October 16 - 18
14th EDITION 2015

NO CONFLICT OF INTEREST TO DECLARE

End-stage renal disease and other arrhythmias: what relationships and clinical implications?

Dr Charlie Ferro

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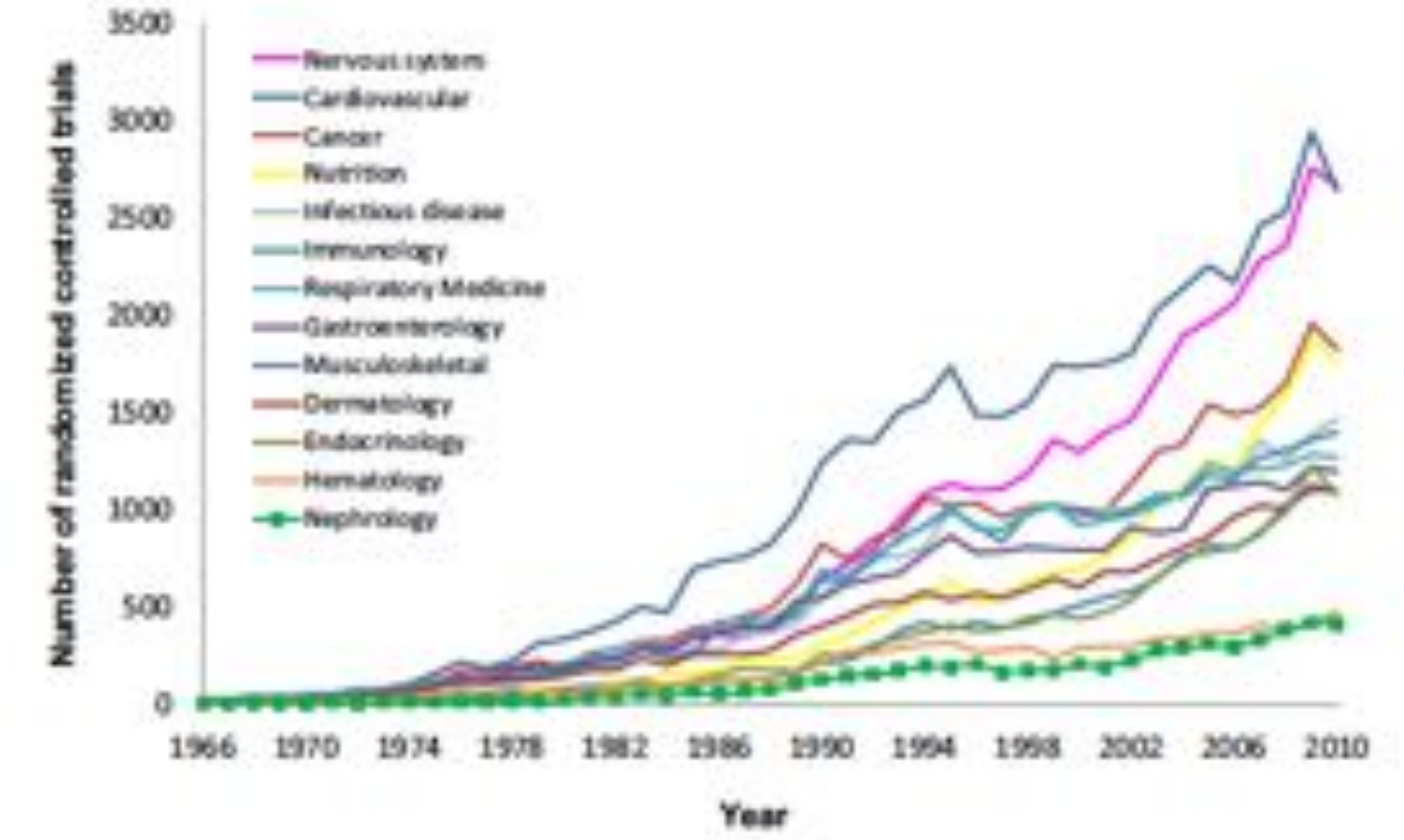
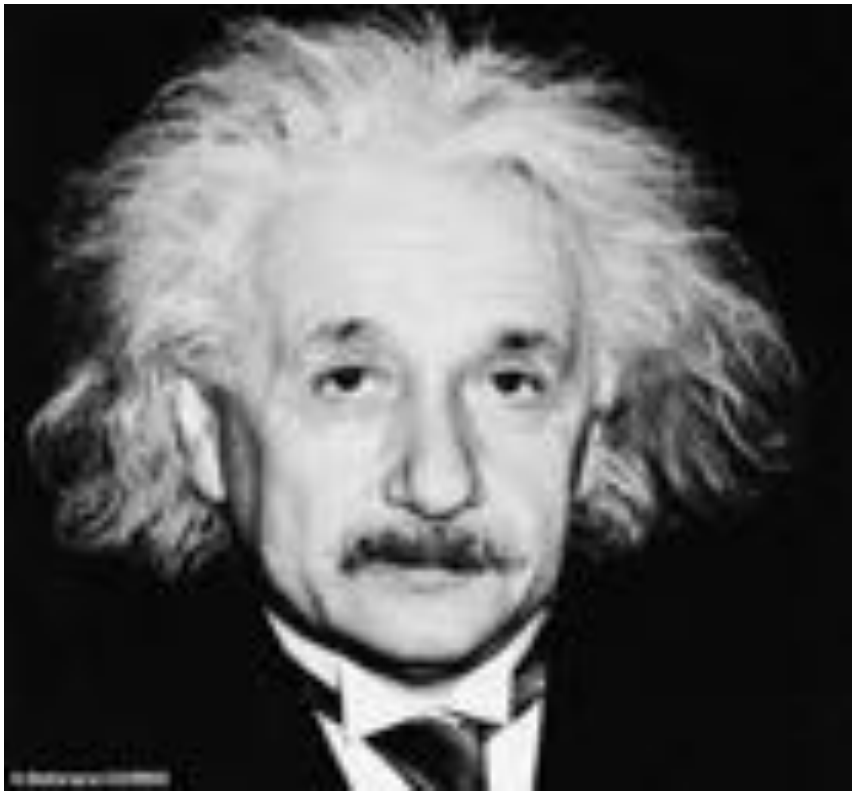
“Birmingham has more miles of canals than Venice and more trees than Paris. But, unfortunately for the canals and trees, they are in Birmingham and not Venice or Paris. This makes them all quite sad.”

Cardiologists and nephrologists



Palmer et al AJKD 2011

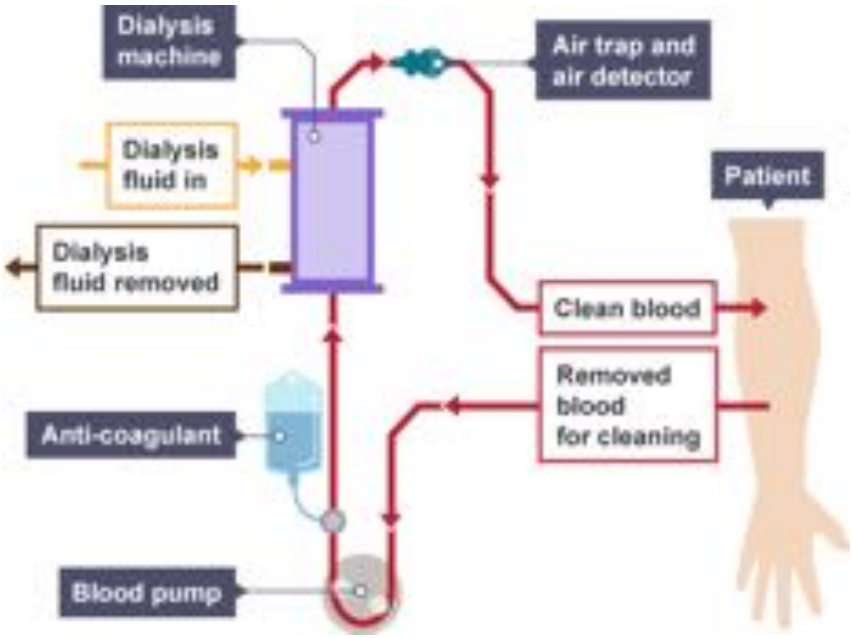
Quality as well as quantity



Plan

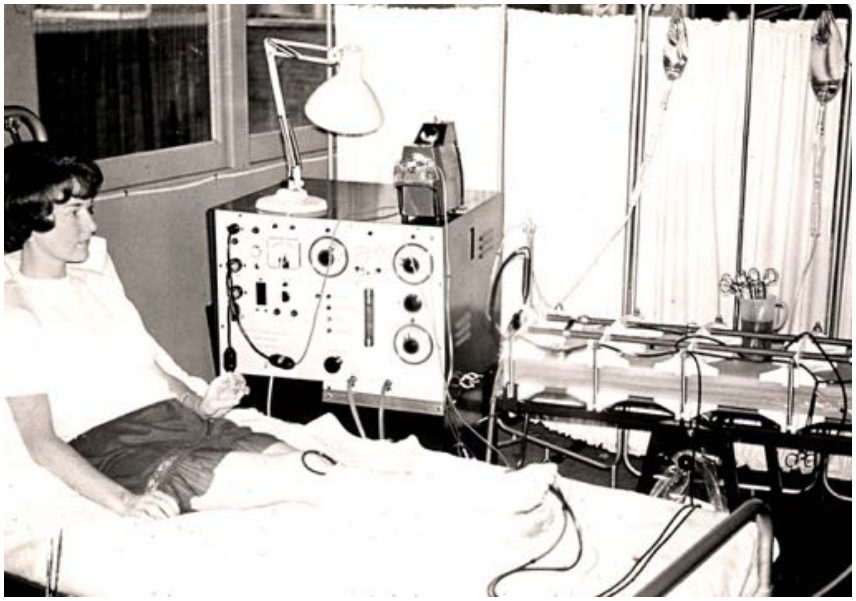
- Haemodialysis?
- Overview of Arrhythmias in ESKD
- Sudden Cardiac Death
- Causes
- Potential therapeutic options
- The Future

Haemodialysis



- 3 x weekly for 4 hours ie intermittent…
- BUT week = 7 days
- Gives a creatinine clearance of approx 10 ml/min
- Does not replace all the other kidney functions:
  - Ca/Phos/Vit D axis
  - Erythropoietin synthesis
  - Middle/large molecule clearance?
  - Etc, etc

Dialysis has not changed much: patients have!



How co-morbid are dialysis patients

Birmingham?

Reality

- Hypertension 89%
- Diabetes 66%
- PVD 30%
- CHF 39%
- MI 16%
- Angina 5%
- COPD 19%
- Cancer 19%
- Rh arthritis 7%

Salter et al BMC Geriatrics 2015

Arrhythmias are common in dialysis patients

Monitoring in Dialysis (MID) Study

- 50 haemodialysis patients – 6 months
- Reveal XT™ Implantable Cardiac Monitoring
- Quantify clinically significant arrhythmias
  - VT ≥ 130 bpm for ≥ 30 seconds
  - Asystole ≥ 3 seconds
  - Bradycardia ≤ 40 bpm for ≥ 6 seconds
  - Symptomatic arrhythmias

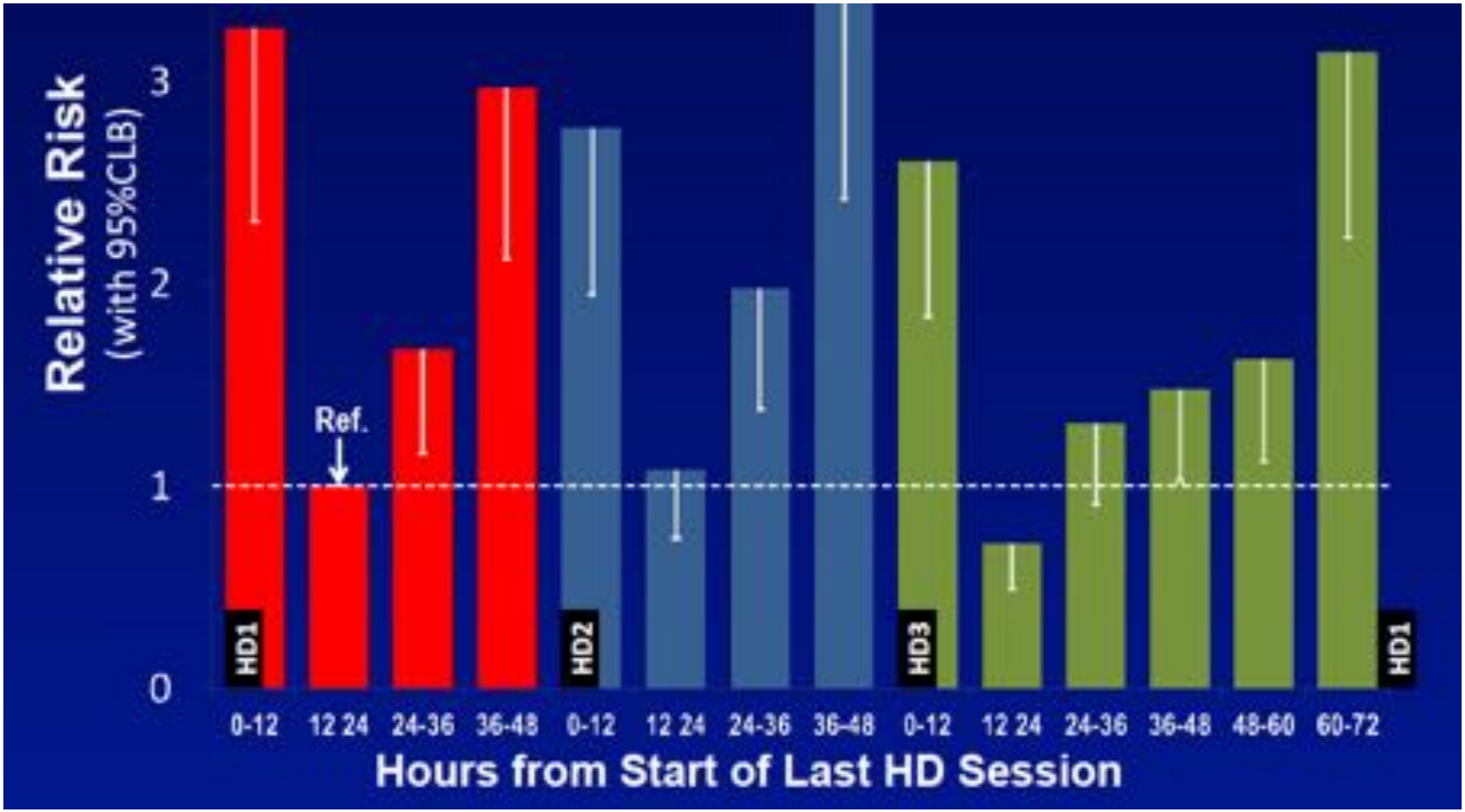
Preliminary results published in abstract form

Arrhythmias Confirmed by ECG Review

	Review Confirmed Arrhythmic episodes	Review-confirmed Arrhythmias by Type:					
		Atrial	**Brady**	**Asystole**	**Ventricular**	**Sinus Tach**	**Patient Marked**
Number of events (% of total)	7801 (100%)	4478 (57.4%)	1197 (15%)	28 (0.4%)	706 (9.1%)	3165 (41%)	183 (2.3%)
Subjects with events (% of implanted)	50 (100%)	46 (92%)	13 (26%)	6 (12%)	38 (76%)	42 (84%)	35 (70%)
Expected events per patient month (95% CI)	29.7 (19.2-46.0)	16.4 (10.2-26.5)	5.2 (1.3-20.0)	0.1 (0-0.3)	2.7 (1.6-4.5)	11.9 (7.0-20.3)	0.7 (04-1.0)

Preliminary results published in abstract form

Timing of Arrhythmias

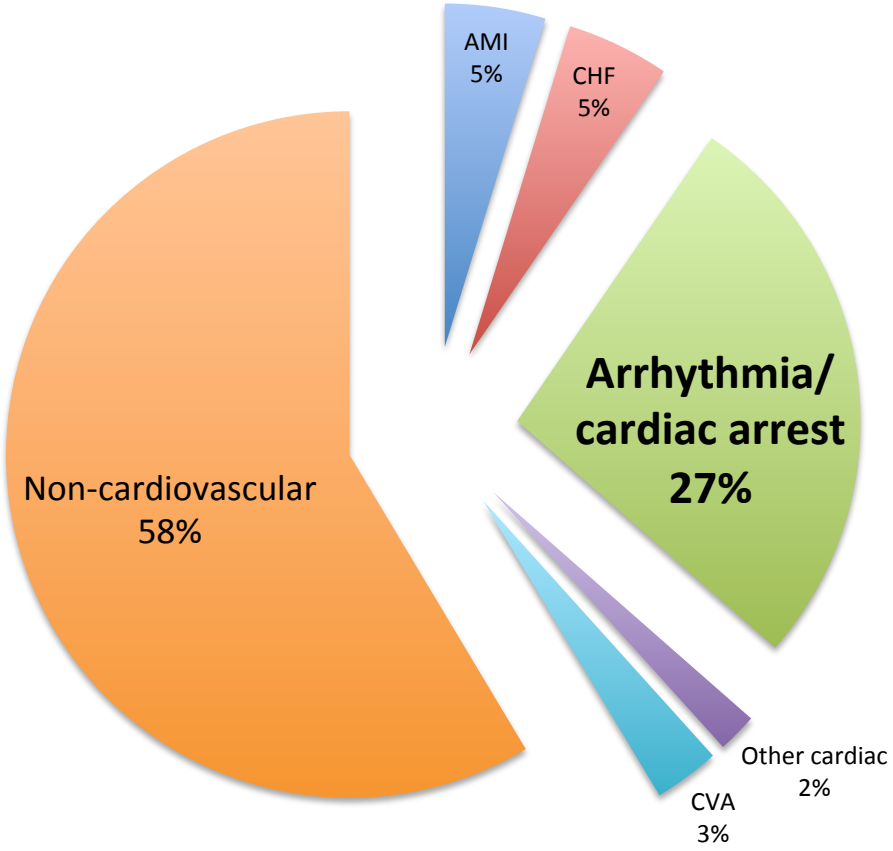


Preliminary results published in abstract form

Sudden Cardiac Death

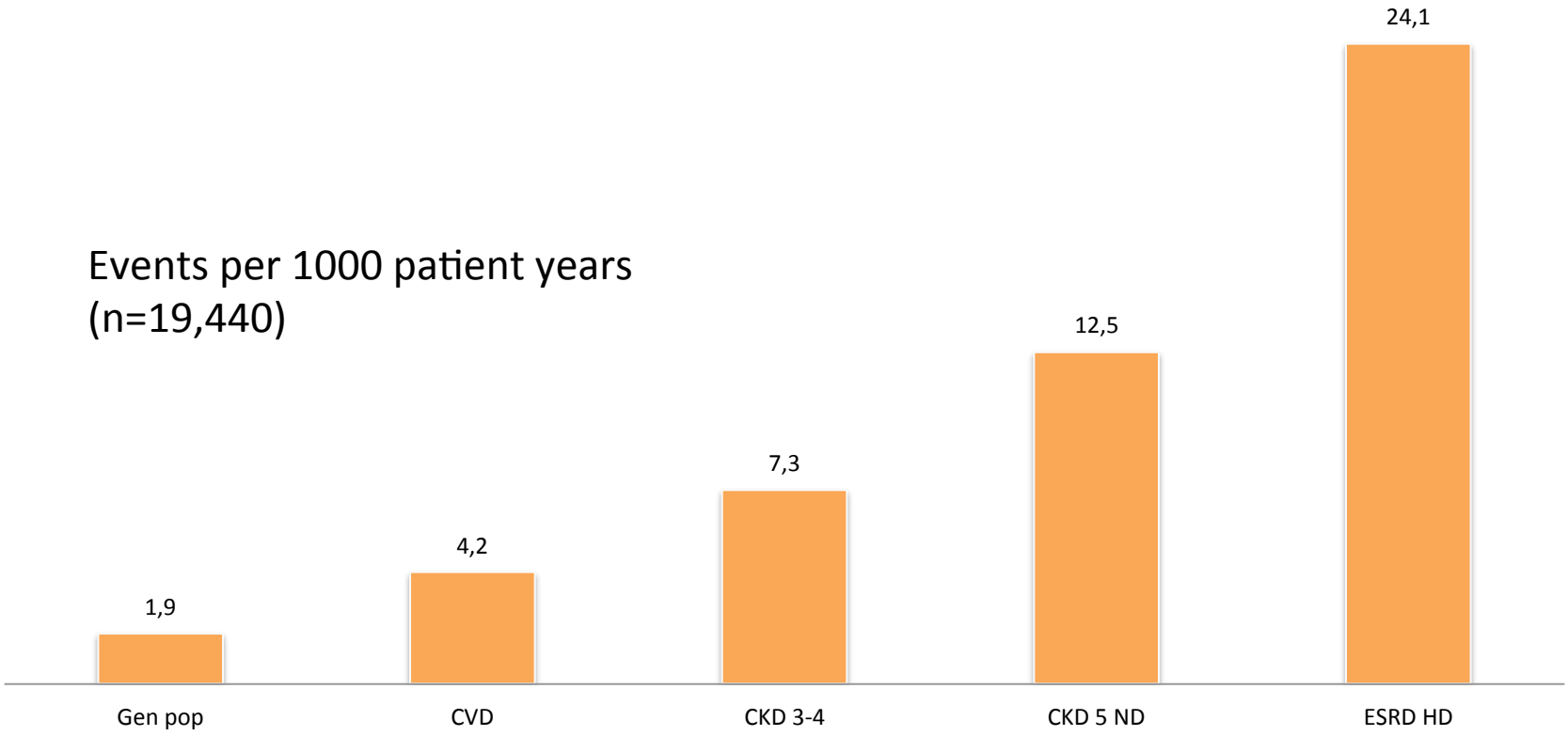
Sudden Cardiac Death is the Leading Cause of Death in Dialysis Patients

Prevalent dialysis patients 2009-2011



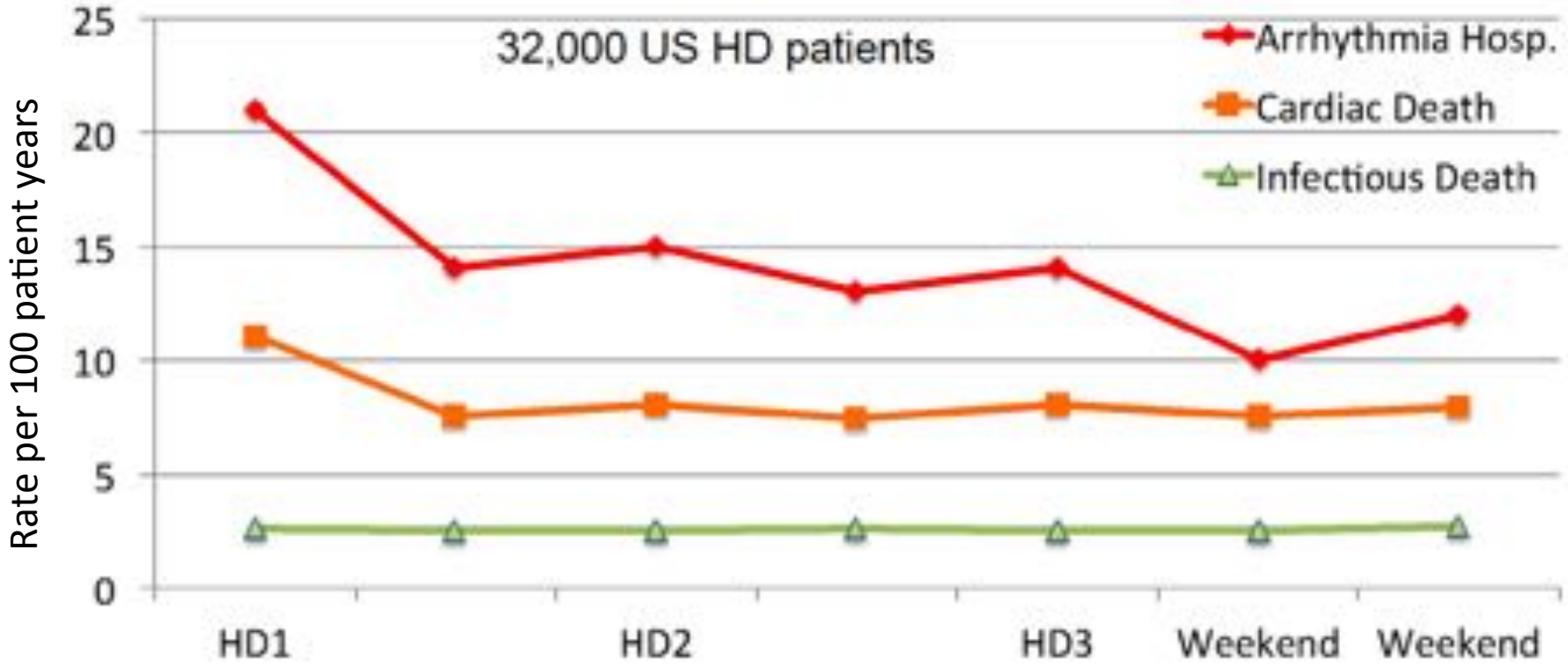
US Renal Data Service Annual Report 20113

Risk of SCD in Haemodialysis Patients is 20x Greater than in General Population



Pun et al Kidney Int 2009

Sudden cardiac death and arrhythmias are more common after the long dialysis break

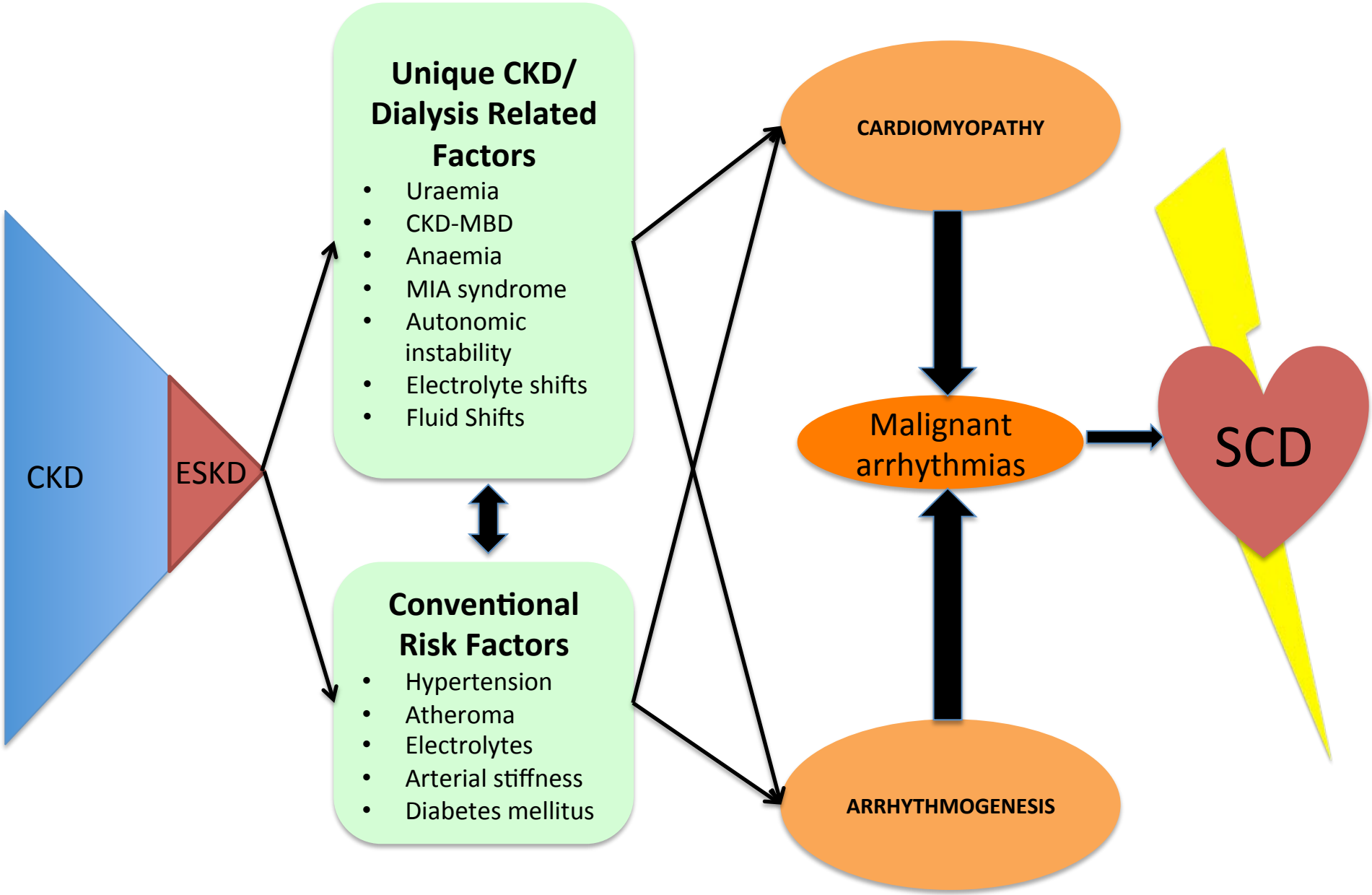


Foley et al. NEJM 2011

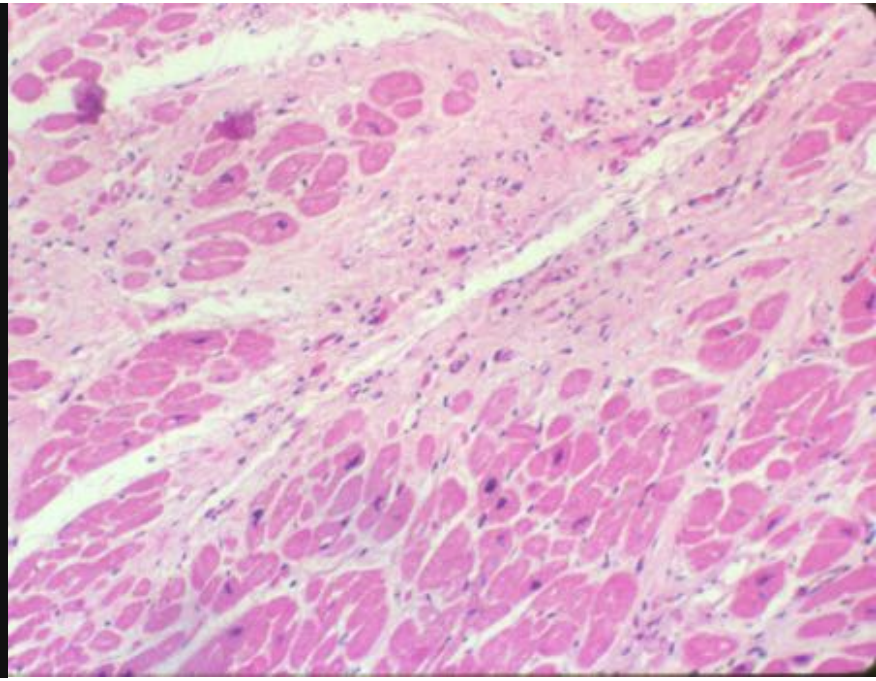
Why?

- Misclassification?
  - Unlikely rates consistent across observational cohorts, registries, interventional trials etc
- Same disease as in general population, only worse?
  - Ischaemic heart disease, diabetes, heart failure
- New disease, novel risk factors?

Sudden Cardiac Death in CKD/ESKD

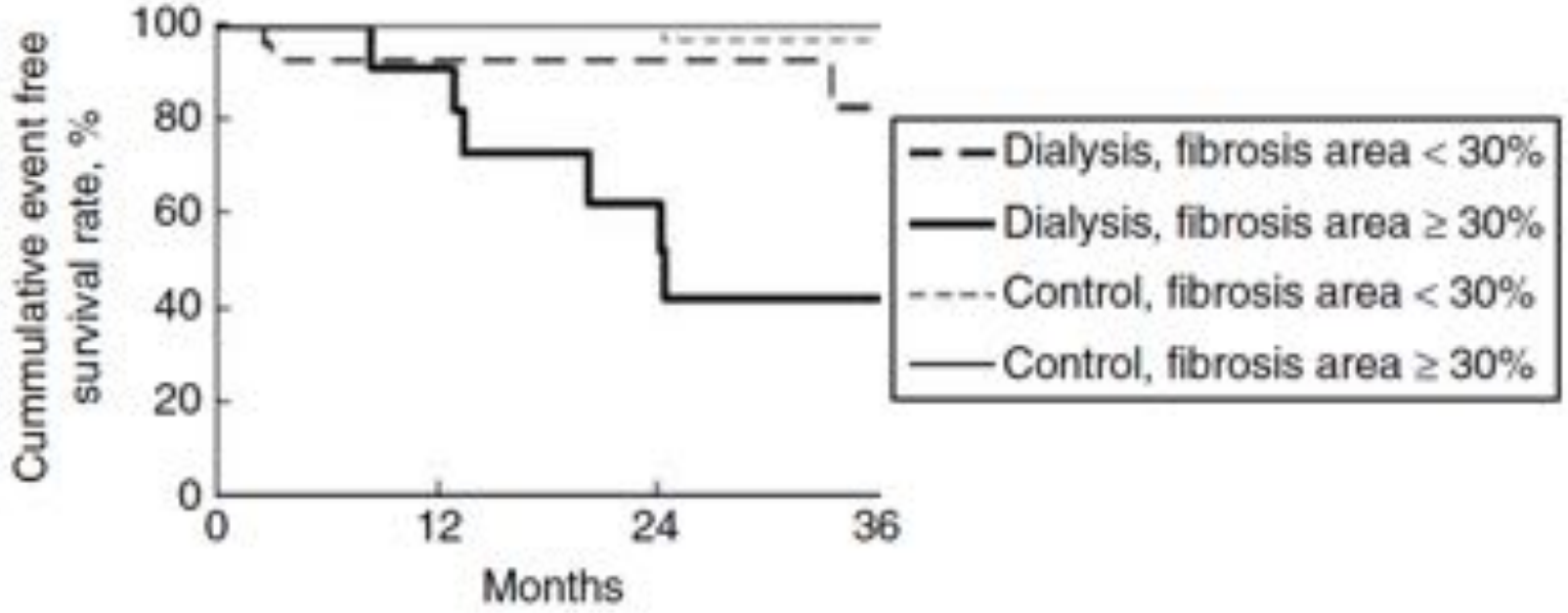


Increased LV Mass and Myocardial Fibrosis



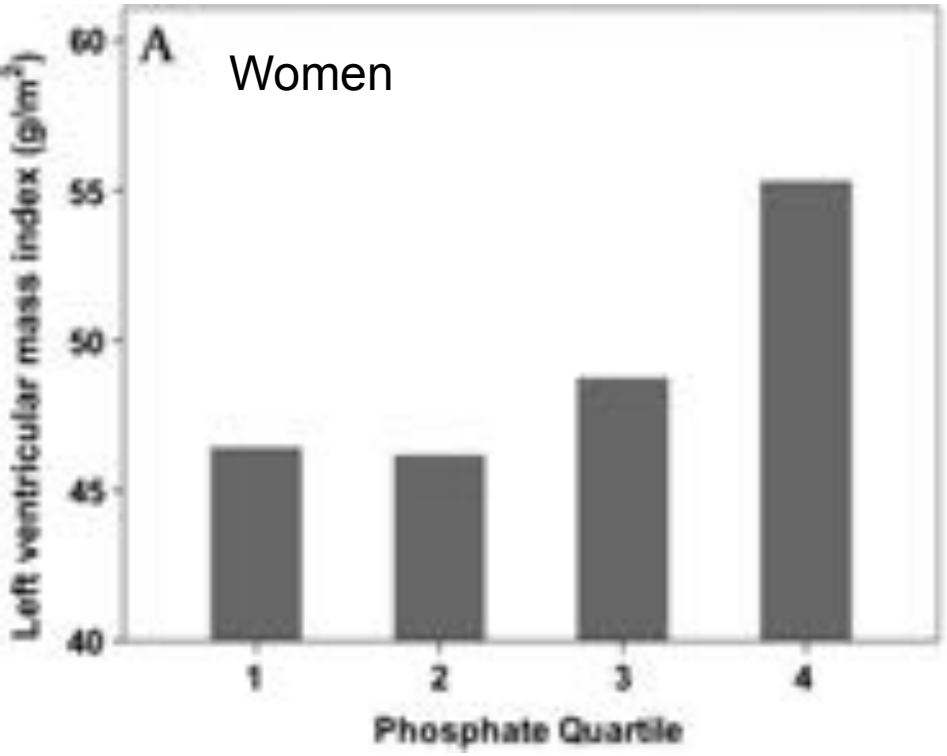
Edwards et al JACC Imaging 2015

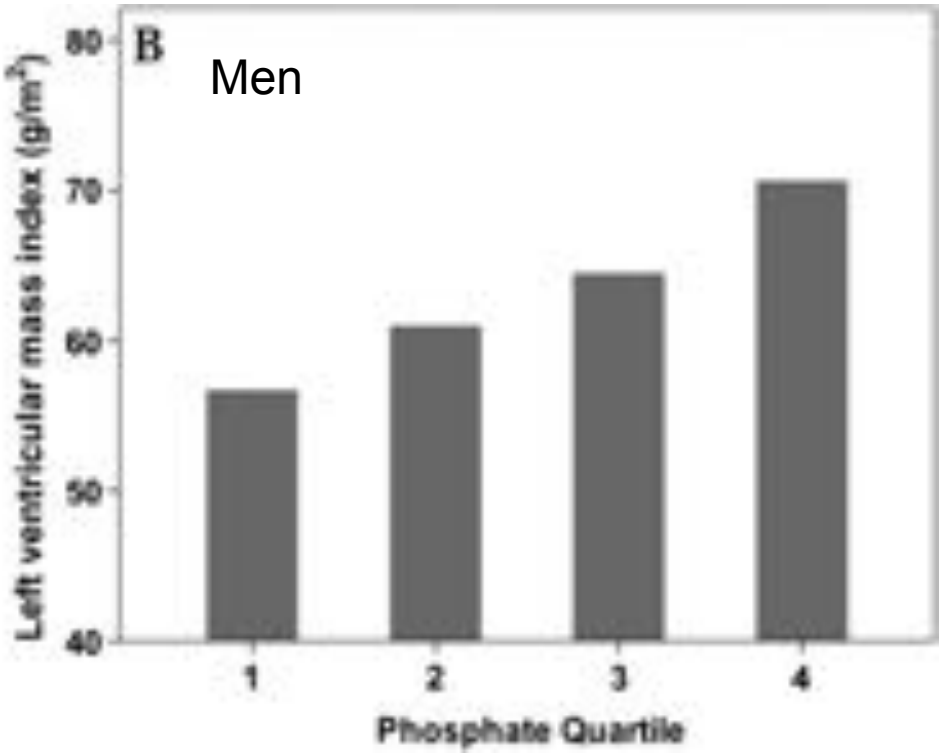
Cardiac fibrosis associated with increased mortality ESRD patients.



Aoki J Kidney Int 2005

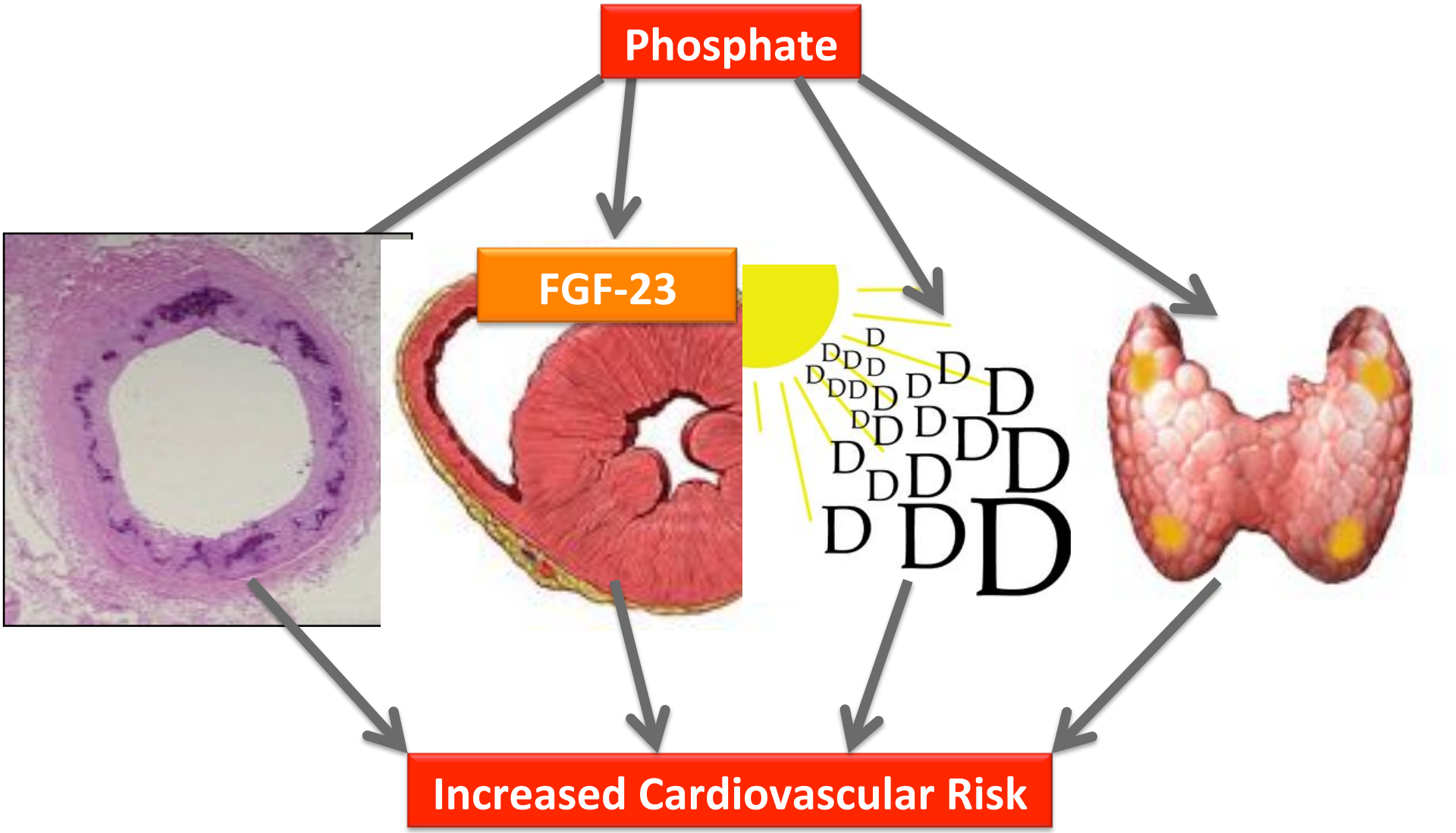
Serum phosphate is associated with LVM in CKD



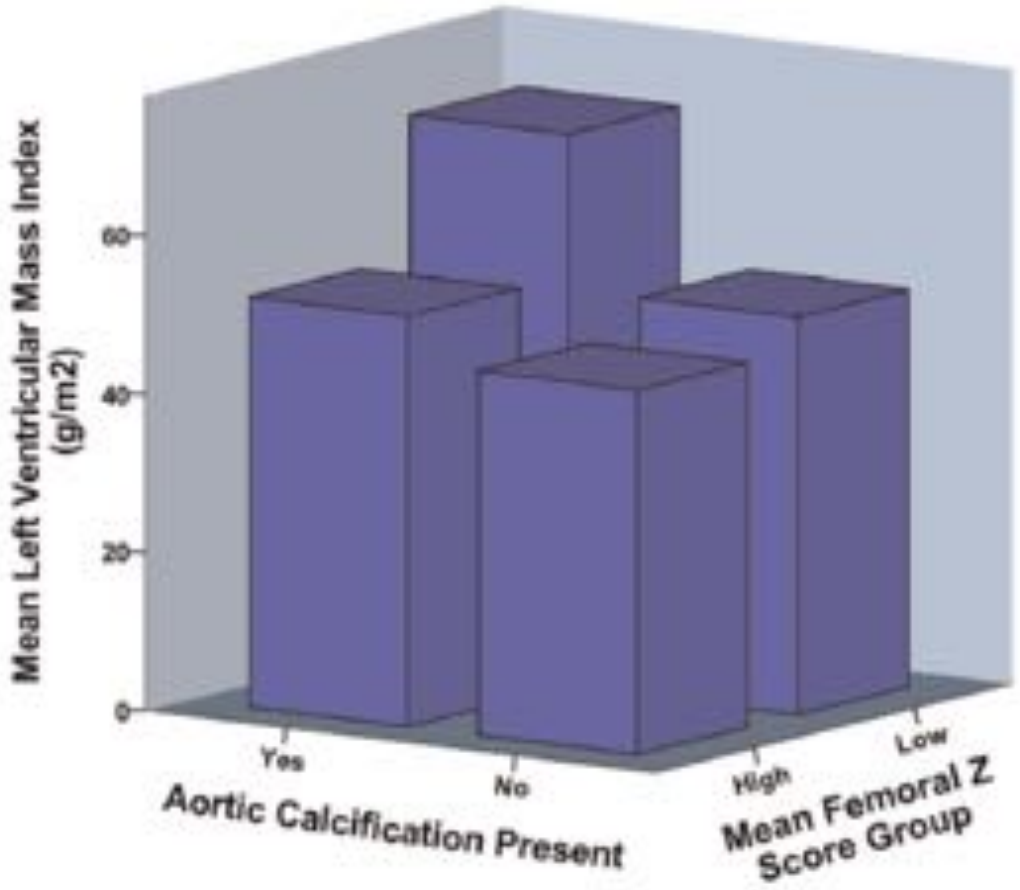


Chue CD, Edwards NC, Moody WE *et al*. *Heart* 2012; **98:** 219–224.

Phosphate is a Mediator of Cardiovascular Disease

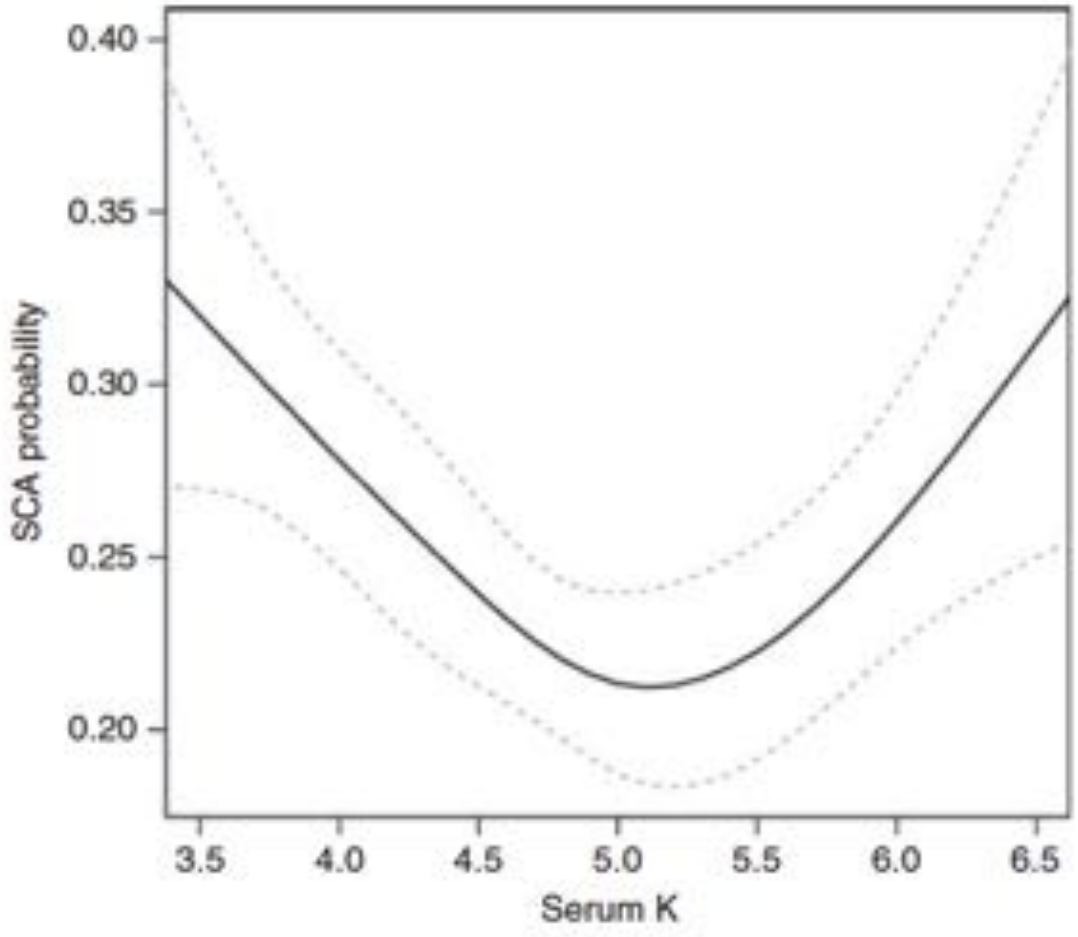


LV Mass Increases with Increasing Aortic Calcification and Decreasing Bone Density



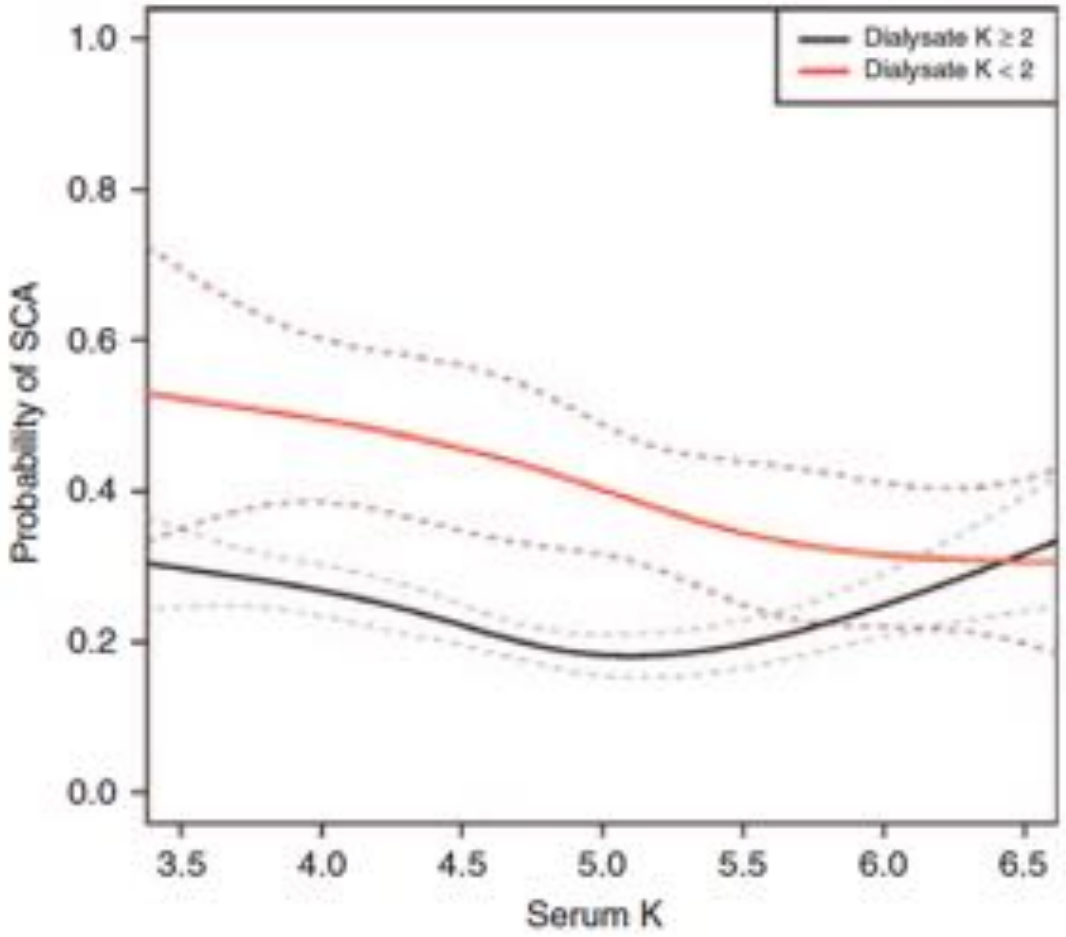
Chue et al Plos One 2013

Pre-dialysis Sudden Cardiac Arrest and Serum Potassium



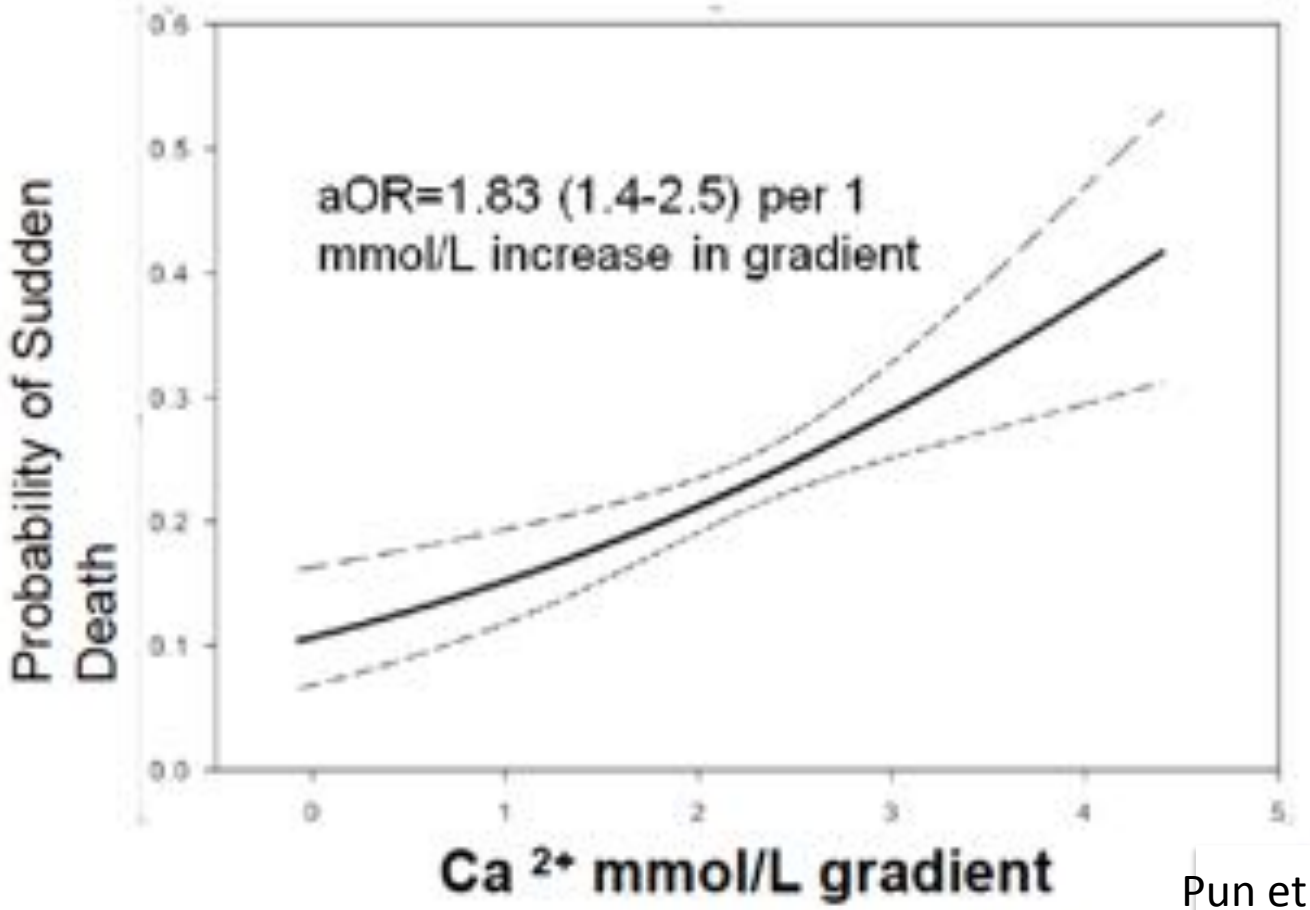
Pun et al. Kidney Int 2011

Low dialysate potassium associated with worse outcomes



Pun et al. Kidney Int 2011

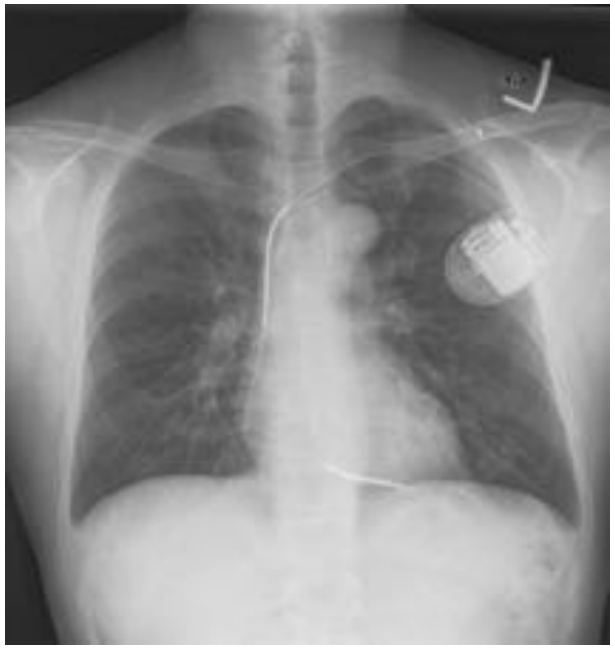
Low calcium dialysate associated with increased risk of SCD



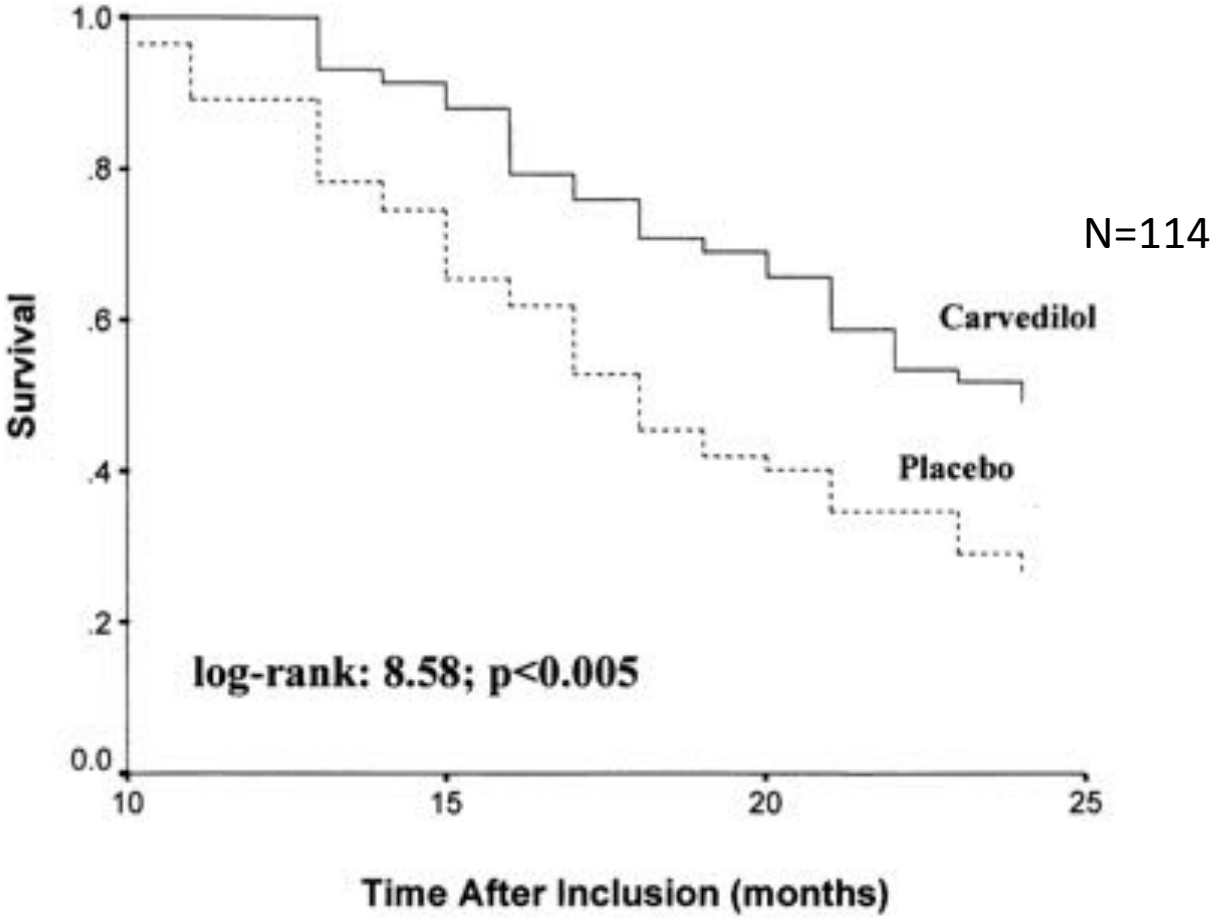
Pun et al cJASN 2013

Potential "Conventional" Treatments

- Beta-blockers
- RAAS Inhibition
- Implantable Cardioverter Defibrillators



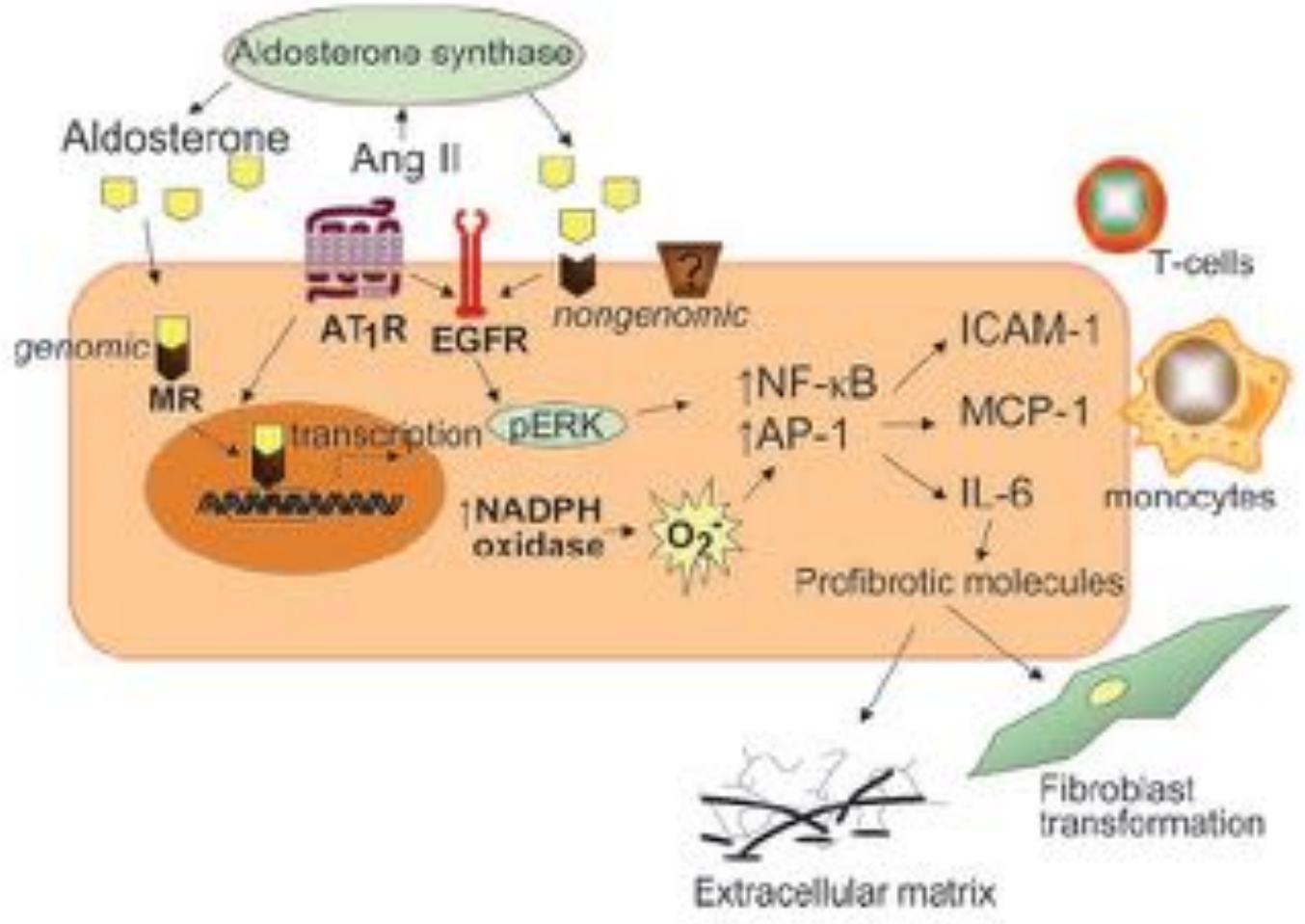
Double-blind RCT of Carvedilol in Dialysis Patients with Dilated Cardiomyopathy



N=114

Cice et al JACC 2003

Aldosterone: a pro-inflammatory and pro-fibrotic stimulus in the heart and vasculature

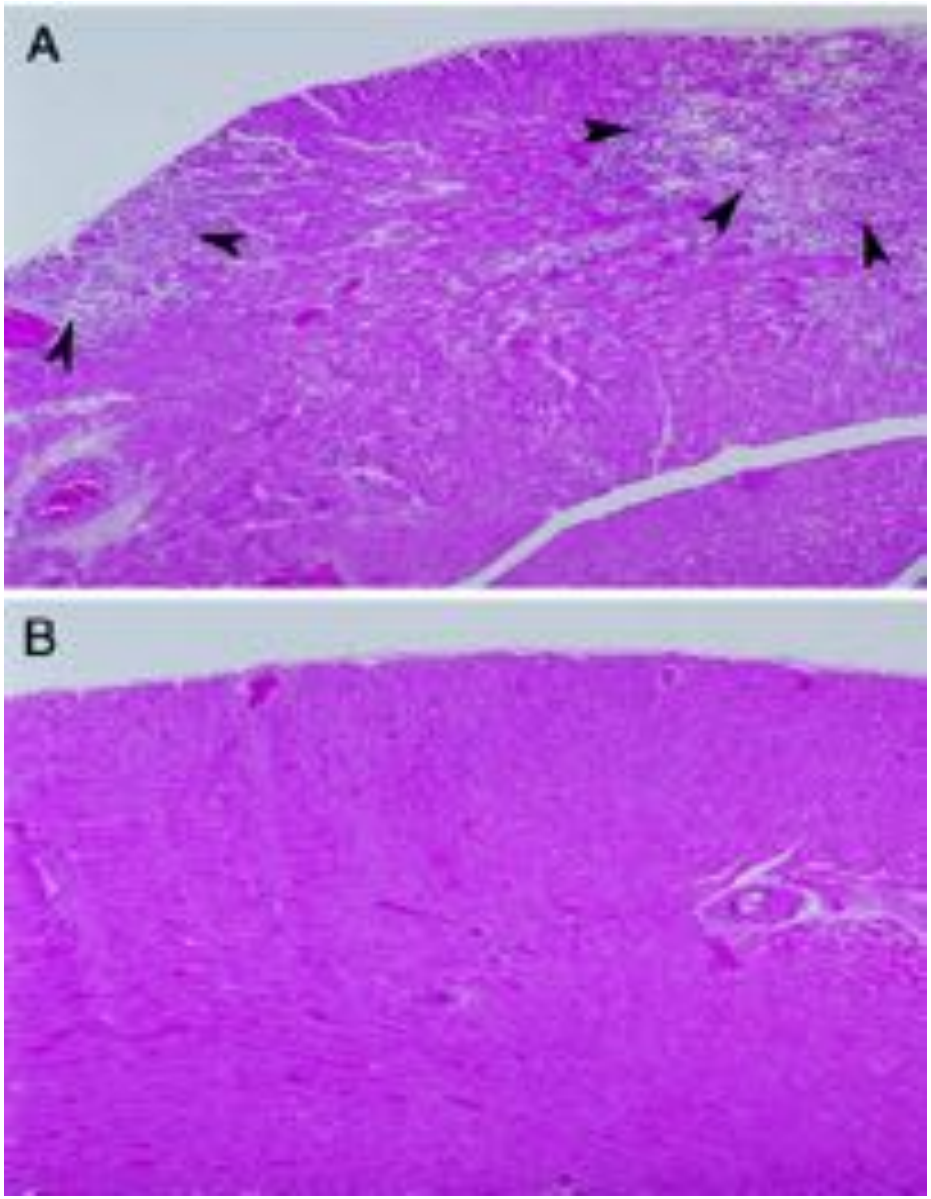


Brown NJ. Hypertension 2008

Aldosterone and Myocardial Necrosis

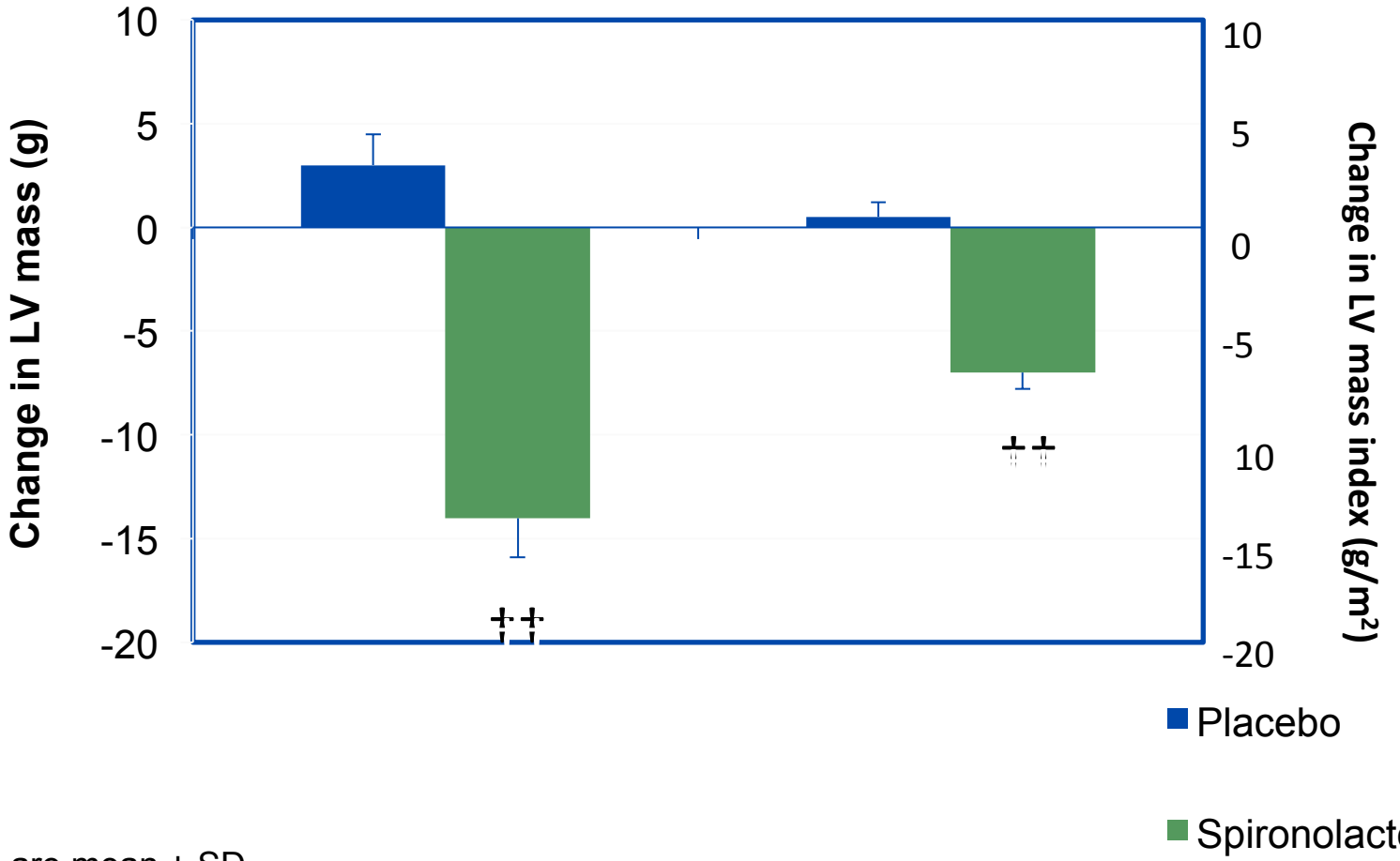
Representative myocardial necrotic lesions induced by L-NAME/Ang II/ NaCl treatment.

Myocardium of an animal Receiving L-NAME/Ang II/NaCl treatment in the presence of eplerenone showing no necrotic lesions.



Rocha et al. Endocrinology 2000; 141: 3871-8

Addition of low dose spironolactone lowers LV Mass independently of blood pressure in optimally managed patients with CKD

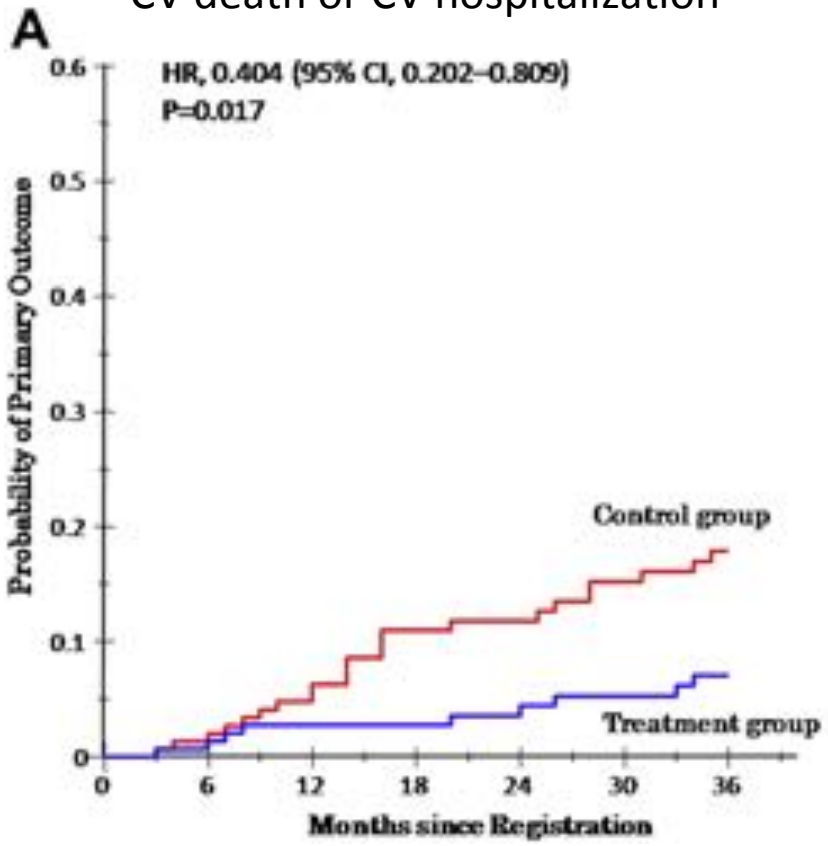


Data are mean ± SD
† p<0.05 †† p<0.01

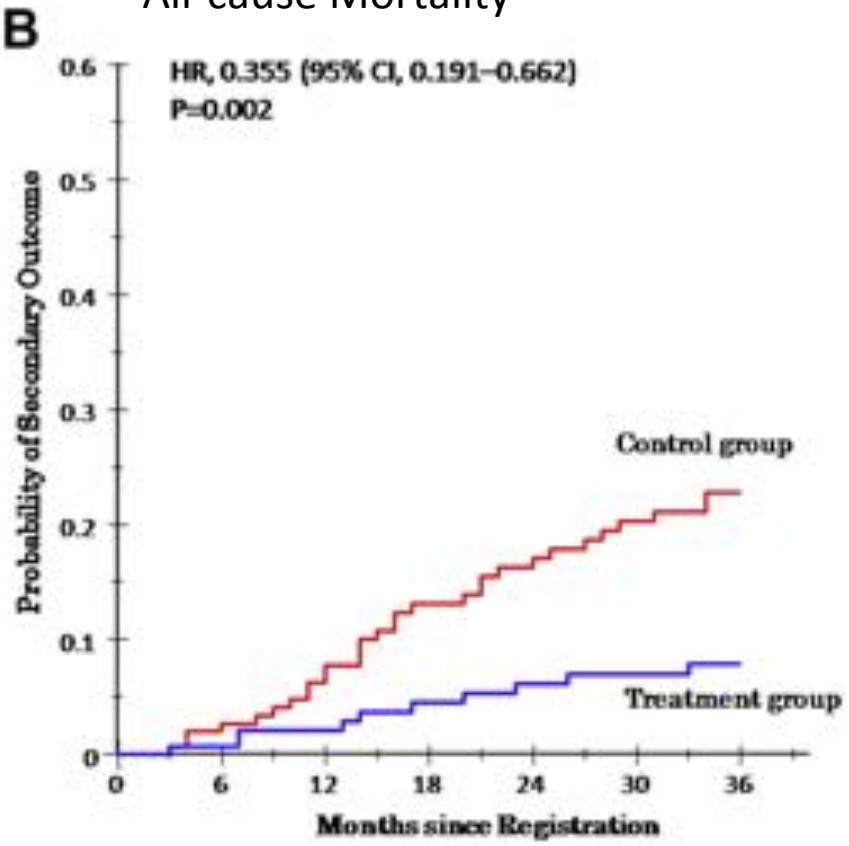
Edwards et al JACC 2009

Spironolactone Reduces Cardiovascular and Cerebrovascular Morbidity and Mortality in Hemodialysis Patients (n=309)

CV death or CV hospitalization



All-cause Mortality



Matsumoto et al. JACC 2014

Implantable Cardioverter Defibrillators in Dialysis Patients

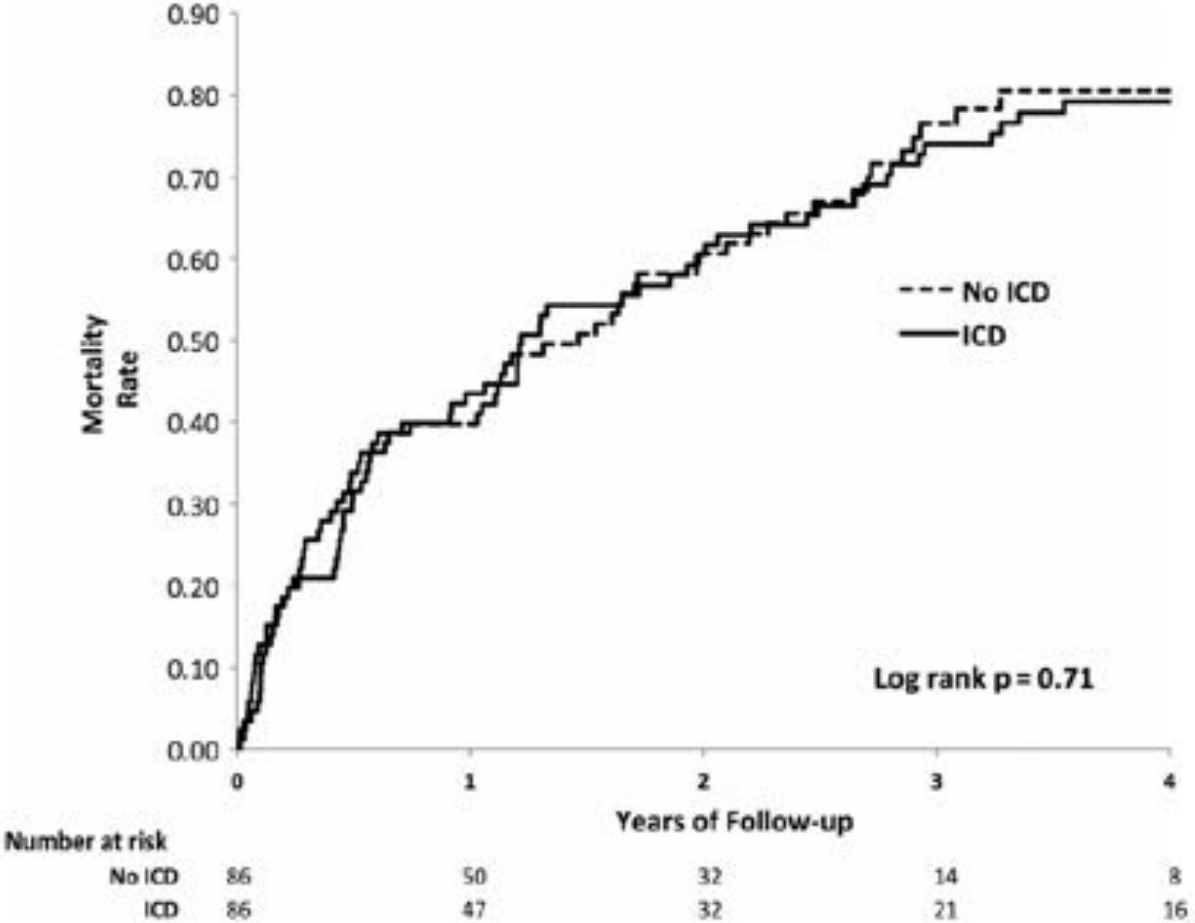
- No dialysis patients included in any RCT
- In secondary prevention:

Observational analyses found survival advantage in cardiac arrest survivors fitted with ICD

  - Confounded by indication

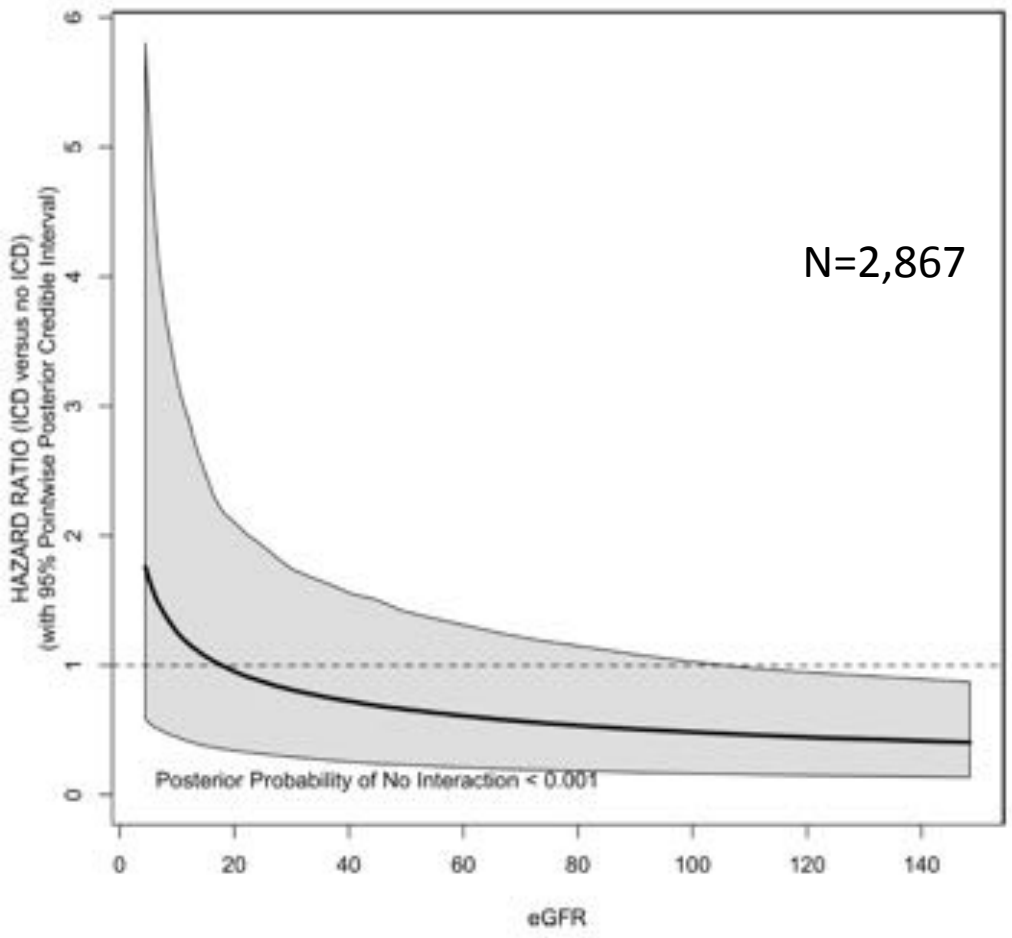
Genovesi, S et al IJC 2015
Charytan et al AJKD 2011
Herzog et al Kidney Int 2005

ICD for primary prevention in dialysis patients: a matched cohort study



Pun et al NDT 2015

Reduced Kidney Function Associated with less benefit from ICD in primary prevention trials: a patient level meta-analysis



Pun et al AJKD 2014

Why Might ICDs Not work in ESKD?

- Increased defibrillation thresholds
- Events might not be “shockable”

(38% of dialysis patients with an ICD still have a sudden death)

- Competing risks
  - High death rate
  - Bacteraemia/endocarditis
  - Associated vascular access problems

Longer or more frequent dialysis associated with less SCD/Arrhythmias?

- Studies relatively small (52 – 245 patients)
- BUT
  - Lower blood pressure
  - Reduce interdialytic weight gain
  - Reduced LV mass
  - Improved blood results – potassium, calcium, phosphate, PTH

All of which theoretically should lower risk (?)

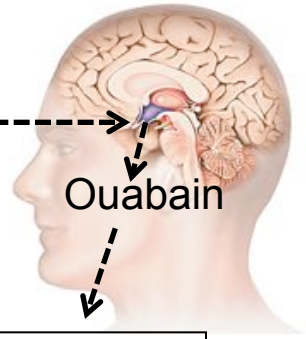
Culleton et al JAMA 2007
Chertow et al NEJM 2010

Current therapeutic options

- Prevent/treat cardiomyopathy
  - Beta-blockers in dilated cardiomyopathy
  - Treat elements of CKD MBD

- Avoid precipitating factors
  - Avoid low potassium and calcium dialysates
  - Reduce IDWG/large fluid shifts
  - Adjust dialysis prescription – daily dialysis?

Cardiotonic Steroids?



Brain
High NaCl

Ouabain

ACTH
Angiotensin II

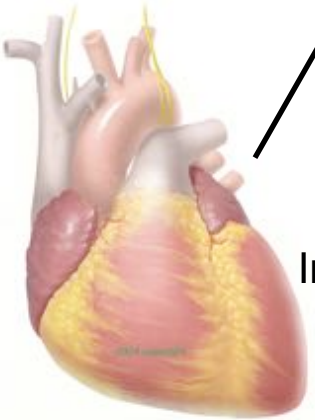
Short term:
Natriuresis
Long term adaptation:
Hypertrophy
Glomerulosclerosis

adrenal gland

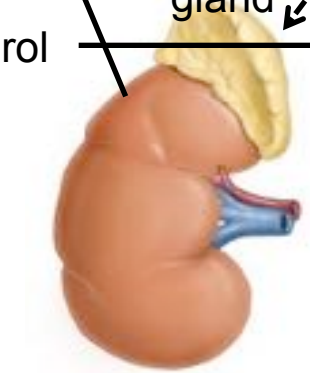
cholesterol

Ouabain
MBG
Bufalin
Telocinobufagin

Short term:
Inotropy
Long term adaptation:
Hypertrophy
Fibrosis
Diastolic dysfunction
Arrhythmogenesis



Cardiac NKA
Inhibition/signalling
α1, α2, α3
Na/K ATPase



Kidney NKA
Inhibition/signalling
α1, α2, α3
Na/K ATPase

Arterial Wall
Inhibition/signaling
α1, α2, α3
Na/K ATPase

Short term:
Vasoconstriction
Long term adaptation:
Arterial hypertension
Muscle hypertrophy

Pavlovic D Nephron 2014

EDITORIAL

THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE

Randomised-controlled trials in chronic kidney disease – a call to arms!

Misery acquaints a man with strange bedfellows.
Trinculo, The Tempest by William Shakespeare

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