Cardio-renal and reno-cardiac Challenges

May 31, 2018

Cardiorenal syndrome (CRS)

- **DEFINITION:**

Disorder of *heart and kidneys* where dysfunction in one organ leads to dysfunction in the other organ.

This can be either acute or chronic.

Cardio-Renal Syndromes

- Term was first coined 63 years ago in **1951** to describe this clinical entity – relationship between heart and kidneys

- Since about 2000 there has been a renewed interest in better defining it - with a view to guiding research into the pathogenesis and treatment

- Recognition of the high risk of repeat hospital admissions and mortality of these patients

Cardio-renal Syndrome: Epidemiology

- Cardiovascular disease (CVD): an independent risk factor for worsening renal function (34%) and development of new kidney disease (6%)

Atherosclerosis Risk in Communities (ARIC) & Cardiovascular Health Study (CHS)

- Congenital heart disease adults: 45% have CKD with 3 fold risk of mortality

Circulation 2008 117:18 p 2320

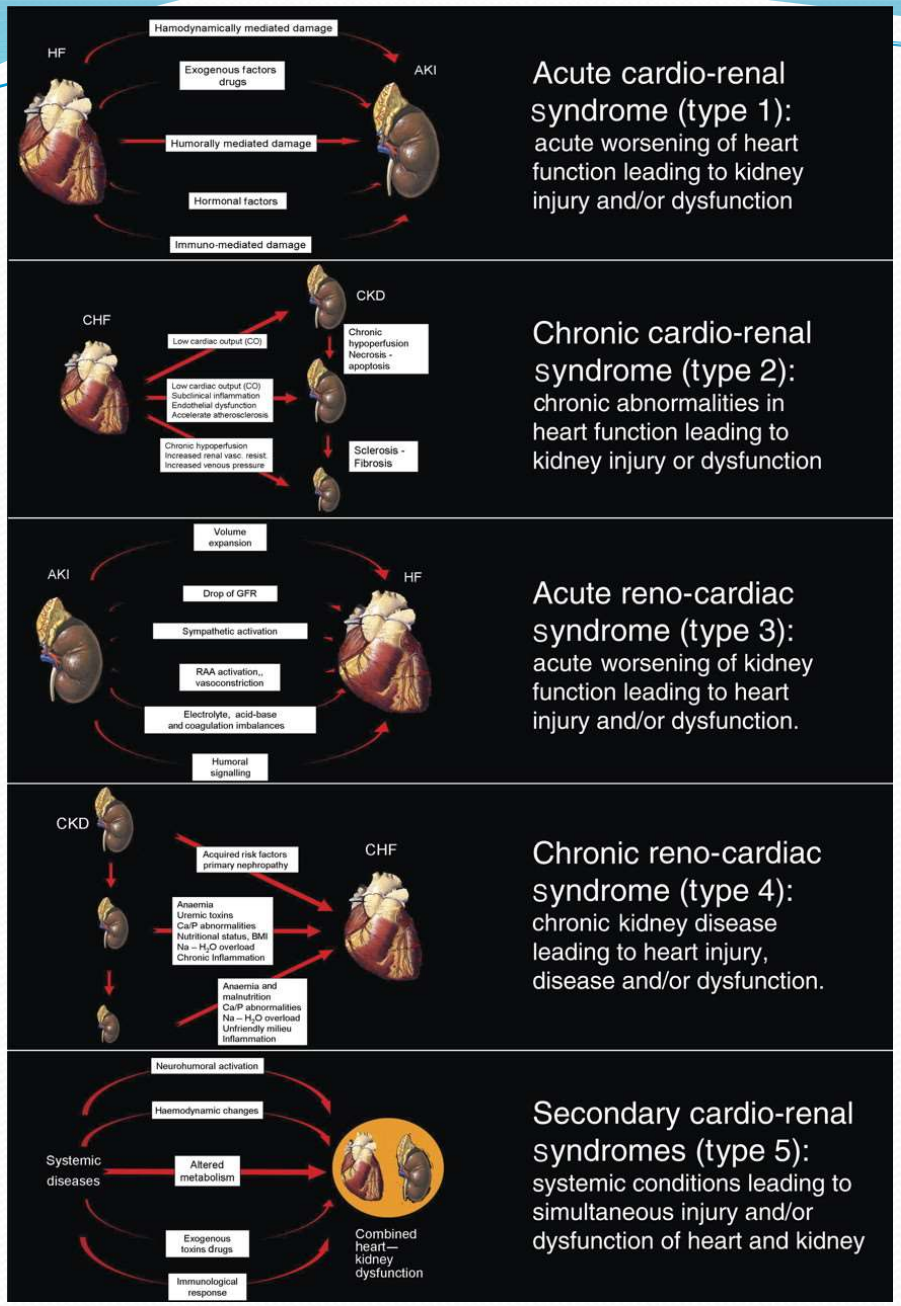
Cardio-renal Syndrome: Epidemiology

- Acute decompensated heart failure (ADHF):
  20 to 35% have AKI and of those patients, 50% have persistent kidney dysfunction and high rates of readmission
- 6 month mortality reported as:
  17 % with no AKI
  20 % with transient change in renal function
  46 % with persistent change in renal function

Aronson J of Cardiac failure 2010 16:7 p541

IMPACT OF CARDIORENAL SYNDROME

- As many as 1 in 7 patients (15%) of hospital admissions to internal medicine have diagnosis of cardiorenal syndrome
- A GFR between 30 to 40 ml/min is associated with 1.5 times the risk of cardiovascular disease when compared with better kidney function
- Patients with congestive heart failure who develop kidney disease or dropping GFR have a significant increase in mortality



Decompensated Heart Failure

Chronic cardio-renal Syndrome

Chronic Reno-cardiac Syndrome

Mr. B

- 53 year old man with a dilated non-ischemic cardiomyopathy diagnosed in 2001 with LVEF 15-20%
- Comorbidities: atrial fibrillation, type 2 diabetes, obesity, hypertension, peripheral vascular disease
- Increasing symptoms by 2011: on cozaar, carvedilol, spironolactone,furosemide, lipitor, metformin, insulin
- Serum creatinine 130 to 150 umol/L (eGFR 40 ml/min)

Mr. B

- August 2012: decompensated HF with AKI diuresed for 8 Kg - Cozaar discontinued
- September 2012: CHF with AKI treated with inotropes (milronone) and IV furosemide and metolazone
- Hemodialysis (few runs) for AKI and volume removal – run of VT on hemodialysis terminated by his ICD
- November 2012: CHF (creatinine 200 umol/L) treated with IV furosemide and milronone
- Peritoneal dialysis catheter inserted complicated by bleeding at exit site

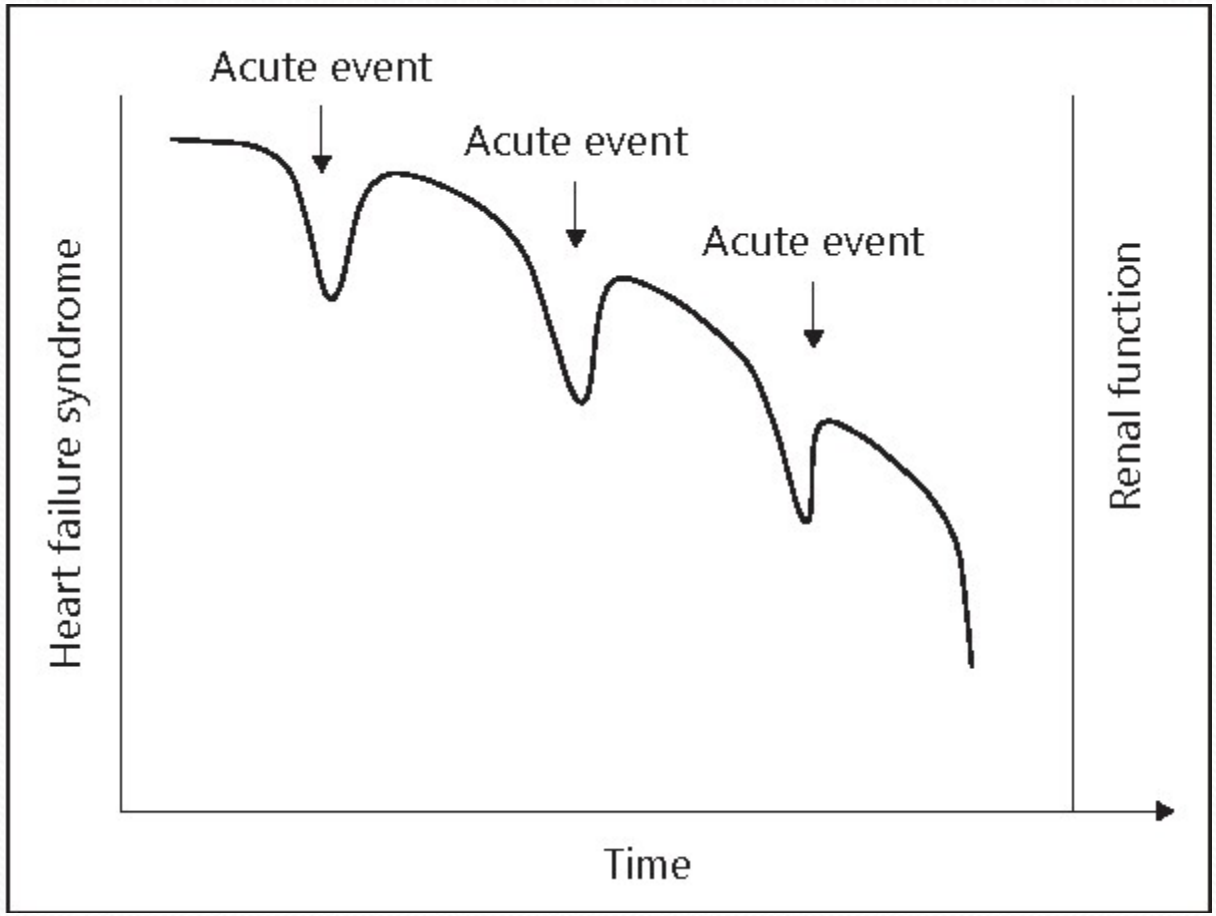
Mr. B

- January 2013 LVAD inserted with improvement – PD catheter was removed
- April 2013: decompensated again with AKI
- LVAD had cardiac output of 10 L
- Had several hemodialysis runs for ultrafiltration
- Eventually improved and discharged home off HD with creatinine of 160 umol\L

Mr B

- Heart transplant February 7, 2014 uneventful with MAP 70 to 80
- Preop creatinine 160 umol/l
- Postop AKI needing 2 hemodialysis runs for clearance and ultrafiltration and then recovered with creatinine now at 120 to 140 umol/l

Heart failure events and worsening renal function



Pathophysiology of CRS

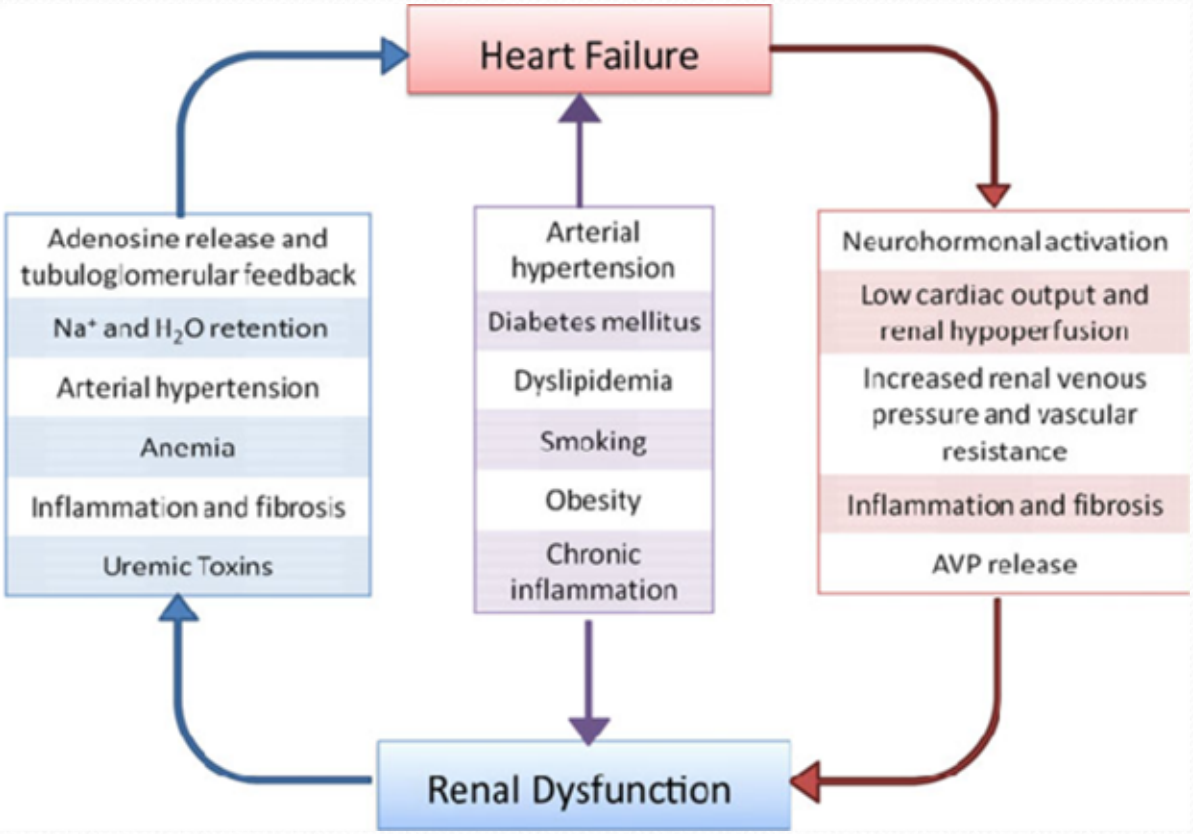
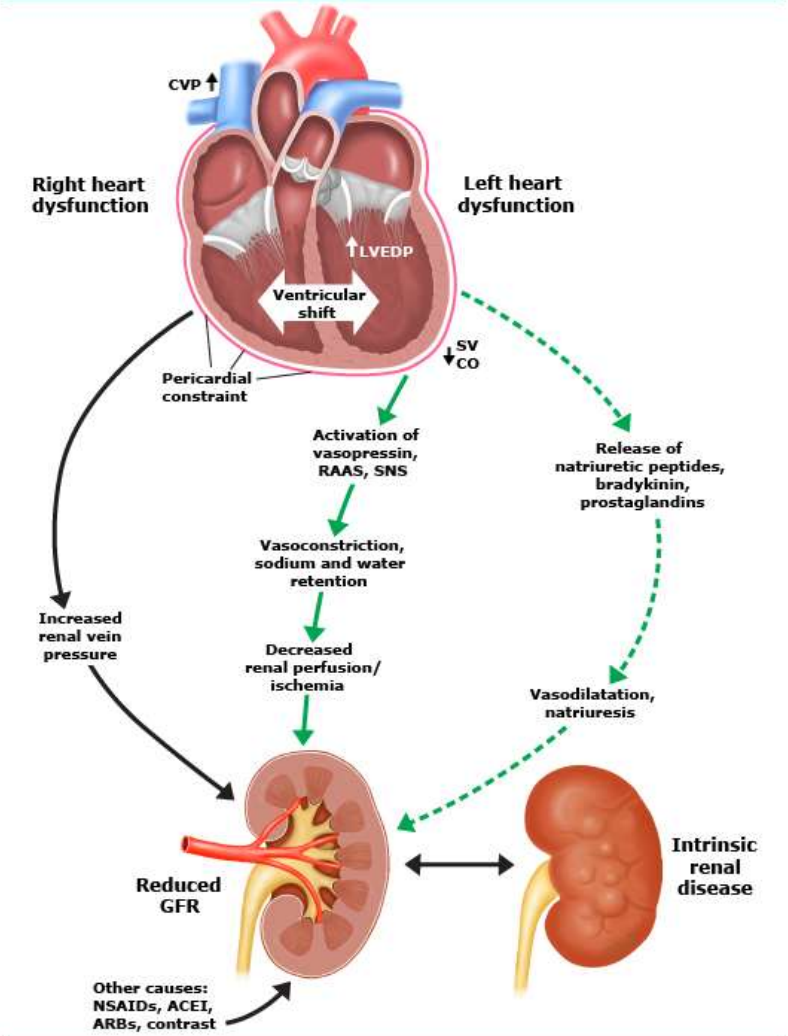


Fig. 1 Mechanisms of cardiorenal syndrome. *AVP* Arginine vasopressin

Pathophysiology of cardiorenal syndrome



ACEI: angiotensin converting enzyme inhibitor; ARBs: angiotensin II receptor blockers; CO: cardiac output; CVP: central venous pressure; LVEDP: left ventricular end-diastolic pressure; ETs: endothelins; NO: nitric oxide; NP: natriuretic peptides; NSAIDs: nonsteroidal antiinflammatory drugs; RAAS: renal angiotensin aldosterone system; SNS: sympathetic nervous system; SV: stroke volume; GFR: glomerular filtration rate.

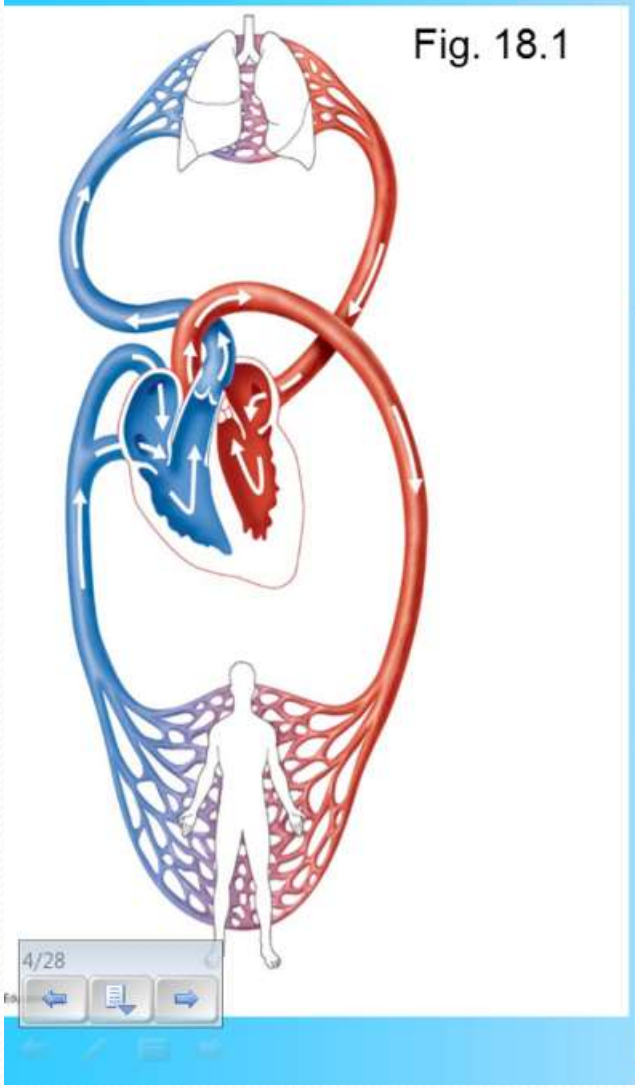
Cardio-renal Syndrome - ADHF

Pathophysiology:

Decreased cardiac function leads to:

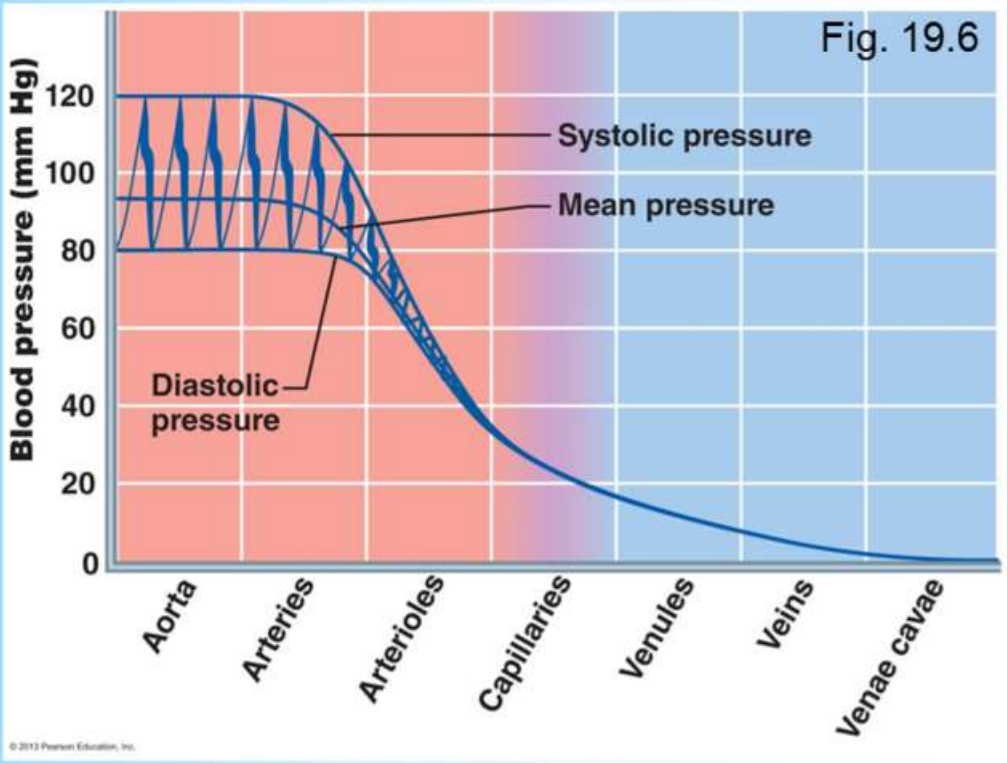
- Decreased renal blood flow and perfusion
- Decreased GFR
- Acute ischemia and AKI and eventually renal fibrosis and CKD
- Right sided heart failure and venous congestion – also causing AKI and possibly CKD

Physiology of Circulation



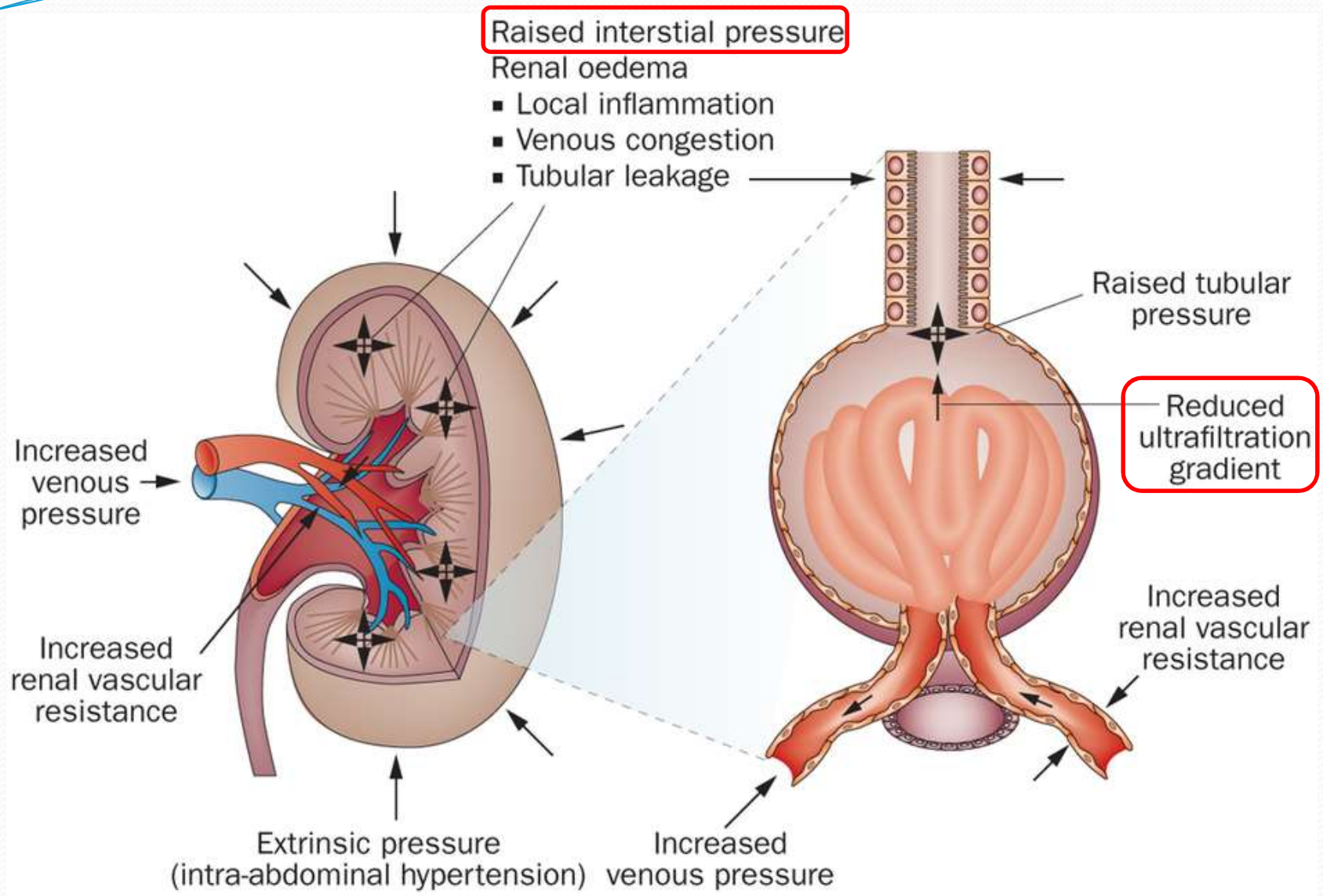
Mean Arterial Pressure (MAP)…

Diastolic + 1/3 pulse pressure



Pathophysiology involves more than just poor forward flow

- Inotropic support to increase MAP helps some patients in short term, but not all
- ESCAPE trial (2005) (to assess benefit of PAC in ADHF)found no correlation between cardiac index and baseline renal function


Raised interstial pressure
Renal oedema
Local inflammation
Venous congestion
Tubular leakage
Raised tubular pressure
Reduced ultrafiltration gradient
Increased venous pressure
Increased renal vascular resistance
Increased renal vascular resistance
Extrinsic pressure (intra-abdominal hypertension)
Increased venous pressure

Cardio-renal Syndrome - ADHF

Pathophysiology:

Activation of sympathetic nervous system:

- Systemic and renal vasoconstriction
- Increased proximal tubule Na and H_2O reabsorption
- Activates Renin-angiotensin-aldosterone system

Activation of RAAS:

- Systemic & renal vasoconstriction; release aldosterone
- More Na and H_2O retention
- Further cardiac injury via fluid overload

Mr. B

Therapeutic Options:

- Beta- blockers
- RAAS inhibition
- Aldosterone antagonism
- Inotropic support
- Diuretics
- Ultrafiltration
- LVAD as bridge to cardiac transplantation

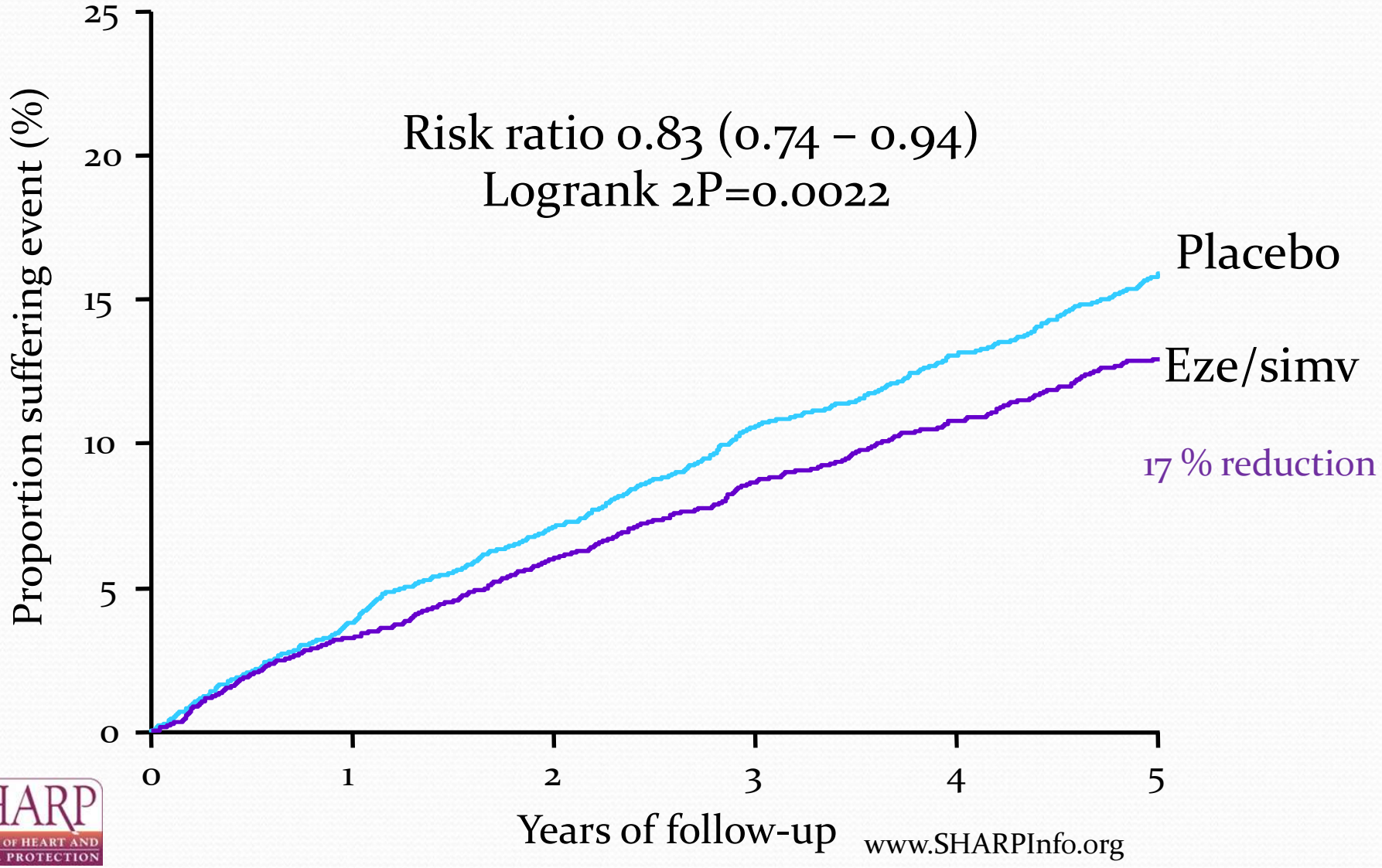
CRS:PREVENTING DECOMPENSATION

Involves interventions and expertise we already practice in our kidney care clinics

CRS: preventing decompensation

- **Sodium** and fluid control
- **Blood pressure** control
- **Glycemic** control
- **Weight** reduction
- **Smoking** cessation
- **Anemia** management
- **AKI** prevention (medications, contrast)
- **Statin** use: not entirely clear for overall prognosis but have been shown to reduce hospitalizations for congestive heart failure (better with higher doses)

SHARP: Major Atherosclerotic Events



SHARP
STUDY OF HEART AND RENAL PROTECTION

SHARP Study

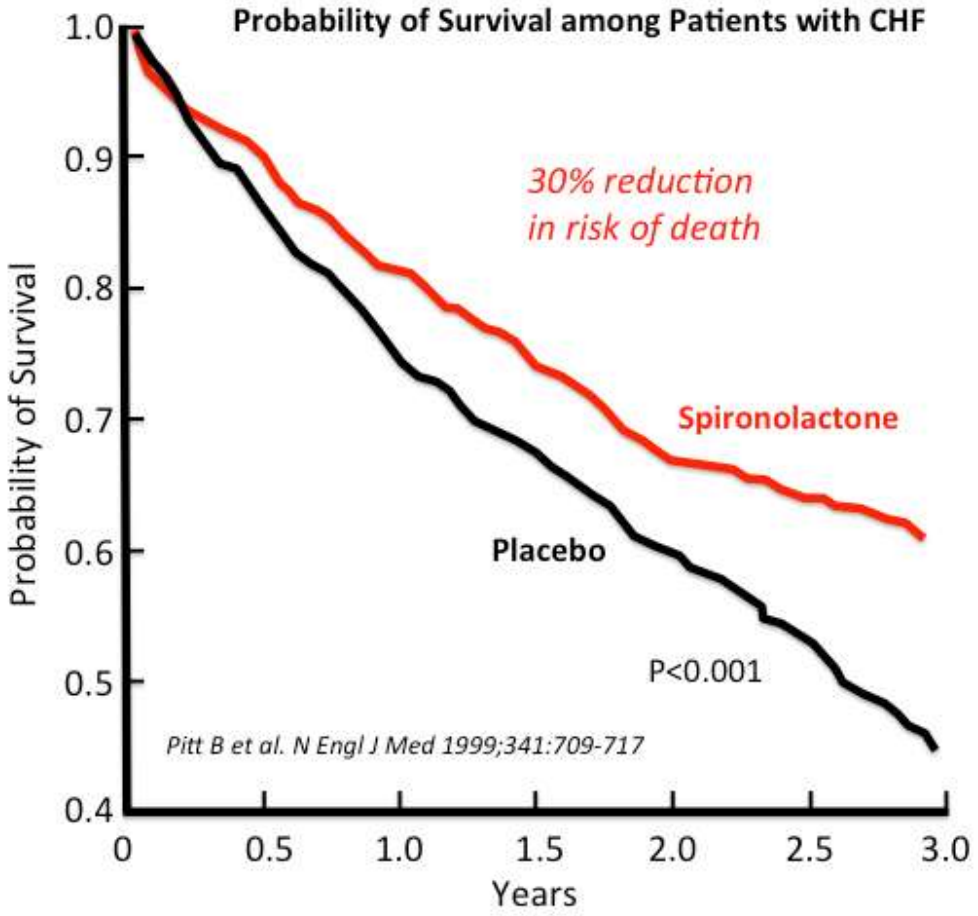
- Most of the risk reduction was in decreasing strokes and peripheral vascular disease with less impact on coronary events
- No impact on overall mortality
- Other studies however have shown that in those with heart failure statins reduce heart failure hospital admissions

CRS: Preventing decompensation

- Appropriate use of **diuretics** for maintenance of euvolemia
- **Beta- blockers** for decreasing sympathetic activity
- Renin angiotensin aldosterone system **(RAAS)** inhibition increases cardiac survival even in patients with low GFR: ACE inhibitors
  Angiotensin receptor blockers
  Aldosterone blockers

Spironolactone well tolerated in patients with serum creatinine less than 200 umol/l. Patients with worse renal function excluded from studies.

Additional benefits in CKD:
Anti-fibrotic effects in kidneys
Anti-proteinuric effects



Randomized Aldactone Evaluation Study
RALES Trial NEJM 1999 341: 709

SGLT2 inhibitors in heart failure

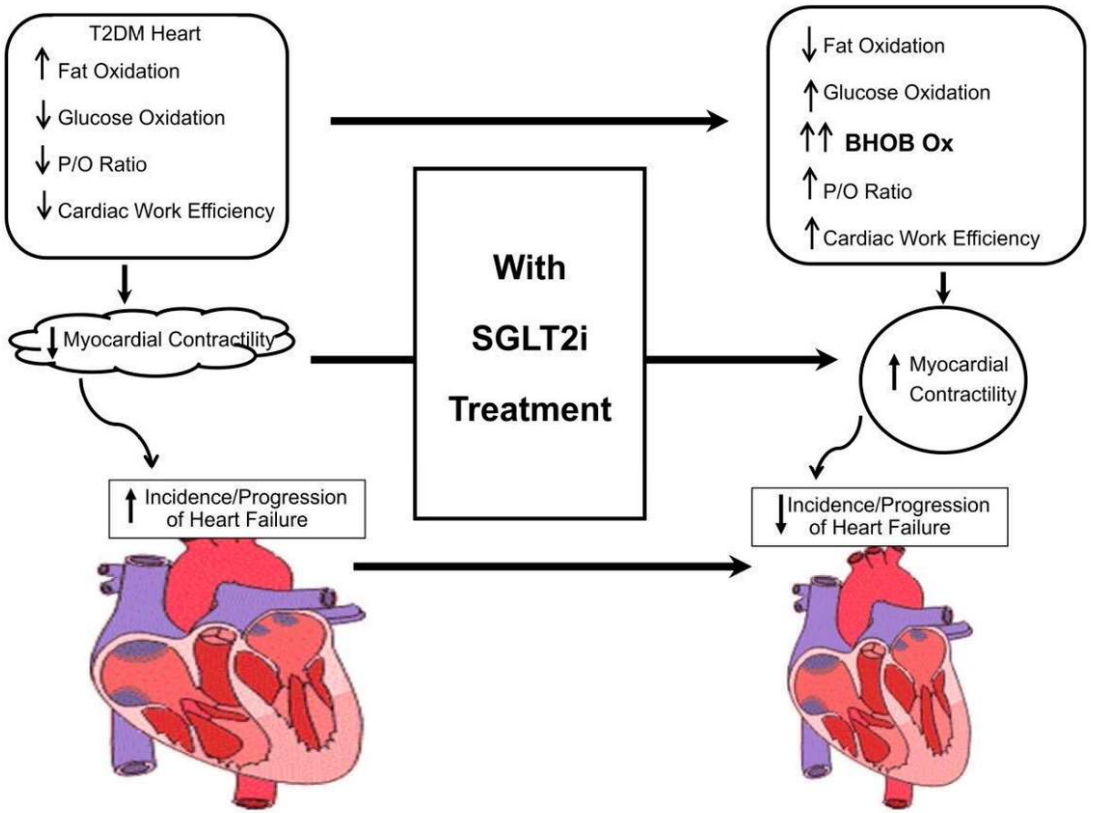
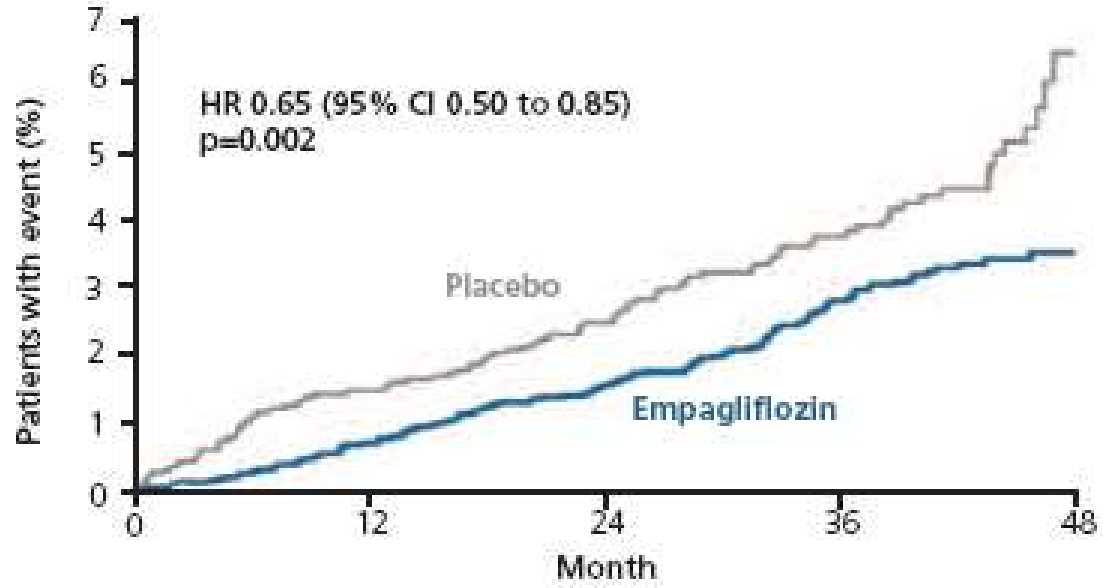


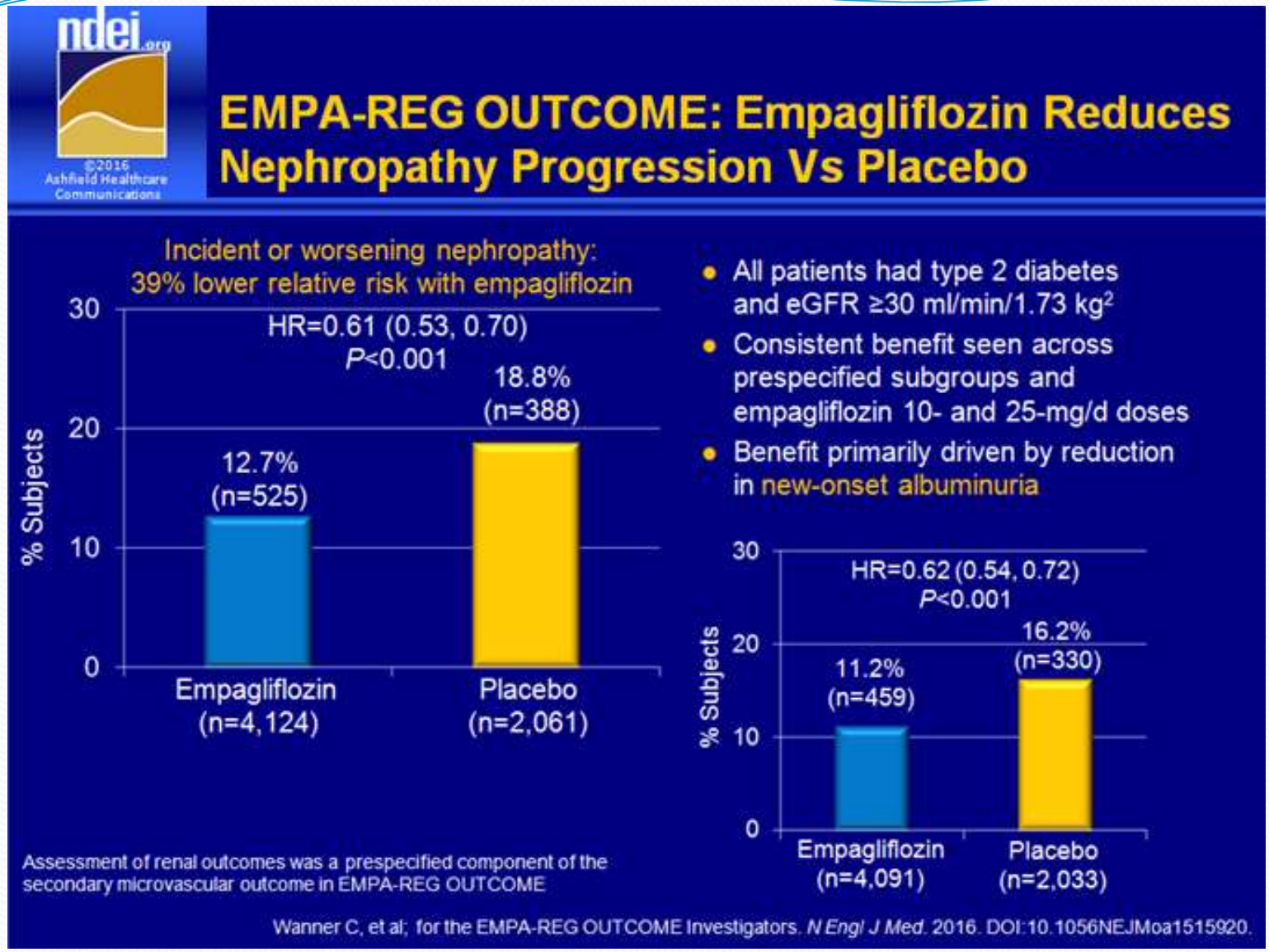
Figure 1—Postulated changes in myocardium fuel metabolism before and after SGLT2 inhibitor (SGLT2i) therapy. P/O ratio reflects the number of molecules of ATP produced per atom of oxygen reduced by the mitochondrial electron transport chain.

Decreased hospitalizations for heart failure in empa group

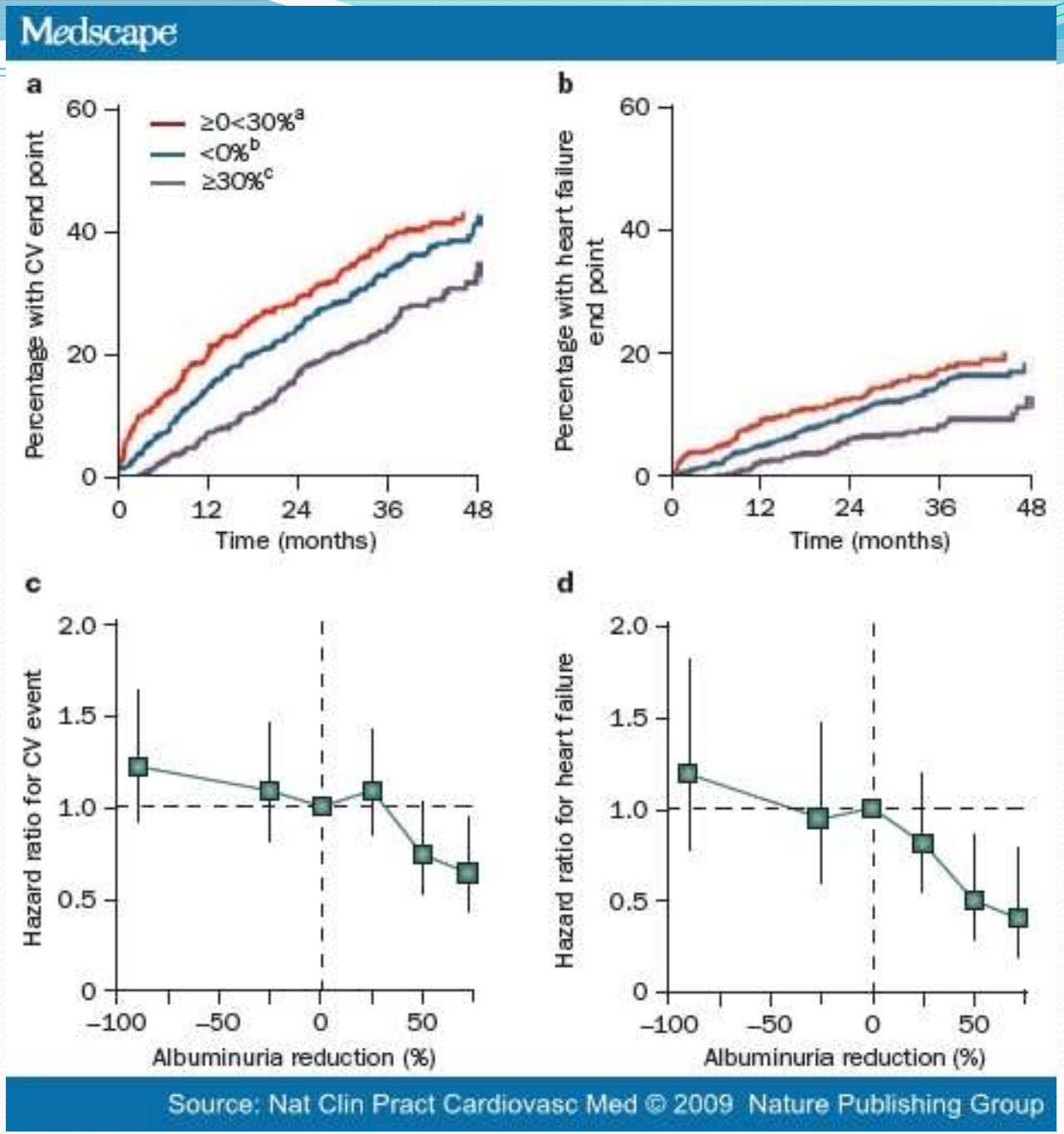
Figure 6. The cumulative incidence of hospitalisation for heart failure in the empagliflozin group versus placebo in the EMPA-REG OUTCOME study

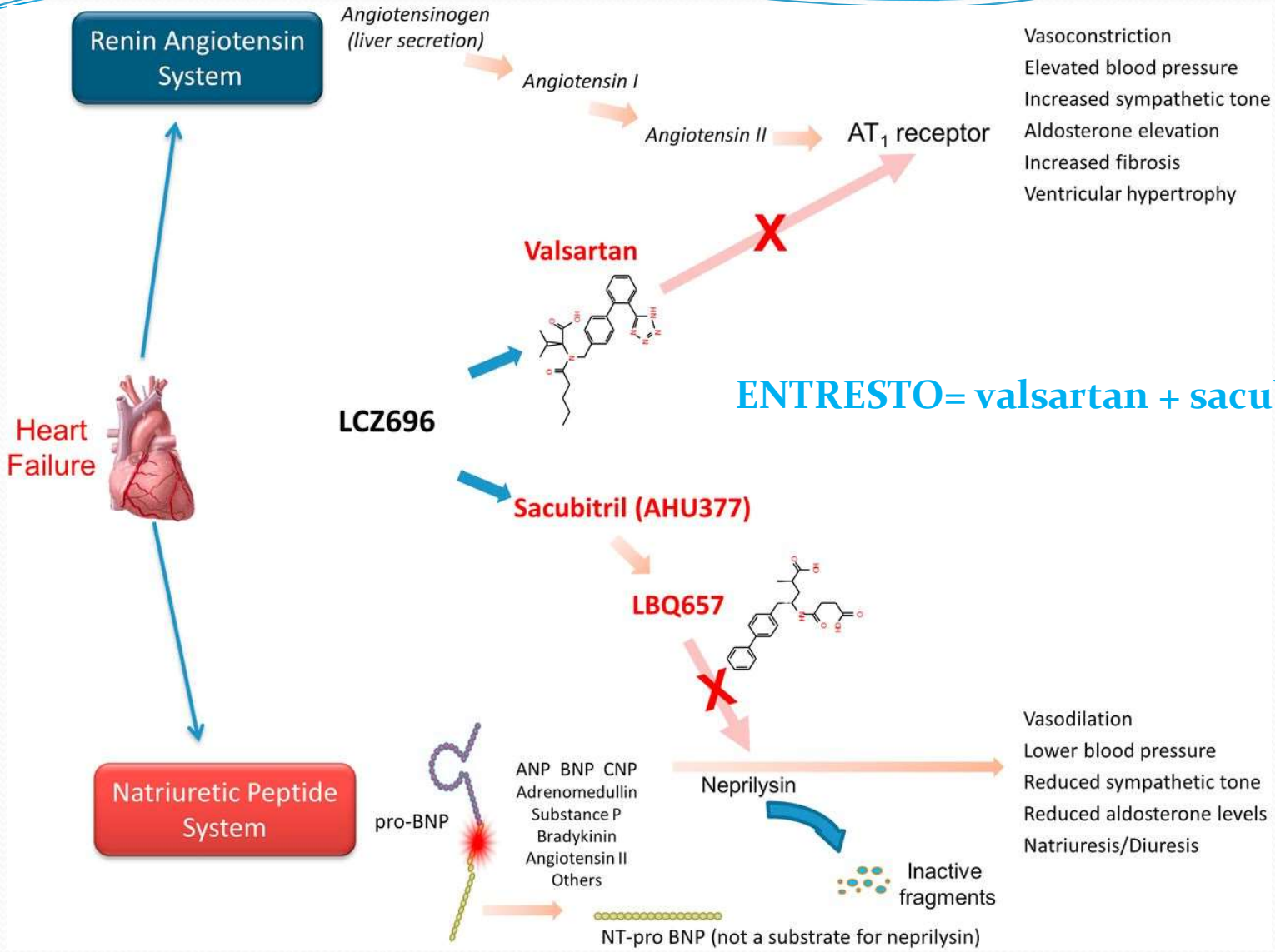


Hazard ratios (HR) are based on Cox regression analysis. Reproduced with permission from ref 2.


ndei.org
©2016 Ashfield Healthcare Communications
EMPA-REG OUTCOME: Empagliflozin Reduces Nephropathy Progression Vs Placebo
Incident or worsening nephropathy:
39% lower relative risk with empagliflozin
HR=0.61 (0.53, 0.70)
P<0.001
18.8%
(n=388)
12.7%
(n=525)
% Subjects
30
20
10
0
Empagliflozin
(n=4,124)
Placebo
(n=2,061)
All patients had type 2 diabetes and eGFR ≥30 ml/min/1.73 kg²
Consistent benefit seen across prespecified subgroups and empagliflozin 10- and 25-mg/d doses
Benefit primarily driven by reduction in new-onset albuminuria
HR=0.62 (0.54, 0.72)
P<0.001
16.2%
(n=330)
11.2%
(n=459)
% Subjects
30
20
10
0
Empagliflozin
(n=4,091)
Placebo
(n=2,033)
Assessment of renal outcomes was a prespecified component of the secondary microvascular outcome in EMPA-REG OUTCOME
Wanner C, et al; for the EMPA-REG OUTCOME Investigators. N Engl J Med. 2016. DOI:10.1056NEJMoa1515920.

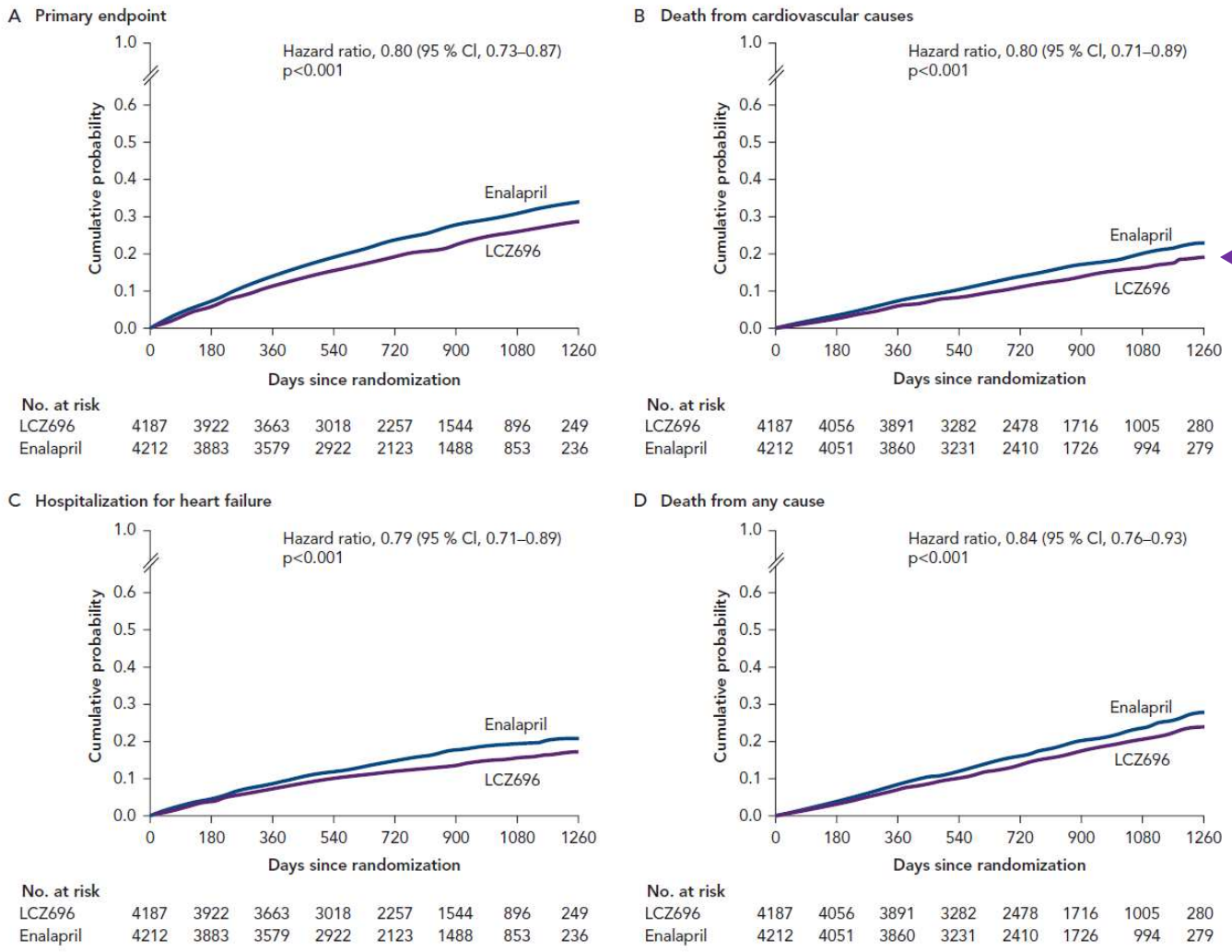
REDUCTION IN CARDIOVASCULAR EVENTS WITH ALBUMINURIA REDUCTION





Orly Vardeny et al. JCHF 2014;2:663-670

Figure 1: Kaplan–Meier curves for key study outcomes of PARADIGM-HF trial according to study group: probabilities of the primary composite endpoint (death from cardiovascular causes or first hospitalization for heart failure; A), death from cardiovascular causes (B), first hospitalization for heart failure (C), and death from any cause (D). PARADIGM-HF = Prospective Comparison of Angiotensin Receptor-neprilysin Inhibitor with Angiotensin Converting Enzyme Inhibitors to Determine Impact on Global Mortality and Morbidity in Heart Failure



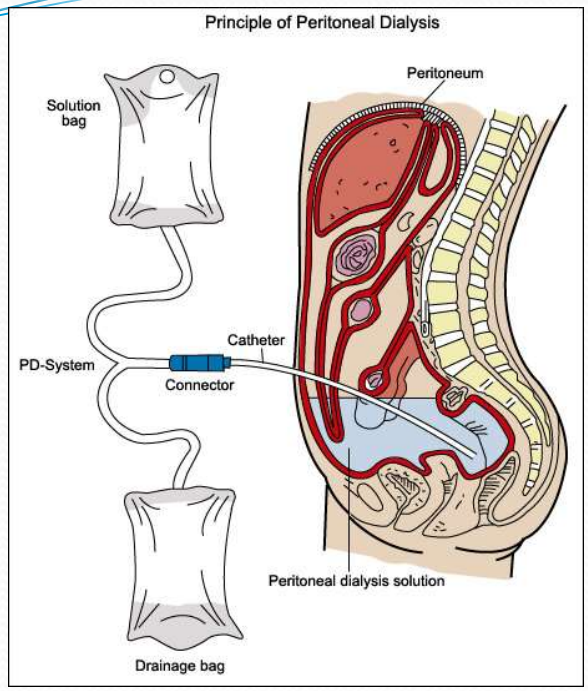
Source: McMurray, et al., 2014.[3] Reprinted with permission from Massachusetts Medical Society.

ENTRESTO

US Cardiology Review 2017;11(2):62–6

ACUTE DECOMPENSATED HEART FAILURE (ADHF)

- Will require hospital admission
- Intravenous diuretics
- Inotropic support to increase cardiac output
- May require ultrafiltration with dialysis
- In appropriate patients, a left ventricular assist device (LVAD) may be needed as a bridge to transplantation
- At this point in Canada LVAD not usually used as destination therapy



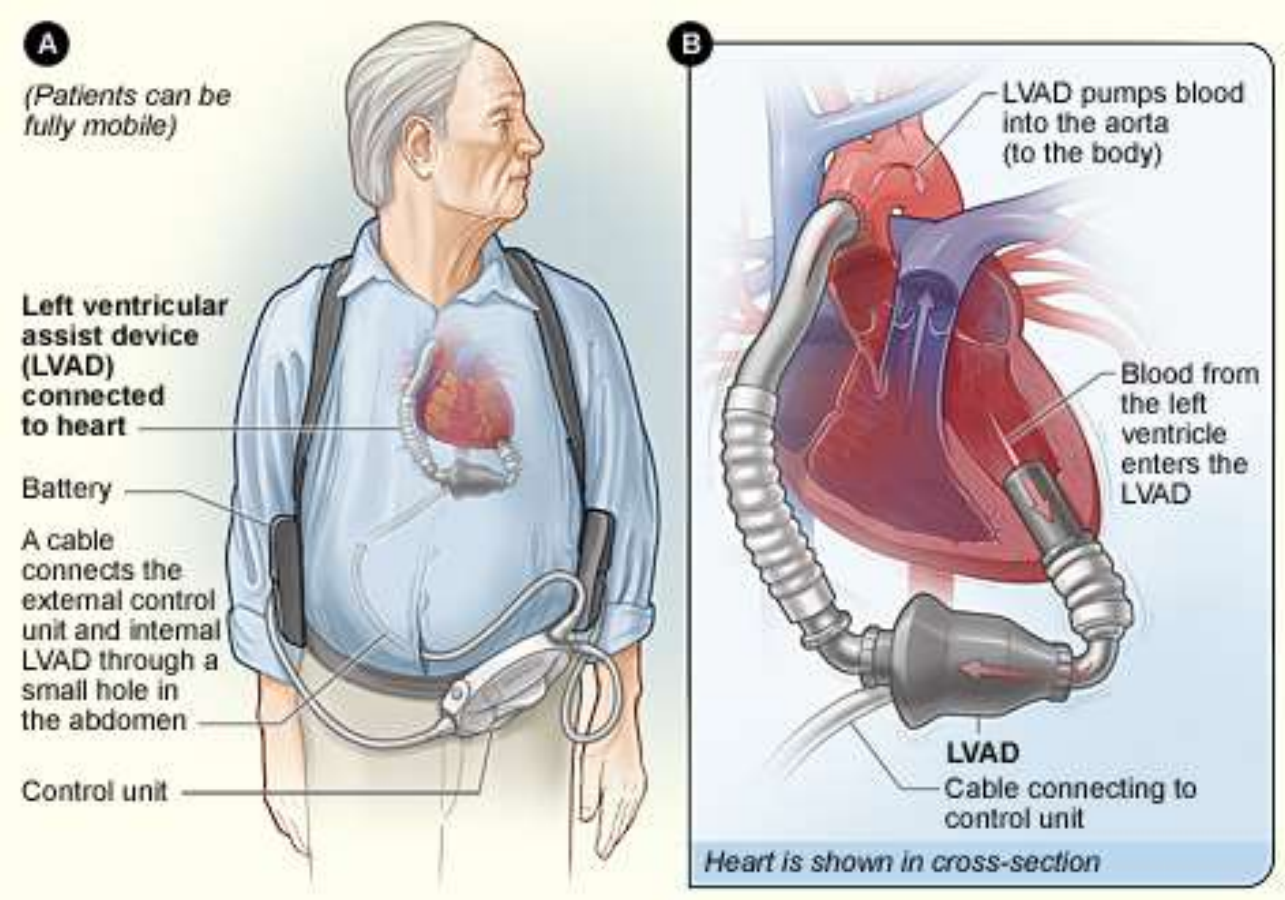
PERITONEAL DIALYSIS

- Associated with longer preservation of residual renal function
- More stable volume status and hemodynamic status
- Peritoneal membrane is more biocompatible

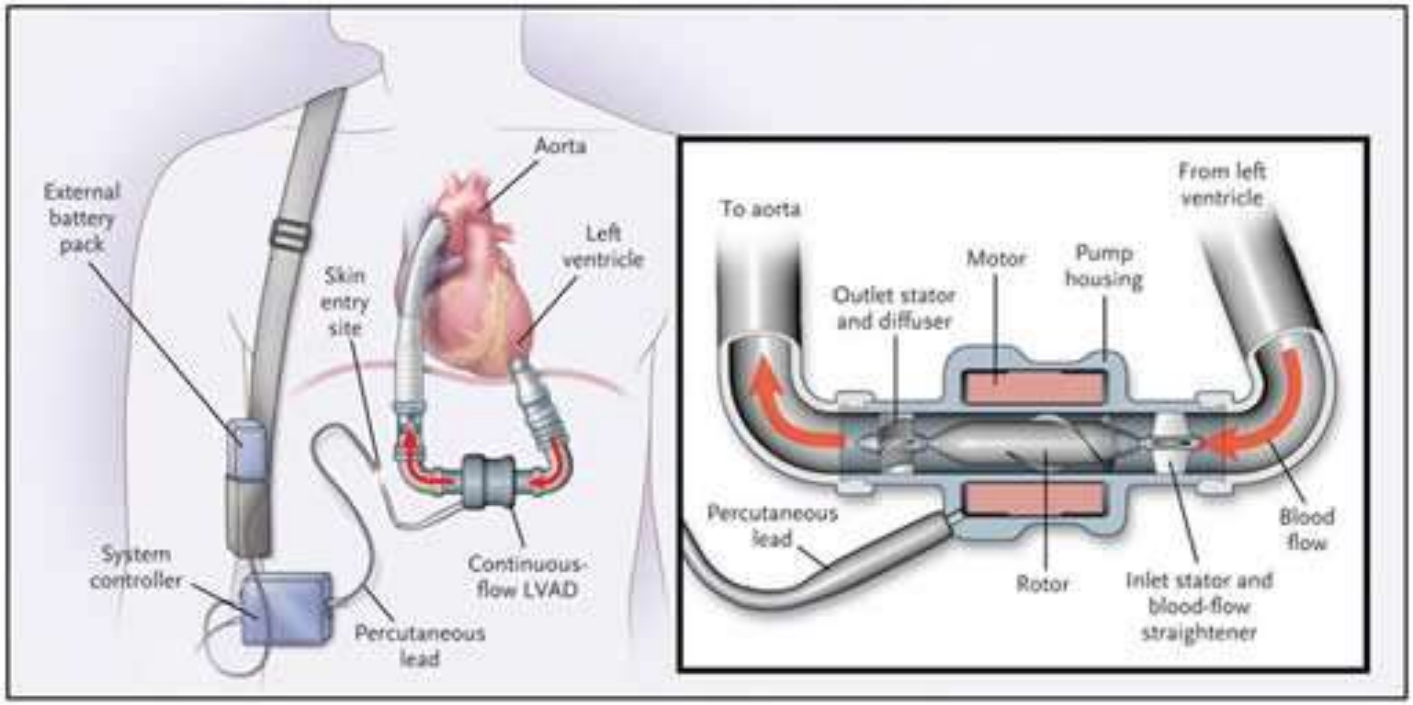
➢ Provides more independence than hemodialysis

Left ventricular assist devices

Teaching old nephrology teams new tricks


A
(Patients can be fully mobile)
Left ventricular assist device (LVAD) connected to heart
Battery
A cable connects the external control unit and internal LVAD through a small hole in the abdomen
Control unit
B
LVAD pumps blood into the aorta (to the body)
Blood from the left ventricle enters the LVAD
LVAD
Cable connecting to control unit
Heart is shown in cross-section

Continuous Flow LVAD



Non Pulsatile LVAD

- Studies have shown improved and preserved renal function as well as cognitive function
- Can generate blood flows of 3 to 8 liters per minute
- Levels of ANP, aldosterone, renin usually decreased
- Animal studies: renal arterial smooth muscle hyperplasia and interstitial nephritis in long term use

Renal challenges with LVAD

- Risk of AKI post implantation varies between 7 to 30 % depending on pre-operative hemodynamic stability
- AKI and need for CRRT is associated with higher mortality
- Those with AKI have higher risk of needing long-term hemodialysis (either from repeated ischemic injury or other intrinsic renal disease) and mortality in these patients is high

Long-term renal replacement challenges

- Vascular access: arterio-venous graft is preferred access
  Lines carry high risk of infection
  AV fistulas may be difficult – higher risk clotting

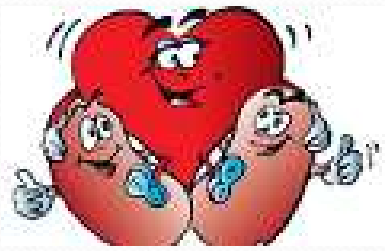
- Blood pressure monitoring: impossible or unreliable

- Excessive ultrafiltration could drop LVAD pump flow and therefore evaluation and monitoring of dry weight is potential challenge

- Peritoneal dialysis is possible with new LVAD

Reno-Cardiac Challenges

Chronic kidney disease increasing risk of cardiovascular disease



Mr. C

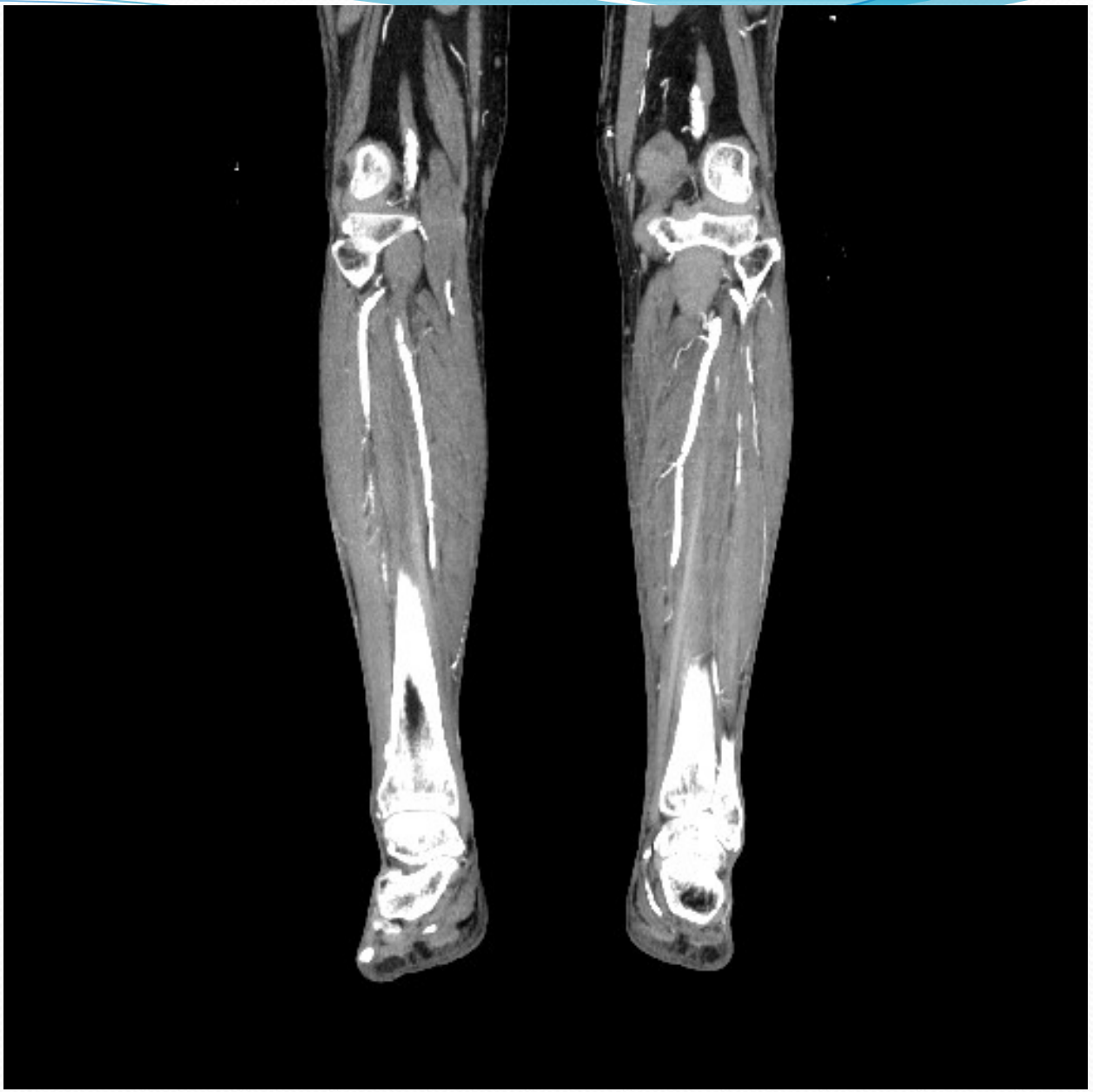
- 60 year old man with ESRF due to diabetic nephropathy starting dialysis in 2008
- Diabetes complicated by retinopathy, neuropathy and PVD
- Comorbidities: gout, sleep apnea, pneumonia
- 2010: ACS -angioplasty and RCA stent with immediate in stent thrombosis, RV infarct and cardiogenic shock
- 2013: ACS – CABG x 2 and aortic and mitral valve replacements complicated by sepsis and weakness
- LVEF on echo was 55%

Mr. C

- Sept 2013 (7 mons later) low BP on dialysis with MIBI showing LVEF of 33%, anterior wall ischemia with transient ischemic LV dilatation
- Angiogram showed his grafts were 70% occluded with ostial lesions too high risk for angioplasty
- November 2013: admitted with ischemic feet and intractable pain with no re-constructable disease on CT
- He chose to withdraw from dialysis and died comfortably with palliative care team support

Mr C.

CT Angiogram
November 2013



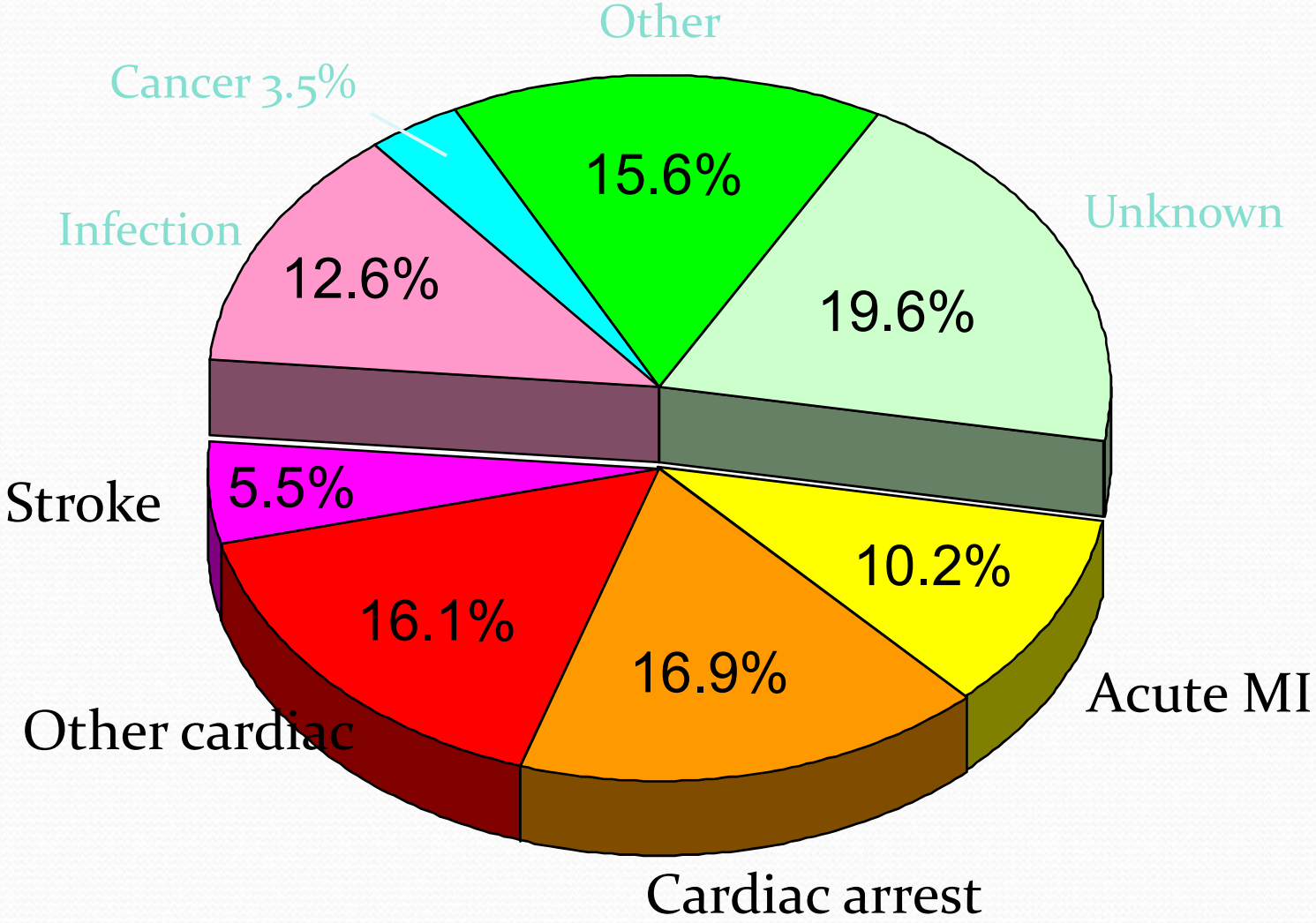
CRS – OMINOUS CO-EXISTENCE

2-year mortality and incidence of ESRD in a 5% sample of Medicare patients from the USA (1.1 million patients)

	2 Year mortality %	2 Year Incidence of ESRD%
No Anaemia/ CHF/ CKI	7.7	0.1
Anaemia	16.6	0.1
CHF	26.1	0.2
CHF & Anaemia	34.6	0.3
CKI	16.4	2.6
CKI & Anaemia	27.3	5.4
CHF & CKI	38.4	3.5
CHF, CKI & Anaemia	45.6	5.9

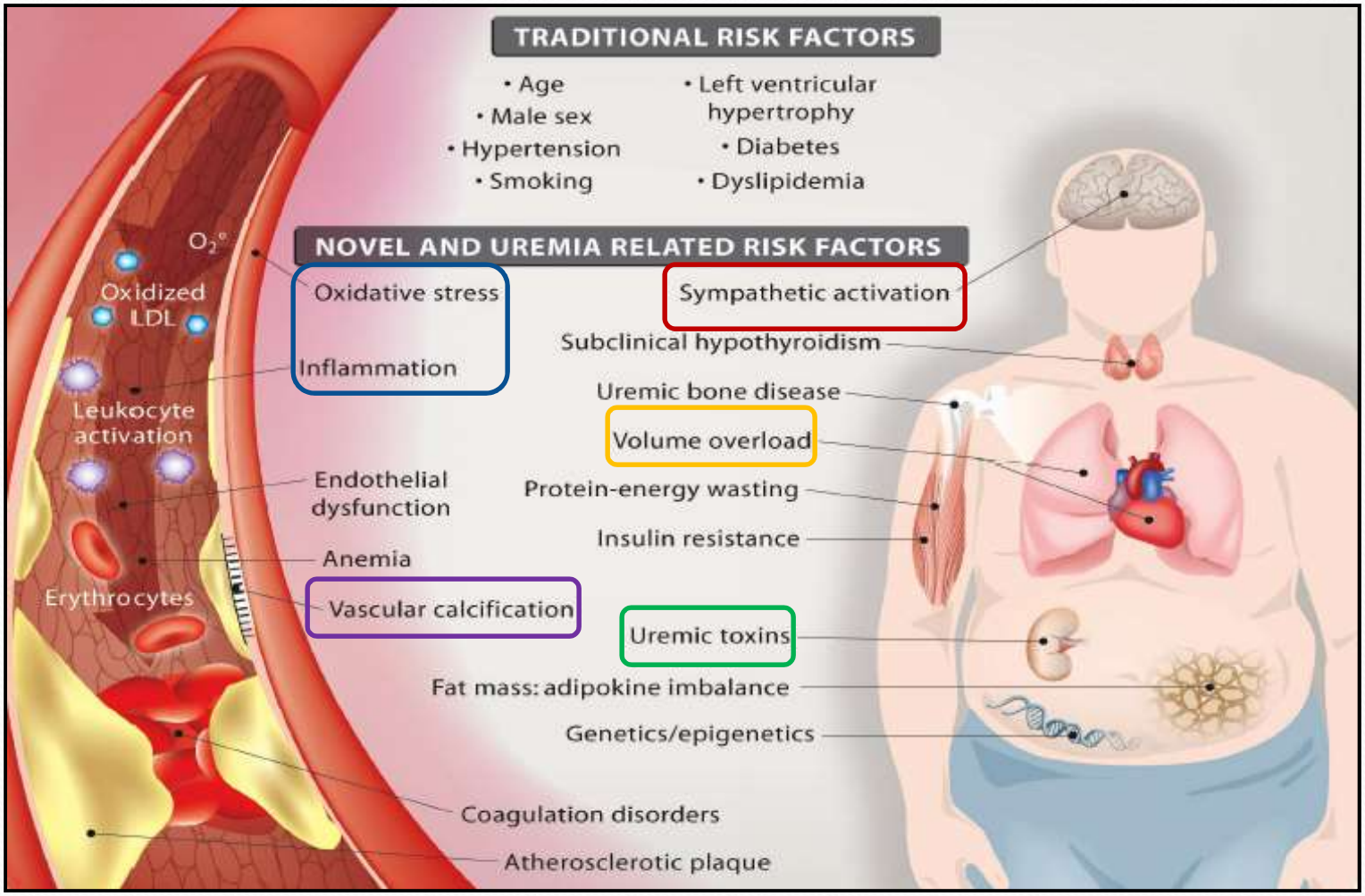
Gilbertson D. *J Am Soc Nephrol* 2002;13:SA848

Causes of death in dialysis patients



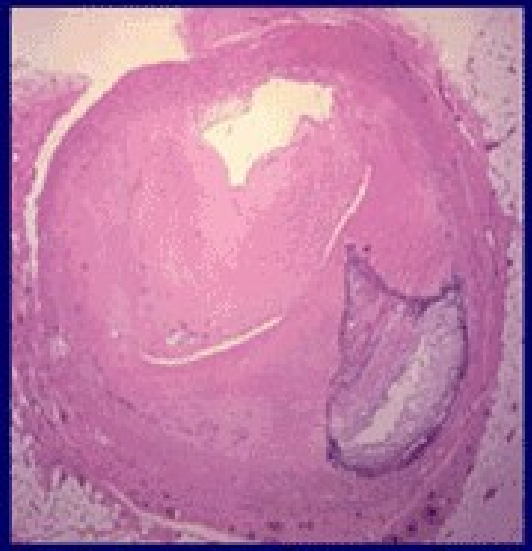
USRDS 1996 Annual Data Report

Traditional and non-traditional risk factors for CVD in CKD patients

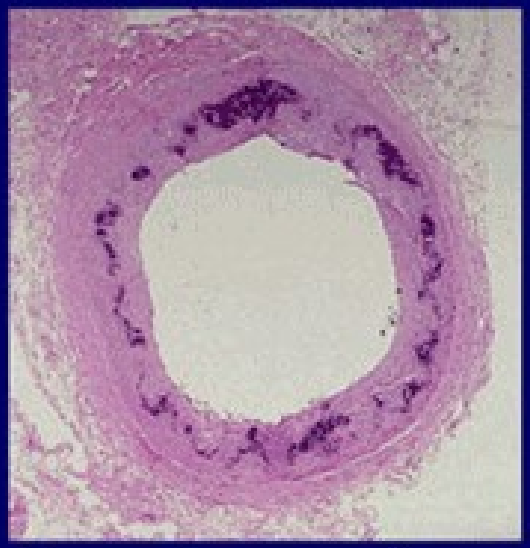


Stenvinkel P. Clin J Am Soc Nephrol 3: 505-521, 2008.

Types of Vascular Calcification in Chronic Kidney Disease



Atherosclerosis



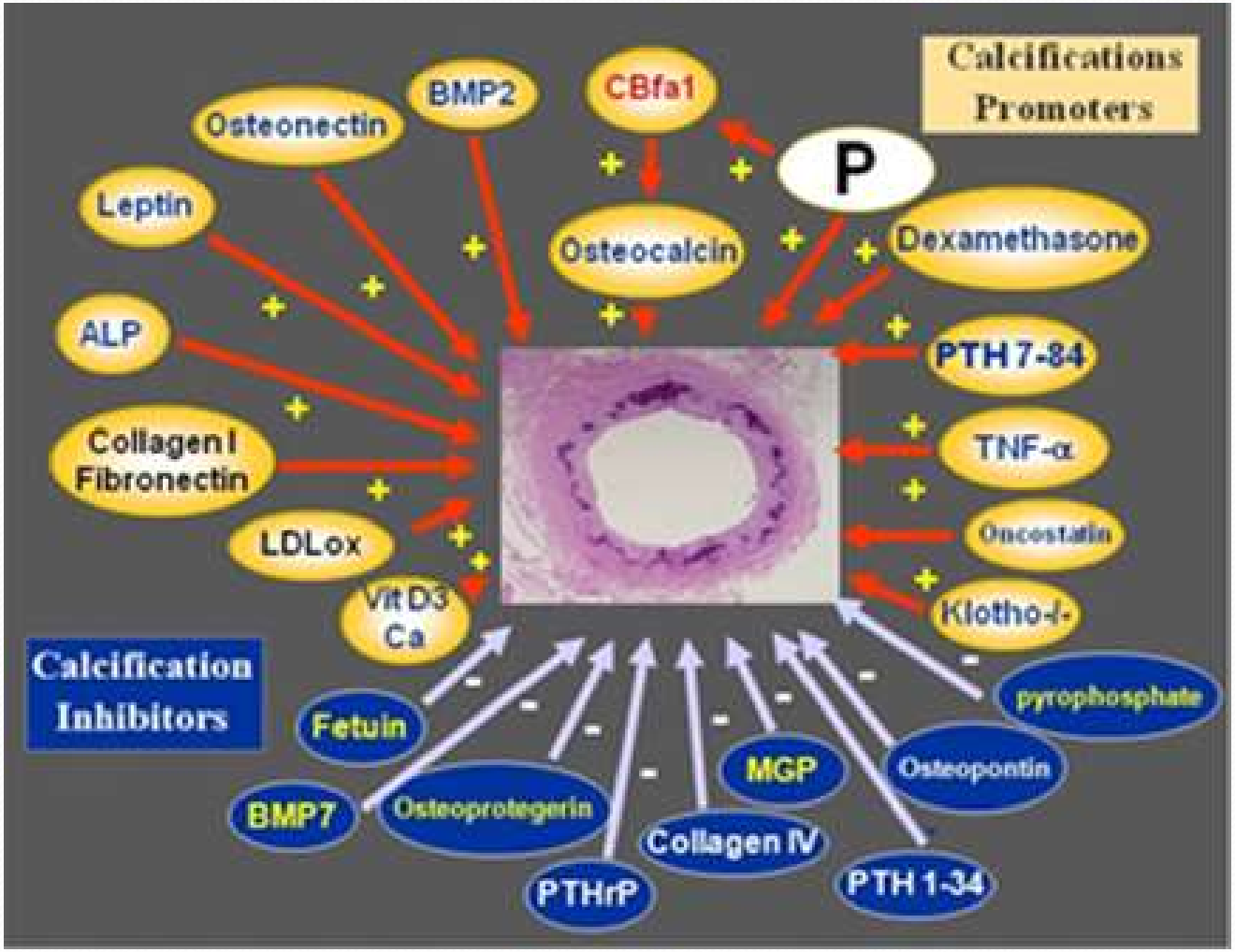
Uremic arteriopathy

What is the role of elevated phosphorus levels in vascular calcification and CVD??

- Elegant in vitro and in vivo (mice) experiments showing that PO_4 causes vascular calcification by increasing expression of **ostrix** – osteoblast specific transcription factor (by the vascular cell) JASN 2008 19(6): 1092

- But phosphate control in humans has proven disappointing in its impact on vascular calcification, CVD and mortality

In addition to *phosphate* there is a multitude of potential *inflammatory mediators* in CKD



How Can We Help?

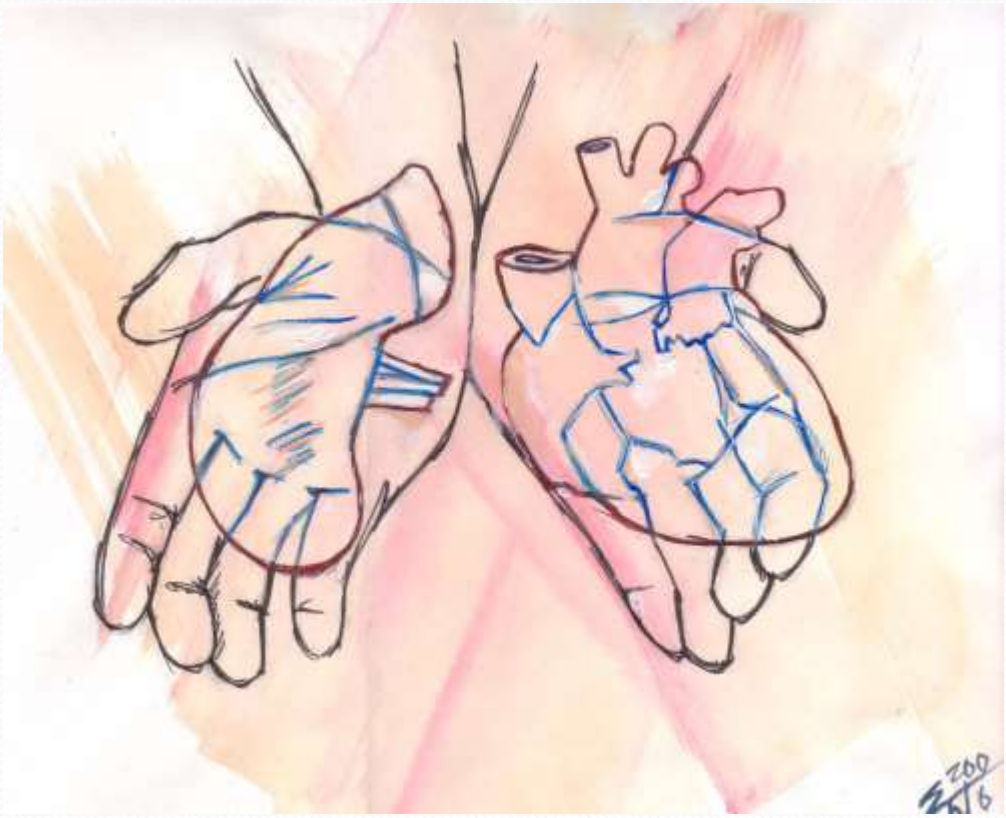
1. Control of DRY WEIGHT with salt intake control, fluid intake advice and diuretics as needed
2. Blood pressure control
3. RAAS inhibition
4. Beta-blockers
5. Use of statins
6. Glycemic control
7. Consider probable renal and cardiac benefits of SGLT2 inhibitors
8. Smoking cessation
9. Maintain activity
10. Phosphate and PTH control

Approach to primary and secondary prevention of CVD in CKD patients

- Even though our CKD patients have a higher risk of side effects from CHF and CVD medications (e.g. hyperkalemia), they should be treated in similar ways as non-renal patients *(statins, beta-blockers, RAAS inhibition, aldosterone blockade)*

- Even though they may have a higher risk of AKI, they should still be investigated with angiography and proceed with angioplasty or CABG as indicated by their coronary anatomy

Thank You



Questions ?

Conclusion

- Cardio-renal and reno-cardiac syndrome patients remain a big challenge to our multidisciplinary teams
- We have come a long way in last 60 years in understanding the pathophysiology, clinical presentations and therapeutic options
- There are many unanswered questions for interested young clinicians and researchers.

Acknowledgments:

- I am extremely grateful to my wonderful colleagues:
- Doctors:

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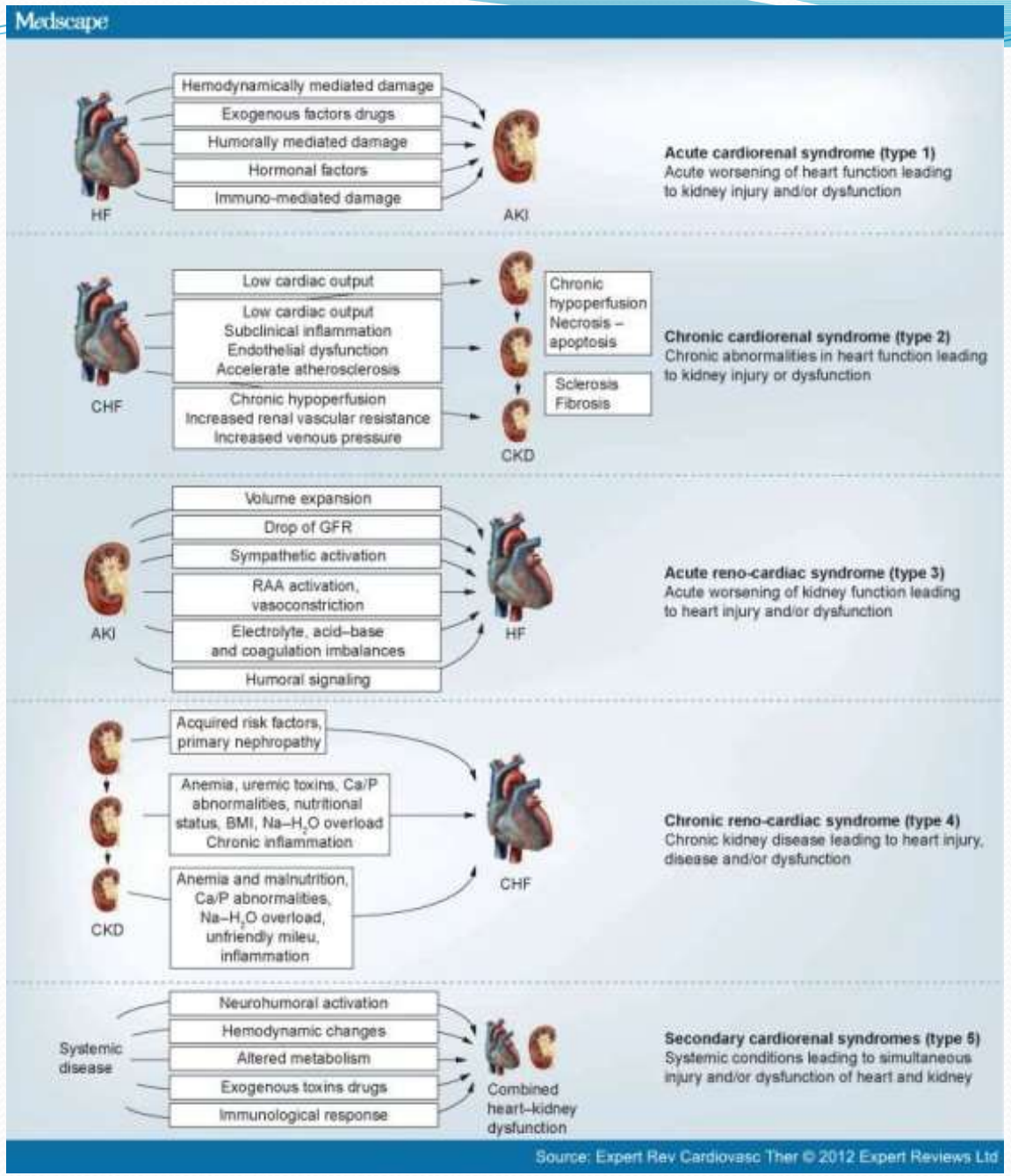
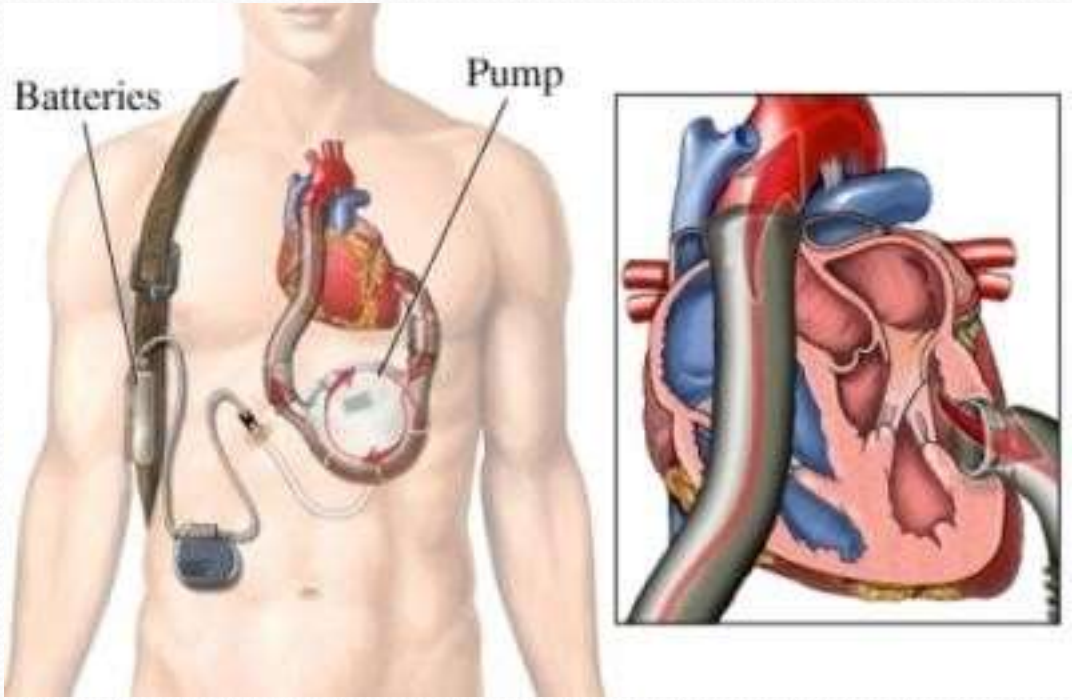
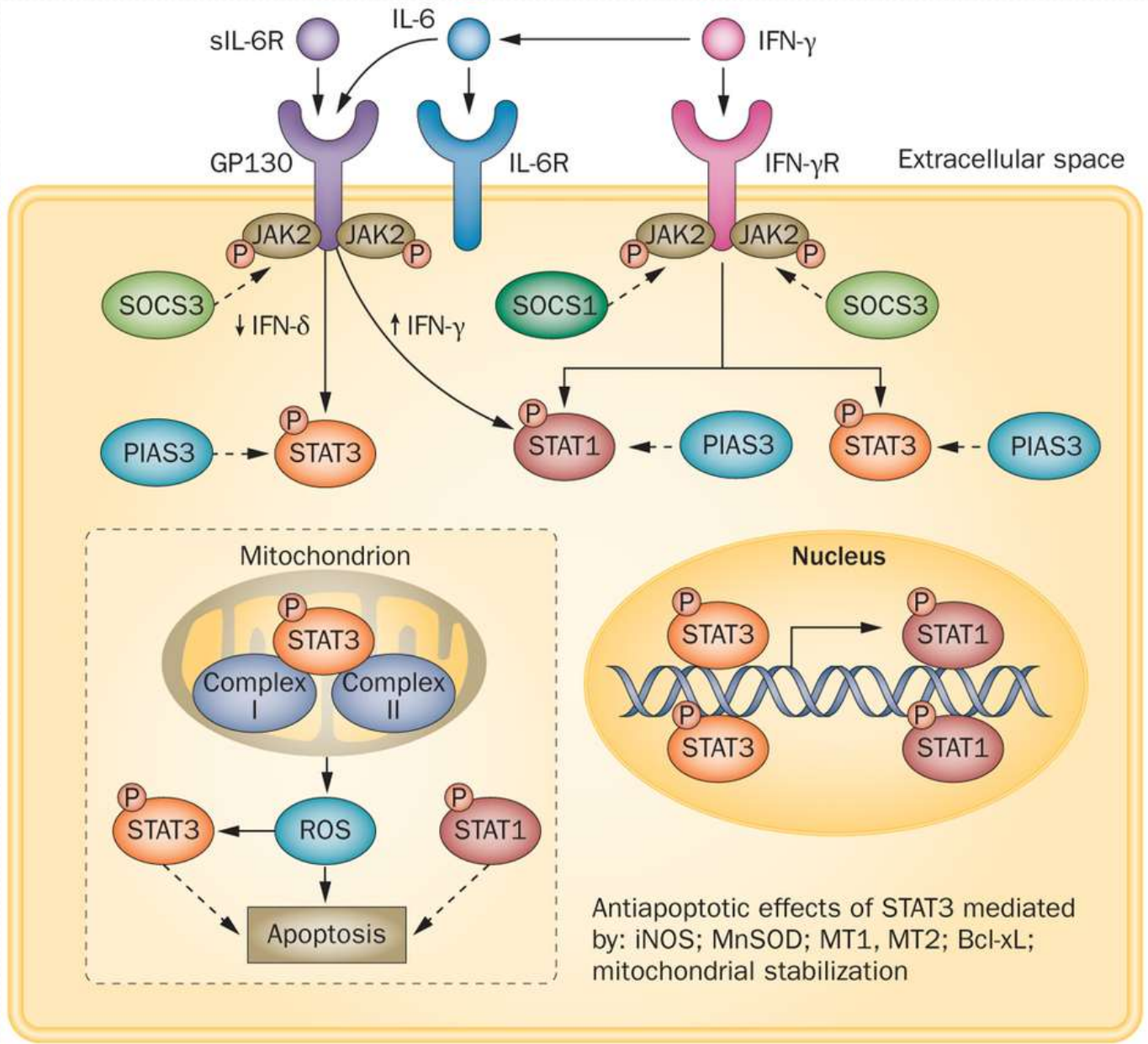
  Abeed Jamal
  Beverley Jung
  Mercedeh Kiaii
  David Landsberg
  Adeera Levin
  Gary Nussbaumer
  David Prchal
  Paul Taylor
- Nurse Practitioner:

  Stan Marchuk
- For all our wonderful nursing and allied staff
- And for our amazing fellows, medical residents and students whose contributions to our professional satisfaction, integrity and education are immeasurable!


Medscape
Hemodynamically mediated damage
Exogenous factors drugs
Humorally mediated damage
Hormonal factors
Immuno-mediated damage
HF
AKI
Acute cardiorenal syndrome (type 1)
Acute worsening of heart function leading to kidney injury and/or dysfunction
Low cardiac output
Low cardiac output
Subclinical inflammation
Endothelial dysfunction
Accelerate atherosclerosis
Chronic hypoperfusion
Increased renal vascular resistance
Increased venous pressure
CHF
Chronic hypoperfusion
Necrosis – apoptosis
Sclerosis
Fibrosis
CKD
Chronic cardiorenal syndrome (type 2)
Chronic abnormalities in heart function leading to kidney injury or dysfunction
Volume expansion
Drop of GFR
Sympathetic activation
RAA activation, vasoconstriction
Electrolyte, acid–base and coagulation imbalances
Humoral signaling
AKI
HF
Acute reno-cardiac syndrome (type 3)
Acute worsening of kidney function leading to heart injury and/or dysfunction
Acquired risk factors, primary nephropathy
Anemia, uremic toxins, Ca/P abnormalities, nutritional status, BMI, Na–H2O overload
Chronic inflammation
Anemia and malnutrition, Ca/P abnormalities, Na–H2O overload, unfriendly mileu, inflammation
CKD
CHF
Chronic reno-cardiac syndrome (type 4)
Chronic kidney disease leading to heart injury, disease and/or dysfunction
Neurohumoral activation
Hemodynamic changes
Altered metabolism
Exogenous toxins drugs
Immunological response
Systemic disease
Combined heart–kidney dysfunction
Secondary cardiorenal syndromes (type 5)
Systemic conditions leading to simultaneous injury and/or dysfunction of heart and kidney
Source: Expert Rev Cardiovasc Ther © 2012 Expert Reviews Ltd


Batteries
Pump


sIL-6R
IL-6
IFN-γ
GP130
IL-6R
IFN-γR
Extracellular space
JAK2
JAK2
JAK2
JAK2
P
SOCS3
↓ IFN-δ
↑ IFN-γ
SOCS1
SOCS3
PIAS3
STAT3
STAT1
PIAS3
STAT3
PIAS3
Mitochondrion
Complex I
Complex II
ROS
Apoptosis
Nucleus
Antiapoptotic effects of STAT3 mediated by: iNOS; MnSOD; MT1, MT2; Bcl-xL; mitochondrial stabilization

Renin Angiotensin System Activation

- Decreased renal artery perfusion
- Increased renal venous pressure
- Decreased distal nephron sodium delivery
- Activation of the sympathetic nervous system

All of these occur in ADHF

From: Diuretics and Ultrafiltration in Acute Decompensated Heart Failure

J Am Coll Cardiol. 2012;59(24):2145-2153. doi:10.1016/j.jacc.2011.10.910

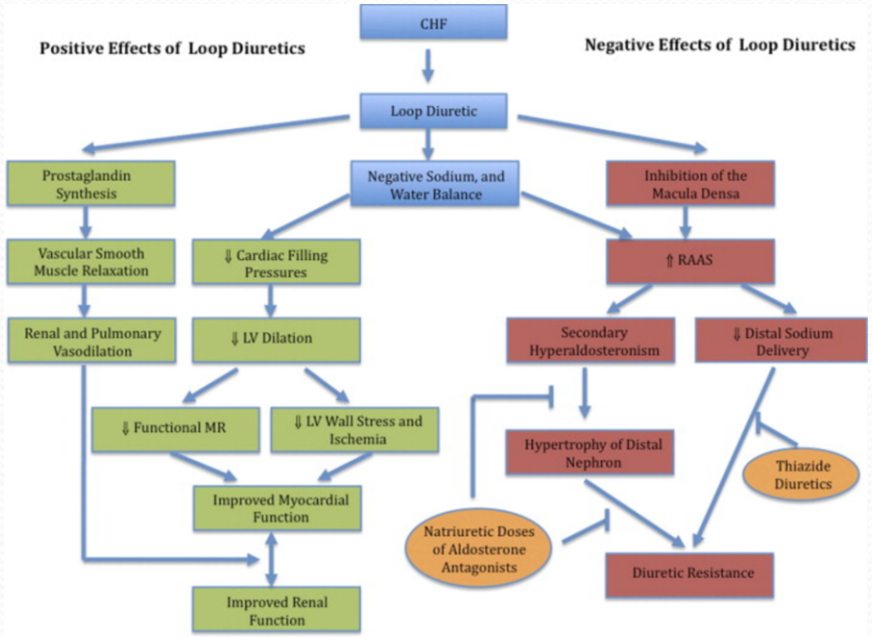
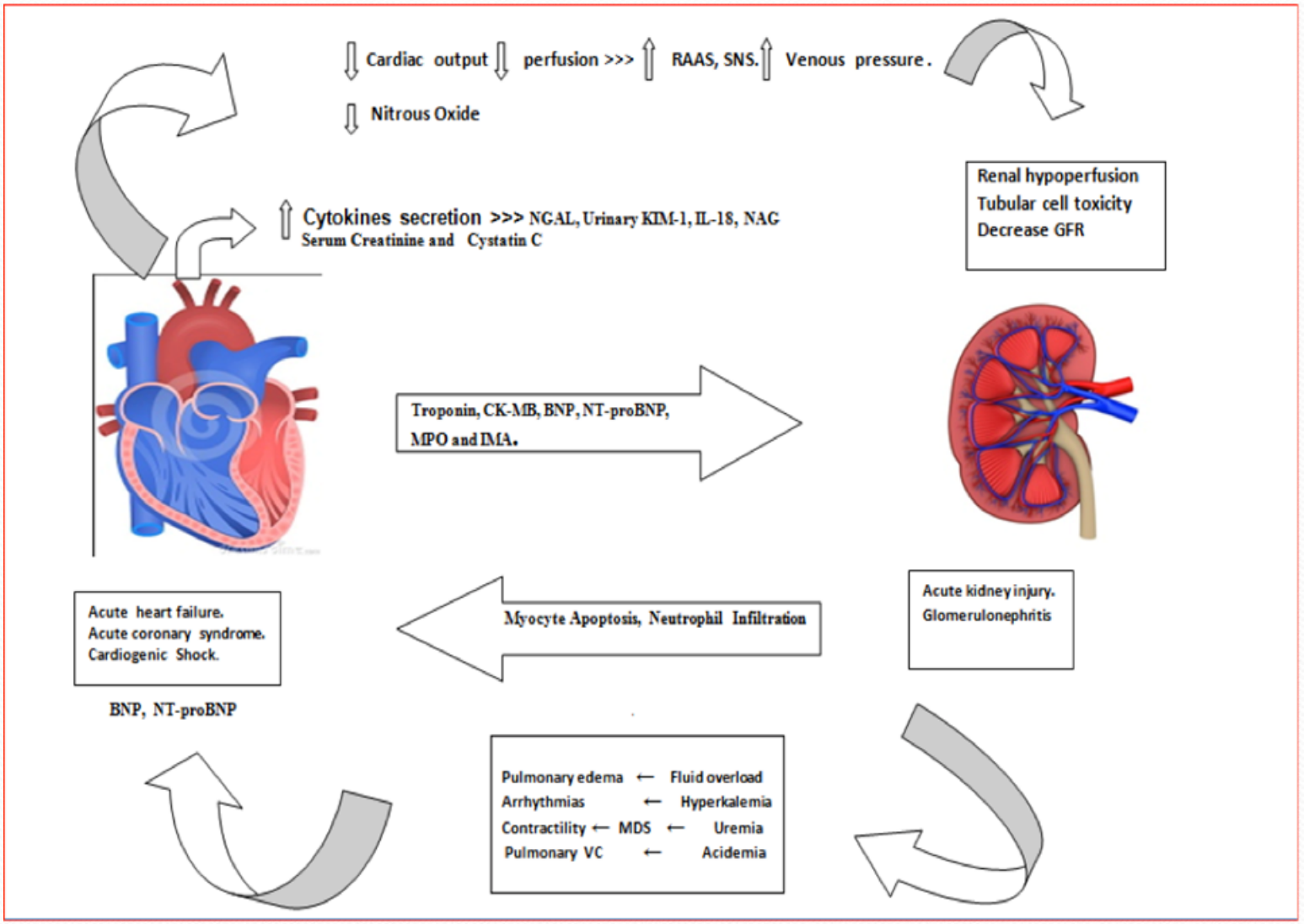


Figure Legend:

Diuretic Mechanisms

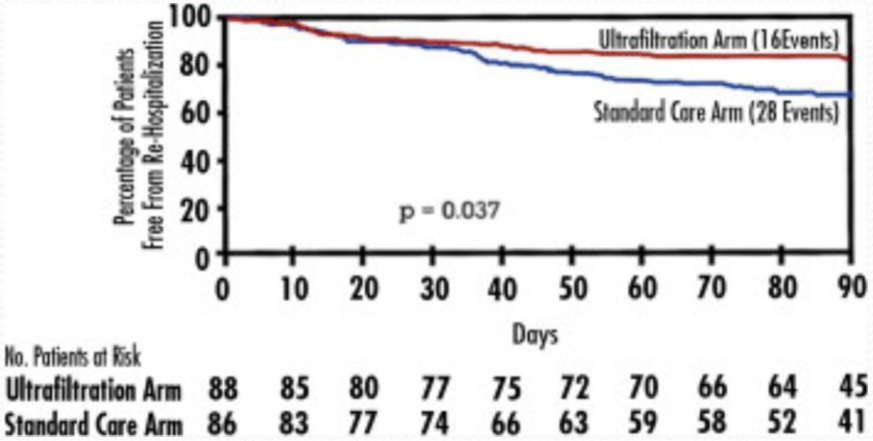
Proposed positive and negative effects of loop diuretics as well as sites of action for thiazide diuretics and natriuretic doses of aldosterone antagonists. CHF = congestive heart failure; LV = left ventricular; MR = mitral regurgitation; RAAS = renin-angiotensin-aldosterone system.


Cardiac output
perfusion >>>
RAAS, SNS.
Venous pressure.
Nitrous Oxide
Renal hypoperfusion
Tubular cell toxicity
Decrease GFR
Cytokines secretion >>> NGAL, Urinary KIM-1, IL-18, NAG
Serum Creatinine and Cystatin C
Troponin, CK-MB, BNP, NT-proBNP,
MPO and IMA.
Acute heart failure.
Acute coronary syndrome.
Cardiogenic Shock.
Myocyte Apoptosis, Neutrophil Infiltration
Acute kidney injury.
Glomerulonephritis
BNP, NT-proBNP
Pulmonary edema ← Fluid overload
Arrhythmias ← Hyperkalemia
Contractility ← MDS ← Uremia
Pulmonary VC ← Acidemia

JACC Journals

From: Diuretics and Ultrafiltration in Acute Decompensated Heart Failure

J Am Coll Cardiol. 2012;59(24):2145-2153. doi:10.1016/j.jacc.2011.10.910



UNLOAD trial
2010

Figure Legend:

Freedom From Heart Failure Rehospitalization

Kaplan-Meier estimate of freedom from rehospitalization for heart failure within 90 days after discharge in the ultrafiltration (red line) and standard care (blue line) groups.

From: Diuretics and Ultrafiltration in Acute Decompensated Heart Failure

J Am Coll Cardiol. 2012;59(24):2145-2153. doi:10.1016/j.jacc.2011.10.910

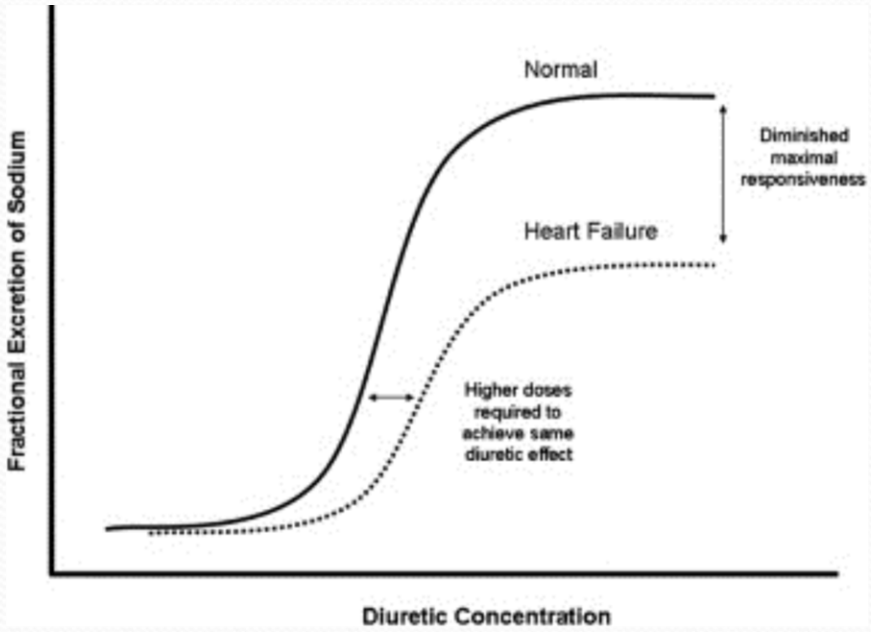
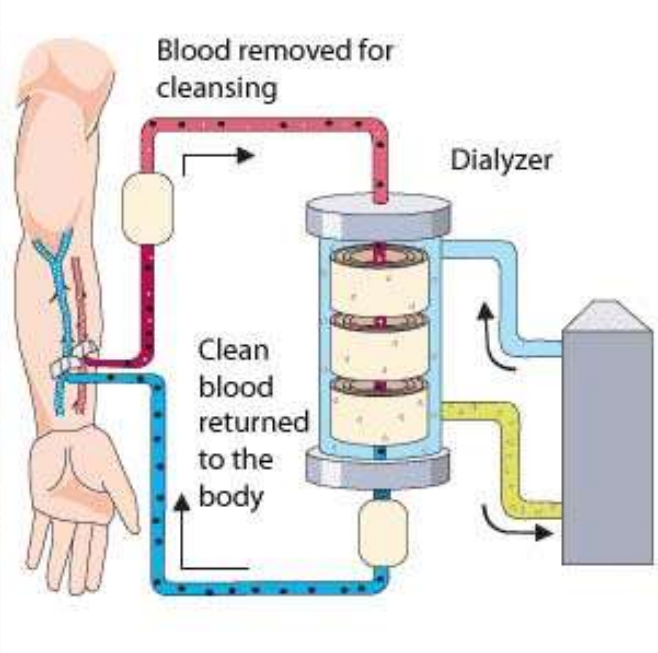


Figure Legend:

Schematic of Dose–Response Curve of Loop Diuretics in Heart Failure Patients Compared With Normal Controls
In heart failure patients, higher doses are required to achieve a given diuretic effect and the maximal effect is blunted.

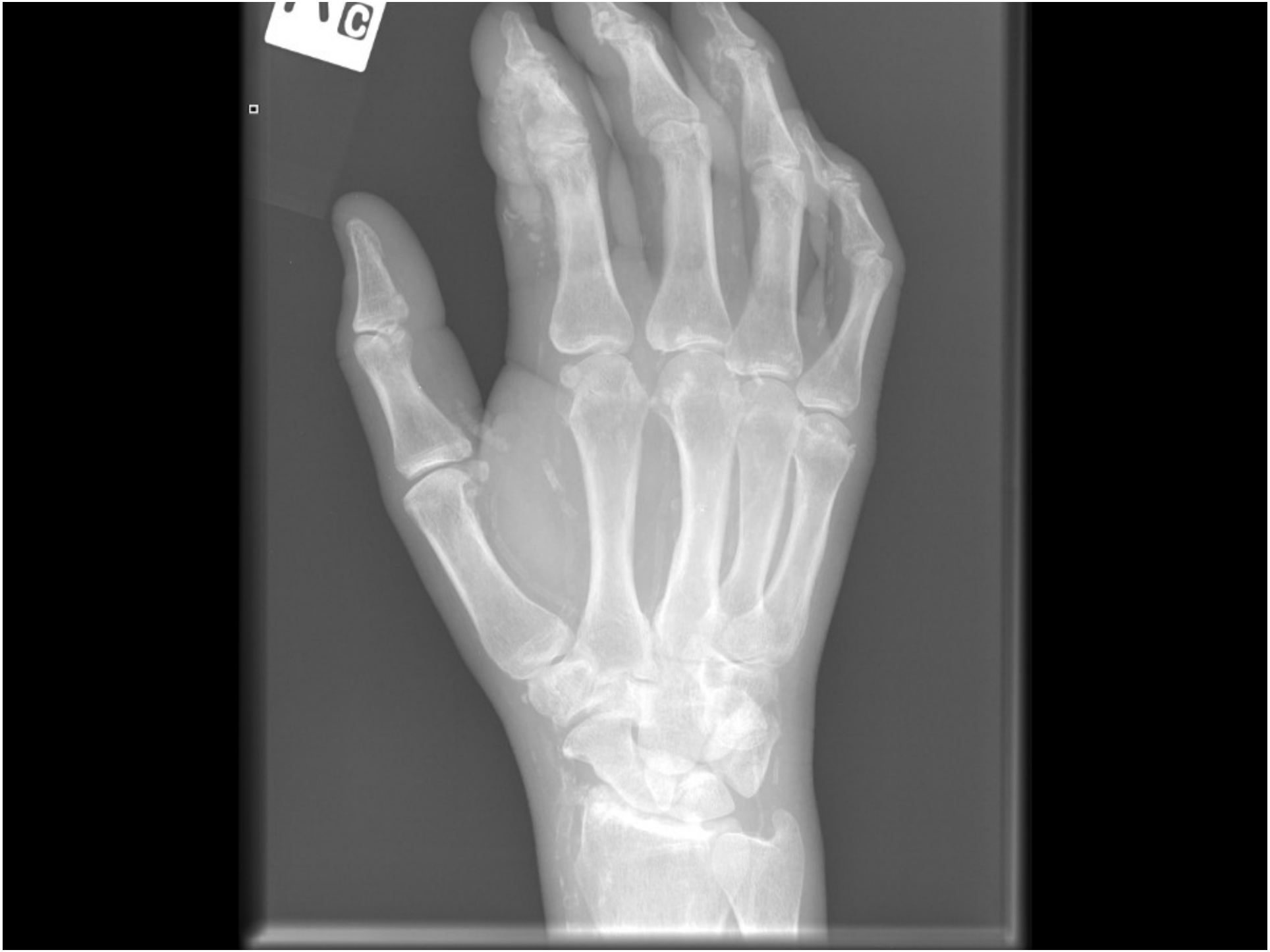


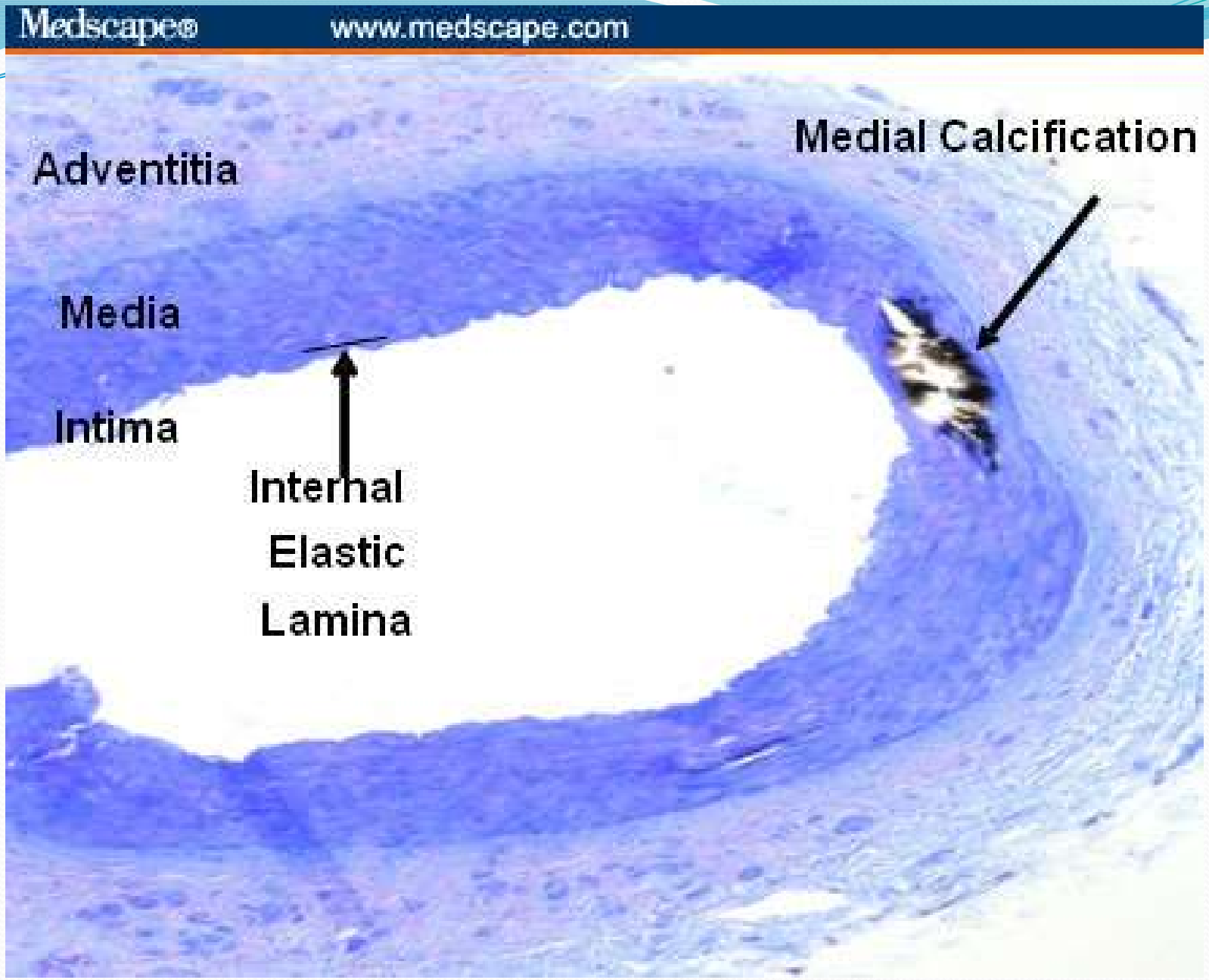
HEMODIALYSIS - over time leads to loss of residual renal function

Intra-dialytic hypotension

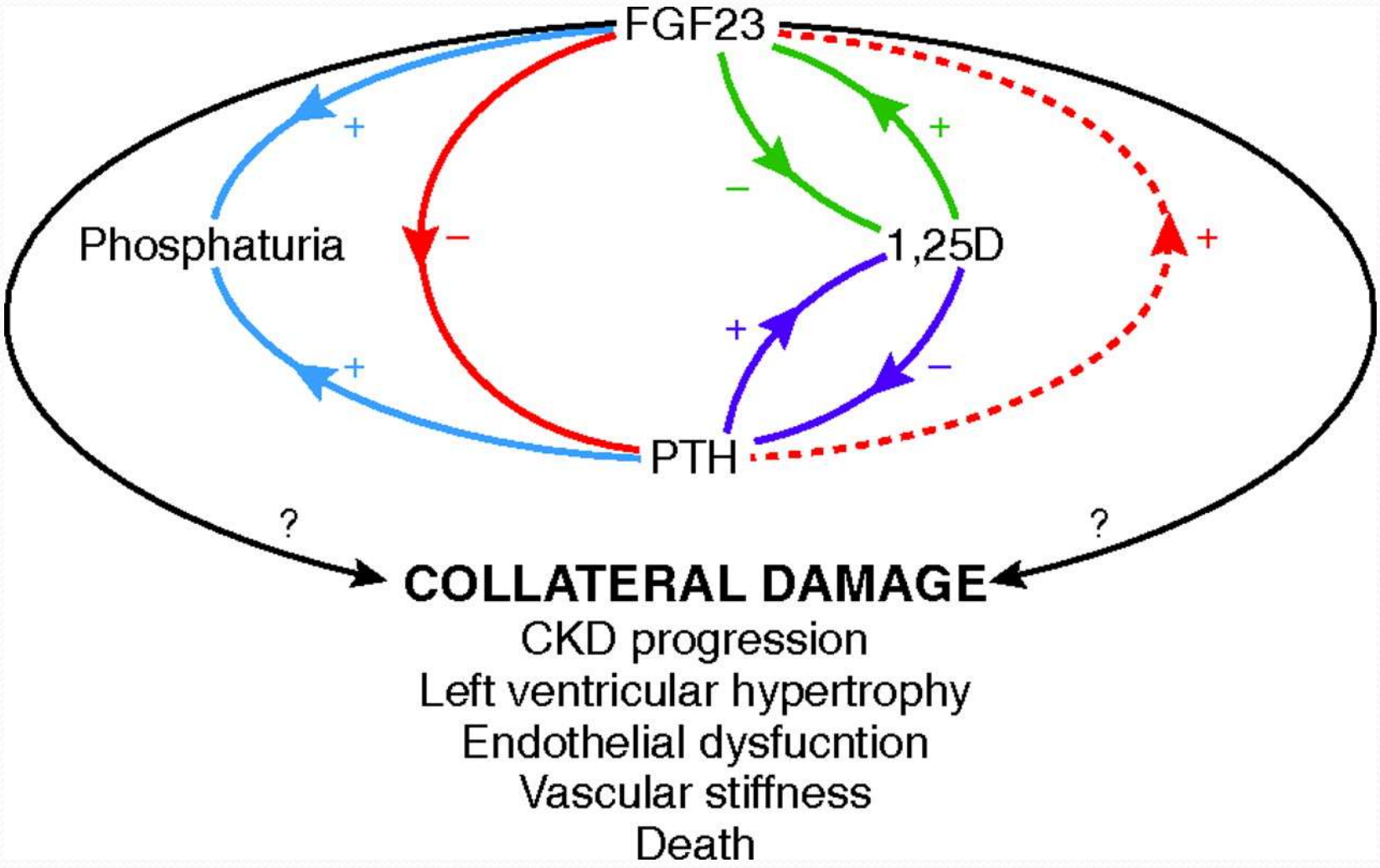
Release of cytokines due to exposure of blood to Membrane

Platelet - platelet and
platelet - leukocyte aggregation




Medscape®
www.medscape.com
Adventitia
Medial Calcification
Media
Intima
Internal
Elastic
Lamina

Collateral Damage from Excess FGF23



Wolf M JASN 2010;21:1427-1435

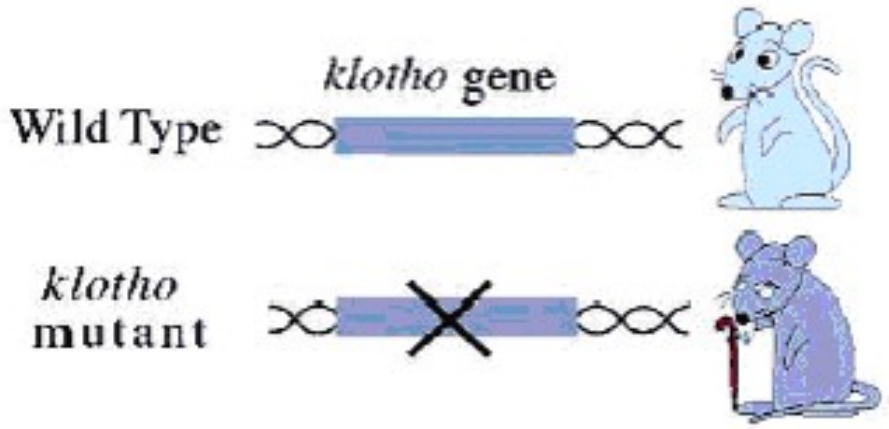
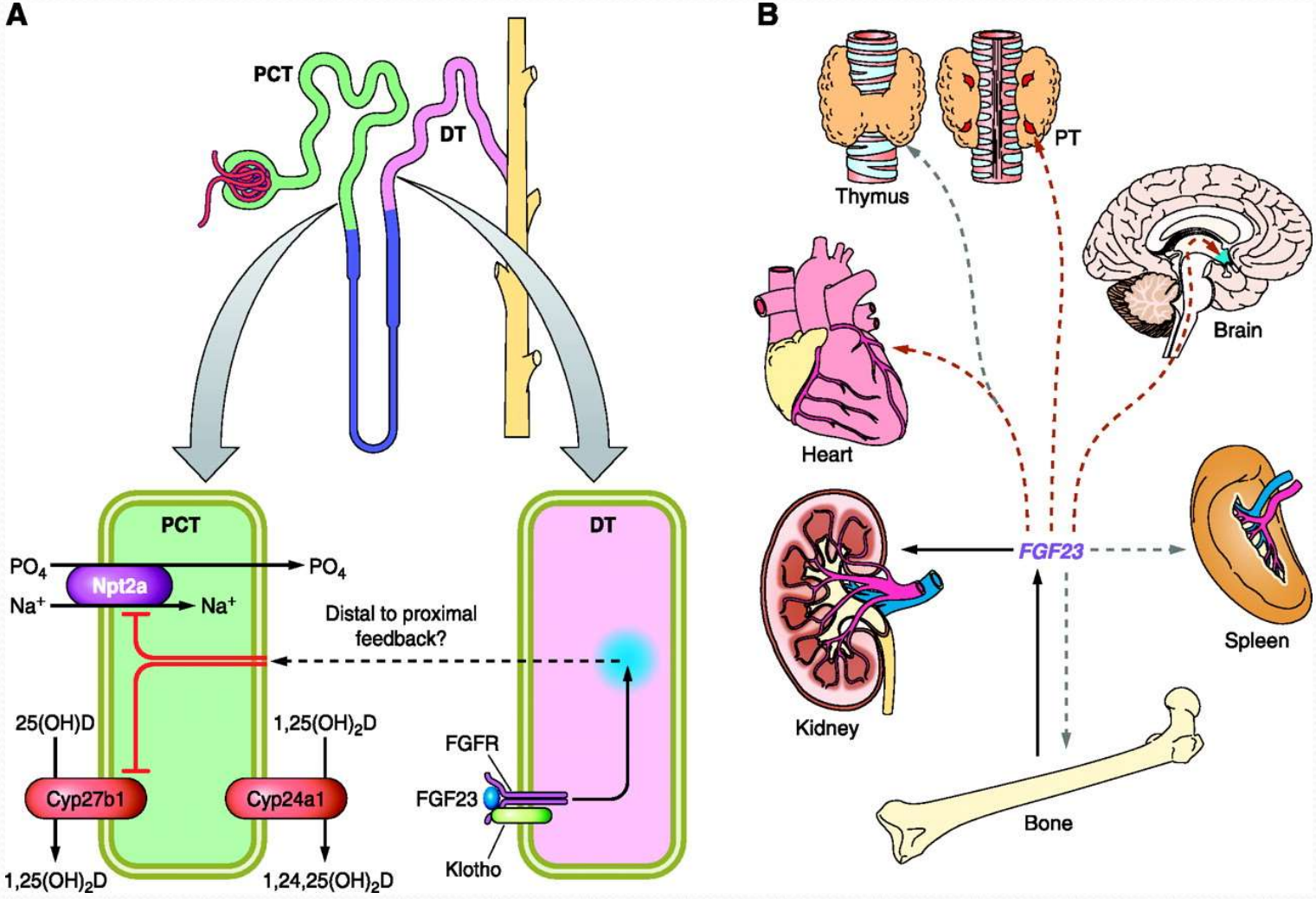


Fig. 1. A mutant model mouse is useful for studies of aging. The *klotho* phenotype (premature aging) is caused by a disruption of the single gene, *klotho*.

Renal and extrarenal functions of FGF23.

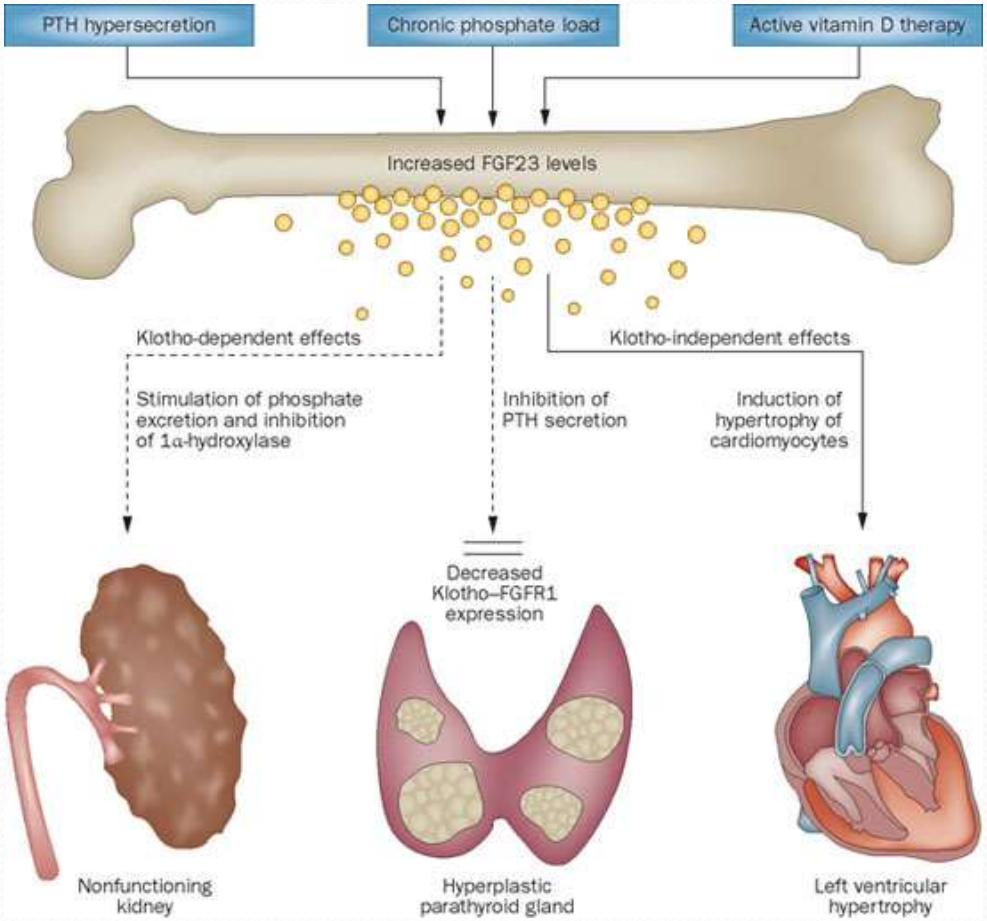


Martin A et al. Physiol Rev 2012;92:131-155

Physiological Reviews

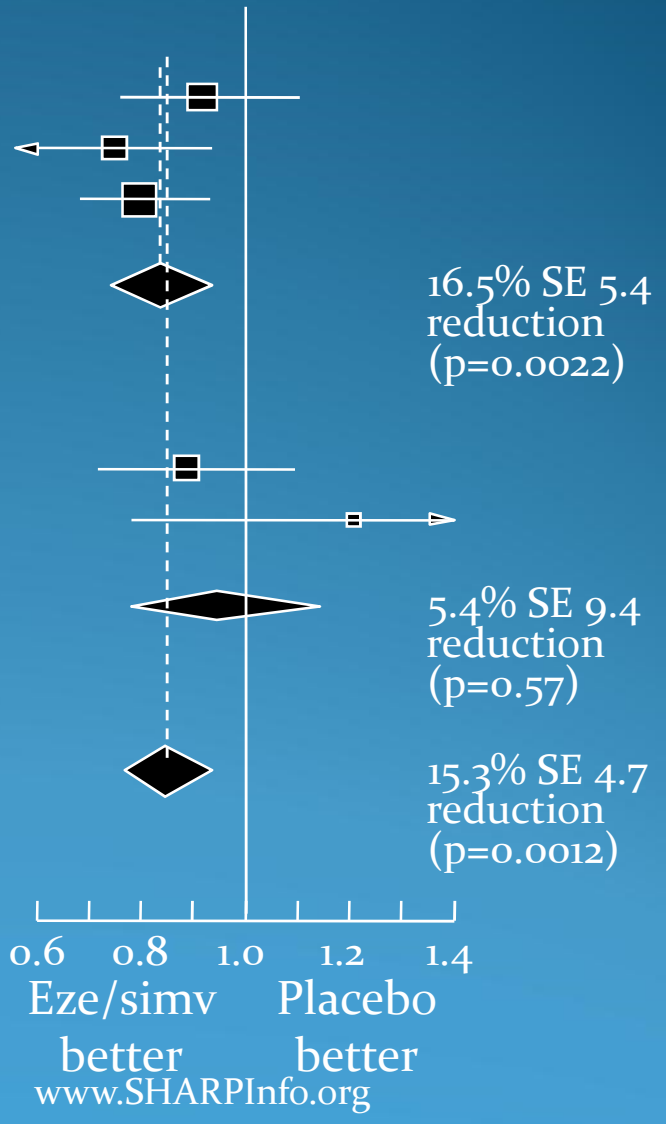
FGF23 Induces Left Ventricular Hypertrophy

- Induces hypertrophy of isolated cardiomyocytes in vitro
- Mice develop LVH with injection of FGF23
- Ascending quartiles of FGF23 associated with significantly increased LV mass index


PTH hypersecretion
Chronic phosphate load
Active vitamin D therapy
Increased FGF23 levels
Klotho-dependent effects
Klotho-independent effects
Stimulation of phosphate excretion and inhibition of 1α-hydroxylase
Inhibition of PTH secretion
Induction of hypertrophy of cardiomyocytes
Decreased Klotho–FGFR1 expression
Nonfunctioning kidney
Hyperplastic parathyroid gland
Left ventricular hypertrophy

SHARP: Major Atherosclerotic Events

Event	Eze/simv (n=4650)		Placebo (n=4620)	
Major coronary event	213	(4.6%)	230	(5.0%)
Non-hemorrhagic stroke	131	(2.8%)	174	(3.8%)
Any revascularization	284	(6.1%)	352	(7.6%)
Major atherosclerotic event	526	(11.3%)	619	(13.4%)
Other cardiac death	162	(3.5%)	182	(3.9%)
Hemorrhagic stroke	45	(1.0%)	37	(0.8%)
Other major vascular events	207	(4.5%)	218	(4.7%)
Major vascular event	701	(15.1%)	814	(17.6%)

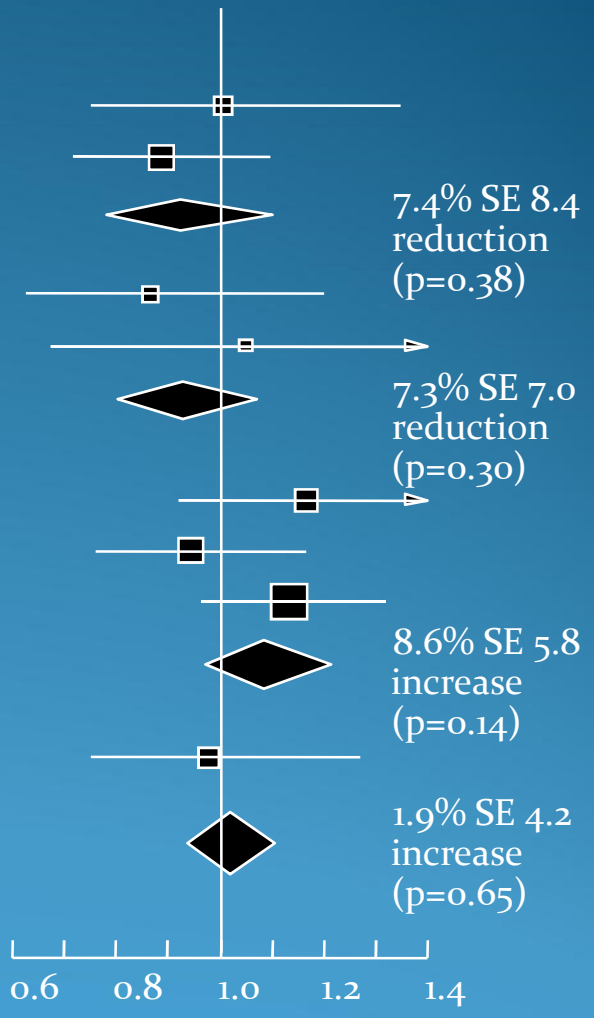


SHARP
STUDY OF HEART AND RENAL PROTECTION

www.SHARPInfo.org

SHARP: Cause-specific mortality

Event	Eze/simv (n=4650)		Placebo (n=4620)	
Coronary	91	(2.0%)	90	(1.9%)
Other cardiac	162	(3.5%)	182	(3.9%)
Subtotal: Any cardiac	253	(5.4%)	272	(5.9%)
Stroke	68	(1.5%)	78	(1.7%)
Other vascular	40	(0.9%)	38	(0.8%)
Subtotal: Any vascular	361	(7.8%)	388	(8.4%)
Cancer	150	(3.2%)	128	(2.8%)
Renal	164	(3.5%)	173	(3.7%)
Other non-vascular	354	(7.6%)	311	(6.7%)
Subtotal: Any non-vascular	668	(14.4%)	612	(13.2%)
Unknown cause	113	(2.4%)	115	(2.5%)
Total: Any death	1142	(24.6%)	1115	(24.1%)



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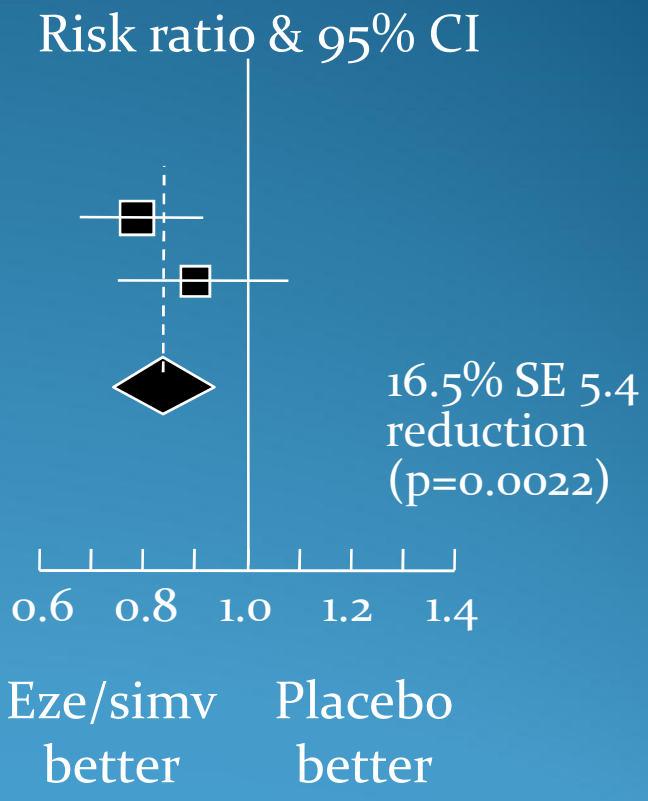
SHARP: Major Atherosclerotic Events by renal status at randomization

	Eze/simv (n=4650)	Placebo (n=4620)
Non-dialysis (n=6247)	296 (9.5%)	373 (11.9%)
Dialysis (n=3023)	230 (15.0%)	246 (16.5%)
Major atherosclerotic event	526 (11.3%)	619 (13.4%)



No significant heterogeneity between non-dialysis and dialysis patients (p=0.25)

SHARP
STUDY OF HEART AND RENAL PROTECTION

www.SHARPInfo.org

Objectives

- 1. To better understand the relationship between cardiac and renal disease and the pathophysiological mechanisms involved
- To review benefits and challenges of therapies

Renal blood flow and GFR
decrease significantly when
MAP falls below 60

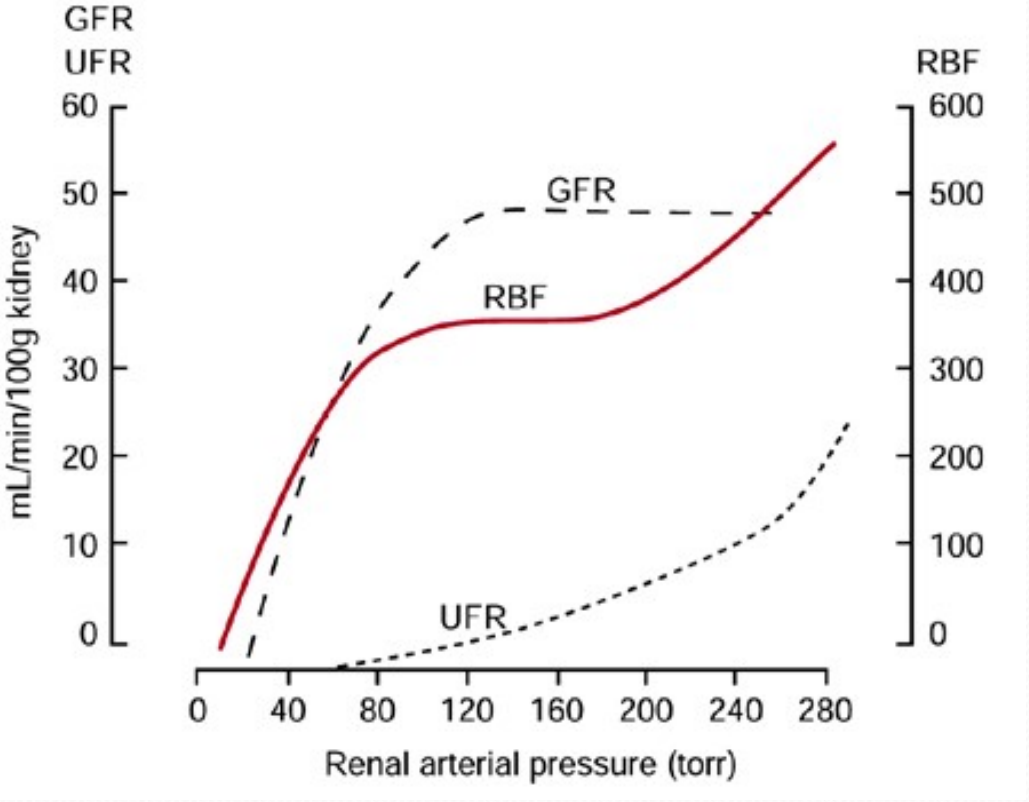
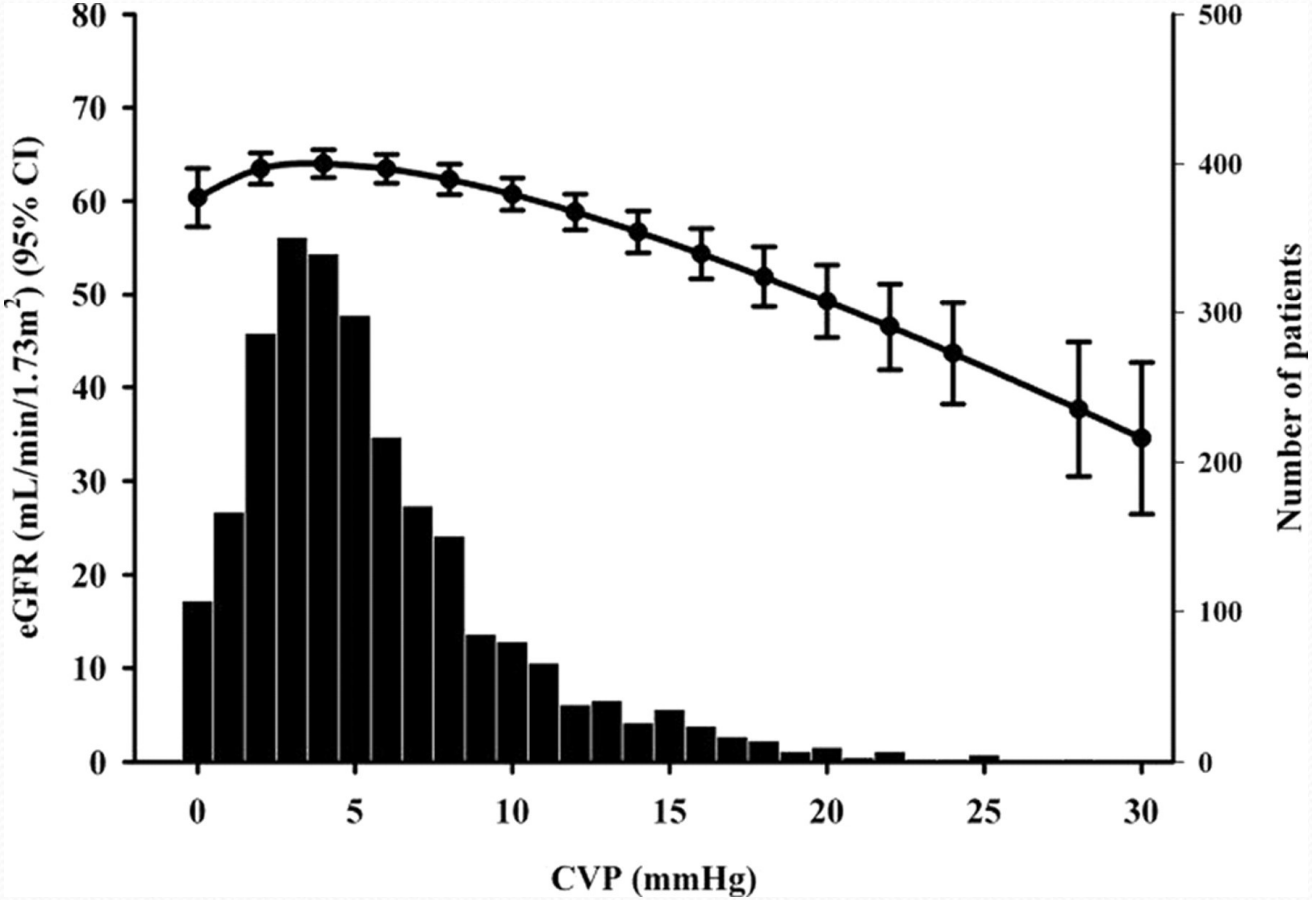


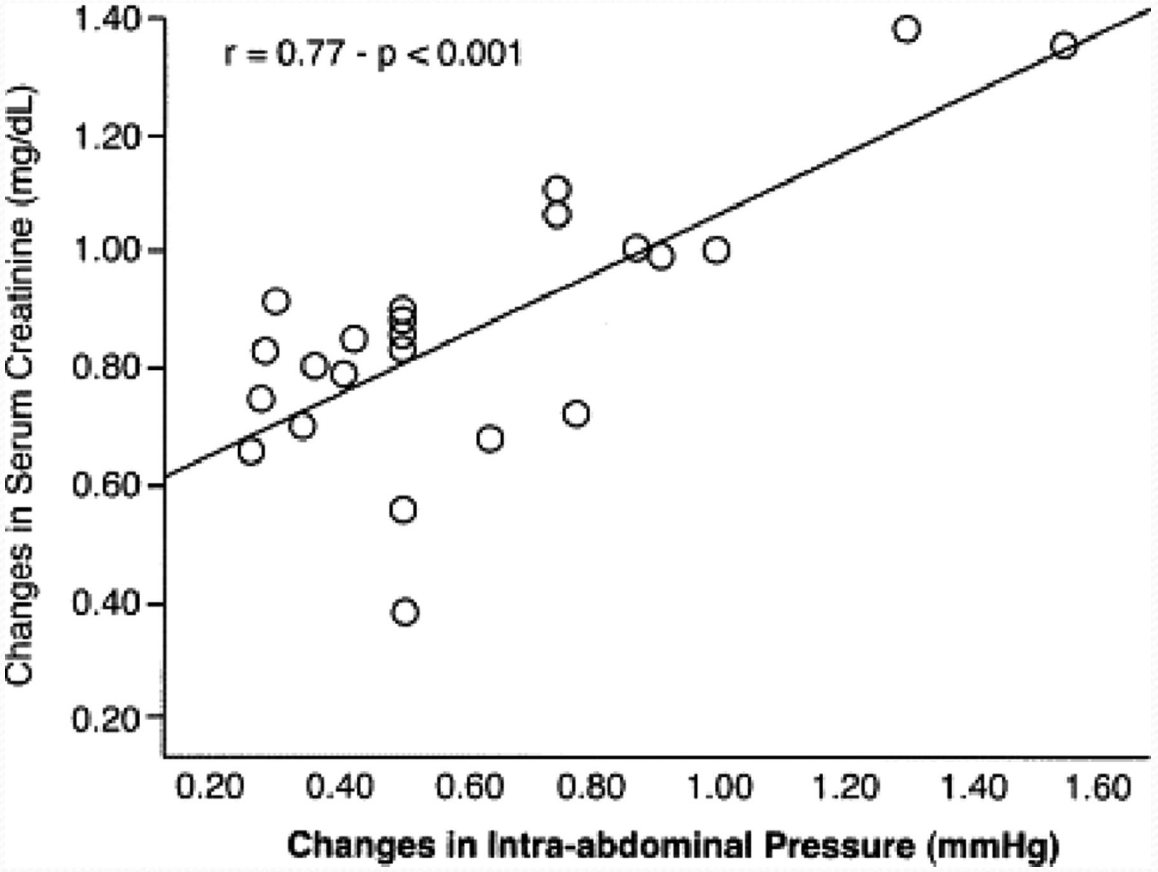
Figure 3. Distribution of central venous pressure (CVP) and the relationship between CVP and estimated GFR in 2557 patients.



American Heart Association.

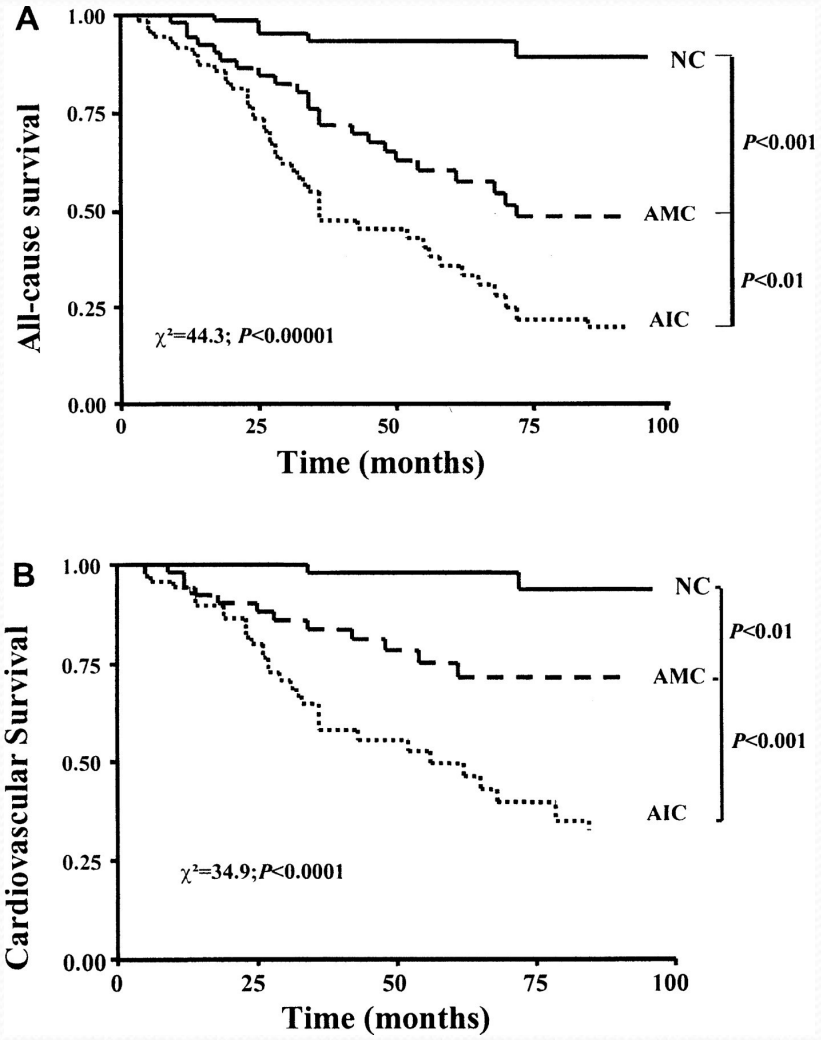
Bock J S , and Gottlieb S S *Circulation*. 2010;121:2592-2600

Figure 2. The relationship between changes in IAP with diuresis and the change in serum creatinine.



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

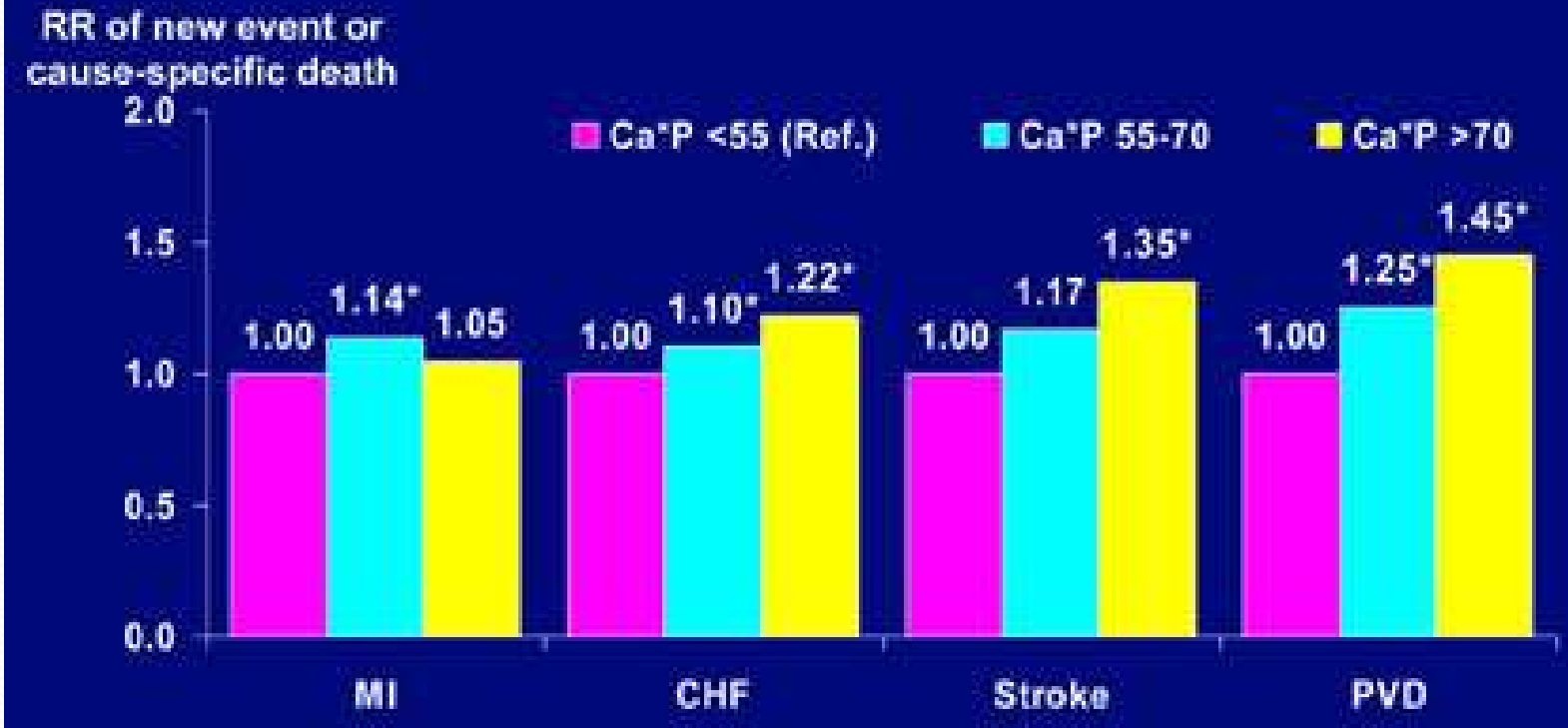
All-cause (A) and CV mortality (B) of ESRD patients as a function of their arterial calcification status.



London G M et al. Nephrol. Dial. Transplant. 2003;18:1731-1740

NDT Nephrology Dialysis Transplantation

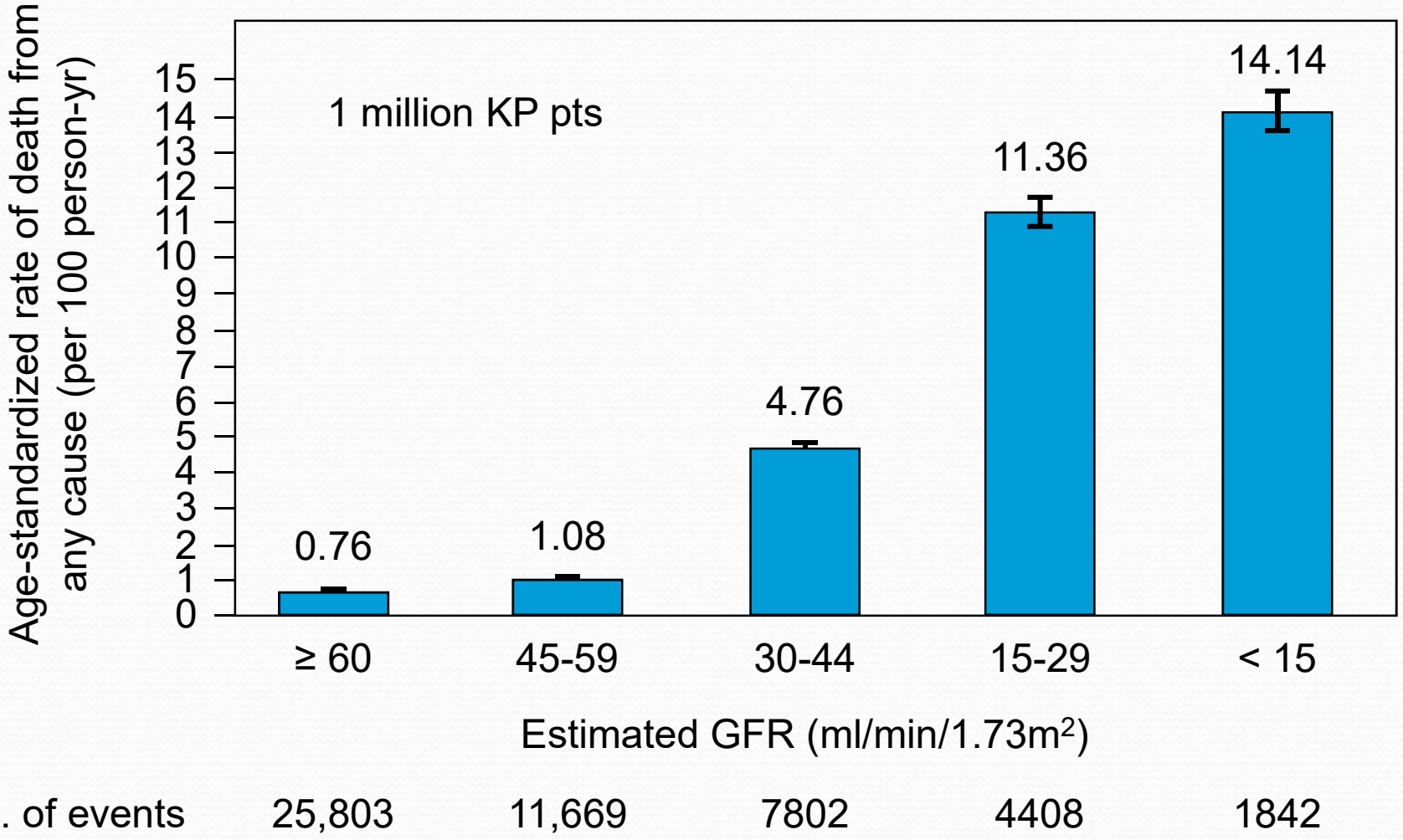
Association of Baseline Ca*P Levels With Incidence of New Cardiovascular Events



DOPPS

*p-value ≤0.03 ; adjusted for age, sex, race, years on dialysis, hemoglobin, albumin, Ca*P, and 14 comorbid conditions; stratified by region (US, Japan, Europe/Australia-New Zealand/Canada)

Mortality increases as GFR declines



Go et al. NEJM 2004; 351:1296-305

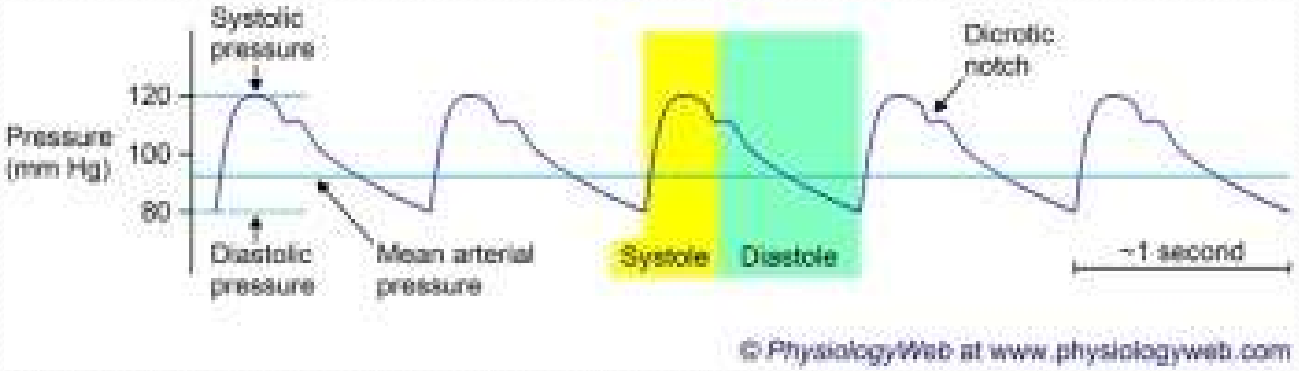
Our patients with LVAD's

- Patients like Mr B whose renal function stabilized
- Patients who have been on hemodialysis, went on to have heart transplant and then later a kidney transplant
- Mrs S who was on hemodialysis and has now changed to peritoneal dialysis
- Mr N. who was on dialysis in remote community unit and recently had a combined heart kidney transplant

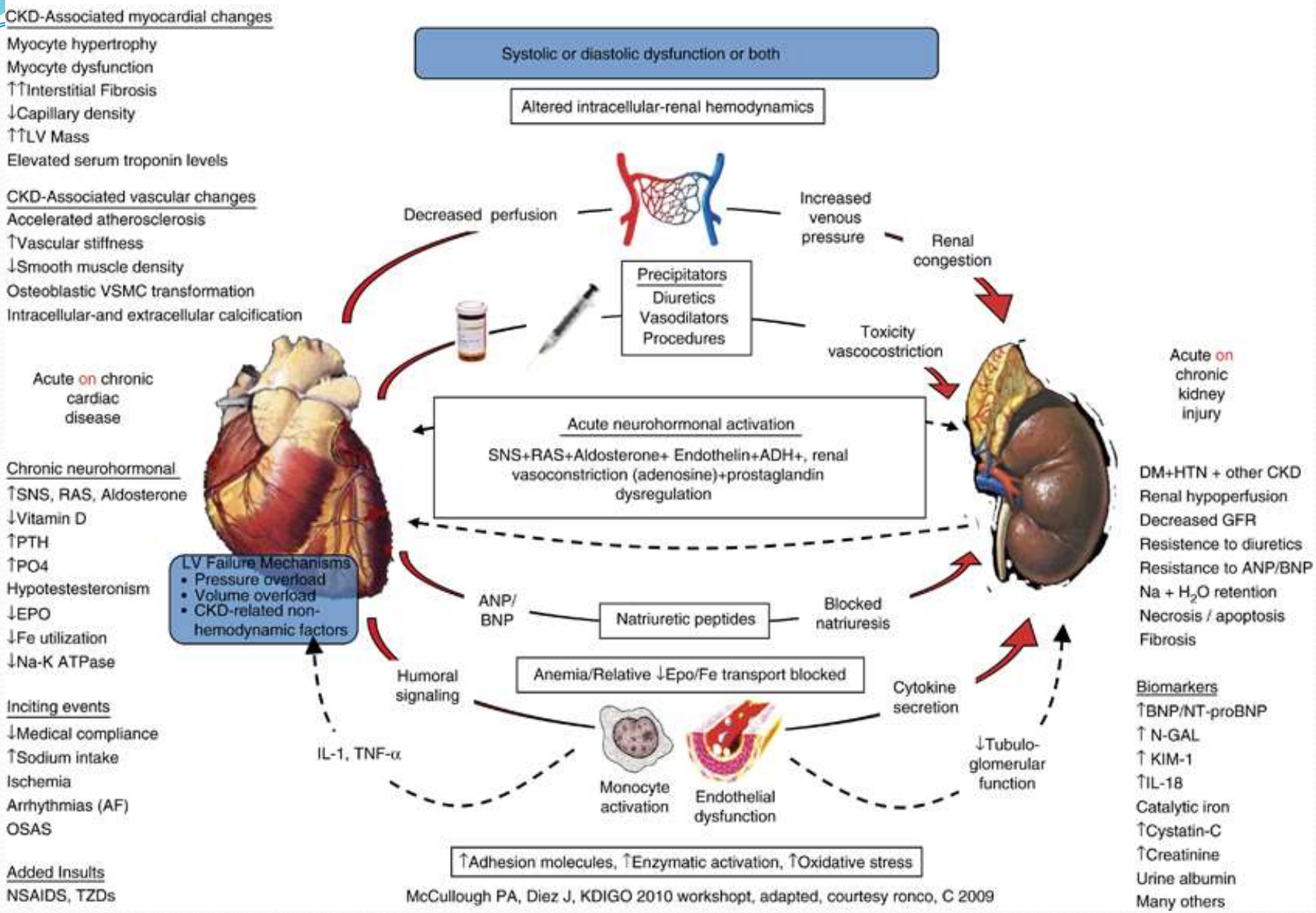
Mean arterial pressure

MAP = Pdiastolic+ 1/3 pulse pressure (Psystolic –Pdiastolic)

$$MAP = \frac{Psystolic + 2(Pdiastolic)}{3}$$

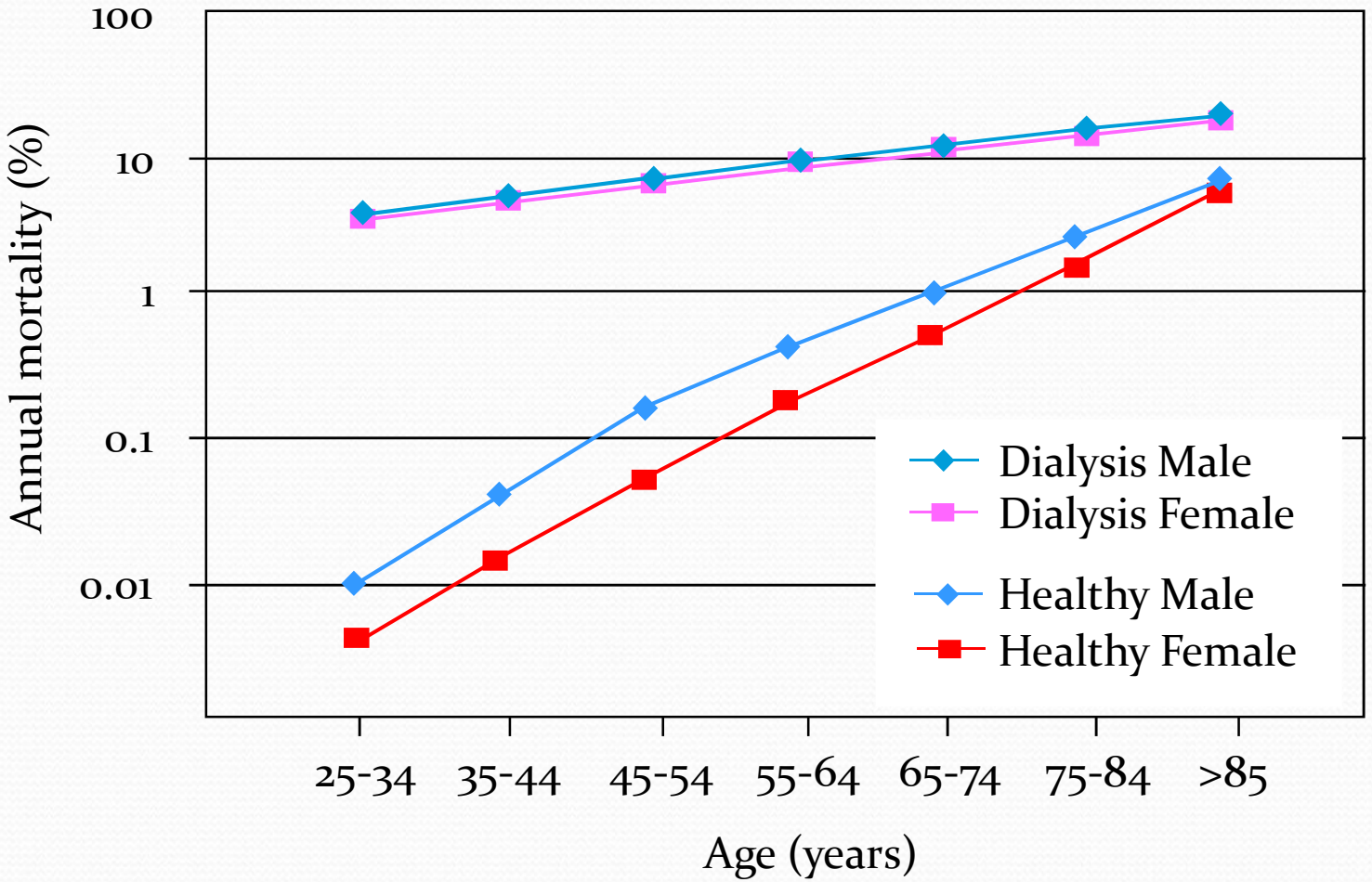


Cardio-renal syndrome pathophysiology

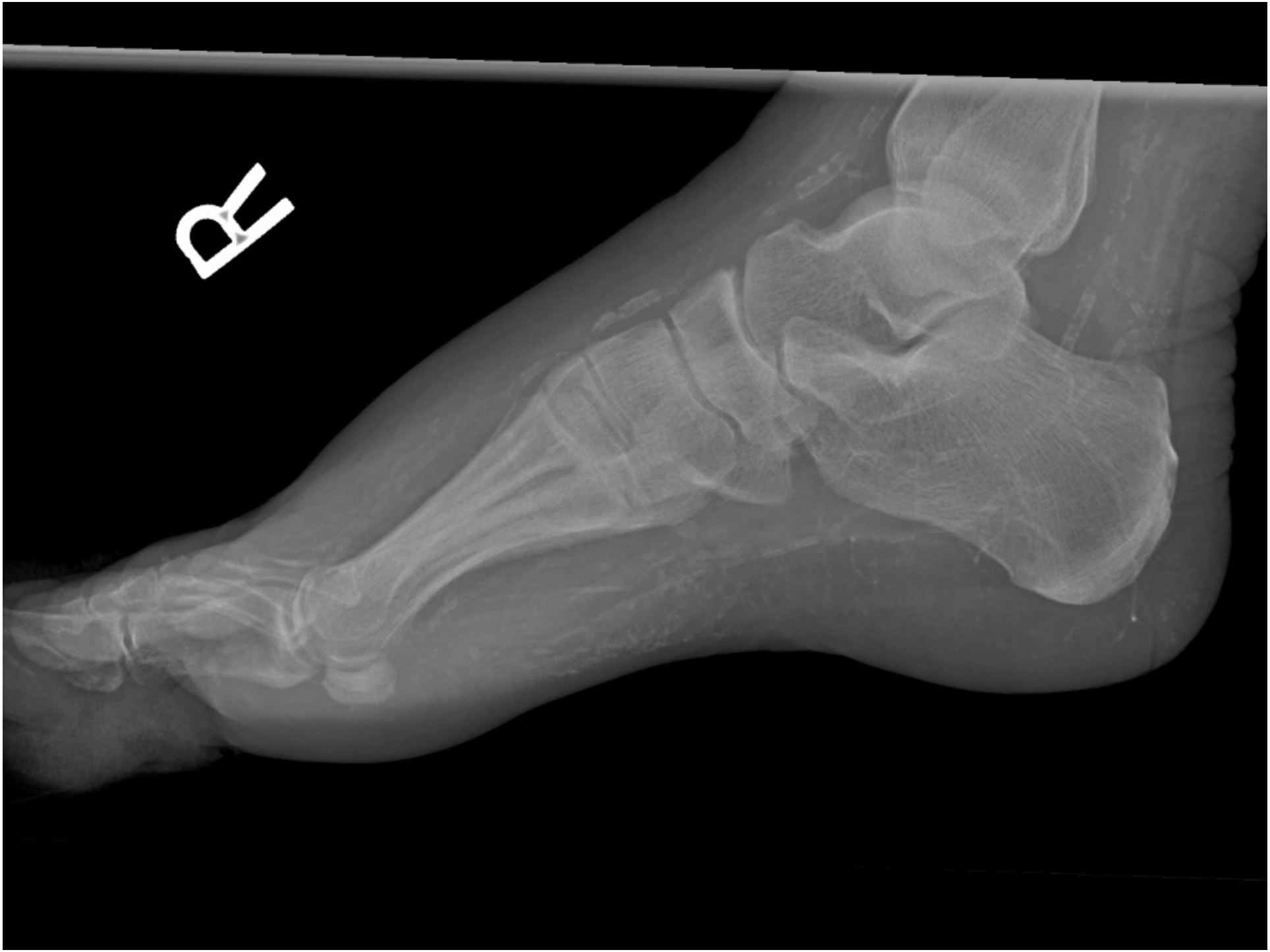


McCullough PA, Diez J, KDIGO 2010 workshopt, adapted, courtesy ronco, C 2009

Epidemiology of cardiovascular disease in haemodialysis patients



Foley et al. AJKD 1998; 32:S112-9



Fibroblast Growth Factor 23
FGF23

- Phosphate regulating hormone synthesized by osteoclasts and osteoblasts in bone

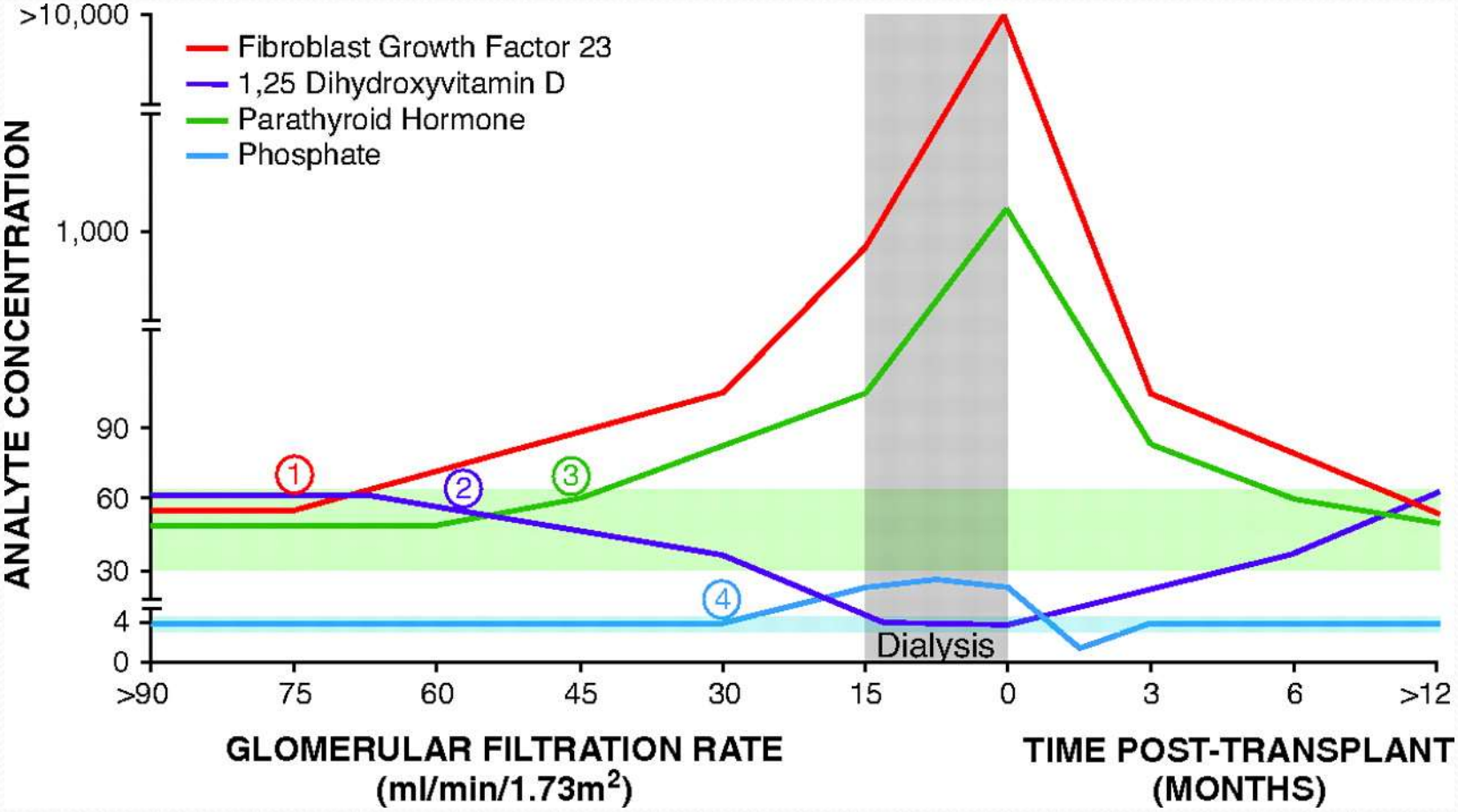
- Phosphate, 1,25 (OH)2D and PTH all activate the promoter of the gene and cause an increase circulating levels of FGF23

Fibroblast Growth Factor 23
FGF23

- Promotes phosphate excretion by the kidney and therefore links bone phosphate flux to kidney handling of phosphate

- Has important biological roles: e.g. Congenital excess (gene mutation) is linked to autosomal dominant hypophosphatemic rickets

Temporal aspects of disordered phosphorus metabolism in progressive CKD and after kidney transplantation.

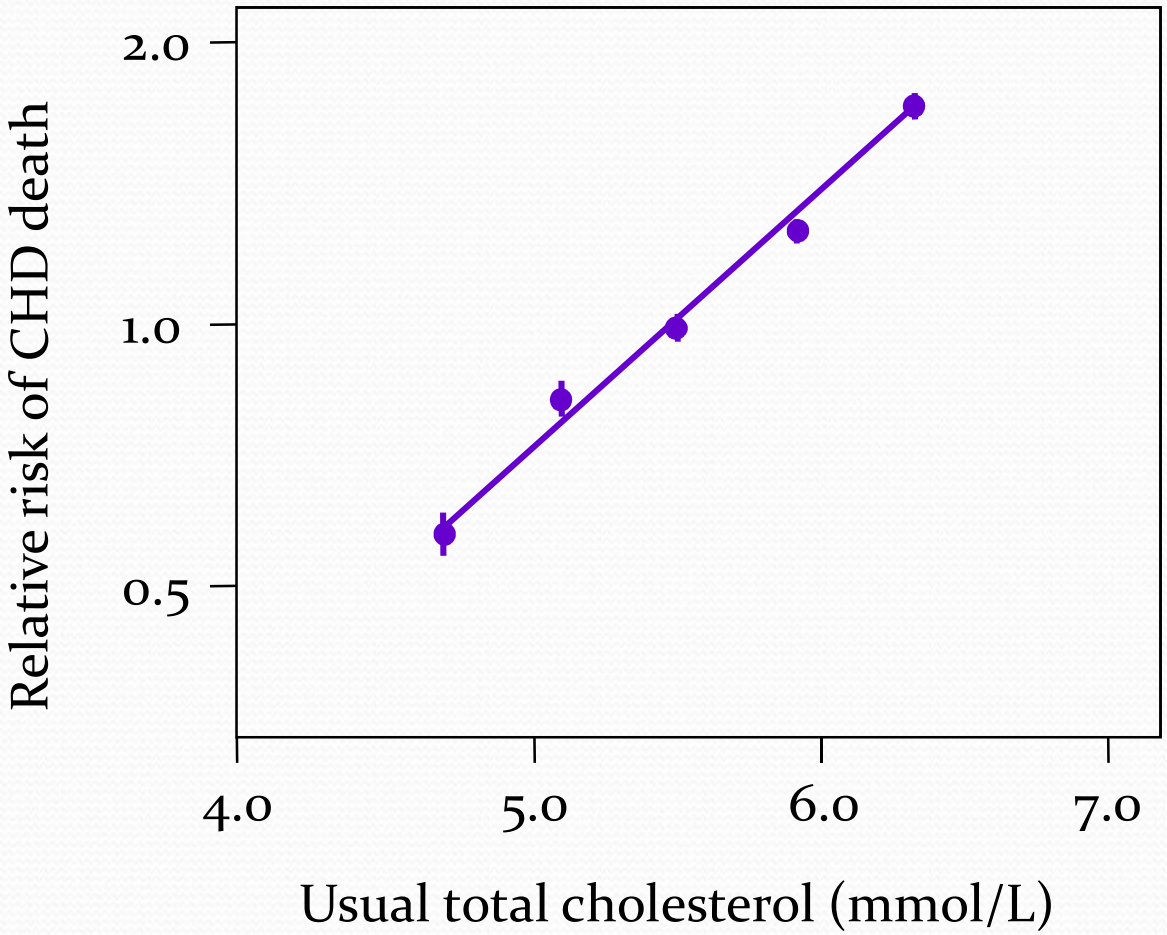


Wolf M JASN 2010;21:1427-1435

Functions of Klotho

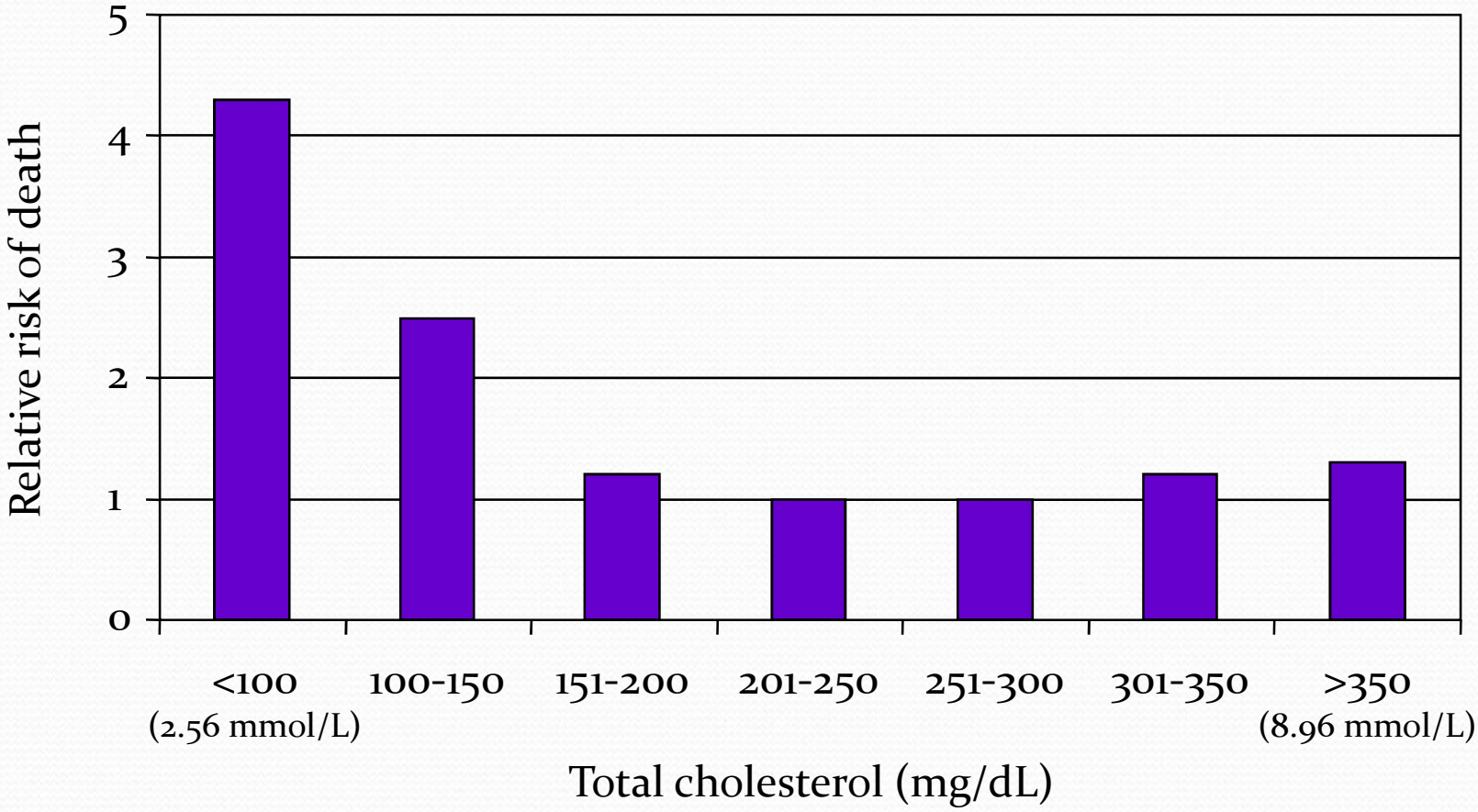
- Cofactor in FGF23 signalling (membrane)
- Enzymatic activity modulating calcium transporters in the kidney promoting reabsorption of Ca (shed or soluble forms)
- Has direct effects to inhibit the NaPi cotransporter causing phosphaturia
- Protective effect against oxidative stress by increasing the expression of superoxide desmutase

Total cholesterol and CV mortality among 350,000 men: MRFIT prospective study



Martin et al. Lancet 1986; 2(8513):933-36

Total cholesterol and all-cause mortality among 12,000 haemodialysis patients



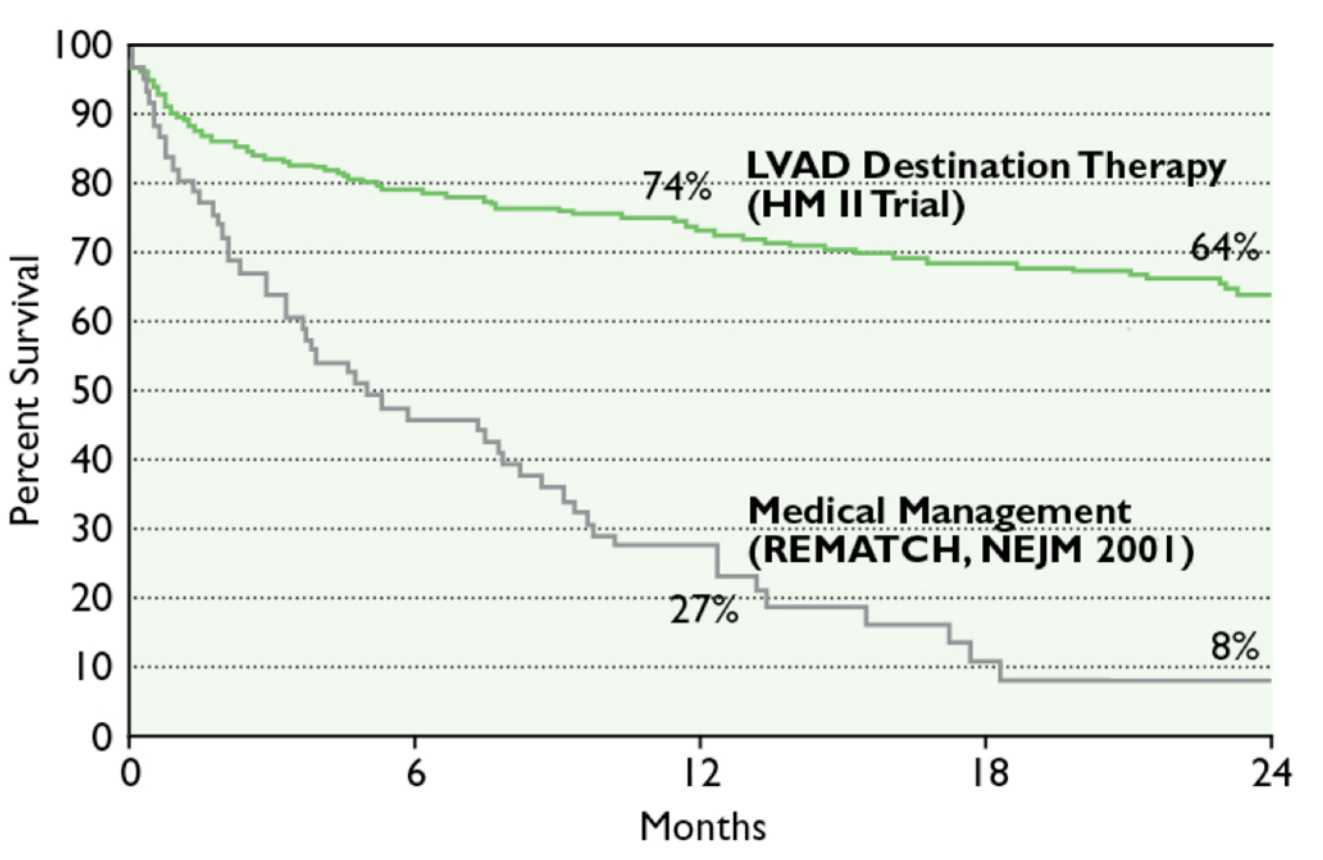
Lowrie & Lew AJKD 1990; 15:458-82

Large-scale statin studies enrolling CKD patients

- ALERT
  - 2100 renal transplant patients
  - Fluvastatin *vs*. placebo; mean FU 5.1 years
  - Results published Lancet June 2003
- 4D
  - 1300 diabetic haemodialysis patients
  - Atorvastatin *vs*. placebo
  - Results published NEJM June 2005
- AURORA
  - 2700 haemodialysis patients
  - Rosuvastatin *vs*. placebo
  - Results published in NEJM April 2009 .
- SHARP
  - Pre-dialysis 6247 patients : dialysis 3023
  - Ezetimibe 10 mg/simvastatin 20 mg *vs*. placebo
  - Lancet 2011 vol 377

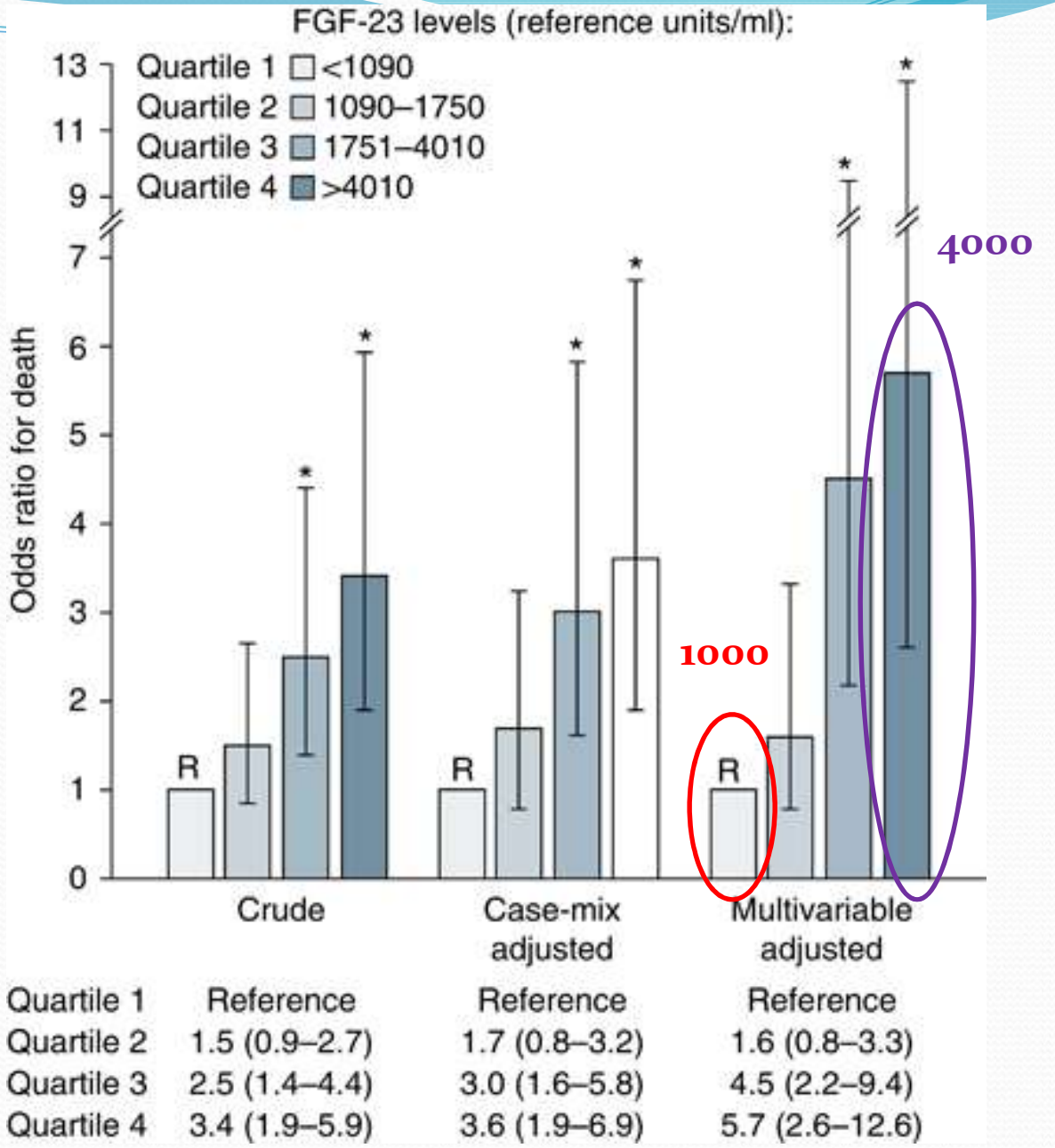
LVAD can be used as:

- Bridge to recovery
- Bridge to heart transplant
- Destination therapy



FGF-23 in CKD

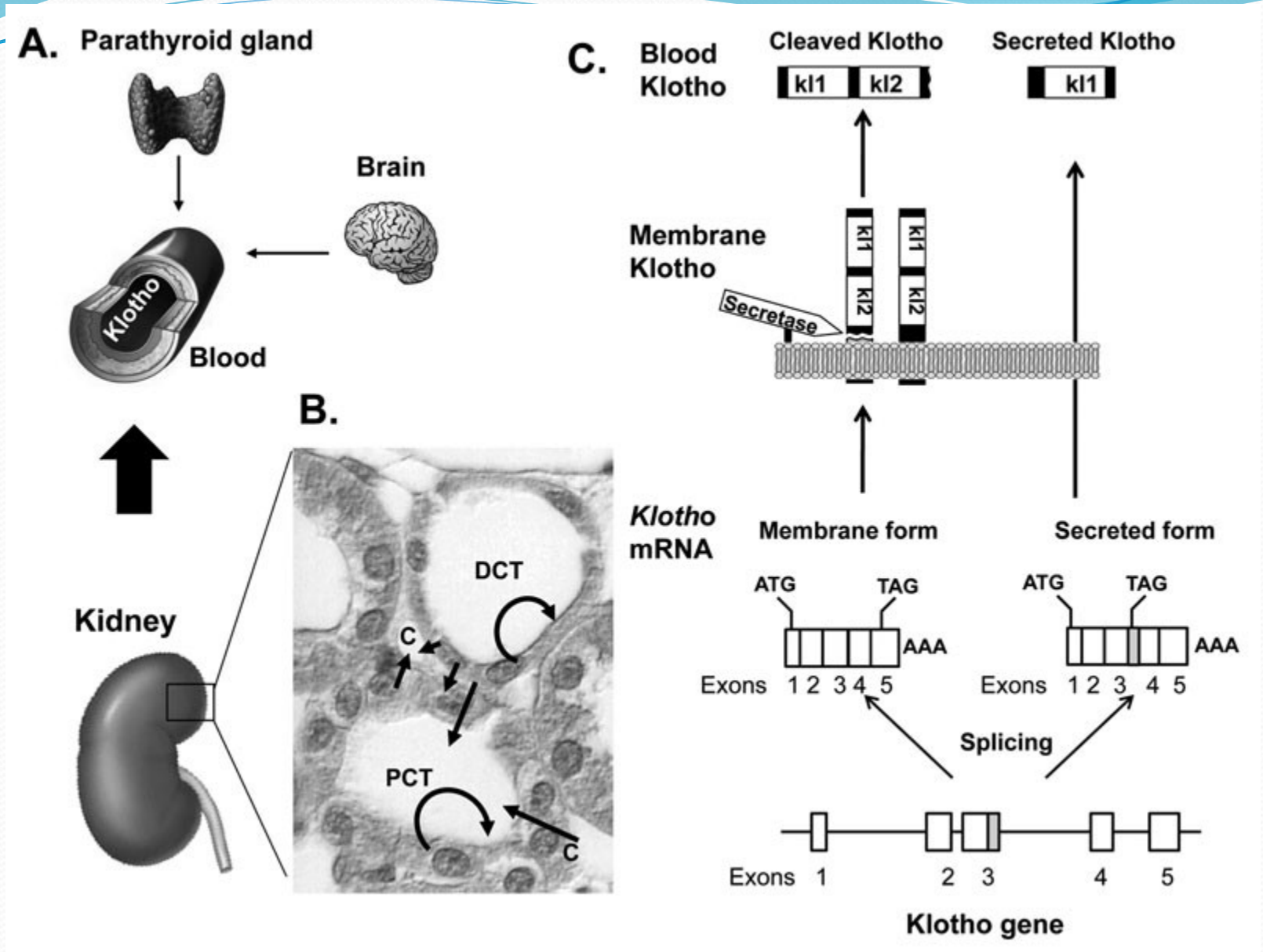
Kidney Inter Suppl
2011;1:130-135



	Crude	Case-mix adjusted	Multivariable adjusted
Quartile 1	Reference	Reference	Reference
Quartile 2	1.5 (0.9–2.7)	1.7 (0.8–3.2)	1.6 (0.8–3.3)
Quartile 3	2.5 (1.4–4.4)	3.0 (1.6–5.8)	4.5 (2.2–9.4)
Quartile 4	3.4 (1.9–5.9)	3.6 (1.9–6.9)	5.7 (2.6–12.6)

Klotho

Wall in Berlin Cemetery


A.
Parathyroid gland
Brain
Klotho
Blood
Kidney
B.
DCT
C
PCT
C
C.
Blood Klotho
Cleaved Klotho
Secreted Klotho
kl1
kl2
kl1
Membrane Klotho
kl1
kl2
kl1
kl2
Secretase
Klotho mRNA
Membrane form
Secreted form
ATG
TAG
AAA
Exons 1 2 3 4 5
ATG
TAG
AAA
Exons 1 2 3 4 5
Splicing
Exons 1 2 3 4 5
Klotho gene

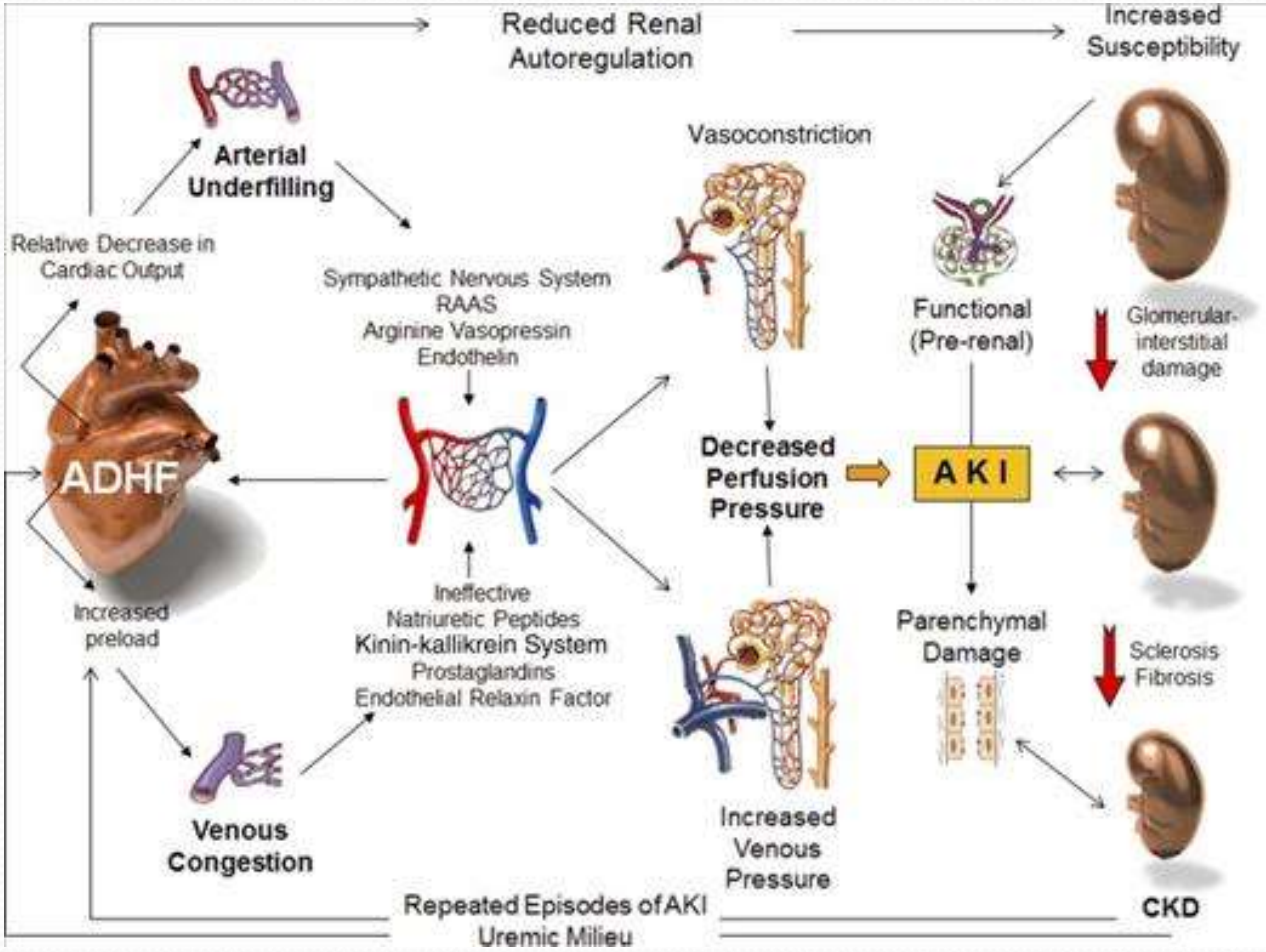
Outline: cardio-renal challenges

- Review epidemiology and basic pathophysiology cardio-renal syndrome – primarily addressing acute decompensated heart failure (ADHF)
- Present the case of a patient who underwent most of the available treatments for ADHF
- A review of some of those treatments especially the ones which involve the nephrology team

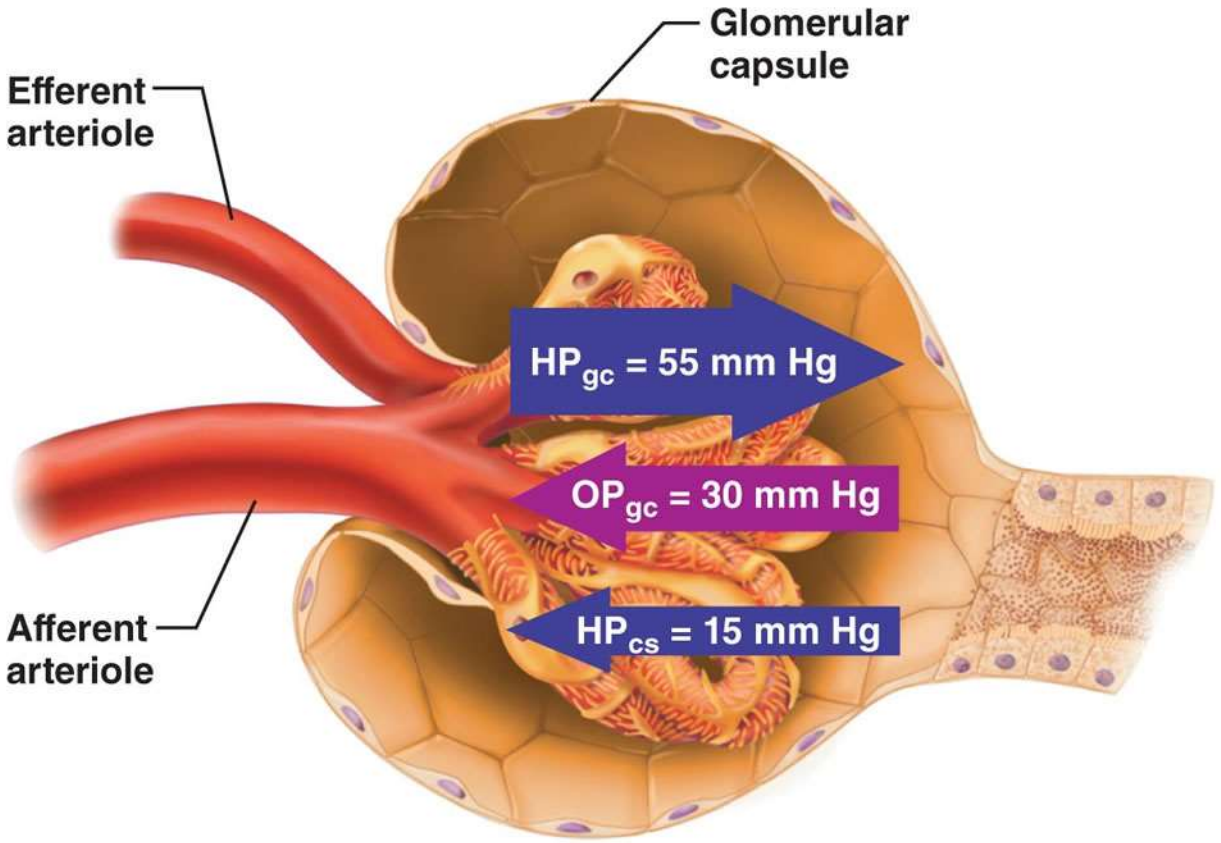
Outline: reno-cardiac challenges

- Case presentation of dialysis patient with extensive cardiac disease and vascular disease
- Review of the pathophysiology of vascular disease in patients with CKD and ESRF
- Review of some of the therapeutic options

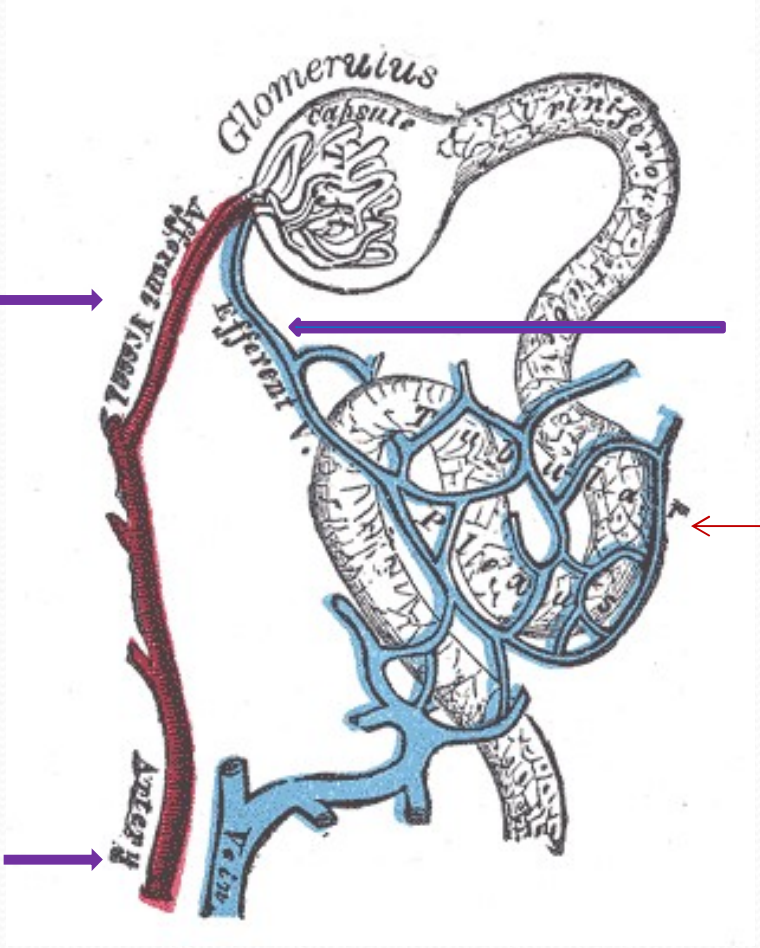
Decreased forward flow



Venous congestion



NFP = Net filtration pressure
= outward pressures – inward pressures
= $(HP_{gc}) – (HP_{cs} + OP_{gc})$
= (55) – (15 + 30)
= 10 mm Hg



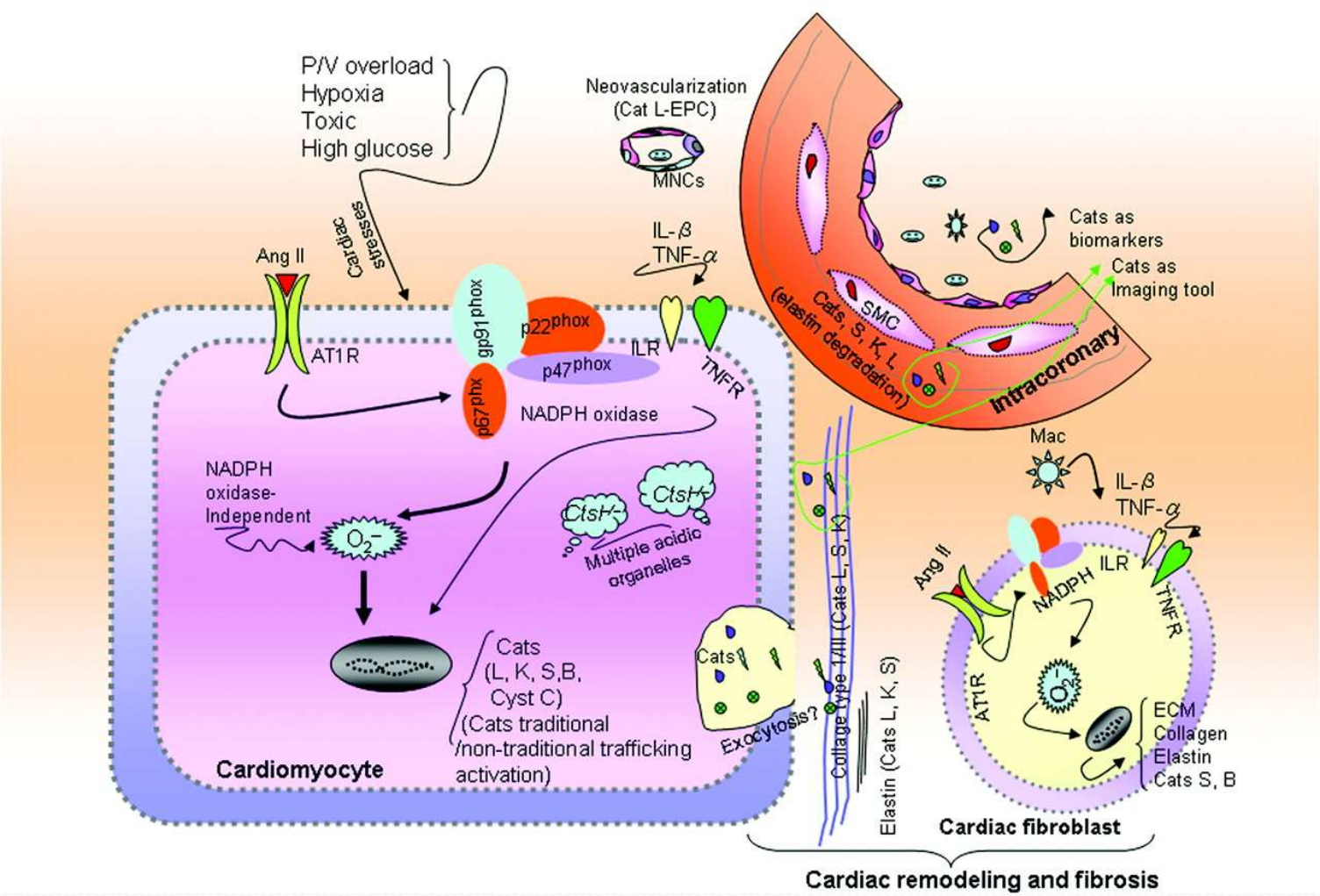
Afferent arteriole

Efferent arteriole

Oxygen supply

Interlobular artery

Angiotensin II Direct Inflammatory Effects

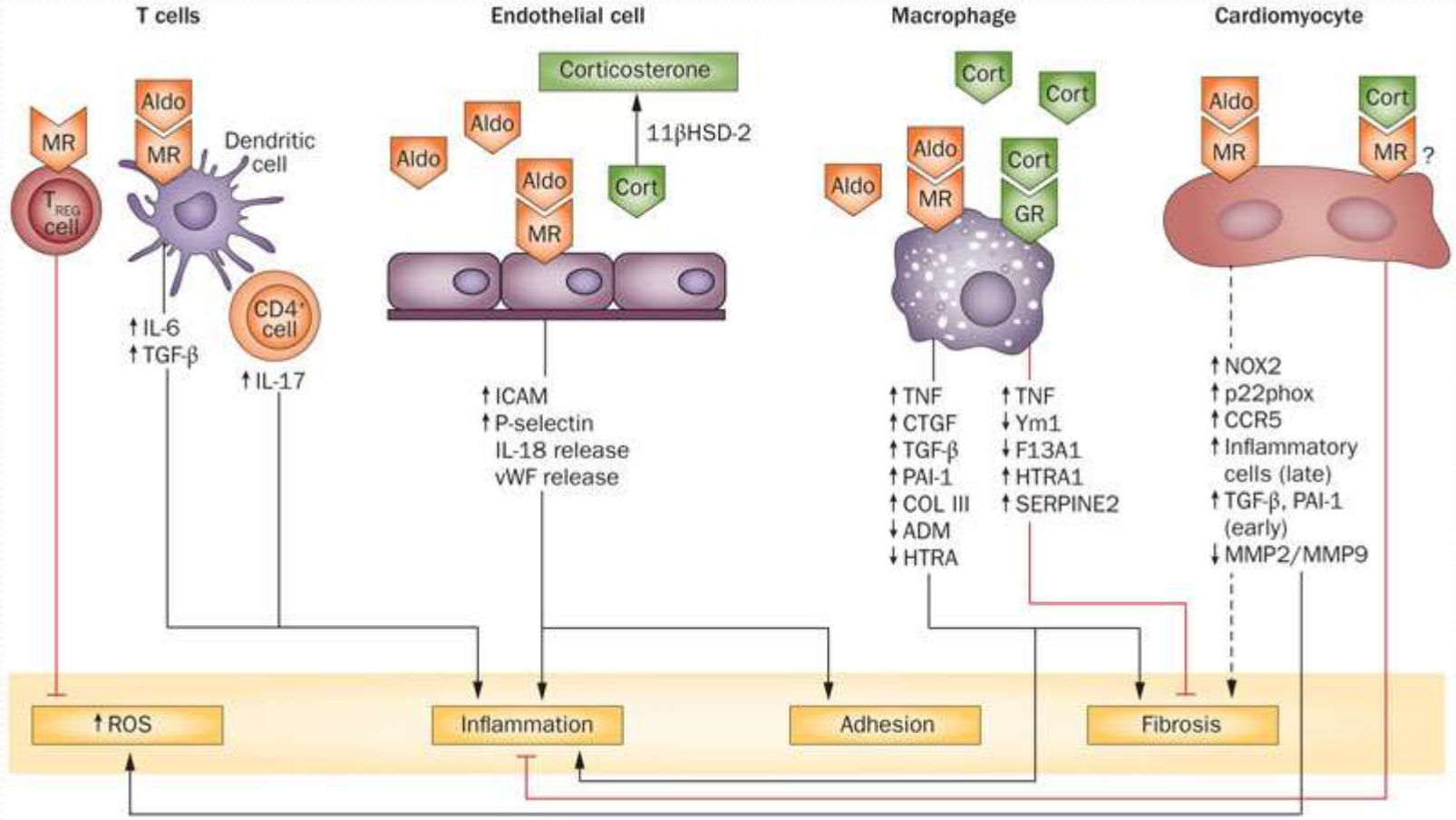


Ultrafiltration Machine

Aquadex Flex Flow (Gambro)

- Fluid removal rate usually 200ml/hour (max 500)
- Blood flow rate 40ml/min
- Can be used with 2 large peripheral lines
- Central line often required

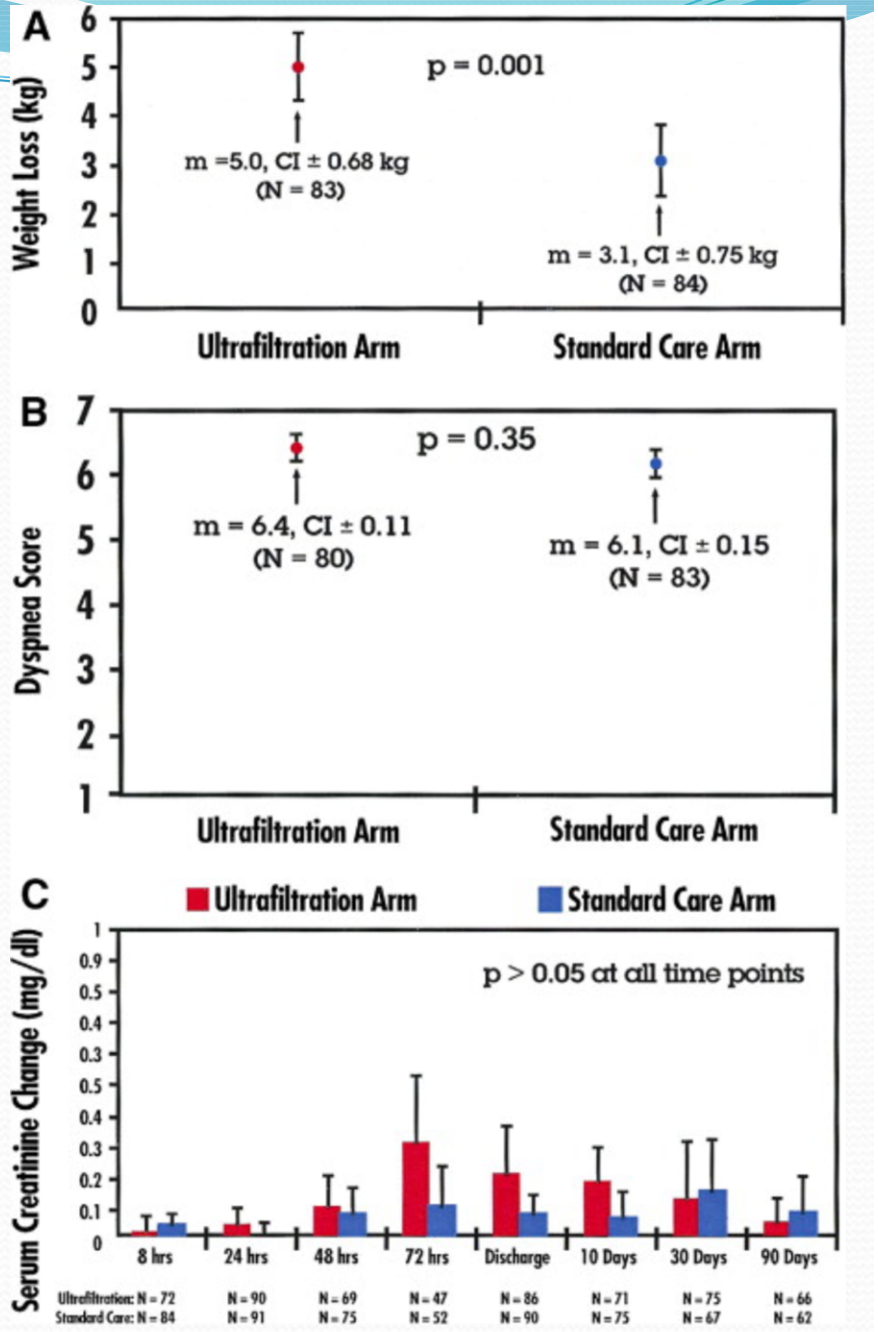
Aldosterone Direct Inflammatory Effects

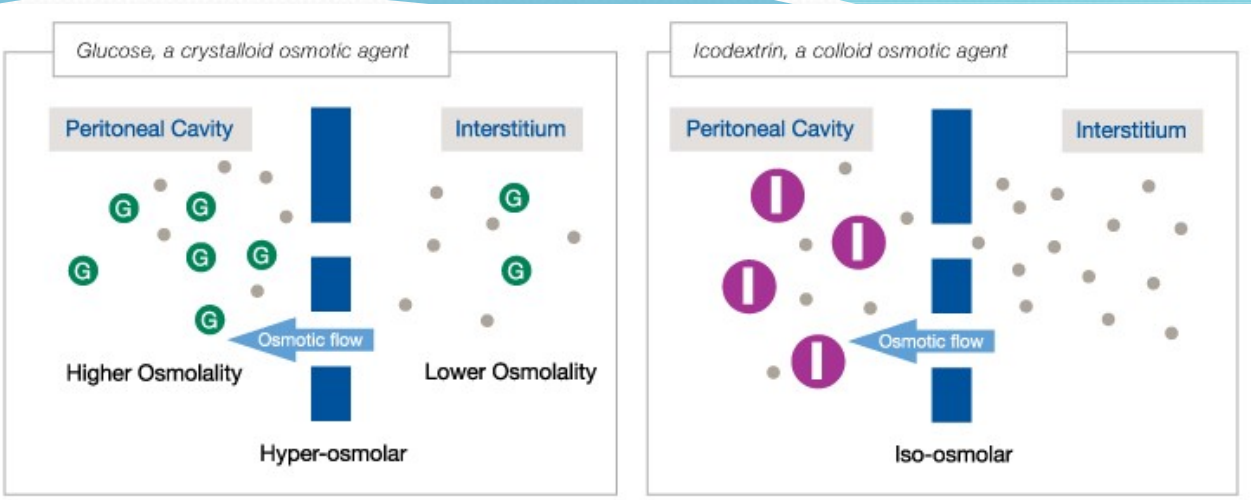


UNLOAD
Costanzo et al. J Am Coll Cardiol 2007 49: 675-83

- 200 patients multicenter randomized to UF or diuretics (either IV or bolus at physician discretion)
- Diuretics were at about 2 times the oral dose prior to admission
- 48 hour treatment

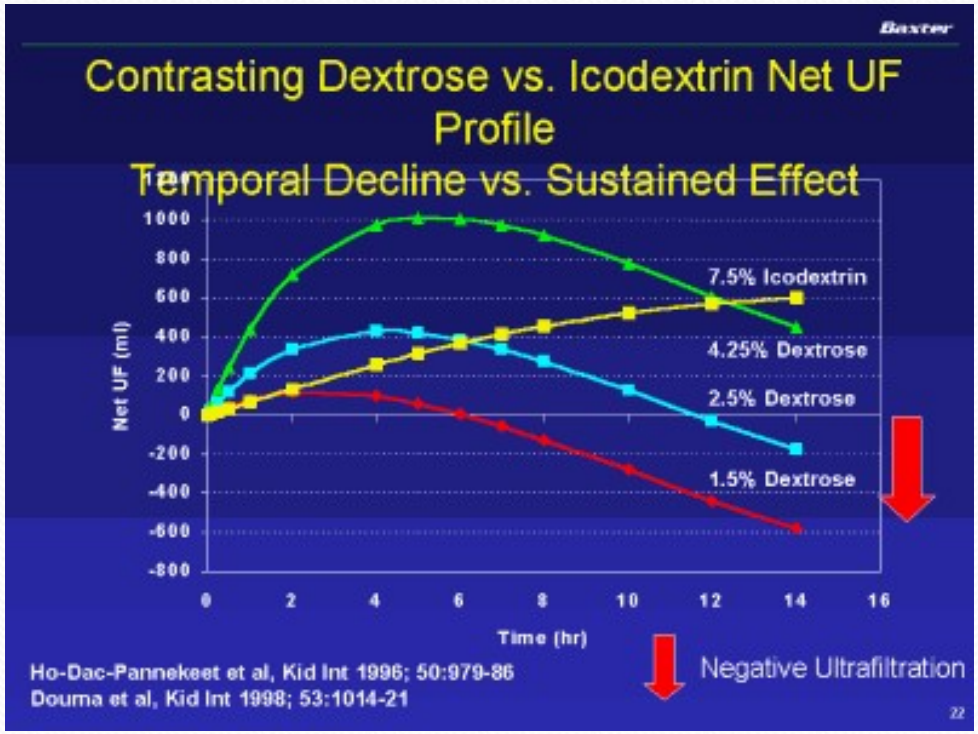
- **Results:**
- Higher weight loss in UF group
- No symptomatic difference
- Trend towards creatinine rise with UF



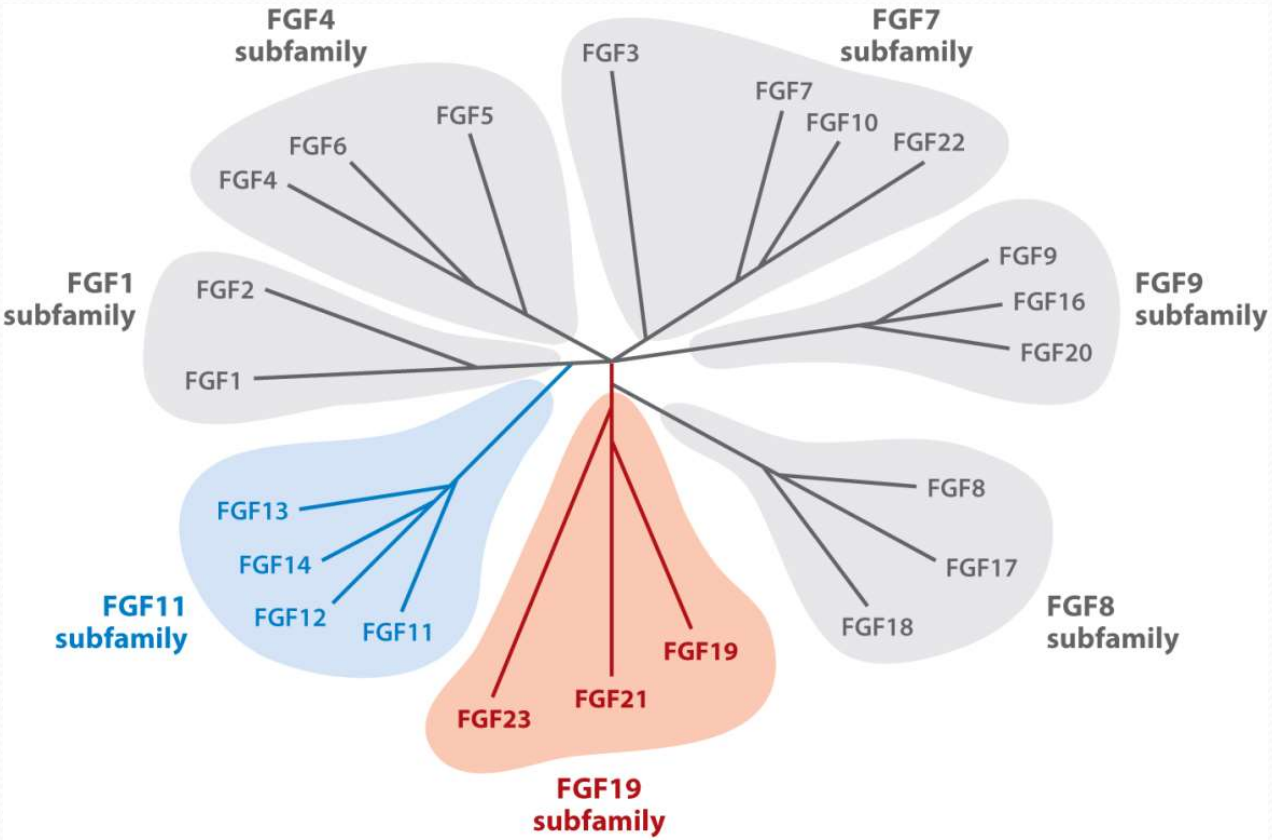


ICODEXTRIN:

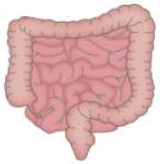
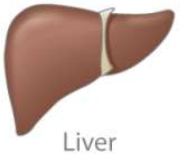
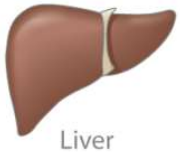
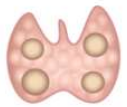
- Cornstarch-like
- Absorbed very slowly from peritoneum therefore UF continues for over 12 hours



Fibroblast growth factor - FGF-23



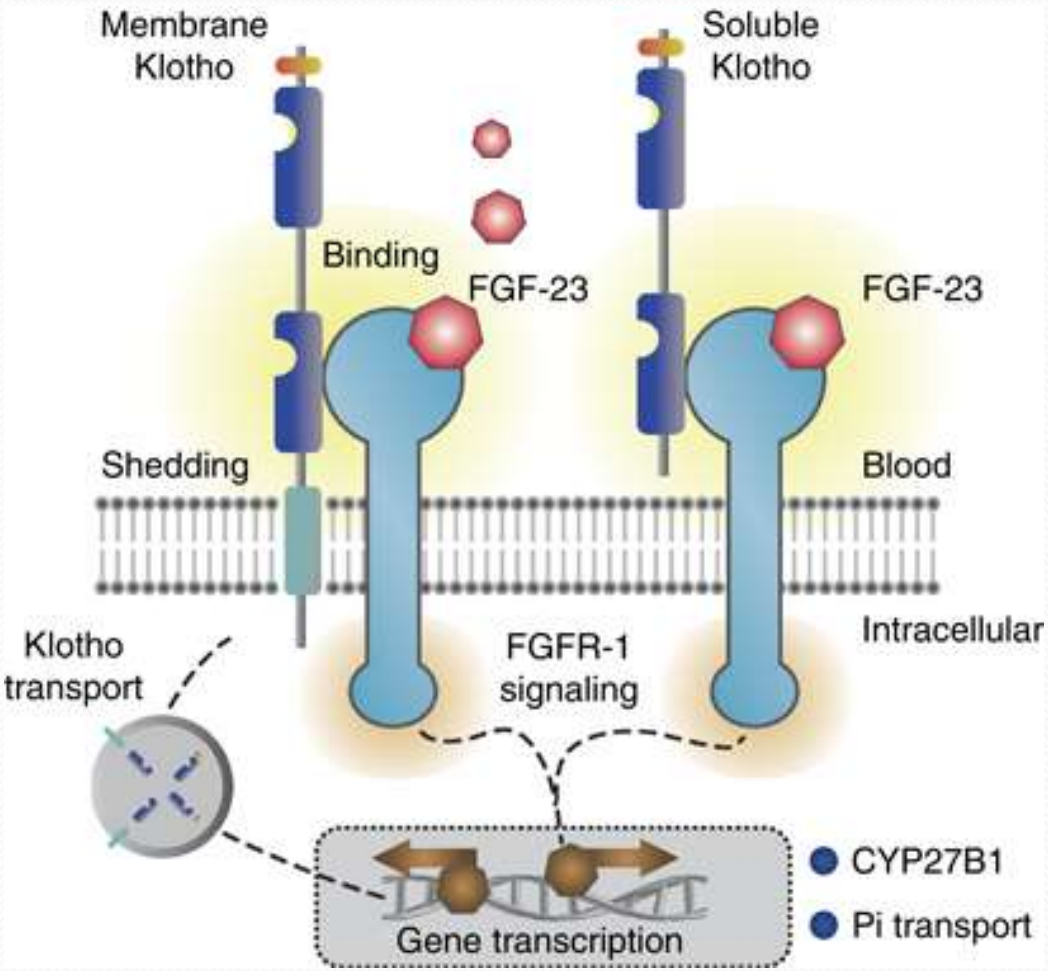
Hu MC, et al. 2013.
Annu. Rev. Physiol. 75:503–33

		FGF15/19		FGF21	FGF23
Induction	Ligand	Bile acid		Fatty acid	Vitamin D
	Receptor	FXR		PPARα	VDR
Source		 Intestines		 Liver	 Bone
Principal target organ		 Liver	 Gallbladder	 Adipocyte	 Kidney  Parathyroid
Receptor complex	FGFR	FGFR4	FGFR1c	FGFR1c	FGFR1c, -3c, -4
	Klotho	βKlotho			αKlotho
Bioactivity		**Postprandial:** ↓ Bile acid synthesis ↑ Glycogen and protein synthesis ↓ Gluconeogenesis	**Postprandial:** Relaxation and filling	**Fasting:** Fatty acid oxidation Torpor	**Phosphate homeostasis** ↑ Urinary P_i excretion ↓ PTH ↓ Calcitriol synthesis

Hu MC, et al. 2013.
Annu. Rev. Physiol. 75:503–33

⬅ **Gene is activated by PO_4, PTH & 1,25 (OH)2D**

In kidney FGF-23 needs Klotho to bind



Chronic Kidney Disease and FGF23

- FGF23 increases very early in CKD before serum PO_4 levels are elevated

- Helps to maintain serum PO_4 at normal level and early on is probably helpful in preventing phosphate induced vascular calcification

Chronic Kidney Disease and FGF23

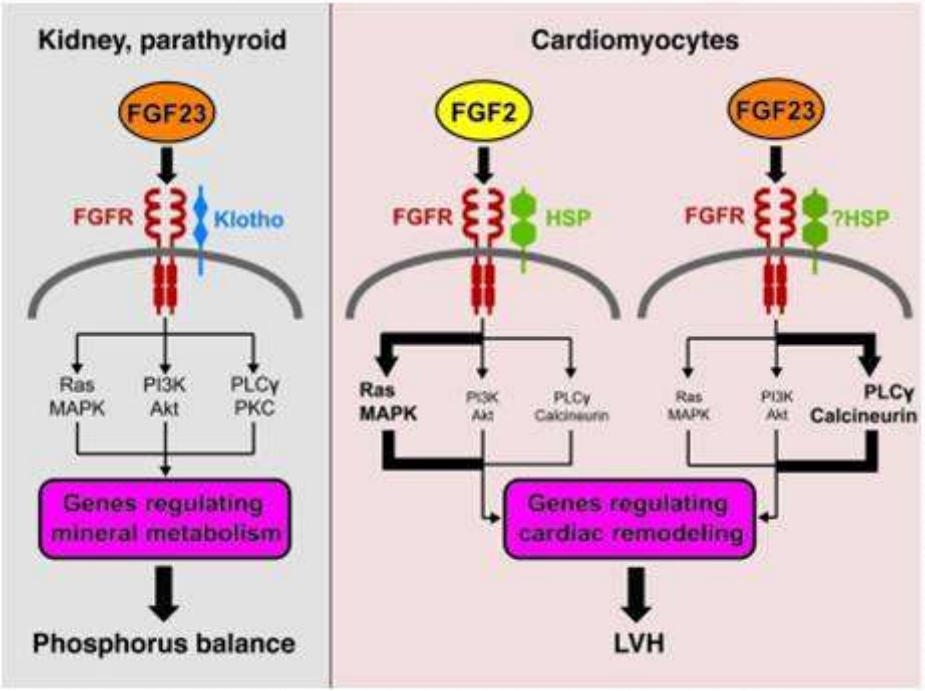
- With decreased renal mass FGF23 loses its effectiveness as a phosphaturic hormone but serum levels still continue to rise

- In dialysis patients FGF23 levels can be increased 1000 fold and at that point are correlated with mortality

Directly harmful or just a marker??

Left ventricular hypertrophy and FGF-23

- In vitro FGF-23 induces hypertrophy of isolated cardiomyocytes
- Mice injected with FGF-23 develop LVH



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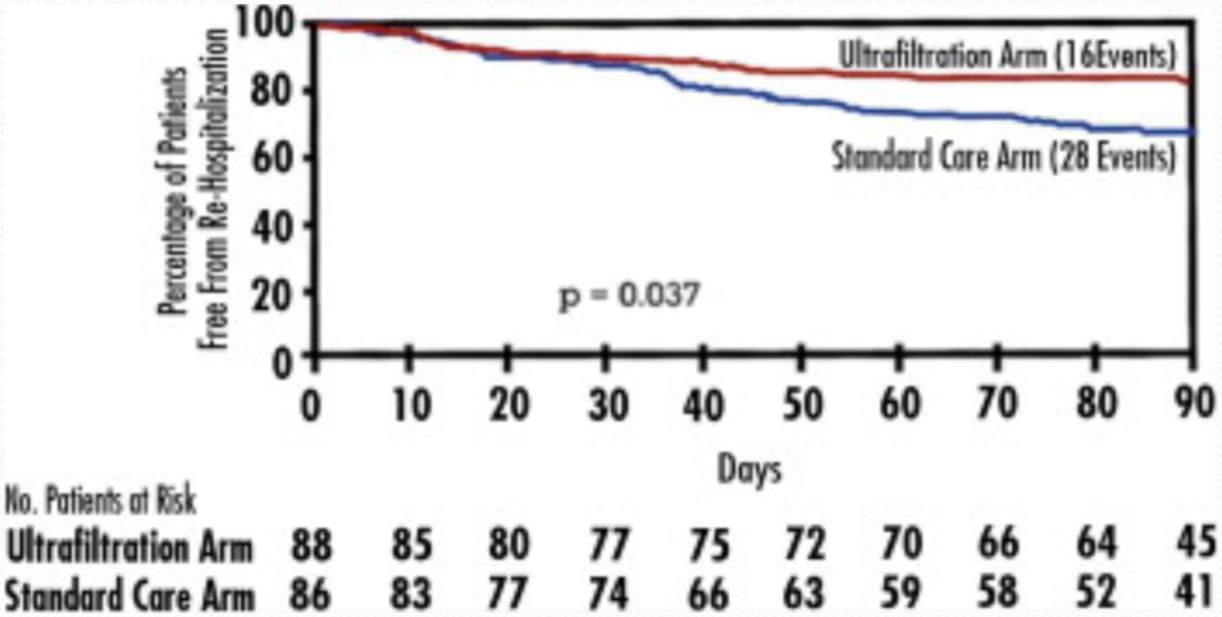


- Decreased re-hospitalization in UF group
- Secondary end- point in a subset of patients

Klotho spins the thread of life!

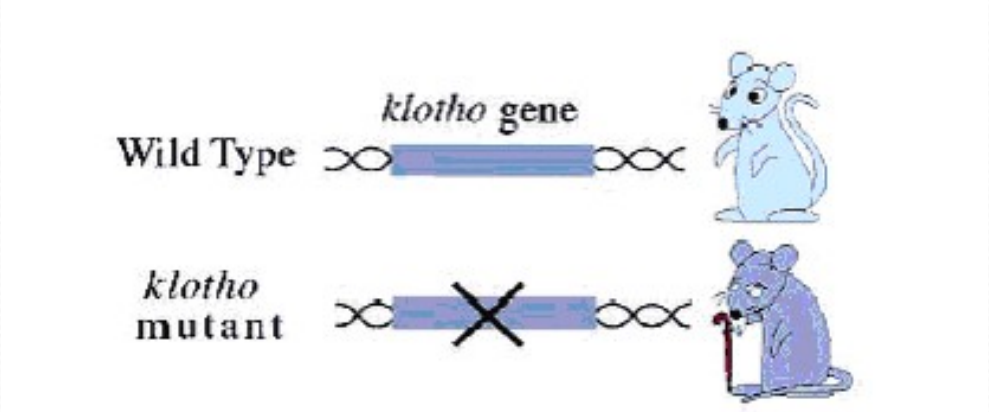


Fig. 1. A mutant model mouse is useful for studies of aging. The *klotho* phenotype (premature aging) is caused by a disruption of the single gene, *klotho*.

- 1997 **Kuro-o** describes a mouse with short life-span, osteoporosis, emphysema, arteriosclerosis, skin atrophy, hyperphosphatemia and ectopic calcifications.
- He identified the gene for **Klotho**, which when over-expressed causes mice to live longer.

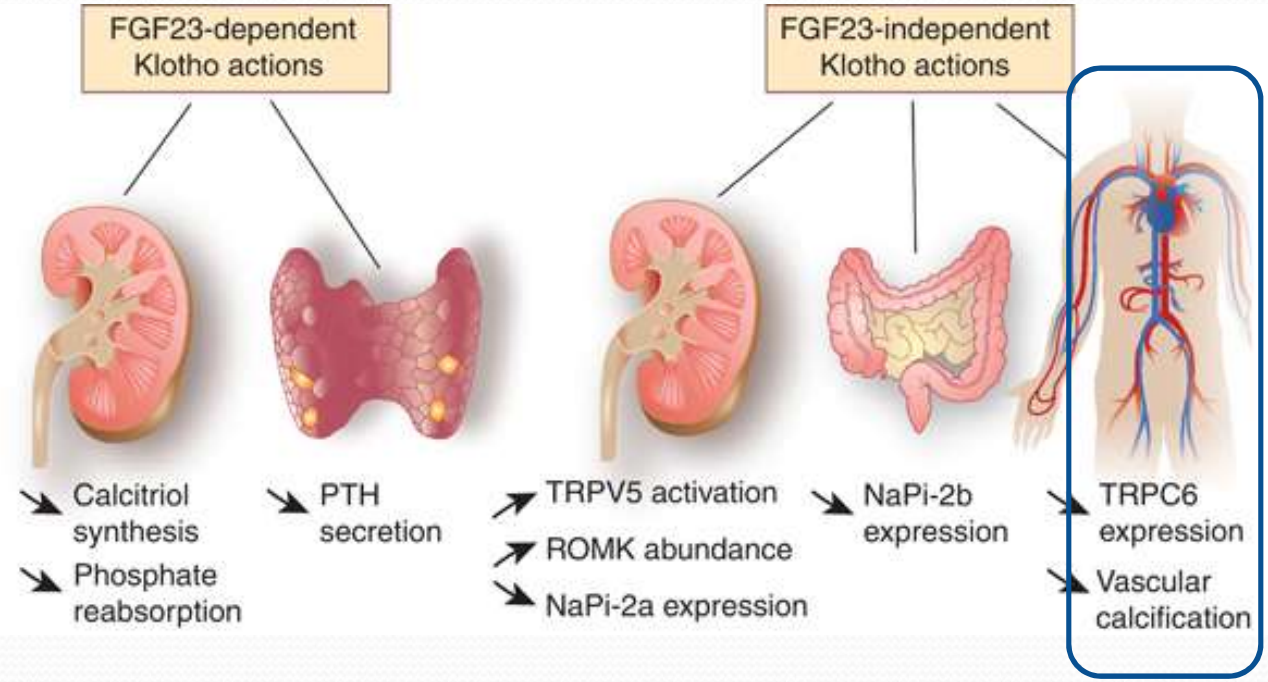
The Moirai – The Fates

Daughters of Zeus (the god of fate) and Themis

Klotho -spinner Lakhesis-measures Atropos–cuts thread of life

The thread of life

Klotho Actions



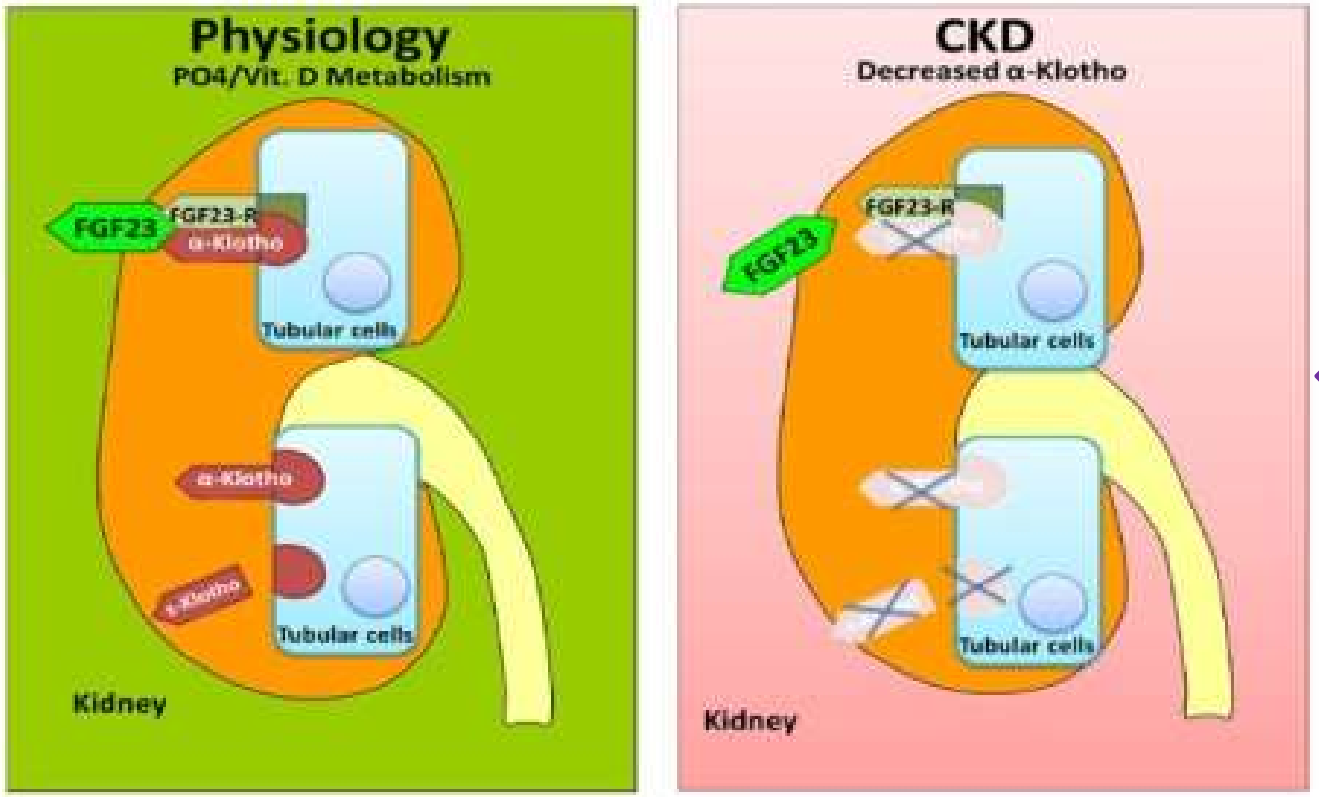
Functions of Klotho

- Involved in endothelial integrity and endothelial dependent vasodilation
- Protective against oxidative stress
- Inhibits TGF-B signaling and suppresses interstitial fibrosis in animal models
- Expressed in the sino-atrial node and decreased expression leads to SA node malfunction and premature death

- ***Circulating levels of Klotho are decreased in CKD***

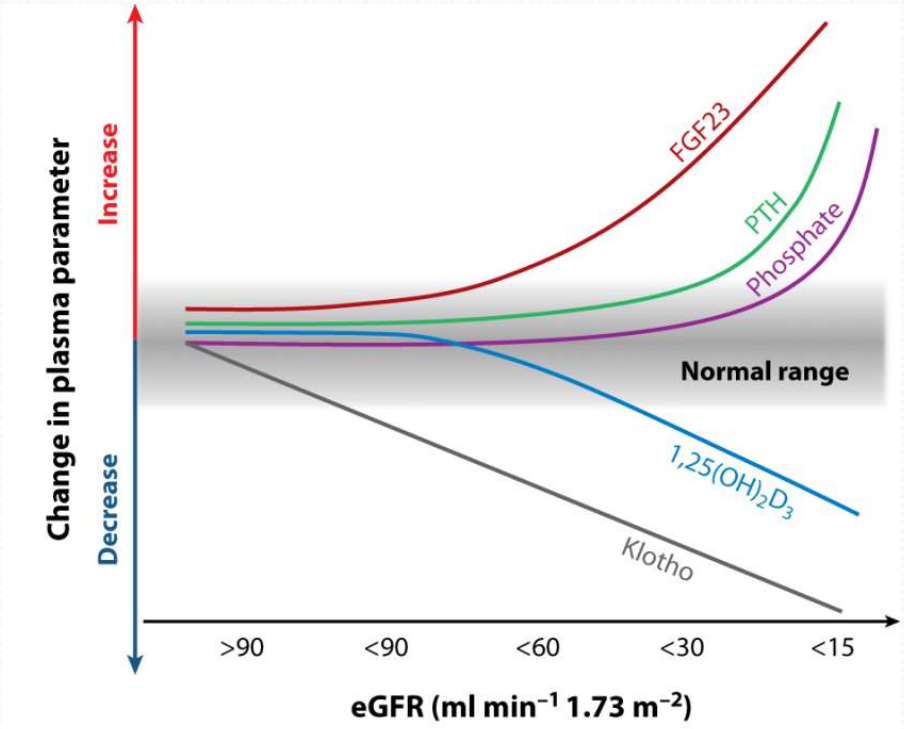
Normal renal function

Chronic kidney disease



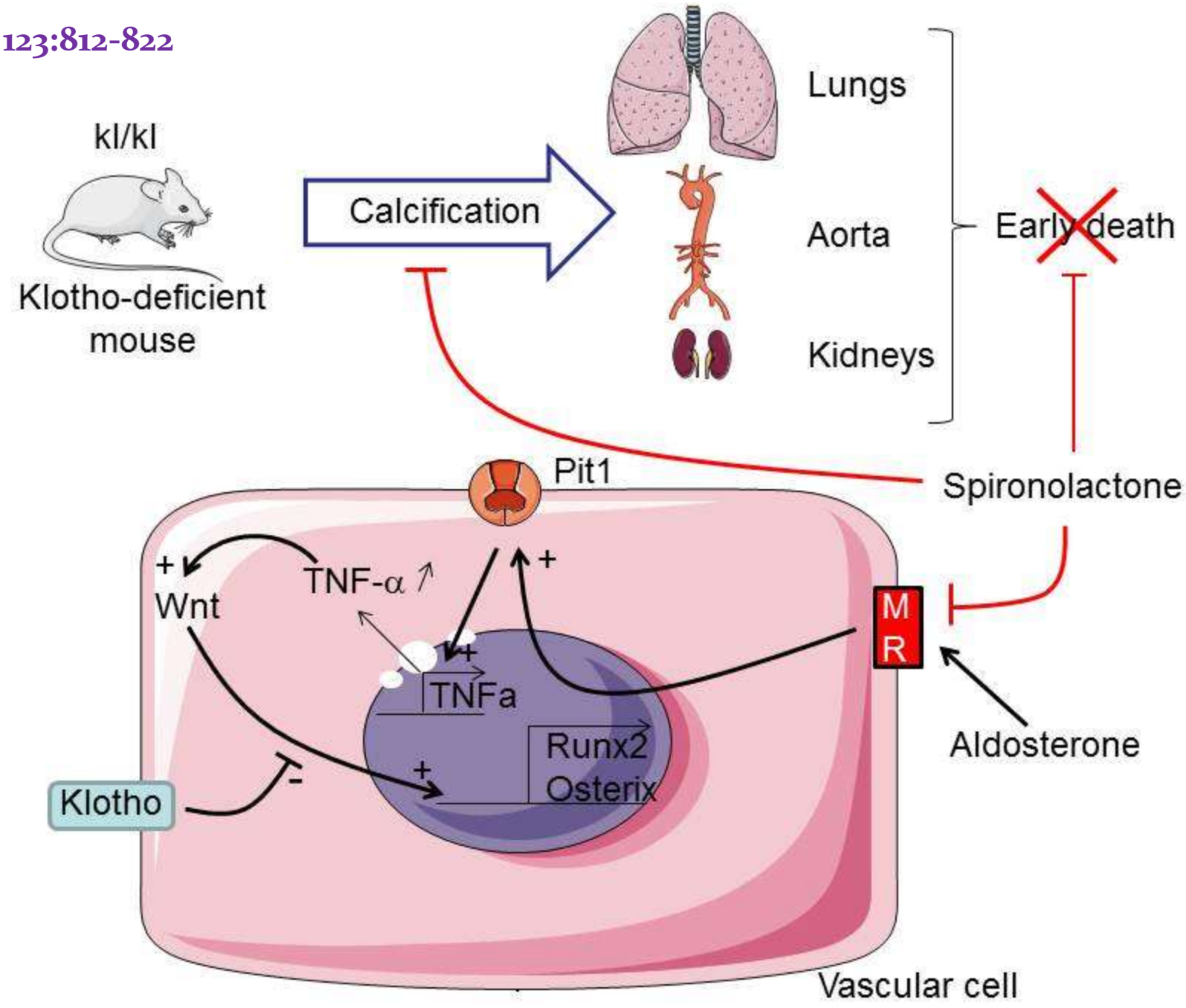
Decreased circulating Klotho and increased FGF-23

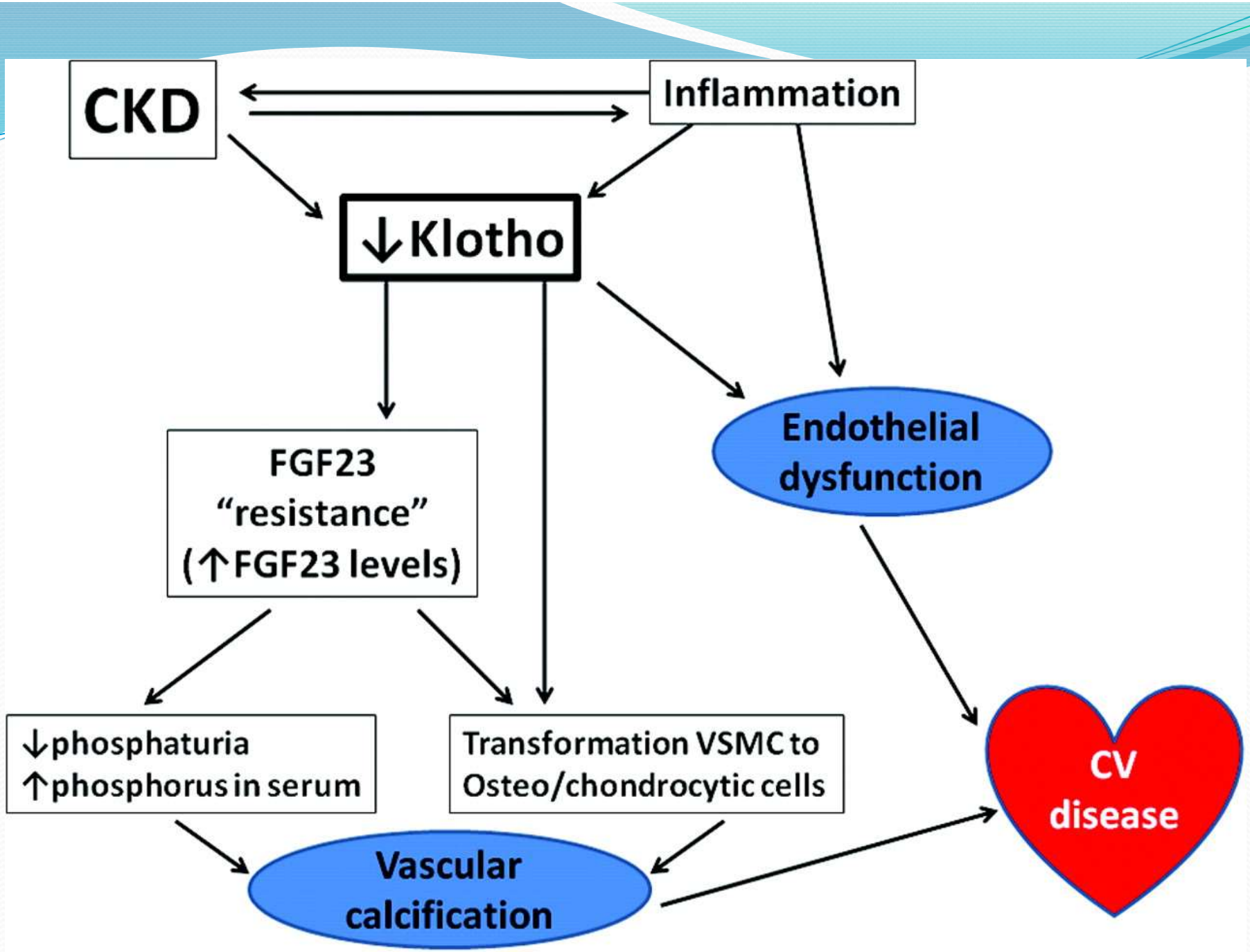
FGF-23 and Klotho plasma levels with progressive renal failure



Hu MC, et al. 2013.
Annu. Rev. Physiol. 75:503–33

JCI 2013; 123:812-822



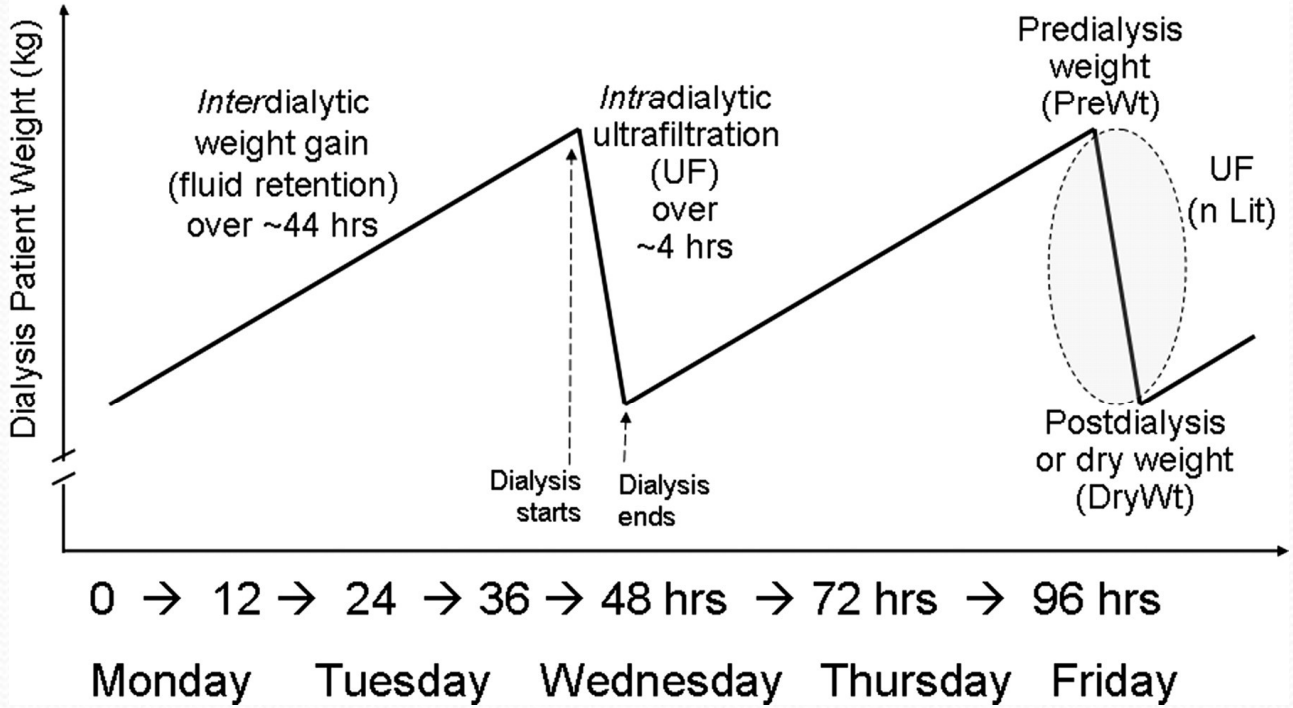

CKD
Inflammation
↓Klotho
FGF23
"resistance"
(↑FGF23 levels)
Endothelial
dysfunction
↓phosphaturia
↑phosphorus in serum
Transformation VSMC to
Osteo/chondrocytic cells
CV
disease
Vascular
calcification

FGF-23 and Klotho in CKD and Vascular Disease

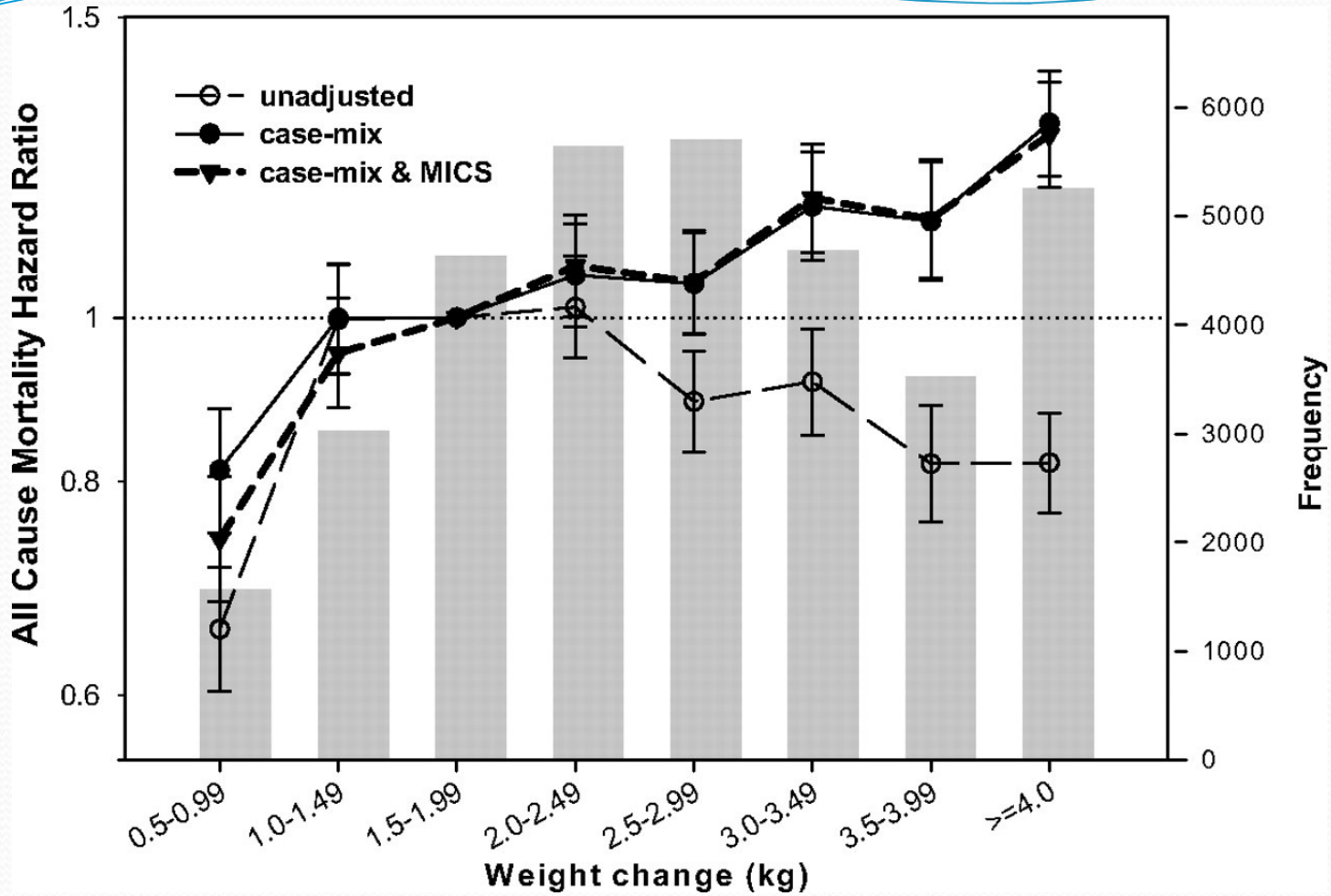
- Intriguing and generating significant research interest
- But at this point the research has not led to any potential therapies in humans

DryWt = PreWt – UF

UF = Fluid Retention



Circulation 2009; 119:671-679
34,000 patients Prospective cohort, multicenter



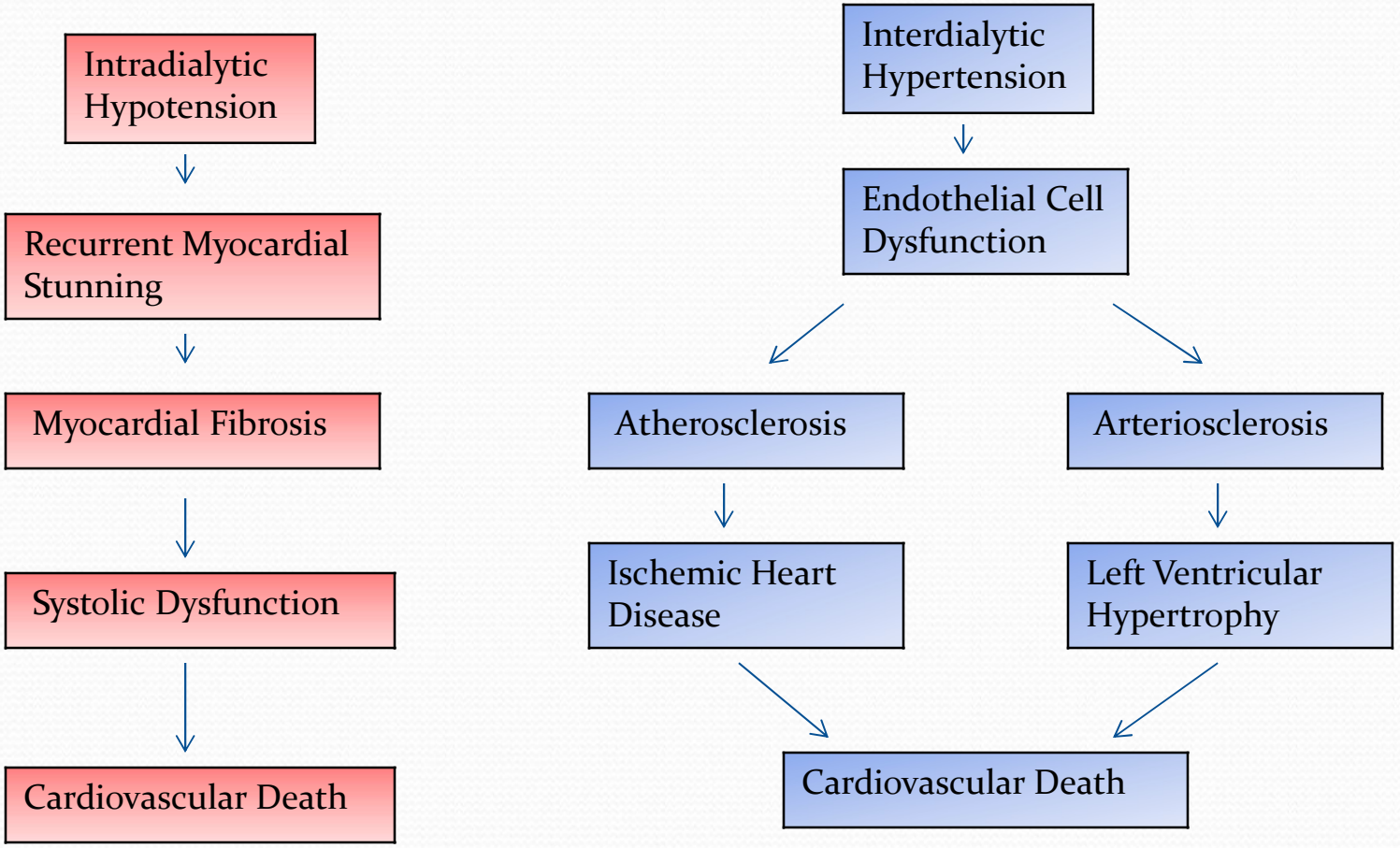
Circulation 2009; 119:671-679

34,000 patients Prospective cohort, multicenter

How Can We Help

BLOOD PRESSURE STABILITY

Blood Pressure Challenges on Dialysis



Inrig, J. KI 2013 84, 641-644

Pathophysiology

Cardio-renal syndrome - ADHF

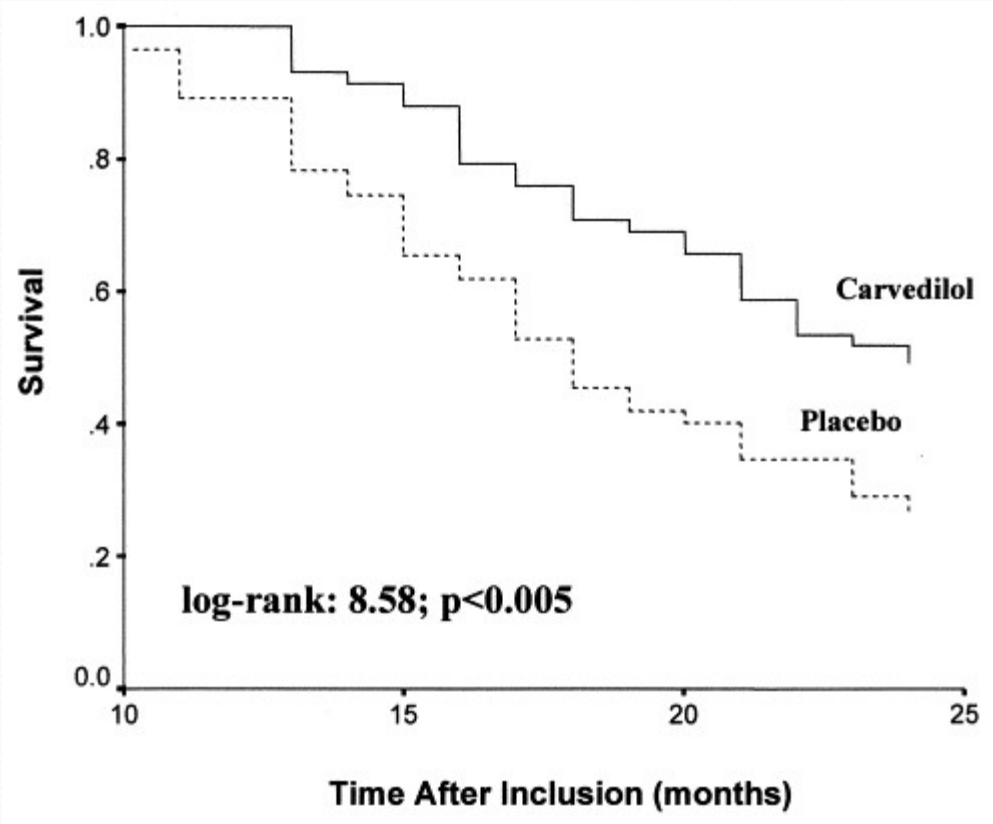
Other contributors to cardiac and renal injury

- Treatment related worsening of renal function: diuretics, RAAS inhibition, aldosterone receptor antagonists

- Contrast mediated renal injury during investigations

How Can We Help

BETA BLOCKERS



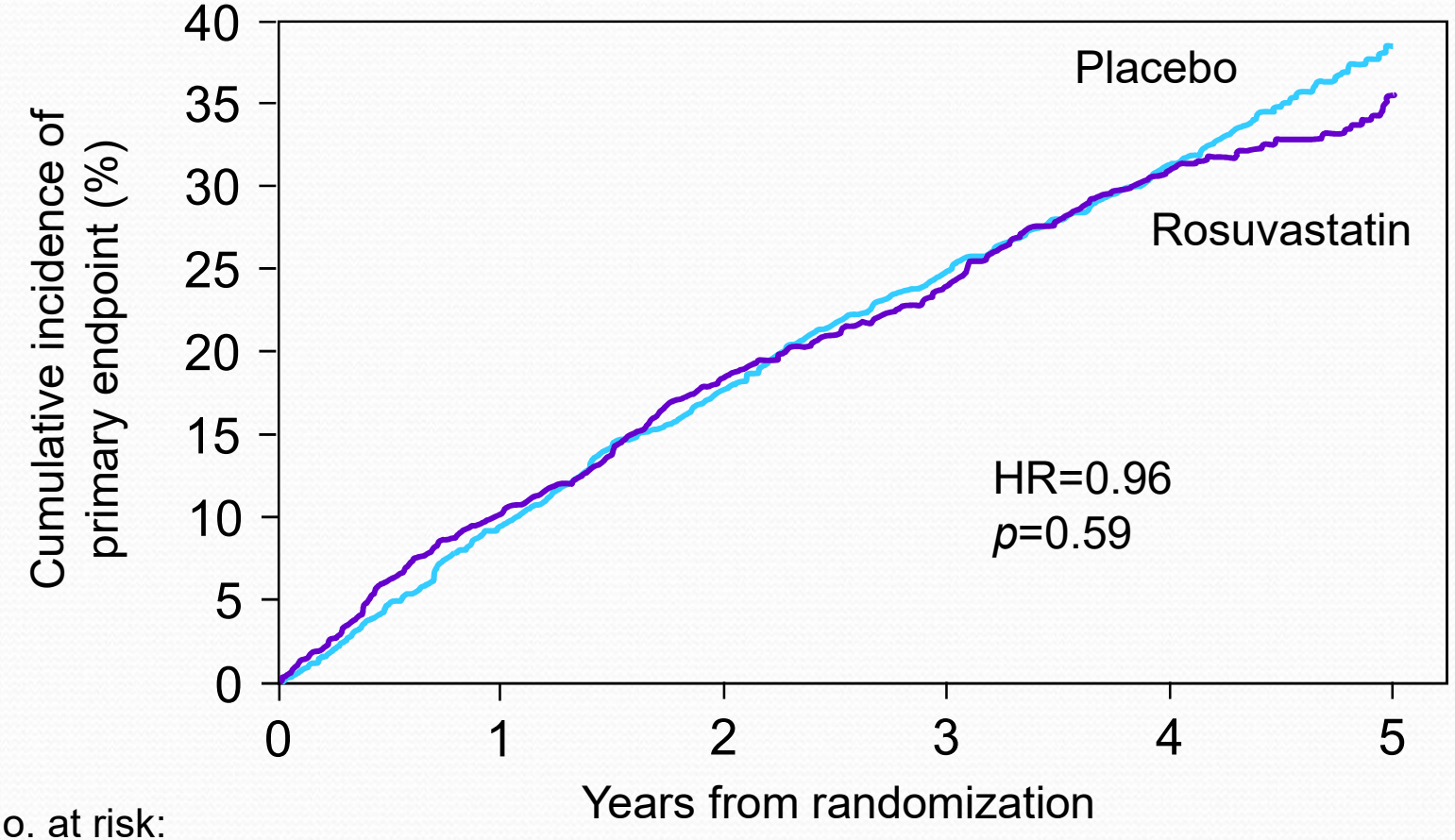
J Am Coll Cardiol 2003 41:1438
114 hemodialysis patients with dilated cardiomyopathy ; max dose 25mg BID

How Can We Help

LIPID CONTROL

AURORA: Primary endpoint

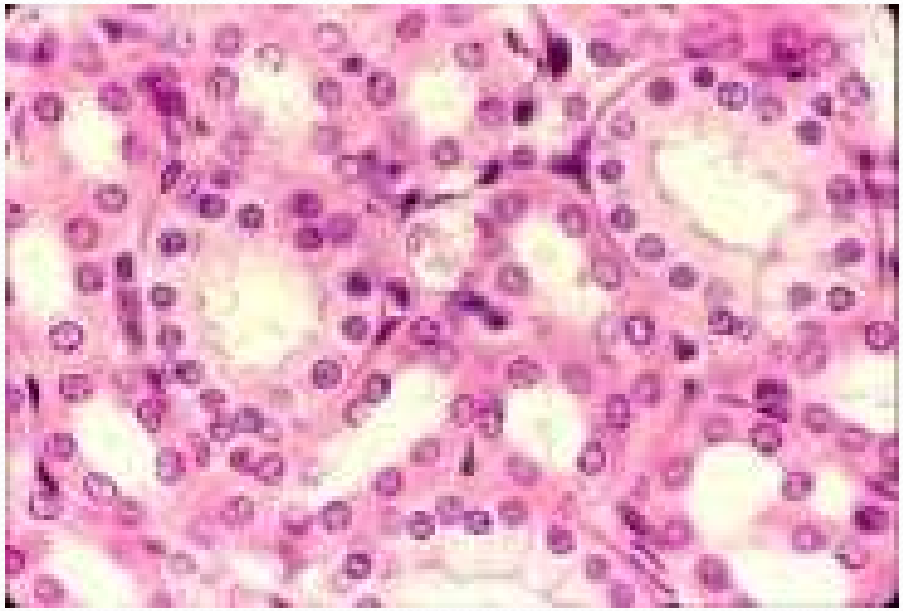
Kaplan-Meier estimate of time-first major CV event



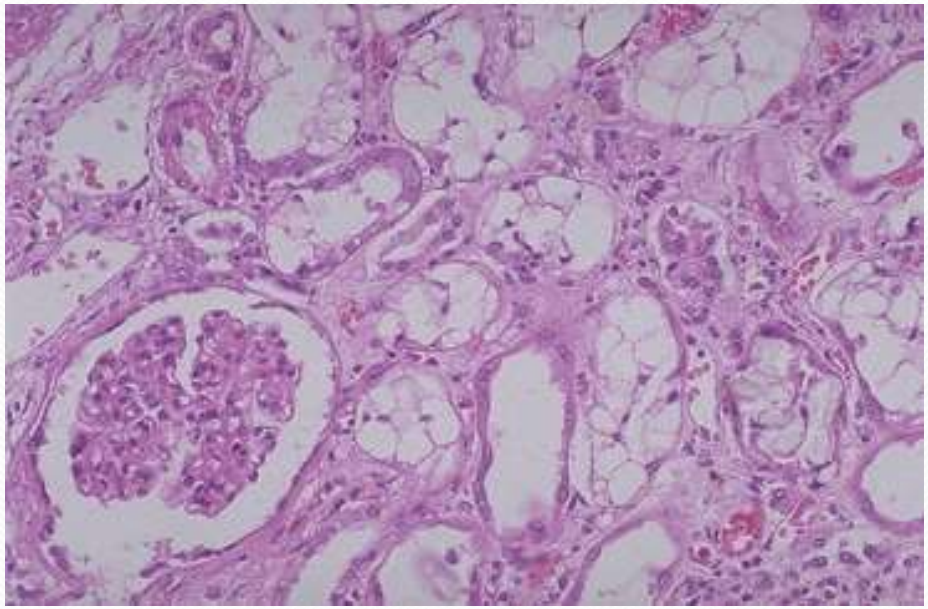
No. at risk:						
Rosuvastatin	1,390	1,152	962	826	551	148
Placebo	1,384	1,163	952	809	534	153

Fellström BC et al. N Engl J Med 2009; 360:1395-407

Normal renal tubules



Mr B. Acute tubular necrosis with dilatation flattened epithelium and vacuoles



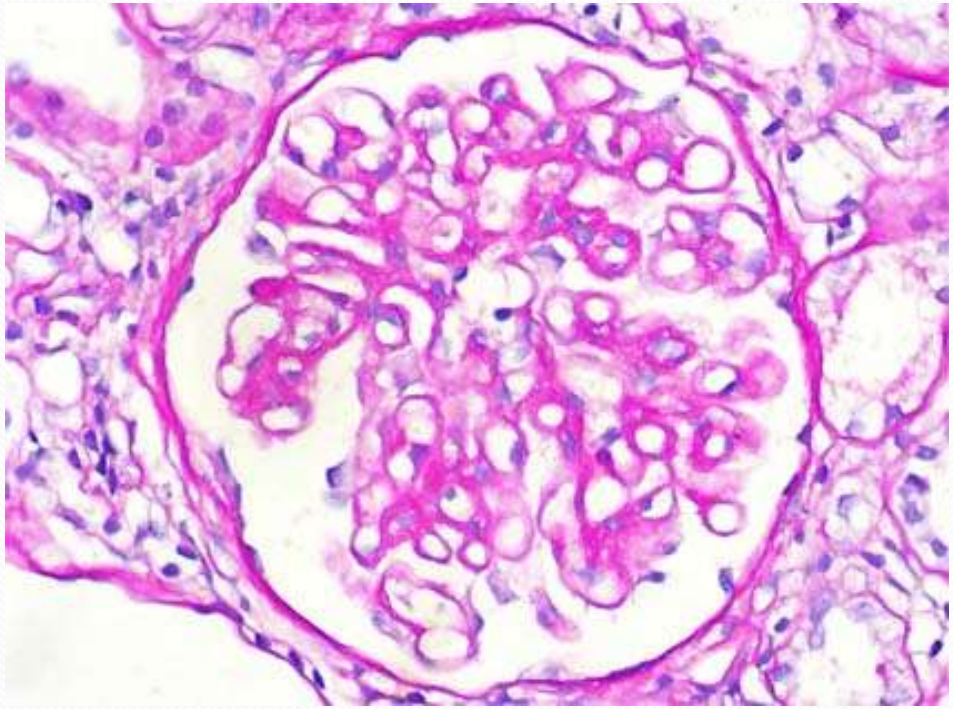
Normal glomerulus

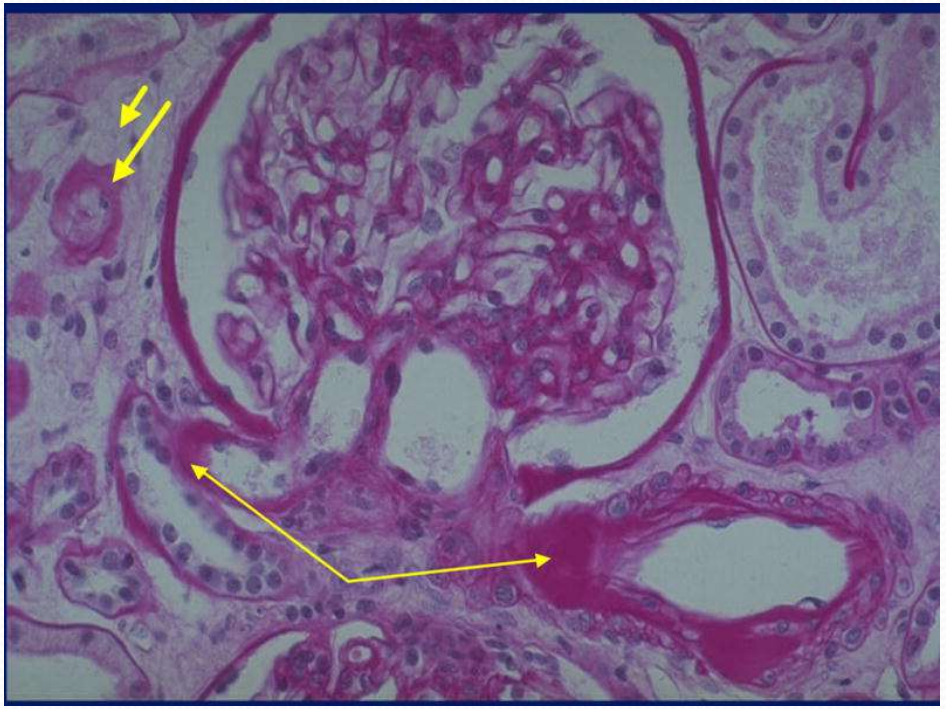
- Mr B. * Acute tubular injury

*Chronic tubular atrophy, interstitial fibrosis

*Mild to moderate mesangial expansion from diabetes

*Arteriolar hyalinosis (arrows)





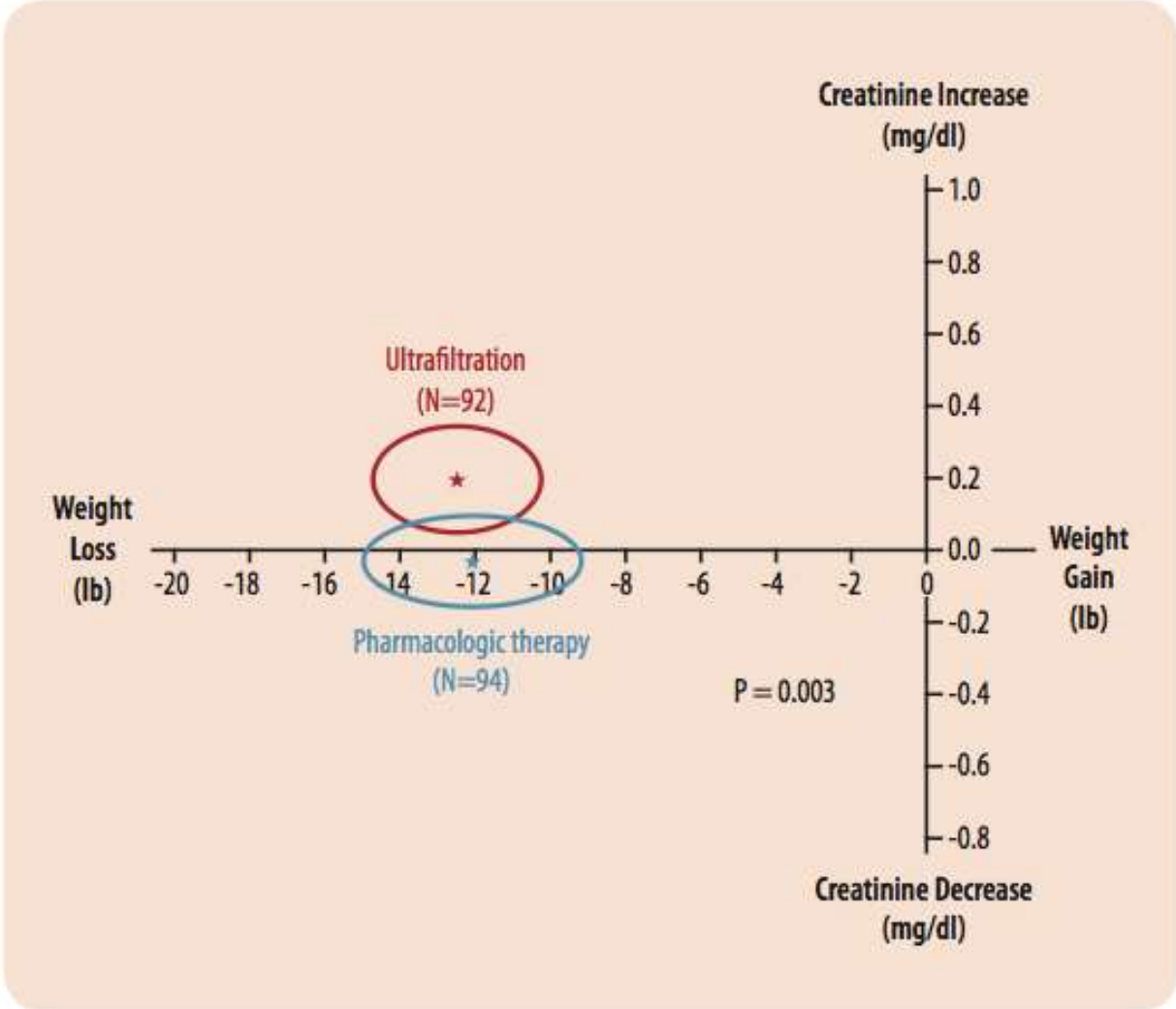
Use of Ultrafiltration in Decompensated Heart Failure

Cardiorenal Rescue Study in ADHF: CARRESS-HF NEJM 2012 367:24

- 188 patients randomized to ultrafiltration at rate of 200ml per hour or to Intravenous diuretics titrated to achieve urine output of 3 to 5 liters per day
- Treatment period was about 4 days and follow-up was 60 days
- Small improvement in symptoms was similar in both groups

CARESS-HF

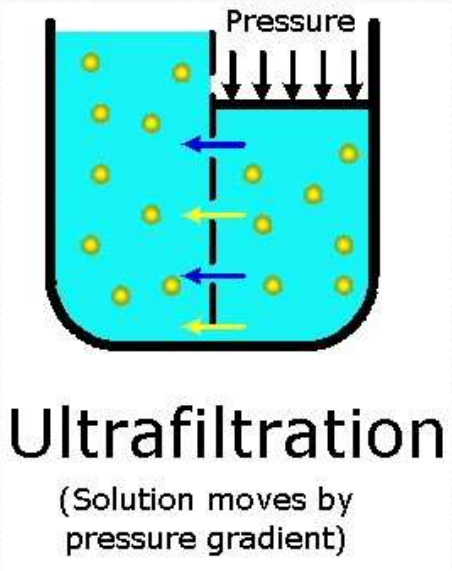
- Both groups had average 5.5 kg weight loss after 4 days
- Increased creatinine in UF group
- Higher risk of bleeding, bacteremia and cellulitis in UF group

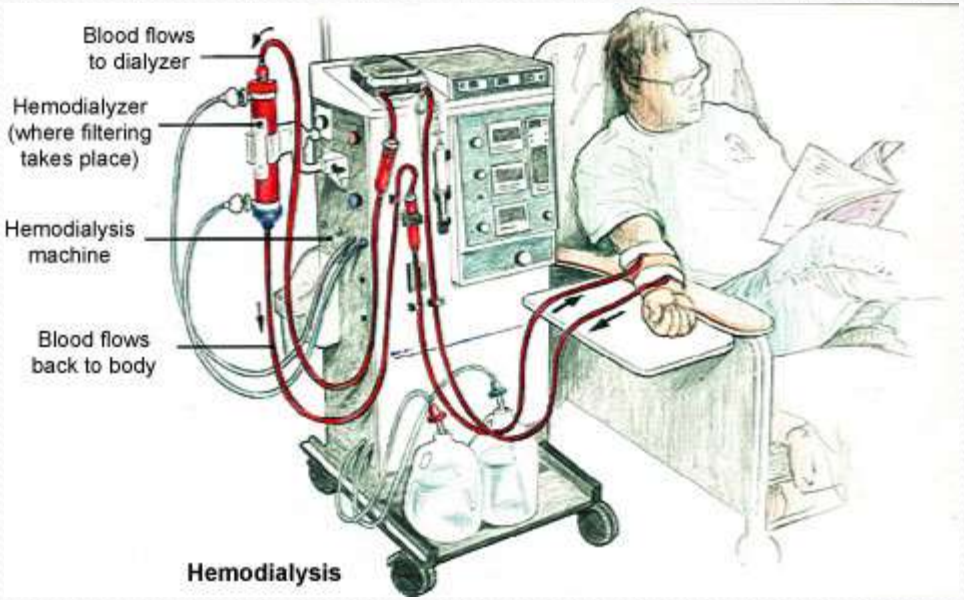


Mr B. needed both isolated ultrafiltration and hemodialysis for worsening renal function.

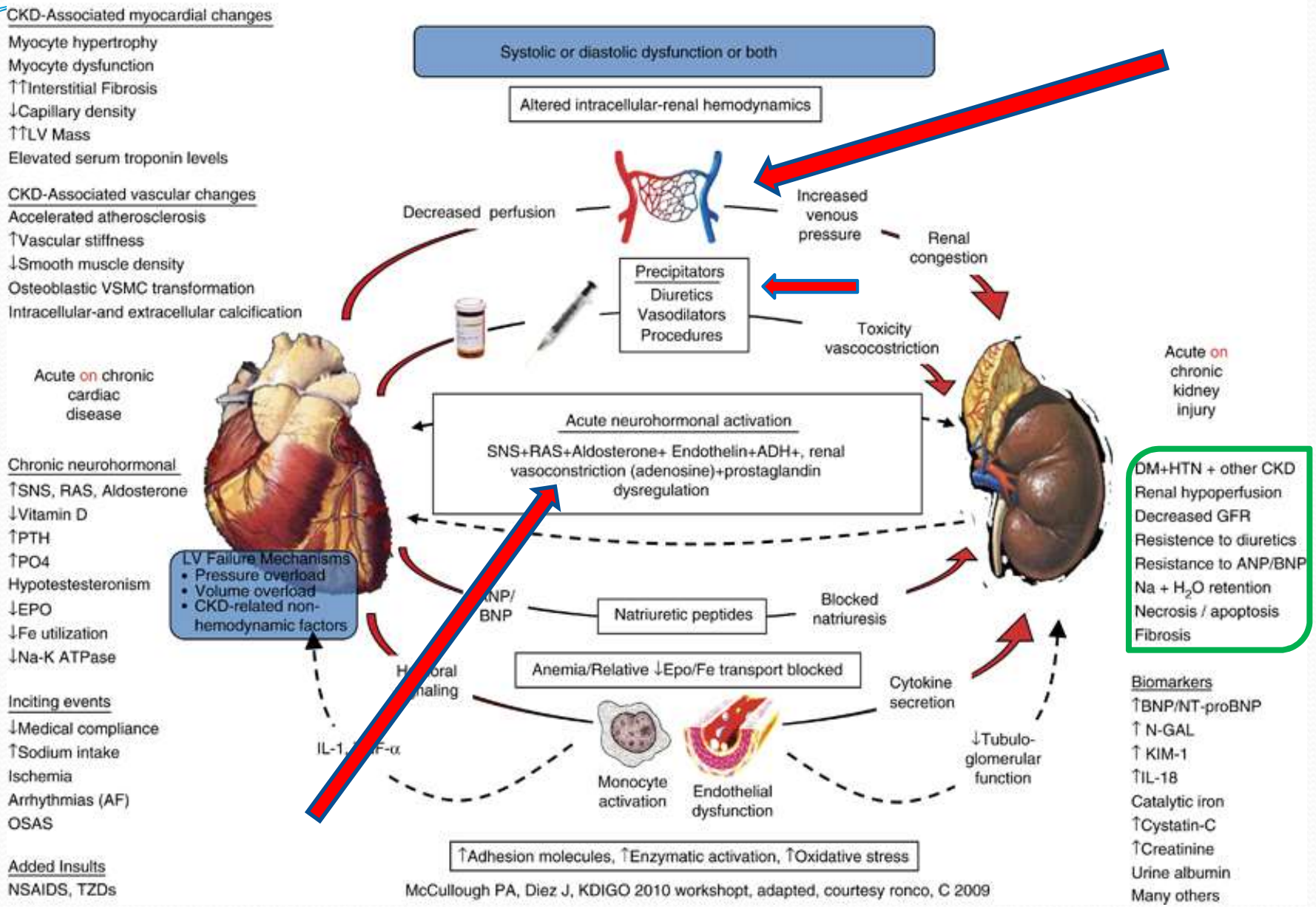
Sometimes with prolonged UF/HD there is loss of residual kidney function and HD dependency due to:

- Hypotension
- Cytokine activation (blood-filter contact)
- platelet- leukocyte aggregation



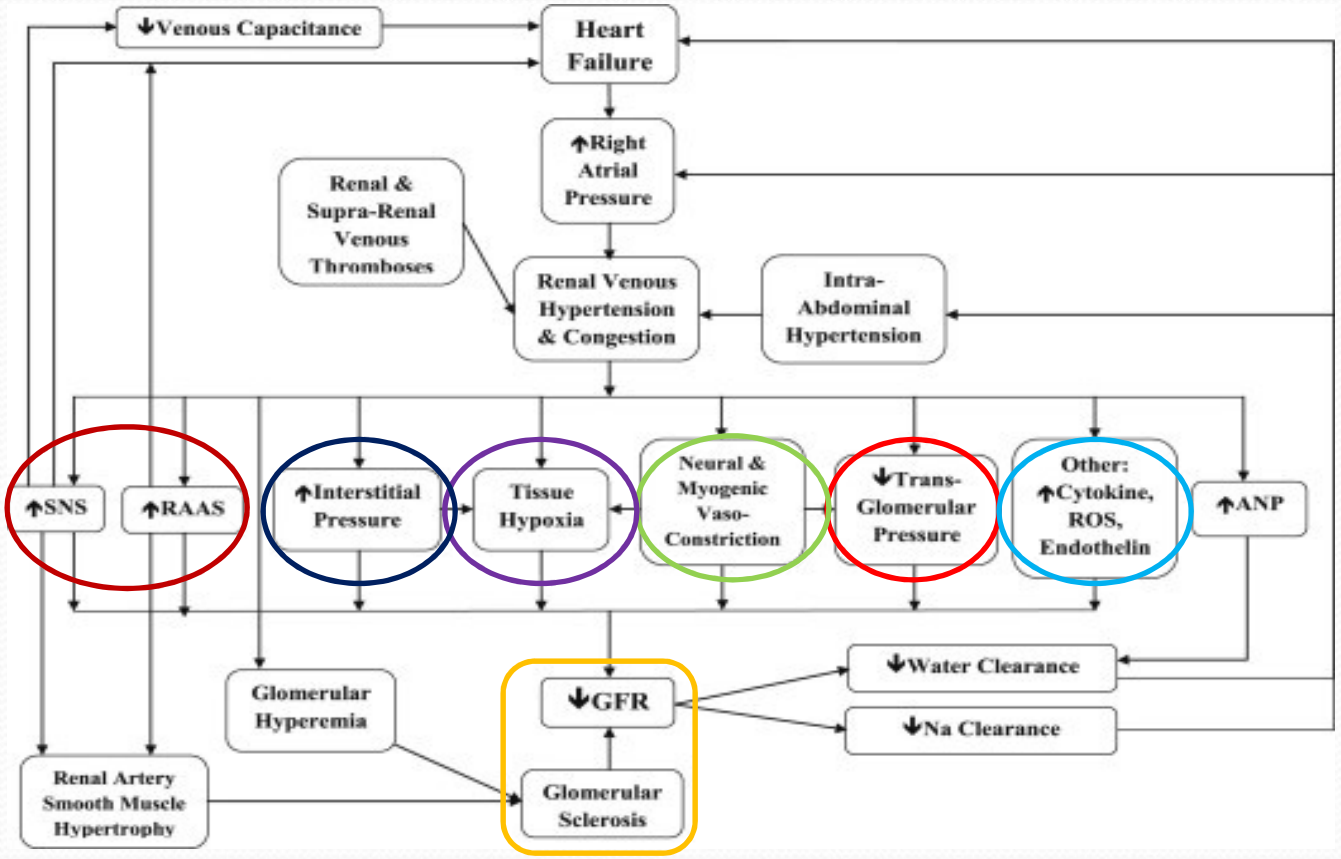


Cardio-renal syndrome pathophysiology



McCullough PA, Diez J, KDIGO 2010 workshopt, adapted, courtesy ronco, C 2009

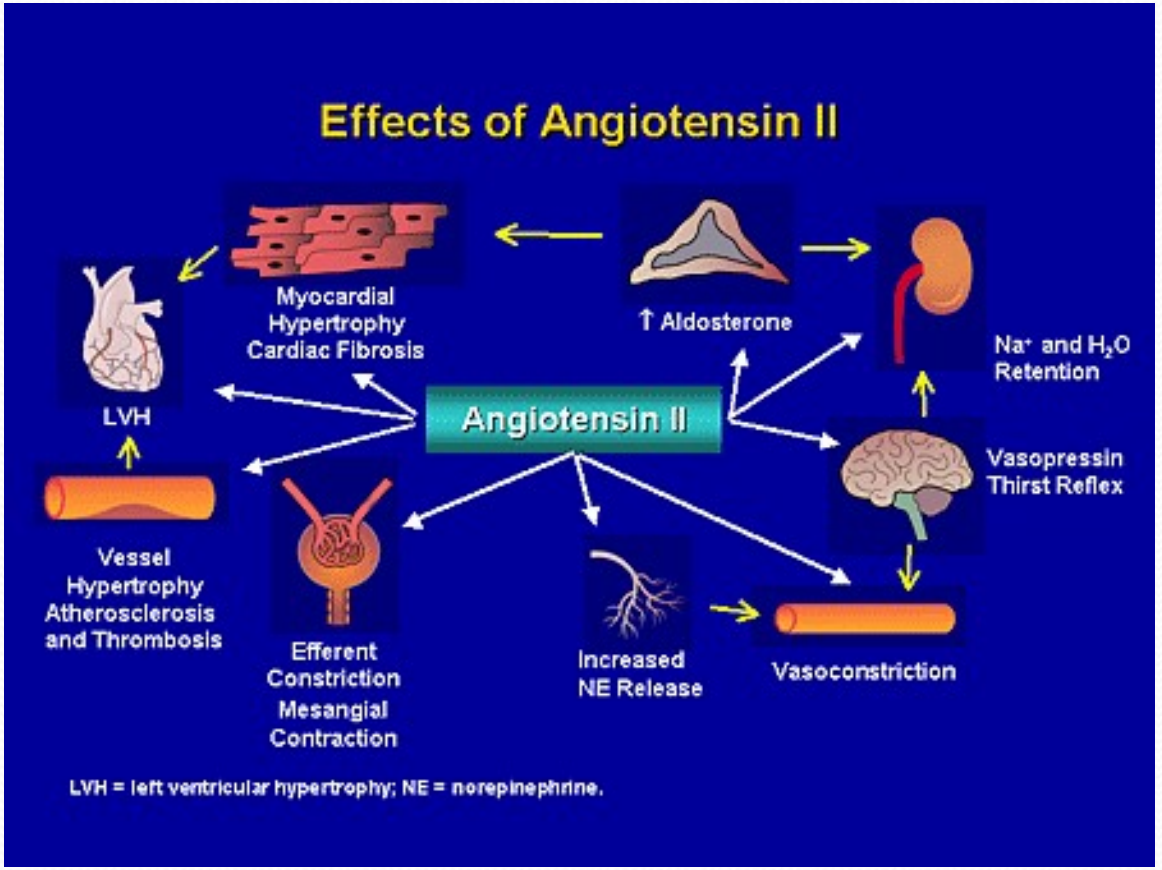
Proposed pathophysiology of renal venous hypertension, congestion, and dysfunction



Journal of Cardiac Failure Volume 18, Issue 12 2012 930 - 938

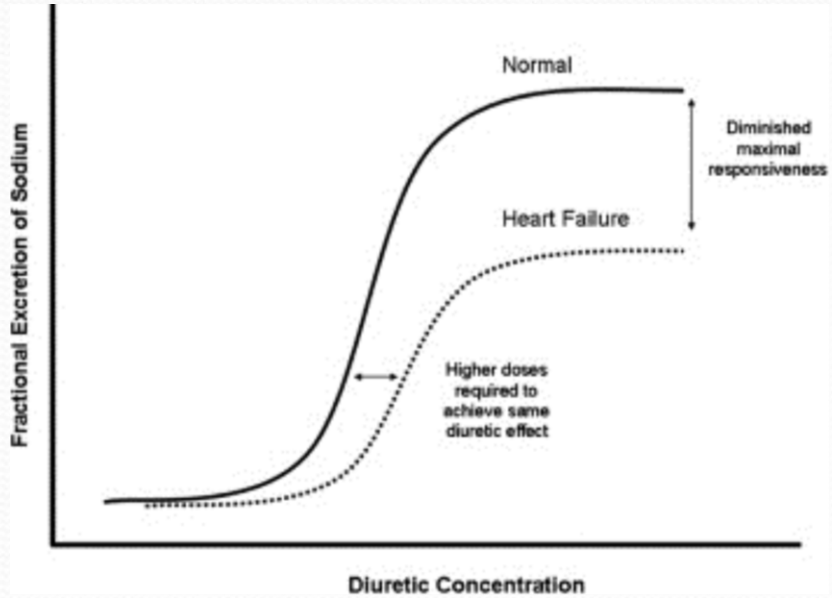
RAAS Inhibition

- Most studies exclude patients with significant renal failure
- Concerns include worsening of renal function and hyperkalemia
- Patients unable to tolerate RAAS Inhibition have higher mortality: is this a marker of poor prognosis or are we stopping these medications too soon?



Questions about diuretics in ADHF

- Dose required
- Diuretic resistance
- Rebound fluid retention with short action of furosemide
- Is continuous infusion better than bolus administration



Diuretic Strategies in Patients with ADHF (DOSE trial) NEJM 2011 364:9

- 308 randomized patients treated for 72 hours
- 60 days of follow-up

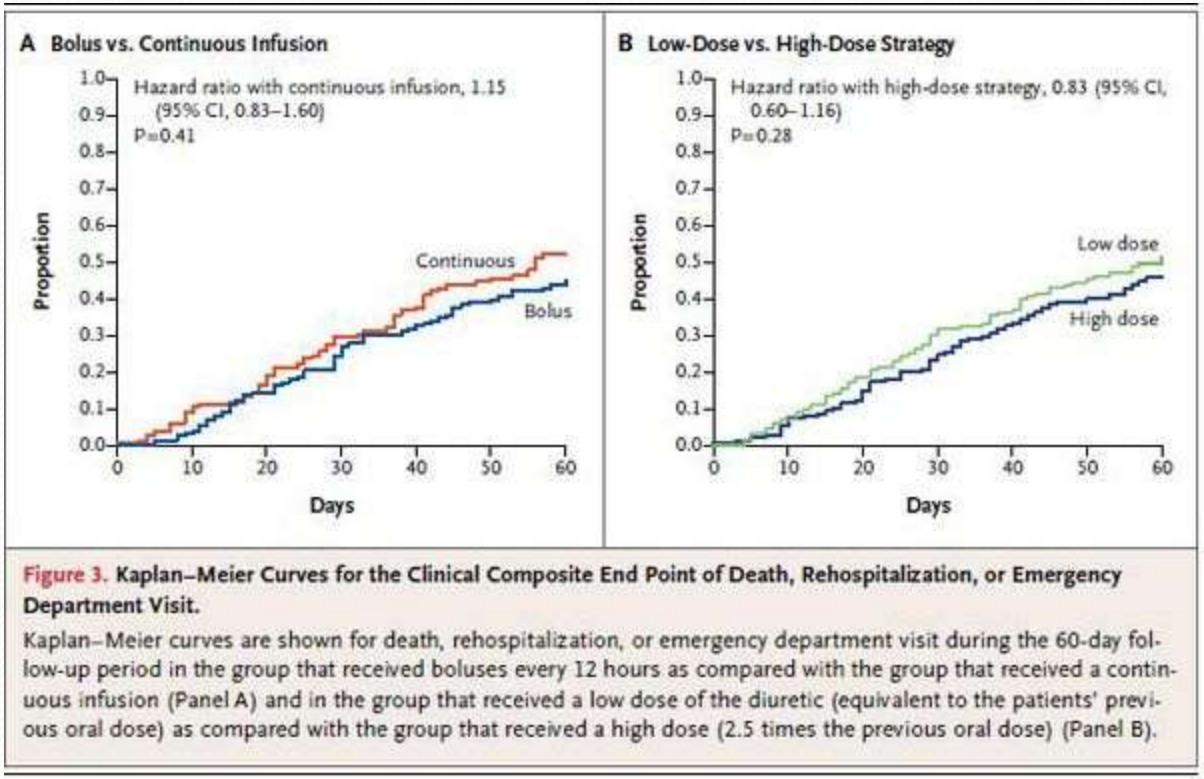


Figure 3. Kaplan–Meier Curves for the Clinical Composite End Point of Death, Rehospitalization, or Emergency Department Visit.

Kaplan–Meier curves are shown for death, rehospitalization, or emergency department visit during the 60-day follow-up period in the group that received boluses every 12 hours as compared with the group that received a continuous infusion (Panel A) and in the group that received a low dose of the diuretic (equivalent to the patients' previous oral dose) as compared with the group that received a high dose (2.5 times the previous oral dose) (Panel B).

Low dose = total home oral dose per day
High dose = 2.5 times oral dose

DOSE Trial

- Trend towards higher creatinine with high dose : no difference at 60 days
- No significant differences in patients' global assessment of symptoms

Use what works for each patient

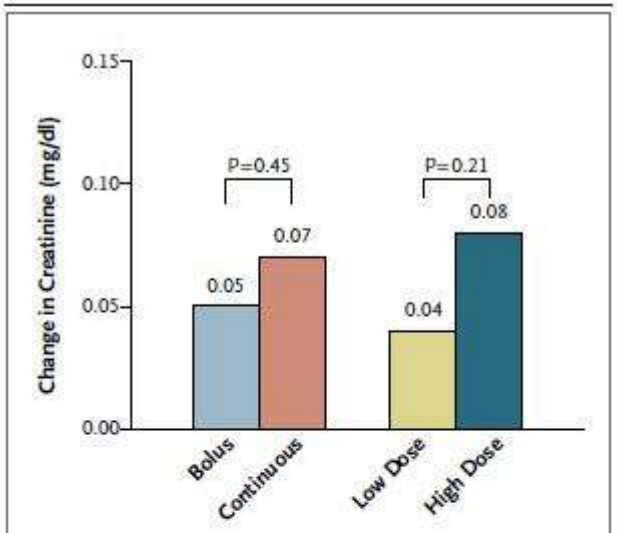
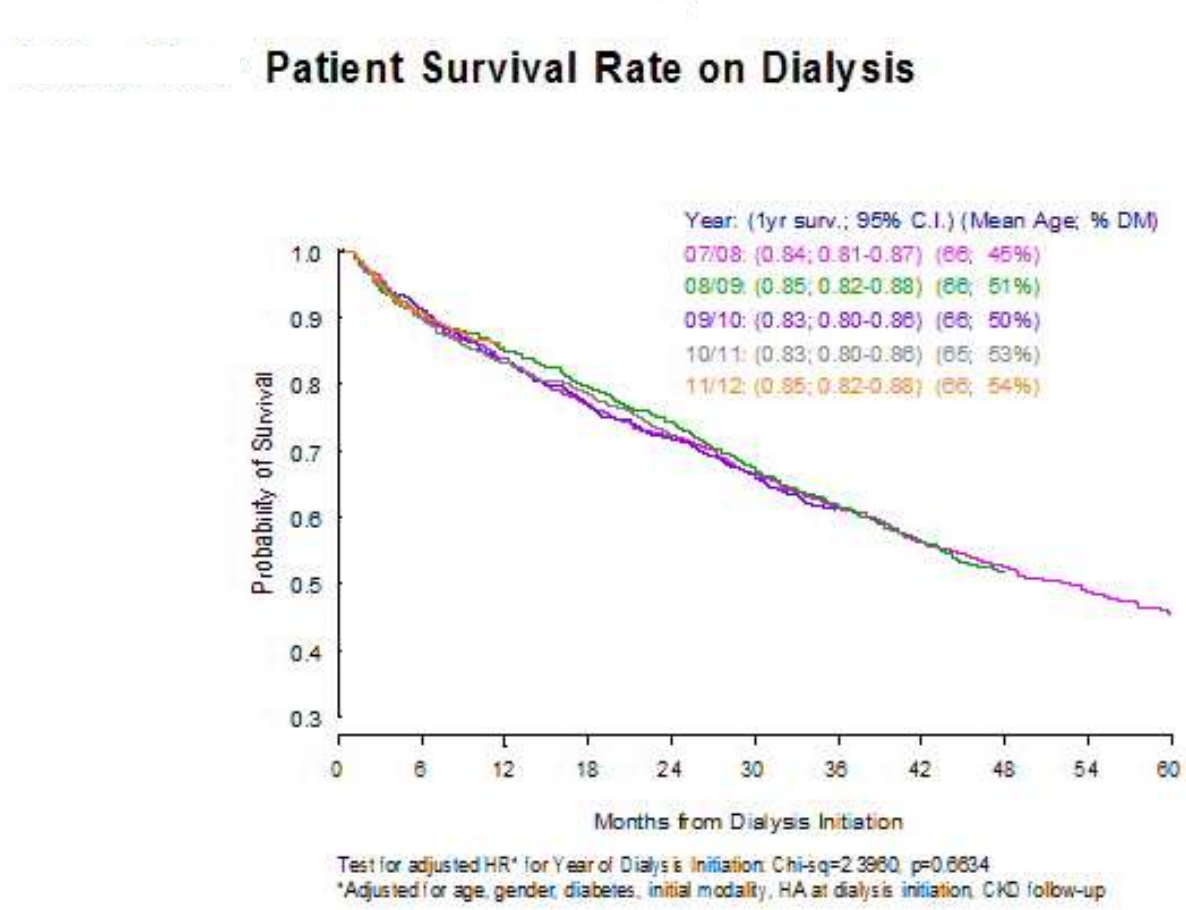


Figure 2. Mean Change in Serum Creatinine Level.
The mean change in the serum creatinine level over the course of the 72-hour study-treatment period is shown for the group that received boluses every 12 hours as compared with the group that received a continuous infusion and for the group that received a low dose of the diuretic (equivalent to the patients' previous oral dose) as compared with the group that received a high dose (2.5 times the previous oral dose). To convert the values for creatinine to micromoles per liter, multiply by 88.4.

What should we do?

- Stepped up pharmacologic therapy to ensure adequate diuresis (e.g. addition of metolazone)
- IV bolus or continuous infusion – whichever works
- If BP or cardiac output low – defer to our cardiology colleagues to decide what's next (e.g. ? Inotropes)
- If all fails, consider ultrafiltration or dialysis as needed

British Columbia Data



Renal blood flow and GFR

decrease significantly when MAP falls below 60