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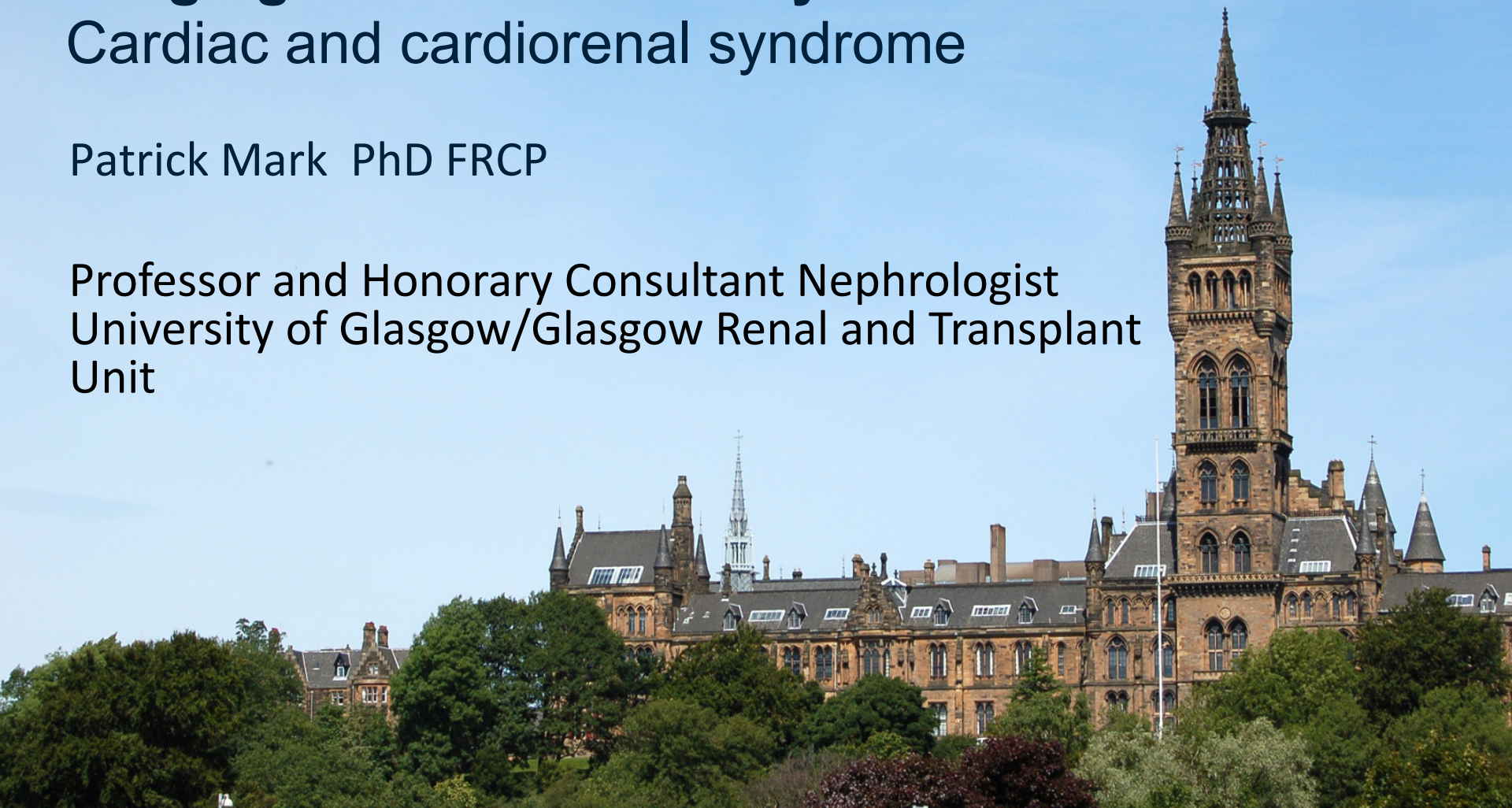
Imaging outside the kidney

Cardiac and cardiorenal syndrome

Patrick Mark PhD FRCP

Professor and Honorary Consultant Nephrologist
University of Glasgow/Glasgow Renal and Transplant Unit



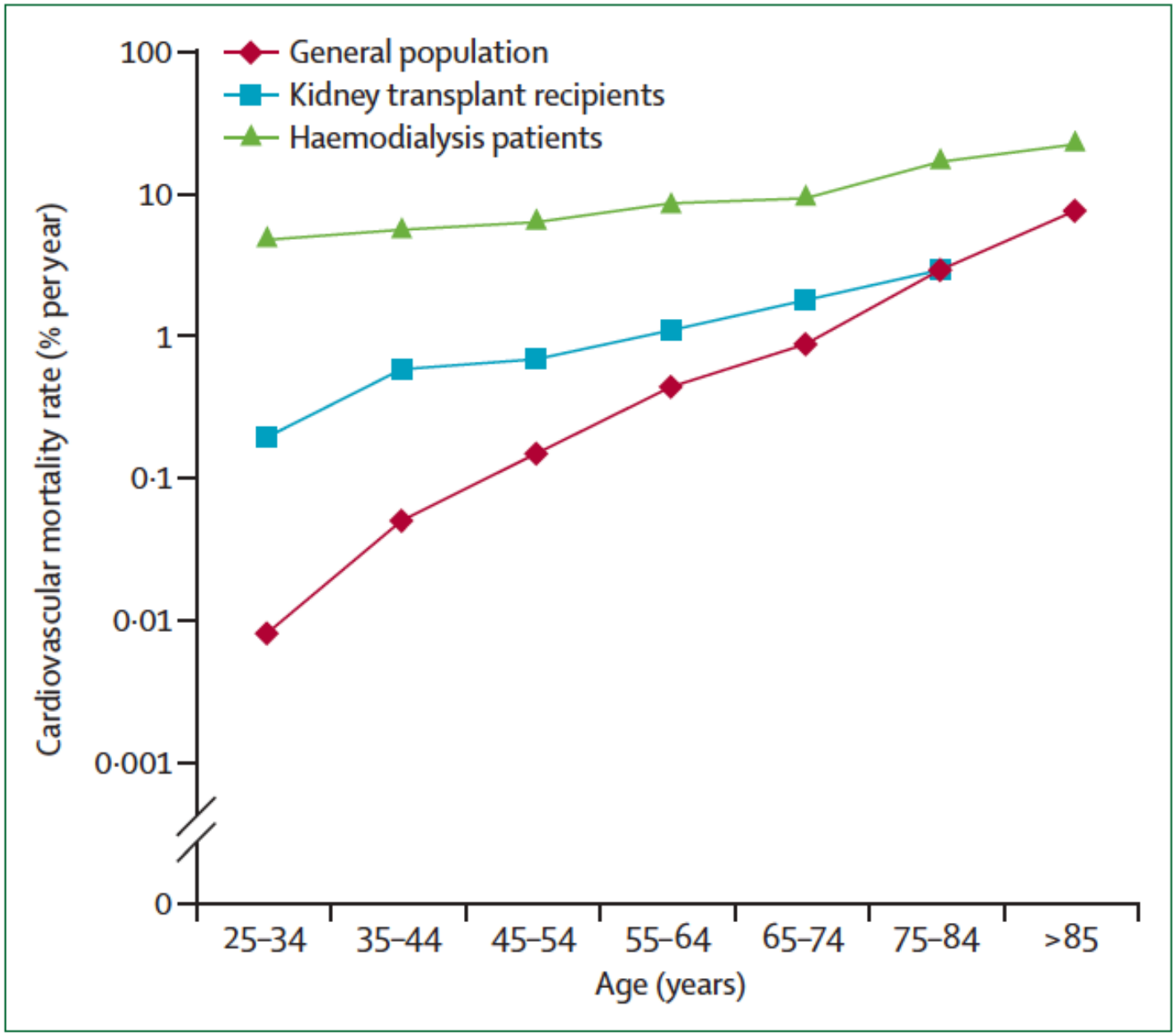


***Figure 1*: Cardiovascular mortality rate by age group**
Adapted from reference 2.

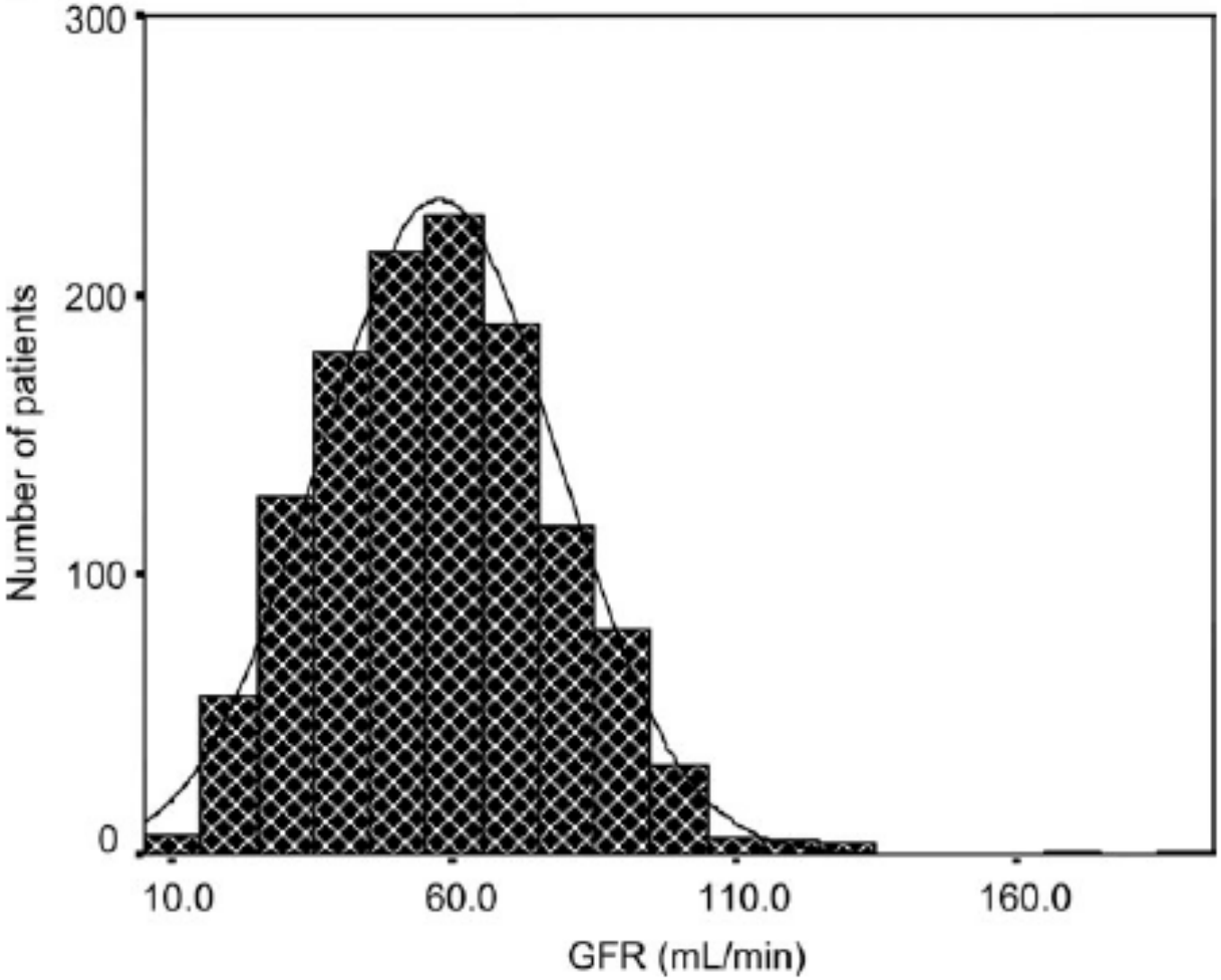
CRS Type I (Acute Cardio-Renal Syndrome)
Abrupt worsening of cardiac function (e.g. decompensated congestive heart failure or acute cardiogenic shock) leading to acute kidney injury
Key Concept: prevent decompensation of stable heart failure

CRS Type II (Chronic Cardio-Renal Syndrome)
Chronic abnormalities in cardiac function (e.g. chronic congestive heart failure) causing progressive and permanent chronic kidney disease
Key Concept: ***optimal medical and device treatment of HF with blood pressure and volume control***

CRS Type III (Acute Reno-Cardiac Syndrome)
Abrupt worsening of renal function (e.g. Contrast or bypass surgery induced AKI) causing acute cardiac disorder (e.g. heart failure, arrhythmia, ischemia)
Key Concept: prevent AKI and reduce the risk of acute Reno-Cardiac Syndrome

CRS Type IV (Chronic Reno-Cardiac Syndrome)
Chronic kidney disease contributing to decreased cardiac function, cardiac hypertrophy and/or increased risk of adverse cardiovascular events
Key Concept: attenuate the progression of CKD and reduce the risk of Chronic Reno-Cardiac Syndrome

CRS Type V (Secondary Cardio-Renal Syndrome)
Systemic condition (e.g. diabetes mellitus, sepsis) causing both cardiac and renal dysfunction
Key Concept: treat the underlying systemic illness to minimize end-organ injury



Distribution of estimated glomerular filtration rate (eGFR) amongst 1 216 patients with chronic stable heart failure. Data from *Eur Heart J* 2006;27:569-81

de Silva R, Nikitin NP, Witte KK, Rigby AS, Goode K, Bhandari S, Clark AL, Cleland JG. Incidence of renal dysfunction over 6 months in patients with chronic heart failure due to left ventricular systolic dysfunction: contributing factors and relationship to prognosis. *Eur Heart J* 2006;**27:**569-81

ELSEVIER

International Journal of Cardiology 128 (2008) 154–165

Cardiology

www.elsevier.com/locate/ijcard

Review

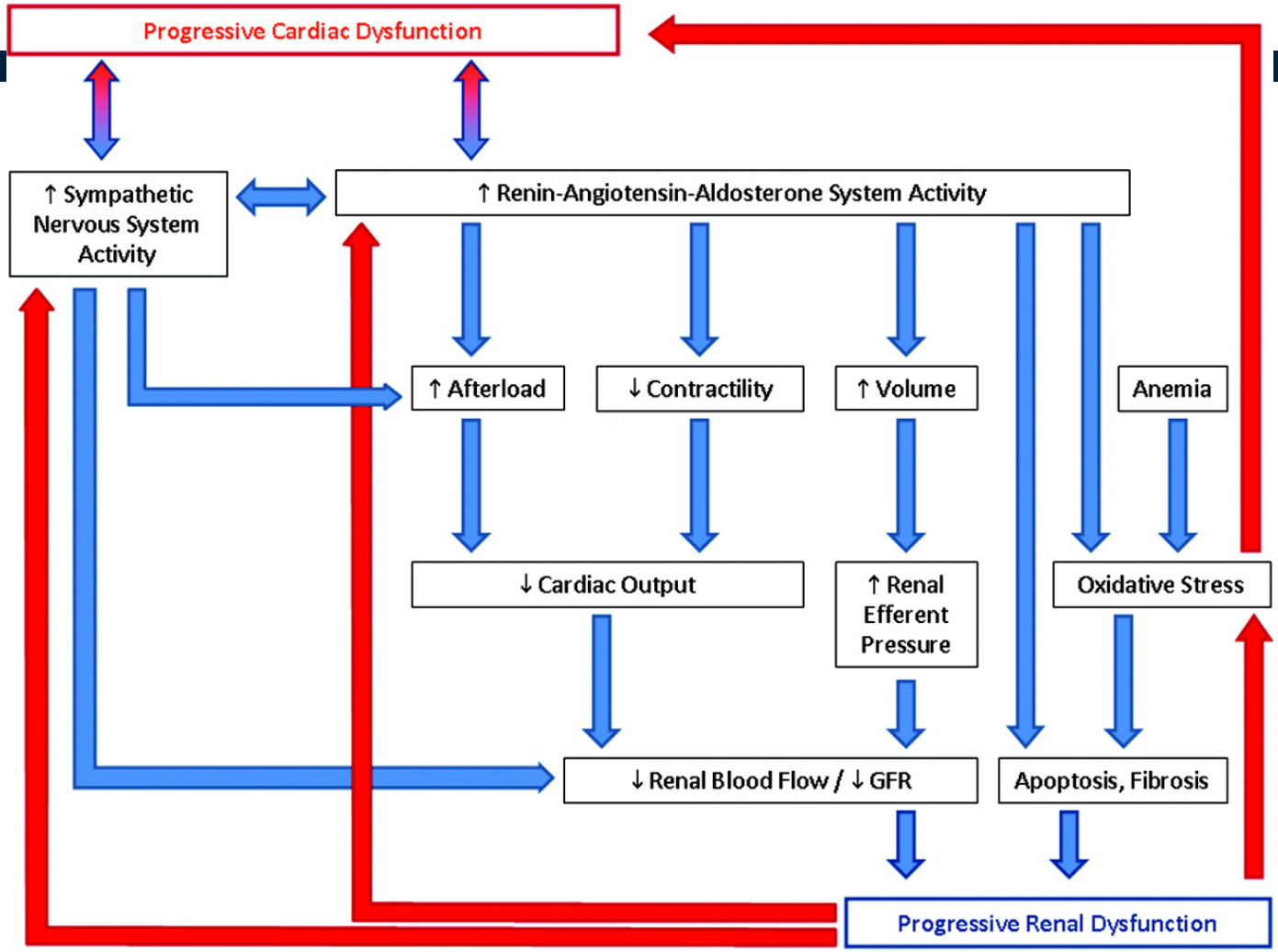
Broken pump or leaky filter? Renal dysfunction in heart failure a contemporary review

Colin J. Petrie [a,*], Partick B. Mark [b], Robin A.P. Weir [a]

[a] *Department of Cardiology, Western Infirmary, Glasgow. G11 6NT, United Kingdom*

[b] *BHF Glasgow Cardiovascular Research Centre, University of Glasgow. 26 University Place, Glasgow G12 8TA, United Kingdom*

Figure 5. Postulated mechanisms underlying the relationship between HF and renal dysfunction.



Bock J S , Gottlieb S S Circulation 2010;121:2592-2600

Global Kidney Disease 5

Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention

Ron T Gansevoort, Ricardo Correa-Rotter, Brenda R Hemmelgarn, Tazeen H Jafar, Hiddo J Lambers Heerspink, Johannes F Mann, Kunihiro Matsushita, Chi Pang Wen

Lancet 2013; 382: 339–52

Published Online
May 31, 2013
http://dx.doi.org/10.1016/
S0140-6736(13)60595-4

Summary of relative risks from categorical meta-analysis (dipstick included) (-,+,±,≥,++)

All-cause morality

	ACR <10	ACR 10-29	ACR 30-299	ACR >300
eGFR >105	1.1	1.5	2.2	5.0
eGFR 90-105	Ref	1.4	1.5	3.1
eGFR 75-90	1.0	1.1	1.7	2.3
eGFR 60-75	1.0	1.0	1.8	2.7
eGFR 45-60	1.3	1.1	2.2	3.6
eGFR 30-45	1.9	2.3	3.3	4.9
eGFR 15-30	5.3	3.6	4.7	6.6

Cardiovascular mortality

	ACR <10	ACR 10-29	ACR 30-299	ACR >300
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

ESRD

	ACR <10	ACR 10-29	ACR 30-299	ACR >300
eGFR >105	Ref	Ref	7.8	18
eGFR 90-105	Ref	Ref	11	20
eGFR 75-90	Ref	Ref	3.8	48
eGFR 60-75	Ref	Ref	7.4	67
eGFR 45-60	5.2	22	40	147
eGFR 30-45	56	74	294	763
eGFR 15-30	433	1044	1056	2286

AKI

	ACR <10	ACR 10-29	ACR 30-299	ACR >300
eGFR >105	Ref	Ref	2.7	8.4
eGFR 90-105	Ref	Ref	2.4	6.8
eGFR 75-90	Ref	Ref	2.5	4.1
eGFR 60-75	Ref	Ref	3.3	6/4
eGFR 45-60	2.7	4.9	6.4	5.9
eGFR 30-45	2.7	10	12	20
eGFR 15-30	17	17	21	29

Progressive CKD

	ACR <10	ACR 10-29	ACR 30-299	ACR >300
eGFR >105	Ref	Ref	0.4	3.0
eGFR 90-105	Ref	Ref	0.9	3.3
eGFR 75-90	Ref	Ref	1.9	5.0
eGFR 60-75	Ref	Ref	3.2	8.1
eGFR 45-60	3.1	4.0	9.4	57
eGFR 30-45	3.0	19	15	22
eGFR 15-30	4.0	12	21	7.7

Adapt
Kidne

; AKI=acute kidney injury; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; ESRD=end-stage renal disease
11;80:17–28

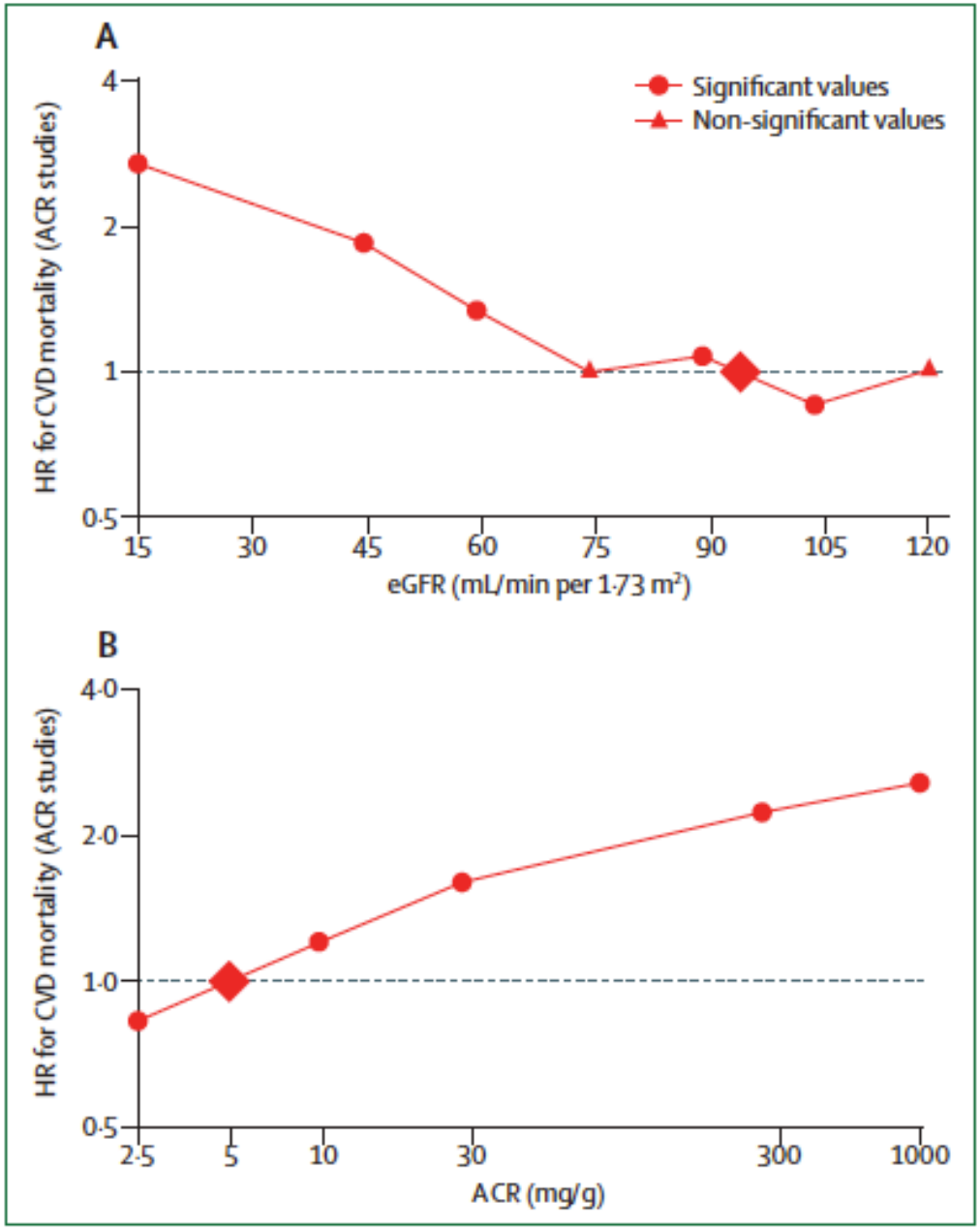


Figure 1: **Independent associations of kidney function and proteinuria with cardiovascular mortality**

Lancet 2013; 382: 339–52

Published Online
May 31, 2013
http://dx.doi.org/10.1016/
S0140-6736(13)60595-4

5 Matsushita K, van der Velde M, Astor BC, et al, for the CKD Prognosis Consortium. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 2010; 375: 2073–81.

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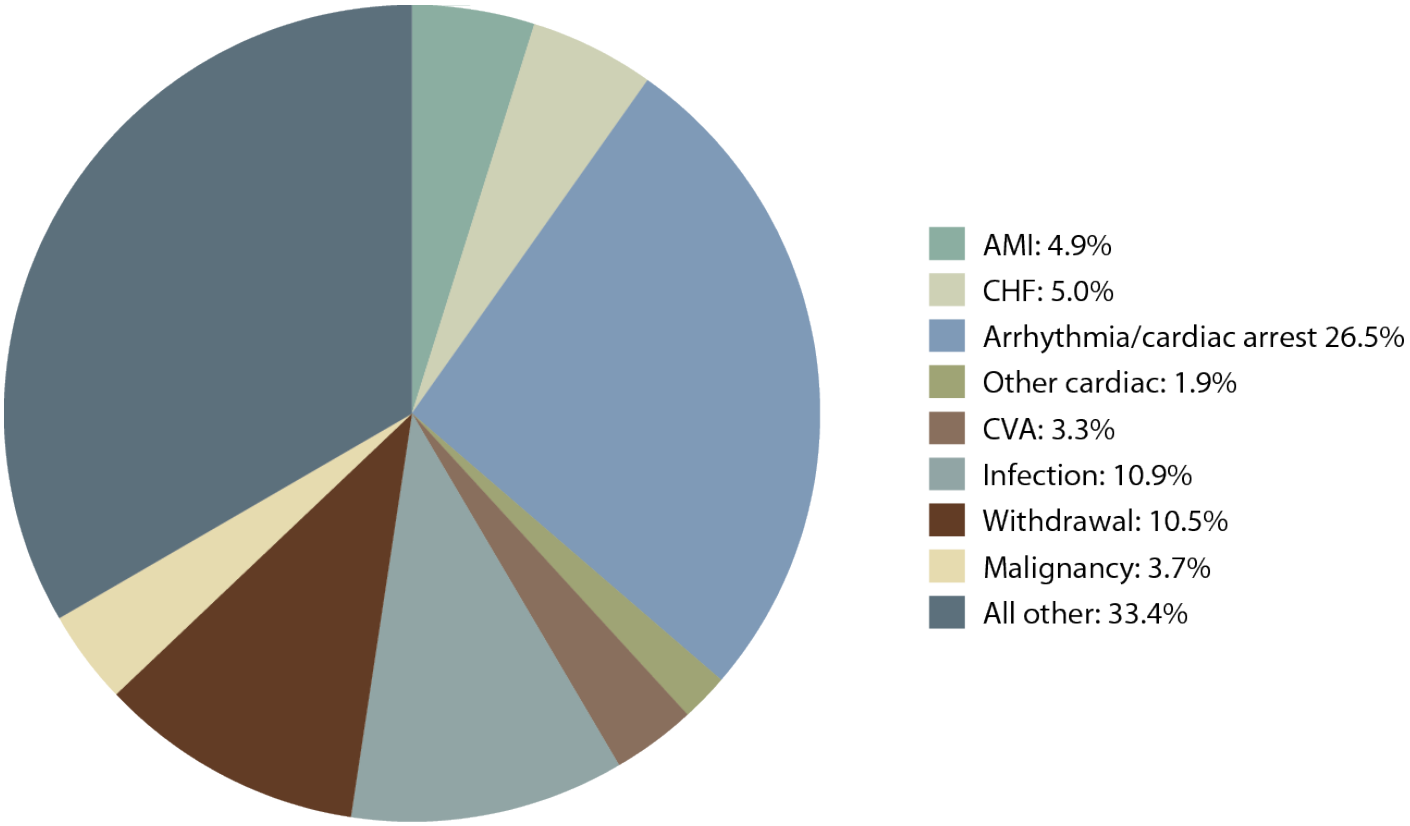
Causes of death in prevalent dialysis patients, 2008–2010

Figure 4.1 (Volume 2)



Incident & prevalent dialysis patients, 2008–2010.

USRDS 2012 ADR

Risk Factors for CVD – gen population

- Older age
- Hypertension
- Hyperlipidaemia
- Diabetes
- Physical inactivity
- Previous MI/CAD/PVD/CVD
- Smoking
- LVH/LVSD

CKD and/orESRD

- Haemodynamic and metabolic factors of CKD
- Proteinuria
- ↑extracellular fluid (ECF) volume
- Electrolyte imbalance
- Anaemia
- Oxidative stress
- Homocysteine
- Arterial calcification
- Phosphate/PTH/Vit D
- Inflammation

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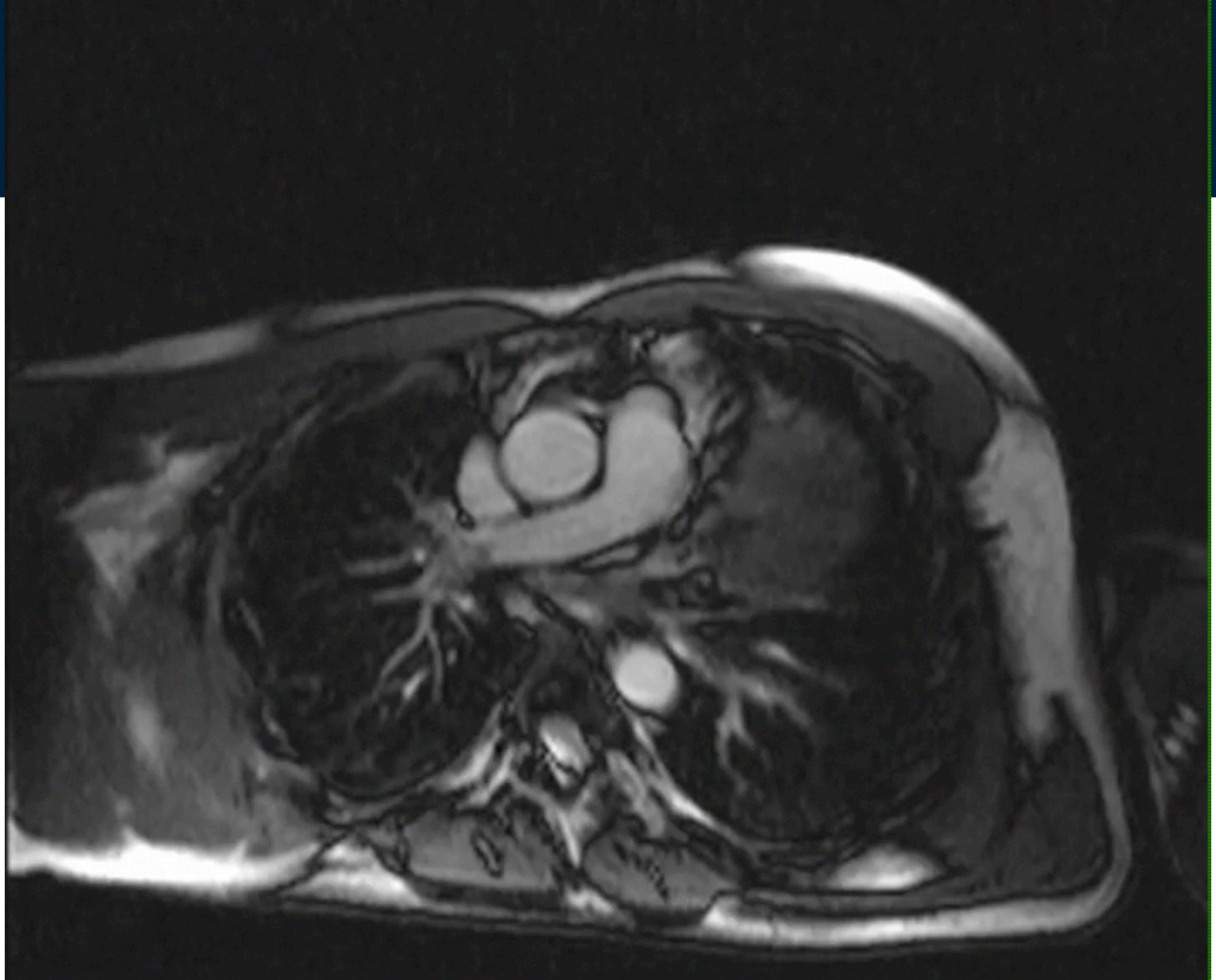
CKD specific mechanisms

- Accelerated atherosclerosis
- Calcification (arteries/valves)
- Vascular stiffening (may be related to calcification)
- Left ventricular hypertrophy (+/- risk of sudden death)



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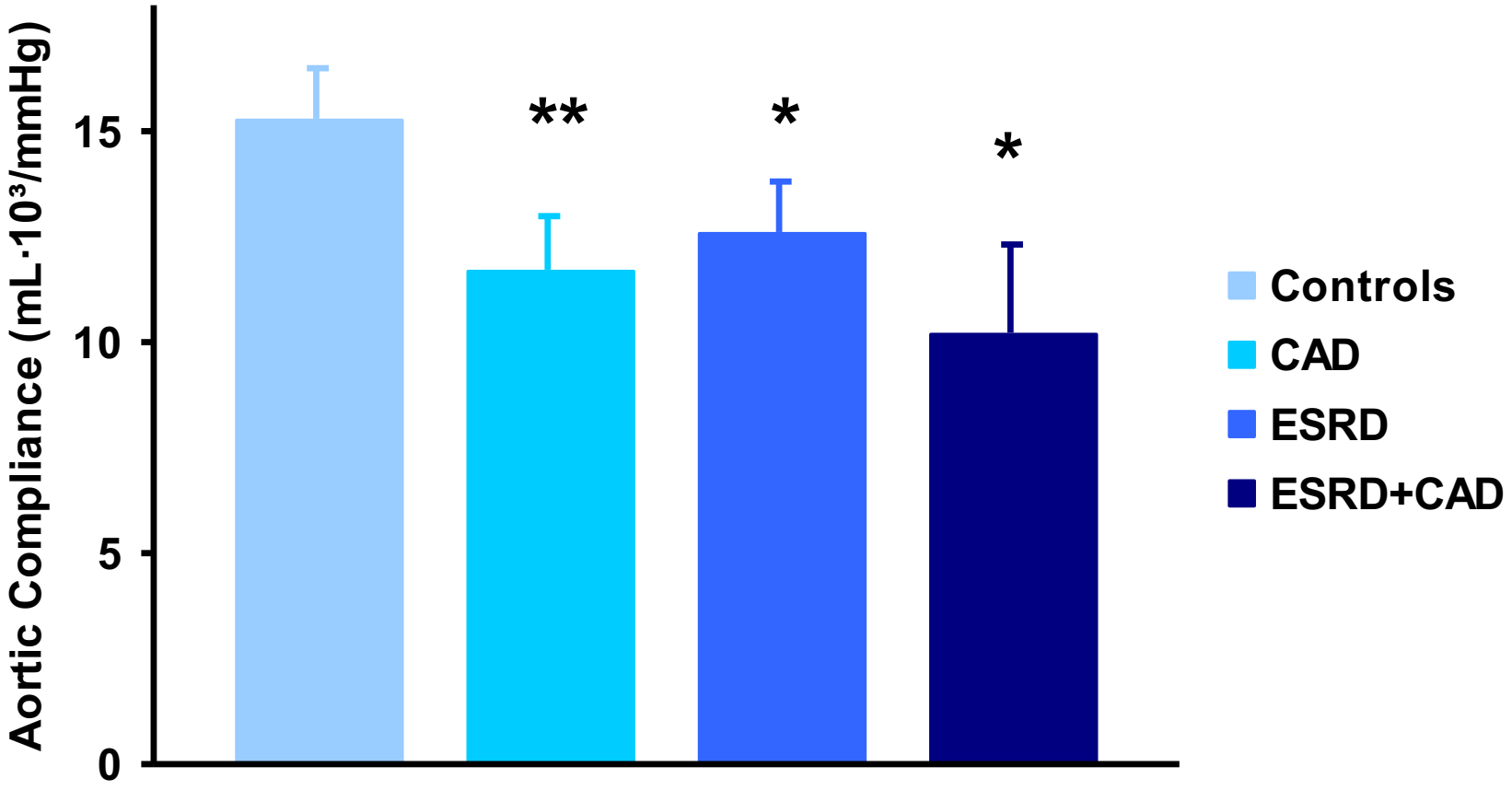
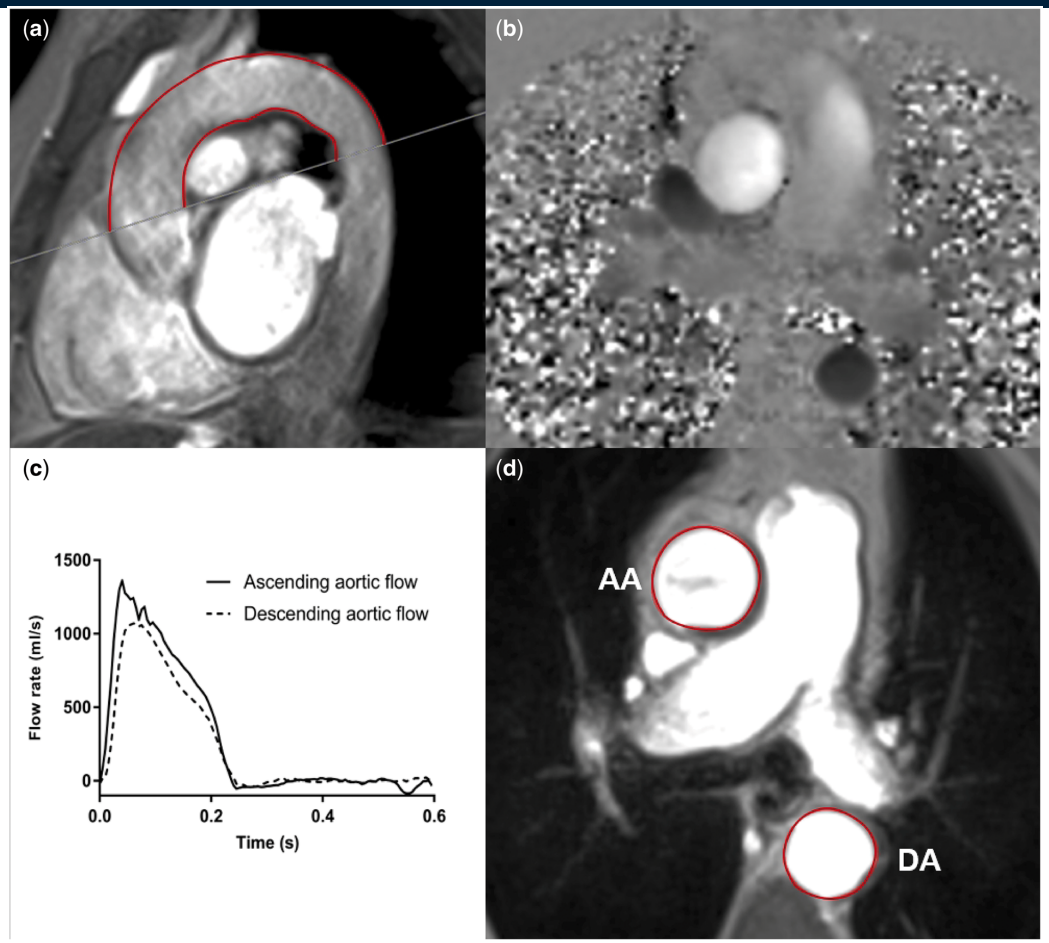
Aortic Compliance

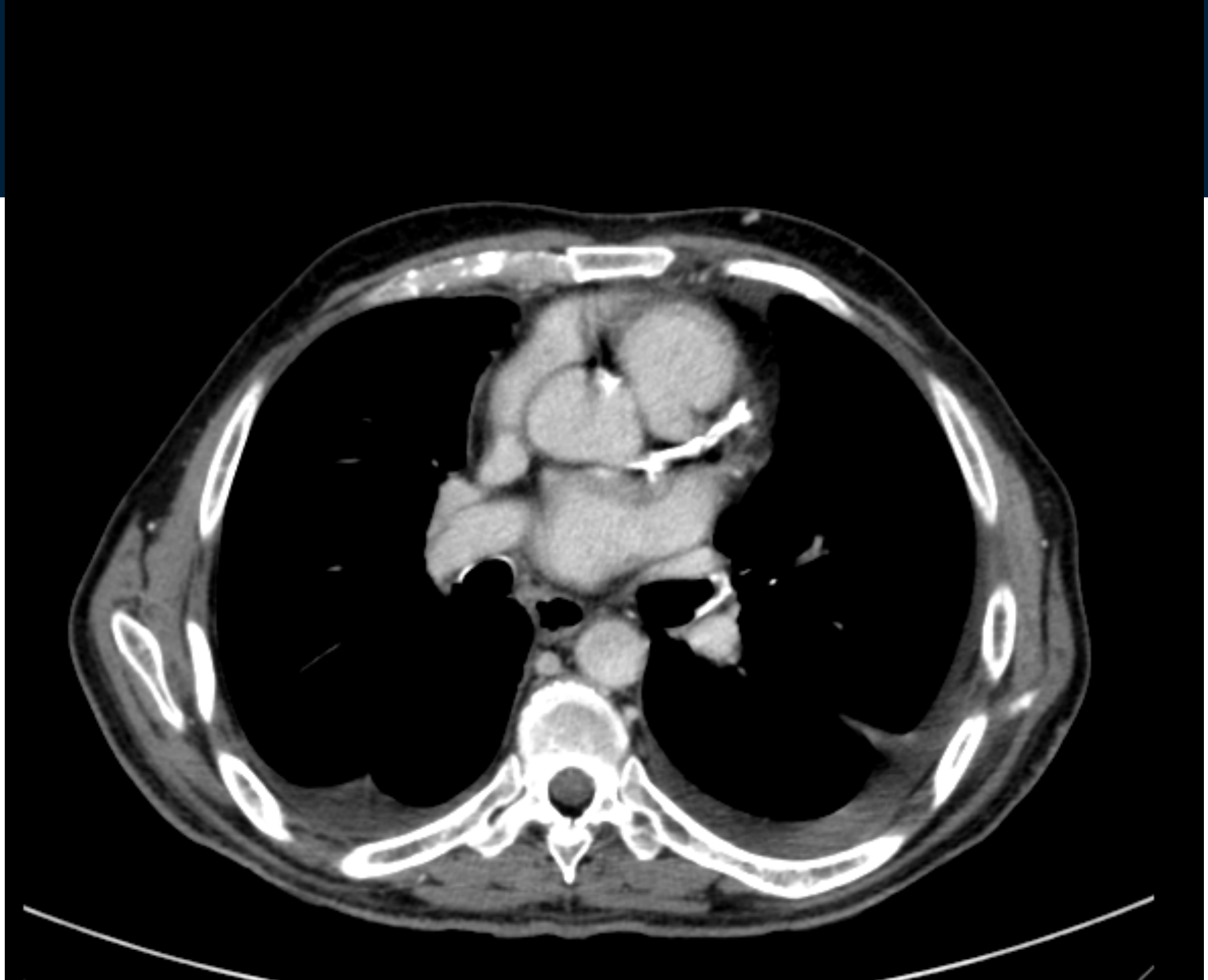


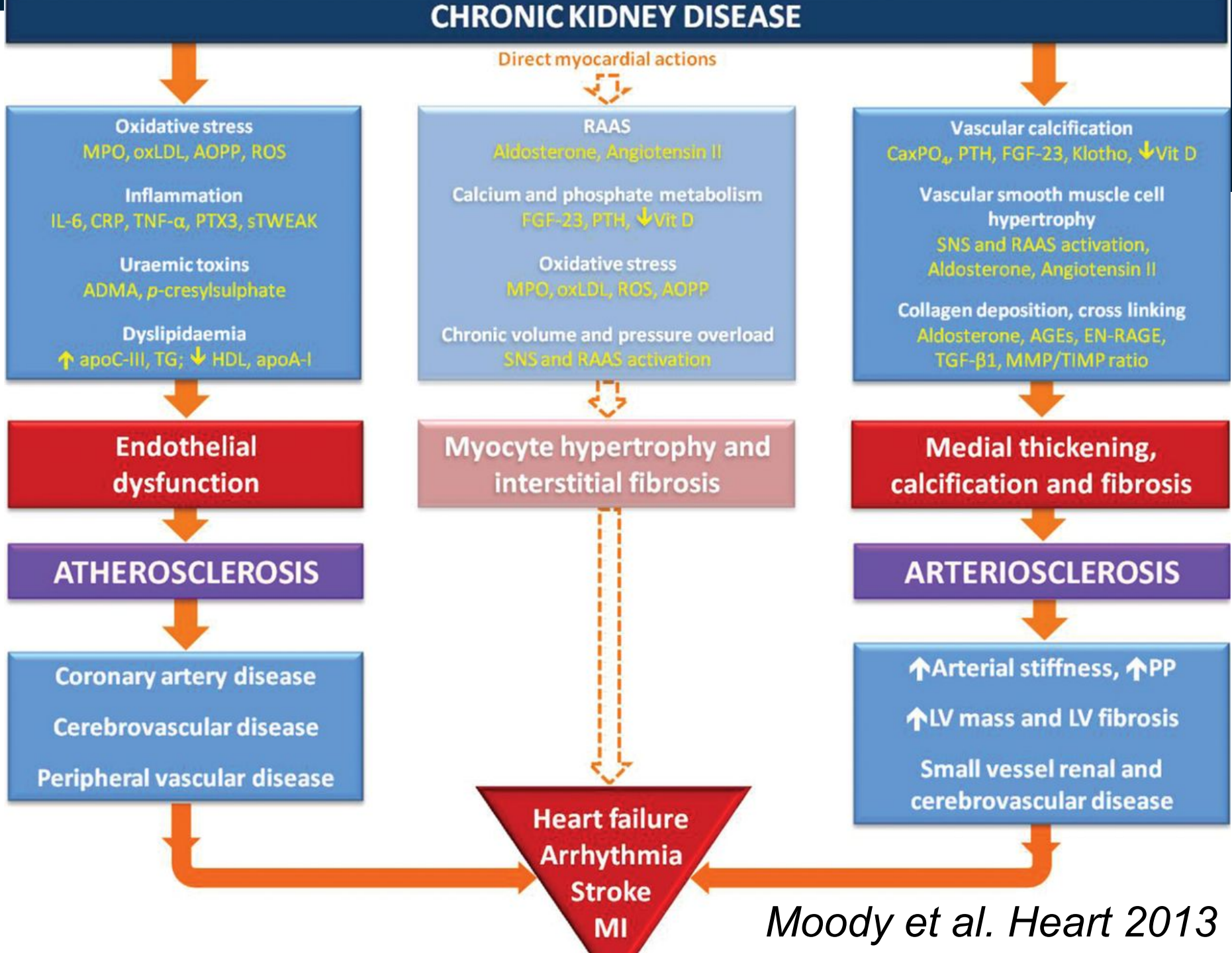
Zimmerli, Mark *et al Kidney Intentional* 2007

FIGURE 1: Assessment of aPWV and AD using two-dimensional phase-contrast CMR.



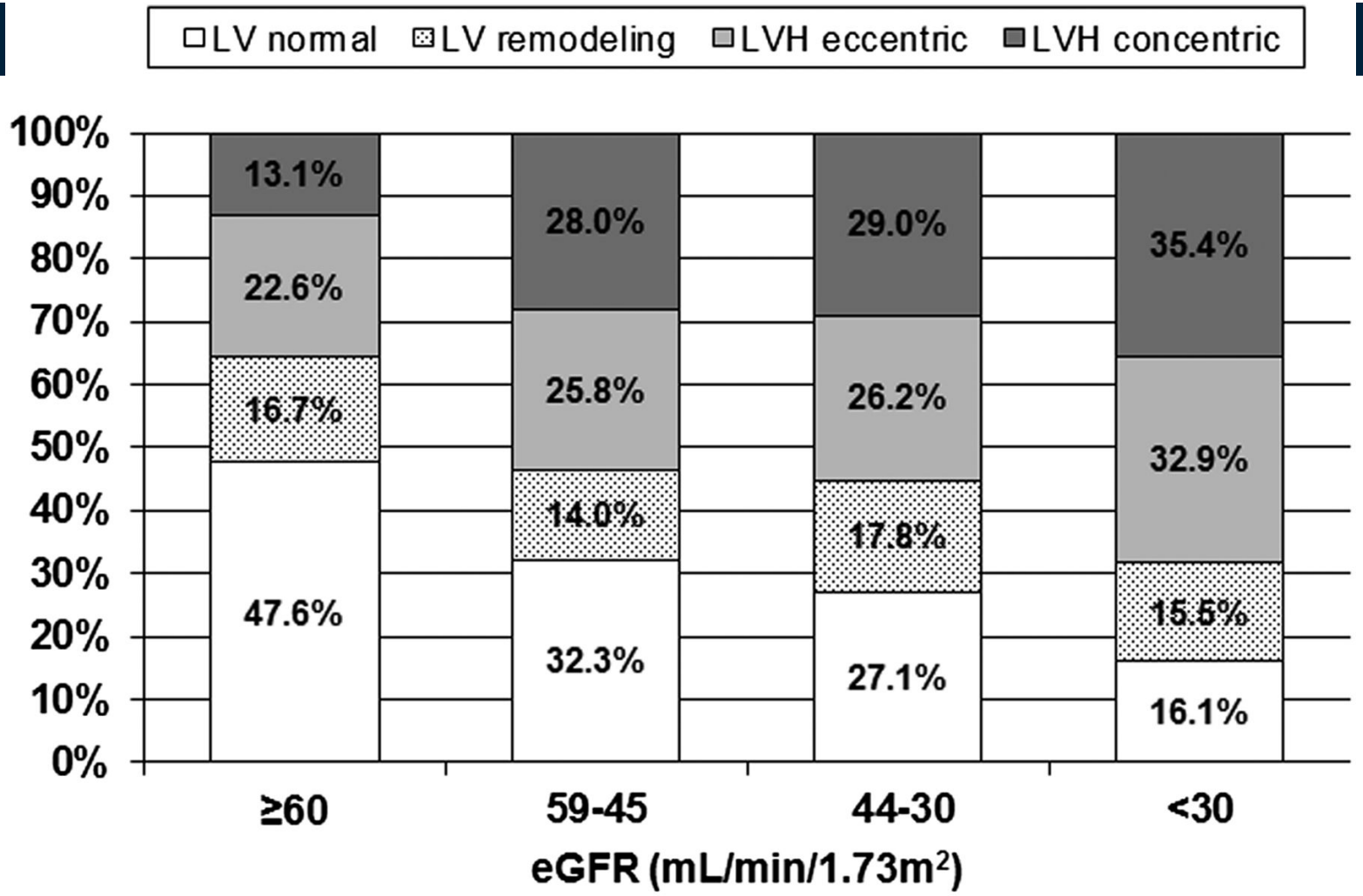
Clinical Kidney Journal, Volume 11, Issue 6, December 2018, Pages 864–873, https://doi.org/10.1093/ckj/sfy042





Moody et al. Heart 2013

Higher prevalence of eccentric and concentric left ventricular hypertrophy (LVH) in patients with lower eGFR.

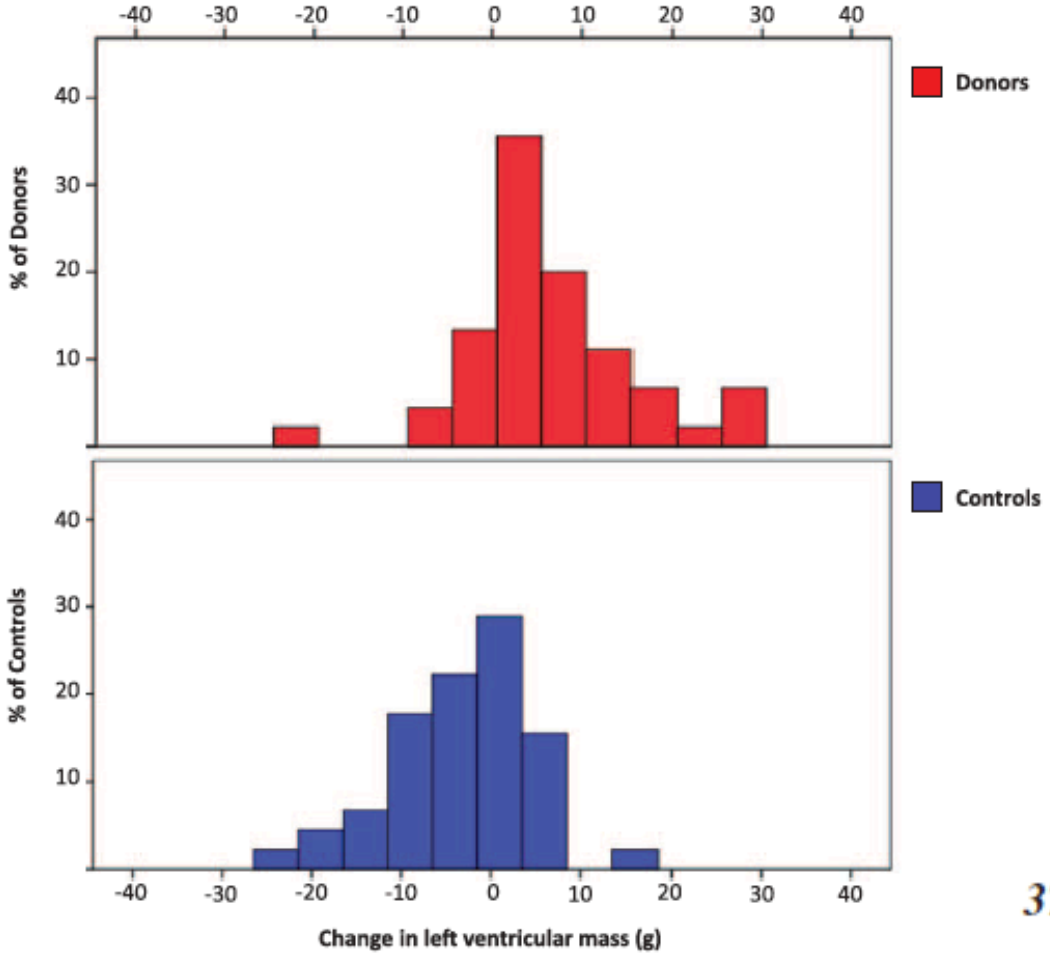


Ernesto Paoletti et al. CJASN 2016;11:271-279

CJASN

Cardiovascular Effects of Unilateral Nephrectomy in Living Kidney Donors

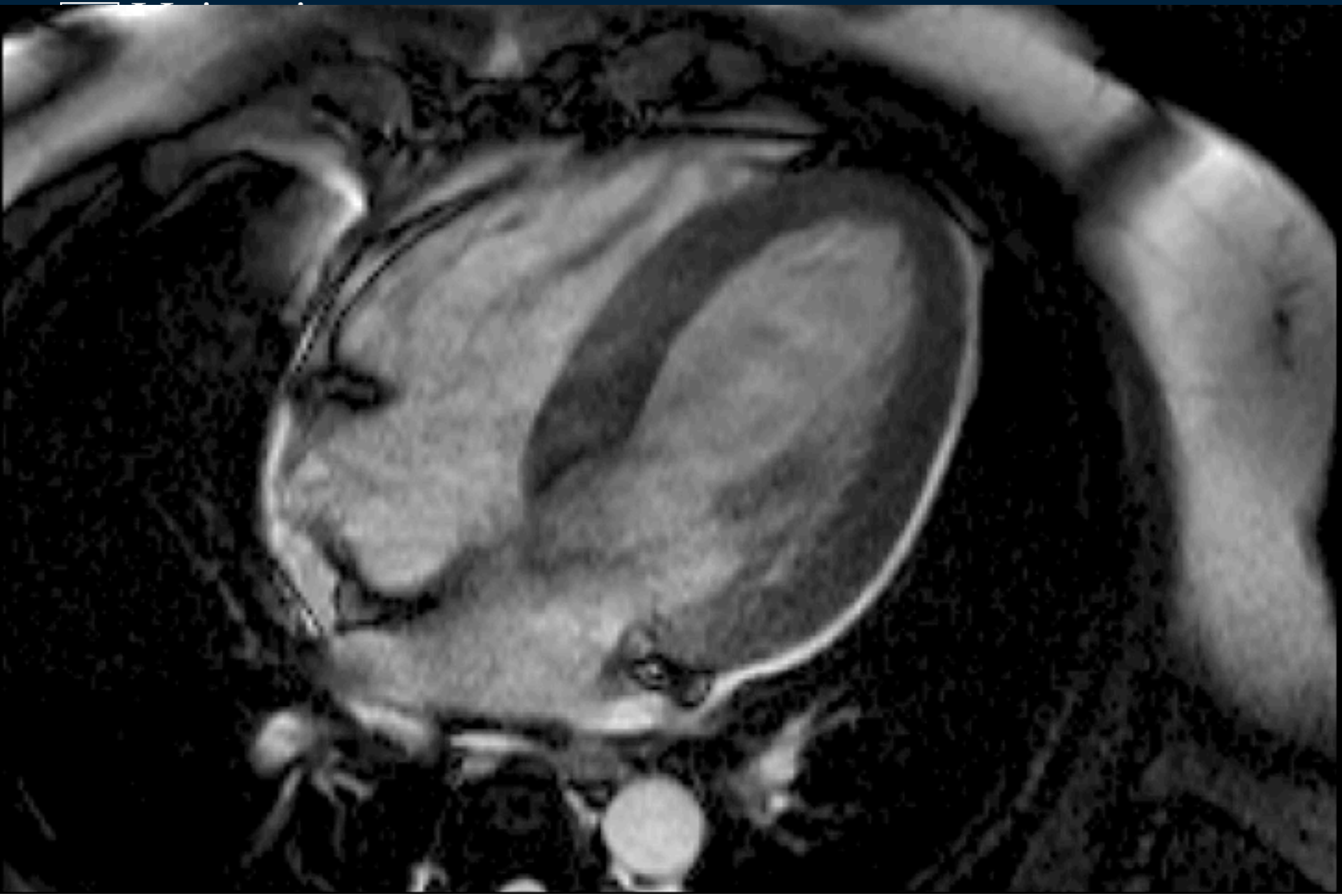
William E. Moody, Charles J. Ferro, Nicola C. Edwards, Colin D. Chue, Erica Lai Sze Lin, Robin J. Taylor, Paul Cockwell, Richard P. Steeds, Jonathan N. Townend; on behalf of the CRIB-Donor Study Investigators



68 kidney donors
56 controls
Difference in LVM 9.8g

Figure 2. Spread of 12-mo change in left ventricular mass among donors vs controls. There was a significant increase in left ventricular mass in donors vs controls at 12 mo with a mean difference in the change >12 mo of 9.8 g (95% confidence interval, 6.2–13.3; $P<0.001$).

F/U GFR
63ml/min
89ml/min



Fibrosis in the CKD/ESRD heart

- Heart in animal models of experimental renal failure shows that LVH is associated with an increase in cardiomyocyte volume➔oxygen diffusion distance and cardiomyocyte ischaemia

- Post mortem specimens of patients with ESRD. It is likely that apoptosis is triggered and increased fibrosis follows progressive myocyte death

- Amann K KI 2003, JASN 1998

Kidney International, Vol. 67 (2005), pp. 333–340

Clinical and pathologic characteristics of dilated cardiomyopathy in hemodialysis patients

JIRO AOKI, YUJI IKARI, HIROYOSHI NAKAJIMA, MASAYA MORI, TOKUICHIRO SUGIMOTO, MITSUHARU HATORI, SHUZOU TANIMOTO, EISUKE AMIYA, and KAZUHIRO HARA

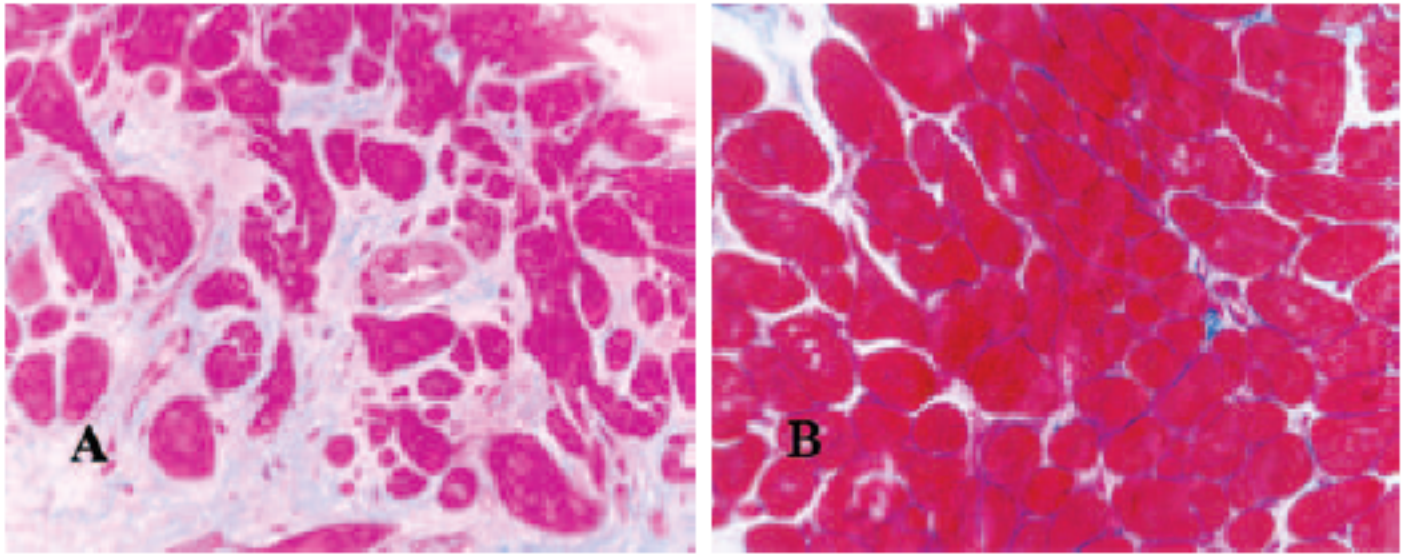
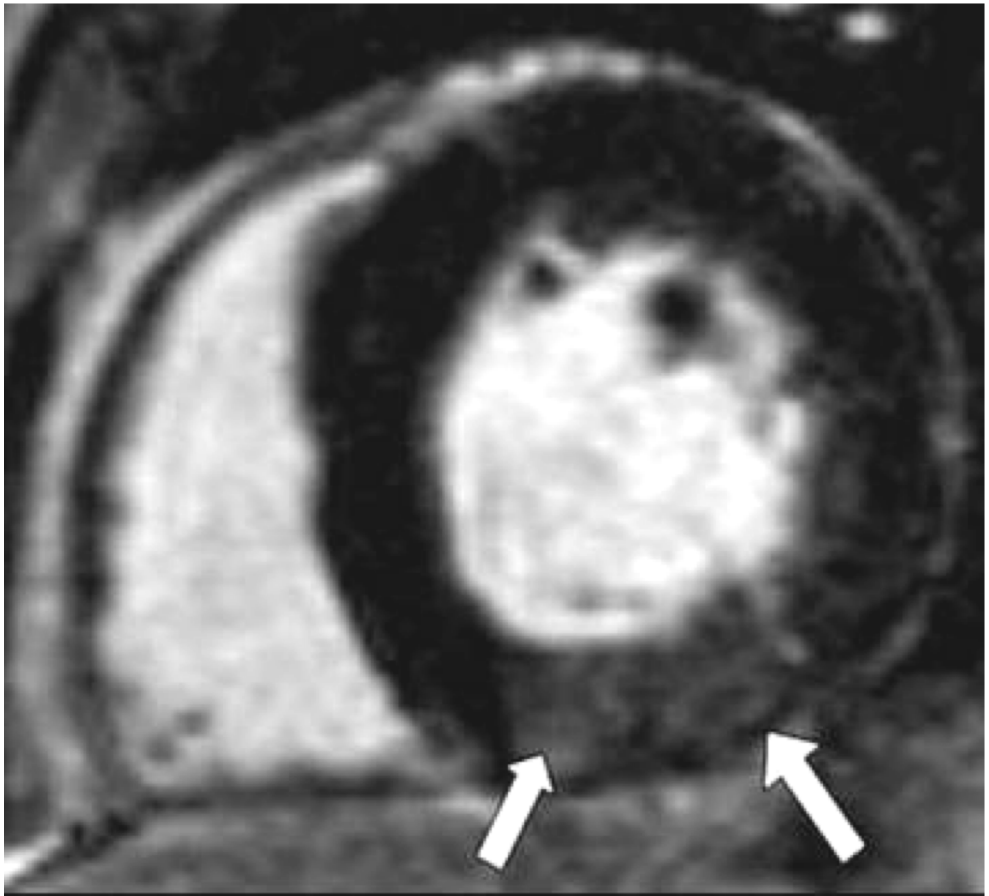


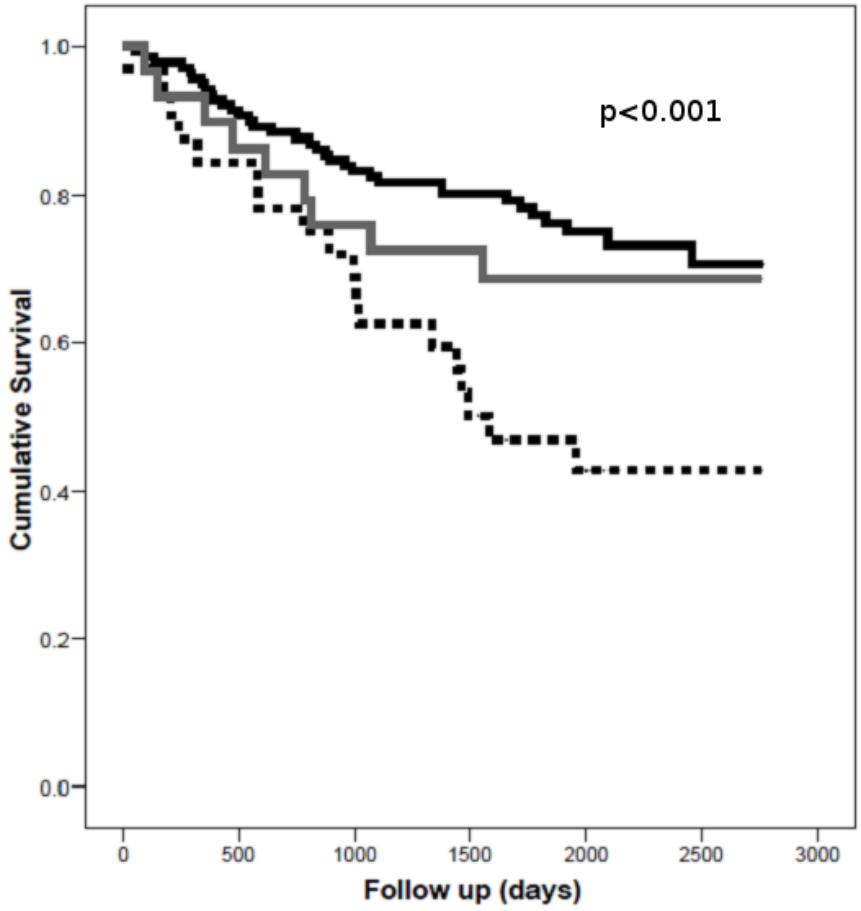
Fig. 3. A 56-year-old male patient on dialysis for 7.1 years (*A*). Widespread fibrosis is present, and interstitial fibrosis surrounds each myocyte (AZ stain, 400×). This patient died of ventricular arrhythmia 1.1 years after biopsy. A 56-year-old male patient on dialysis for 6.8 years (*B*). Only a little interstitial fibrosis is present (AZ stain, 400×). This patient had no cardiac events during 3.8 years of follow-up.

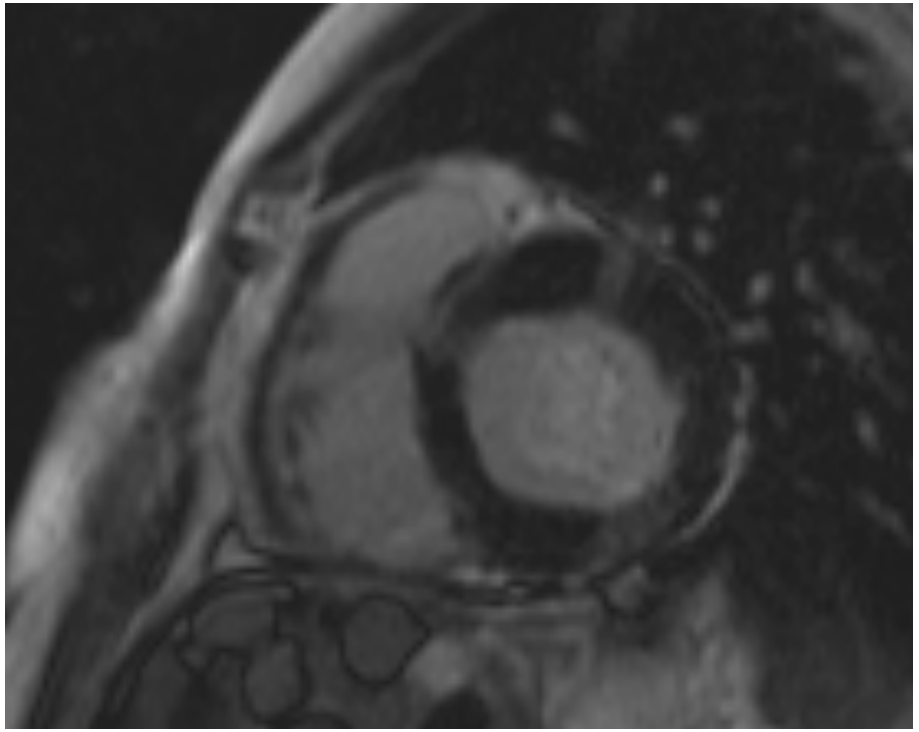
see commentary on page 1711

Redefinition of uremic cardiomyopathy by contrast-enhanced cardiac magnetic resonance imaging

PB Mark[1,2], N Johnston[3], BA Groenning[3], JE Foster[3], KG Blyth[3], TN Martin[3], T Steedman[3], HJ Dargie[3] and AG Jardine[1,2]







1. Mark PB, Johnston N et al KI 2006

2. Schietinger BJ, Brammer GM, Wang H et al. JACC CV Imaging 2008;1:450-6

Interesting Case

Nephrology Dialysis Transplantation

Gadolinium – a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis?

Thomas Grobner

Fast Track

Nephrogenic Systemic Fibrosis: Suspected Causative Role of Gadodiamide Used for Contrast-Enhanced Magnetic Resonance Imaging

Peter Marckmann,* Lone Skov,† Kristian Rossen,‡ Anders Dupont,§ Mette Brimnes Damholt,* James Goya Heaf,* and Henrik S. Thomsen‖

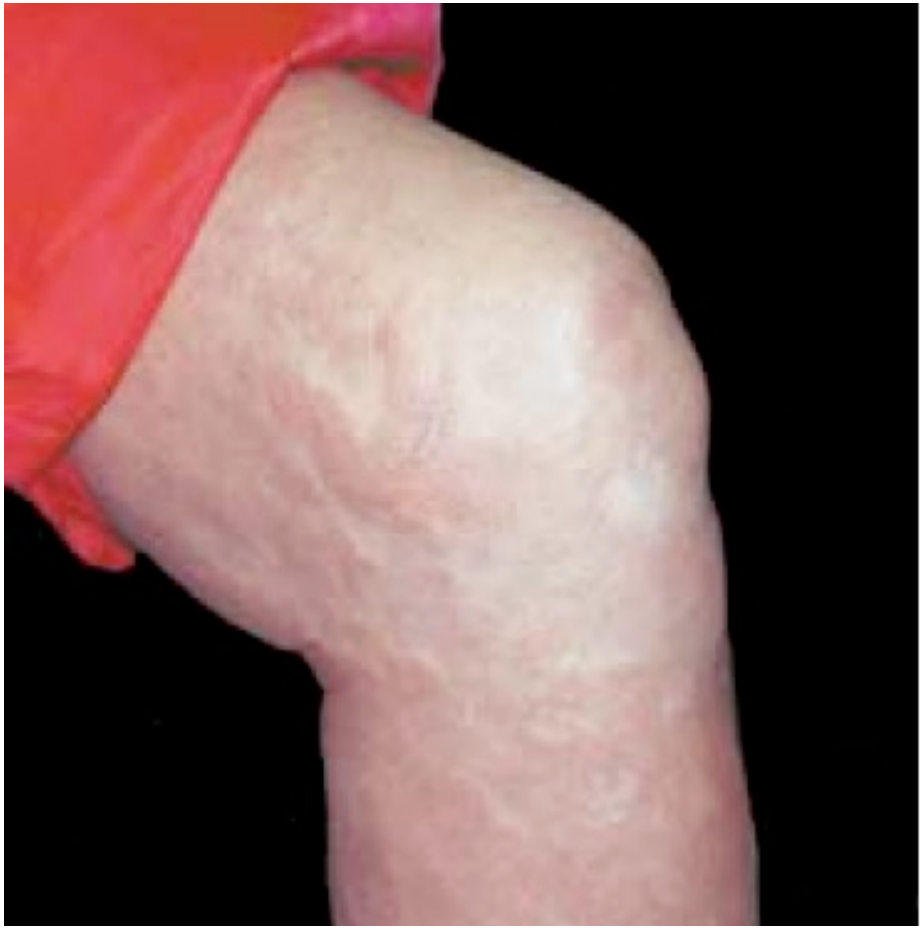
Gadolinium-enhanced MR Imaging and Nephrogenic Systemic Fibrosis: Retrospective Study of a Renal Replacement Therapy Cohort[1]

Radiology

Tara Anne Collidge, MBChB, PhD, MRCP
Peter Campbell Thomson, MBChB, BSc(MedSci), MRCP
Patrick Barry Mark, MBChB, BSc(MedSci), MRCP
James Phillip Traynor, MBChB, MD, MRCP
Alan George Jardine, MBChB, MD, FRCP
Scott Thomas William Morris, MBChB, PhD, FRCP
Keith Simpson, MBChB, FRCP
Giles Hannibal Roditi, MBChB, FRCP, FRCR

Nephrogenic systemic fibrosis

- First described 1997
- Only GFR<15ml/min
- 10% never on RRT
- Symmetrical brawny plaques
- Skin thickened, ‘woody’
- Painful, contractures
- No clear aetiology



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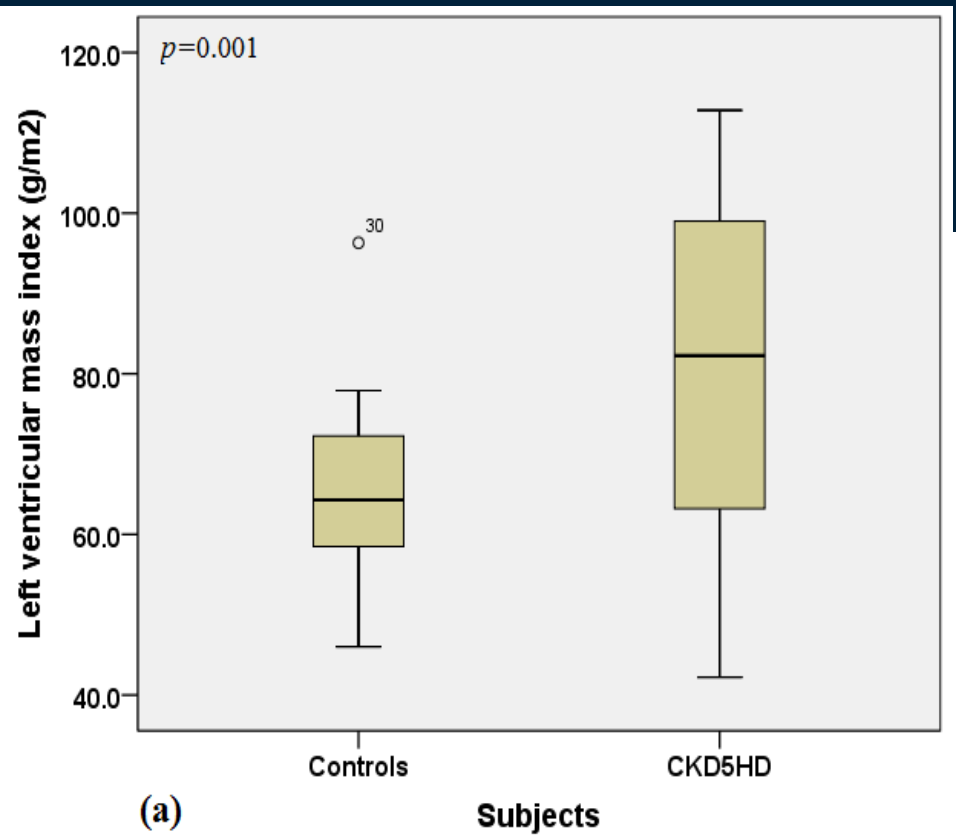
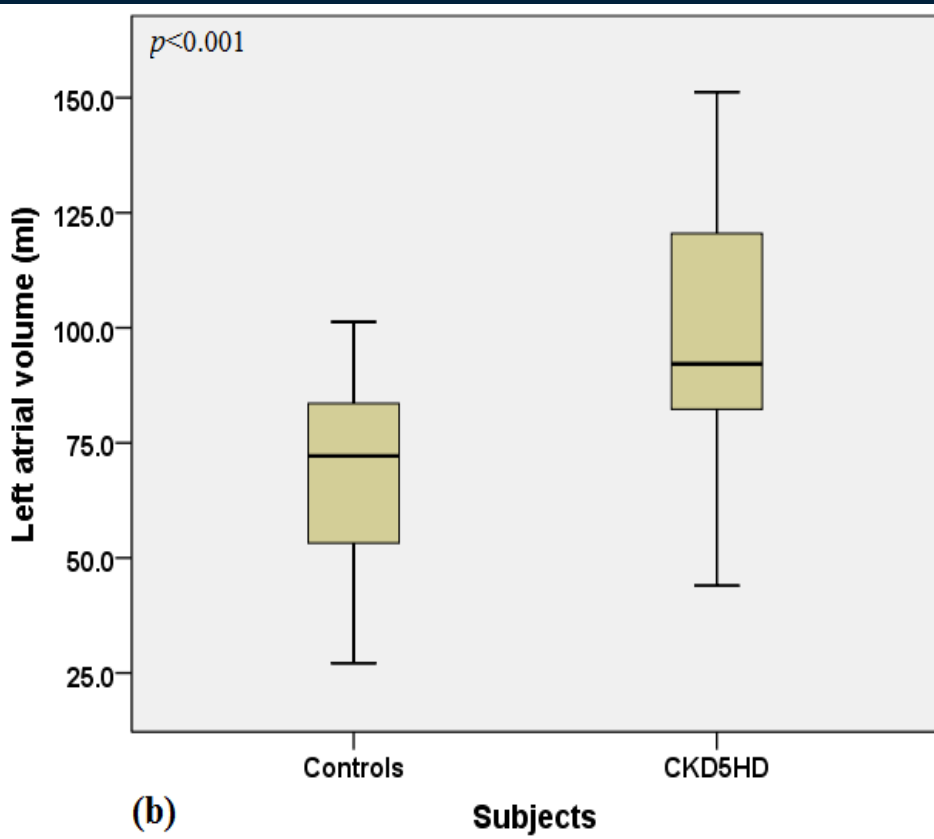
CMR Native T1 Times

- Longitudinal recovery time of hydrogen atoms following their excitation by a magnetic field
- Surrogate marker of myocardial fibrosis in other populations
- CKD 2-4 – Edwards et al AJC 2015
  - Contrast administration





Box plots comparing left ventricular mass index (a) and left atrial volume (b) in CKD5HD and controls

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Hypothesis

- T1 times will be higher in dialysis patients when compared to controls

- T1 times may also be a marker of fibrosis in this population

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Methods

- 28 volunteers v 33 dialysis patients
- 3.0 Tesla MRI
- HD participants all scanned on post dialysis day
- Cardiac function – LV mass
- Global Longitudinal Strain
- T1 maps throughout myocardium
  - American Heart Association model
  - Global, Septal and Mid-septal T1 times calculated

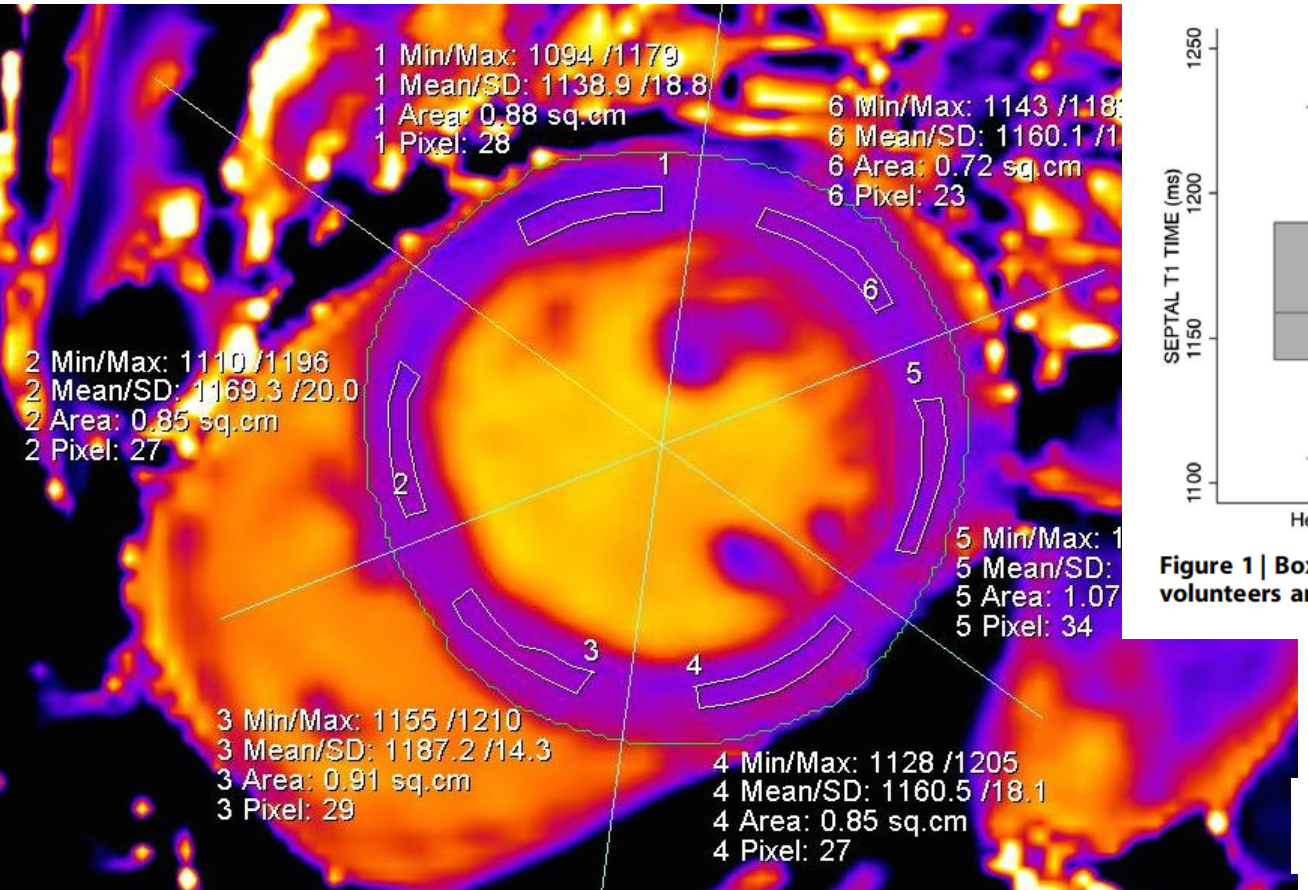
Defining myocardial tissue abnormalities in end-stage renal failure with cardiac magnetic resonance imaging using native T1 mapping

OPEN

see commentary on page 729

Elaine Rutherford[1,2], Mohammed A. Talle[1], Kenneth Mangion[1], Elizabeth Bell[1], Samuli M. Rauhalammi[1], Giles Roditi[1], Christie McComb[1], Aleksandra Radjenovic[1], Paul Welsh[1], Rosemary Woodward[1], Allan D. Struthers[2], Alan G. Jardine[1], Rajan K. Patel[1], Colin Berry[1] and Patrick B. Mark[1]

[1]*Institute of Cardiovascular and Medical Sciences, BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Scotland, UK; and* [2]*University of Dundee, Division of Cardiovascular & Diabetes Medicine, Dundee, Scotland, UK*



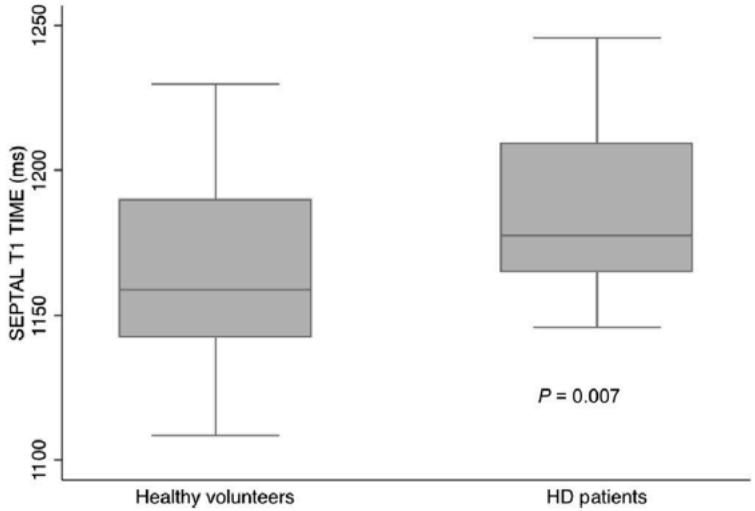
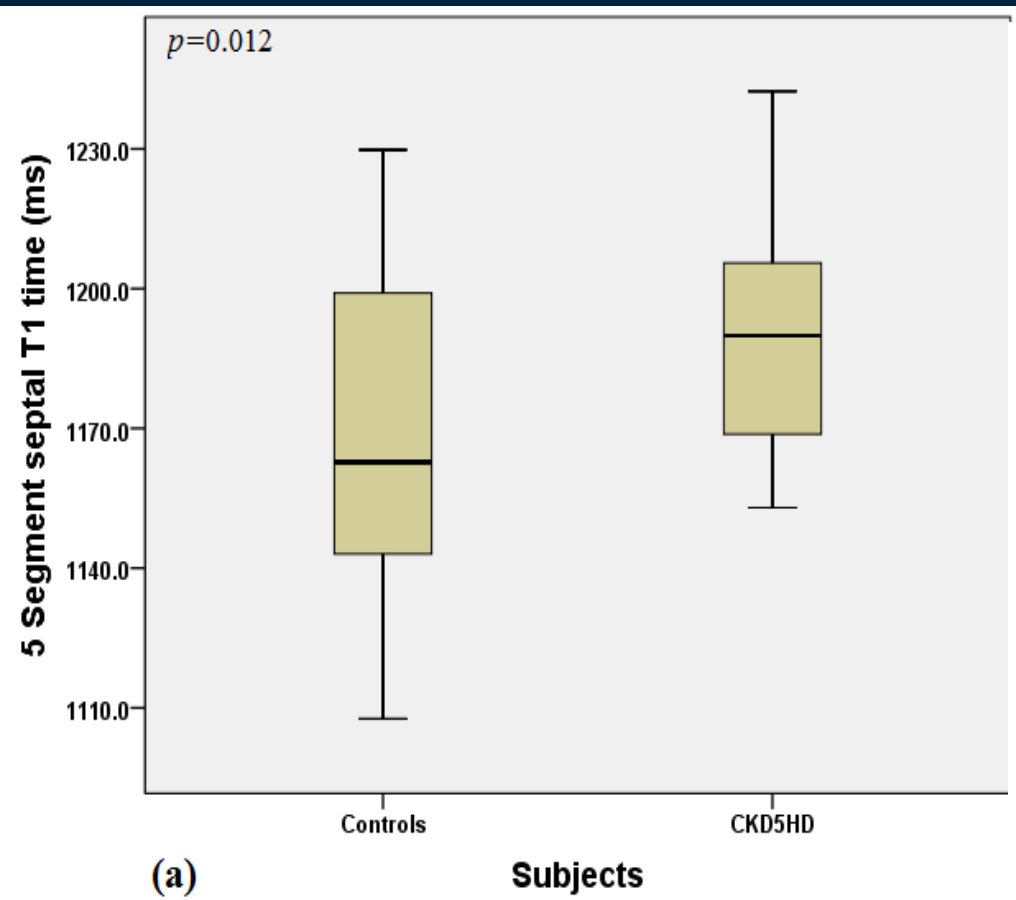
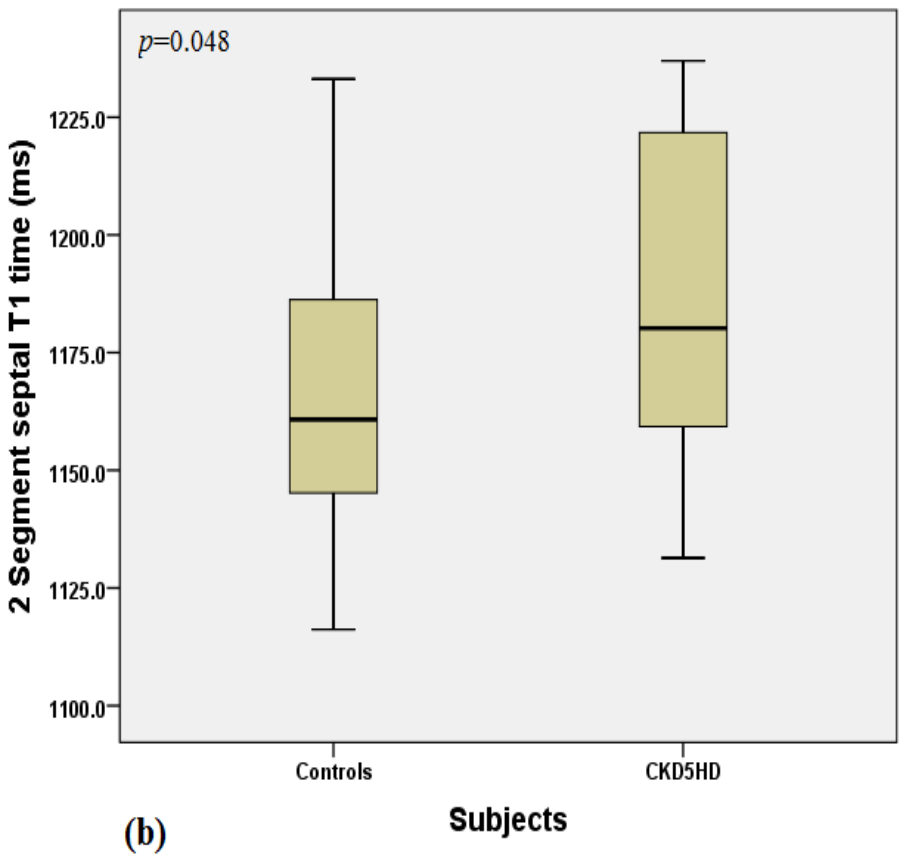


Figure 1 | Boxplot comparing septal T1 times in healthy volunteers and hemodialysis (HD) patients.

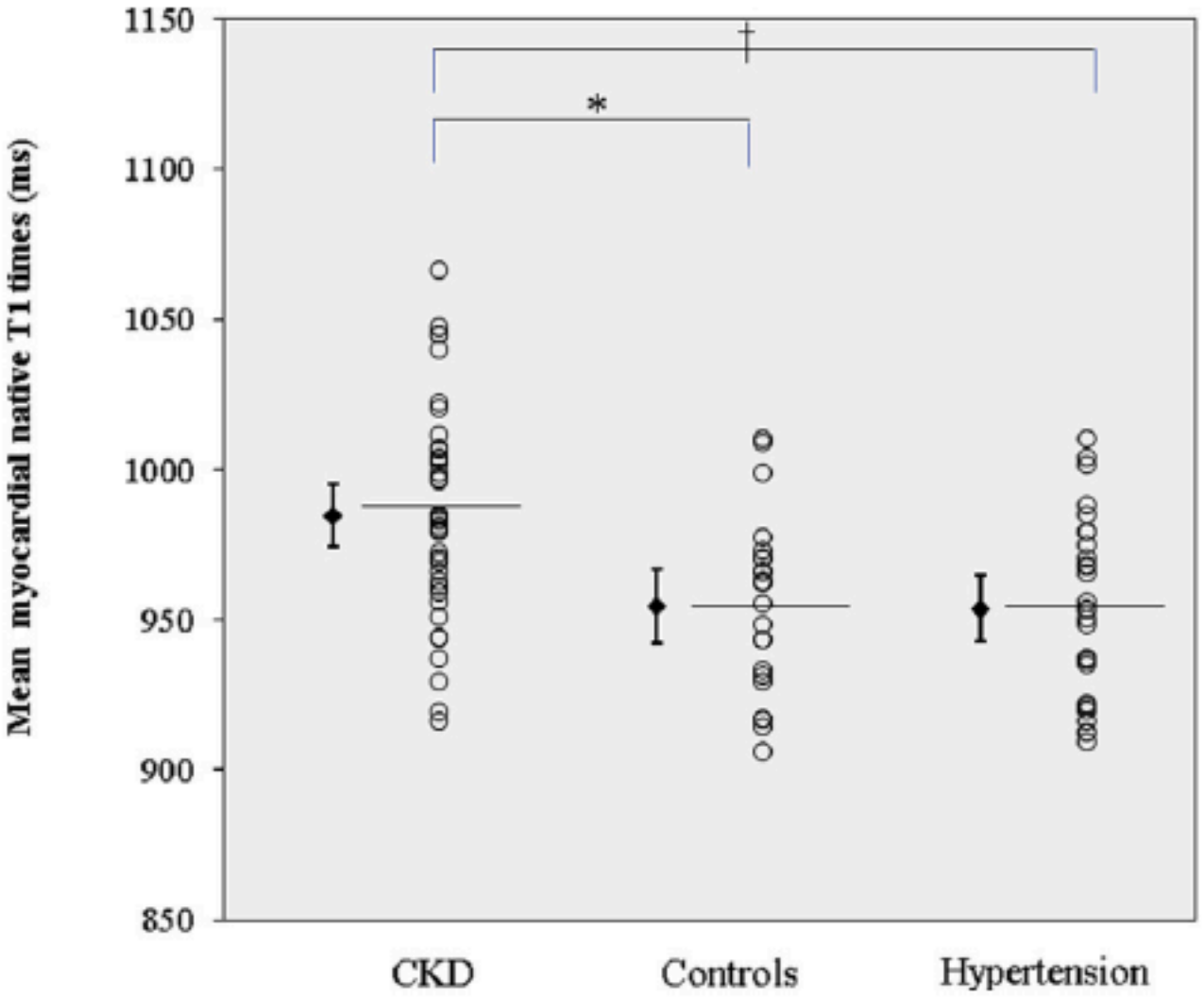




Box plots comparing septal T1 time obtained from 5 septal segments (a) and 2 septal segments (b) in CKD5HD and controls

Diffuse Interstitial Fibrosis and Myocardial Dysfunction in Early Chronic Kidney Disease

Nicola C. Edwards, PhD[a,b,*], William E. Moody, MBChB[a,b], Mengshi Yuan, MBChB[b], Manvir K. Hayer, MBChB[c], Charles J. Ferro, MD[a,c], Jonathan N. Townend, MD[a,b], and Richard P. Steeds, MD[a,b]



Am J Cardiology2015 May 1;115(9):1311-7.

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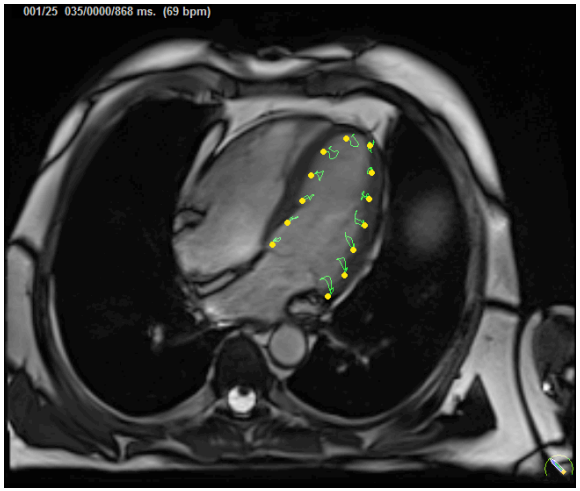
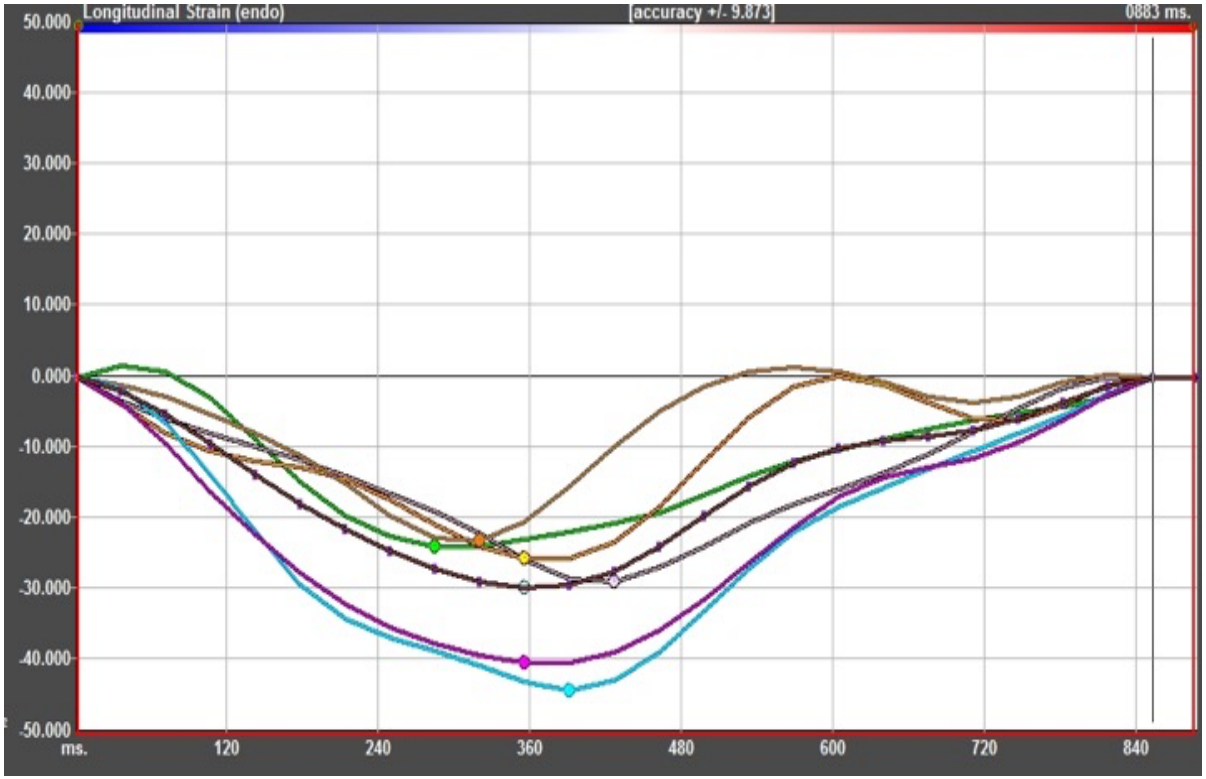
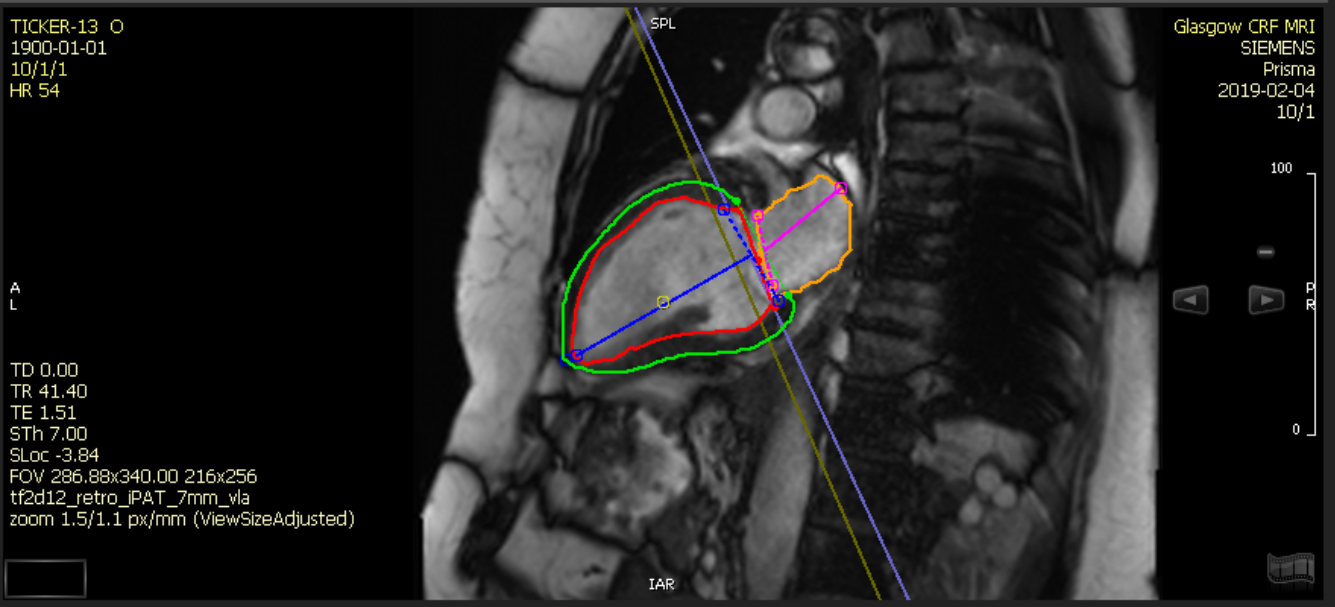
Global Longitudinal Strain

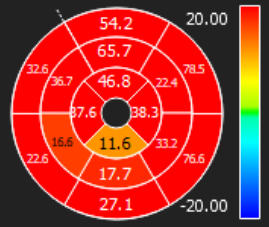




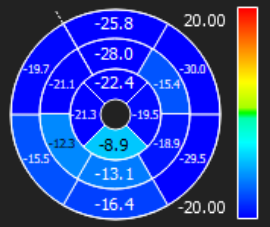
Tissue Tracking



LV Results (2D) | RV Results(2D) | LV Results(3D) | RV Results(3D



Peak Radial Strain (%)
78.6 mm (AHA)



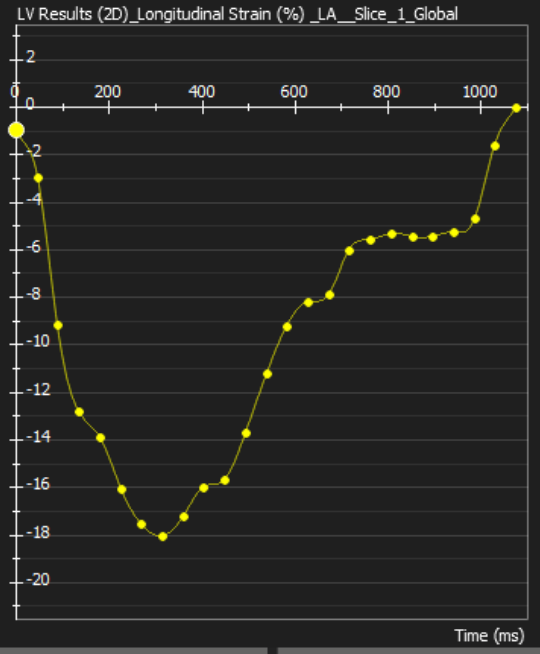
Peak Longitudinal Strain (%)
78.6 mm (AHA)

No Overlay | ROI Count: 6

Peak SI | AHA Segments | Coronary Terr | Restrict Result

SA Series

LA Series



Show Intersections Between Image Planes (Based on Tracking Contours)

Longitudinal Strain (%) | Global Myocardium on curre

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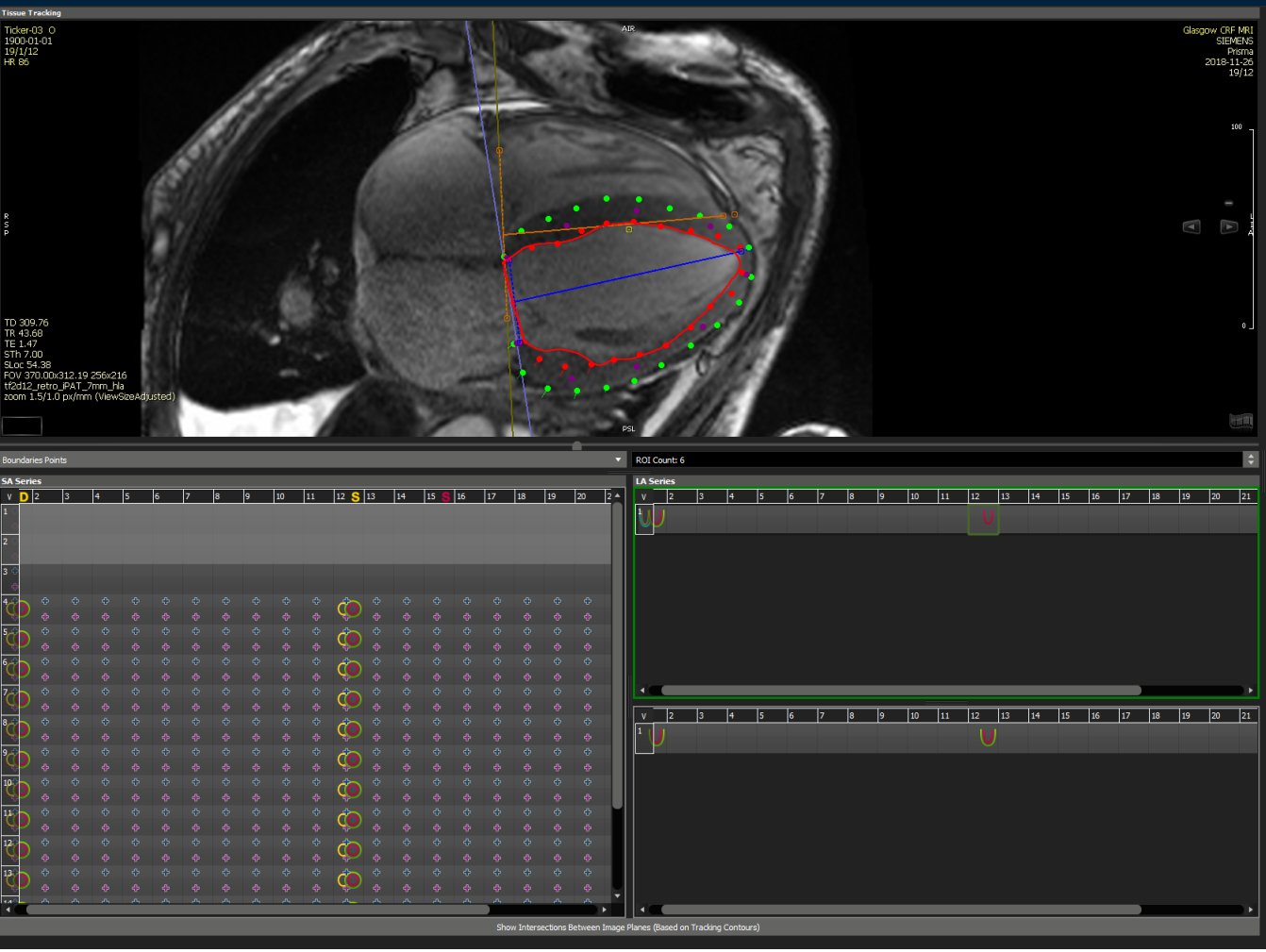


Variable	Healthy Volunteers (n=28)	HD Patients (n=33)	P value
Age (years)	60 (19.5)	56 (21.5)	0.562
Male (%)	57.1	57.6	0.973
LVMI (g/m^2)	55.0 (12.0)	69.8 (28.3)	0.001
LVH (%)	3.6	42.4	0.001
Ejection Fraction (%)	63.3 ± 5.2	63.2 ± 9.3	0.963
Global Longitudinal Strain (%)	-21.8 ± 6.2	-17.7 ± 5.3	0.007

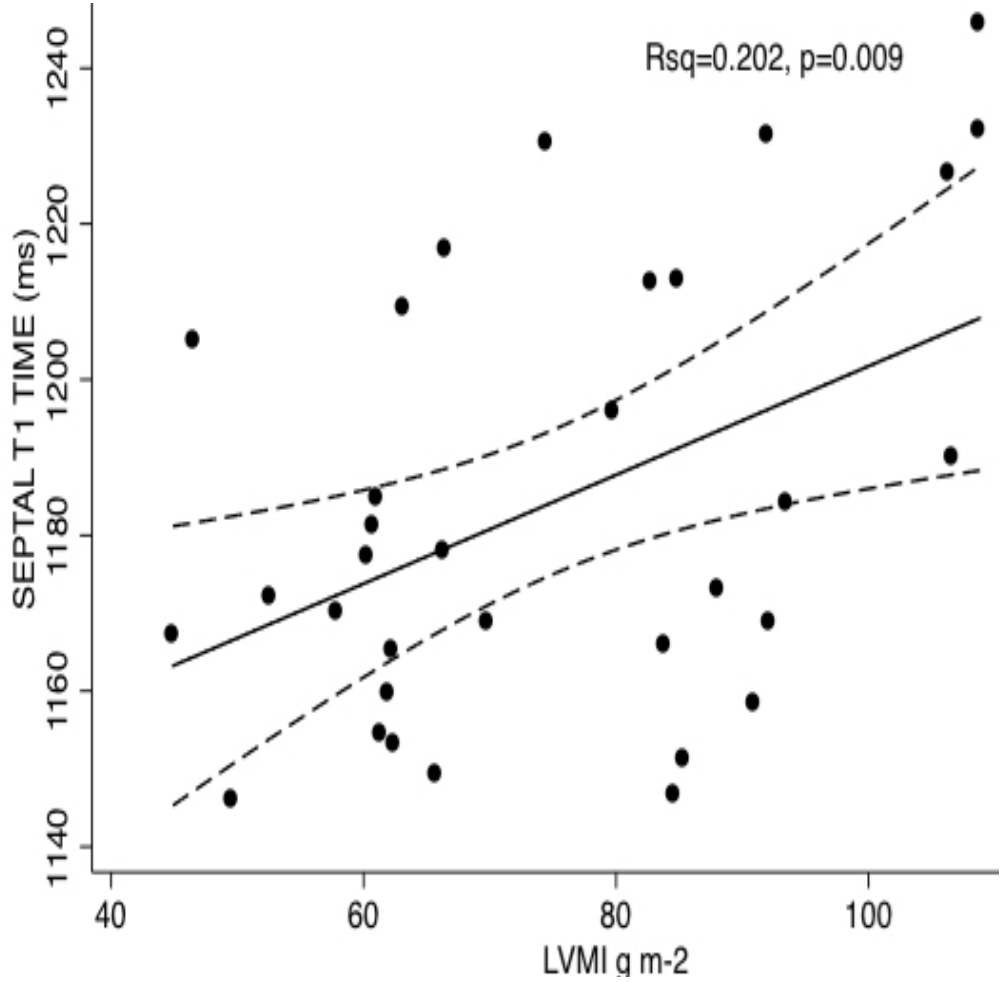
Variable	Healthy Volunteers (n=28)	HD Patients (n=33)	P value
Global T1 (ms)	1154 ± 32	1171 ± 27	0.025
Septal T1 (ms)	1163 ± 30	1184 ± 29	0.007
Mid-septal T1 (ms)	1161 ± 29	1184 ± 34	0.006

Left ventricular mass indices correlated with T1 times

Global T1
R = 0.452 p = 0.008

Septal T1
R = 0.449 p = 0.009

Mid-Septal T1
R = 0.498 p = 0.003



Kidney International (2016) **90,** 845–852

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- T1 times are prolonged in HD
- In the HD population T1 times correlate with LV mass
- Global Longitudinal Strain is reduced in the HD population
- Prolonged T1 times may be representative of myocardial fibrosis known to be found in this population

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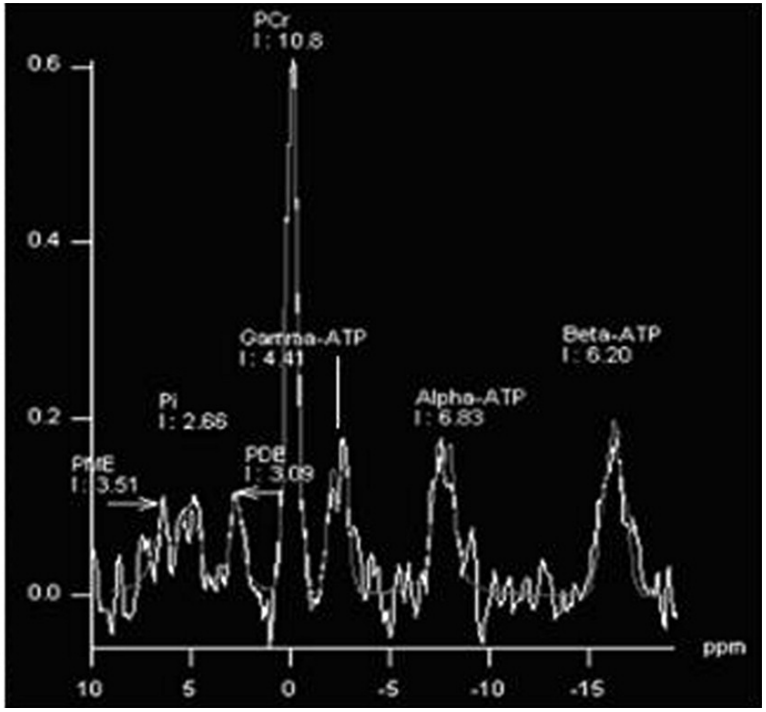
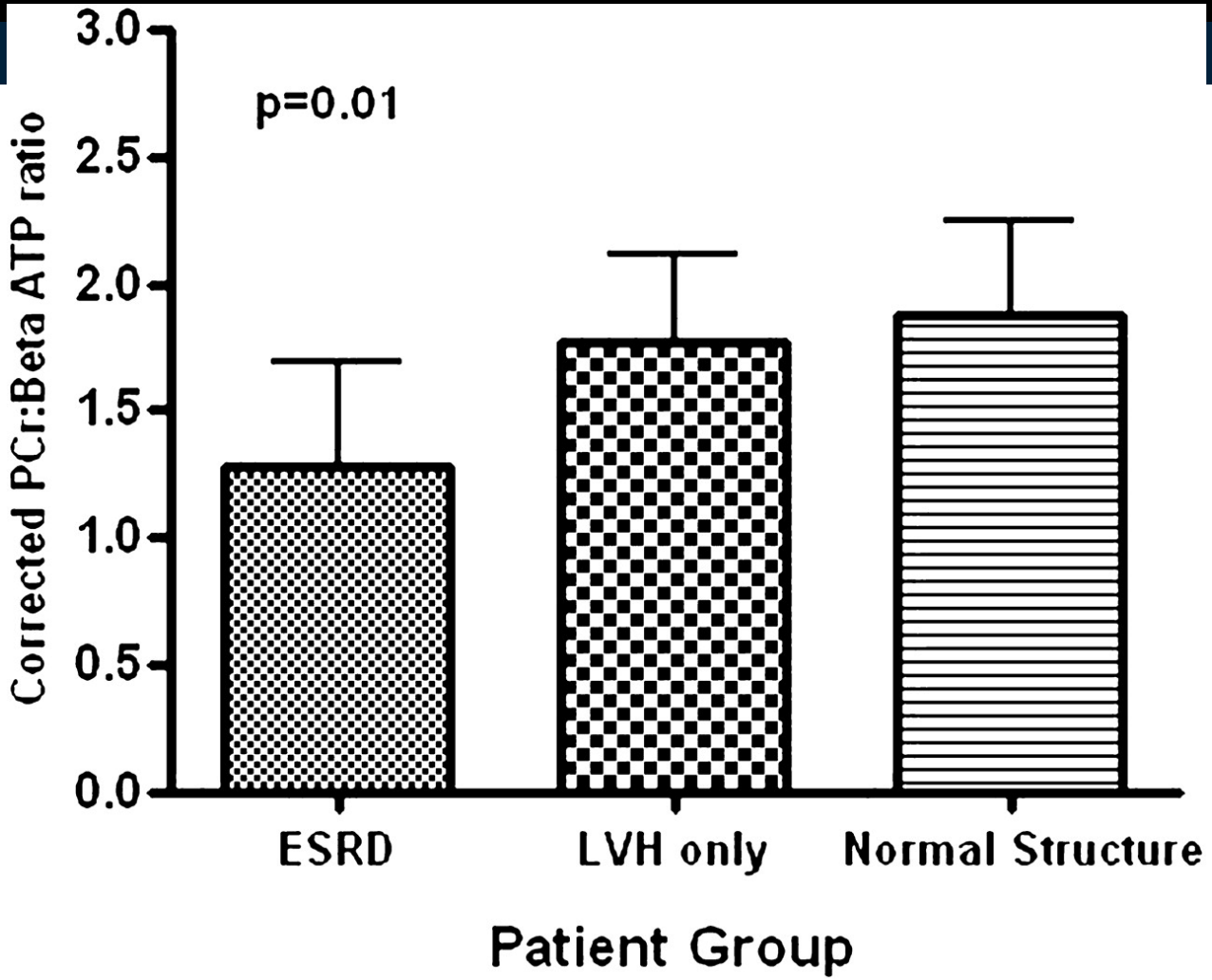
Acquisition of 31P MRS spectra from apex of left ventricle.



Patel R K, Mark PB et al. Nephrol. Dial. Transplant. 2012;27:2446-2451

NDT Nephrology Dialysis Transplantation

Comparison of mean PCr:ATP (±SD) between ESRD, LVH-only and normal patients.

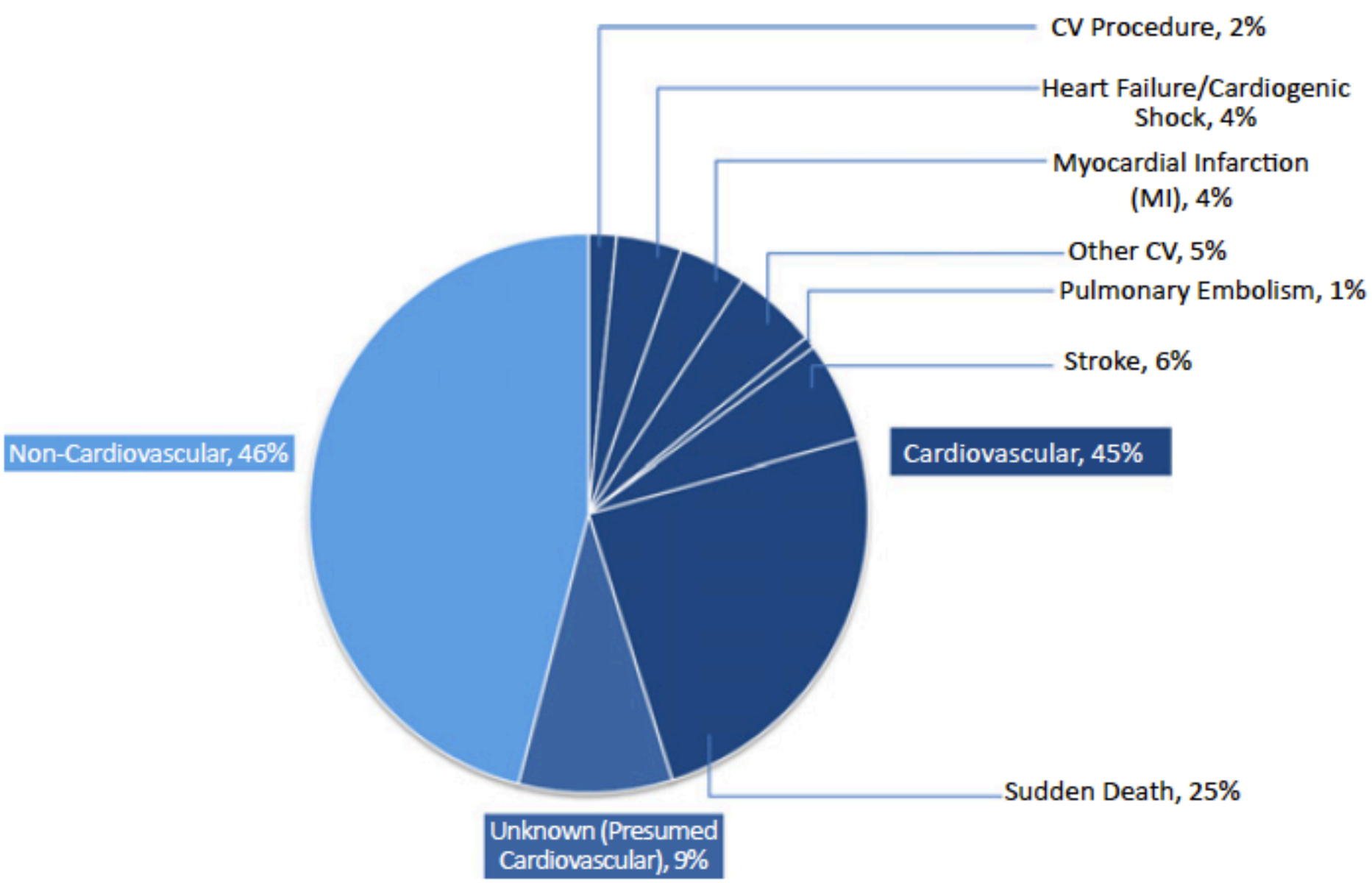


Patel R K et al. Nephrol. Dial. Transplant. 2012;27:2446-2451

NDT Nephrology Dialysis Transplantation

LVH as a CVD risk factor in CKD

- The big CV problem in advanced CKD is NON-atherosclerotic cardiac death
- Arrhythmia focus
- Heart failure with preserved ejection fraction
- Myocyte/capillary mismatch leads to demand/subendocardial ischaemia
- Viscous circle



EVOLVE Cardiovascular Events *Wheeler et al*

Journal of the American Heart Association

Imaging as an end point in trials at reduction of CVD risk specific to CKD

- LV mass
- GLS
- T1 at MRI – tissue fibrosis
- Myocardial energetics – fuel
- Myocardial strain- function
- Calcification scoring (CT)
- Vascular distensibility

- BUT change surrogate biomarker needs to translate into reduction in actual risk of cardiac events/dying

Allopurinol Benefits Left Ventricular Mass and Endothelial Dysfunction in Chronic Kidney Disease

Michelle P. Kao,* Donald S. Ang,* Stephen J. Gandy,† M. Adnan Nadir,* J. Graeme Houston,† Chim C. Lang,* and Allan D. Struthers*

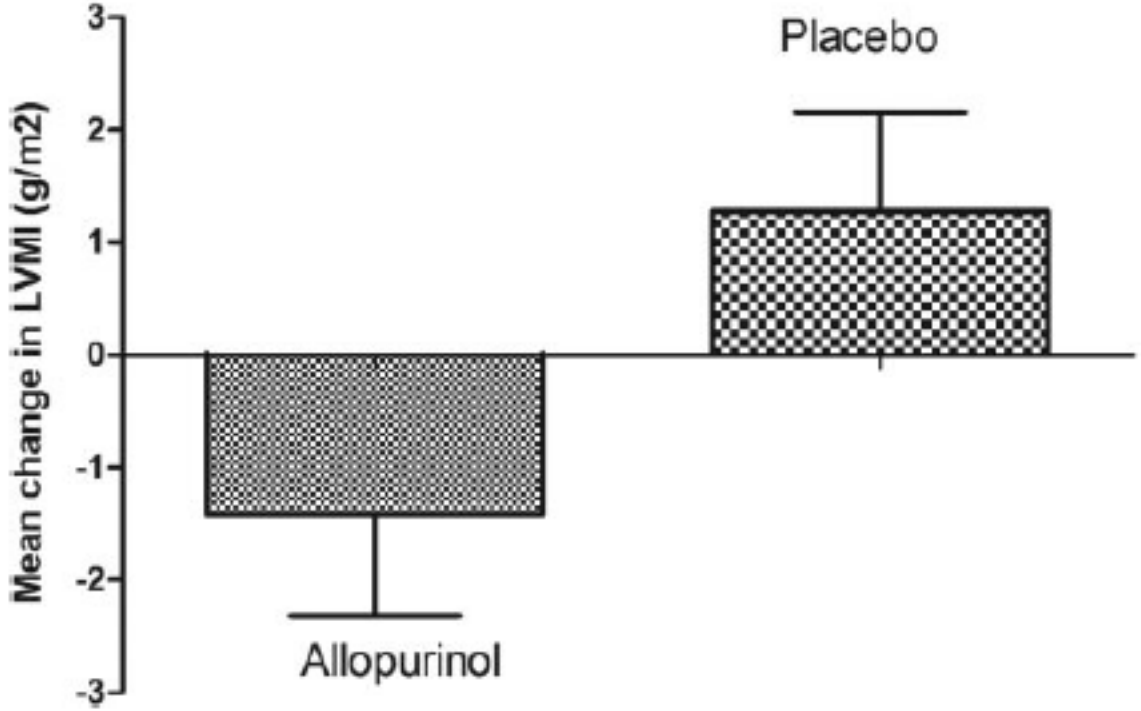


Figure 2. Significant regression of LVMI in the allopurinol group compared to the placebo group after 9 months, as measured by cardiac MRI.

J Am Soc Nephrol **22:** 1382–1389, 2011

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Final thoughts on CKD and CVD

- CKD alone is bad for the heart
- The heart is big and fibrotic
- The vessels are stiff and may be calcified
- T1/LVH/vessel stiffness is a potential surrogate for trials
- More evidence/therapies needed and coming
- Meanwhile kidney transplant still most cardiovascular benefit in the right people