Can We Prevent Sudden Cardiac Death in CKD Patients?

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Introduction

- Dialysis patients have high mortality rates
- Death rate for all U.S. dialysis patients in 2008 was 205 per 1,000 patient years
- Cardiac disease is the major cause of death in dialysis patients - 40% of all-cause mortality
- 14% of cardiac deaths are attributed to AMI in the USRDS database
- 66% of cardiac deaths are sudden/arrhythmic in the USRDS database = 26% of all-cause mortality
- HEMO & 4D trials: 25-26% of all deaths are sudden
Causes of death in prevalent dialysis patients, 2006–2008

Figure 9.1 (Volume 2, 2010 ADR)

- AMI: 5.3%
- CHF: 5.2%
- Arrhythmia/cardiac arrest: 26.1%
- Other cardiac: 2.2%
- CVA: 3.7%
- Infection: 11.8%
- Withdrawal: 9.0%
- Malignancy: 3.7%
- All other: 32.9%

Prevalent dialysis patients, 2006-2008.
Event rates of cardiovascular diagnoses & procedures, by modality

Point prevalent ESRD patients on January 1, 2005

USRDS 2009 ADR
Factors impacting sudden cardiac death in ESRD patients

- Ischemic heart disease — “Obstructive CAD”
- Abnormalities in myocardial ultra-structure & function (cf. Amann & Ritz, et al)
  - Endothelial dysfunction (DM)
  - Interstitial fibrosis
  - Decreased perfusion reserve
  - Diminished ischemia tolerance
- Left ventricular hypertrophy
- Electrolyte shifts in hemodialysis patient
- Autonomic dysfunction (& sleep apnea)
Methods for estimation of sudden cardiac death in dialysis patients

• “Simple Method”: “Cardiac arrest, cause unknown” or “arrhythmia” from CMS Death Notification (2746) form (= 26% all-cause mortality)
  ▪ Excludes other sudden cardiac deaths (e.g. AMI)
  ▪ Includes deaths not truly sudden cardiac (e.g. patients withdrawn from dialysis)
• “CVSSC ADR Method”: ICD-9-CM claims + Form 2746 in context of death location
• Definition of “Inpatient” SCD is problematic
“CVSSC ADR Method” for SCD

- **SCD outside of hospital (including death in ER):**
  - ICD-9-CM codes 427.4 or 427.5 (v.fib/cardiac arrest) and cardiac or unknown cause on Form 2746
  - *OR*
  - If no claim data, primary cause of death is cardiac on Form 2746

- **SCD in-hospital:**
  - Inpatient claim for v.fib/cardiac arrest and primary cause of death due to cardiac disease on Form 2746.
  - *OR*
  - If no claim data, primary cause of death due to cardiac arrest/arrhythmia on Form 2746.

- **Exclusions (both groups):** Sepsis, malignancy, hyperkalemia, or withdrawal from dialysis on Form 2746.
SCD in 2002 U.S. prevalent dialysis patients (followed to 12-31-03)

- **Total Death**: 99,854 (100%)
  - **Out-of-Hospital Death**: 51,298 (51.4%)
    - **Not SCD**: 27,144
      - **SCD**: 5,970
      - **In Hospital Death**: 24,154 (24.2%)
        - **Not SCD**: 18,184
          - **exclude those withdrawing from dialysis; sepsis, malignancy, & hyperkalemia as secondary causes**: 11,481
            - **SCD**: 29,665 (29.7%)
  - **In Hospital Death**: 48,556 (48.6%)
    - **Not SCD**: 34,198
      - **SCD**: 11,481

**Exclusion Criteria**
- Patients withdrawing from dialysis
- Sepsis, malignancy, and hyperkalemia
Prevalent dialysis patients
adjusted SCD rates

SCD-w/withdrawal incl.
SCD_op-w/withdrawal incl.
all-cause death

SCD-w/withdrawal excl.
SCD_op-w/withdrawal excl.
Cumulative probability of SCD & all-cause death
2002 prevalent dialysis patients
Figure 1 | Cumulative incidence of overall mortality and specific causes of death (including sudden cardiac death, other cardiovascular causes and other causes of death) in the CHOICE cohort.

Parekh et al. *Kidney International* 2008;74;1335
Event rates & adjusted event-free survival: cardiac arrest

Event rates

- Rate per 1,000 pt years at risk

Event-free survival

- Percent free of event

- Group 1
- Group 2
- Group 3
- Group 4
- All
Cardiac Arrest in CKD
Unadjusted cardiac arrest event rates

**CKD stages**
1. eGFR ≤ 190, albumin/creatinine ratio (ACR) ≥ 30 mg/g
2. eGFR 45–89, ACR 2–29 mg/g
3. eGFR 10–44
4. eGFR 15–29
5. eGFR <15 (dialysis pts excluded from analyses)
Probability of cardiac arrest in incident patients, overall

Cumulative probability

- CKD
- Hemodialysis
- Peritoneal dialysis
- Transplant

Months

2006 ADR
Probability of cardiac arrest in incident patients, by age

- CKD
  - 66-74
  - 75+
- Hemodialysis
- Peritoneal dialysis
  - 20-44
  - 45-64
  - 65-74
  - 75+
- Transplant

2006 ADR
Probability of cardiac arrest in incident patients, by diabetic status

- **Diabetic**
- **Non-diabetic**

**Cumulative probability**

**Months**: 0, 6, 12, 18, 24, 30, 36

**Conditions**:
- **Peritoneal dialysis**
- **Hemodialysis**
- **Transplant**
Event rates & event-free probabilities, incident patients: cardiac arrest

Event rates

- Rate per 1,000 pt months at risk

- Hemodialysis
- Peritoneal dialysis

Event-free probability

- Event-free probability

- Months after day 90

2006 ADR
Serum Potassium in SCD

  - Prior monthly lab tests: Serum K 4.78±0.94 in cardiac arrest group and 4.90±0.71 in FMCNA reference group
  - Zero or 1.0 mEq/l K dialysate associated with increased risk of sudden death
Serum Potassium in SCD

- Serum K 4.50 mEq/l±0.84 (Mean±SD)
- Serum K range:
  - < 3.5 (13%)
  - 3.5- <4.0 (12%)
  - 4.0- <5.0 (51%)
  - 5.0- <6.0 (18%)
  - ≥6.0 (6%)
Hazard ratios of all-cause mortality for predialysis serum K

Modifiable Risk Factors Associated with Sudden Cardiac Arrest in Hemodialysis Clinics

DaVita Prevalent Dialysis Population
2002-2005 n=43,200

Witnessed Cardiac Arrest N=783

No Cardiac Arrest N=2349
Excluded pts with < 90 days dialysis data.

Case Cohort N=502

Control Cohort N=1646
Sample random matched subgroup 3:1
Potassium Homeostasis and Risk of SCA: Predialysis Potassium

- Risk linked to extremes of serum potassium (K)
- Lowest risk at K ~ 5.0
Potassium Homeostasis and Risk of SCA: Risk of Treatment

- Use of Low K dialysate reduces serum K levels
- ~20% of SCA pts on very low K dialysate at time of event
- Mean Predialysis serum K was in the normal range (4.9 meq/L)
Potassium Homeostasis and Risk of SCA: Risk of Treatment

- Interaction testing: Serum K*Low K dialysate \( p=0.03 \)
- 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
Figure 1. Crude survival curves show decreased survival with digoxin use

Figure 3. The mortality effect associated with a higher serum digoxin level is magnified with decreasing serum K level.

Sudden cardiac death in ESRD patients: therapeutic strategies (a two-tiered approach)

- Reducing the risk of sudden cardiac death
- Improving the likelihood of surviving cardiac arrest
Reducing the risk of sudden cardiac death

*Risk Stratification (Can we identify the highest risk ESRD patients?)*

- Biomarkers - Cardiac Troponin T (CRP, Albumin)
- Electrocardiographic markers
  - Ambulatory ECG (Ventricular ectopy & ST-segment shift)
  - Prolonged Q-T dispersion (a measure of heterogeneity of ventricular repolarization)
  - Abnormal heart rate variability/autonomic dysfunction
  - Microvolt T-wave alternans
  - Heart rate turbulence
BIOMARKERS
Reducing the risk of sudden cardiac death

*Ischemic burden/LV dysfunction*

- Non-invasive stress imaging for detection of “occult CAD”?
- Assessment of left ventricular function in all dialysis patients
Speculative therapeutic strategies (Can we reduce the likelihood of sudden cardiac death?)

- Reduction of Myocardial Ischemic Burden
  - Traditional/“Non-Traditional” Risk Factor Modification
  - Prophylactic coronary revascularization?
  - Prophylactic Beta-blocker therapy?
  - ACE-inhibitors?
  - Improvement of endothelial function/plaque
    - Statins? (No, based on 4D+AURORA)
    - Glycemic control
    - Anti-platelet agents
Reducing the Risk of Sudden Cardiac Death (continued)

“Physiologic Dialysis”

- Frequent long-duration dialysis (for consistent maintenance of euvolemia and avoidance of rapid electrolyte shifts)—Conventional thrice weekly hemodialysis associated with 50% increased death risk on Mondays/Tuesdays (Bleyer et al, 1999).
  
  - Reduction of LVH

- Avoidance of very low K+ (0 or 1.0 mEq/L) dialyzate—nearly two-fold increased risk of cardiac arrest (Karnik et al, 2001).

“Prophylactic” anti-arrhythmic therapy?

- Amiodarone
- Conventional beta-blockers
Probability of all-cause and cause-specific death

CAB (IMG+)

- All-cause: 0.43
- Cardiac: 0.24
- Arrhythmic: 0.14
- MI: 0.06
- Infectious: 0.07
- Other: 0.19

Years

Probability of Event

0.0 0.2 0.4 0.6 0.8 1.0

0.0 0.5 1.0 1.5 2.0 2.5 3.0

Years
Surviving cardiac arrest: strategies for reducing lethality

Device therapy—Implantable cardioverter defibrillators (ICD’s)

- A randomized trial of ICD’s is needed - issue of competing risk of mortality in ESRD (not due to sudden cardiac death)

- Automatic external defibrillators (AED’s) in all dialysis centers (or not: Lehrich et al, JASN 2007)?
Survival after cardiac arrest adjusted for age, gender, race, & ESRD vintage
Cardiac arrest in the dialysis unit

- Cardiac arrest incidence (FMCNA, 10/1998-6/1999) 7/100,000 HD runs (Karnik et al, 2001)
- Cardiac arrest incidence (Gambro, 1/2002-1/2005) 4.5/100,000 HD runs (Lehrich et al, 2007)
- Cardiac arrest incidence (Seattle) 3.8/100,000 HD runs (Davis et al, 2008)
Cardiac Arrest in Seattle/King County Outpatient Dialysis Centers

- 47 cardiac arrests in 9 outpatient dialysis centers from 1990-1996 (from EMS data)
- 41 witnessed events
- Bystander CPR in 41 patients
- 29 patients (62%) rhythm was ventricular fibrillation (VF) or ventricular tachycardia (VT)
- Overall survival to hospital discharge 30%
- Overall survival to hospital discharge 38% for VT/VF despite no AED’s (mortality = 10%/min after cardiac arrest in general population)
- Expected survival even greater with AED’s on site?
Figure 2. Kaplan-Meier survival analysis of patients who sustained cardiac arrest in hemodialysis centers that lacked automated external defibrillators (AED; dotted line) and those where AED were present (solid line)

ICD’s in ESRD Patients
MADIT-2

Survival of dialysis patients after cardiac arrest

Herzog et al, Kidney International, 2005
Figure 1: Kaplan-Meier Appropriate ICD Therapy-Free Survival for VT/VF in ESRD versus non-ESRD Patients

Robin et al, Heart Rhythm 2006
Patients receiving ICDs or CRT-D

Cumulative number & percent of dialysis patients receiving ICDs/CRT-Ds

Figure 9.2 (Volume 2)

USRDS 2010 ADR
Percent of ESRD patients receiving ICDs/CRT-Ds, by modality

Figure 9.3 (Volume 2)

Percent of patients

Peritoneal dialysis
Hemodialysis
Transplant

Period prevalent ESRD patients.
CVD, CVA/TIA, & coronary revascularization in patients receiving ICDs/CRT-Ds, by modality, 1999–2008

Figure 9.4 (Volume 2)

Per period prevalent ESRD patients, 1999-2008.
Demographics of ESRD patients receiving ICDs/CRT-Ds, 1999–2008

Figure 9.5 (Volume 2)

Period prevalent ESRD patients, 1999-2008.
All-cause survival following implantation of ICDs/CRT-Ds, by modality, 1999–2008

Figure 9.6 (Volume 2)

Period prevalent ESRD patients, 1999-2008.
All-cause survival after implantation of ICD/CRT-D

Recipients of first ICD/CRT-D during 1996–2005, age 66 & older (CKD & non-CKD patients), or 20 & older (ESRD patients) on the date of ICD/CRT-D. Survival probabilities are unadjusted.
Survival of patients with cardiovascular diagnoses & procedures, by modality

January 1, 2005 point prevalent ESRD patients, age 20 & older, with a first cardiovascular diagnosis or procedure in 2005–2007. USRDS 2009 ADR
Geographic variations in unadjusted rates of cardiac arrest (per 1,000 patient years), by HSA

1997

2007

Point prevalent ESRD patients age 20 & older. USRDS 2009 ADR
Conclusion

• Sudden cardiac death is the single largest cause of death in dialysis patients
• The usage of ICD’s in dialysis patients has markedly increased over time, (despite their exclusion from clinical trials on device therapy).
• Further studies to reduce the risk of SCD in ESRD patients are warranted.
ICD in Dialysis Patients: Proposed Trial Design
Study Design

Prospective Randomized Clinical Trial

- Equal (1:1) assignment of dialysis patients to ICD implantation or no ICD implantation.
- Target sample size: 1300 patients (650 to receive ICDs).
- Enrollment period: 2 years.
- Follow-up duration: 4 years after enrollment.
- Primary endpoint: all-cause mortality.
- Secondary endpoints: cardiac death, sudden death due to arrhythmia, quality of life, cost effectiveness
- Substudy: serum biomarkers and outcome
Exclusion Criteria

Any of the following:

- Prior ICD implantation or pacemaker, or current established indications for pacemaker, ICD, or CRT therapy.
- Renal transplantation scheduled within the following 12 months (waitlisted patients acceptable).
- Pregnancy.
- Prior history of cardiac arrest.
- Life expectancy < 6 months due to malignancy.
- Inability to give informed consent.
- Current participation in another research study.
- Ongoing sepsis (active infection not adequately controlled).
Infection-free probability after device implant, by device type and implant year

Log-rank test: PM 91-95 vs PM 96-01: P=0.0005
ICD 96-01 vs PM 96-01: P=0.1576

No. at risk
PM 91-95 (N=4,616) 2,978 2,202 1,687 1,288
PM 96-01 (N=9,364) 5,603 3,751 2,532 1,702
ICD 96-01 (N=1,400) 919 599 414 275

ASN 2004

CDRG
LV Ejection Fraction in Dialysis Patients: Observational Data

- Few published cross-sectional data on LVEF in dialysis pts

- Prospective incident Canadian dialysis cohort (n= 433) (Foley et al, 1995); Montreal pts (n=240) had MUGA’s: 9% had LVEF <36% (personal communication, Robert Foley).

- Incident dialysis pt database (n= 500), including Echo (St. Paul’s Hospital, Vancouver, BC): <10% of pts had LVEF <36% (personal communication, Chris Thompson)

LVEF in ESRD SCD

- Few data
- Bleyer et al (KI, 2006): Retrospective study of 88 HD pts (54% African-American) in North Carolina with sudden death, 69 with prior Echo. LVEF 46.6±16.9 (Mean ±SD); LVEF<36% in 17 pts (24.6%); EF 50%+ in 37 pts (53.6%)
- Mangrum et al (Heart Rhythm, S154, 2006): retrospective study of 31 dialysis pts in Virginia with SCD; 71% had normal or mild-moderate LV dysfunction
Power Calculations/Sample Size  
(1300 Patients enrolled in 130 sites)

- High number of expected competing risks in dialysis population, etc mandates conservative assumptions.
- Assumptions:
  - 4 year 50% survival of non-ICD (control) arm
  - SCD responsible for 26% of all-cause mortality (= SCD rate of 13% at 4 years).
  - ICD’s will reduce SCD rate by two-thirds.
  - Estimated treatment effect is based on a detectable reduction in all-cause mortality of ≥17.5%
  - Constant hazard ratio for entire follow-up period.
  - Interim analyses after 70% and 85% of deaths have occurred.
  - Sample size based on two-tailed upper boundary of 0.05(by log rank test)
  - 88% power
  - Two year uniform entry, four year follow-up
  - Attrition rate of 10%/yr in first two years
ICD Trial in Dialysis Patients: Coda (Why should we do this?)

- SCD is single largest cause of death in dialysis patients, with minimal improvement over time.
- The number of U.S. ESRD patients is projected to increase by 700% in the next 25 years, with disproportionate increase in high risk (older, diabetic) patients.
- The magnitude of SCD mortality in dialysis patients will continue to increase with the expanding size of the prevalent ESRD population, both in the U.S. and abroad.
- “Proof of concept”
ICD2 Trial

- 200 dialysis patients (Leiden): ICD vs no ICD
- Ages 55-80
- No central venous catheter for dialysis vascular access
- EF > 35%
- No significant CAD by Multislice CT or “associated pathology” (CT+Echo)
- Primary endpoint: sudden cardiac (“arrhythmic”) death
- Many trial design issues!
- Alternatives strategies: wearable devices, leadless ICD’s
Patients receiving ICDs/CRT-Ds

Incident Medicare dialysis patients & first transplant patients with Medicare as primary payor, age 20 & older, 2004–2006 combined. USRDS 2008 ADR
## Multivariable Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>Wald Chi-Square</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dialysate K &lt; 2 meq/L on last visit</td>
<td>2.12</td>
<td>1.55, 2.89</td>
<td>22.4</td>
</tr>
<tr>
<td>Last recorded creatinine value</td>
<td></td>
<td></td>
<td>20.3</td>
</tr>
<tr>
<td>OR per 1 unit increase starting at 6.5 mg/dl</td>
<td>0.86</td>
<td>0.80, 0.92</td>
<td></td>
</tr>
<tr>
<td>Pre-dialysis serum potassium</td>
<td></td>
<td></td>
<td>12.9</td>
</tr>
<tr>
<td>OR per 1 meq/L decrease below 5.1 meq/L</td>
<td>1.49</td>
<td>1.19, 1.89</td>
<td></td>
</tr>
<tr>
<td>OR per 1 meq/L increase above 5.1 meq/L</td>
<td>1.38</td>
<td>1.03, 1.86</td>
<td></td>
</tr>
<tr>
<td>Anti-Arrhythmic use</td>
<td>1.67</td>
<td>1.27, 2.20</td>
<td>13.3</td>
</tr>
<tr>
<td>EPO dose (weekly mean) (OR per 1000)</td>
<td>1.02</td>
<td>1.01, 1.03</td>
<td>8.4</td>
</tr>
<tr>
<td>Percent fluid removed (mean over 90 days)</td>
<td>1.11</td>
<td>1.03, 1.20</td>
<td>7.7</td>
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<tr>
<td>Last recorded Hemoglobin lab value (OR per 1 g/dl increase)</td>
<td>0.90</td>
<td>0.82, 0.98</td>
<td>6.5</td>
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<tr>
<td>ACEI/ARB use</td>
<td>1.33</td>
<td>1.06, 1.66</td>
<td>6.0</td>
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<tr>
<td>Vitamin D use</td>
<td>1.38</td>
<td>1.06, 1.80</td>
<td>5.7</td>
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<tr>
<td>Dialysate Ca &lt; 2.5 meq/L on last visit</td>
<td>1.50</td>
<td>1.07, 2.11</td>
<td>5.6</td>
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<tr>
<td>Serum Bicarbonate (OR per 1 meq/L increase)</td>
<td>1.03</td>
<td>1.00, 1.06</td>
<td>4.1</td>
</tr>
</tbody>
</table>

Adjusted for gender, race, history of congestive heart failure, diabetes, hypertension, coronary heart disease, hyperlipidemia, history of arrhythmia, tobacco use, medication use (aspirin, beta-blockers, statins) last recorded albumin, calcium, phosphorus, last recorded urea reduction ratio, catheter use). Overall model c-statistic 0.70
Unadjusted SCD Free Survival in CKD and ESRD

Log rank p <0.001

Smarz. et. al. Abstract presentation at 2007 ASN annual meeting
Cumulative probability of SCD & all-cause death
2002 prevalent dialysis patients
Adjusted AMI admission rates in elderly patients

**Medicare (age 66+)**
- CKD: all
- CKD: 66-79
- CKD: 80+

Non-CKD

Admissions per 1,000 patient years

2005 reference year

USRDS 2008 ADR
All-cause survival after acute myocardial infarction, by CKD status

Prevalent Medicare patients age 66+, 2000-2005
USRDS 2008 ADR
Probability of all-cause and cause-specific death

STENT

<table>
<thead>
<tr>
<th>Cause</th>
<th>2 yr P(event)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause</td>
<td>0.48</td>
</tr>
<tr>
<td>Cardiac</td>
<td>0.30</td>
</tr>
<tr>
<td>Arrhythmic</td>
<td>0.17</td>
</tr>
<tr>
<td>MI</td>
<td>0.09</td>
</tr>
<tr>
<td>Infectious</td>
<td>0.07</td>
</tr>
<tr>
<td>Other</td>
<td>0.21</td>
</tr>
</tbody>
</table>
Event rates & adjusted event-free survival: cardiac arrest
Linear Relationship Between SCD Risk and Declining GFR

Smarz. et. al. Abstract presentation at 2007 ASN annual meeting
## Multivariable Model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Chi-Square</th>
<th>P Value</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>NY Heart Association Class (HR per increase in 1 class)</td>
<td>37.5</td>
<td>&lt;0.0001</td>
<td>1.226</td>
<td>1.149, 1.309</td>
</tr>
<tr>
<td>History of Diabetes</td>
<td>27.3</td>
<td>&lt;0.0001</td>
<td>1.631</td>
<td>1.358, 1.960</td>
</tr>
<tr>
<td>GFR (HR per 10 unit decrease)</td>
<td>25.5</td>
<td>&lt;0.0001</td>
<td>1.125</td>
<td>1.075, 1.178</td>
</tr>
<tr>
<td>Number of Diseased Vessels</td>
<td>15.1</td>
<td>0.0001</td>
<td>1.251</td>
<td>1.117, 1.401</td>
</tr>
<tr>
<td>History of MI</td>
<td>15.0</td>
<td>0.0001</td>
<td>1.419</td>
<td>1.189, 1.693</td>
</tr>
<tr>
<td>Any Valvular Disease</td>
<td>12.1</td>
<td>0.0005</td>
<td>1.437</td>
<td>1.172, 1.762</td>
</tr>
<tr>
<td>History of COPD</td>
<td>10.2</td>
<td>0.0014</td>
<td>1.570</td>
<td>1.191, 2.069</td>
</tr>
<tr>
<td>History of Peripheral Vascular Disease</td>
<td>7.2</td>
<td>0.0073</td>
<td>1.376</td>
<td>1.090, 1.737</td>
</tr>
</tbody>
</table>

Overall Chi-Square: 341.7

Smarz, et. al. Abstract presentation at 2007 ASN annual meeting.
Figure 1 | Cumulative incidence of overall mortality and specific causes of death (including sudden cardiac death, other cardiovascular causes and other causes of death) in the CHOICE cohort.

Parekh et al. Kidney International 2008;74;1335