30	14	7.9	4.8	8.1

ACR in mg/mmol
eGFR in ml/min/1.75m²

Levey AS et al, Kidney Inter 2011;80-17-28

High cardiovascular event rates occur within the first weeks of starting hemodialysis

Kai-Uwe Eckardt[1], Iain A. Gillespie[2], Florian Kronenberg[3], Sharon Richards[2], Peter Stenvinkel[4], Stefan D. Anker[5], David C. Wheeler[6], Angel L. de Francisco[7], Daniele Marcelli[8], Marc Froissart[9] and Jürgen Floege[10] on behalf of the ARO Steering Committee[11]
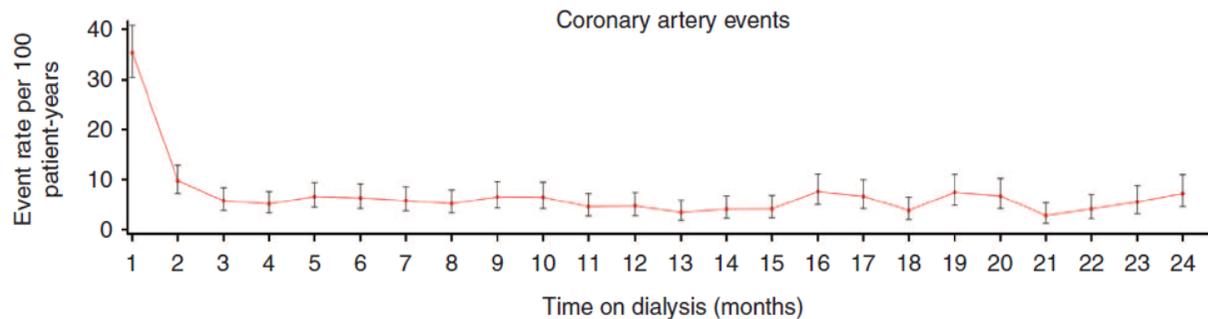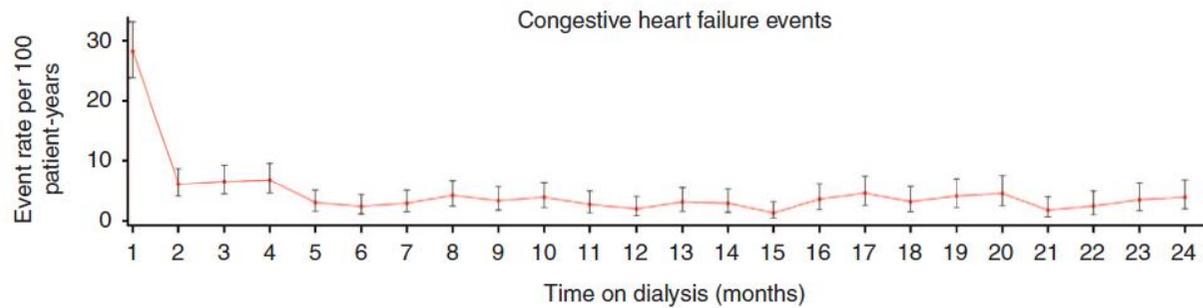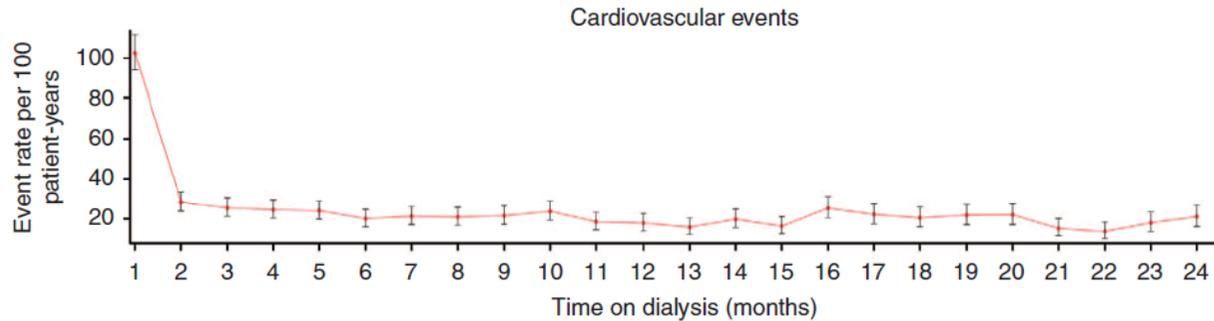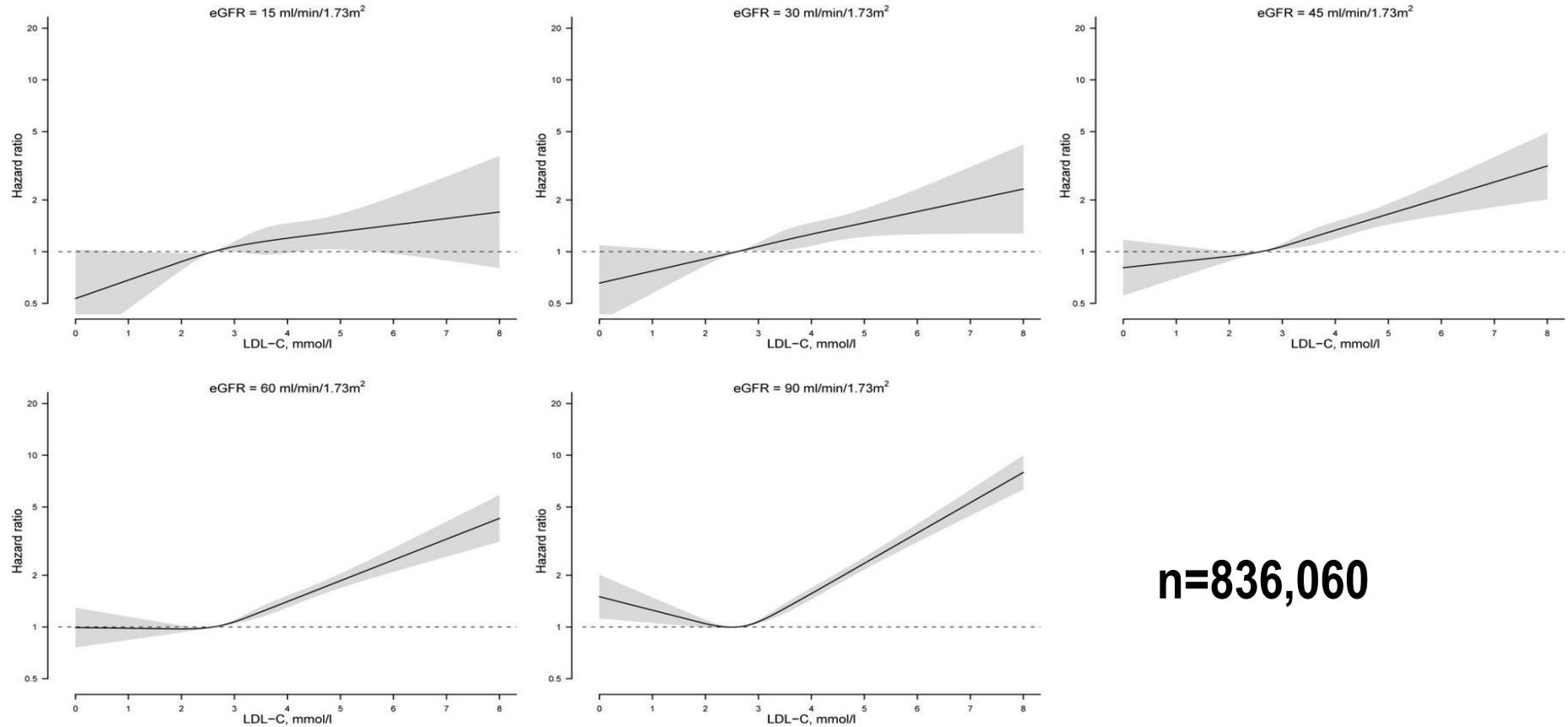
6308 patients commencing HD with 1449 patients experiencing 2405 events

1st year event rate: 30.2/100 person years (95% CI 28.7-31.7)

2nd year event rate: 19.4/100 person years (5% CI 18.1-20.8)

Kidney Int 2015;88:1127-25

Association between LDL and risk of MI in CKD patients

n=836,060

Marcello Tonelli et al. JASN 2013;24:979-986

Are there any new biomarkers?
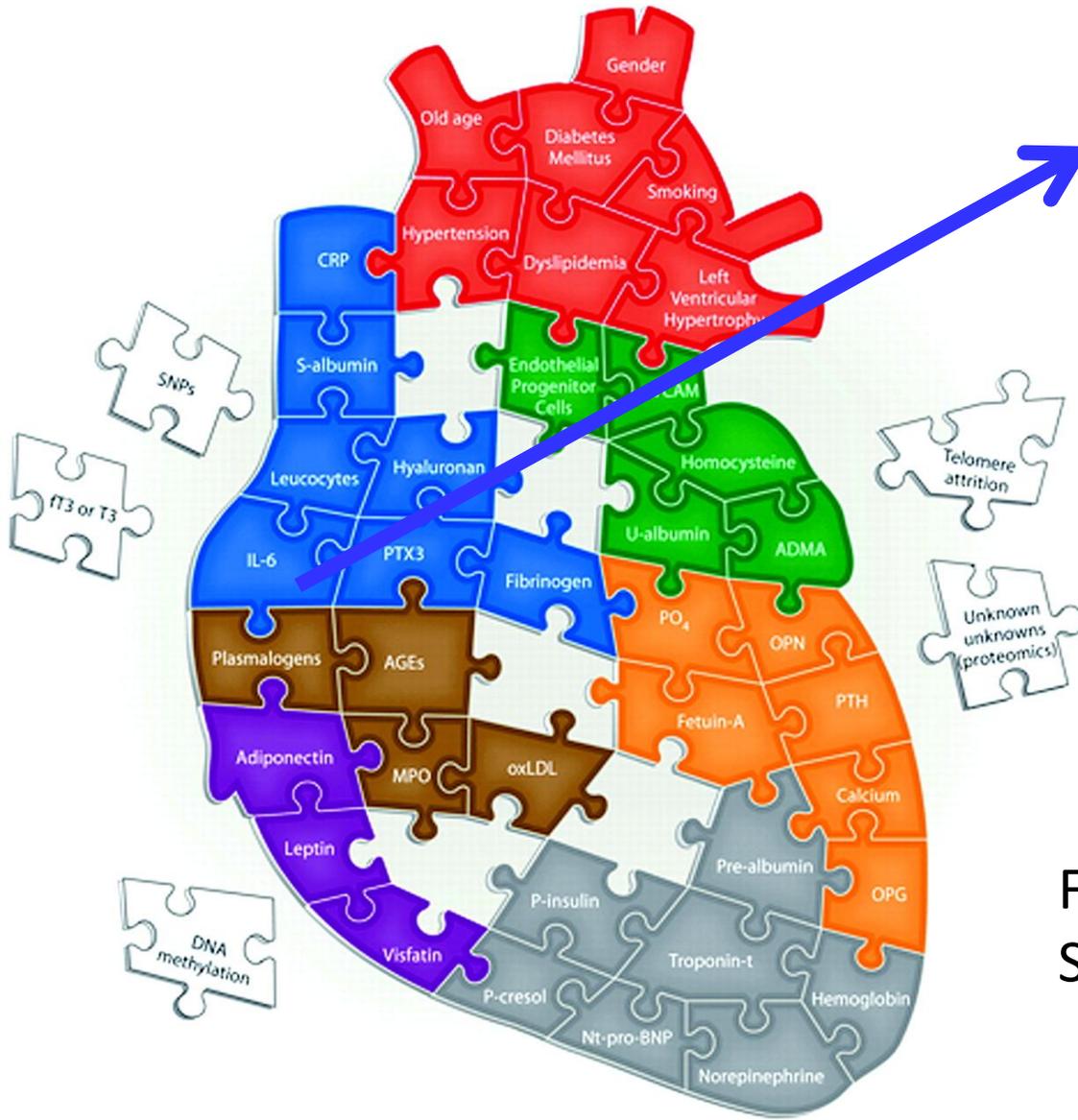
In 543 CKD stage 5 patients, only IL-6
- **correlates with clinical CV disease**
- **predicts all-cause mortality**

Sun et al CJASN June 2016

**Yes, there are biomarkers...
but age and comorbidity are better
predictors!**

Figure from : Stenvinkel et al, Clin J Am
Soc Nephrol. 2008 (2):505-21

Special considerations in renal transplant recipients

- Pre-existing cardiovascular disease is the most important risk factor
- All the other risk factors (general population + CKD) also apply
- But we're not good at using standard secondary prevention post-transplant
  - Only 24% of recipients were taking ACE/ARB at 6 months post-transplant
  - <40% were taking aspirin (only 60% even if pre-existing cardiovascular disease)

DeKAF study, Gaston et al Am J Transplant 2009 (8) 1811

Pathophysiology

- the reason why we still can't predict outcomes in CKD?

CKD alters the cardiovascular system's structure

Renal patients
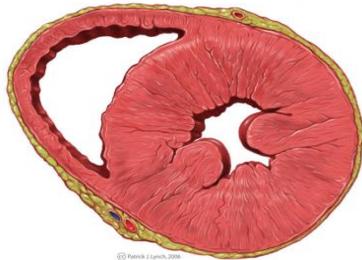
65% of cardiovasc deaths on dialysis are "sudden death"/arrhythmias, 25% to acute MI

Calcific uraemic arteriolopathy
-medial calcification of small arteries
-mortality 60-80%
-no treatment

General population

Most mortality due to acute MI

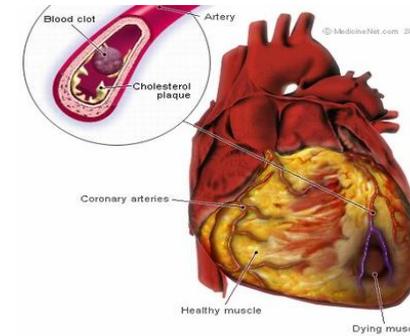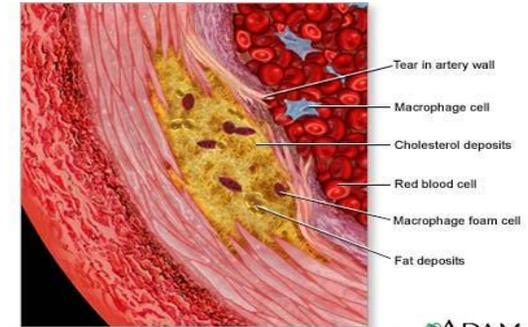

Atherosclerosis

-intimal calcification

These CO-EXIST in renal patients!
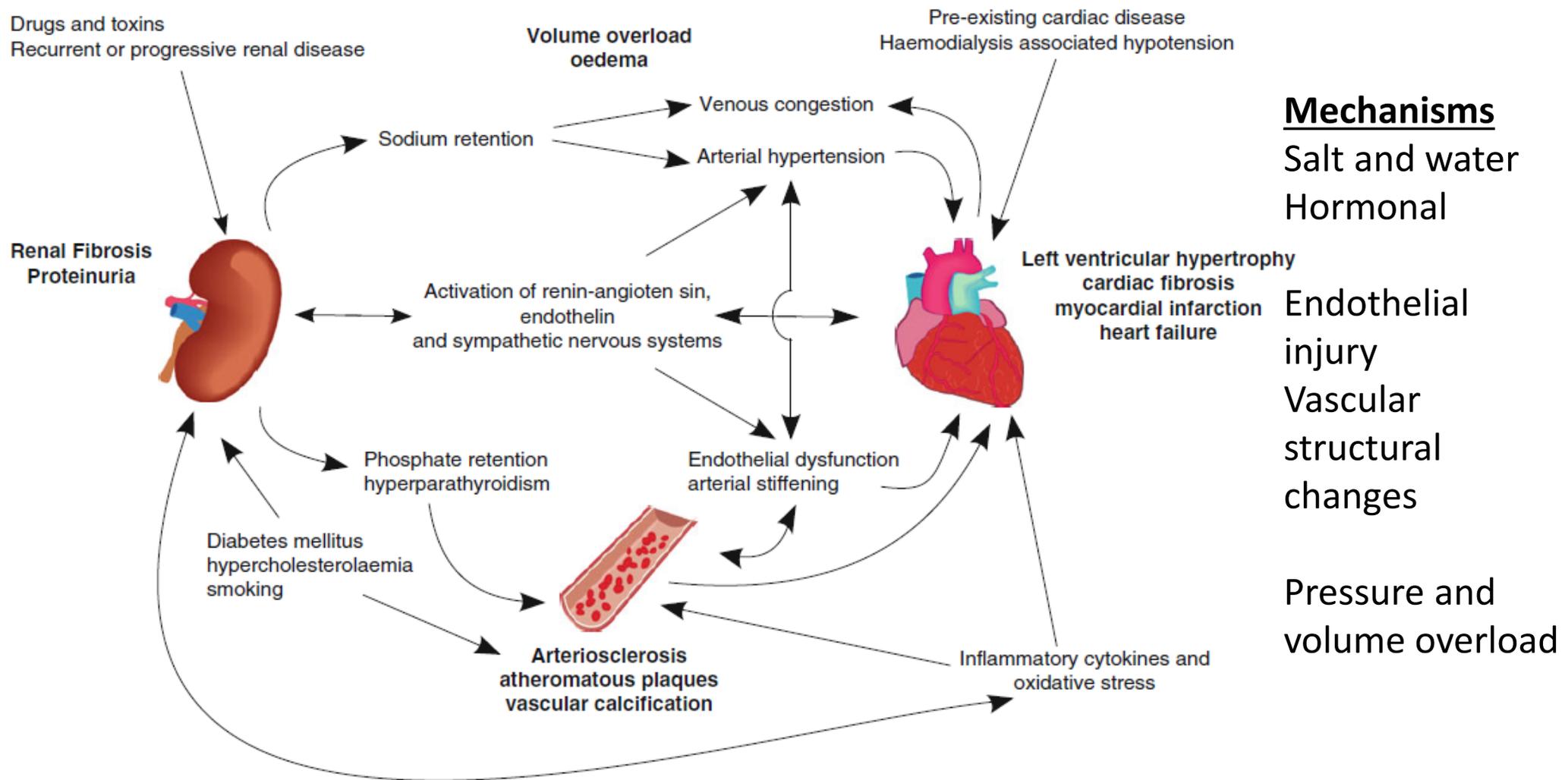
Mechanisms of cardiovascular disease in CKD

(Caplin & Wheeler, Practical Nephrology 2014)

A

Atherosclerosis

Electrical instability & arrhythmia

Calcification

Diastolic dysfunction

Fibrosis

Dilatation

LVH

B

Atherosclerosis

Vascular calcification

Plaque rupture

Thrombosis

High blood pressure
Lipids abnormalities
Insulin resistance
Endothelial dysfunction
Oxidative stress

Uremic toxins
Salt & fluid retention
Calcium-phosphate abnormalities
Vit D & receptors, FGF23 dysregulation
Anaemia & EPO resistant

Chronic Inflammation
Neurohormonal abnormalities
Protein energy wasting
Pro-fibrogenic cytokines
Pro-inflammatory cytokines

Early CKD → Advanced CKD → Dialysis or kidney transplantation

What can we do to reduce cardiovascular risk?

Let's start with what we know

Non-CKD meta-analysis: lower BP is better

123 studies including 613,815 participants

Ettehad D et al Lancet 2016;387:957-67
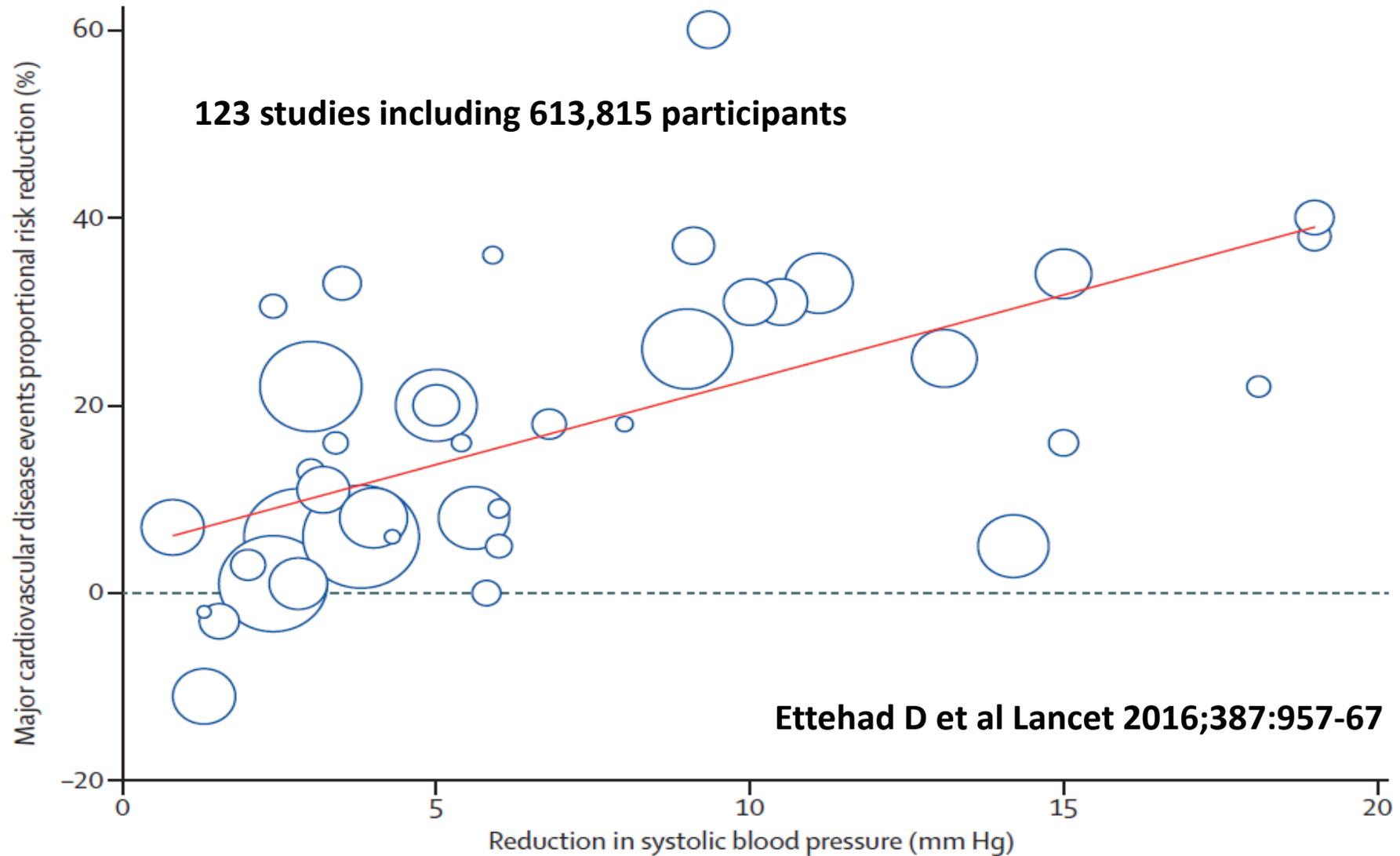
Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis

Dena Ettehad, Connor A Emdin, Amit Kiran, Simon G Anderson, Thomas Callender, Jonathan Emberson, John Chalmers, Anthony Rodgers, Kazem Rahimi

Impact of blood pressure lowering in patients with or without CKD:

Subgroup	Studies	Baseline SBP	Events Intervention	Participants Intervention	Events Control	Participants Control	RR per 10 mmHg lower SBP	RR (95% CI)
Major Cardiovascular Events								
CKD*	6	147	904	4663	818	4106		0.84 [0.73; 0.96]
No CKD	12	145	1788	26103	2277	25306		0.68 [0.62; 0.75]
Fixed effect model								0.73 [0.68; 0.78]

Test for interaction: p=0.0122   p=0.012
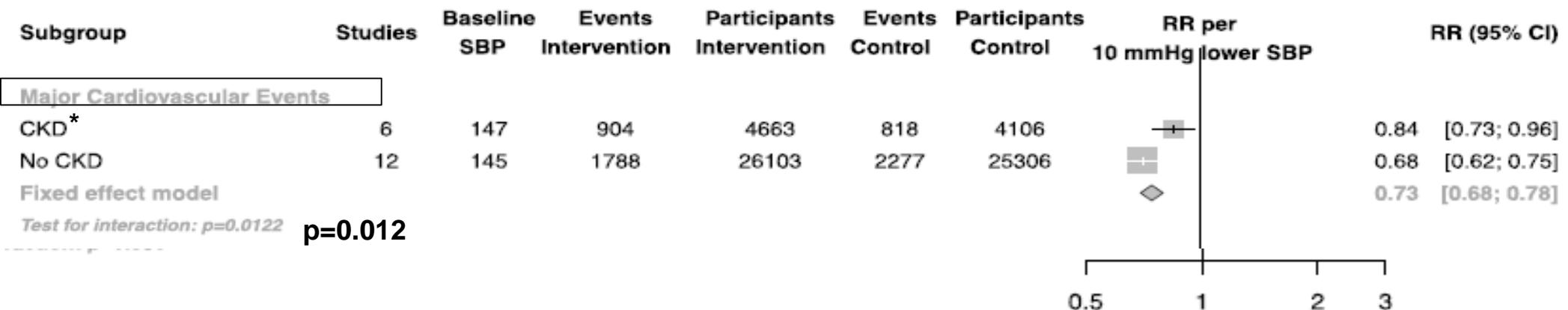
* Predominantly stage 3A CKD

Dyslipidaemia in CKD

	Lipoprotein Pattern	Blood Lipid Abnormality
Nephrotic Syndrome	Accumulation of LDL	High Cholesterol
CKD stages 1-2	Usually normal	Usually normal
CKD stages 3-5	Accumulation of VLDL Smaller denser LDL Modifications of HDL	High triglycerides Normal or low cholesterol

Adapted from Harber M, Practical Clinical Nephrology, Springer-Verlag, London 2014

SHARP: Major Atherosclerotic Events

Lancet 2011;377:2181-92

Risk ratio 0.83 (0.74 – 0.94)
(16.5% reduction in CV events)

Placebo

Ezetimibe 10 mg
/simvastatin 20 mg

Proportion suffering event (%)

Years of follow-up

Atorvastatin and cardiovascular events in haemodialysis patients with type II diabetes

Relative Risk Reduction 8 % (95 % CI: -23%, +10%, P=0.37)

N=1255 HD pts with type 2 diabetes
Cardiac death, non-fatal MI or stroke
Mean follow-up 4 years

— Placebo
— Atorvastatin 20 mg
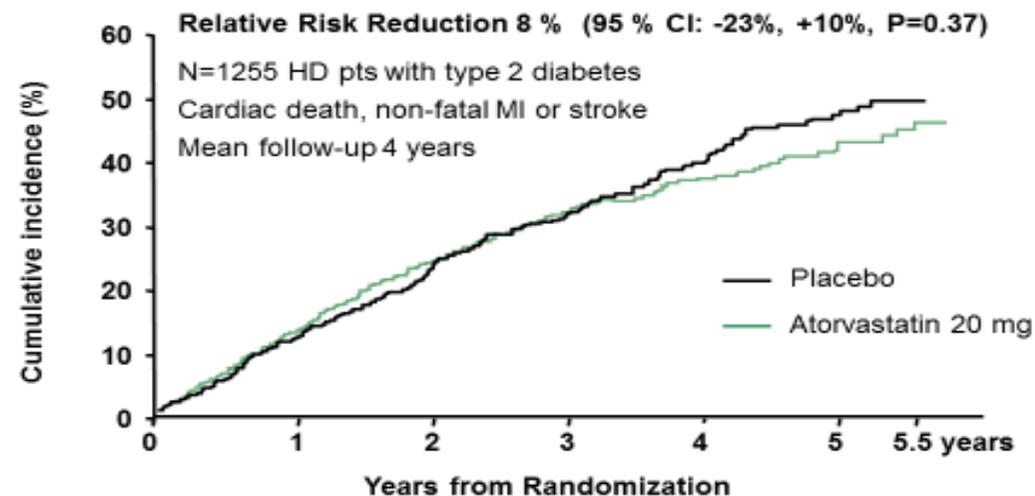
Placebo	636	532	383	252	136	51	29
Atorva	619	515	378	252	136	58	19

Wanner et al NEJM 2006;353:238-48

Rosuvastatin and cardiovascular events in patients undergoing hemodialysis (AURORA)

— Placebo
— Rosuvastatin

Hazard ratio, 0.96
P=0.59
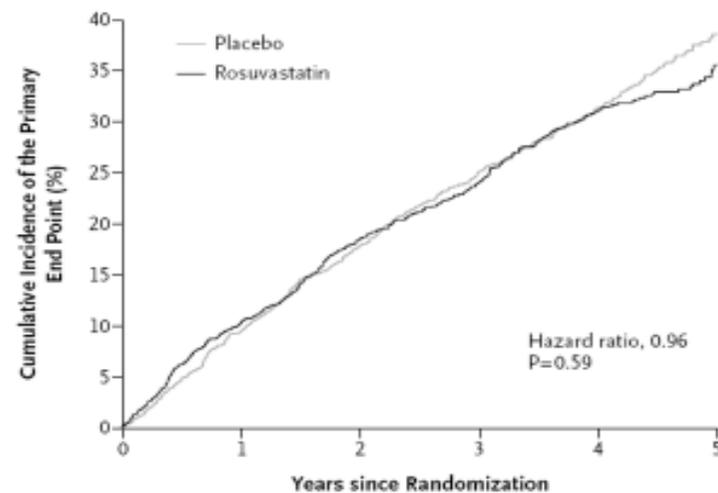
No. at Risk
Placebo	1384	1163	952	809	534	153
Rosuvastatin	1390	1152	962	826	551	148

Felstrom et al NEJM 2009;360:1395-407

RECOMMENDATION 2: PHARMACOLOGICAL CHOLESTEROL LOWERING TREATMENT IN ADULTS

- 2.1.1:	In adults aged ≥50 years with CKD 3-5 ND, we recommend treatment with a statin or statin/ezetimibe combination. (1A)

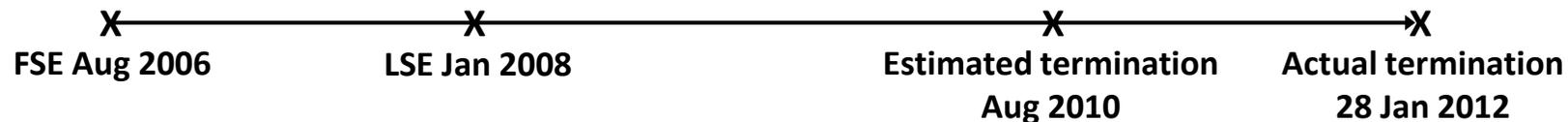- 2.1.2:	In adults aged ≥50 years with CKD 1-2 we recommend treatment with a statin. (1B)

KDIGO Lipid Work Group, KI Suppl 2013 (3) 259

Targetting CKD-MBD – the EVOLVE study

Placebo plus standard care (n=1,935)

Trial Population
- **Haemodialysis**
- **iPTH ≥300 pg/mL**
- **Ca ≥2.1 mmol/L**

- **Randomised (1:1), double-blind, placebo-controlled study**
- **Event-driven: 1,882 events needed for 88% power to detect a 20% treatment effect at an alpha level of 0.044**

Cinacalcet plus standard care (n=1,948)

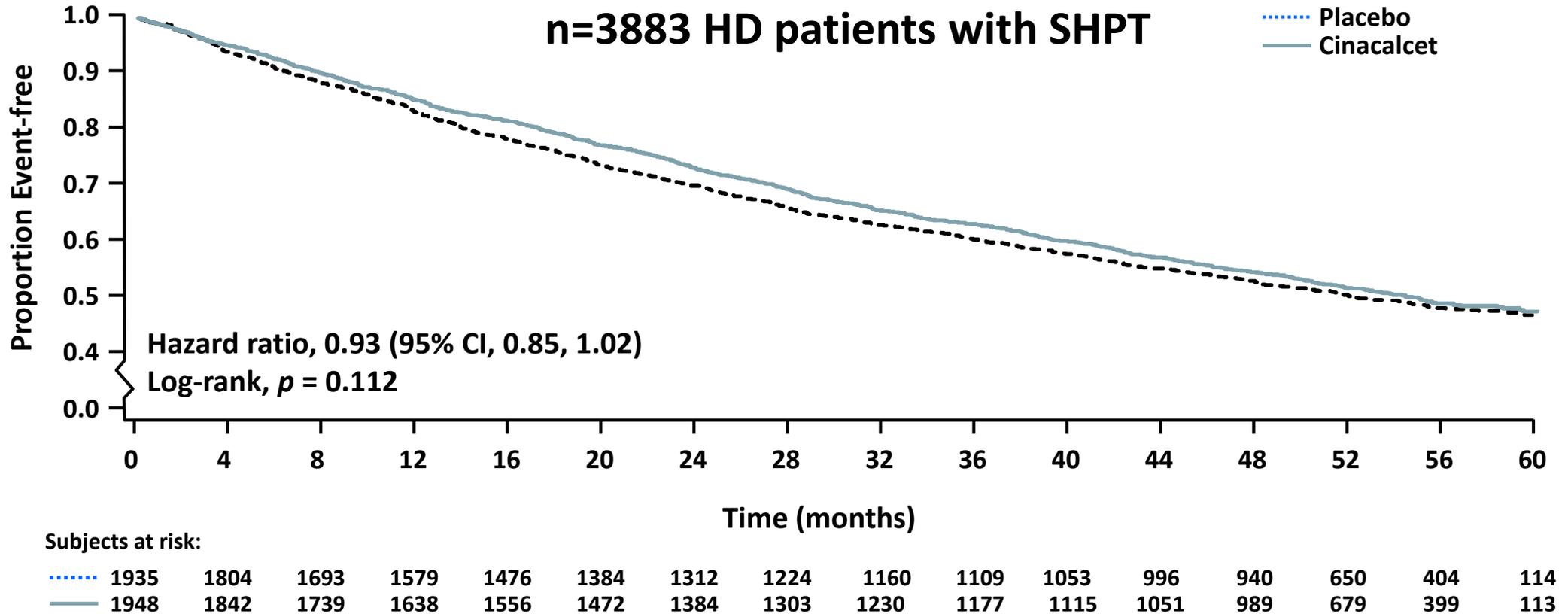|			
FSE Aug 2006	**LSE Jan 2008**	**Estimated termination Aug 2010**	**Actual termination 28 Jan 2012**

Primary endpoint

Time to the primary composite endpoint comprising: all-cause mortality
or nonfatal CV events (myocardial infarction, hospitalisation for unstable angina, heart
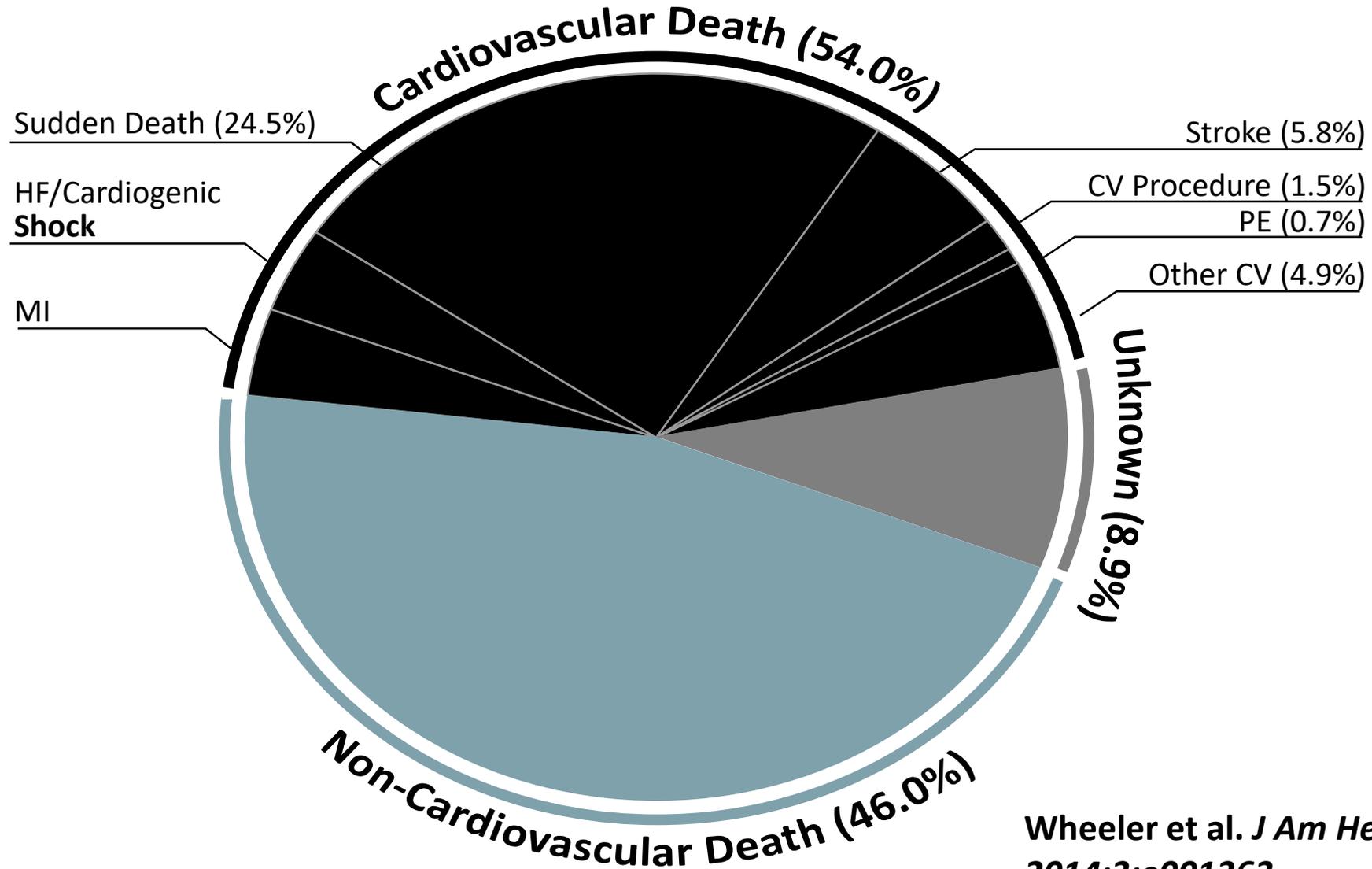failure or peripheral vascular event)

Secondary endpoints

Fracture, PTX, CV death, stroke; components of primary composite endpoint

EVOLVE: Kaplan-Meier Plot of Primary Composite Endpoint (ITT)

n=3883 HD patients with SHPT

Hazard ratio, 0.93 (95% CI, 0.85, 1.02)
Log-rank, *p* = 0.112

Placebo
Cinacalcet

Proportion Event-free

Time (months)

Subjects at risk:

	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60
Placebo	1935	1804	1693	1579	1476	1384	1312	1224	1160	1109	1053	996	940	650	404	114
Cinacalcet	1948	1842	1739	1638	1556	1472	1384	1303	1230	1177	1115	1051	989	679	399	113

Chertow GM et al. N Engl J Med 2012;367:2482–94

Causes of Death in the EVOLVE Study Population

Cardiovascular Death (54.0%)

Sudden Death (24.5%)

HF/Cardiogenic **Shock**

MI

Stroke (5.8%)

CV Procedure (1.5%)

PE (0.7%)

Other CV (4.9%)

Unknown (8.9%)

Non-Cardiovascular Death (46.0%)
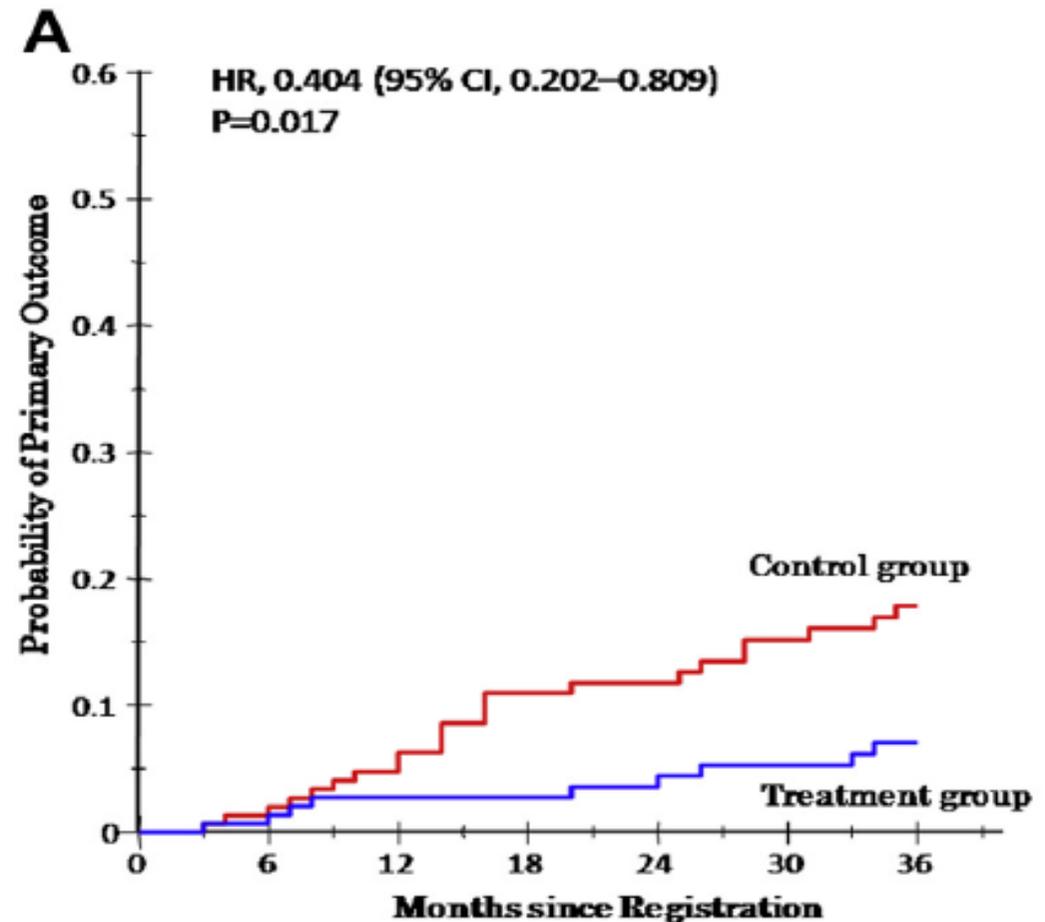
Wheeler et al. *J Am Heart Assoc. 2014;3:e001363.*

Spironolactone associated with lower mortality in haemodialysis patients

Open label, n=309 oliguric HD patients
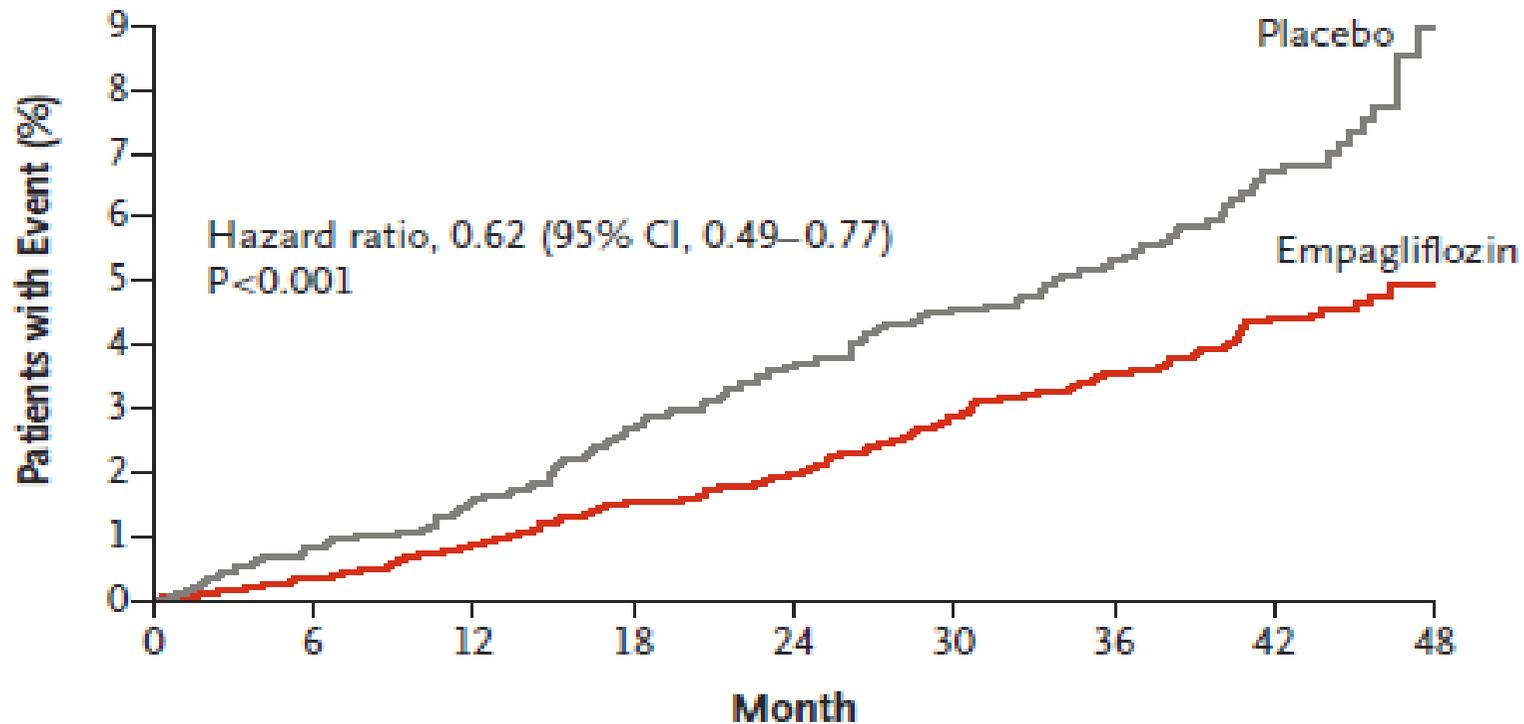157 assigned Spironolactone 25mg
152 controls

Primary Outcome Fatal and non Fatal CV events

HR 0.404 (95% CI) 0.202-0.809 p<0.017

65% mortality reduction

Matsumoto et al J Am Coll Cardiol 2014;63:528-536.

SGLT-2 inhibitor: deaths from cardiovascular causes

Hazard ratio, 0.62 (95% CI, 0.49–0.77)
P<0.001

Zinman B et al NEJM 2015;373:2117-2128

Conclusions

- Atherosclerosis is one of several cardiovascular pathologies observed in CKD becoming relatively less important in ESRD
- Decreased eGFR and increased urinary albumin excretion independently predict higher risk of cardiovascular disease.
- Statin-based regimens safely reduce the risk of atherosclerotic cardiovascular events in CKD patients (less benefit in ESRD)

With thanks to Professor David Wheeler

Thank you