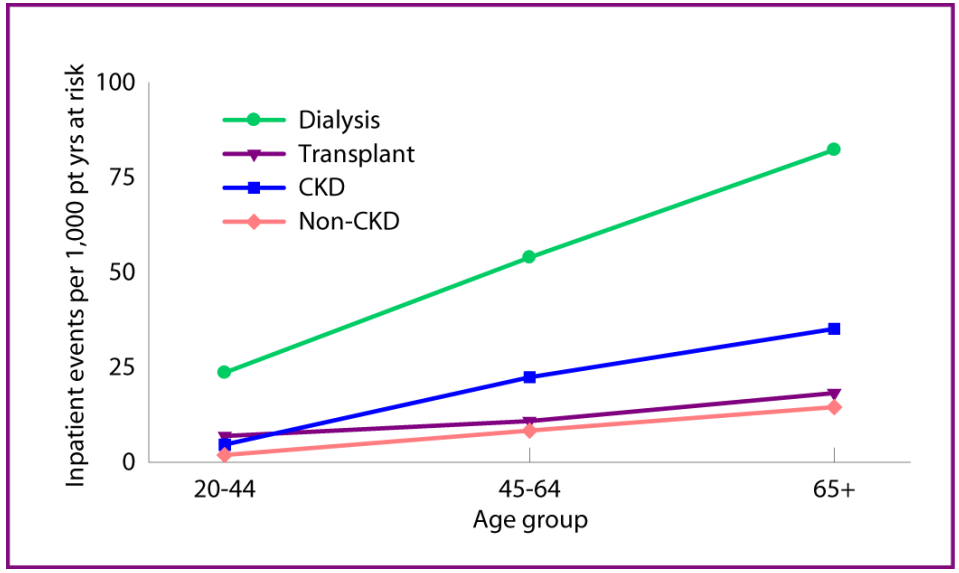
ASN DIALYSIS ADVISORY GROUP

ASN DIALYSIS CURRICULUM

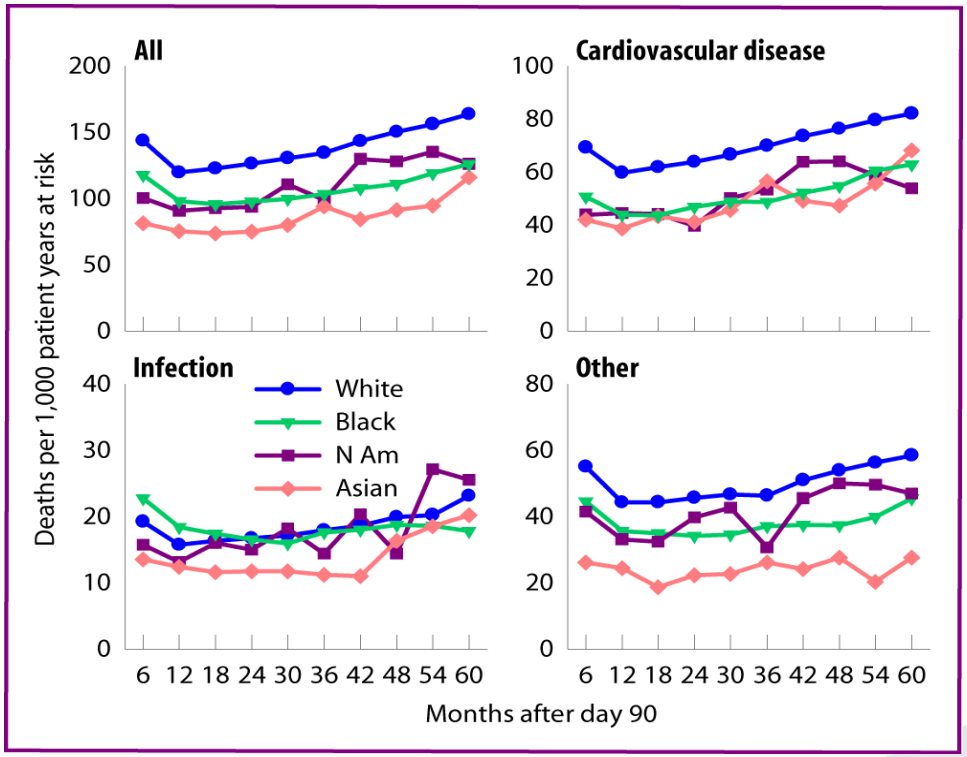
Management of Non-Traditional CV Risk Factors in ESRD

David Charytan, MD, MSc
Brigham & Women's Hospital
Harvard Medical School
Boston, MA

(A) Adjusted age-specific MI rates Dialysis vs. Other



(B) Adjusted cause-specific mortality rates in incident Dialysis Patients



USRDS; 2005 ADR.

Etiology of Increased Risk of CVD Events in ESRD

- Hypertension
- Hyperlipidemia
- Age
- Diabetes

Traditional Risk Factors

- Inflammation
- Oxidative stress
- CKD-Mineral and Bone Metabolism
- Myocardial changes
- Hyperuricemia
- Hyperhomocystinemia
- ADMA
- Arterial Calcification
- Volume Overload
- Myocardial Stunning
- Sleep apnea

Non-Traditional Risk Factors

Left Ventricular Hypertrophy is Common in ESRD

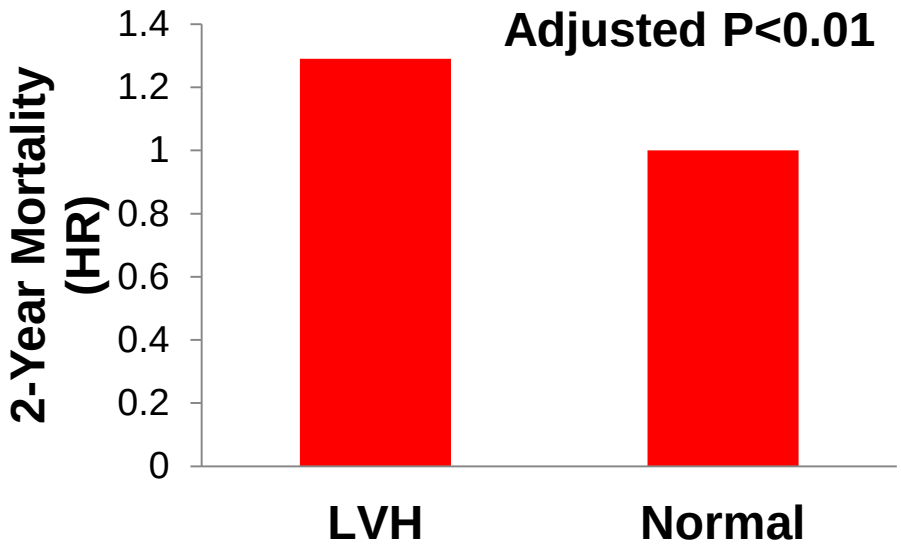
- Prevalence increases in stage 4 CKD compared with earlier CKD
- Present in approximately 75-85% of incident dialysis patients
- May be present in eccentric form (volume overload) or concentric form

Variable	Moderate CKD	Severe CKD	ESRD	P
LVH (%)	70	83	85	0.20
LVMI (g/m^2)	58.2	63.6	60.2	0.20
EF <50% (%)	21	33	46	0.005

Foley RN. KI. 1995;47:186-92
Bansal N. CJASN. 2000;8:355-62

Left Ventricular Hypertrophy is Associated with Mortality

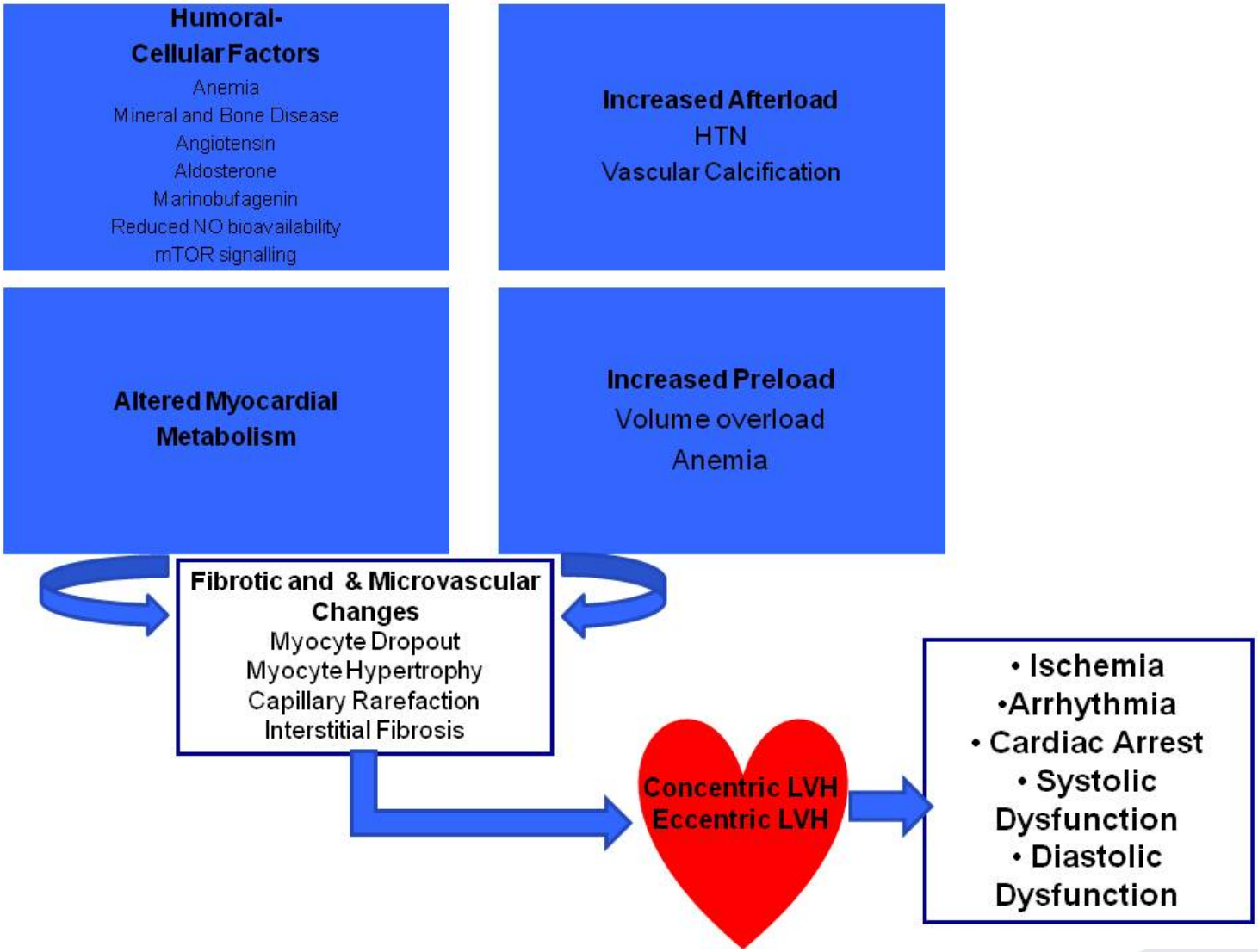
- **Baseline LVH and progression of LVH associated with risk of death and CV events during follow-up**
  - **Strong univariate associations for baseline LVH but not all data confirms independent effect**
  - **LVH progression independently associated with CV outcomes**



Association between LVH and Mortality in 2584 incident HD patients

Stack AG. AJKD. 2002;40:1202-10

Etiology of Left Ventricular Hypertrophy in ESRD



Glassock RJ. CJASN. 2009;Supplement1:S79-91.

Left Ventricular Hypertrophy Regression in ESRD

- LVH progression is not inevitable in ESRD
  - With usual care LVH regresses in ~40% of hemodialysis patients
  - LVH regression or stabilization in majority of patients in non-randomized trials of multi-factorial intervention optimizing anemia, BP and volume control
  - No impact of anemia correction in best RCTs but non-randomized data consistent with benefit when anemia severe
  - Quotidian dialysis RCT data
    - Significant reduction in LVMI with short daily vs. 3x/week HD
    - Similar effect estimate but non significant in smaller (underpowered?) trial of nocturnal hemodialysis
  - Small RCTs consistent with significant LVMI reduction with RAS blockade vs. control therapy

Foley RN. CJASN. 2010;5:805-13
London GM. JASN. 2001;12:2759-2767
Hampl H. Am J Nephrol. 2005;25:211-220
Chan CT. CJASN. 2013;8:2106-16
Ito Y. JASN. 2014.125:1094-1102

Treatment/ Prevention of Left Ventricular Hypertrophy

- Regression of LVH is feasible and may result in improved clinical outcomes

- RCT-based recommendations-

  - Switch to daily dialysis if feasible

  - RAS blockade for BP control

  - Anemia correction for LVH control cannot be recommended in majority of patients

Treatment/ Prevention of Left Ventricular Hypertrophy

- Opinion-based recommendations without strong RCT support
  - Optimize volume control/limit inter-dialytic weight gains
  - Optimize BP control
    - Ideal BP target uncertain
  - Optimize control of mineral and bone disease parameters

ESRD is a State of Inflammation and Oxidative Stress

- Persistent elevation of inflammation, oxidative stress biomarkers in ESRD patients
- CRP and IL-6 most widely studied but multiple markers including albumin, ferritin, F2 isoprotanes elevated
- Both transient and persistent inflammation associated with increased risk of all-cause and CV death in ESRD
  - persistently elevated (>10mg/L) in 20% of dialysis and transiently in 26% of patients

Wendy PJ. NDT. 2006;21:1588-1595
Wanner C. NDT. 2002;17:29-32
Ferraro B. KI. 2003;63:2207-13

Factors Contributing to Inflammation and Oxidative Stress in ESRD

- Repetitive exposure to artificial membranes
- Decreased clearance of pro-inflammatory factor as GFR declines
- Tunneled catheters
- Non-pure dialysate/endotoxin exposure
- Nutritional depletion or dialytic loss of anti-oxidants
- Altered microbiome and increased intestinal permeability
- Intravenous iron

Ferrara B. KI. 2003;63:2207-13
Payson BP. KI. 2004;65:1009-1016
Coli L. Int J Atif Organs. 2011;34:481-8
Honda H. Blood Purif. 2009;28:29-39
Nakayam K. Clin Exp Nephrol. 2007;11:218-24
Anders HJ. KI. 2013;83:1010-6
Tovbin D. AJKD. 2002;40:1005-12

Management of Inflammation and Oxidative Stress

- Early removal of tunneled catheter in favor of native access to minimize infection and colonization
- Ultrapure dialysate to minimize endotoxin exposure
- Minimize intra-dialytic hypotension to limit gut translocation of endotoxin
- Biocompatible membranes
- Minimize use of intravenous iron
- Efficacy of anti-oxidant strategies or probiotics unproven
  - No effect of randomization to 6 months of mixed tocopherols + ±-lipoic acid vs. matching placebo on markers of inflammation in 353 hemodialysis patients

Himmelfarb J. JASN. 2014: 25:623-33

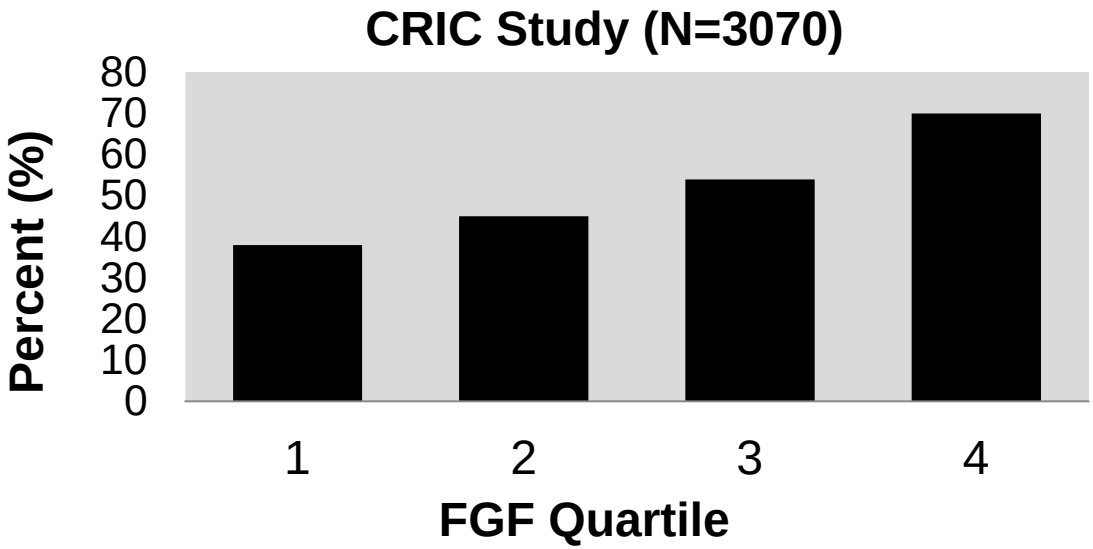
Mineral and Bone Metabolism Factors Implicated in Cardiovascular Disease

- PTH
- Vitamin D
- FGF-23
- Positive calcium balance/Hypercalcemia
- Hyperphosphatemia
- Vascular calcification

Evenepoel P. Semin Nephrol. 2014;34:151-63

Mineral Bone Disease and Left Ventricular Hypertrophy

- **Left ventricular hypertrophy**
  - **Vitamin D deficiency, hyperparathyroidism and increased FGF-23 all associated with ventricular hypertrophy and myocardial fibrosis in experimental and clinical studies**



Faul F. JCI. 2011;121:4393-4408

Mizobuchi M. J Steroid Biochem Mol Biol.2010;121:188-92
van Ballegooijen AJ. Am J Cardiol. 2013;111:418-24
Gutierrez OM. Circulation. 2009;119:2545-52

Mineral Bone Disease and Vascular Calcification

- **Vitamin D deficiency, hyperparathyroidism , calcium balance/binders, hyperphoshatemia, and increased FGF-23 all associated with vascular calcification in experimental and clinical studies**
- **Present in high proportion of patients before dialysis initiation**
- **Progressive over time**
- **More rapid progression with high phosphorous, use of calcium containing binders, high FGF-23, high PTH**

Chertow GM. NDT. 2004;19:1489-96
Khan AM. CJASN. 2012;7:2017-22
Bhan I. CJASN. 2009;Suppl :S102-5.

Mineral Bone Disease and Vascular Calcification

- **Coronary Calcification more common in ESRD or CKD than with normal renal function, particularly among those with diabetes**
- **Most accurately detected with EBCT, but peripheral/central vascular calcification associated with coronary calcification and can be detected with chest/abdominal/forearm plain films**
- **Independently linked to risk of CV death in both ESRD and normal controls**
- **Coronary calcification is correlated with presence of coronary atherosclerosis**

Goodman WG. NEJM. 2000;18:1478-83
Kramer H. JASN 2005;16:507-13
Matsuoka M. Clin Exp Neph 2004
8:54-58. Block GA. KI 2007;78:438-41

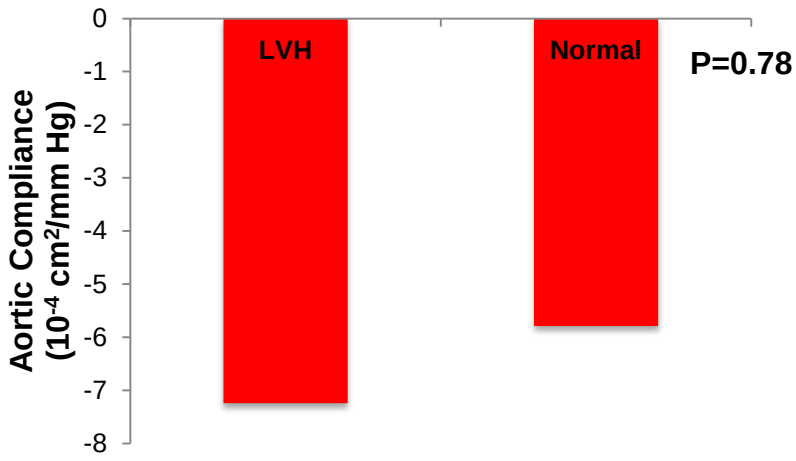
Mineral Bone Disease and Vascular Calcification

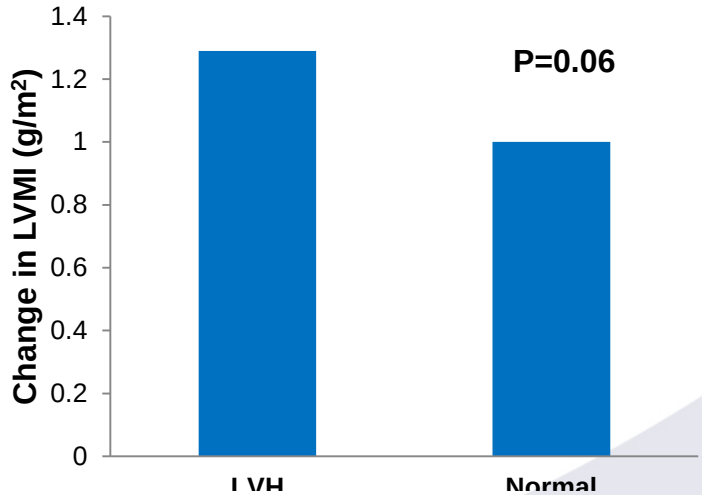
- Excellent marker of all-cause and cardiovascular mortality risks
- Pathogenic role of coronary calcification uncertain
  - May play a protective or compensatory role—response to atherosclerosis rather than underlying cause
    - Experimental studies suggest stabilization of plaque by calcification
- Extra-coronary vascular calcification
  - Decreased arterial compliance/increased afterload
  - Increased blood pressure
    - Secondary consequences
      - LVH
      - Vascular damage

Virmani R. Circ 2001;103:1051-1056
Haydar AA. KI. 2004;65:1790-4

Management of Mineral Bone Disease and Vascular Calcification

- Activated or 25OH Vitamin D
  - Multiple trials demonstrate impact on parameters of MBD
  - No RCT evidence of impact on mortality in ESRD
  - Primo Study
    - 227 patients with CKD randomized to placebo or paricalcitol
    - No improvement in LV mass or aortic compliance at 48 weeks despite significant differences in PTH





Thadani R. JAMA. 2012;307:674-684

Management of Mineral Bone Disease and Vascular Calcification

- Cinacalcet
  - Improved FGF 23 and PTH
  - No evidence for improvement in CV outcomes
  - EVOLVE trial
    - 3883 hemodialysis patients randomized to cinacalcet vs. placebo
    - Primary endpoint death or non-fatal CV event
      - HR 0.93 (95% CI: 0.85-1.02), P=0.11
      - Significant benefit in adjusted analysis (post-hoc)
- Sevelamer
  - Early trials consistent with decreased arterial calcification with non-calcium containing compared with calcium-based binders
  - No evidence for improvement in CV outcomes
  - DCOR trial
    - 2103 hemodialysis patients randomized to sevelamer vs. calcium containing binder
    - All-cause mortality—HR 0.93 (95% CI: 0.79-1.10), P=0.40
    - CV Mortality—HR 0.93 (95% CI: 0.74–1.17), P=0.53
    - Evidence of benefit in post-hoc analysis of long-term users

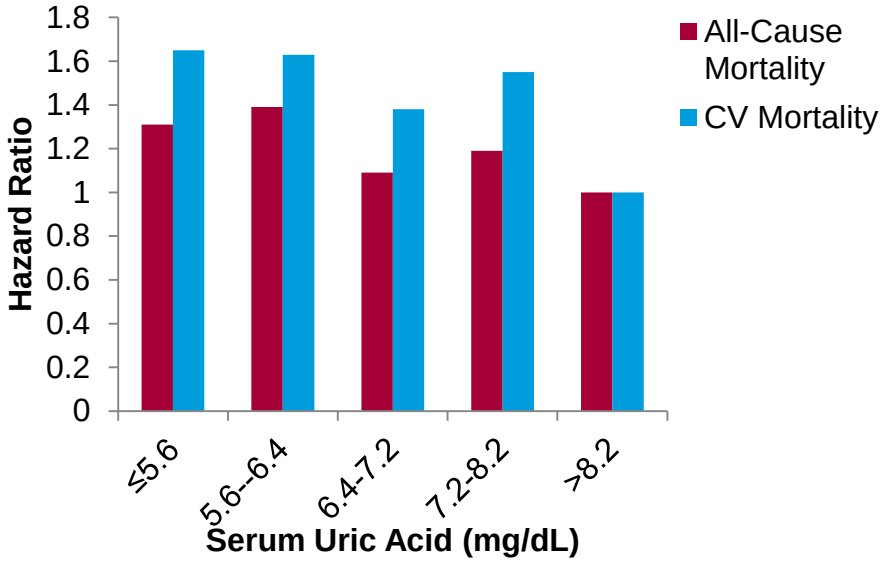
Chertow GM. NEJM. 2012;367:2482-94
Suki W. KI. 2007;72:1130-1137

Management of Mineral Bone Disease and Vascular Calcification Conclusions

- Disorders of calcium, phosphorous, PTH, vitamin D and FGS-23 linked to LVH, arterial calcification, and mortality
- Available agents effectively improve parameters of MBD but have not been proven to improve CV outcomes
- Reasonable to limit intake of calcium containing phosphate binders to low doses
- Suggestion of benefit with cinacalcet but no definite evidence
- Evidence for benefit from vitamin D analogues lacking

Hyperuricemia

- Uric acid levels frequently elevated in CKD and ESRD
- Hyperuricemia associated with poor outcomes in general and CKD populations and with endothelial dysfunction in ESRD
- Small RCT of allopurinol vs. placebo in CKD→ improved LVH
- Largest ESRD study—increased risk of CV outcomes with *lower* UA
- Premature to recommend urate lowering therapy in ESRD at current time



Latif W. CJASN. 2011;6:2740-2747 Kao MP. JASN. 2011;22:1382-9

Asymmetric Dimethyl Arginine

- ADMA
  - Potent inhibitor of nitric oxide synthase (NOS)→reduced NO availability
  - Concentration dramatically elevated in ESRD and CKD due to decreased degradation and increased production
  - Strongly associated with risk of CV and all-cause mortality
  - Nitric Oxide Donors or L-arginine (NOS substrate) increase NO availability
    - Improved LVH and BP in trial of 140 HD patients randomized to isorsorbide mononitrate vs. placebo for 24 weeks.
  - Conclusions
    - Potent risk factor with available therapeutic options
    - Limited evidence is promising but premature to advocate routine use of nitrate donors or L-arginine in ESRD

Zoccali C. Lancet. 2001;358:2113-7 Li H. J Nephrol. 2011;24:236-245

Homocysteine

- Concentrations elevated in ~85% of CKD patients due to reduced metabolism, impaired renal excretion, and folate losses in dialysate
- Increased HCY contributes to oxidative stress and atherosclerosis
- Strong associations with mortality and CV risk in ESRD
- Levels can be decreased by folate and/or Vitamin B12 supplementation
- RCT of 650 HD patients high-dose MVI (folate/B_6/B_{12}) vs. low-dose MVI
  - Mortality—HR 1.13 (95% CI: 0.85-1.50), P=0.51
  - CV events—HR 0.80 (95% CI: 0.60-1.07), P=0.13
  - Negative results in FAVORIT trial (4110 transplant patients)
- Conclusions
  - Potent risk factor with available therapeutic options
  - Evidence does not support high dose therapy to lower HCY

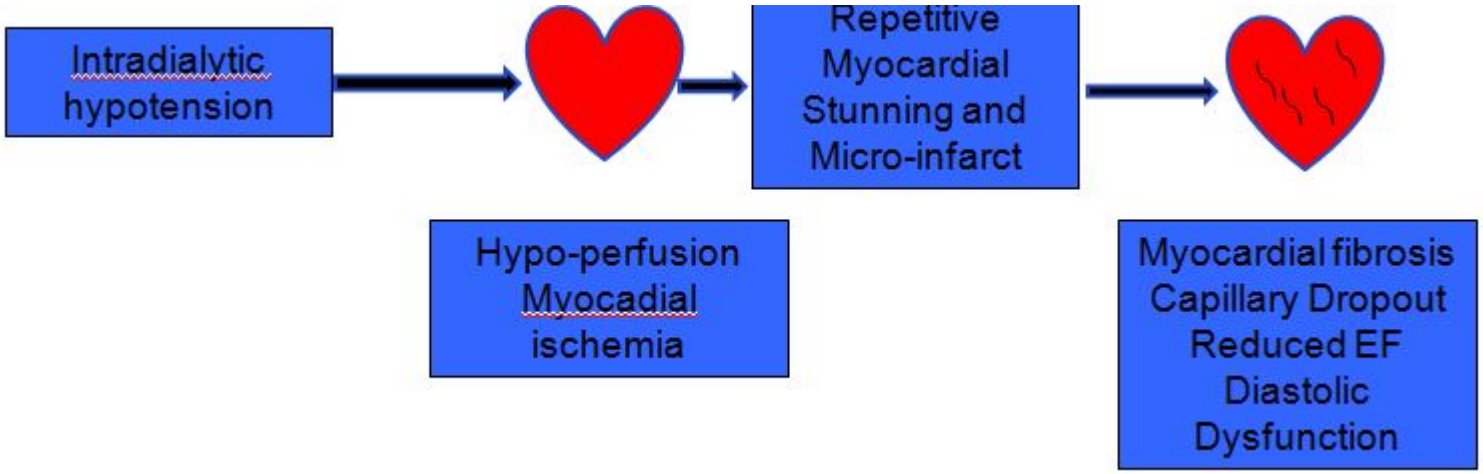
Wu CC. Clin Biochem. 2012;45:1286-94 Heinz J. Circ. 2010;121:1432-8
Bostom AG. Circ. 2011;123:1763-70

Myocardial Stunning

- **Myocardial perfusion decreases early in dialysis prior to significant ultrafiltration**

- **Changes in myocardial blood flow associated with regional wall motion abnormalities—"myocardial stunning" that reverse after dialysis**

- **May be preventable with cool dialysate or other modalities to preventing hypotension**



- **Mortality CV benefits of cool dialysate unknown but intervention is well-tolerated and cost-free**

McIntyre C. CJASN. 2008;3:19-26
Selby NM. CJASN. 2006;1:1216-1225.

Volume Overload

- **Frank volume overload/large interdialytic weight gains (without frank overload) ubiquitous in HD population, less prevalent in PD**

- **Volume overload frequently present even at perceived EDW & difficult to define in individual patients**

- **Markers of volume overload strongly associated with all-cause and CV mortality as well as markers of myocardial damage and inflammation**
  - **Gains > 3kg independently associated with CV and all-cause mortality**

- **Improvements in survival/seen in Frequent Hemodialysis Network trials and non-randomized studies may be due to better volume control with quotidan dialysis**

- **Achieving true EDW/limiting IDWG may accomplished with cool dialysate, low sodium dialysate, dietary counseling, blood volume monitoring but no randomized data showing impact on mortality**

Voroneanu L. Int Urol Nephrol. 2010;42:789-97

Paniagua R. NDT. 2010;25:551-7

Kalantar-Zadeh. Circ. 2009;119:671-9.

Sleep Apnea

- Sleep apnea linked to LVH in general population
  - Small studies demonstrate similar associations in ESRD
  - Associated with presence of hypertension and inflammation

- Volume overload/pulmonary congestion may be key underlying factors

- Non-randomized crossover trial of 14 patients demonstrated improved nocturnal oxygenation with nocturnal HD compared with standard 3x/week IHD
  - Similar findings with change from CAPD to Nocturnal cycler-assisted PD in small, non-randomized study

- No data on outcomes but optimization of volume control, treatment with CPAP and switch to frequent hemodialysis or cycler-assisted PD reasonable when sleep apnea identified

Zoccali C. NDT. 2001;16:70-7
Abdel-Kader. J Hyperten. 2012;30:960-6
Hanly PJ. NEJM. 2001;344:102-107
Tang SC. JASN 2006. 17:2607-16

Conclusions

- Multiple non-traditional risk factors likely contribute to CVD and mortality in ESRD

- LVH, inflammation, and MBD parameters are potent risk factors

- No trials definitively demonstrating reduction in mortality with targeting of non-traditional risk factors but good evidence exists that many are modifiable

- Opinion-based recommendations can be made for reasonable steps to target non-traditional CV risk factors in the absence of high-quality studies

- Prospective, mortality-powered RCTS are urgently needed to determine the efficacy of targeting modifiable non-traditional CV risk factors in ESRD