Can we prevent Sudden Death in Dialysis Patients?

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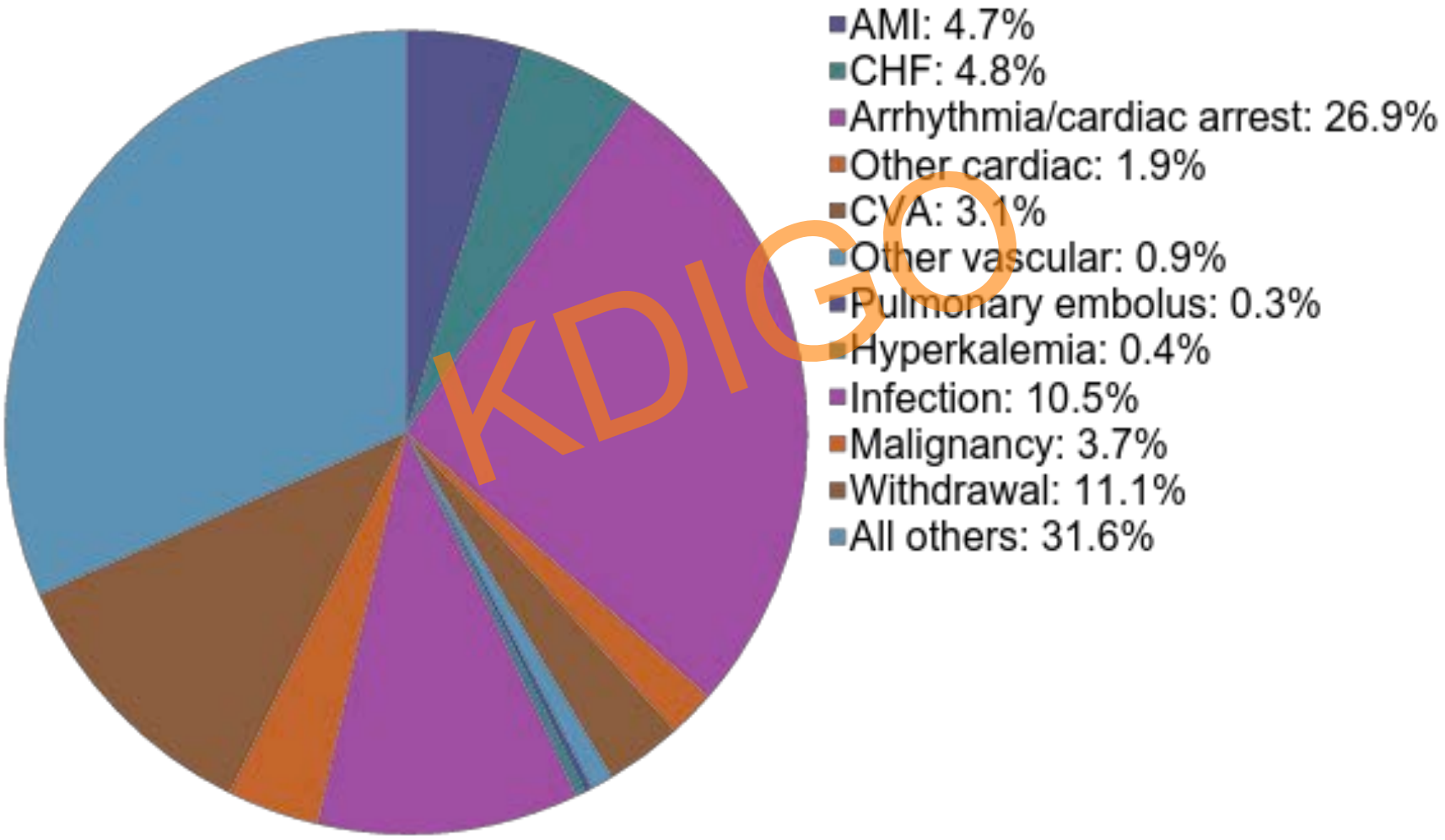
This presentation will include information on the WED-HED (Wearable Cardioverter Defibrillator in Hemodialysis Patients) Study (ClinicalTrials.gov Identifier: NCT02481206), an FDA-approved randomized trial evaluating a commercially available device, the LifeVest (wearable defibrillator), made by Zoll.

Introduction

- Dialysis patients have high mortality rates
- Death rate for all U.S. dialysis patients in 2013 was 182 per 1,000 patient years
- Cardiac disease is the major cause of death in dialysis patients - 39% 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: 22-26% of all deaths are sudden
- 468,386 US dialysis (421,349 HD) and 193,262 renal transplant pts on 12/31/2013.

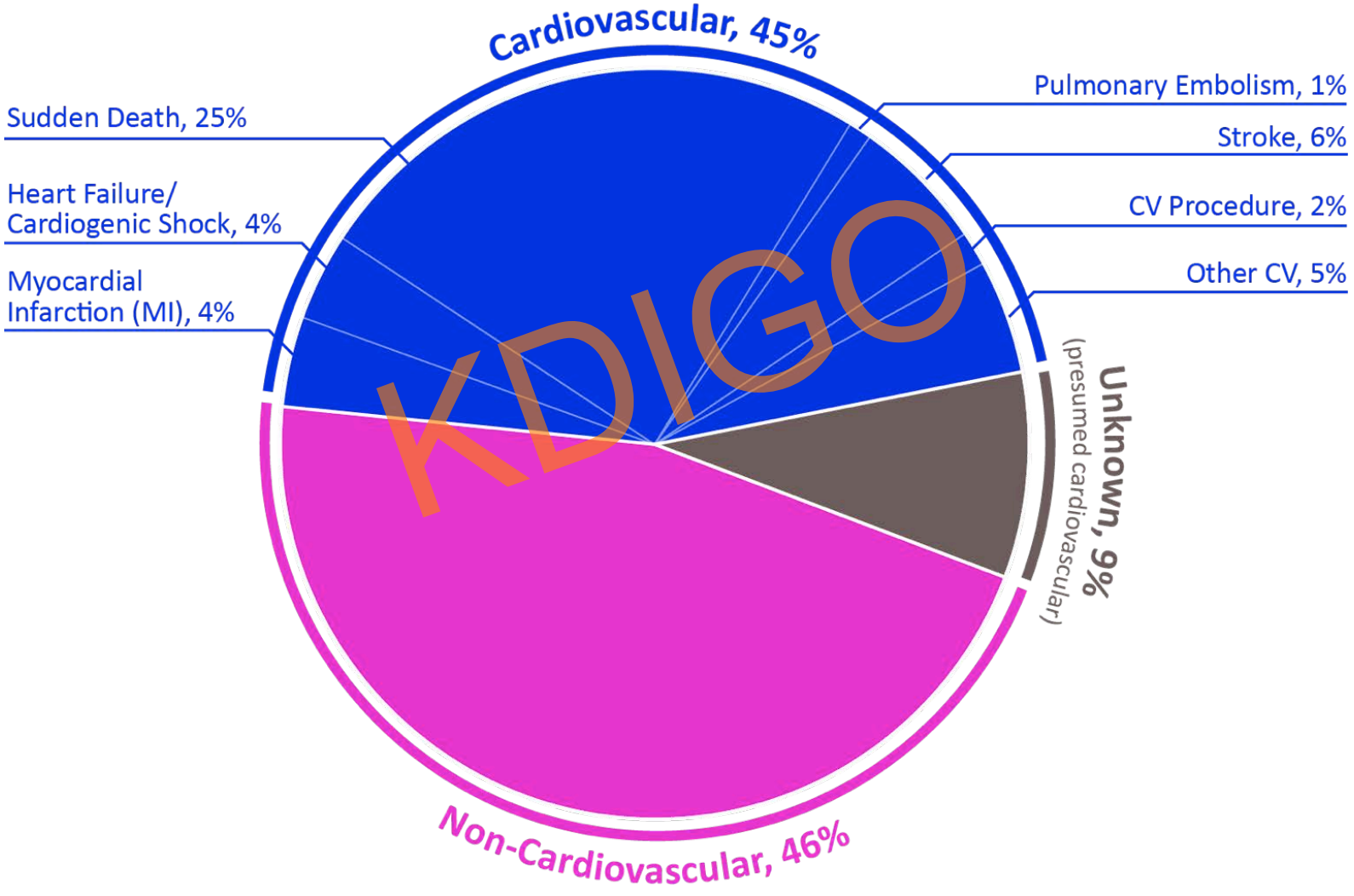
Causes of death in prevalent dialysis patients, 2009-2011



USRDS 2013 ADR; Figure 4.1 (Volume 2)

Prevalent dialysis patients, 2009–2011

Adjudicated causes of death in the EVOLVE study population

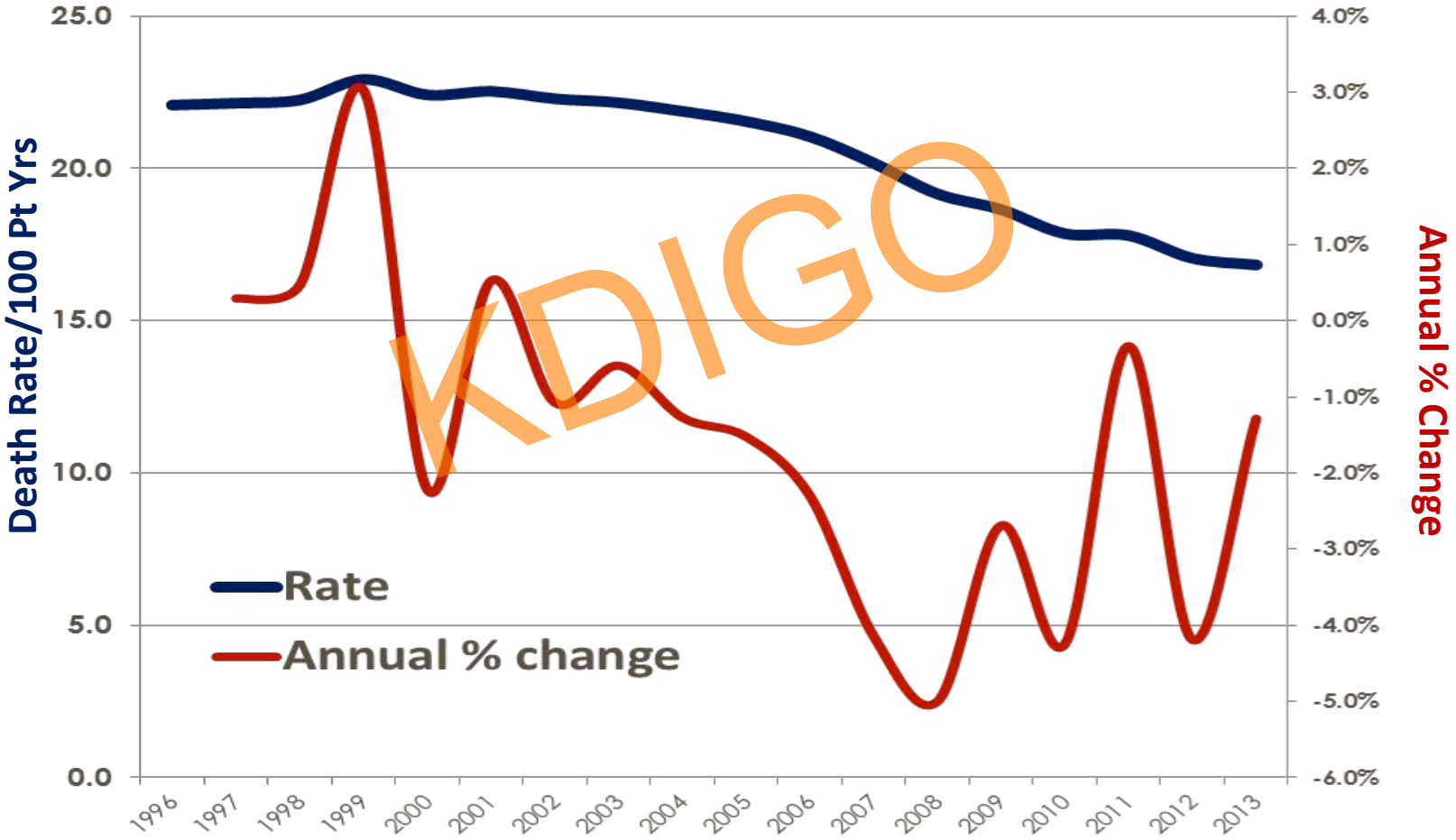


Wheeler et al, JAHA, 2014;3(6):e001363

Factors impacting sudden cardiac death in ESRD patients

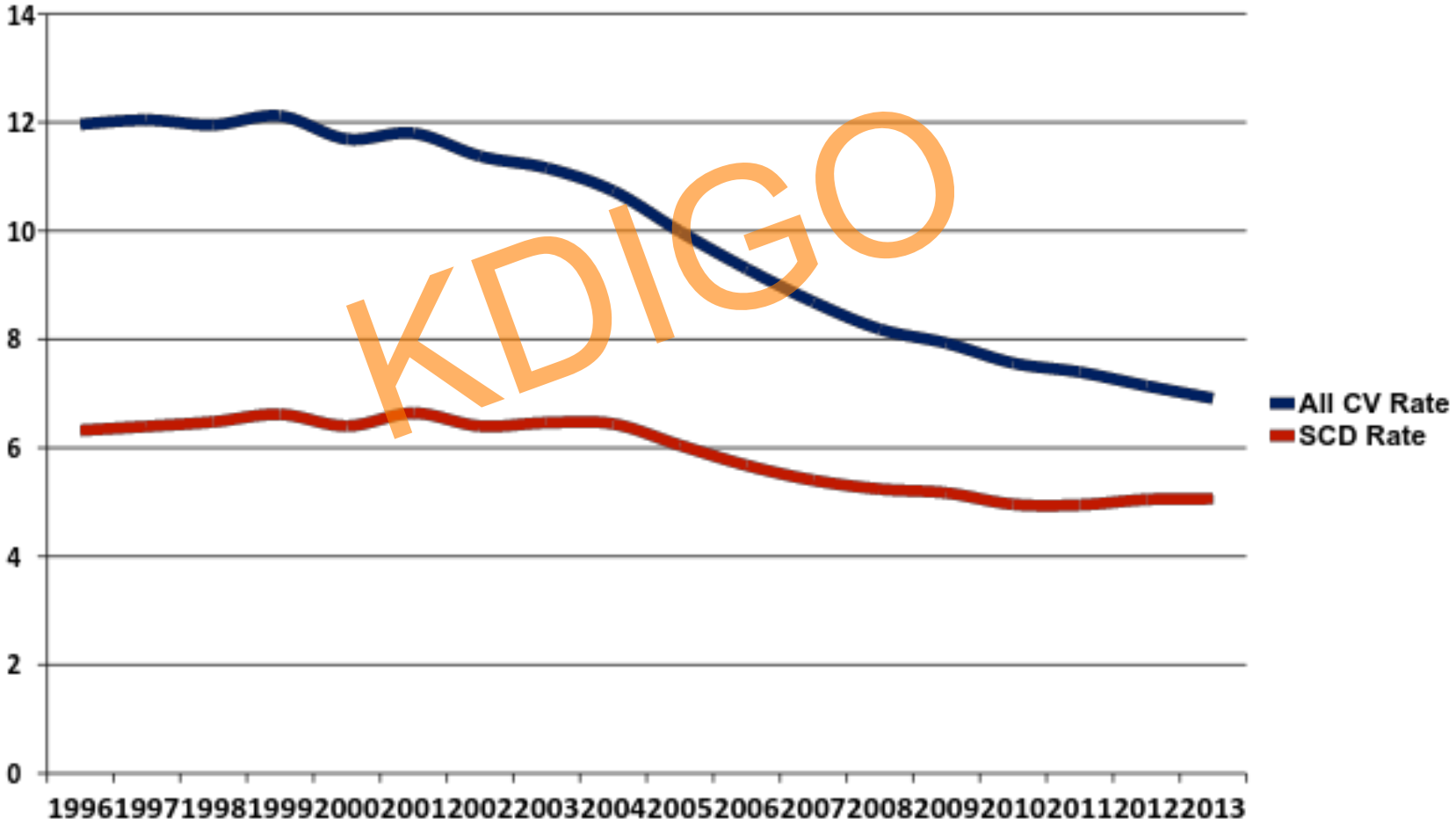
- Ischemic heart disease — “Obstructive CAD”
- Abnormalities in myocardial ultra-structure & function (cf. Amann & Ritz, et al)
  - Endothelial dysfunction (DM)
  - Interstitial fibrosis
  - Decreased perfusion reserve
  - Diminished ischemia tolerance
- Left ventricular hypertrophy
- Electrolyte shifts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

Trends in Death rates per 100 pt yrs & Annual % Change 1996 to 2013



Peer Kidney Care Initiative 2016

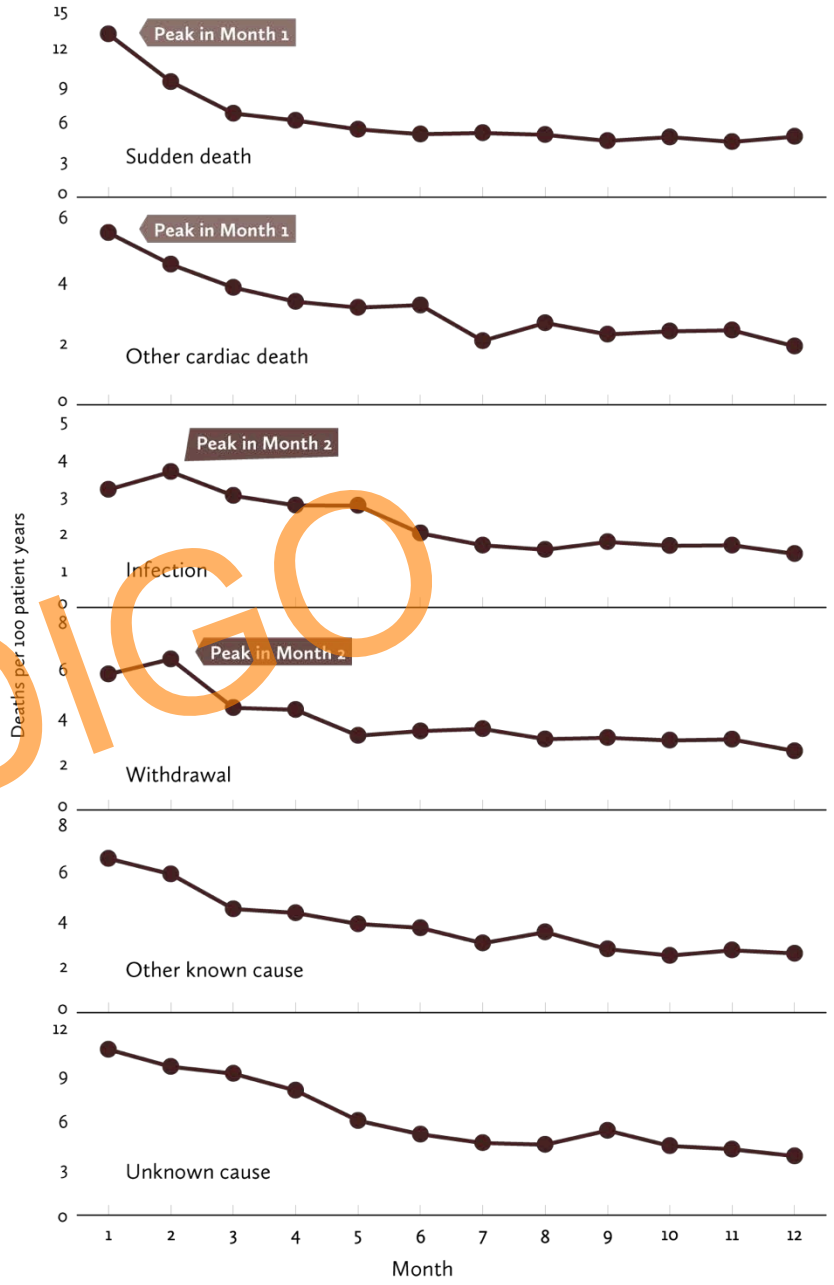
All Cause CV vs Sudden Cardiac (SCD) Death per 100 Pt Yrs in US



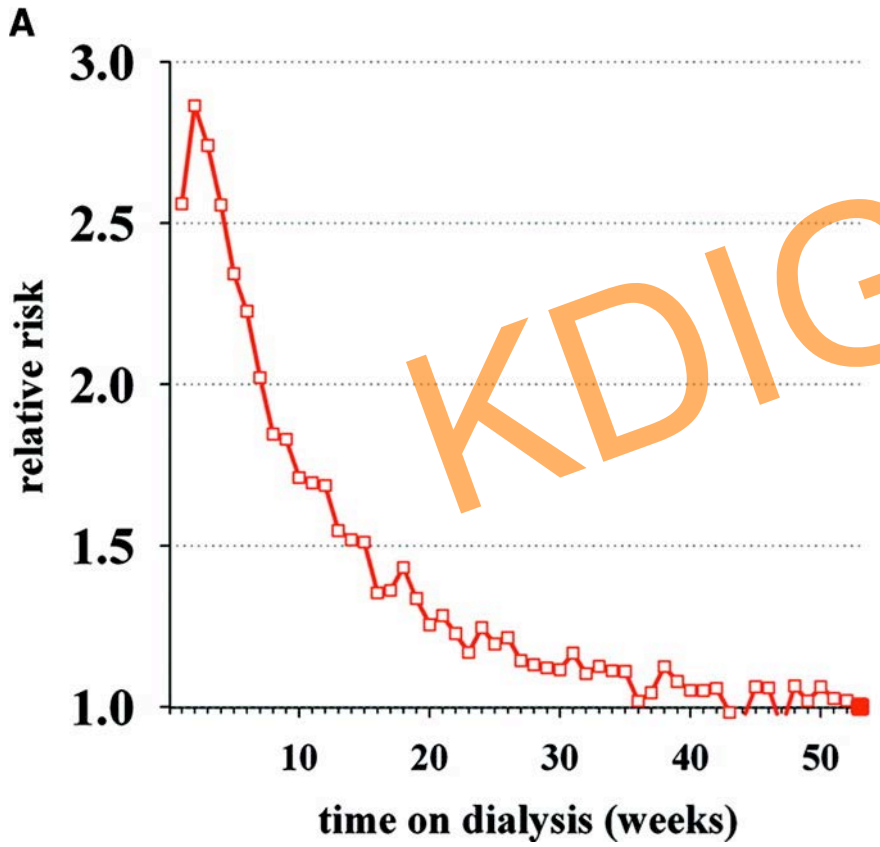
Peer Kidney Care Initiative 2016

Cause-specific mortality in incident dialysis patients

After first dialysis session in a freestanding facility



(A) Among patients starting chronic dialysis (n = 303,289) the relative risk of death at each 1-week interval



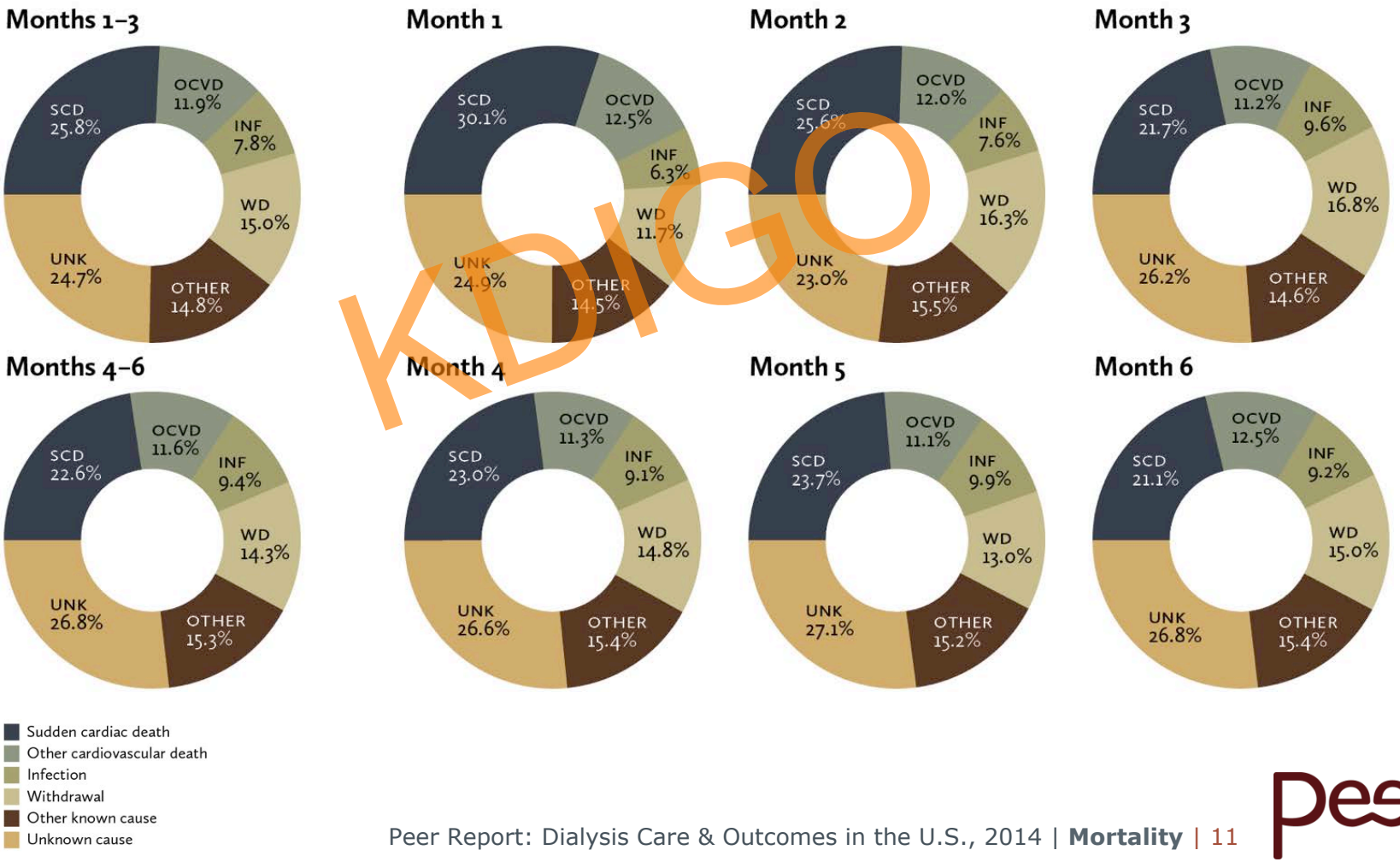
(A) Among patients starting chronic dialysis (n = 303,289), the relative risk of death at each 1-week interval was compared with a reference group of patients who survived the first year of dialysis.

Kevin E. Chan et al. CJASN 2011;6:2642-2649

CJASN

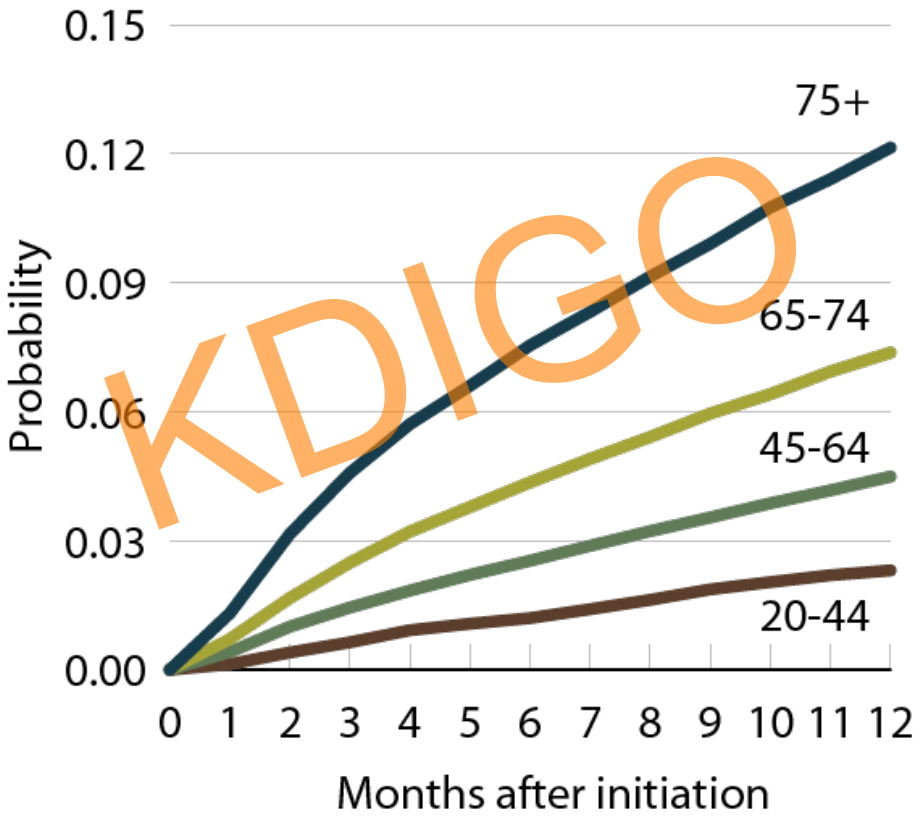
Distribution of causes of death during the first year of dialysis

According to the Death Notification Form



Probability of sudden cardiac death in incident dialysis patients, by age, 2009

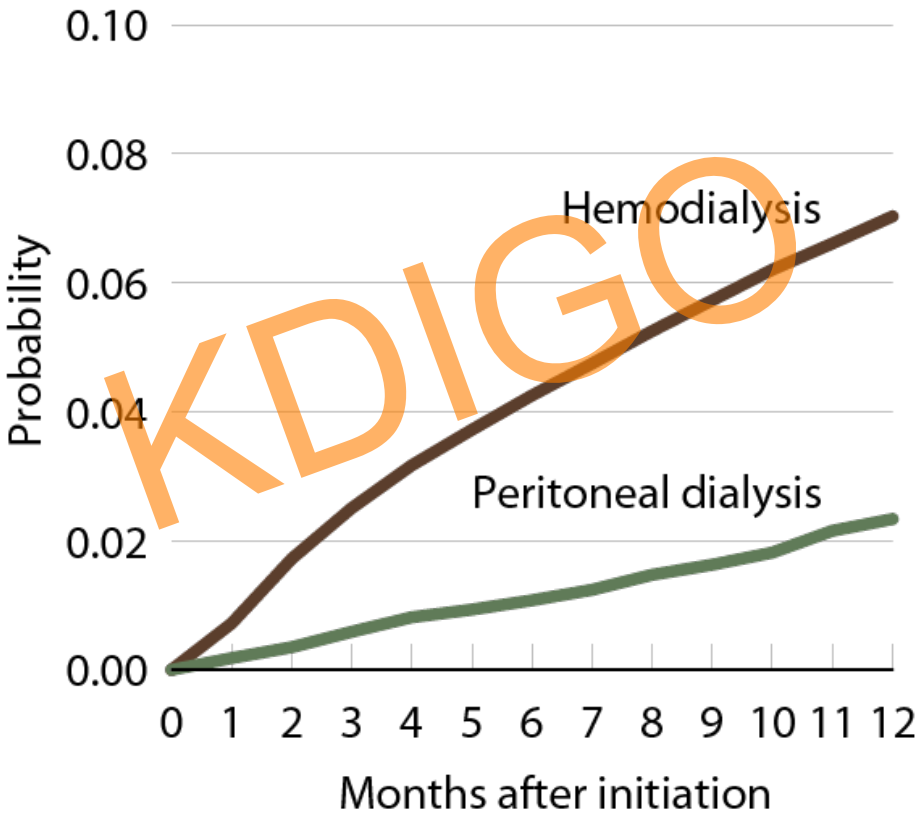
Figure 4.9 (Volume 2)



Incident dialysis patients, age 20 & older, unadjusted.

Probability of sudden cardiac death in incident dialysis patients, by modality, 2009

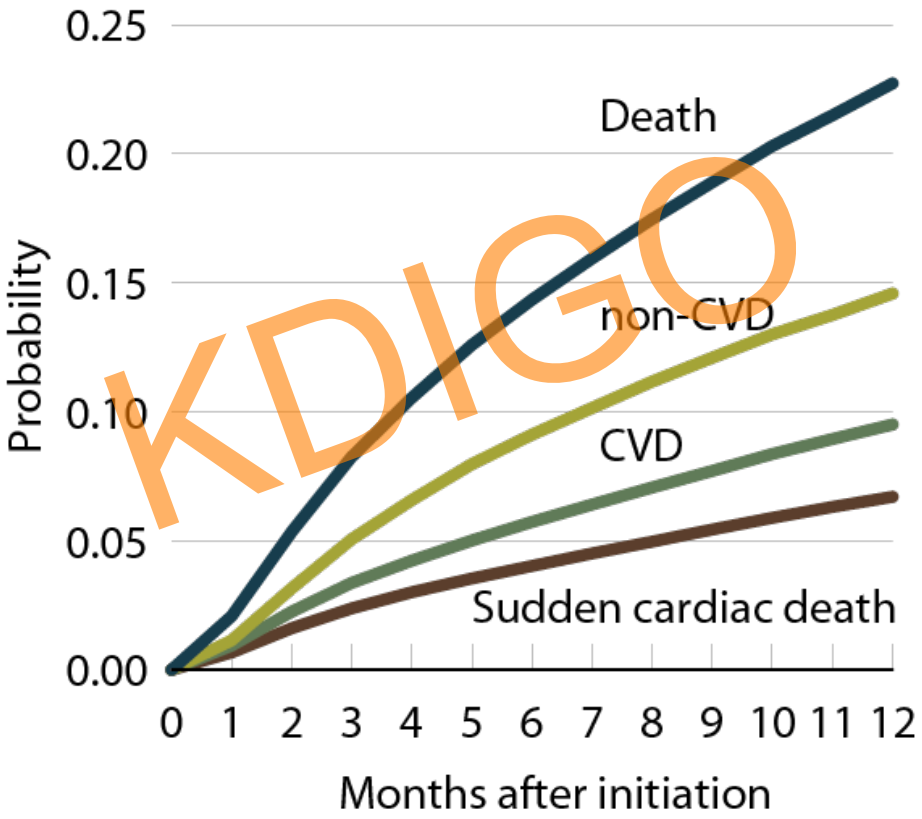
Figure 4.12 (Volume 2)



Incident dialysis patients, age 20 & older, unadjusted.

Probability of death in incident dialysis patients, by cause of death, 2009

Figure 4.8 (Volume 2)



Incident dialysis patients, age 20 & older, unadjusted.

Medical Interventions in the Dialysis Clinic to Reduce SCD

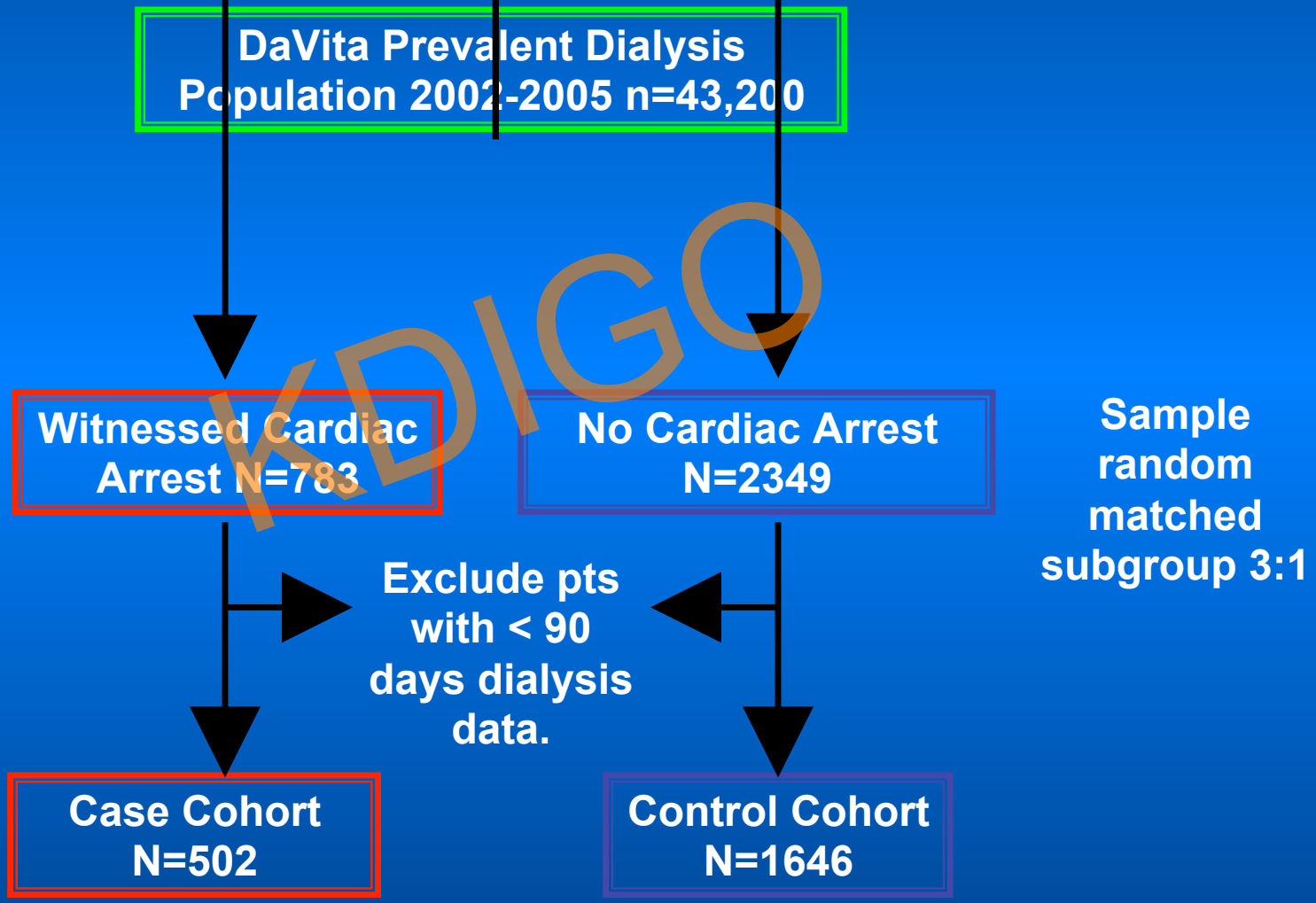
Avoid low K/Ca/Mg dialysate

Avoid medications known to cause SCD

Serum Potassium in SCD

- Karnik et al (*Kidney Int* 2001;60:350-357):
  400 in-HD center cardiac arrests in 10/98 - 6/99 in Fresenius Medical Care North America HD pts (n= 77,000)
  - 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

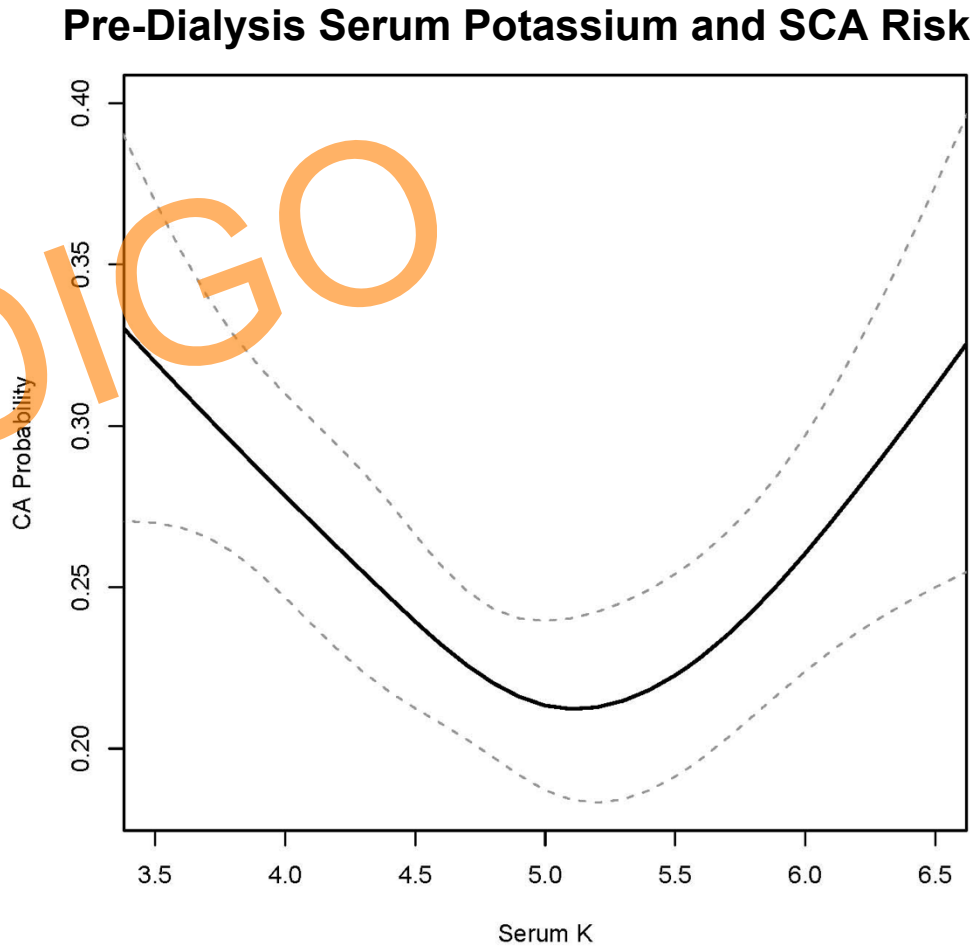
Modifiable Risk Factors Associated with Sudden Cardiac Arrest in Hemodialysis Clinics



(Pun et al, *Kidney Int*, 2011;79:218)

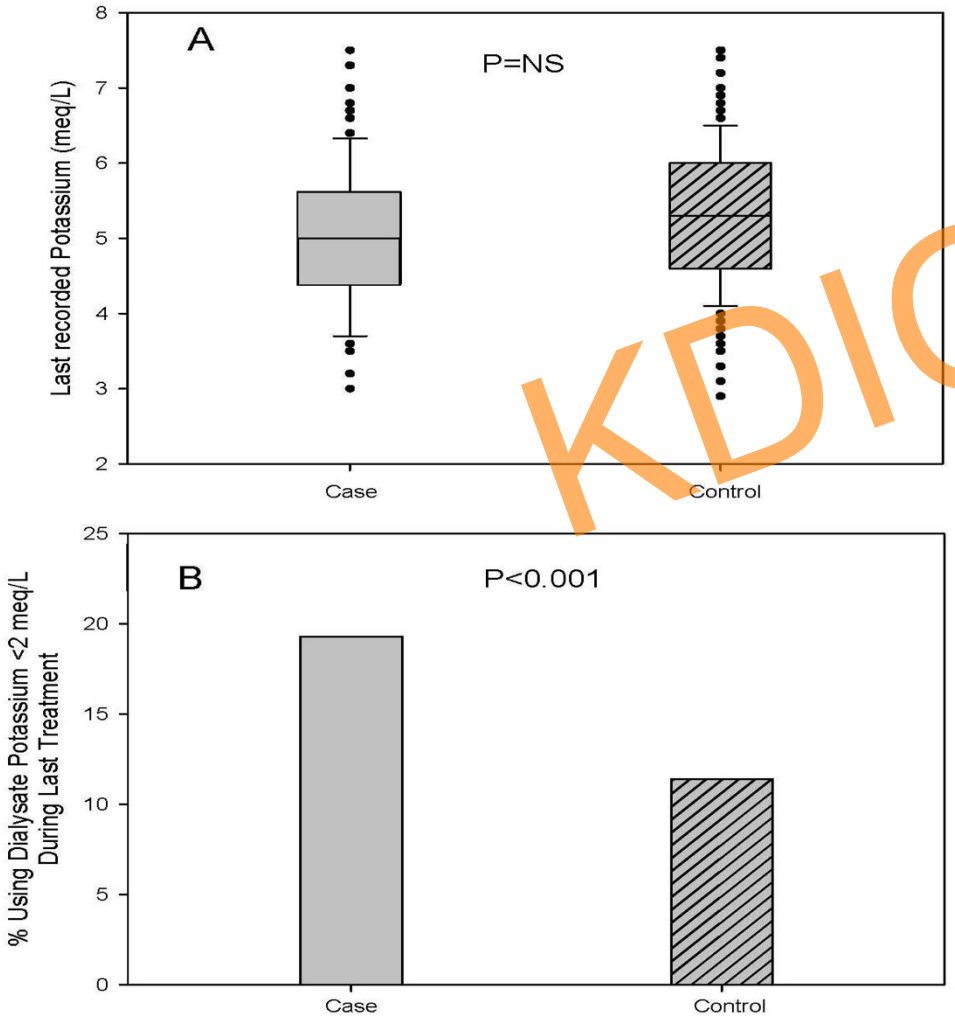
Potassium Homeostasis and Risk of SCA: Predialysis Potassium

- Risk linked to extremes of serum potassium (K)
- Lowest risk at K ~ 5.0



(Pun et al, Kidney Int, 2011;79:218

Potassium Homeostasis and Risk of SCA: Risk of Treatment

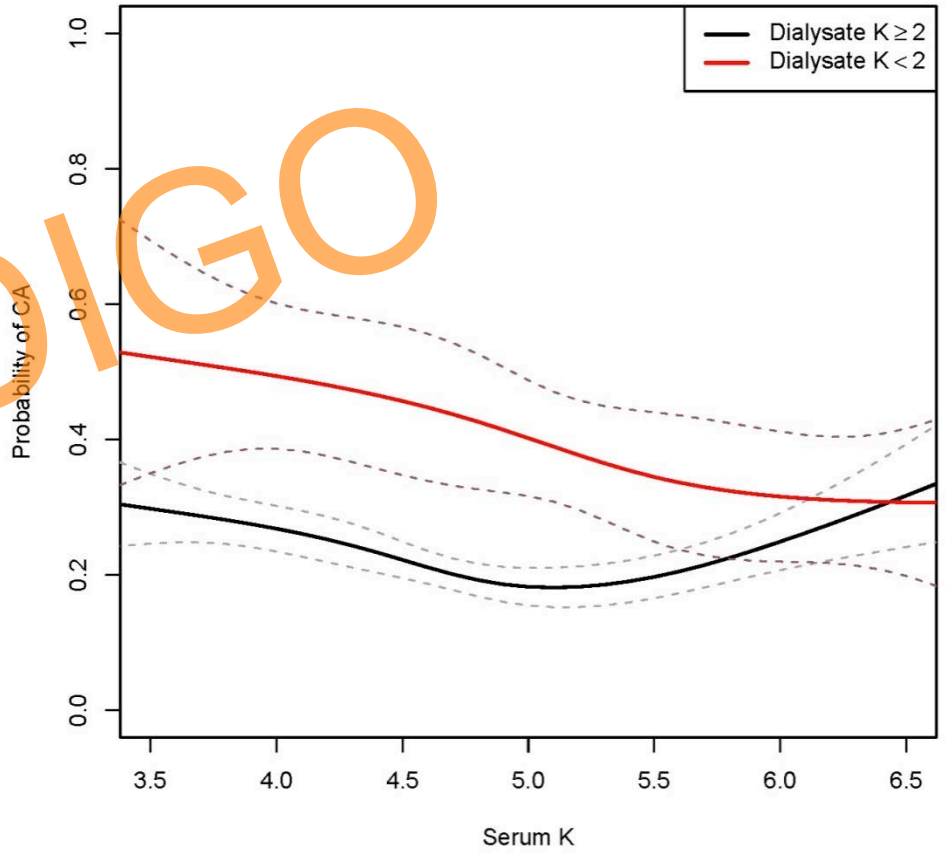


- Use of Low K dialysate reduces serum K levels
- ~20% of SCA pts on very low K dialysate at time of event
- Mean Predialysis serum K was in the normal range (4.9 meq/L)

(Pun et al, Kidney Int, 2011;79:218

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



(Pun et al, Kidney Int, 2011;79:218

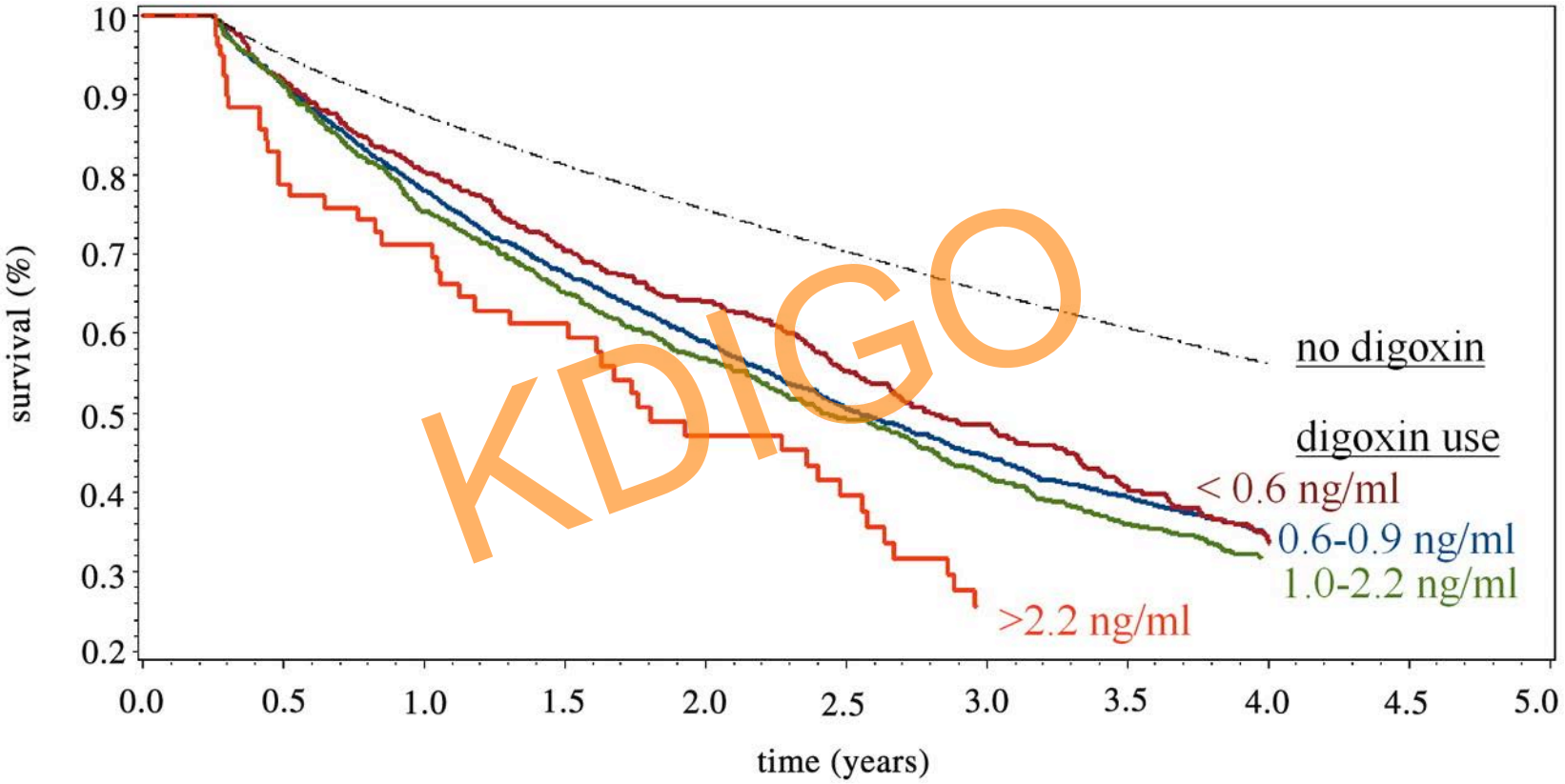
Unadjusted and adjusted associations between relevant factors related to calcium homeostasis and risk of sudden cardiac arrest

Parameter	Unadjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Predialysis corrected serum calcium (per 1 mg/dl increase)	1.10 (1.00–1.20)	0.05	1.10 (1.00–1.30)	0.05
Dialysate calcium <2.5 meq/L	2.00 (1.40–2.80)	<0.001	2.00 (1.40–2.90)	<0.001
Serum-to-dialysate calcium gradient (per 1 meq/L increase)	1.40 (1.10–1.60)	<0.001	1.40 (1.10–1.80)	0.002
QT medication exposure	1.20 (1.00–1.50)	0.06	1.00 (0.80–1.30)	0.80

Pun P H et al. CJASN 2013;8:797-803

CJASN

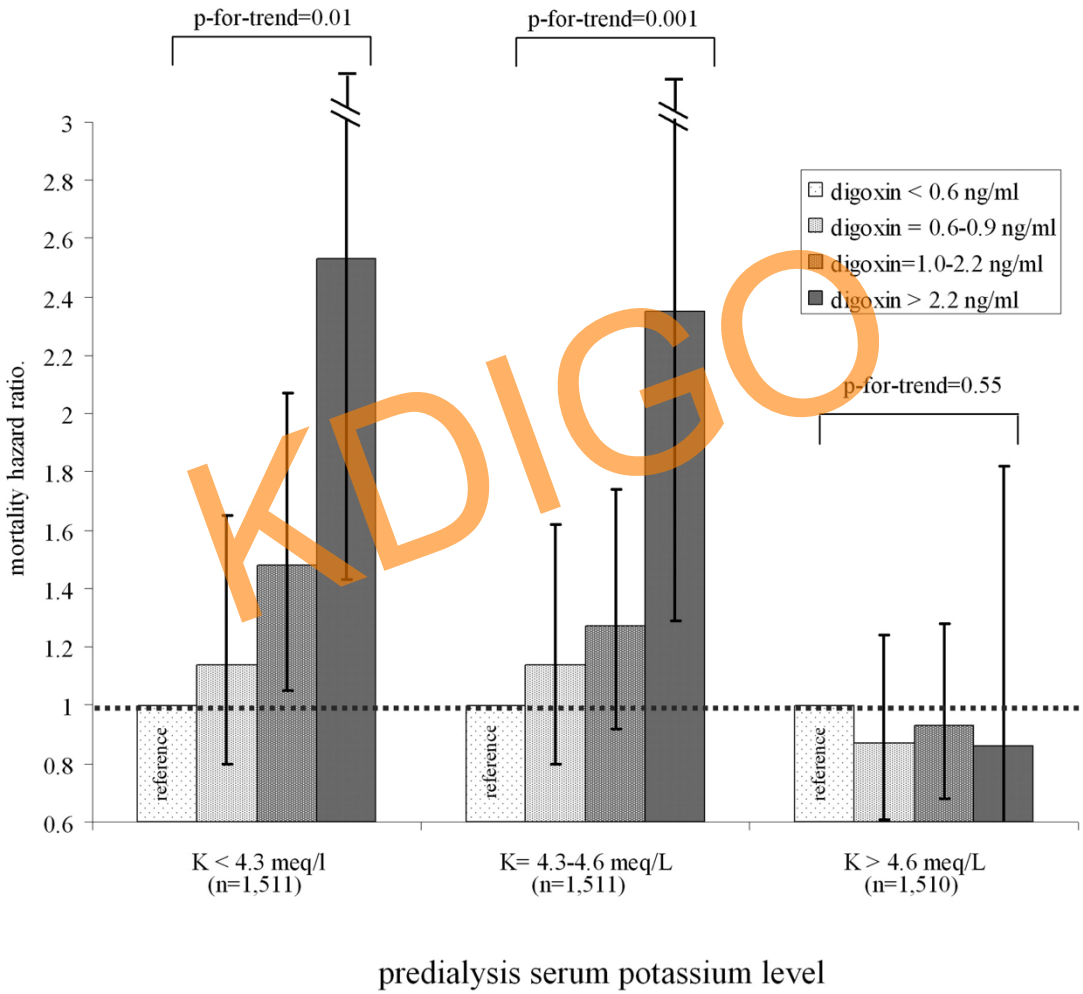
Crude survival curves show decreased survival with digoxin use



Chan, K. E. et al. J Am Soc Nephrol 2010;21:1550-1559

JASN

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



Chan, K. E. et al. *J Am Soc Nephrol* 2010;21:1550-9

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

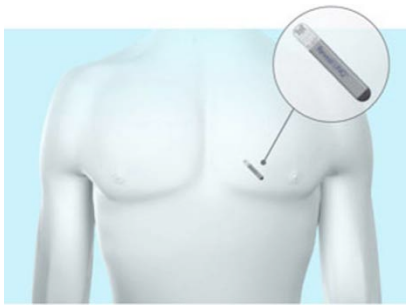
- Reducing the risk of sudden cardiac death
- Improving the likelihood of surviving cardiac arrest

Reducing the risk of sudden cardiac death

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

- Biomarkers-Cardiac Troponins (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
  - Atrial fibrillation (Genovesi et al, NDT, 2009).

Reveal® LINQ ICM (Implantable Cardiac Monitor)



Wireless

Cellular

Mobile Alerts

Reveal® LINQ Features:

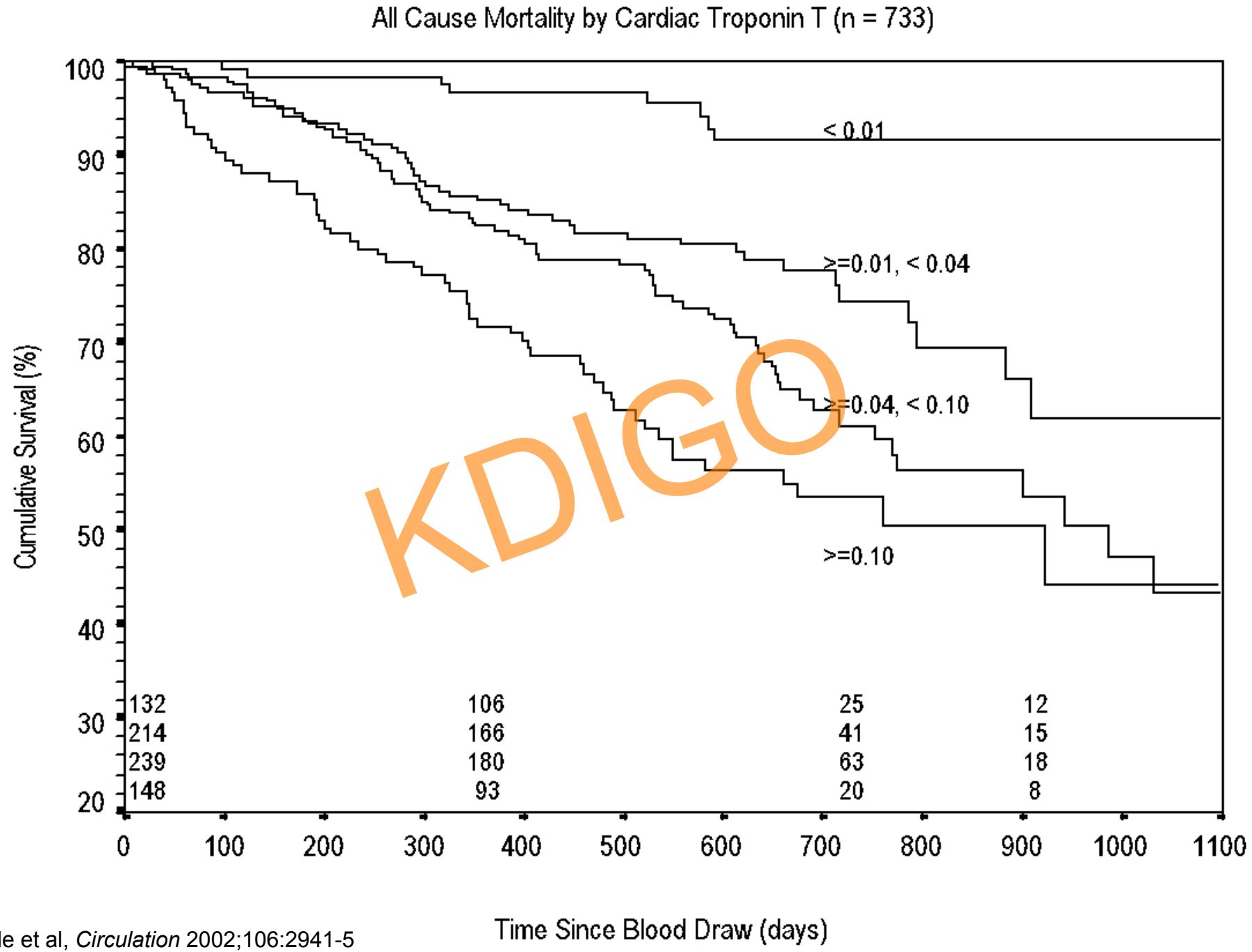
- AF algorithm accurately detects AF in 98.5% of patients[1]
- 3-year longevity for long-term monitoring[2]
- MR-Conditional at 1.5 and 3.0 Tesla[3]
- Proven diagnostic yields with clinically actionable reports[4-7]

Reveal® LINQ Indications for Use:

- Patients with clinical syndromes or situations at increased risk for cardiac arrhythmias
- Patients who experience transient symptoms such as dizziness, palpitation, syncope and chest pain, that may suggest a cardiac arrhythmia

1. Hindricks G, et al. Performance of a new leadless implantable cardiac monitor in detecting and quantifying atrial fibrillation: Results of the XPECT Trial. *Circ Arrhythm Electrophysi.* 3(2):141-147.
2. Reference the Reveal LINQ ICM Clinician Manual for usage parameters.
3. Reveal LINQ ICM has been demonstrated to pose no known hazards in a specified MR environment with specified conditions of use. Reference the Reveal LINQ ICM clinician manual for more details.
4. Edvardsson N, et al. Use of an implantable loop recorder to increase the diagnostic yield in unexplained syncope: results from the PICTURE registry. Europace.13(2):262-269.
5. Krahn AD, et al. Final results from a pilot study with an implantable loop recorder to determine the etiology of syncope in patients with negative noninvasive and invasive testing. Am J Cardiol. 82(1):117-119.
6. Krahn AD, et. al. Use of an extended monitoring strategy in patients with problematic syncope. Reveal Investigators. Circulation. 99(3):406-410.
7. Krahn AD, et. al. Cost implications of testing strategy in patients with syncope: randomized assessment of syncope trial. J Am Coll Cardiol. 42(3):495-501.

BIOMARKERS



Apple et al, *Circulation* 2002;106:2941-5

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
- < 10% of dialysis patients have LVEF of < 36%.

Reducing the risk of sudden cardiac death (continued)

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? (ISCHEMIA-CKD trial)
  - Prophylactic Beta-blocker therapy?
  - ACE-inhibitors?
  - Improvement of endothelial function/plaque
    - Statins? (No, based on 4D+AURORA/ SHARP had "atherosclerotic" endpoints)
    - Glycemic control
    - Anti-platelet agents

Reducing the risk of sudden cardiac death (continued)

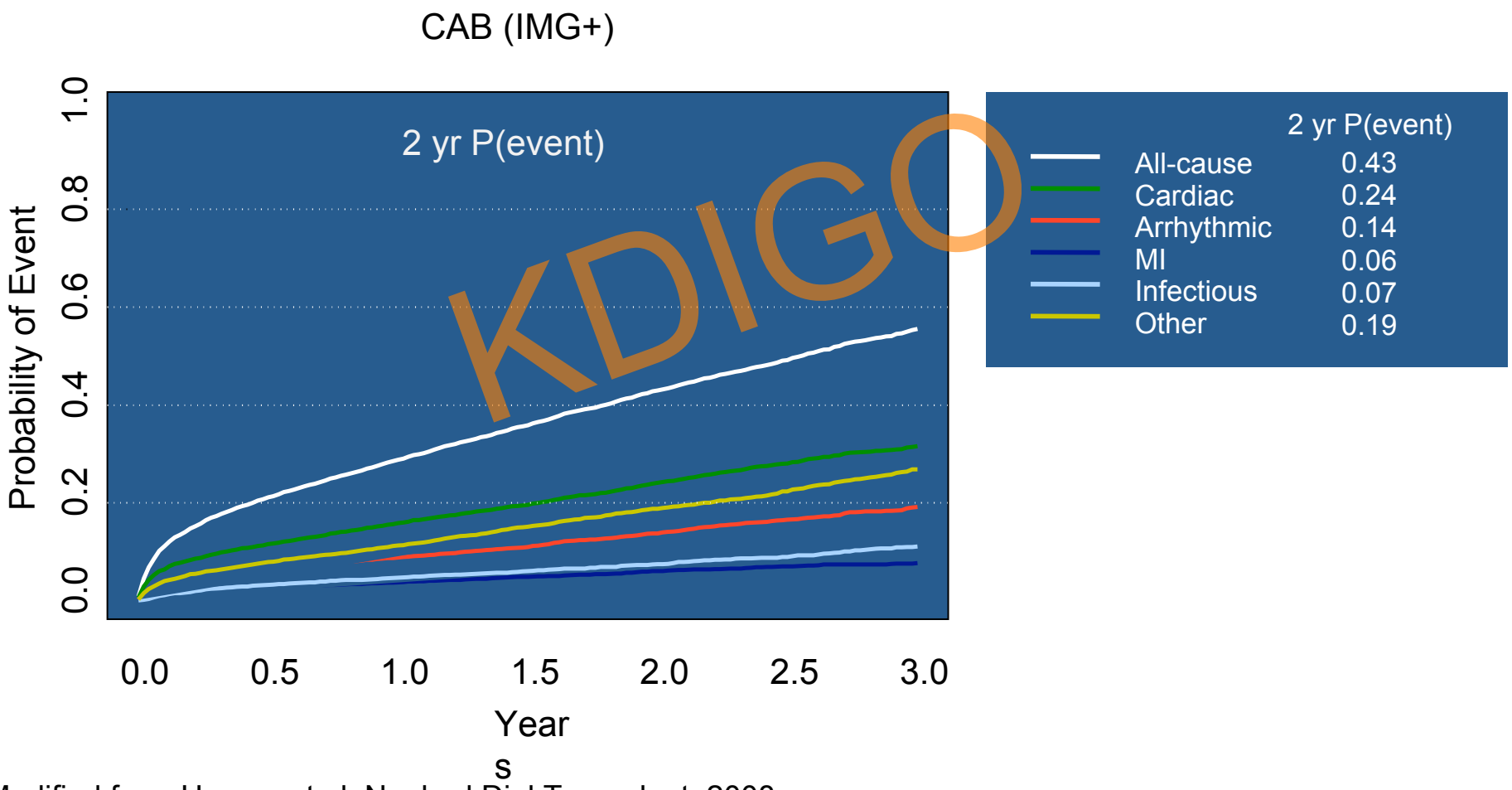
"Physiologic Dialysis"

- 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; Foley et al, 2011).
  - 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 with low dialyzability (Weir et al, JASN,2014)
- Fish oil?

Probability of all-cause and cause-specific death



Modified from Herzog et al, Nephrol Dial Transplant, 2008

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)?
- Wearable external defibrillators?

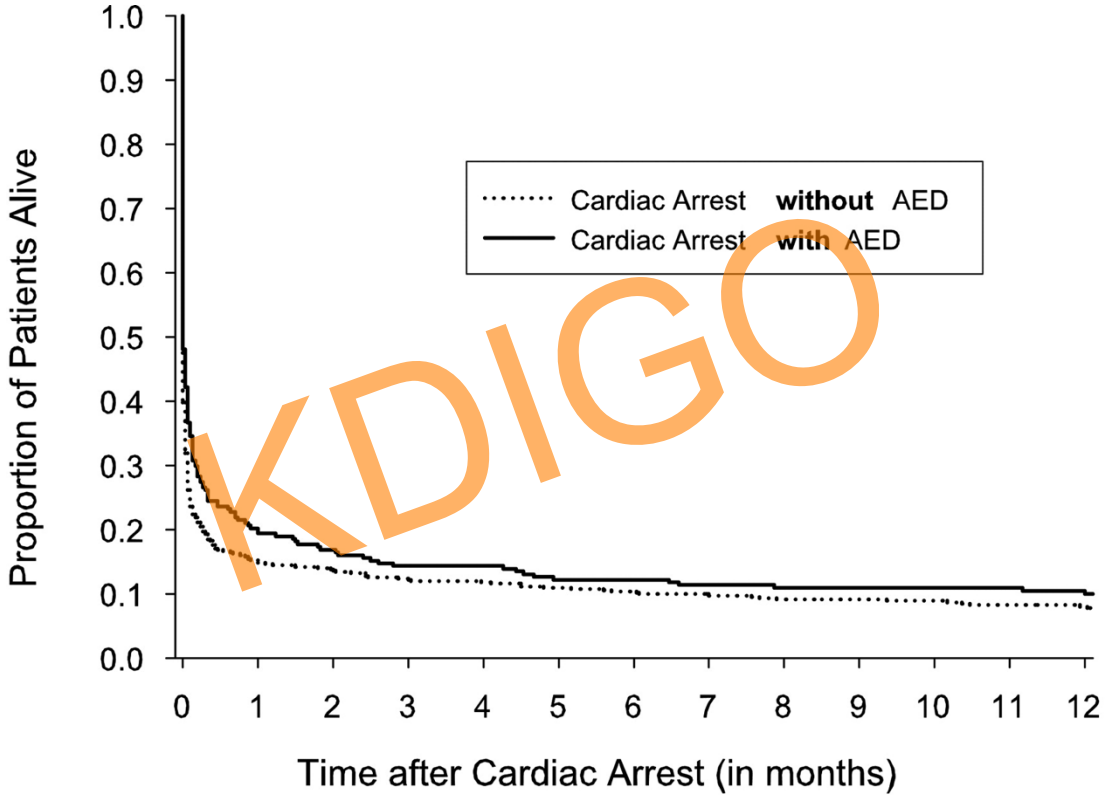
Cardiac arrest in the dialysis unit

- 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)
- Abysmal outcome after CPR (without rapid defibrillation): 92-100% in-hospital mortality (Moss et al,1992; Lai et al, 1999).

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?

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)



Without AED	492	68	58	51	44	41	35
With AED	237	40	34	29	25	24	20

Number of Patients at Risk

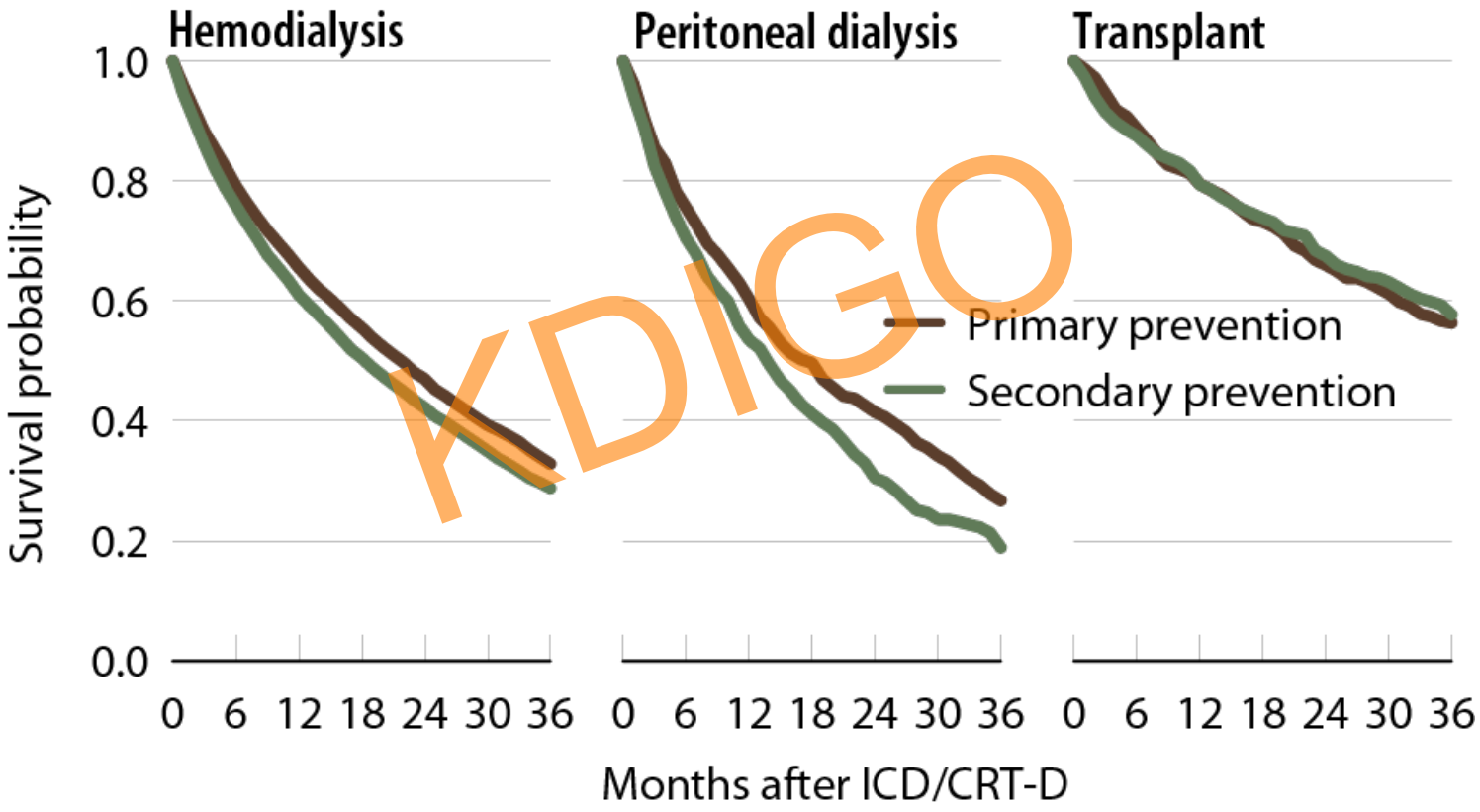
Lehrich, R. W. et al. *J Am Soc Nephrol* 2007;18:312-320

JASN

ICD's and WCD's in ESRD Patients

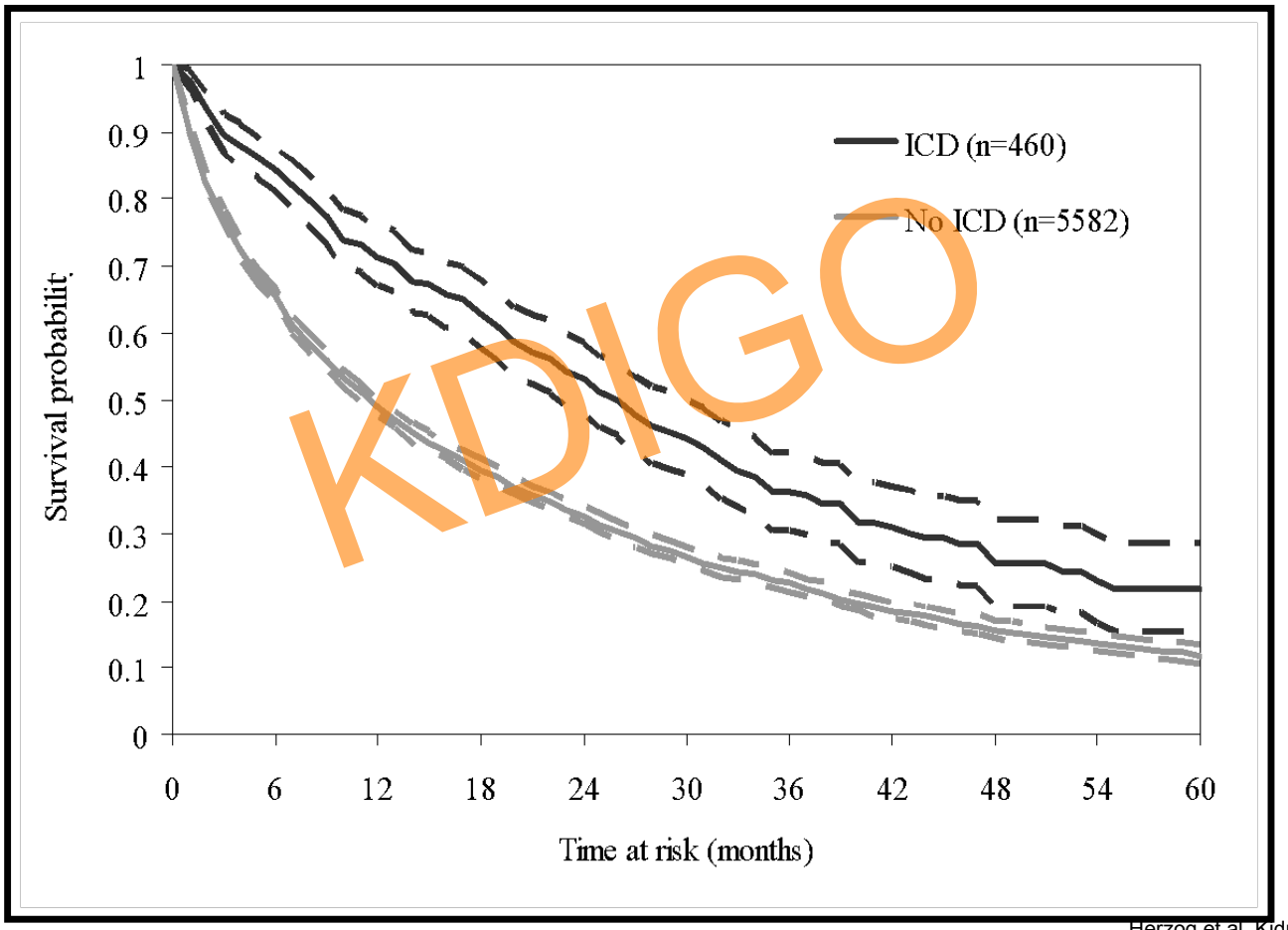
All-cause survival following implantation of first ICD/CRT-D, by modality, 1999–2010

Figure 4.16 (Volume 2)



Dialysis & transplant patients receiving their first ICDs/CRT-Ds in 1999–2010.

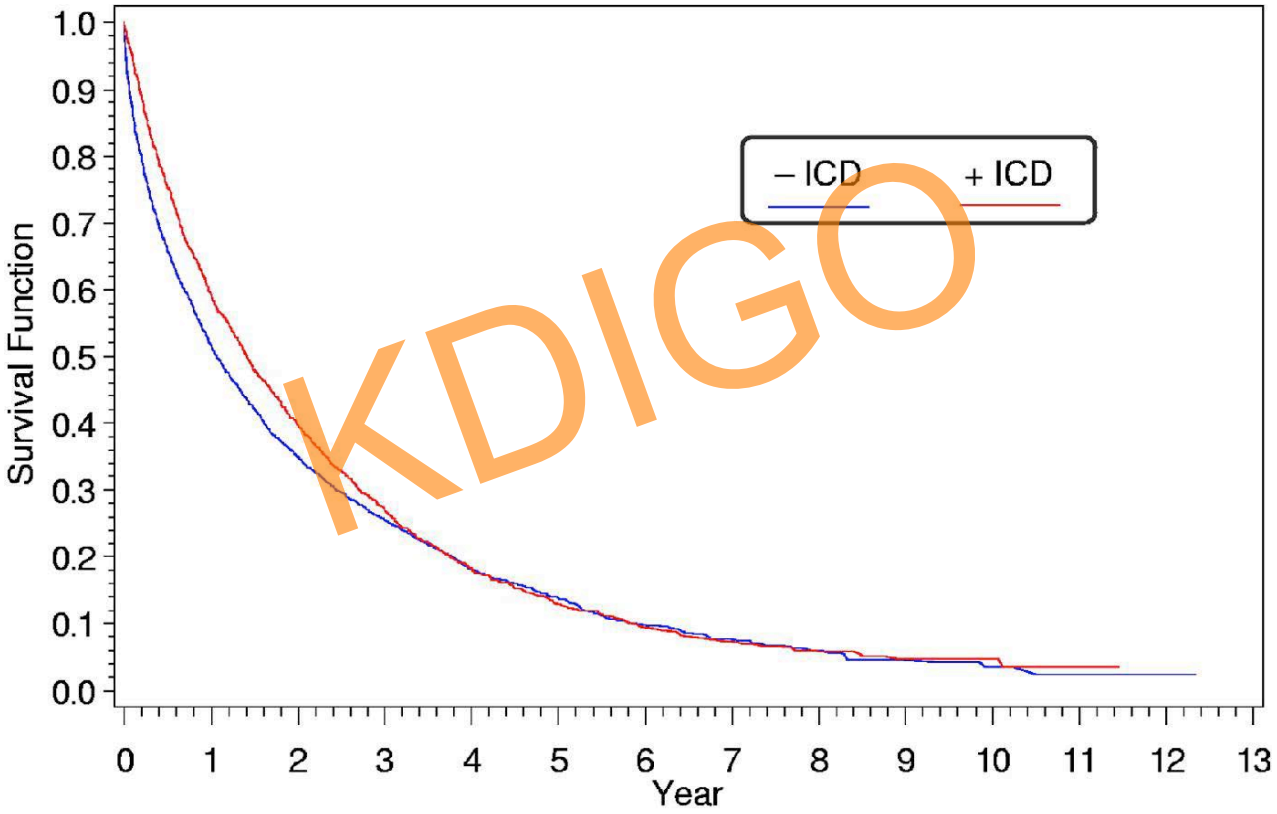
Survival of dialysis patients after cardiac arrest



Number at risk:					
No ICD	2,239	1,149	562	246	100
ICD	243	136	61	25	12

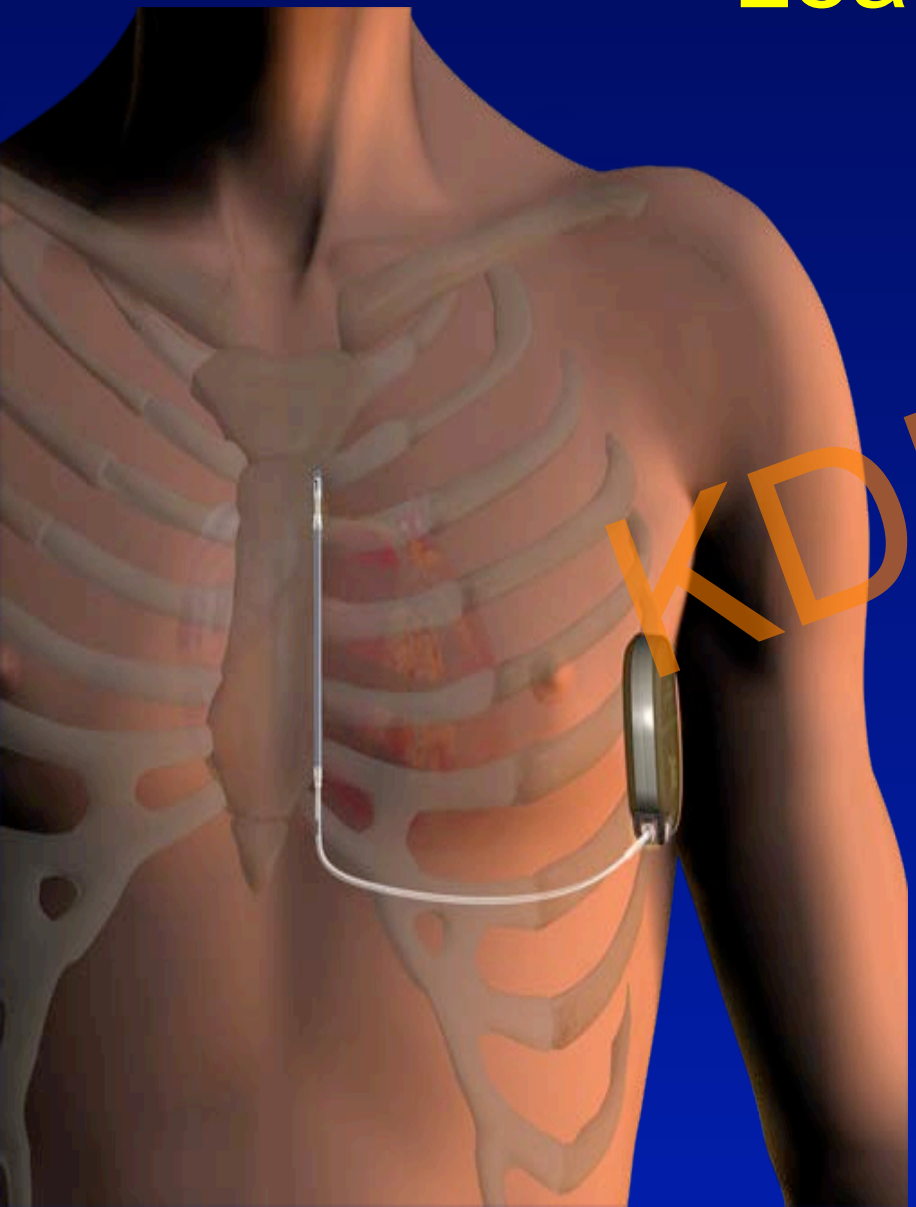
Herzog et al, Kidney International, 2005

Survival of patients who received an implantable cardioverter-defibrillator (ICD) for secondary prevention compared with matched controls.



Source: Charytan et al American Journal of Kidney Diseases 2011; 58:409-417

Defibrillation Without Transvenous Leads



The S-ICD System

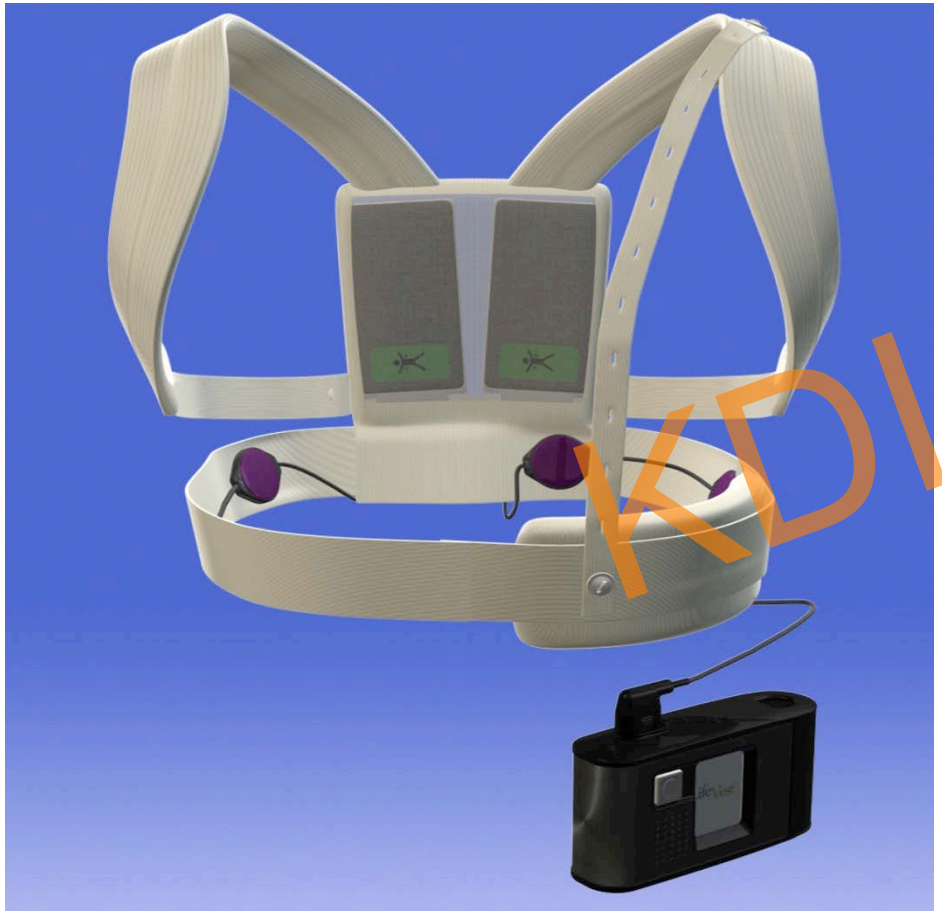
- Completely subcutaneous
- Does not require leads in the heart, leaving the vasculature untouched
- Placed strictly by anatomical landmarks, removing the need for fluoroscopy at implant
- Efficacy and safety not well studied in dialysis patients- absence of vascular access complications is appealing

WED-HED

(Clinicaltrials.gov identifier NCT02481206)

- ***WE****arable* **Cardioverter** ***D*****efibrillator (in)** ***HE*****mo*****D*****ialysis Patients**

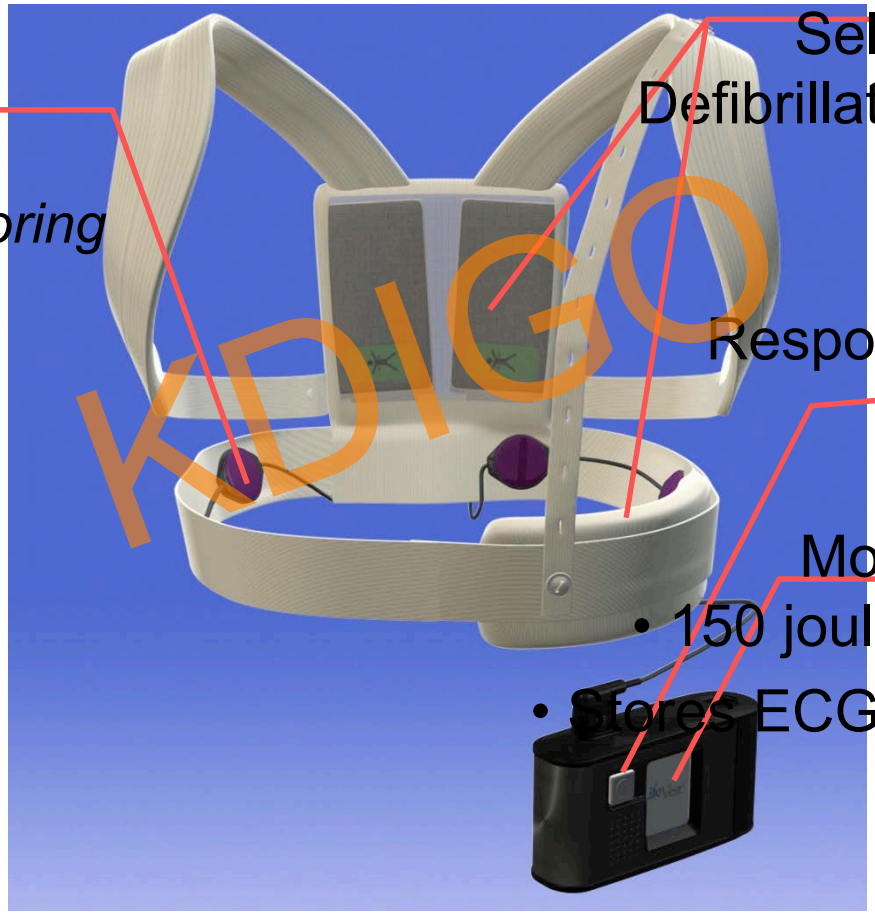
LifeVest Overview



- The LifeVest is indicated for adult patients who are at risk for sudden cardiac arrest and are not candidates for or who refuse an implantable defibrillator.

LifeVest System

lectrodes
on-adhesive
g 2 channels of monitoring



Self-Gelling
Defibrillation Electrodes

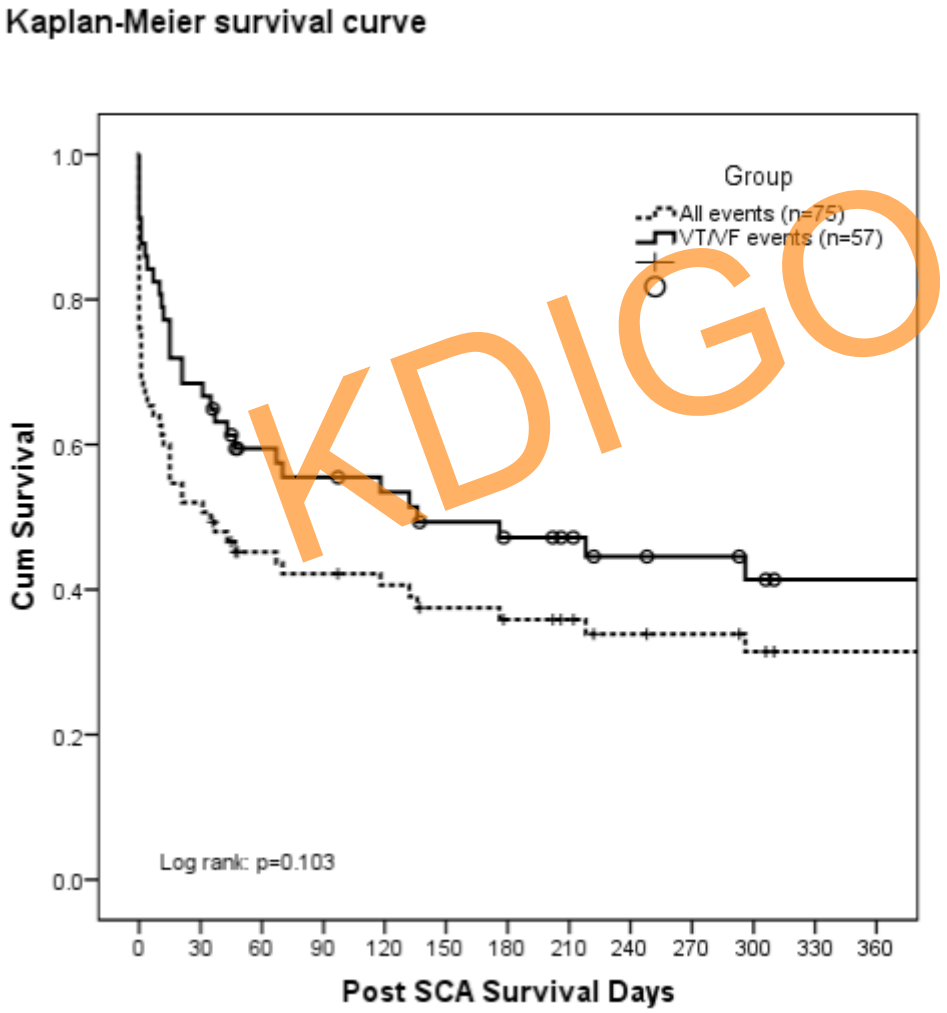
Response Buttons

Monitor
- 150 joules biphasic
- Stores ECG, daily use, etc.

LifeVest Patient Use Data

- Over 200,000 patients have worn LifeVest
- 98% first shock success rate
- 92% shocked event survival (conscious ER arrival or stayed at home)
- Most (73%) treated within 60 seconds (remaining delayed from response button use or VT programming)
- Average duration of use is 2 to 3 months
- Median daily use is 22.5 hours/day
- VT/VF was 78% of SCA events in 75 HD pts (Wan et al 2013)

Survival of ESRD after Cardiac Arrest



Wan C et al. *Annals of Noninvasive Electrocardiol*.2013

Sudden Cardiac Events in Dialysis Patients with WCD

Characteristic	N =84
Initial rhythm	
VT	54 (64.3%)
VF	12 (14.3%)
Asystole	18 (21.4%)
Location of event occurrence	
Home	30 (35.7%)
Hospital	13 (15.5%)
Dialysis unit	23 (27.4%)
Rehab/Nursing home	1 (1.2%)
Others	1 (1.2%)
Unknown	16 (19.0%)

Wan C et al. *Annals of Noninvasive Electrocardiology*, 2013

WCD – Treated VT/VF in Dialysis Patient

Wan C et al. *Annals of Noninvasive Electrocardiology*, 2013

Proposed Study Objective

- To determine if the wearable cardioverter defibrillator (WCD) will reduce the incidence of sudden cardiac death in patients with ESRD on hemodialysis with no prior SCA
  - **LVEF > 35% and age 50+**

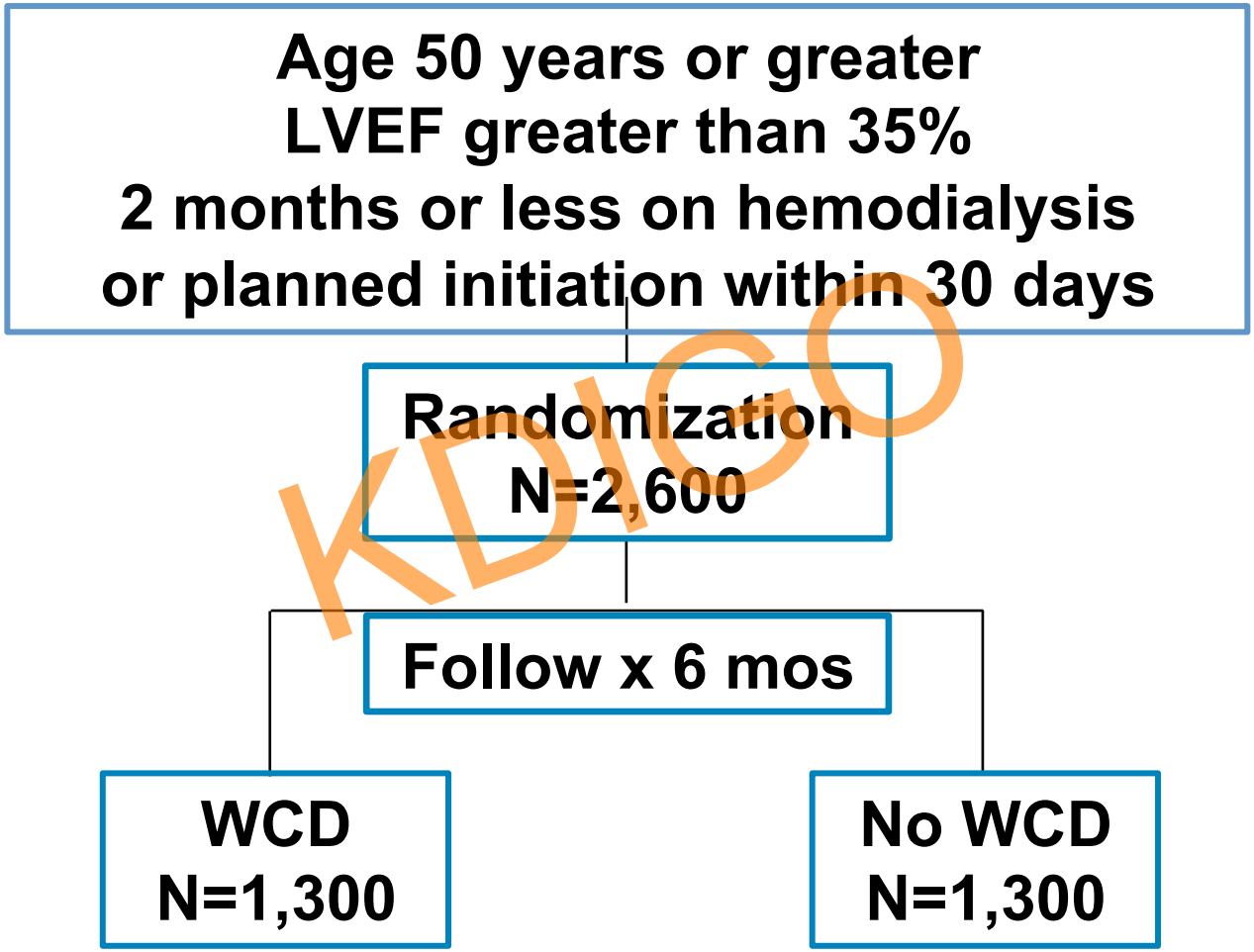
    and *newly incident:*

    Started dialysis within 60 days

    or

    Dialysis initiation planned within 30 days

Clinical Trial Design



Primary Endpoint: Adjudicated SCD

Conclusion

- Sudden cardiac death is the single largest cause of death in dialysis patients
- Modifiable risk factors for sudden cardiac death include very low potassium dialyzate
- Further studies to reduce the risk of SCD in ESRD patients are warranted: WED-HED

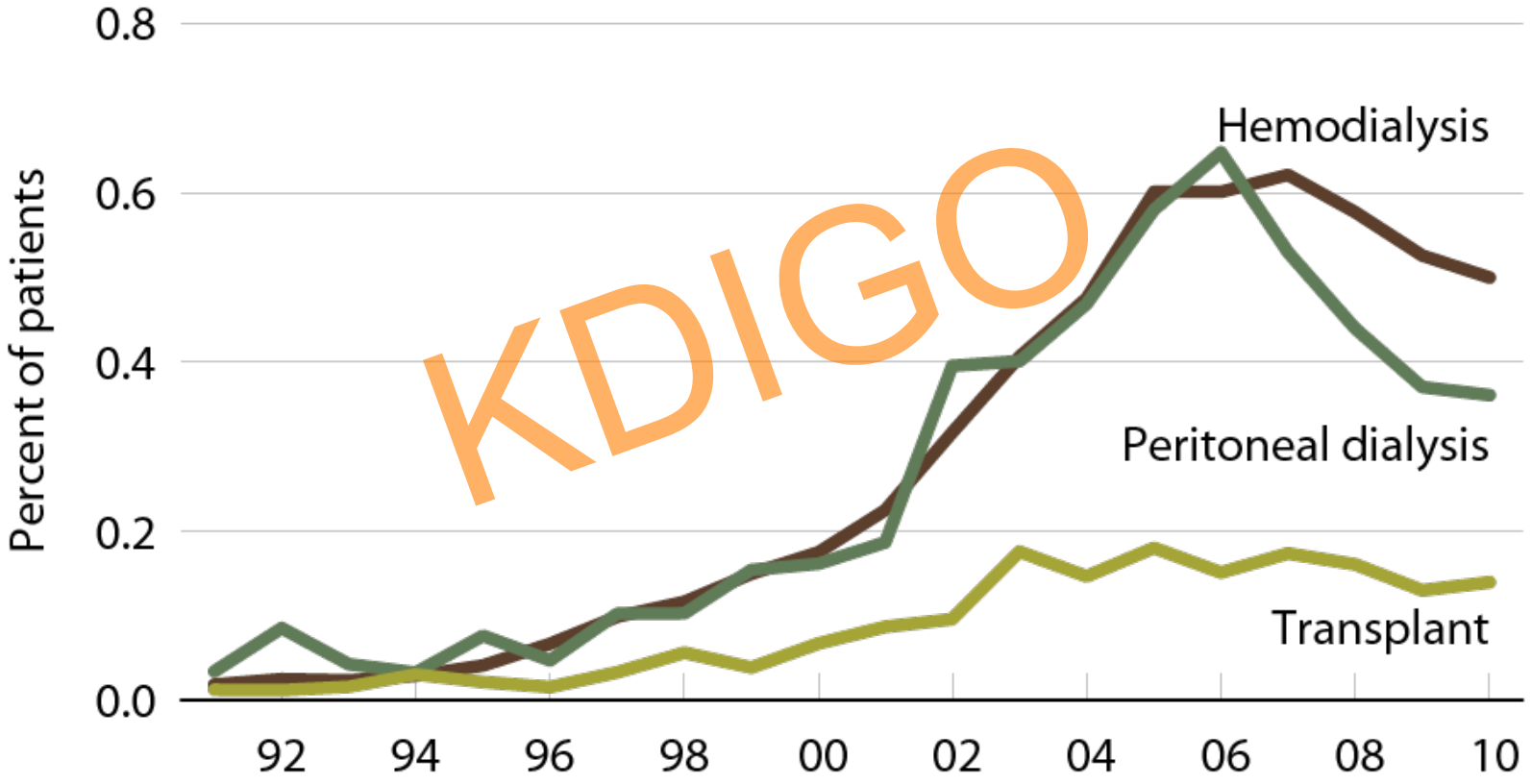
Cumulative number & percent of dialysis patients receiving ICDs/CRT-Ds

Figure 4.13 (Volume 2)

Period prevalent patients; dialysis patients 1992–2010.

Patients receiving ICDs/CRT-Ds, modality

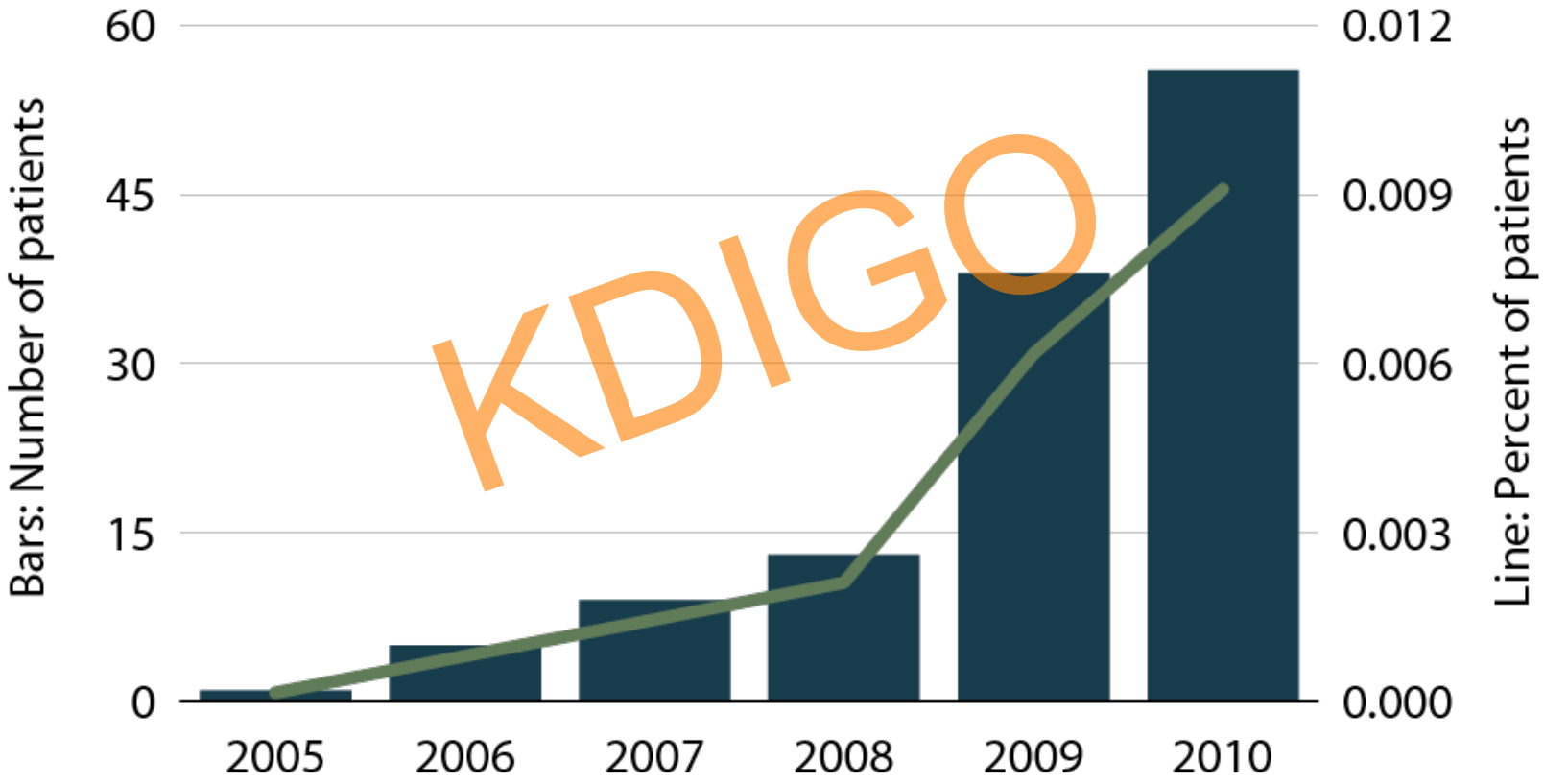
Figure 4.14 (Volume 2)



Dialysis or transplant patients in each year 1992–2010.

Cumulative number & percent of dialysis patients using a wearable cardioverter defibrillator

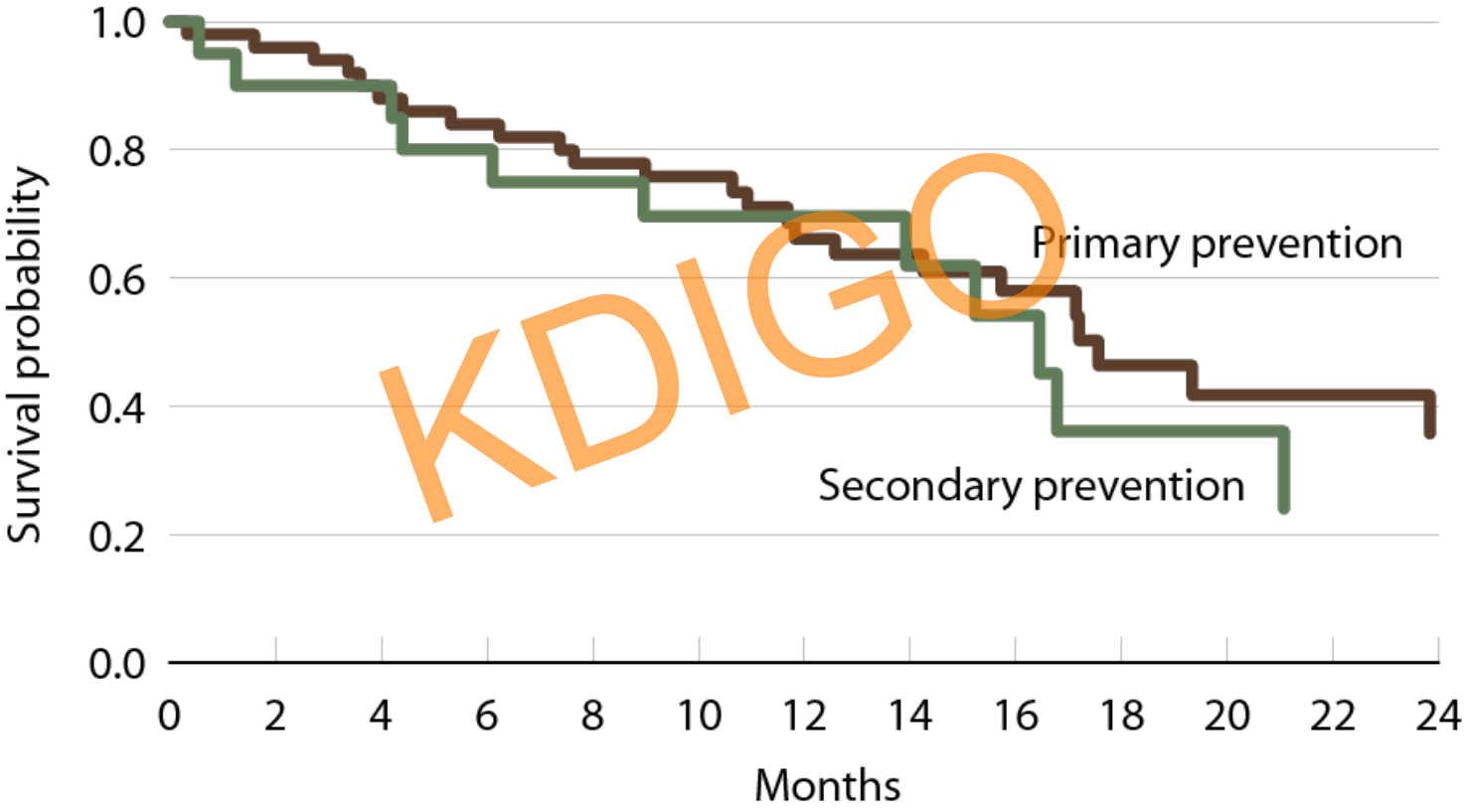
Figure 4.15 (Volume 2)



Dialysis patients 2005–2010.

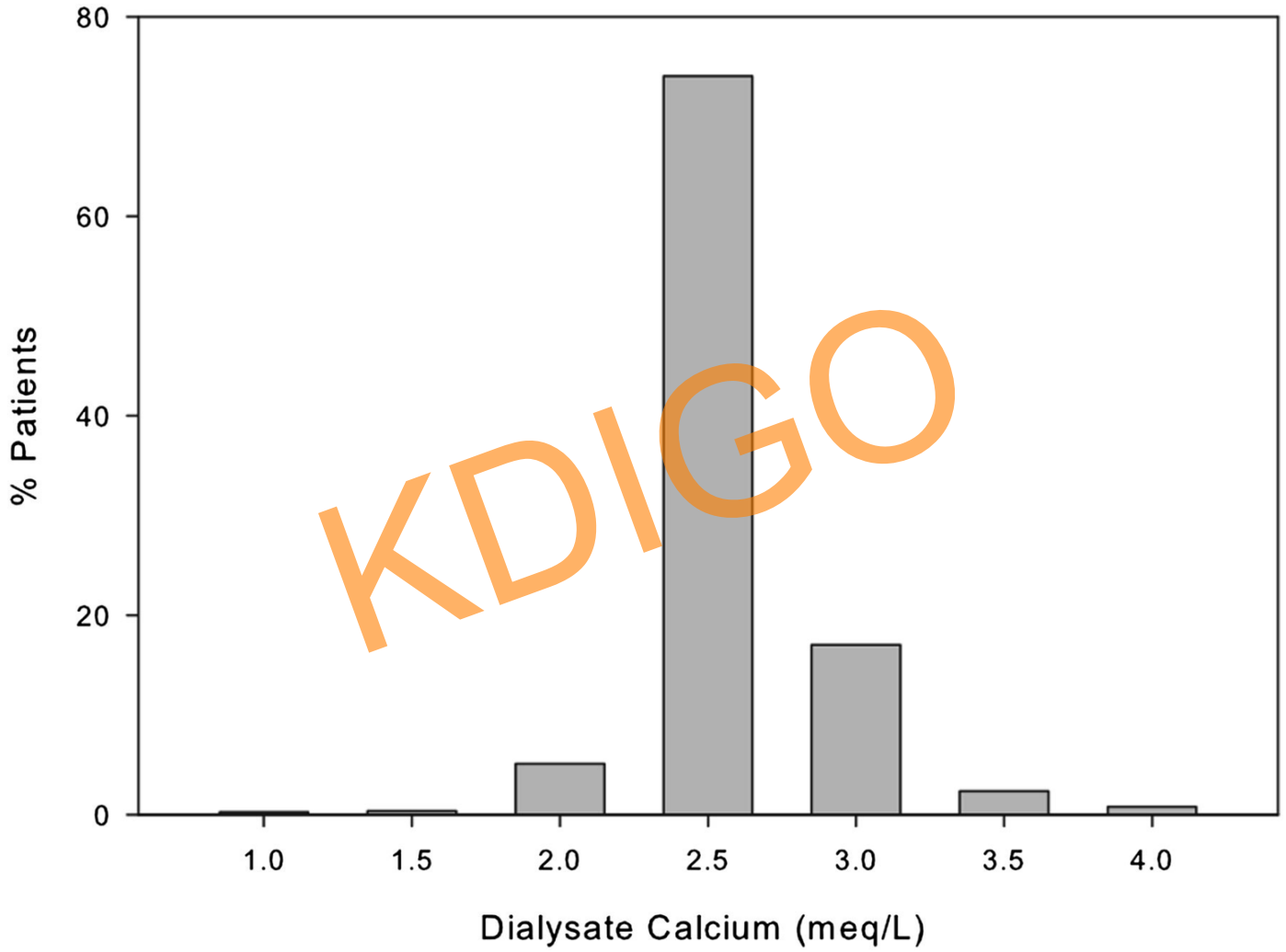
All-cause survival in dialysis patients using first wearable cardioverter defibrillator (WCD), 2005–2010

Figure 4.17 (Volume 2)



Dialysis patients receiving first WCD in 2005–2010.

Distribution of dialysate calcium assignment in the study cohort.



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