ASN DIALYSIS ADVISORY GROUP

ASN DIALYSIS CURRICULUM
The Challenge of Sudden Cardiac Death in Hemodialysis Patients

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Learning Objectives

Describe the epidemic of sudden cardiac death (SCD) among CKD (and particularly ESKD) patients

Describe unique risk factors which may explain the high risk of SCD in hemodialysis patients

Describe what we know about SCD prevention and management in hemodialysis patients
Sudden Death is the Leading Cause of Death in Dialysis Patients

Prevalent Dialysis Patients, 2007-2009:

- **ScD**: 26.1%
- **AMI**:
- **CHF**:
- **Arrhythmia/SCA**:
- **CVA**:
- **Other cardiac**:
- **Infection**:
- **Withdrawal**:
- **Malignancy**:
- **All other**:

USRDS ADR 2011
The risk of SCD in ESKD-HD is 20x greater than the general population

Duke catheterization database:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Events/1000 pt-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gen Pop</td>
<td>1.89</td>
</tr>
<tr>
<td>CVD</td>
<td>4.2</td>
</tr>
<tr>
<td>CKD3-4</td>
<td>7.3</td>
</tr>
<tr>
<td>CKD 5 ND</td>
<td>12.5</td>
</tr>
<tr>
<td>ESRD-HD</td>
<td>24.1</td>
</tr>
</tbody>
</table>

N=19,440

11% increase risk per 10 ml/min GFR decline

Pun et. al. Kidney Int. 2009 Sep;76(6):652-8
What is also clear is that the risk of SCD increases in relationship to the number of years on dialysis. Again data from the USRDS showing the increasing cumulative probability of SCD with each passing month on HD.
Why is the SCD rate so high?
Possible explanations

Misclassification

Same disease as general population, just worse

Novel risk factors → New Disease
SCD Traditional Definitions

• **Witnessed cardiac arrest**
  - Within an hour of symptom onset

• **Unwitnessed death**
  - Unexpected
  - Patient known to be well in the last 24 hours
  - No other clear non-cardiac cause of death

• **Out of hospital occurrence of unanticipated non-traumatic cardiac death**

• **Usually due to ventricular tachyarrhythmia**

• **Does this apply to dialysis patients?**
Probably not just due to misclassification: Some assurances

Registry/death certificate data prone to misclassification?

**363 HD patients with witnessed outpt SCD**

- Sensitivity of registry definition 70-83%
- Specificity of registry definition 90%

**SCD rate is consistent across data sources**

- In clinical trials [HEMO trial, 4D trial]
- In prospective HD cohorts [CHOICE cohort]

**Increased rate of SCD unlikely due to just misclassification**

Herzog et al. Kidney Int. 2011 Sep;80(6):572-86
SCD Pathophysiology Cardiomyopathy + Acute Trigger=SCA

- Cardiomyopathy (Decreased EF)
- Malignant Arrhythmias
- Arrhythmic Triggers (Ischemia)

Conventional CHD-related Risk Factors

CKD Patients

HD patients
Underlying cardiac disease in CKD SCD is rarely traditional ischemic cardiomyopathy with systolic dysfunction

- Only 7% Systolic Dysfunction in CRiC
- 5% in incident HD cohort
- Increased SCA risk cannot be explained by SD/ IHD disease alone
Differences in Structural Heart Disease: LVH and Diffuse Myocardial Scarring are more Common

Left Ventricular Hypertrophy
• 56% of HD pts without CAD

Etiologic associations with
• Chronic ECFV excess/ vascular access
• Pressure loading/ hypertension
• Anemia
• Mineral-bone-disease/ hyperphosphatemia
• Aluminum

LVMI>125 g/m² = 30% increased risk of death at 5 yrs

LVH= Increased rate of arrhythmias

Increased myocardial fibrosis with diffuse subendocardial enhancement

Meier et. al. Nephron. 2001 Mar;87(3):199-214
Silverberg et. al. KI 1989
Ayus et. al. JASN 2005
SCD Acute Triggers: SCD and Arrhythmias occur most frequently on the first hemodialysis day of the week.

Mortality and CV events on Days of the Dialysis Week

32,000 US HD patients

Foley et. al. NEJM 2011: 365: 1099
Hemodialysis as an acute trigger for SCD

Potentially due to rapid shifts in:

• Potassium?

• Calcium?

• Fluid?
Role of Serum Potassium in SCA

Study of 500 witnessed peridialytic SCA vs. 1600 matched controls

Risk linked to extremes of serum potassium (K)

Lowest risk at K ~ 5.0

Role of Dialysate Potassium in SCA

Use of low potassium dialysate (<2 meq/L) was associated with a two-fold increase in risk of SCA

Mean Predialysis serum K was in the normal range (4.9 meq/L)

Potassium Homeostasis and Risk of SCA: Low [K] bath for High Pt [K]?

Difference in risk between low and high K dialysate decreases as serum K increases.

No indication of benefit for low K dialysate at any level of serum K.

Calcium: Low Calcium Dialysate Associates With Increased risk of SCD

Matched Case Control Study of 2100 patients

- 50% Increase in SCA risk with dialysate calcium <2.5 meq/L
- Risk rises incrementally with increasing serum: dialysate gradient


\[ \text{aOR} = 1.83 \ (1.4-2.5) \ \text{per 1 mmol/L increase in gradient} \]
Amount and Rate of Fluid Removal During HD Associates With Myocardial “Stunning”

- Hemodialysis procedure can reduce myocardial blood flow, even in absence of significant CAD.
- A myocardial “stun” may be detected from echocardiogram regional wall motion abnormalities (RWMAs).
- RWMAs present in 50-64% of patients, and associated with poor outcomes.

<table>
<thead>
<tr>
<th>HD Exposure</th>
<th>Odds Ratio</th>
</tr>
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<tbody>
<tr>
<td>1L Fluid Removal on HD</td>
<td>5.1</td>
</tr>
<tr>
<td>1.5L Fluid Removal on HD</td>
<td>11.6</td>
</tr>
<tr>
<td>2L Fluid Removal on HD</td>
<td>26.2</td>
</tr>
</tbody>
</table>

SCA in CKD: A complex interplay of traditional and CKD-related risk factors

- **CKD**
- **ESKD-HD patients**
- **Conventional CHD-related Risk Factors**
- **Unique CKD-related Risk factors**
- **Cardiomyopathy**
- **Malignant Arrhythmias**
- **Arrhythmic Triggers**
- **SCA**

Risk factors include:
- Inflammation
- Malnutrition
- Uremia
- LVH
- Anemia
- CaPhos
- PTH
- Electrolyte shifts
- Autonomic instability
- Dialysis reactions
- Volume shifts
Management of SCD

Prevent Sudden Cardiac Arrest
• Medical therapies to treat underlying cardiac disease
• Reduce exposure to triggers

Improve survival following SCA
• Defibrillation
Medical Therapies for SCD Prevention: Beta Blockers

- Beta Blockers shown to be helpful for prevention in pts with minimal or no CKD.

- Poor Implementation: Only 24% of dialysis patients with CAD or prior MI are on beta blockers

- Only one randomized trial of beta-blockers in ESRD
  - 114 pts with DCM randomized to Carvedilol or placebo
  - Significant survival advantage: non significant reduction (24%) in SCD

Cice: J ACC 2003; 41:1438-44
Medical Therapies for SCD Prevention: Phosphorus/SHPT

Hyperphosphatemia can provoke vascular calcification, endothelial dysfunction and atherosclerosis.

Observational study of 12,833 HD patients
• 6% increase in SCD per 1 mg/dl increase in Phos
• 7% increase in SCD per 10 mg/dl increase is CaxPhos product
• 20% increase with phos >6.5
• 6% increase with PTH>495

Ganesh et. Al. JASN 2001
Other Medical Therapies for SCD Prevention?

Benefit in ESRD not clearly known for:

- Statins
  - 4D, AURORA studies negative
  - SHARP: Reduction in coronary revascularization cardiac events seen only in 2/3 pts with predialysis CKD not in 1/3 pts with ESRD
- ACEI/ARB
- Antiplatelet agents
- Vitamin D
Implantable Cardioverter Defibrillators in HD patients:

No ESRD patients included in any randomized trials

- **Secondary prevention ICD (ICD after cardiac arrest)**
  - Two retrospective studies show benefit ICD after cardiac arrest compared to patients with cardiac arrest and no ICD
    - HR 0.86 (95% CI 0.81-0.91)
    - Subject to indication bias
  
- **Primary prevention (prophylactic ICD)**
  - No data on mortality benefit in ESRD compared to controls
  - Increased mortality, risk of complications, in ESRD compared to non-ESRD ICD recipients


Diminishing Benefit of Primary ICD with CKD

Meta-analysis of 3 randomized controlled trials
- 2,867 patients
- 36.3% with eGFR <60; no HD patients
- Diminishing survival benefit of ICD vs. no ICD with lower eGFR
Why might primary ICDs not be beneficial?

• Increased defibrillation thresholds in CKD and ESRD pts compared to normal

• ESRD patients not having “shockable” events; 38% of ICD recipients on dialysis still die of arrhythmia!

• Competing risks may outweigh benefits:
  • Death: 45% annually
  • Bacteremia: 52%
  • Device infection: 4.2% (vs. 0.7%)
  • Generator replacement: 3.9% (vs <2%)
  • Vascular Access Complications

Wase J Interv Card Electrophysiol. 2004 Dec;11(3):199-204
Charytan et. al Am J Kidney Dis. 2011 Sep;58(3):409-17
Drew et. al Am. J. Kidney Dis. 2011 Sep;58(3):494-496
Rising to the Challenge of SCD in Hemodialysis Patients

Treat Cardiomyopathy:
• Assess at baseline and q3yrs (2005 K/DOQI guideline)
• Use beta-blocker for dilated cardiomyopathy EF <35%
• Control SHPT and phosphorus
• Unclear if other proven therapeutic interventions will also be beneficial in dialysis patients

Reduce and monitor triggers
• Avoid low potassium and low calcium dialysate
• Review and adjust prescription dialysis regularly in response to laboratory data
• Reduce IDWG/avoid large volume shifts
• More frequent/longer dialysis sessions?
Rising to the Challenge of SCD in Hemodialysis Patients

ICDs

• No evidence to support prophylactic primary ICDs in dialysis patients
  • Counsel patients regarding likelihood of decreased benefits and increased risks compared to general population

• Consider ICDs for secondary prevention

• Coordinated care b/t nephrologists and EP
Rising to the Challenge of SCD in Hemodialysis Patients

We need:

• Large cohort studies assessing risk factors with carefully adjudicated endpoints
  • Clinical variables
  • Dialysis variables
  • Cardiac/EP variables
  • Biomarkers

• RCT
  • Beta blockers
  • Potassium management
  • ICDs (ICD2 trial, wearable ICD, subQ ICD?)