ASN DIALYSIS ADVISORY GROUP

ASN DIALYSIS CURRICULUM

ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

The Challenge of Sudden Cardiac Death in Hemodialysis Patients

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Learning Objectives

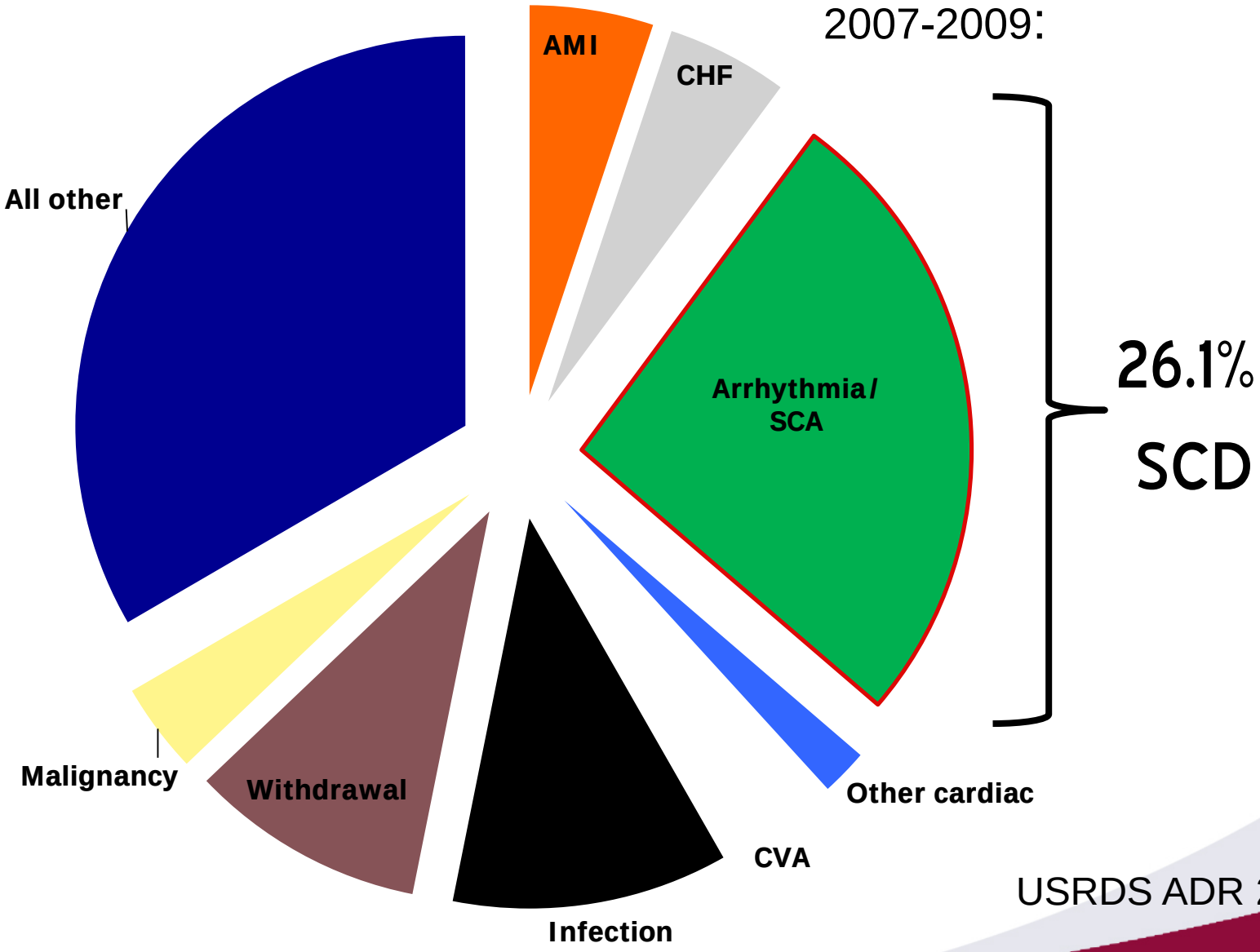
Describe the epidemic of sudden cardiac death (SCD) among CKD (and particularly ESKD) patients

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

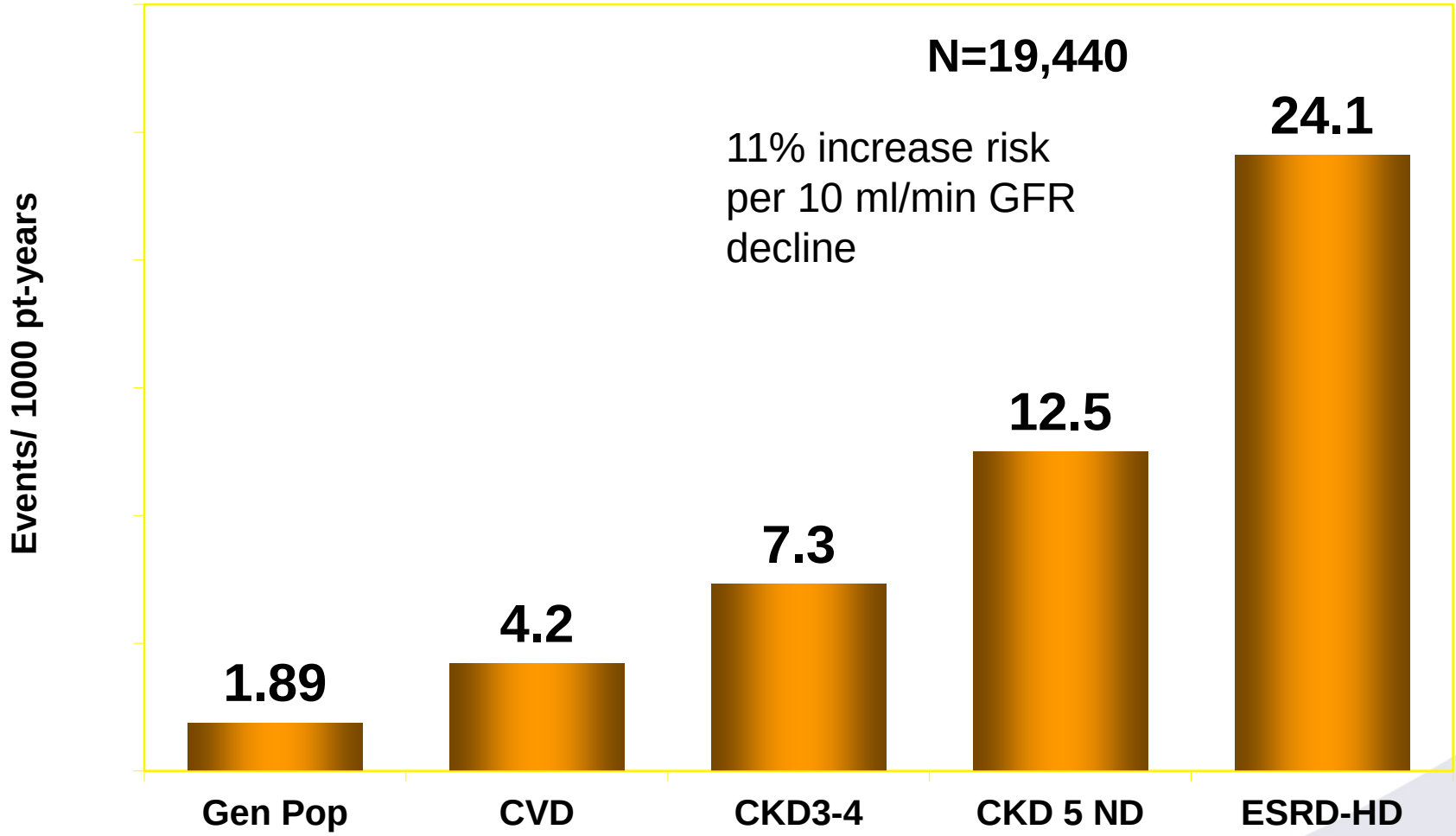
Prevalent Dialysis Patients, 2007-2009:



USRDS ADR 2011

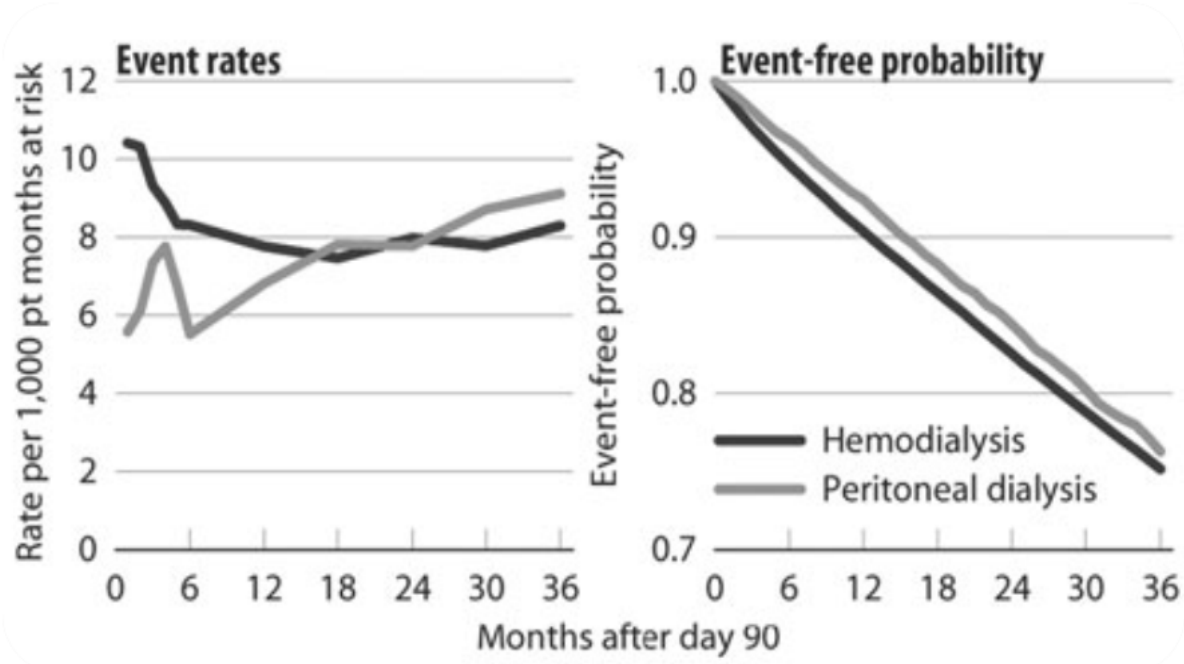
The risk of SCD in ESKD-HD is 20x greater than the general population

Duke catheterization database:



Pun et. al. Kidney Int. 2009 Sep;76(6):652-8

Risk of Sudden Cardiac Death after Dialysis Initiation: PD vs. HD



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.

USRDS ADR 2011

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%

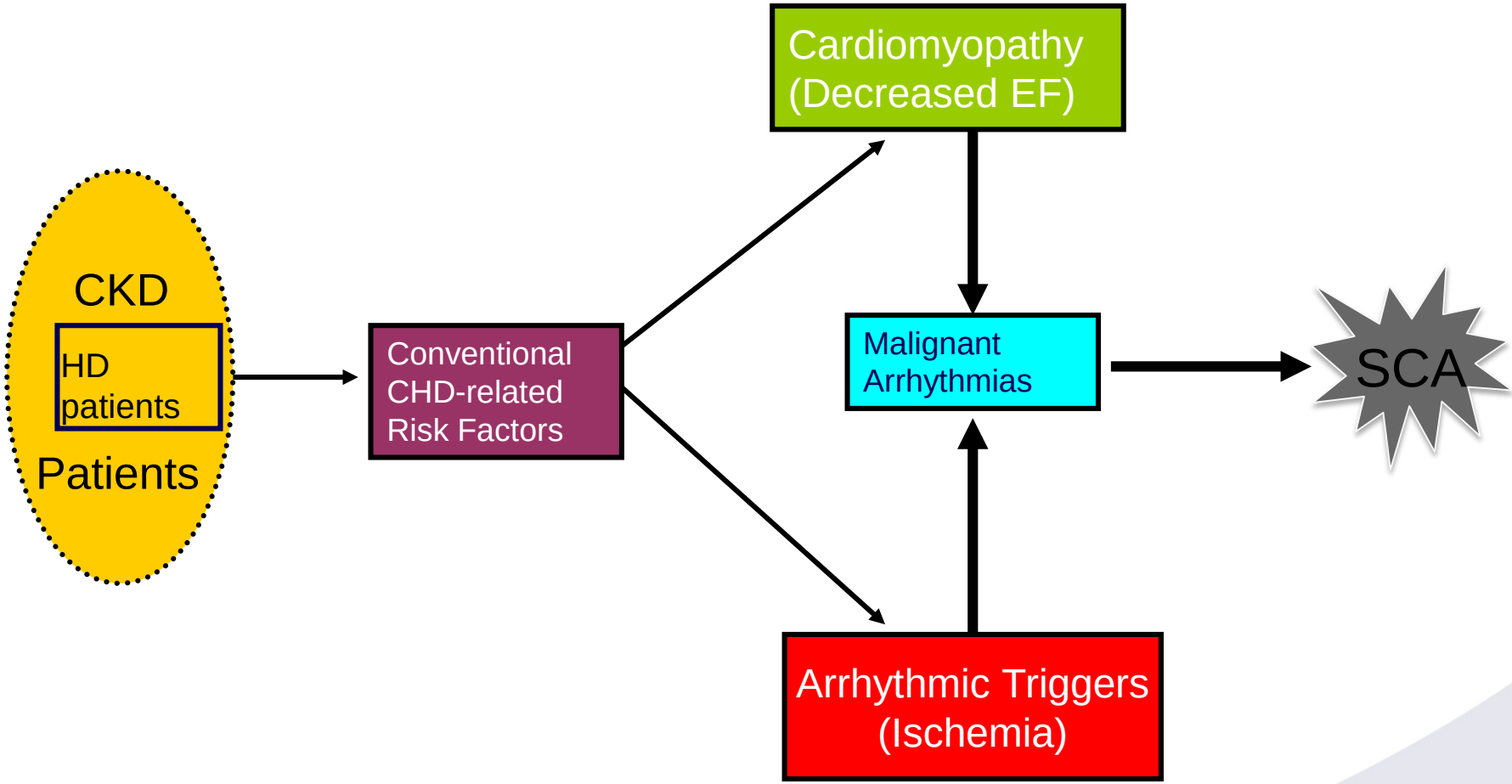
SCD rate is consistent across data sources

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

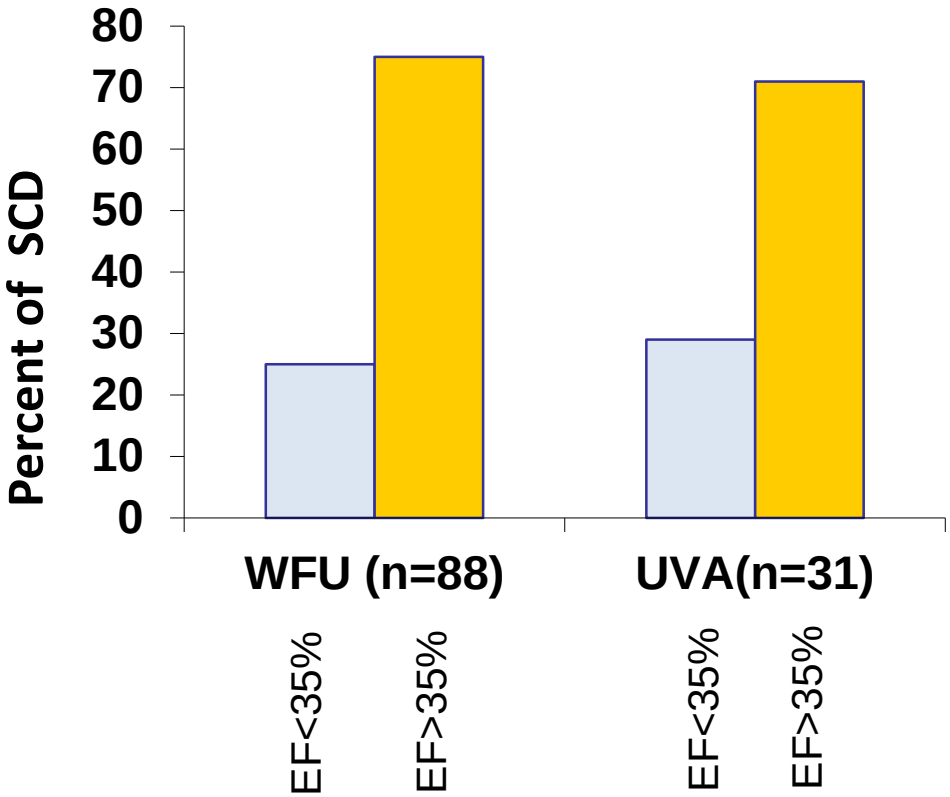
Increased rate of SCD unlikely due to just misclassfication

Pun et al. Clin J Am Soc Nephrol. 2012 Jan;7(1):116-22
Herzog et al. Kidney Int. 2011 Sep;80(6):572-86

SCD Pathophysiology Cardiomyopathy + Acute Trigger=SCA



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**

Bleyer Kidney Int. 2006 Jun;69(12):2268-73
Yamada Clin J Am Soc Nephrol. 2010 Oct;5(10):1793-8
Mangrum et. al Heart Rhythm 2005 2(5):S41
Park et. al J Am Soc Nephrol. 2012 Oct;23(10):1725-34

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/m^2 = 30% increased risk of death at 5 yrs**

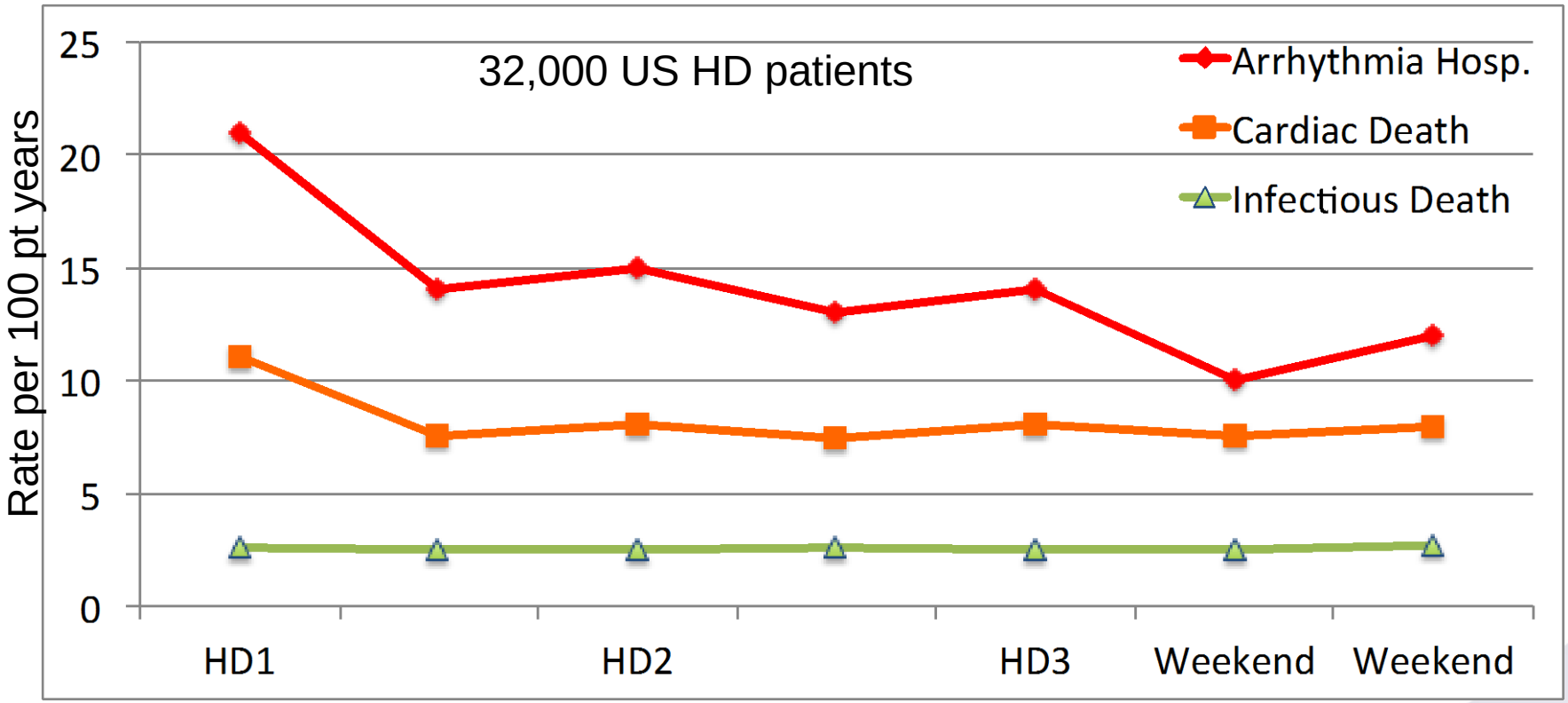
- **LVH= Increased rate of arrhythmias**

- **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
Mark PB et al. *Kidney International* (2006) 69: 1839–1845

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



Foley et. al. NEJM 2011: 365: 1099

Hemodialysis as an acute trigger for SCD

Potentially due to rapid shifts in:

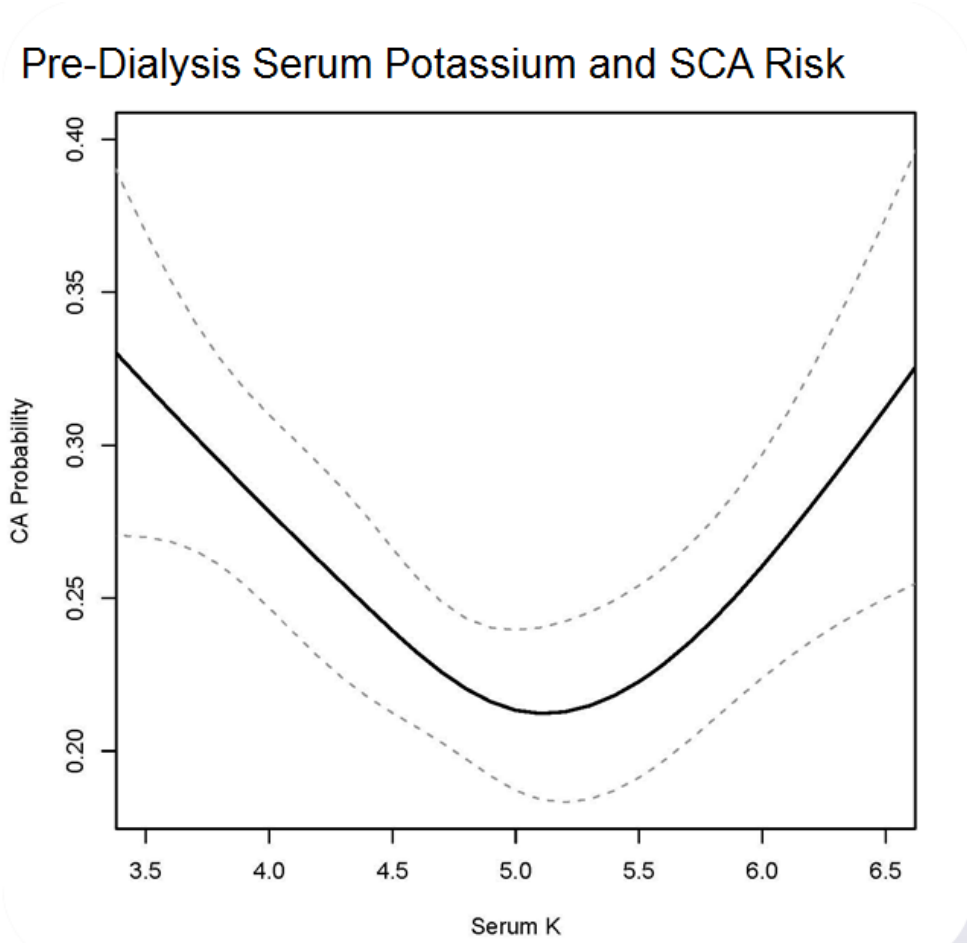
- Potassium?
- Calcium?
- Fluid?

Role of Serum Potassium in SCA

Study of 500 witnessed peridialytic SCA vs. 1600 matched controls

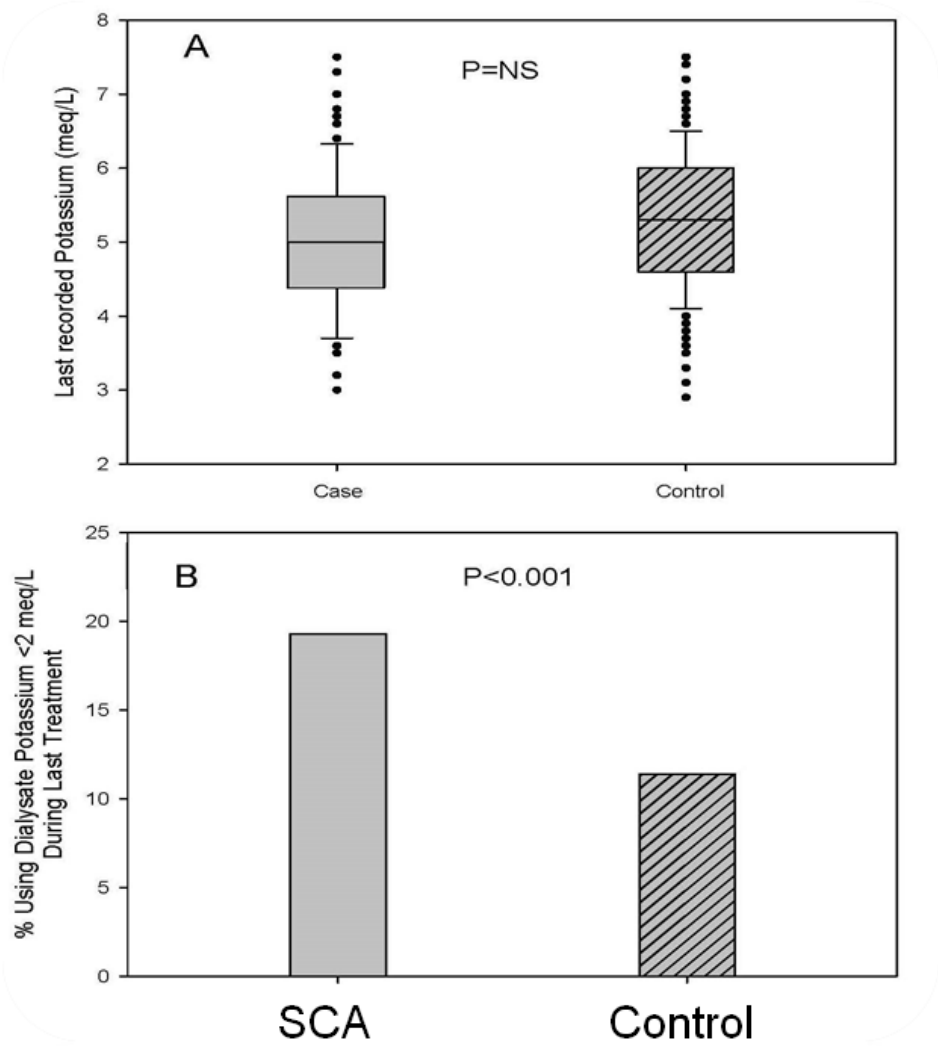
Risk linked to extremes of serum potassium (K)

Lowest risk at K ~ 5.0



Pun et. al. Kidney Int. 2011 Jan;79(2):218-27

Role of Dialysate Potassium in SCA



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

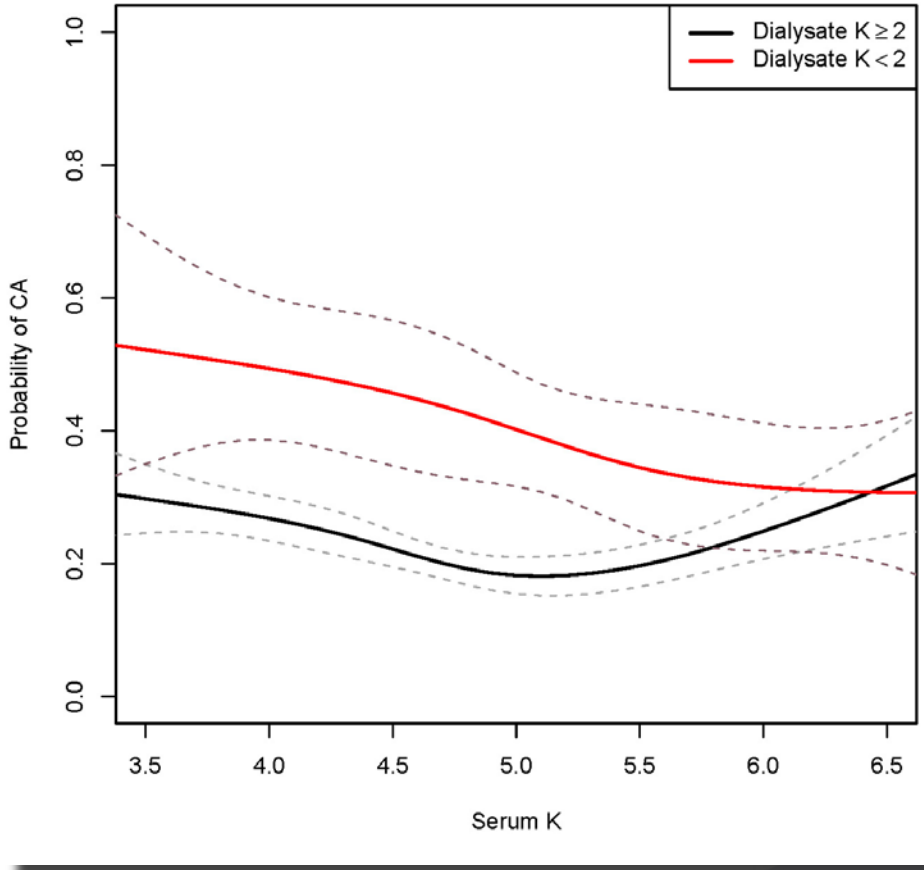
Mean Predialysis serum K was in the normal range (4.9 meq/L)

Pun et. al. Kidney Int. 2011 Jan;79(2):218-27

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

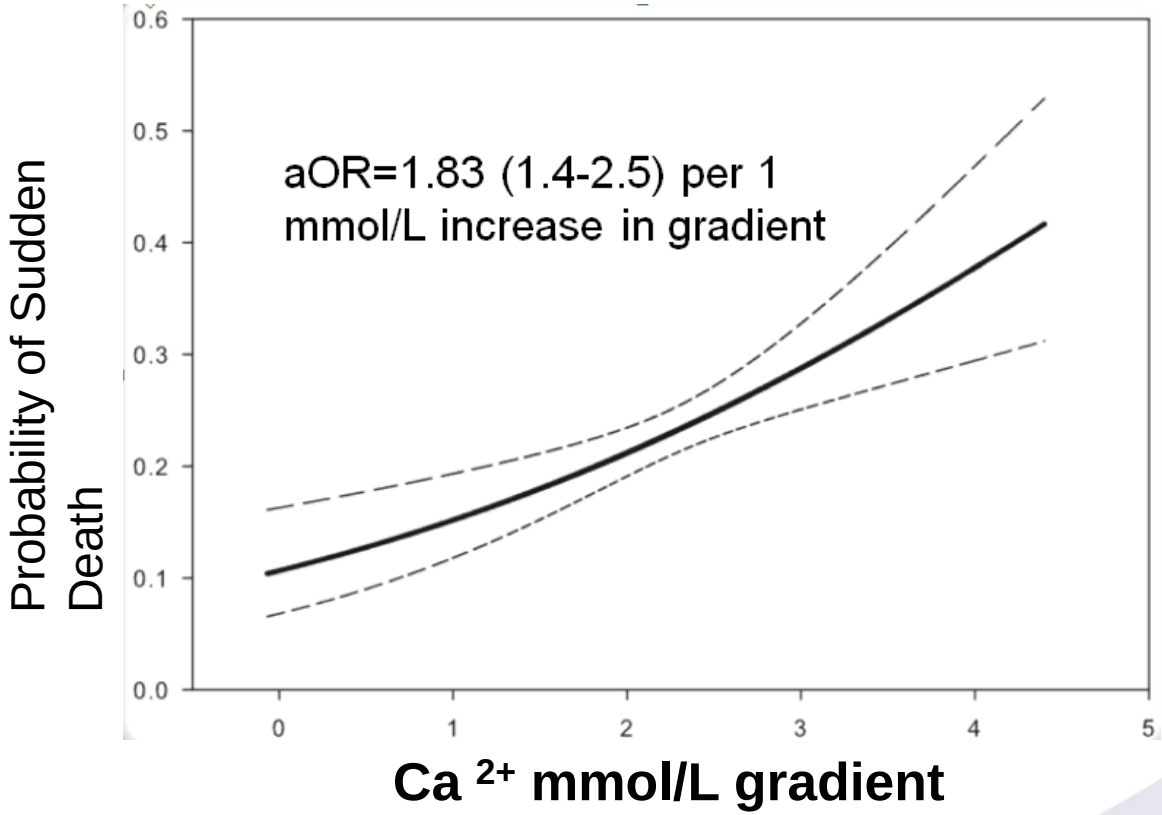


Pun et. al. Kidney Int. 2011 Jan;79(2):218-27

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



Pun et. Al. Clin J Am Soc Nephrol. 2013 May;8(5):797-803

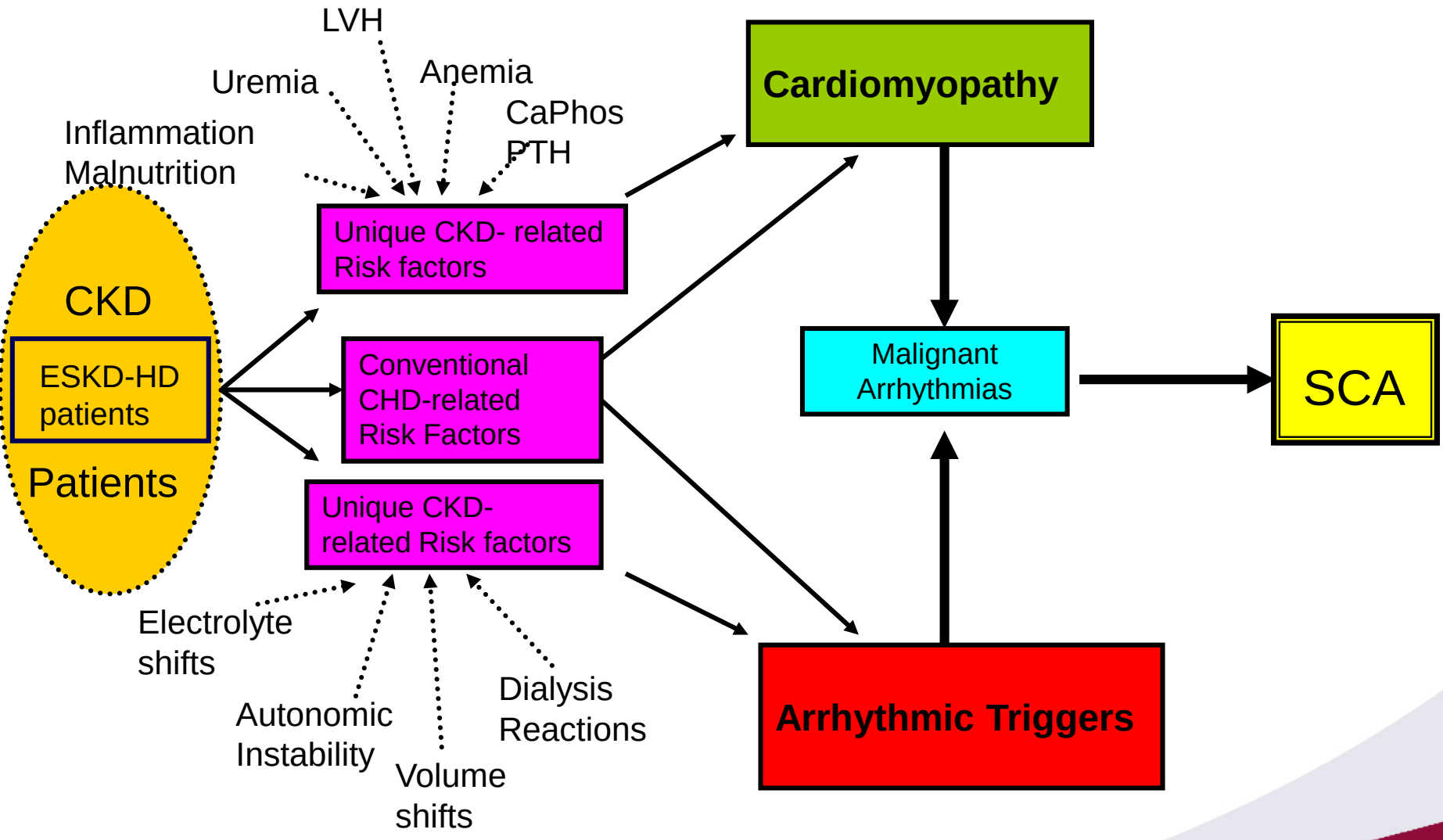
Amount and Rate of Fluid Removal During HD Associates With Myocardial "Stunning"

HD Exposure	Odds Ratio
1L Fluid Removal on HD	5.1
1.5L Fluid Removal on HD	11.6
2L Fluid Removal on HD	26.2

- 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.

Burton JO et al. *Clin J Am Soc Nephrol* (2009) 4: 914-920

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



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: JACC 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

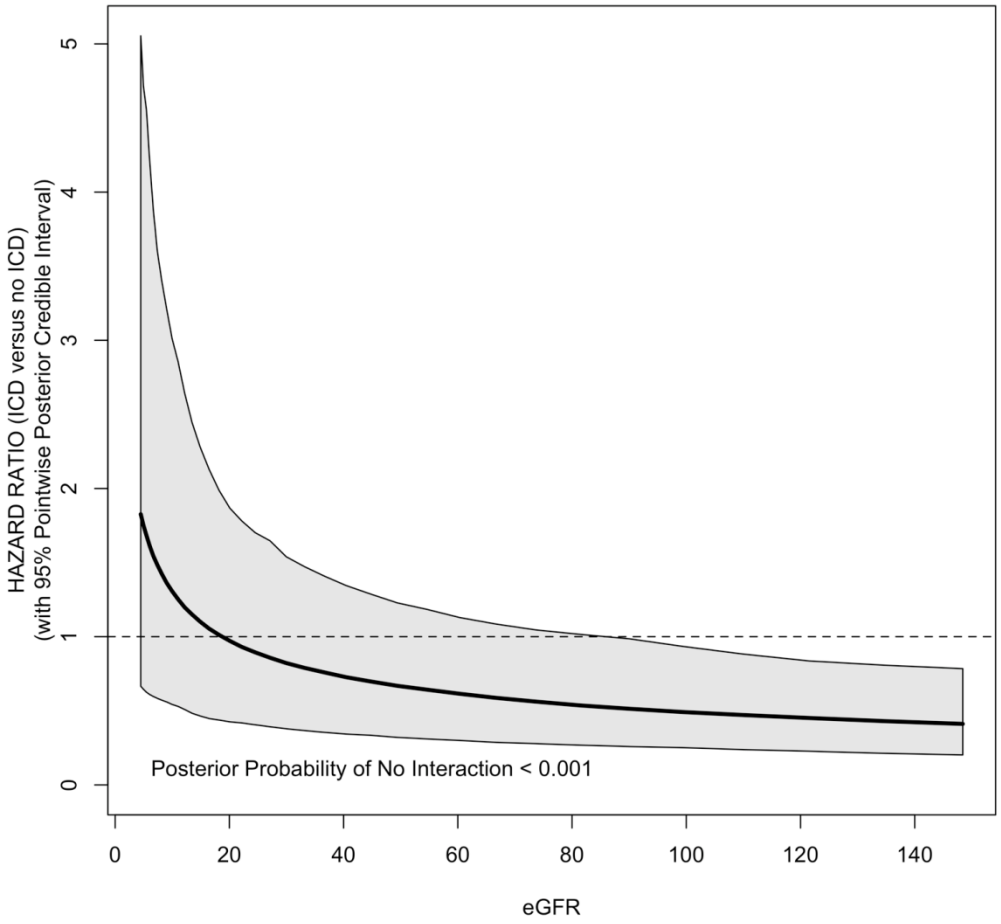
Charytan et. al. Am J Kidney Dis. 2011 Sep;58(3):409-17

Herzog et. al. Kidney Int. 2005 Aug;68(2):818-25

- **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

Agarwal et al. Heart Rhythm. 2009 Nov;6(11):1565-71

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

Pun et. al. Am J Kidney Dis. 2014 Feb 8.epub ahead of print

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?)