Management of Non-Traditional CV Risk Factors in ESRD

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

(B) Adjusted cause-specific mortality rates in incident Dialysis Patients
Etiology of Increased Risk of CVD Events in ESRD

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

Traditional Risk Factors

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Moderate CKD</th>
<th>Severe CKD</th>
<th>ESRD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVH (%)</td>
<td>70</td>
<td>83</td>
<td>85</td>
<td>0.20</td>
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<tr>
<td>LVMI (g/m²)</td>
<td>58.2</td>
<td>63.6</td>
<td>60.2</td>
<td>0.20</td>
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<td>EF &lt;50% (%)</td>
<td>21</td>
<td>33</td>
<td>46</td>
<td>0.005</td>
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</tbody>
</table>

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

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

Association between LVH and Mortality in 2584 incident HD patients
Etiology of Left Ventricular Hypertrophy in ESRD

**Humoral-Cellular Factors**
- Anemia
- Mineral and Bone Disease
- Angiotensin
- Aldosterone
- Mammalian target of rapamycin
- Reduced NO bioavailability
- mTOR signalling

**Altered Myocardial Metabolism**

**Increased Afterload**
- HTN
- Vascular Calcification

**Increased Preload**
- Volume overload
- Anemia

**Fibrotic and Microvascular Changes**
- Myocyte Dropout
- Myocyte Hypertrophy
- Capillary Rarefaction
- Interstitial Fibrosis

**Concentric LVH**

**Eccentric LVH**

- Ischemia
- Arrhythmia
- Cardiac Arrest
- Systolic Dysfunction
- Diastolic Dysfunction

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. CJ ASN. 2010;5:805-13
Chan CT. CJ ASN. 2013;8:2106-16
Ito Y. J ASN. 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

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Wendy PJ. NDT. 2006;21:1588-1595
Wanner C. NDT. 2002;17:29-32
Ferraro B. Kl. 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
Anders HJ. KI. 2013;83:1010-6
Tovbin D. AJ KD. 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

CRIC Study (N=3070)

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

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, hyperphosphatemia, 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
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

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

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

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. CJ ASN. 2008;3:19-26
Selby NM. CJ ASN. 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

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
Hanly PJ. NEJ M. 2001;344:102-107
Tang SC. J ASN 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