CKD/ESRD «Cardiomyopathy» Pathophysiology and Therapy

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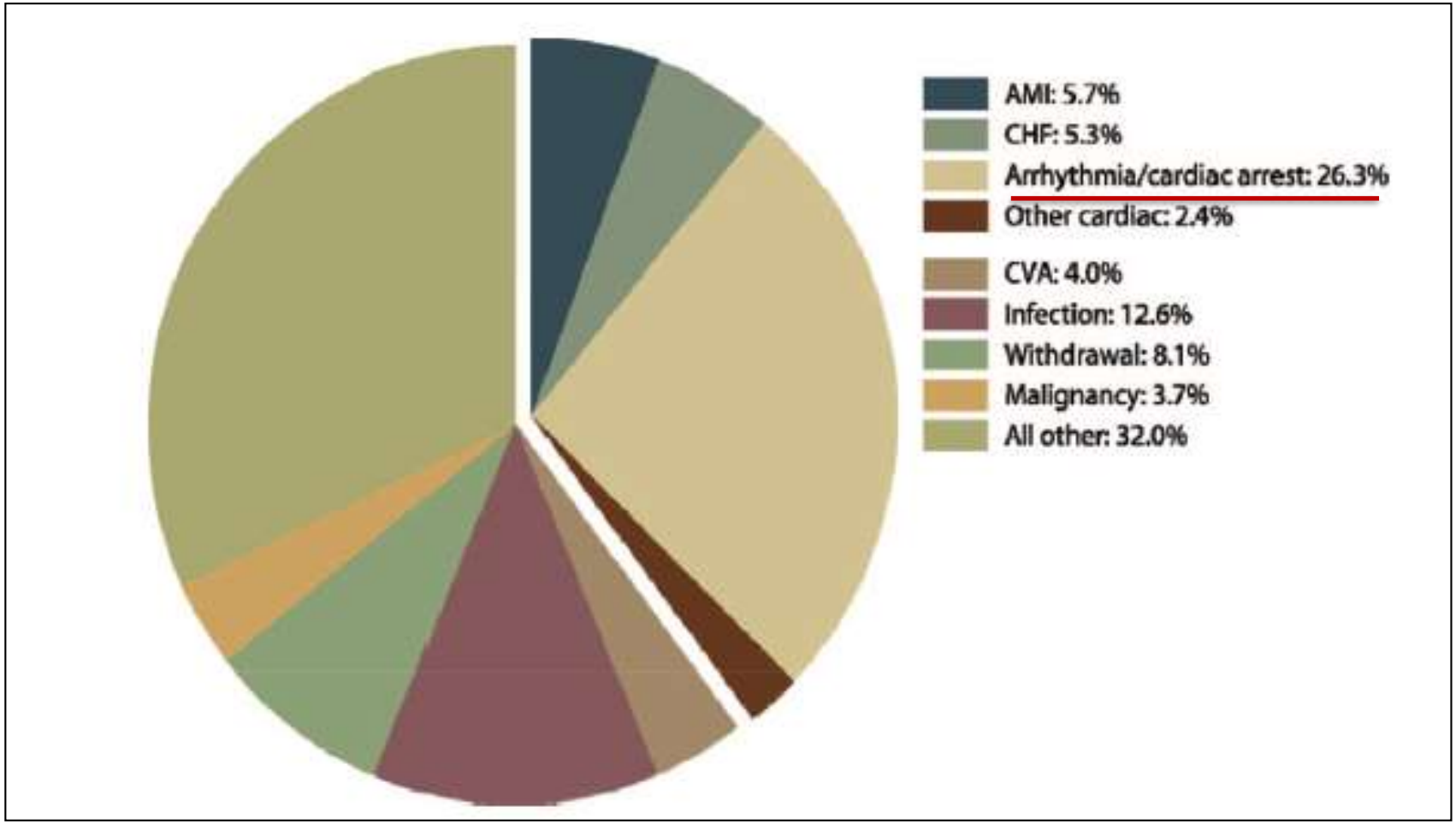
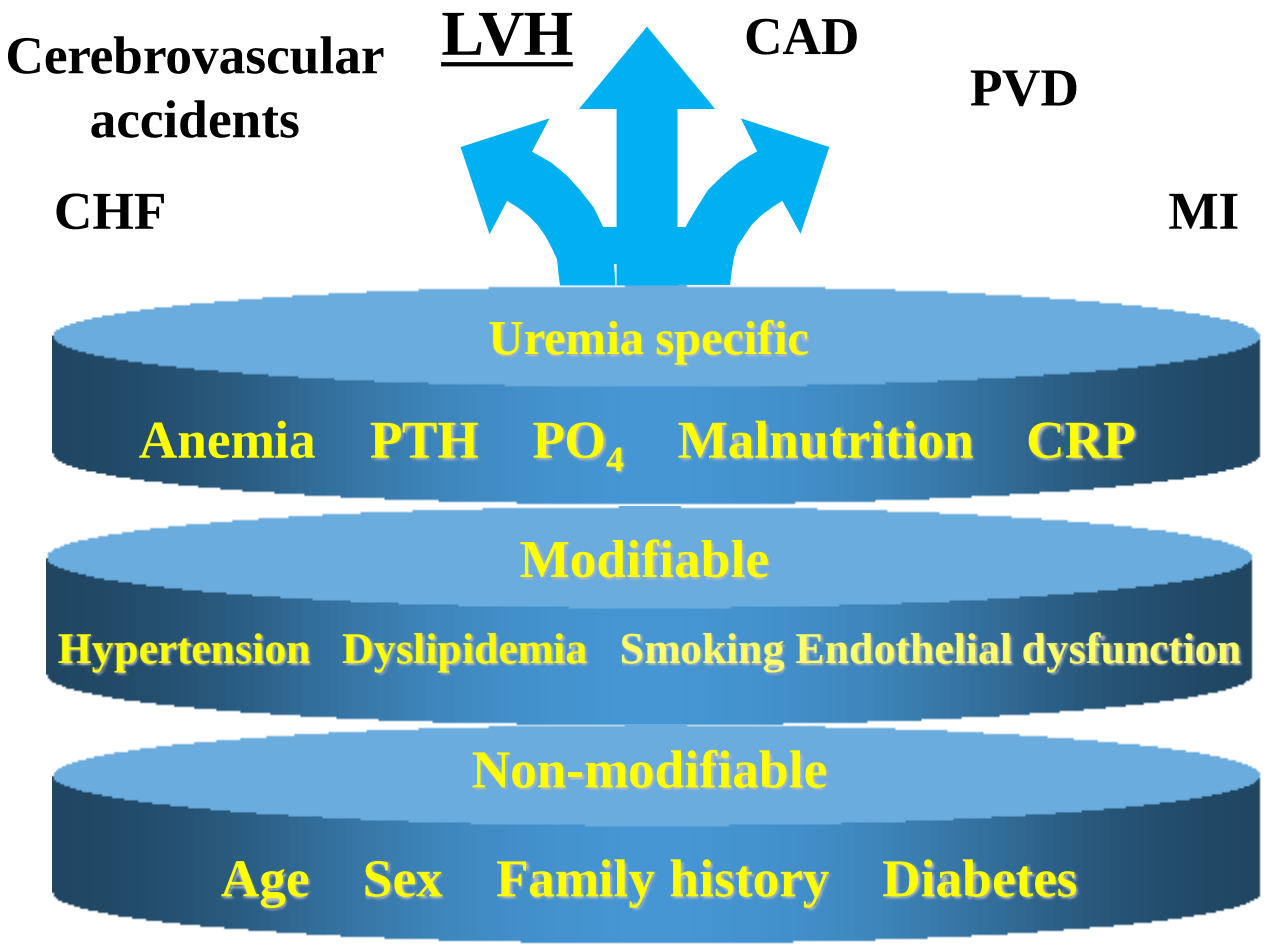
Causes of death in hemodialysis USA 2005-2007

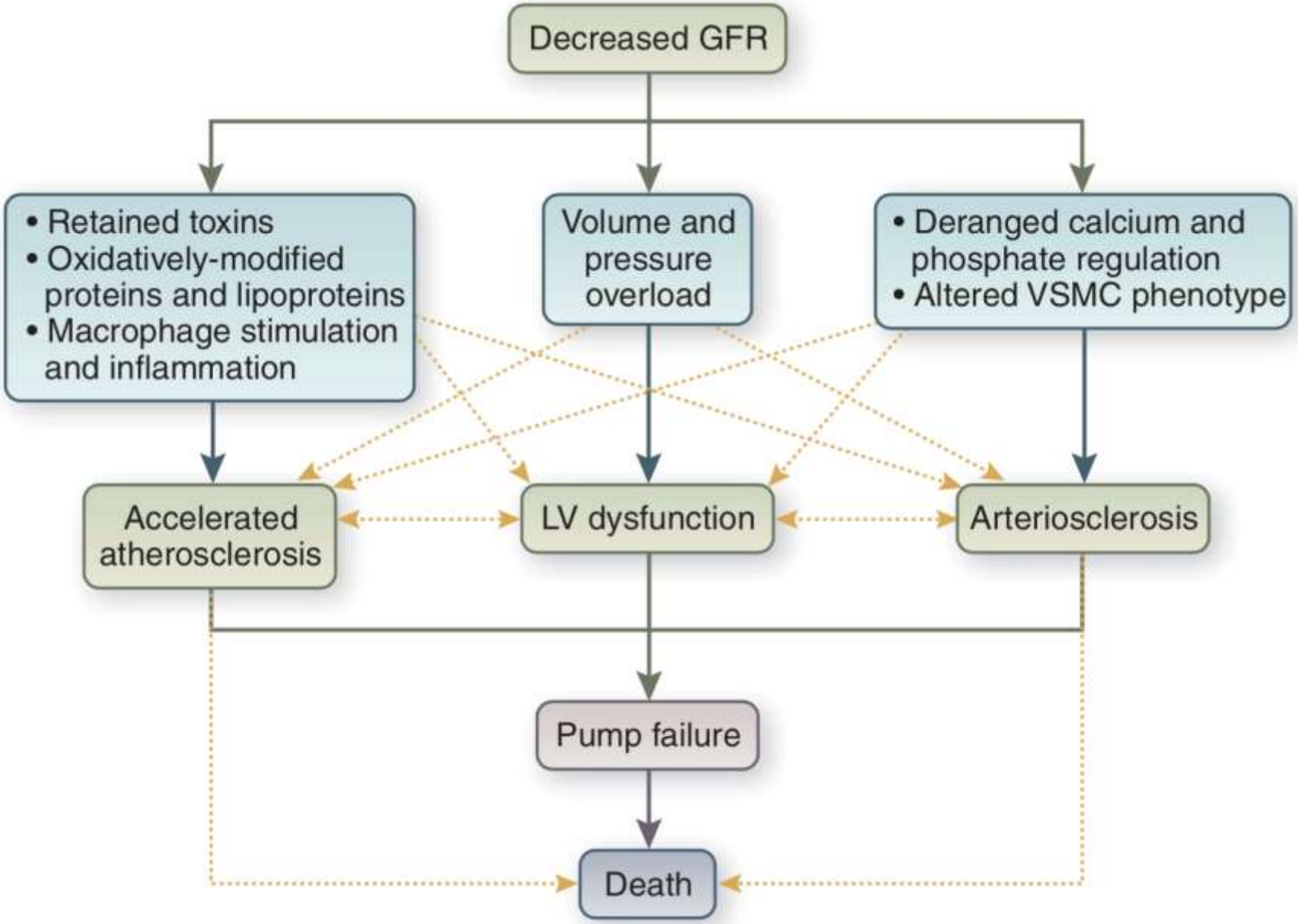


***Circ Arrhythm Electrophysiol*. 2010;3:553-559.)**

Cumulative Risk Factors for CVD in CKD



CVD = cerebrovascular disease; CKD = chronic kidney disease; CHF = congestive heart failure; CAD = coronary artery disease; PVD = peripheral vascular disease; PTH = parathyroid hormone; GFR = glomerular filtration rate; CRP = C-reactive protein; tHcy = homocysteine


Decreased GFR
• Retained toxins
• Oxidatively-modified proteins and lipoproteins
• Macrophage stimulation and inflammation
Volume and pressure overload
• Deranged calcium and phosphate regulation
• Altered VSMC phenotype
Accelerated atherosclerosis
LV dysfunction
Arteriosclerosis
Pump failure
Death

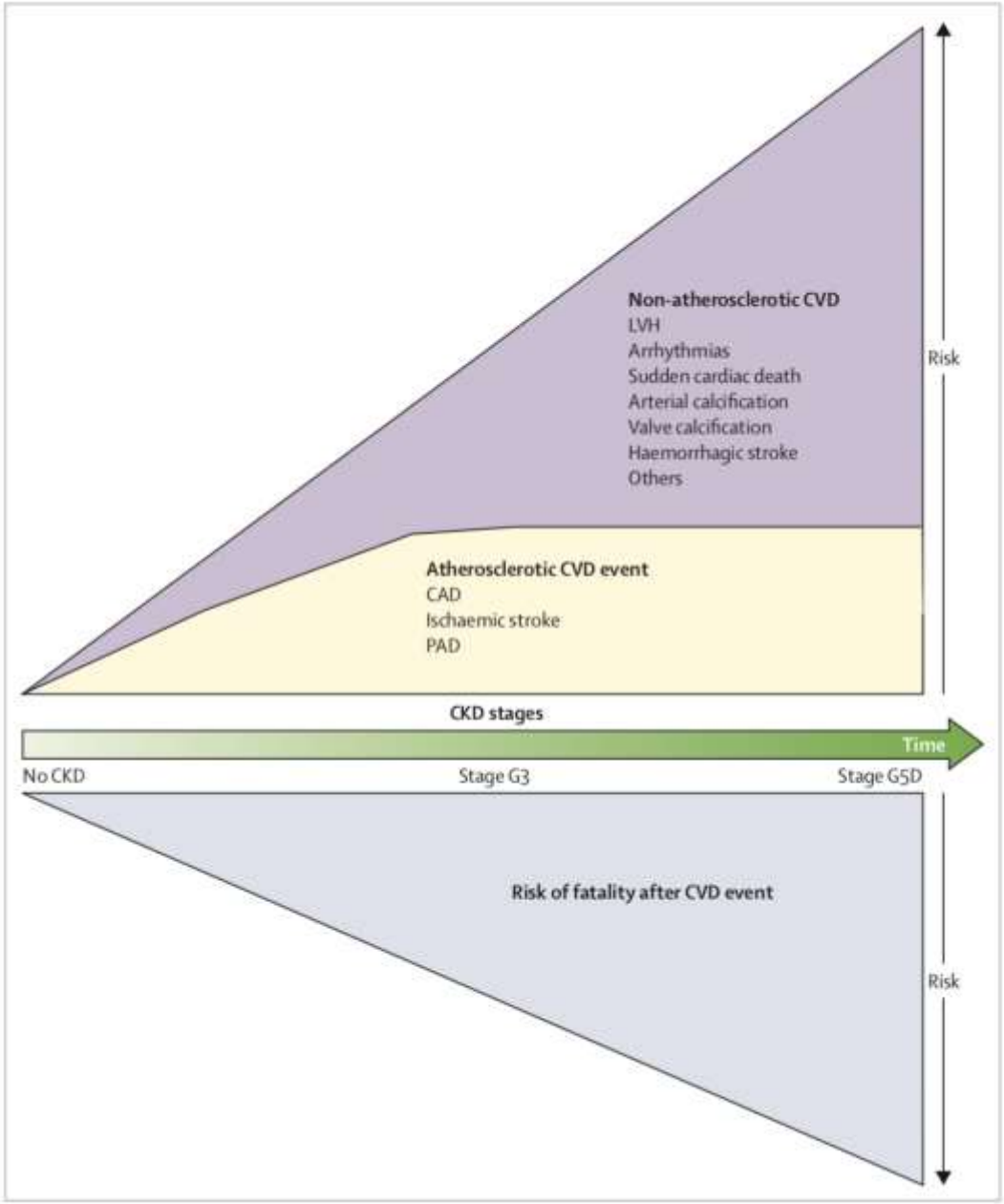
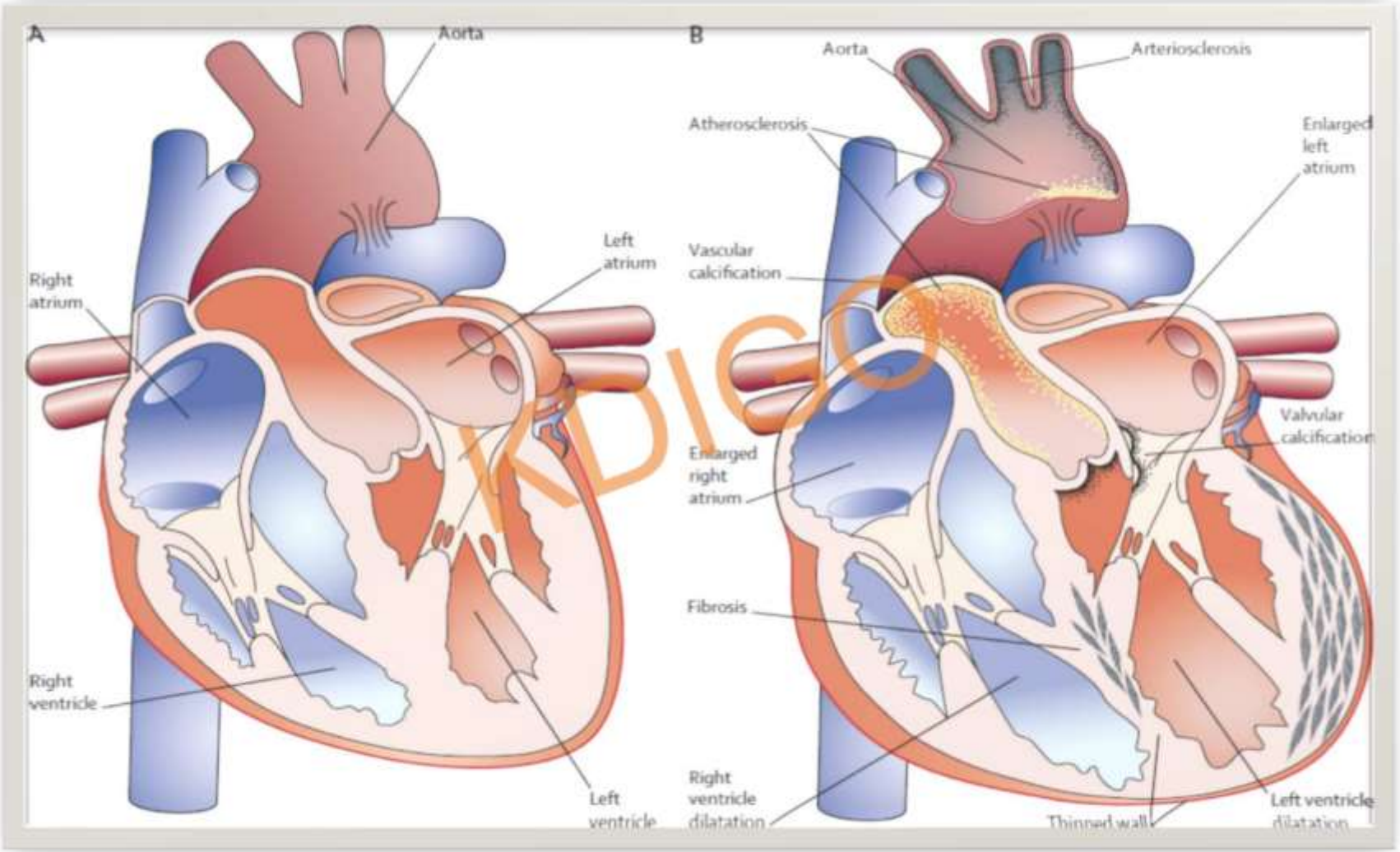


Figure 2: Change in cardiovascular risk during chronic kidney disease progression

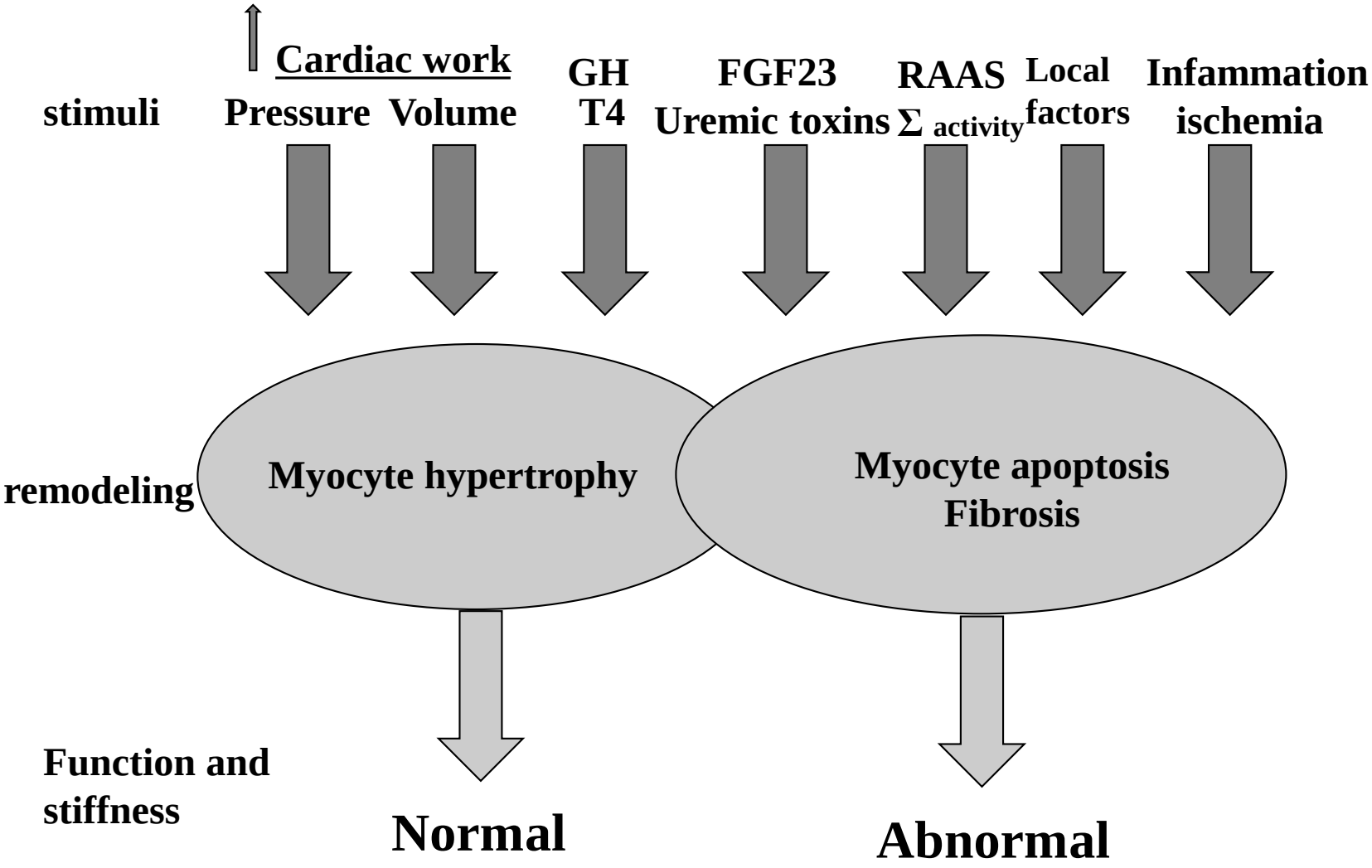
Wanner C et al. Lancet 2016;388:276-84

Changes in uremic cardiomyopathy



Wanner C, Amann K, Shoji T. Lancet 2016

Stimuli to myocardial remodelig and their impact on stiffness and function



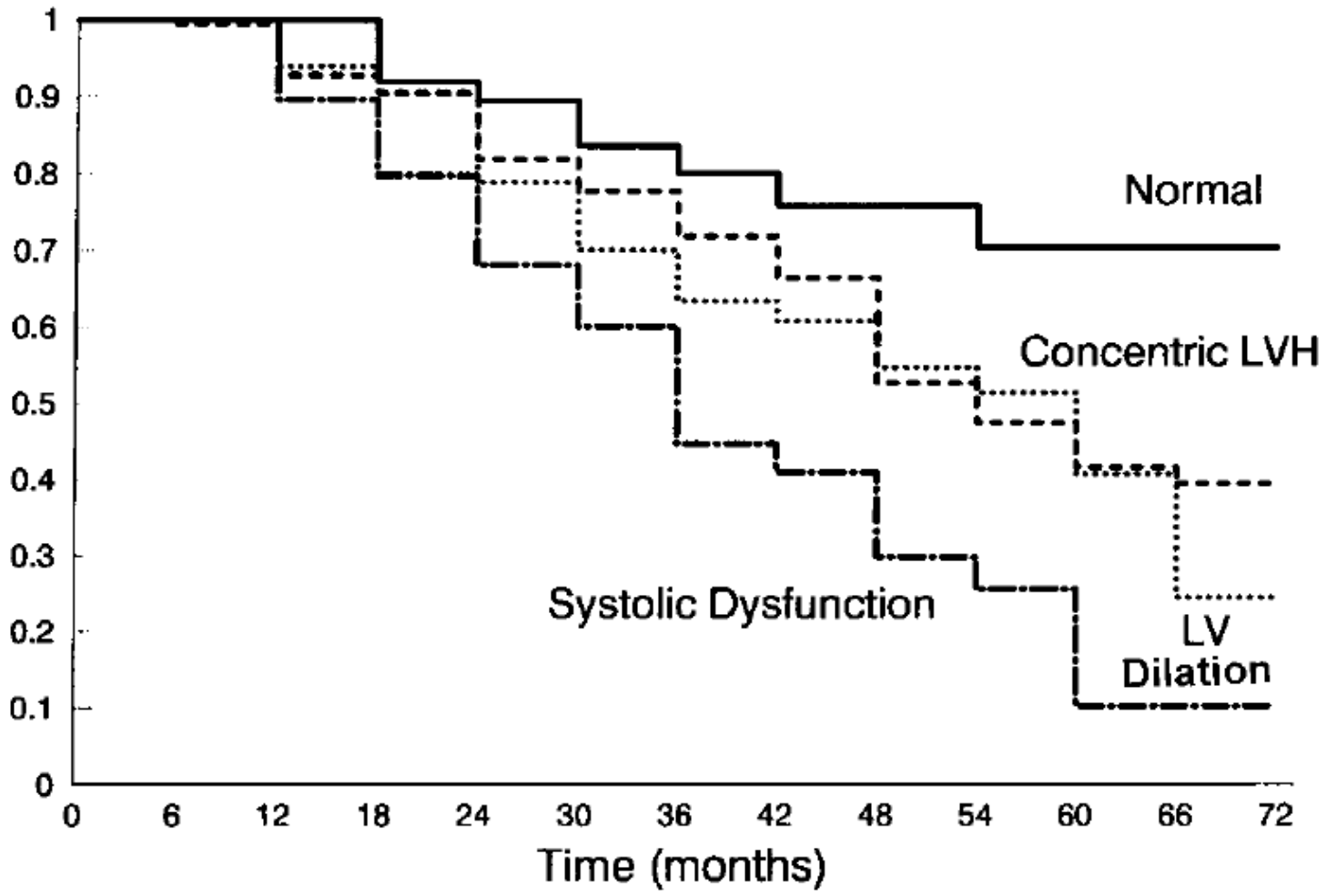
Adapted from Weber et al Blood Press 1991

Causes of LV hypertrophy

Volume overload	Pressure overload

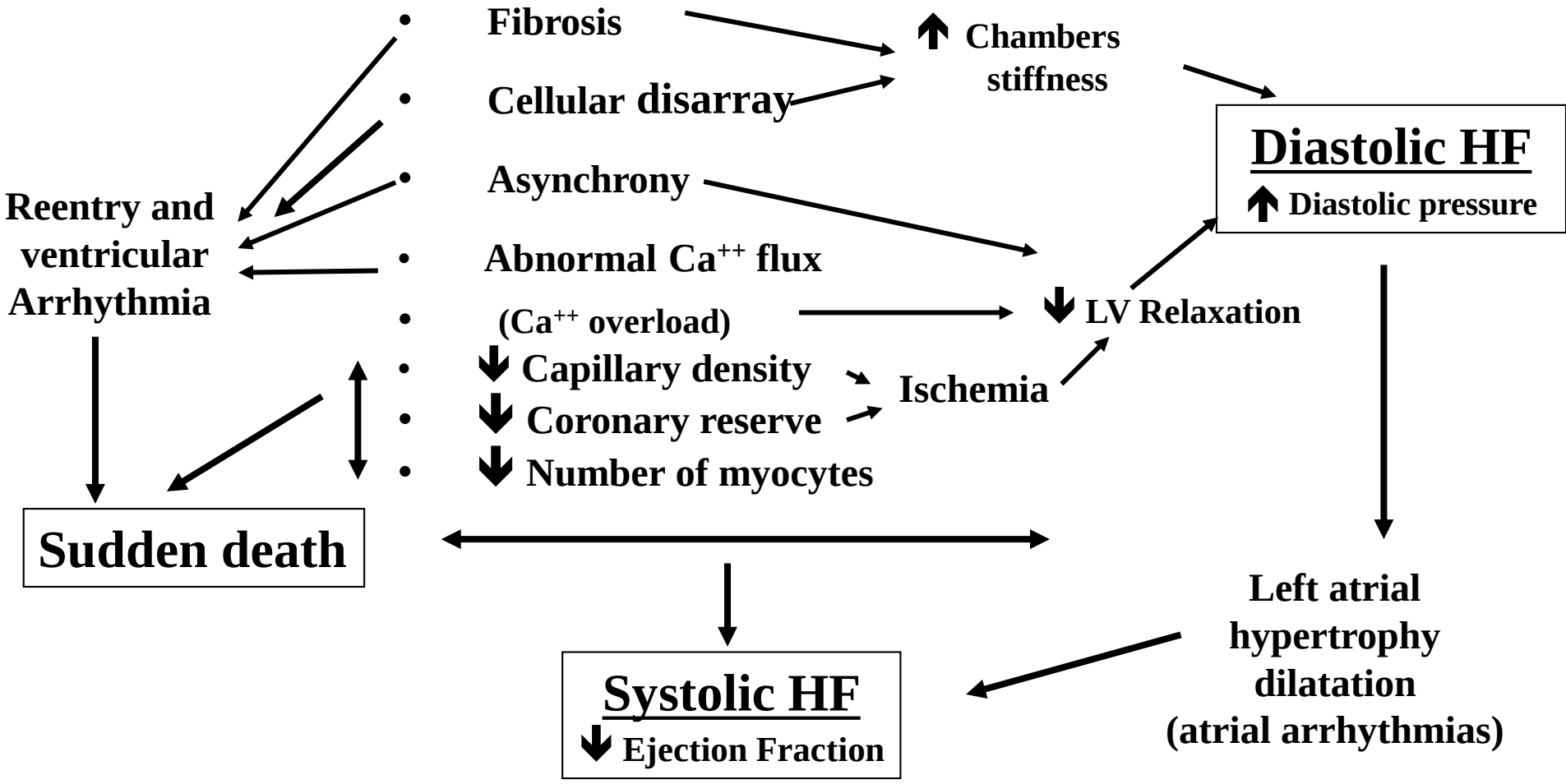
• A-V fistula
• $Na+/H_20$ retention
• Chronic anemia
  – increased stroke volume
  – increased heart rate
	• Hypertension
	• Arteriosclerosis/stiffness
	• Aortic stenosis

Cumulative survival in ESRD patients according to echocardiography

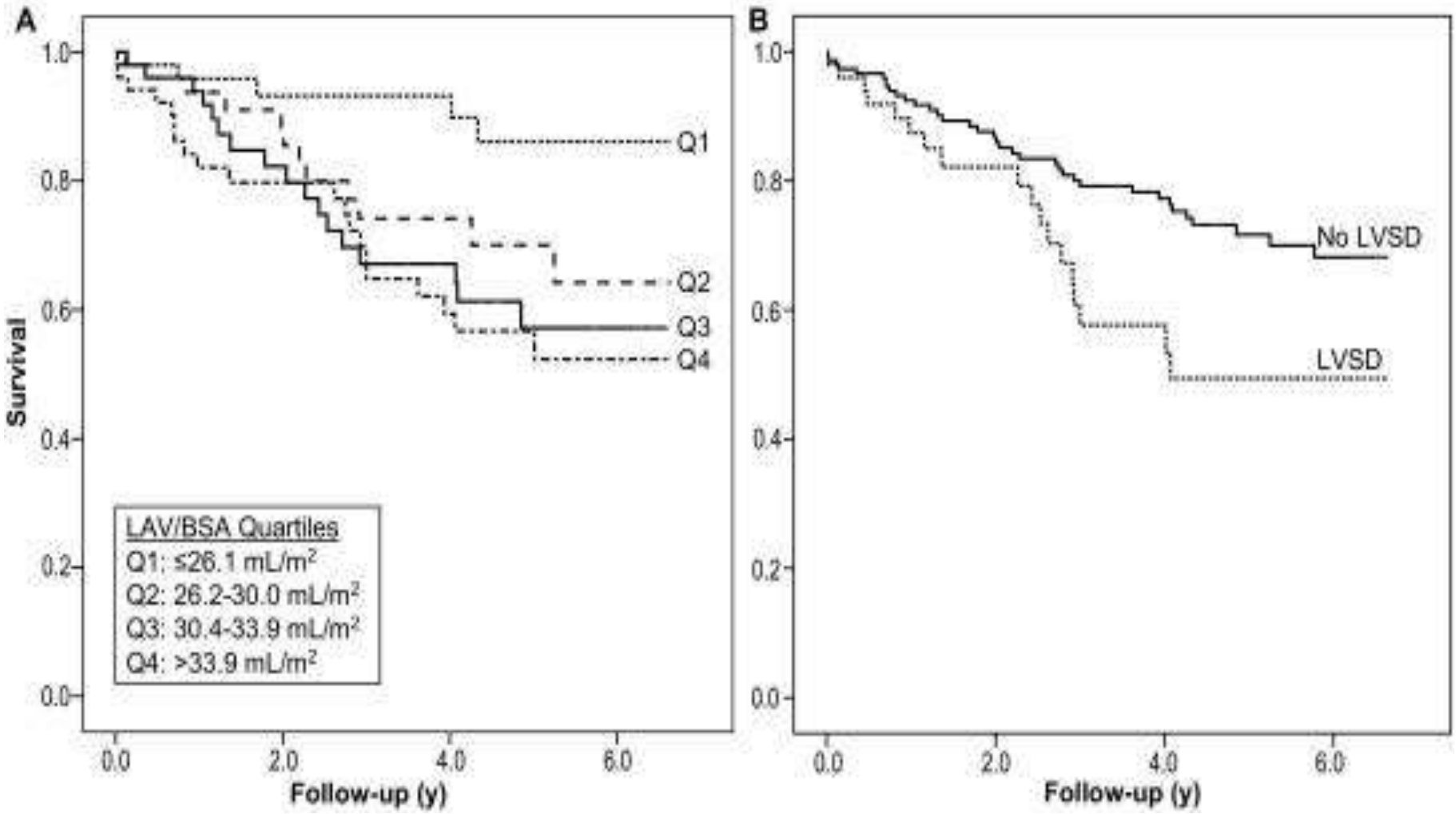


Parfrey P and Foley B JASN 1999;10:1606

Adverse effects associated with LV hypertrophy

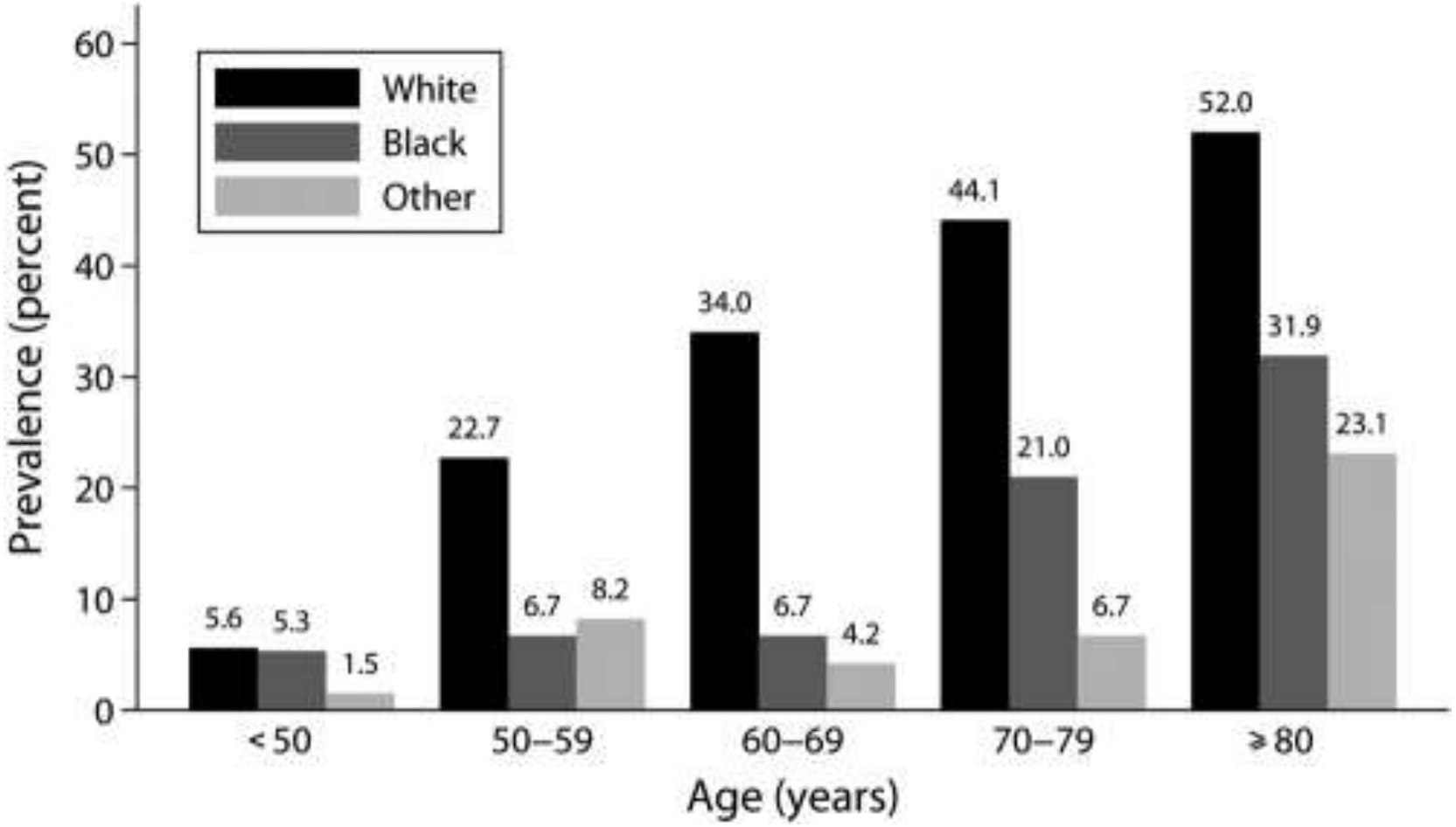


Association of left atrial volume with mortality among ESRD



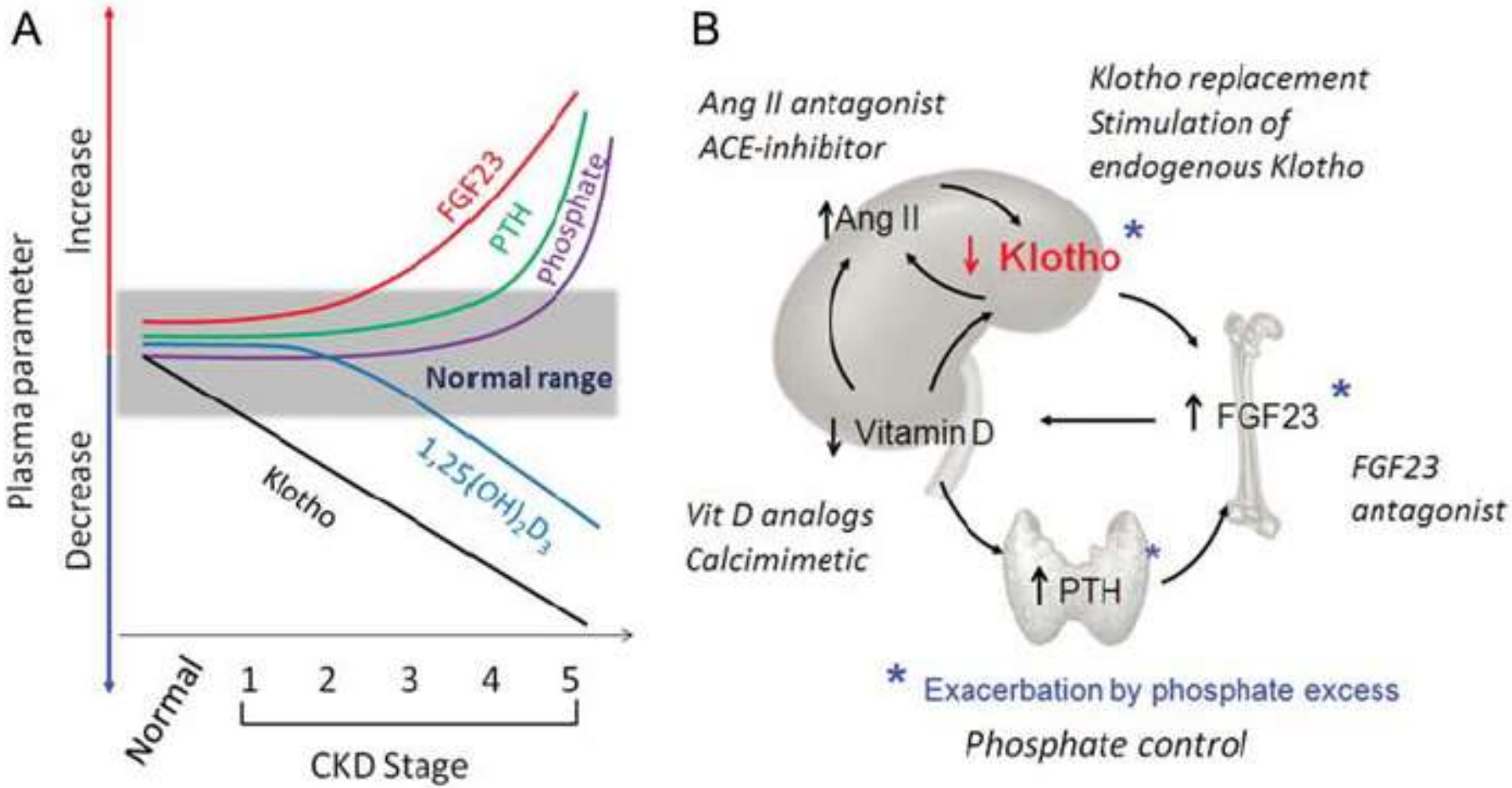
Patel RK et al AJKD 2010;55:1088-96

Prevalence of atrial fibrillation among nondialysis patients with CKD stratified by age and race



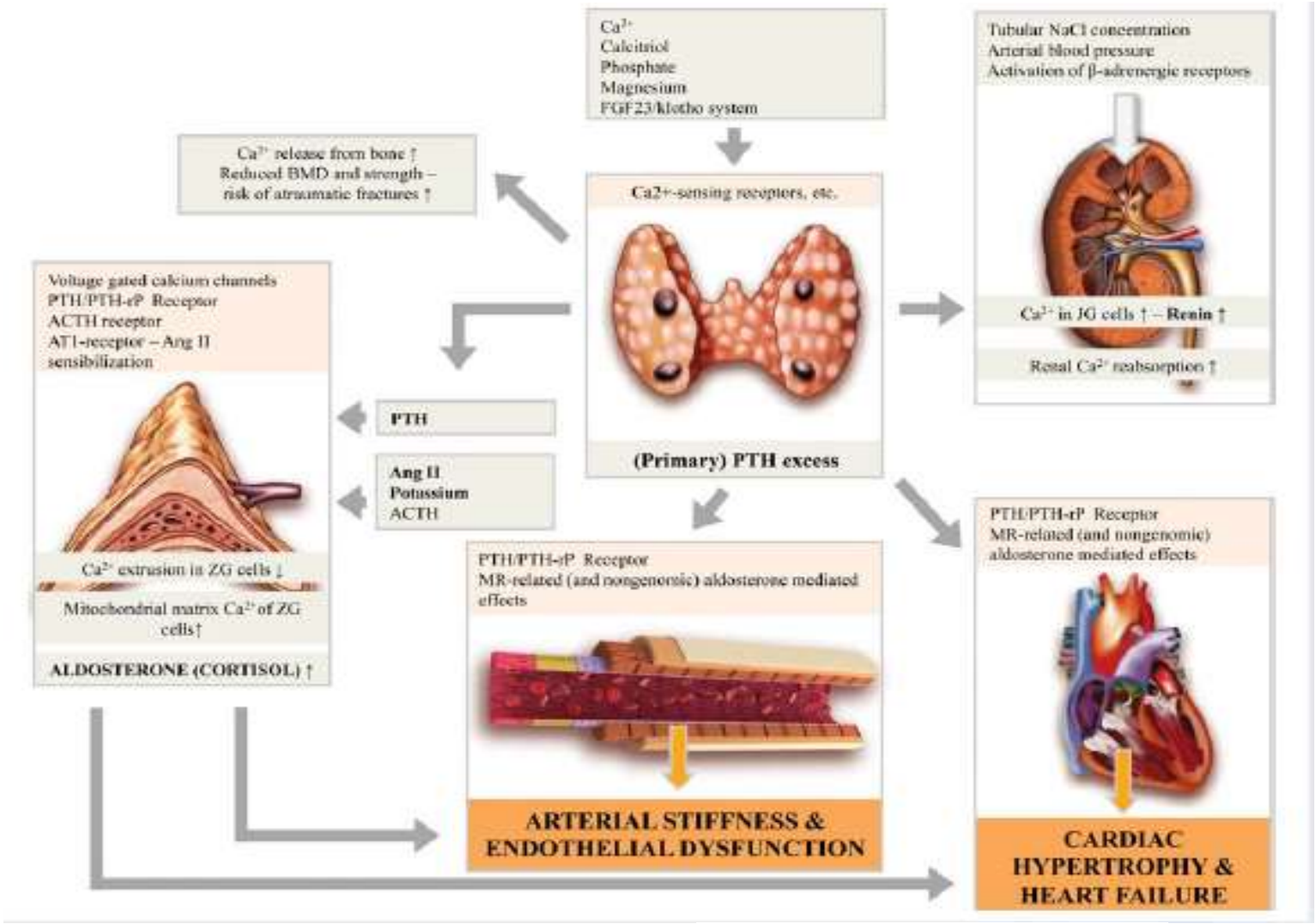
Uremic «toxicity »

ADMA, TMAO, Indoxyl Sulfate, Uric Ac., PO4, PTH, *FGF23*, Neurohumoral factor -Σ activity ROS, Inflammation,……



Nephrol Dial Transplant (2012) 27: 2650–2657

Aldosterone and parathyroid hormone: a precarious couple for cardiovascular disease



Cardiovascular Research (2012) **94**, 10–19

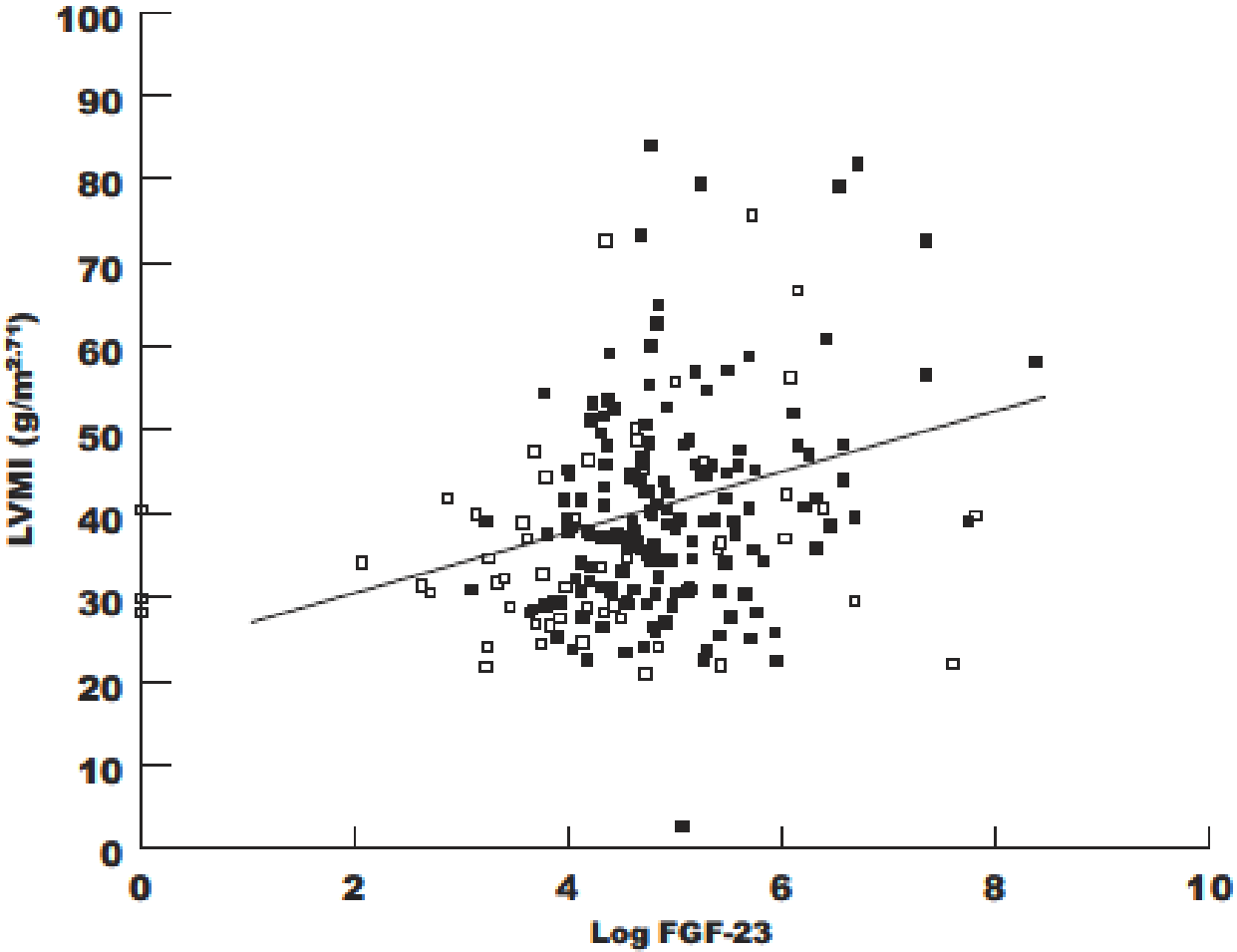
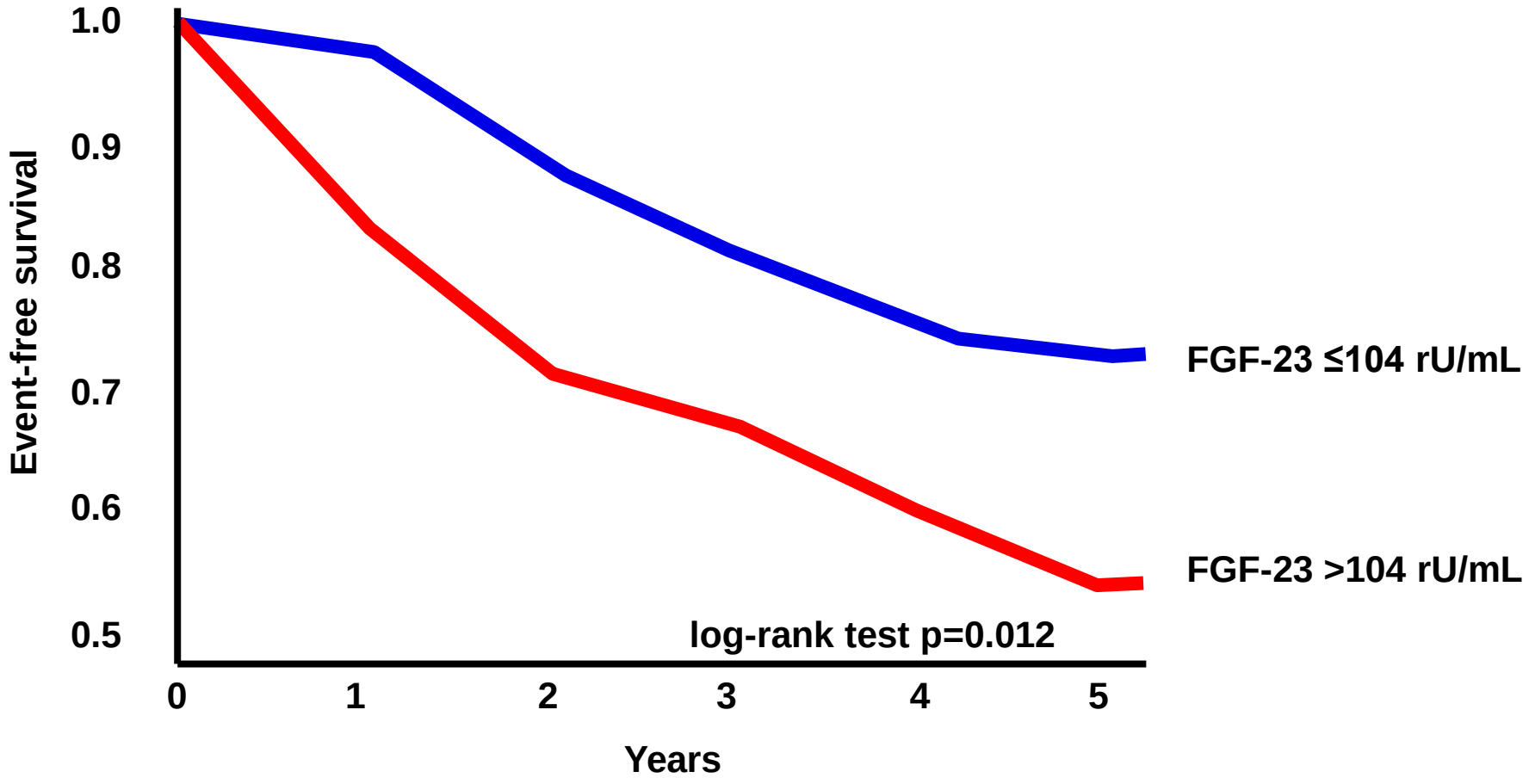


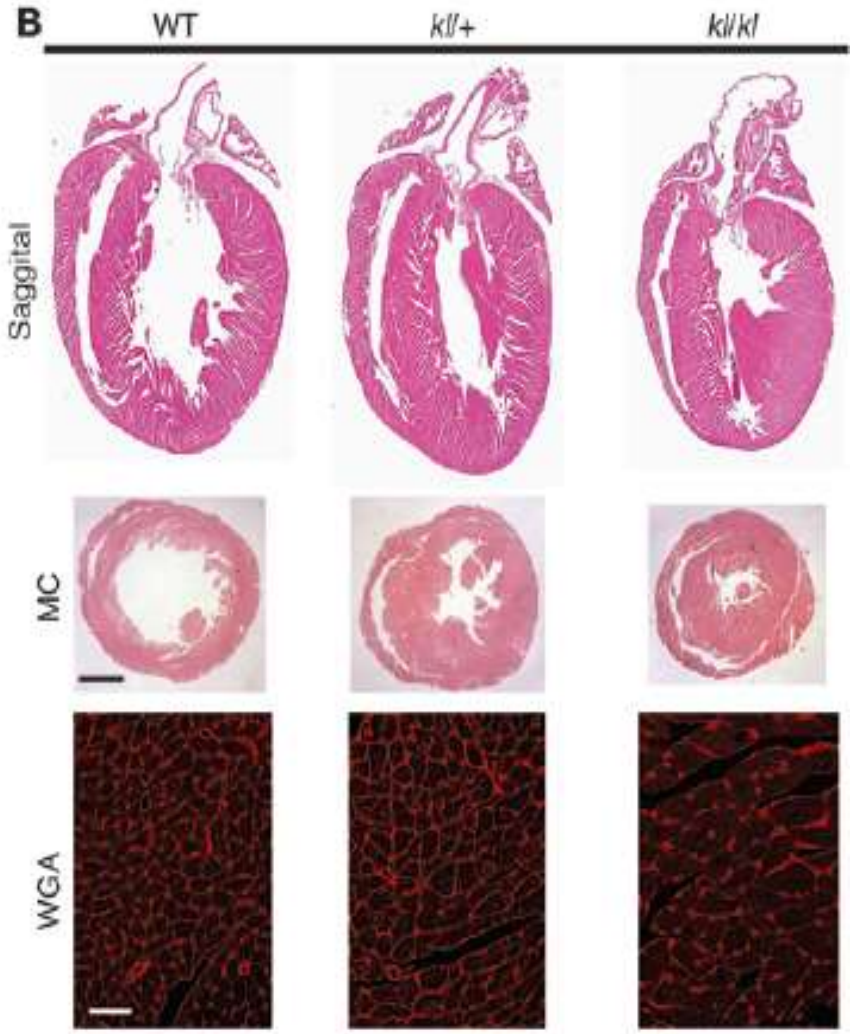
Figure 2. Correlation between log FGF-23 and LVMI (r=0.27, P<0.001). □ Indicates non-CKD subjects; ■, subjects with CKD.

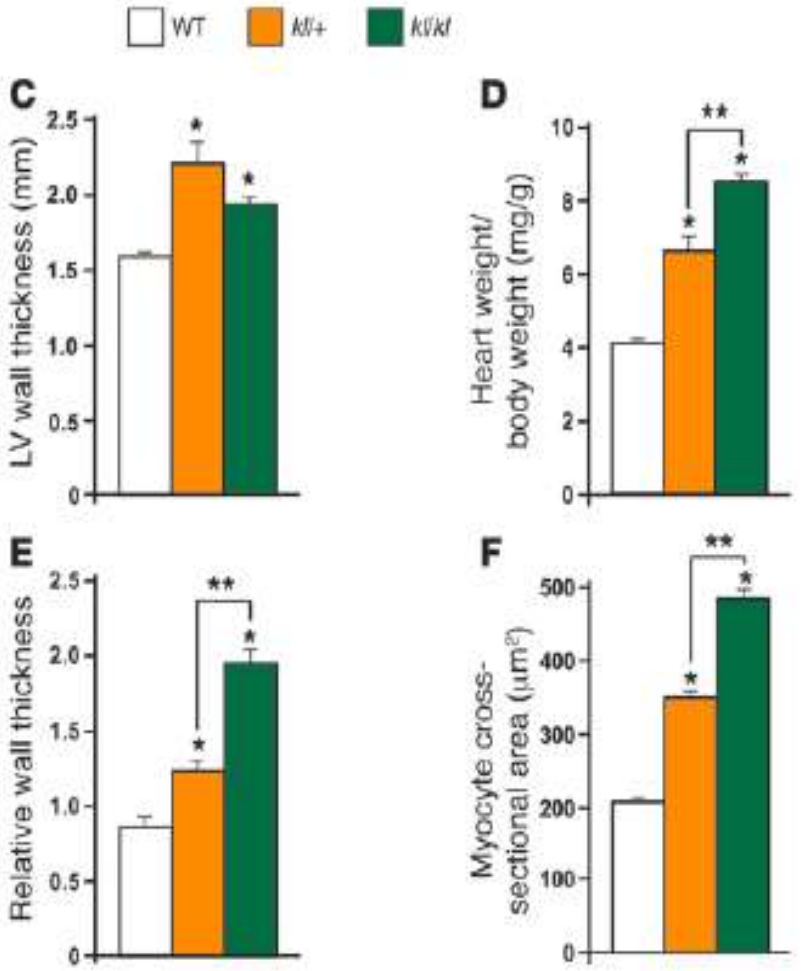
FGF-23 levels are linked to future cardiovascular events



Seiler S et al. *Nephrol Dial Transplant* 2010;25:3983–3989

FGF-23 excess leads to klotho-independent increase in LVH in mice





J Clin Invest. 2011;121(11):4393–4408

Klotho-deficiency is associated with cardiac hypertrophy and fibrosis

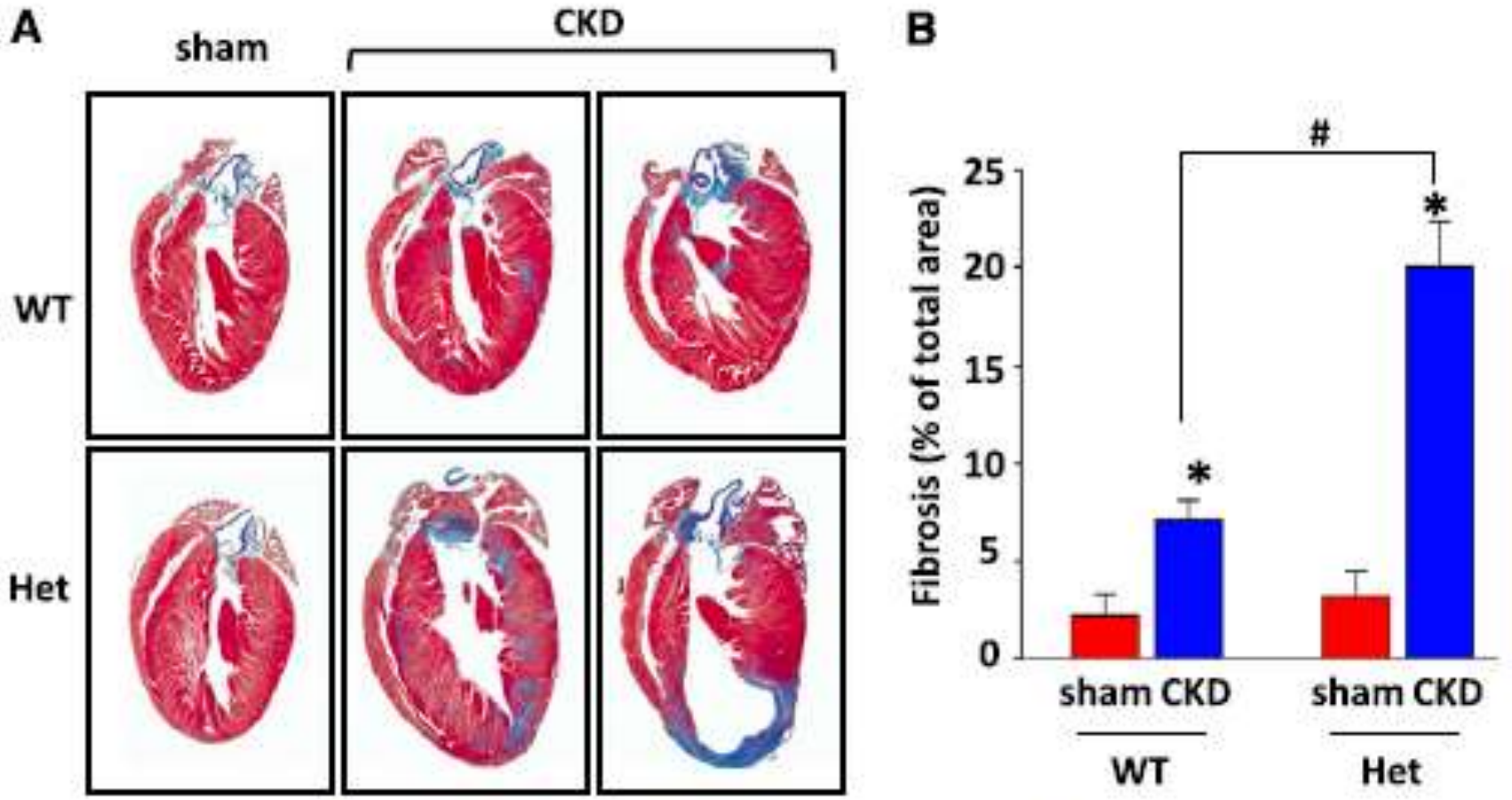


Figure 4. Klotho-deficient CKD mice have aggravated cardiac fibrosis compared with WT

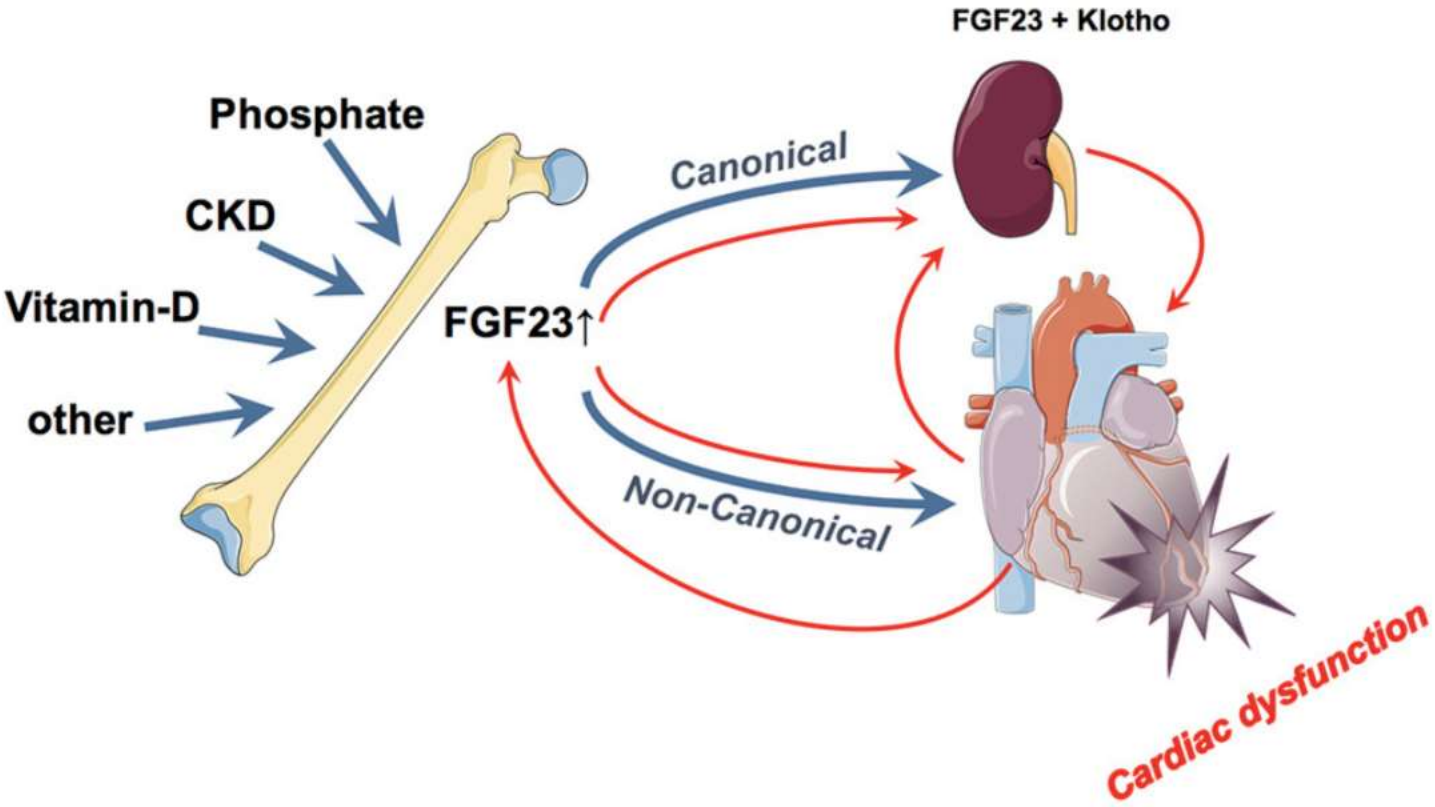


FIGURE 2 | Summary of the currently hypothesized canonical and non-canonical effects of FGF23 on the myocardium and vice-versa. In blue is illustrated the "bone damages heart via FGF23 model" while the red pathways illustrate the "heart damage induces FGF23 alterations model".

The elevation of circulating fibroblast growth factor 23 without kidney disease does not increase cardiovascular disease risk
Kidney International (2018) 94, 49–59

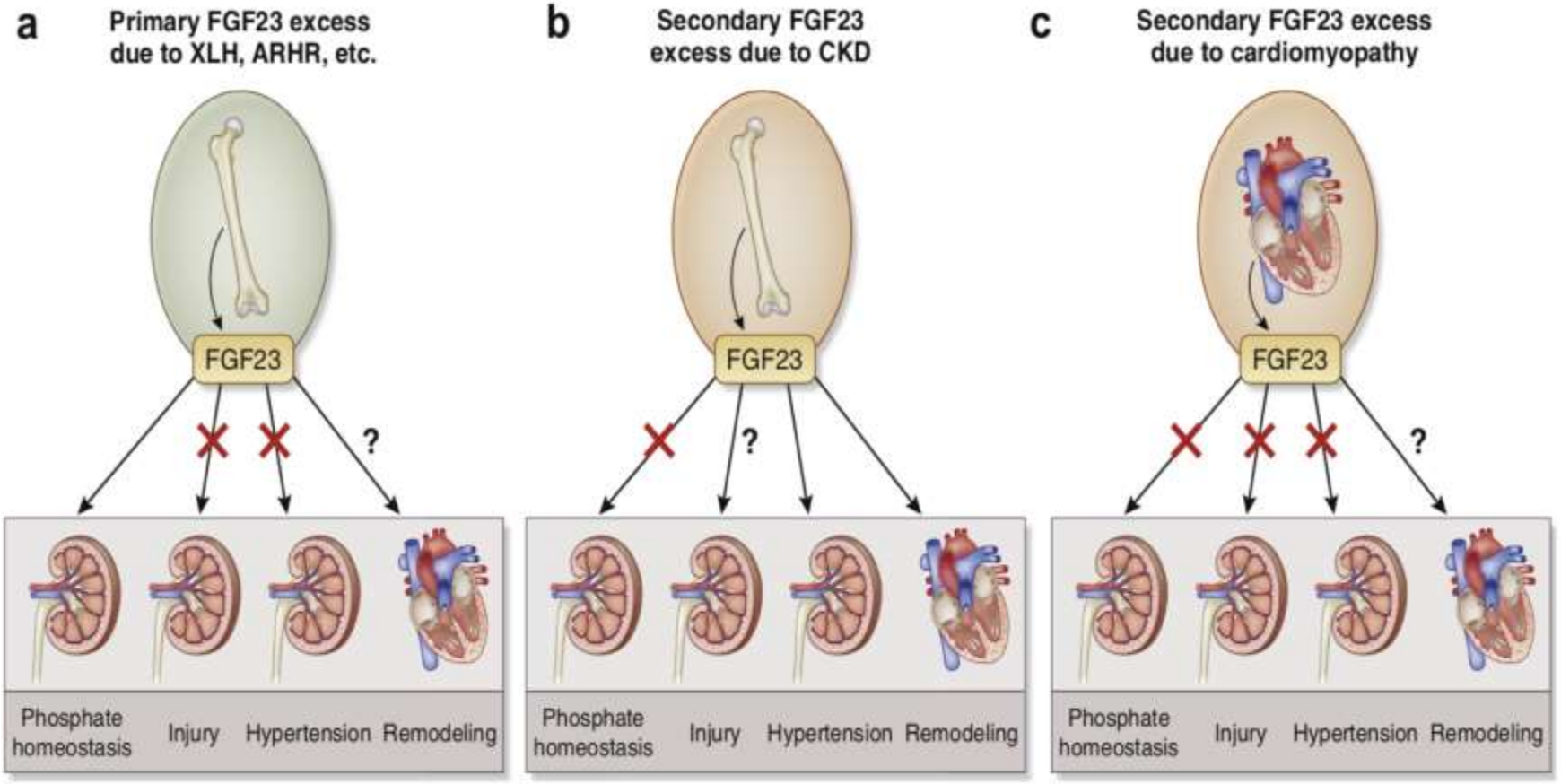
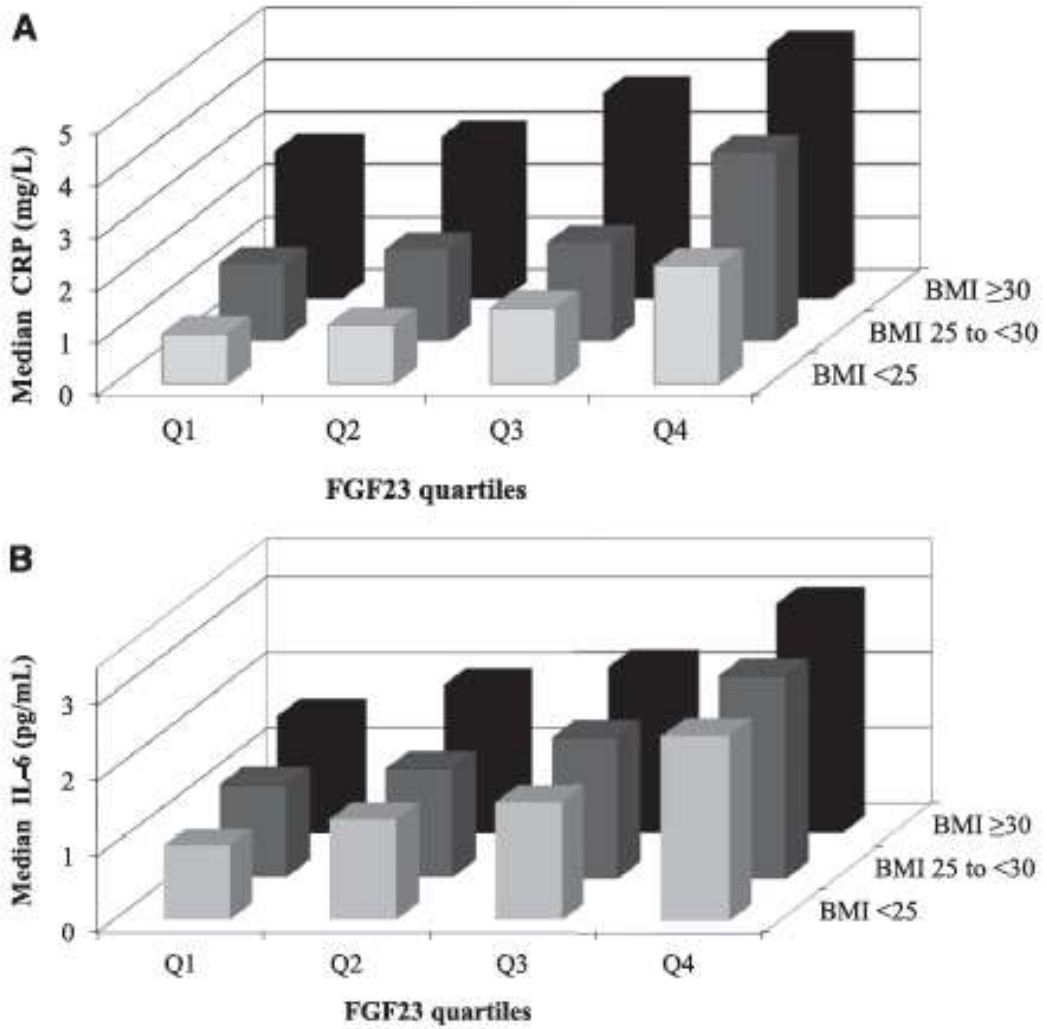


Figure 1 | Effects of fibroblast growth factor 23 (FGF23) on the kidney and heart depend on the source and context of FGF23 elevation.

Fibroblast Growth Factor 23 and Inflammation in CKD

Jair Munoz Mendoza, Tamara Isakova, Ana C. Ricardo, Huiliang Xie, Sankar D. Navaneethan, Amanda H. Anderson, Lydia A. Bazzano, Dawei Xie, Matthias Kretzler, Lisa Nessel, L. Lee Hamm, Lavinia Negrea, Mary B. Leonard, Dominic Raj, and Myles Wolf, for the Chronic Renal Insufficiency Cohort



Median inflammatory marker levels across fibroblast growth factor 23 (FGF23) quartiles and body mass index (BMI) categories

Clin J Am Soc Nephrol 7: 1155–1162, 2012

PTH and Cardiovascular risk

The cardiovascular system is a target organ for parathyroid hormone and the action of this hormone on the myocardium may be mediated through the ability of PTH to increase cytosolic calcium ([Ca2+]i) in the myocardial cells. This action is receptor-mediated and is produced by activation of the L-type calcium channels following stimulation of G protein(s), the rise in [Ca2+]i is due to both augmented entry of calcium into the myocytes and mobilization of calcium from sarcoplasmic reticulum by a calcium-induced calcium release mechanism. These effects could be observed in primary and secondary hyperparathyroidism

High serum PTH is a risk factor for hypertension in association with increased serum calcium in Japanese with primary hyperPT

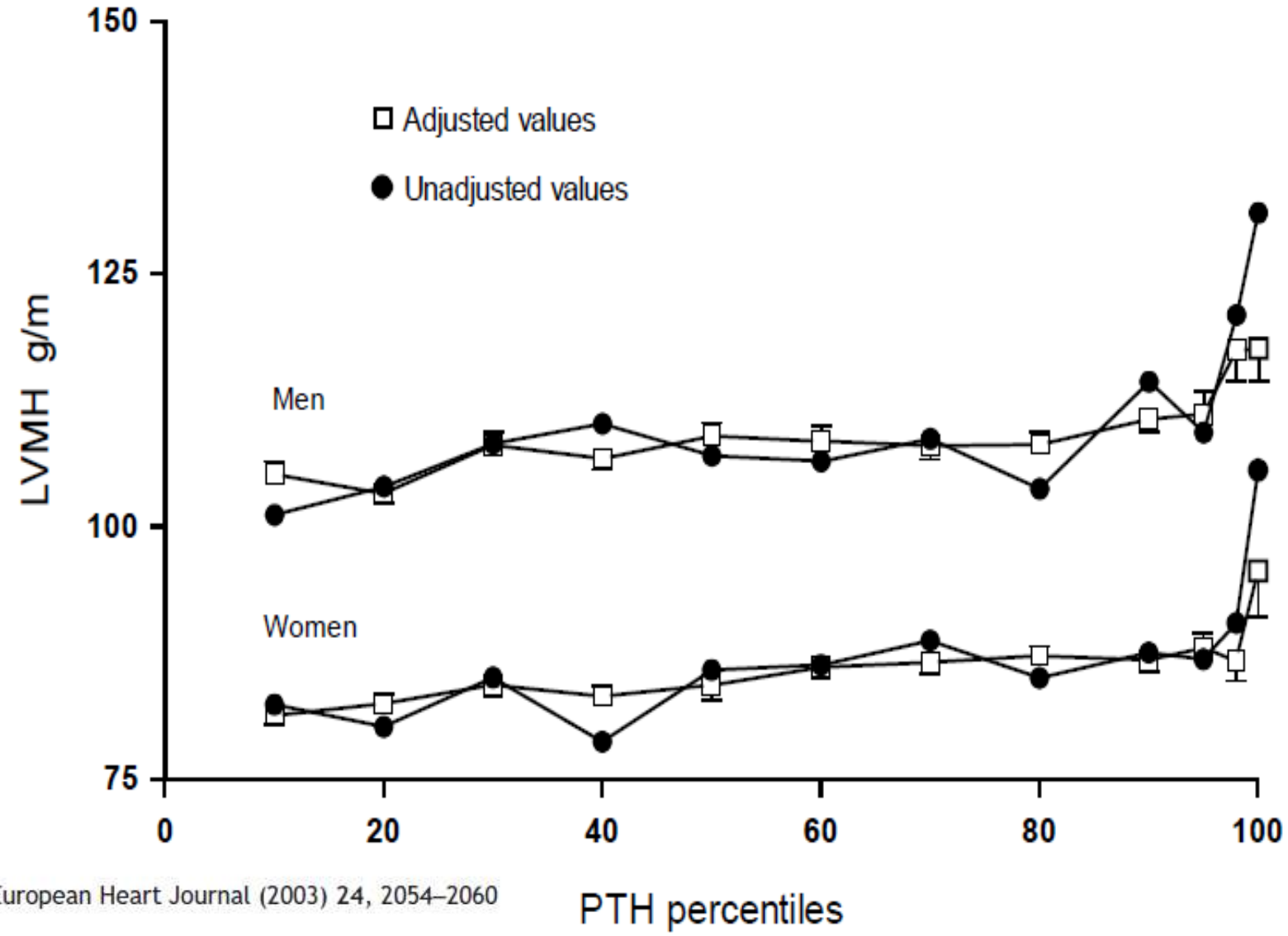
Table 2 Clinical characteristics of the patients according to the combination of serum calcium and parathyroid hormone levels

Variables	Normocalcemia Low PTH	Normocalcemia High PTH	Hypercalcemia Low PTH	Hypercalcemia High PTH	*P*-value
Number of patients	33 (28.9%)	15 (13.2%)	17 (14.9%)	49 (43.0%)	-
Male	14 (42.4%)	3 (20.0%)	9 (52.9%)	10 (20.4%)	-
Age (years)	51.5 ± 14.1	55.7 ± 16.4	54.2 ± 19.8	61.3 ± 12.1	0.03
Body mass index	23.1 ± 5.7	24.0 ± 6.5	23.3 ± 4.8	23.7 ± 3.6	0.92
Systolic BP (mmHg)	124.4 ± 14.0	130.3 ± 12.9	128.3 ± 19.4	139.8 ± 20.6	0.003
Diastolic BP (mmHg)	74.8 ± 11.0	72.9 ± 9.4	78.6 ± 11.1	76.6 ± 16.5	0.66
Serum calcium (mg/dL)	9.9 ± 0.1	9.9 ± 0.1	10.3 ± 0.2	11.2 ± 0.8	<0.001
Serum albumin (g/dL)	4.3 ± 0.3	4.3 ± 0.4	4.1 ± 0.6	4.1 ± 0.4	0.099
Corrected serum calcium (mg/dL)	9.9 ± 0.1	10.0 ± 0.1	10.4 ± 0.2	11.3 ± 0.8	<0.001
Serum PTH (pg/mL)	28.0 ± 9.0	85.4 ± 43.4	33.1 ± 12.5	142.5 ± 81.4	<0.001
eGFR(mL/min/1.73m^2)	77.0 ± 19.6	77.1 ± 29.3	73.1 ± 23.0	70.1 ± 23.7	0.54
Complications					
Diabetes mellitus	12 (36.4%)	7 (46.7%)	3 (17.6%)	14 (28.6%)	-
Hyperlipidemia	9 (27.3%)	7 (46.7%)	3 (17.6%)	29 (59.2%)	-

BP, blood pressure; PTH, parathyroid hormone; eGFR, estimated glomerular filtration rate

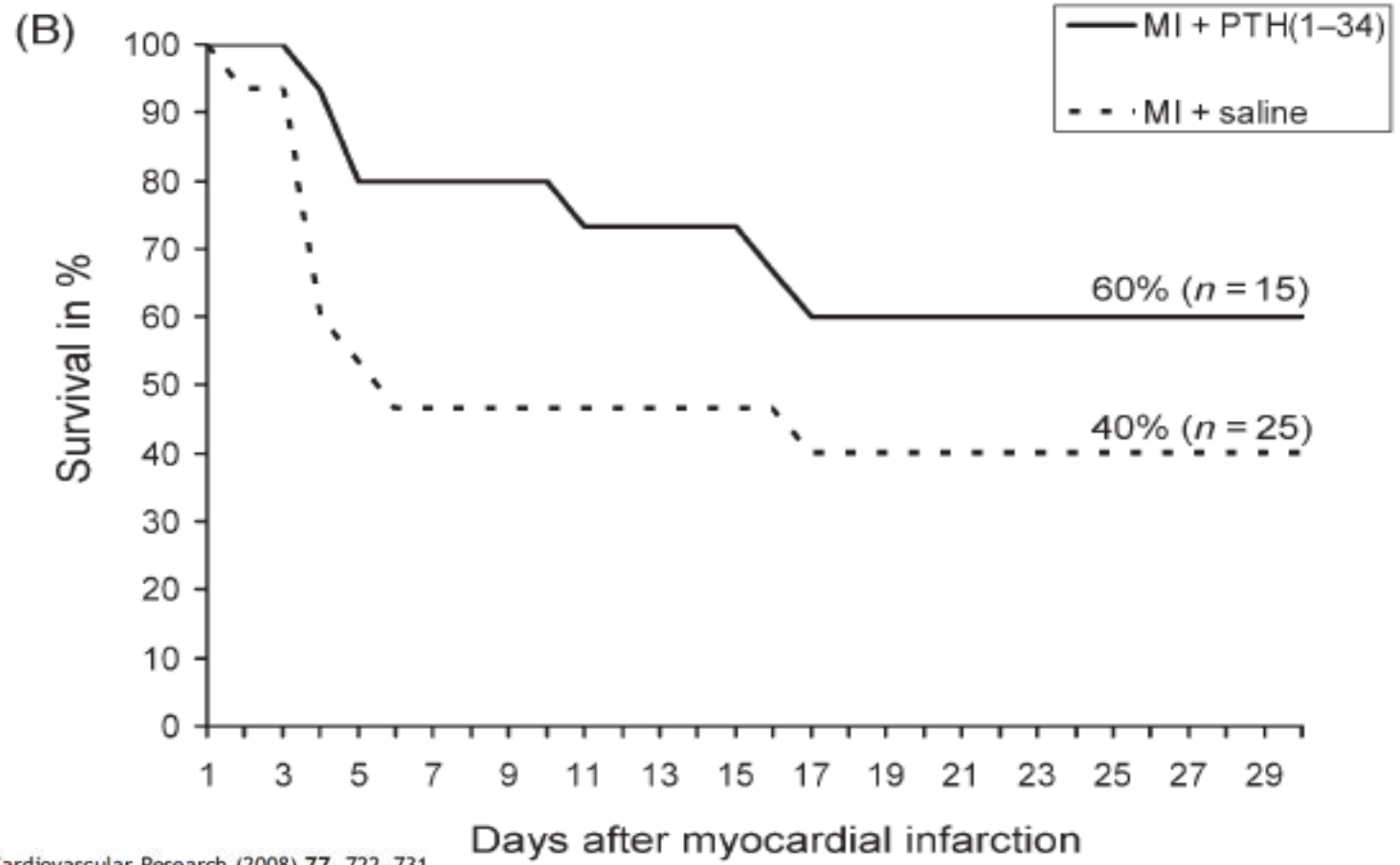
Normocalcemia, 9.8–10.1 mg/dL; hypercalcemia, 10.2–13.4 mg/dL; low PTH, 8–49 pg/mL; high PTH, 50–440 pg/mL

Endocrine Journal 2014, **61** (7), 727-733



European Heart Journal (2003) 24, 2054–2060

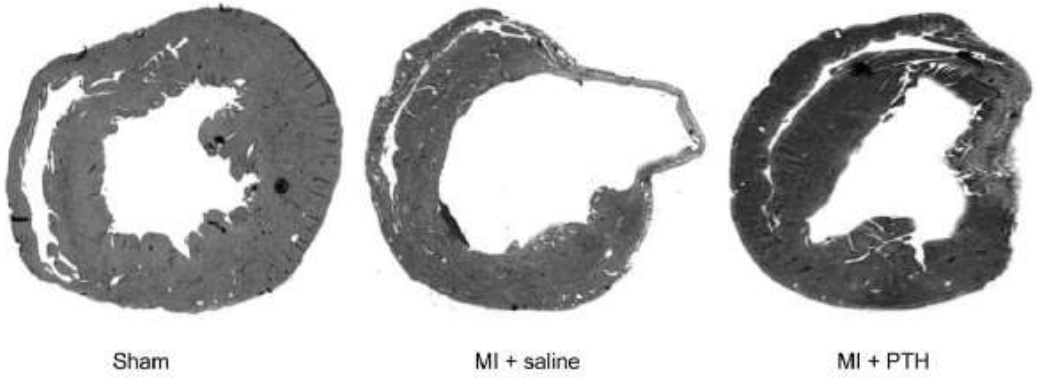
Parathyroid hormone treatment after myocardial infarction promotes cardiac repair by enhanced neovascularization and cell survival

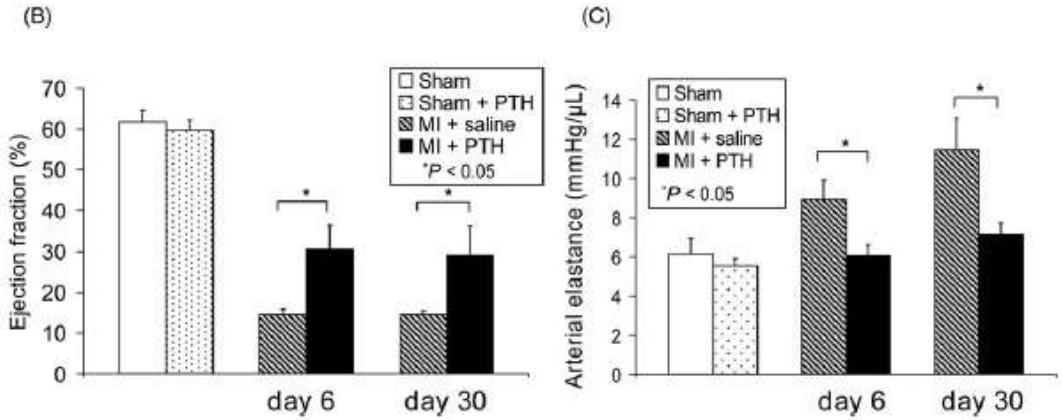


Cardiovascular Research (2008) **77**, 722–731

Parathyroid hormone treatment after myocardial infarction promotes cardiac repair by enhanced neovascularization and cell survival

Cardiovascular Research (2008) **77**, 722–731





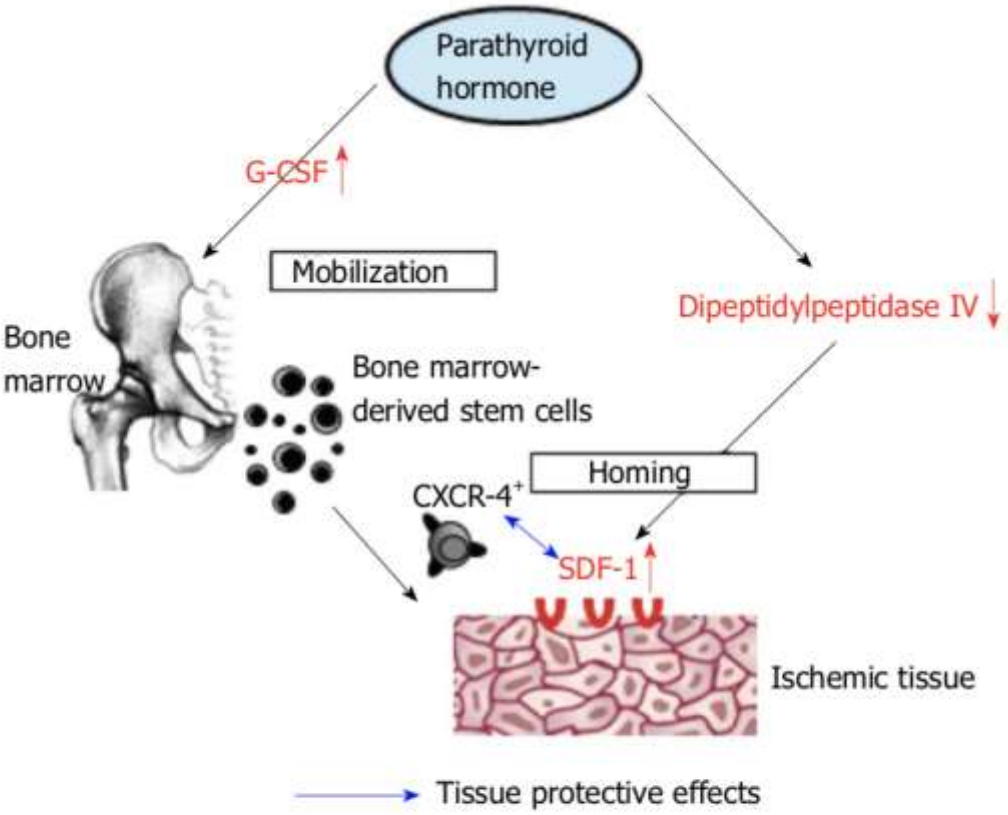


Figure 1 Impact of parathyroid hormone on mobilization and homing of bone marrow-derived stem cells. Left axis: PTH administration results in mobilization of BMCs from bone marrow into peripheral blood *via* endogenous release of G-CSF. Right axis: PTH results in down-regulation of DPPIV, which inhibits inactivation of SDF-1 and therefore promotes homing of CXCR4+ BMCs.

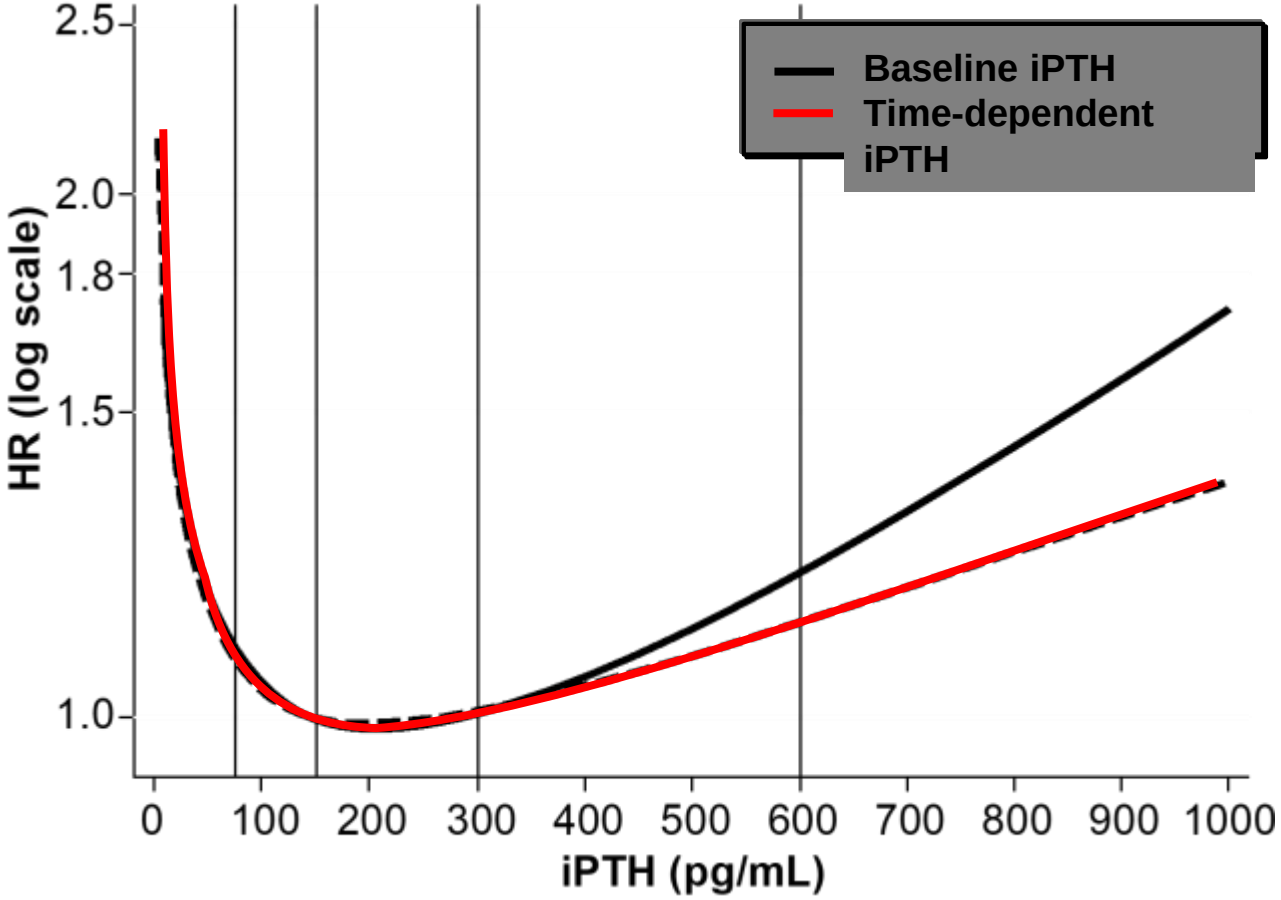
Abnormal mineral metabolism and mortality in hemodialysis patients with secondary hyperparathyroidism: evidence from marginal structural models used to adjust for time-dependent confounding.
Fukagawa M, Kido R, Komaba H, Onishi Y, Yamaguchi T, Hasegawa T, Kurita N, Fukuma S, Akizawa T, Fukuhara S.
Am J Kidney Dis. 2014 Jun;63(6):979-87
RESULTS:
The association between phosphorus level and mortality appeared U-shaped, although only higher phosphorus level categories reached statistical significance: compared to those with phosphorus levels of 5.0-5.9 mg/dL (1.61-1.93 mmol/L), patients with the highest (≥9.0 mg/dL [≥2.90 mmol/L]) phosphorus levels had 9.4 excess deaths/100 person-years (rate ratio, 2.79 [95% CI, 1.26-6.15]), whereas no association was found for the lowest phosphorus category (<3.0 mg/dL [<0.97 mmol/L]; rate ratio, 1.54 [95% CI, 0.87-2.71]). Similarly, hypercalcemia (≥10.0 mg/dL [≥2.50 mmol/L]) was associated with excess deaths, and the highest level of hypercalcemia (≥11.0 mg/dL [≥2.75 mmol/L]) was associated with 5.8 excess deaths/100 person-years (rate ratio, 2.38 [95% CI, 1.77-3.21]) compared to those with levels of 9.0-9.4 mg/dL (2.25-2.37 mmol/L). Abnormally high parathyroid hormone levels were not associated with excess deaths.
CONCLUSIONS:
These results reinforce the idea that serum calcium (in addition to phosphorus) level is an important predictor of the absolute risk of death in hemodialysis patients with secondary hyperparathyroidism.

Association of Nonoxidized Parathyroid Hormone with Cardiovascular and Kidney Disease Outcomes in Chronic Kidney Disease.
Seiler-Mussler S1, Limbach AS2, Emrich IE2, Pickering JW3,4, Roth HJ5, Fliser D2, Heine GH
Clin J Am Soc Nephrol. 2018 Apr 6;13(4):569-576
CONCLUSIONS:
In a cohort of patients with CKD, PTH was associated with all-cause mortality; there was no association of nonoxidized PTH with any of the clinical outcomes examined

Increased active PTH(1-84) fraction as a predictor of poor mortality in male hemodialysis patients.
Inaba M1, Okuno S, Imanishi Y, Ishimura E, Yamakawa T, Shoji S.
Osteoporos Int. 2013 Nov;24(11):2863-70
CONCLUSION:
Higher PTH(1-84)/intact PTH ratio, which provides a relevant marker for parathyroid function, may be a significant

predictor of All Causes Mortality in male hemodialysis patients.

Mortality Risk in CKD Patients Increases if iPTH Levels are Outside Targets



N=7970

Adapted from Floege, J et al. *Nephrol Dial Transplant.* 2011;261948-1955

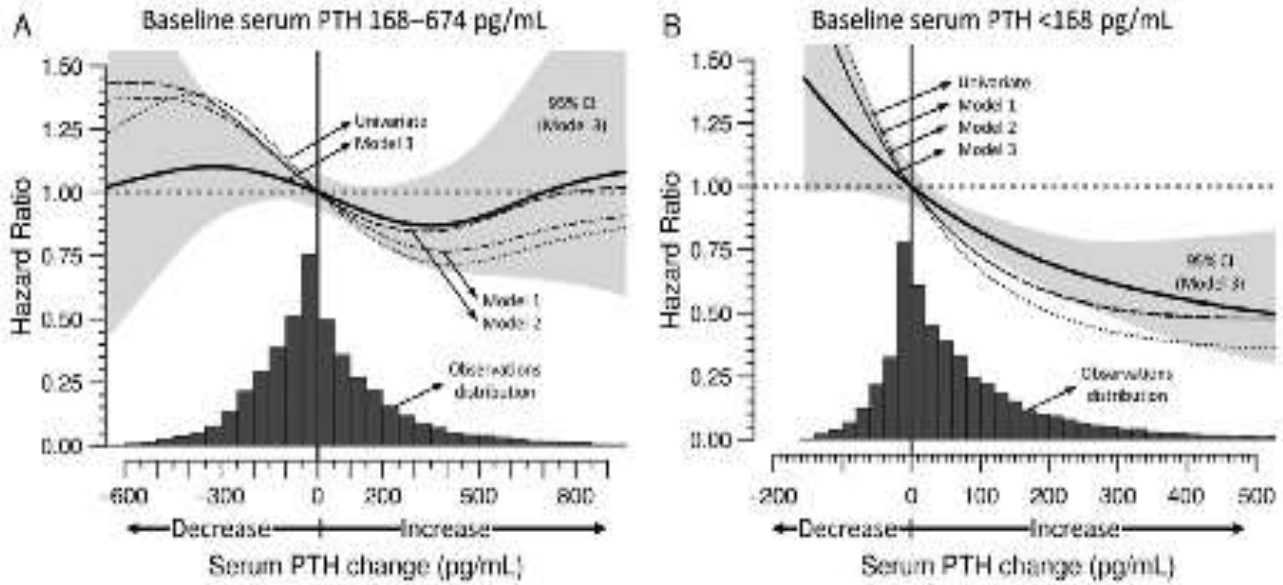
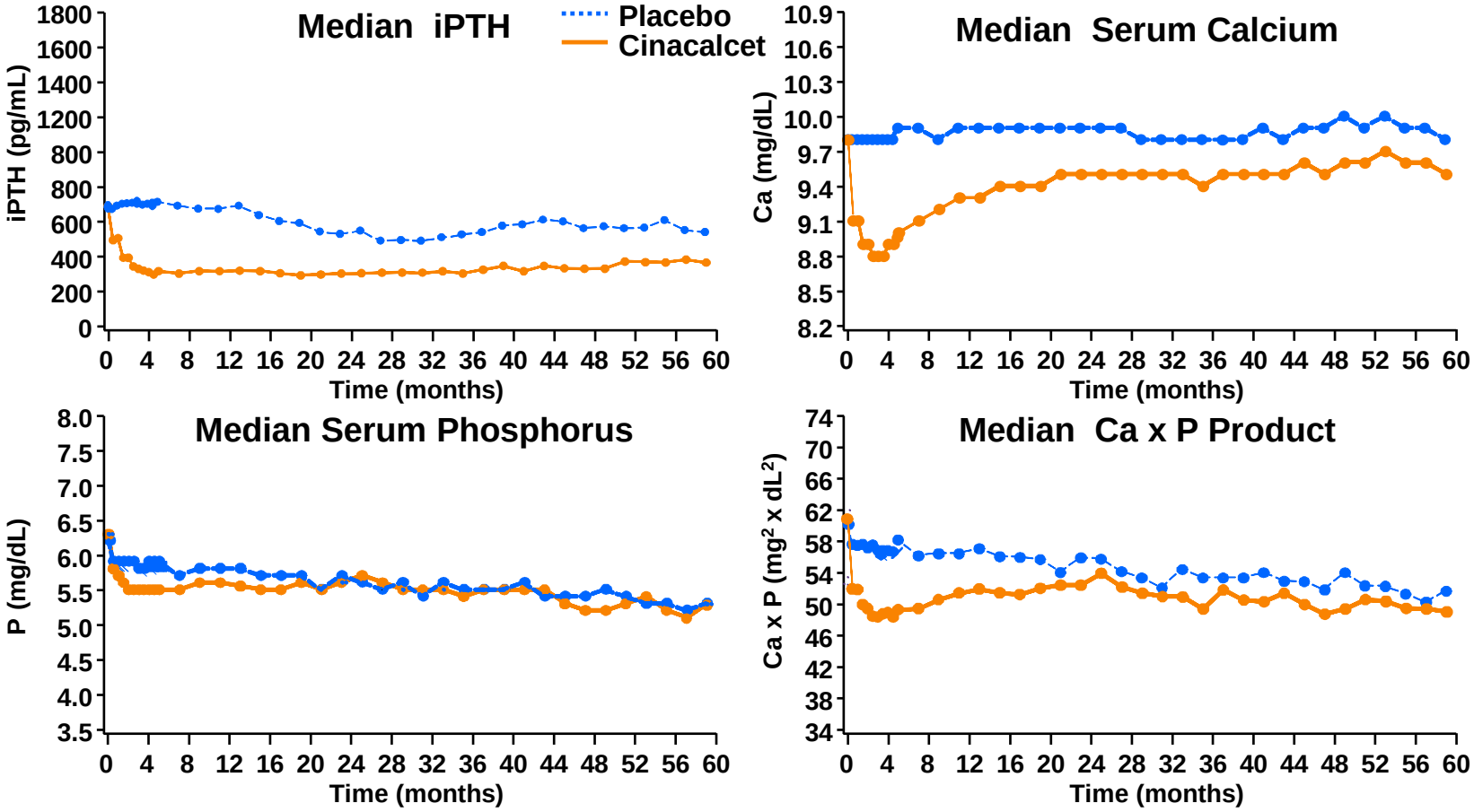


FIGURE 4: Serum PTH changes from baseline and relative risk of mortality. (A) Patients with baseline serum PTH between 168 and 674 pg/mL (patients with a HR < 1.1 in Figure 1C, number of observations: 11 070). (B) Patients with baseline serum PTH lower than 168 pg/mL. Multivariate models were the same described in Figure 1 (number of observations: 9271). Serum PTH changes from baseline were considered as a time-varying variable. The multivariate Model 3 included serum phosphorus and calcium (both as time-varying variables). Serum PTH changes from baseline equal to 0 (no change) were used as reference (HR = 1.0) in both graphs.

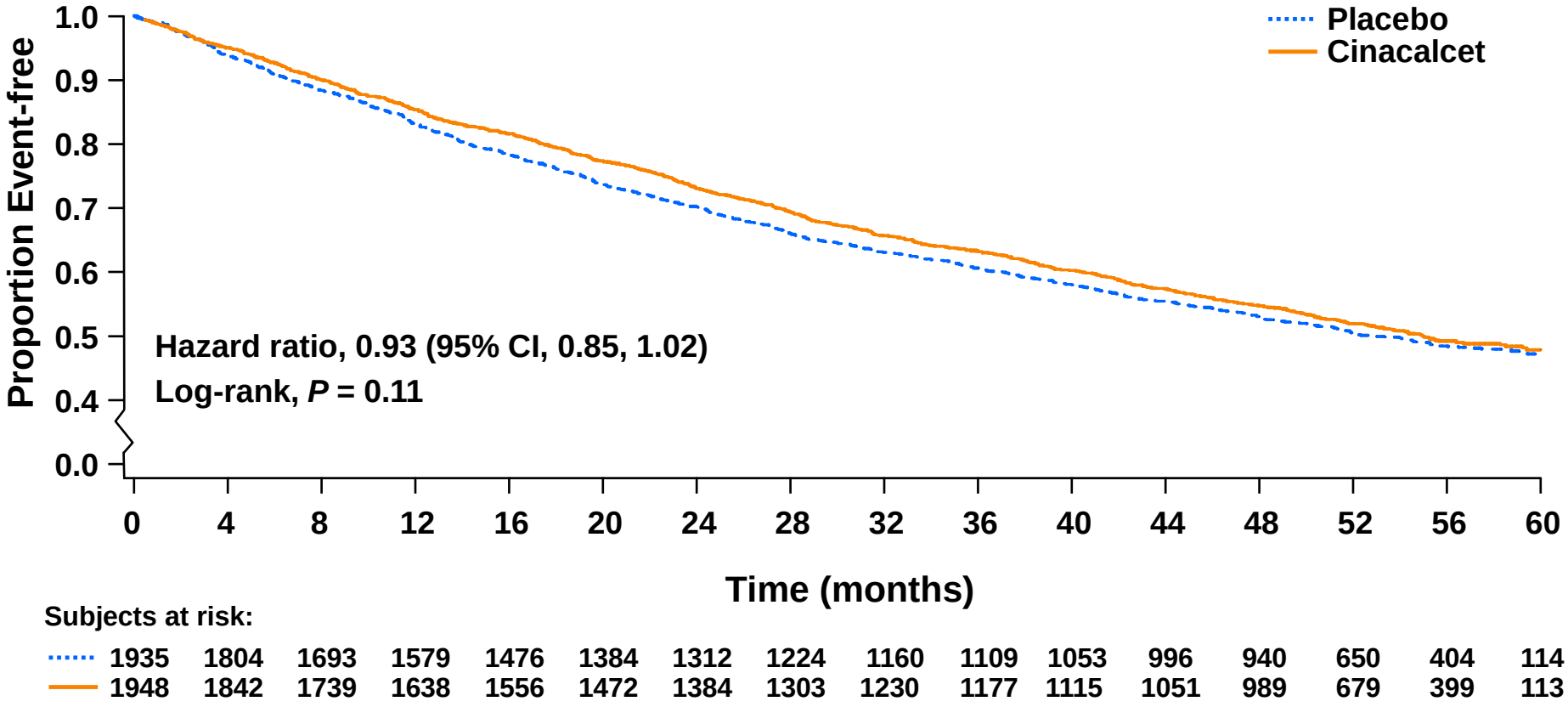


iPTH = intact parathyroid hormone; P = phosphorus; Ca = calcium; Ca x P = calcium phosphorus product.

Adapted from Chertow GM, et al. *N Engl J Med*. Epub 2012 Nov 3; DOI: 10.1056/NEJMoa1205624

Primary Composite Endpoint (ITT) not met: Non-significant 7% Reduction in the Risk of Death or Cardiovascular Events

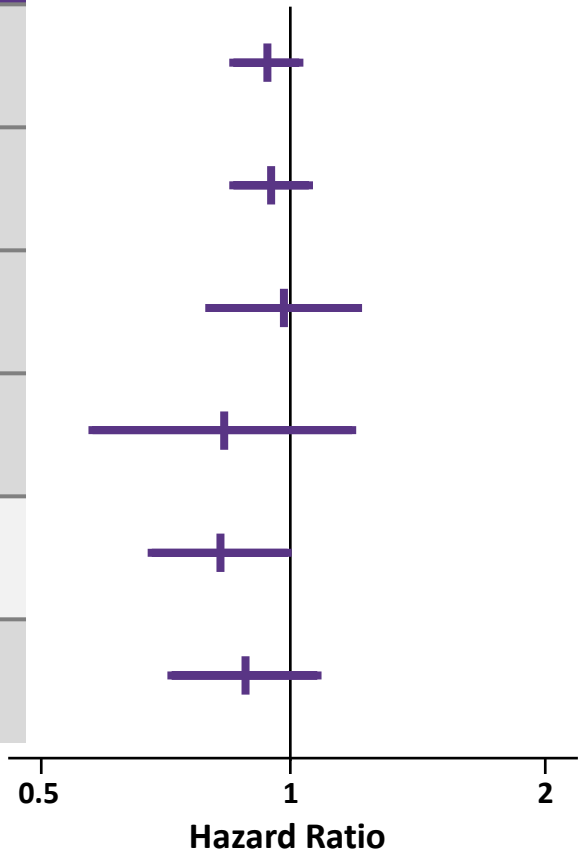
Kaplan-Meir plot of the time to the primary composite endpoint (death, myocardial infarction, hospitalization for unstable angina, heart failure, or peripheral vascular event) in EVOLVE™.



Chertow GM, et al. *N Engl J Med*. Epub 2012 Nov 3; DOI: 10.1056/NEJMoa1205624

Mortality and Cardiovascular Outcomes (ITT Analysis)

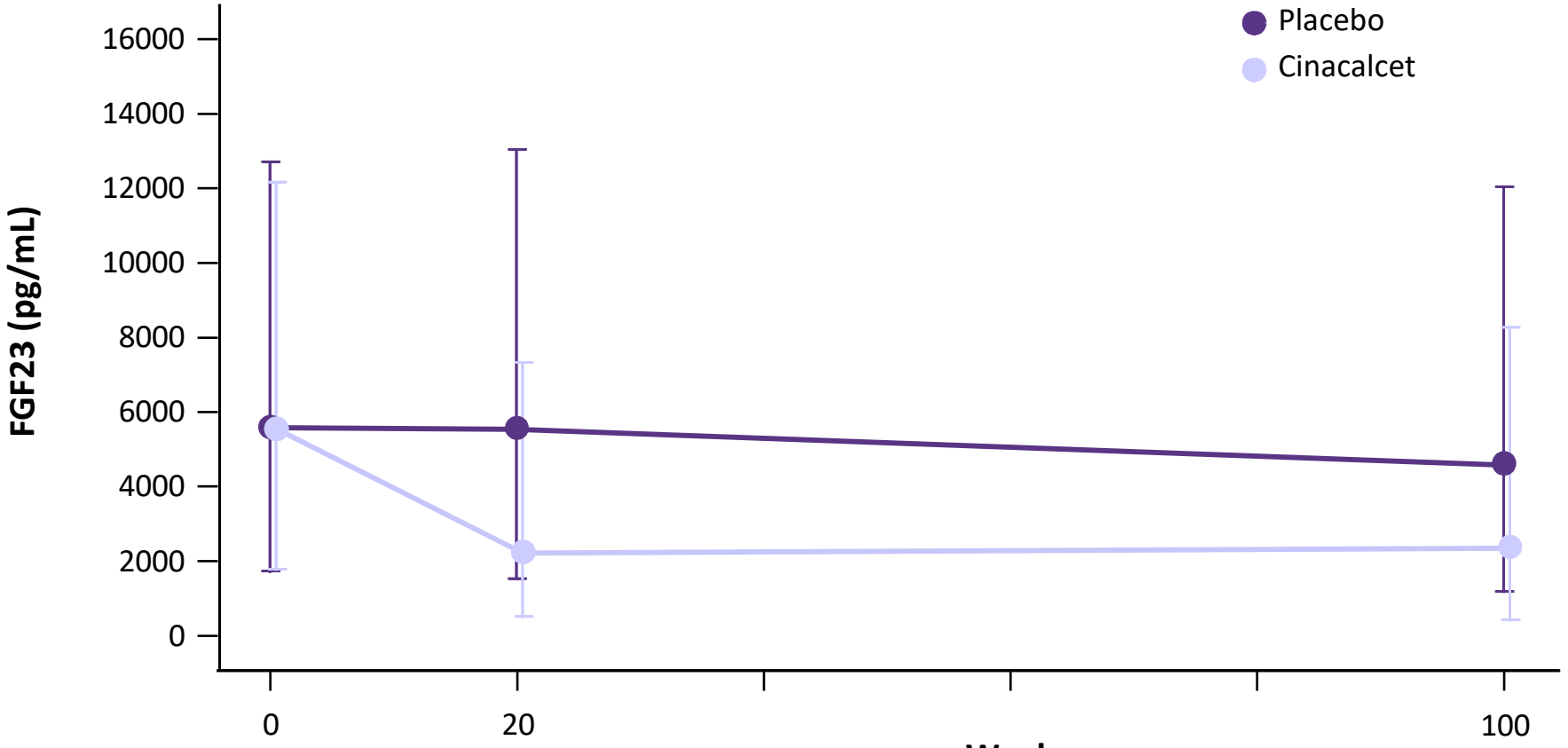
Endpoint	Cinacalcet n = 1,948	Placebo n = 1,935	HR (95% CI)	P Value
Primary composite endpoint*	938	952	0.93 (0.85, 1.02)	0.112
All-cause mortality	703	718	0.94 (0.85, 1.04)	0.249
Myocardial infarction	187	183	0.97 (0.79, 1.19)	0.800
Hospitalization for unstable angina	56	66	0.82 (0.58, 1.18)	0.283
Heart failure	**206**	**236**	**0.82 (0.68, 0.99)**	**0.034**
Peripheral vascular event	184	200	0.87 (0.72, 1.07)	0.190



*** The trial did not meet its primary endpoint in the intent-to-treat analysis**

Adapted from Chertow GM, et al. *N Engl J Med*. Epub 2012 Nov 3; DOI: 10.1056/NEJMoa1205624

Reduction in FGF23 from Baseline was Observed at Week 20 and 100 in Cinacalcet Subjects (FGF23 Cohort)



	0	20	100
Placebo n:	1264	1264	830
On commercial cinacalcet **n_1 (%):**	0	**32 (3%)**	**108 (13%)**
Cinacalcet n:	1338	1338	921
On study drug **n_1 (%):**	0	**1215 (91%)**	**724 (79%)**

Subjects with baseline and week 20 FGF23 values are included

Median (Q1, Q3) are presented

n = Number of subjects with laboratory value at the study visit, **n_1** = number of placebo subjects on commercial cinacalcet, cinacalcet subjects on study drug. % based on n

Heart Failure in the EVOLVE Trial

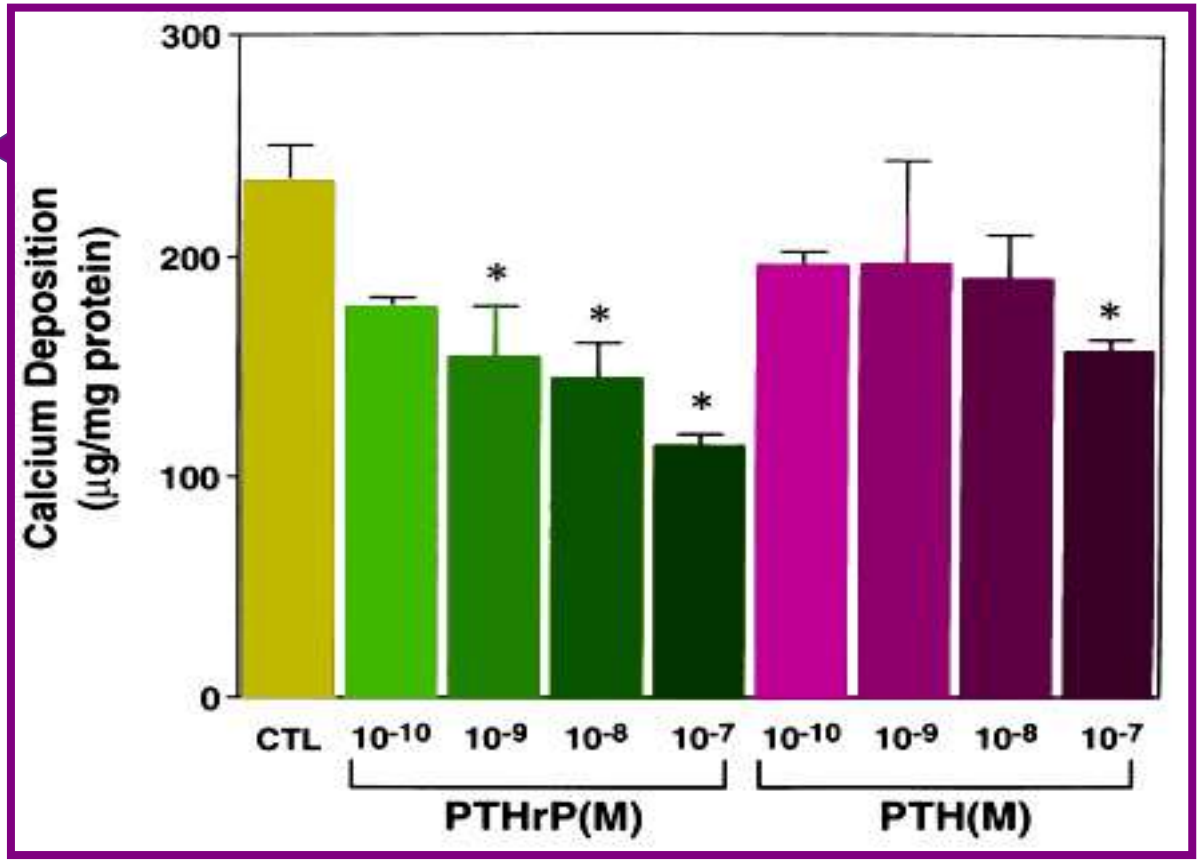
Background

- Increased levels of parathyroid hormone (PTH), calcium and phosphorus can cause **arterial calcification and arteriosclerosis**, which predispose to left ventricular hypertrophy and heart failure

Hypothesis

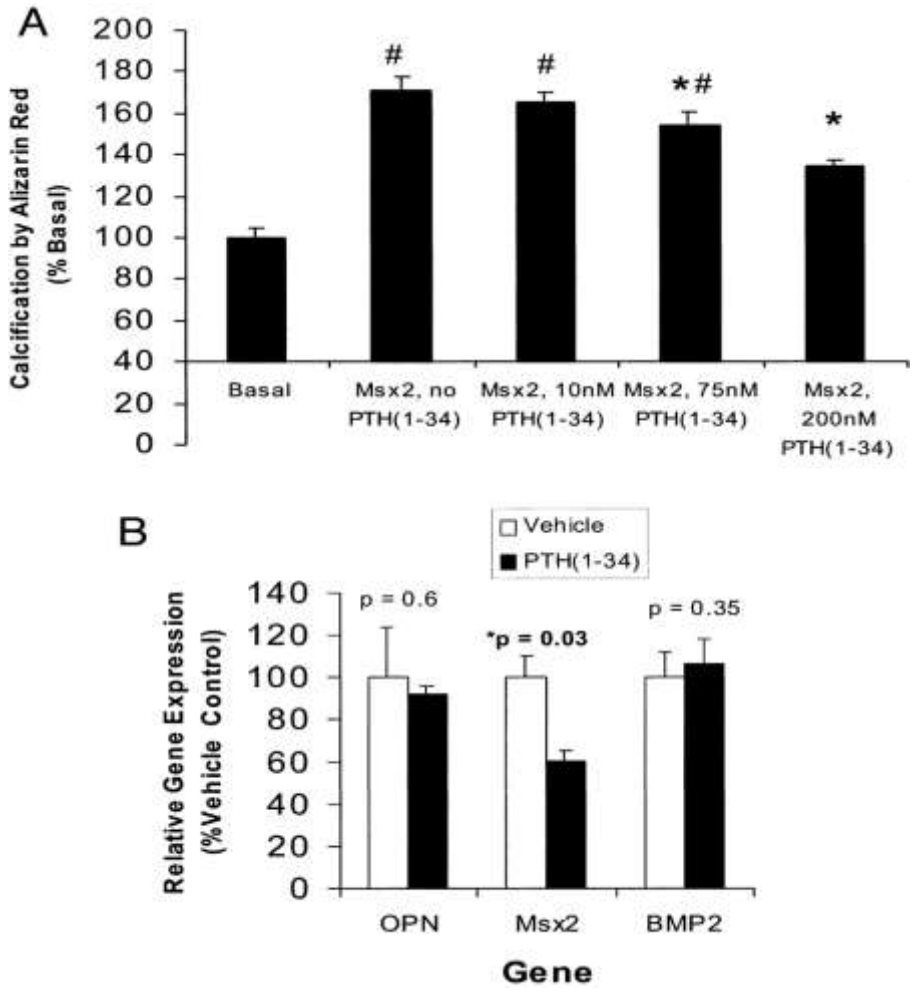
- ***Calcimimetic cinacalcet [+ conventional therapy for secondary hyperparathyroidism (sHPT)] would reduce the risk of mortality and cardiovascular events in patients on hemodialysis with moderate to severe sHPT***

Effects of human PTHrP and PTH (1-34) on BVSMC calcification CTL- calcified controls. PTH and PTHrP decrease vascular calcification



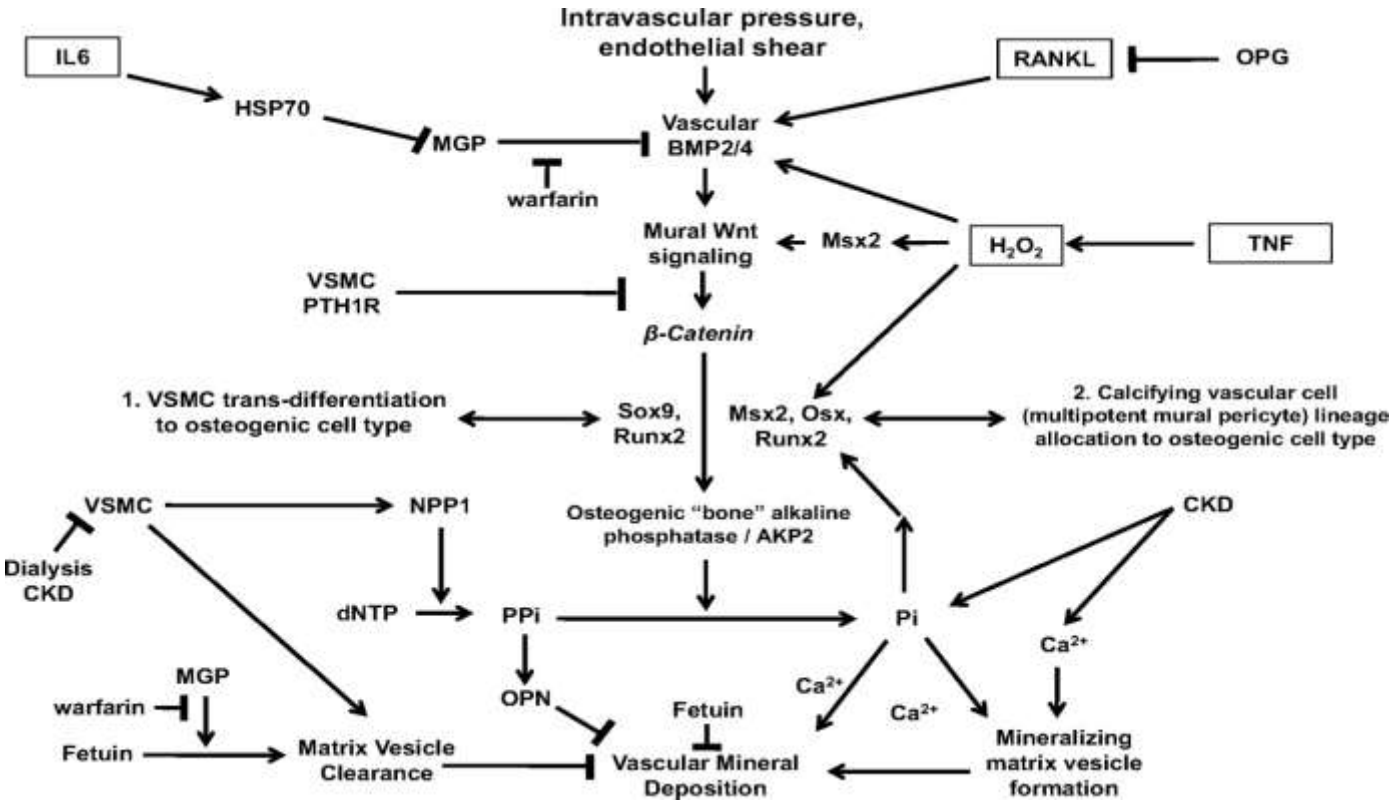
Jono et al. Arterioscler Thromb Vasc Biol. 1997 J;17::1135-42.

PTH(1–34) inhibits Msx2-dependent mineralization and down-regulates Msx2 expression in cultured aortic myofibroblasts.



Shao J et al. J. Biol. Chem. 2003;278:50195-50202

Inflammation and osteogenic regulation of vascular calcification: a review and working model



Shao, J.-S. et al. Hypertension 2010;55:579-592

Management of HF in CKD G4+

Approach	Are there data in CKD G4+?	Limitations for use in CKD G4+?
β-Blockers	Yes: observational data and small trials	May have more adverse effects
RAAS inhibitors	No	Hyperkalemia Risk of progressive loss of eGFR
MRAs	Ongoing trials	Hyperkalemia Risk of progressive loss of eGFR
Neprilysin inhibitors	No	May have higher risk of hyperkalemia Unknown dose
Treatment of anemia	Yes	May be linked with worse outcomes
Treat mineral metabolism abnormalities	Yes	Not a clear benefit
Frequent dialysis	Yes	Many patients cannot do home therapies, and frequent in-center dialysis is not always available
Ultrafiltration	Small observational studies and trials	May cause intradialytic hypotension and/or myocardial stunning
Cardiac resynchronization therapy	Small observational studies	May have more adverse effects, such as infections

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HF, heart failure; MRA, mineralocorticoid receptor antagonist; RAAS, renin-angiotensin-aldosterone system.