Can We Prevent Sudden Cardiac Death in CKD Patients?

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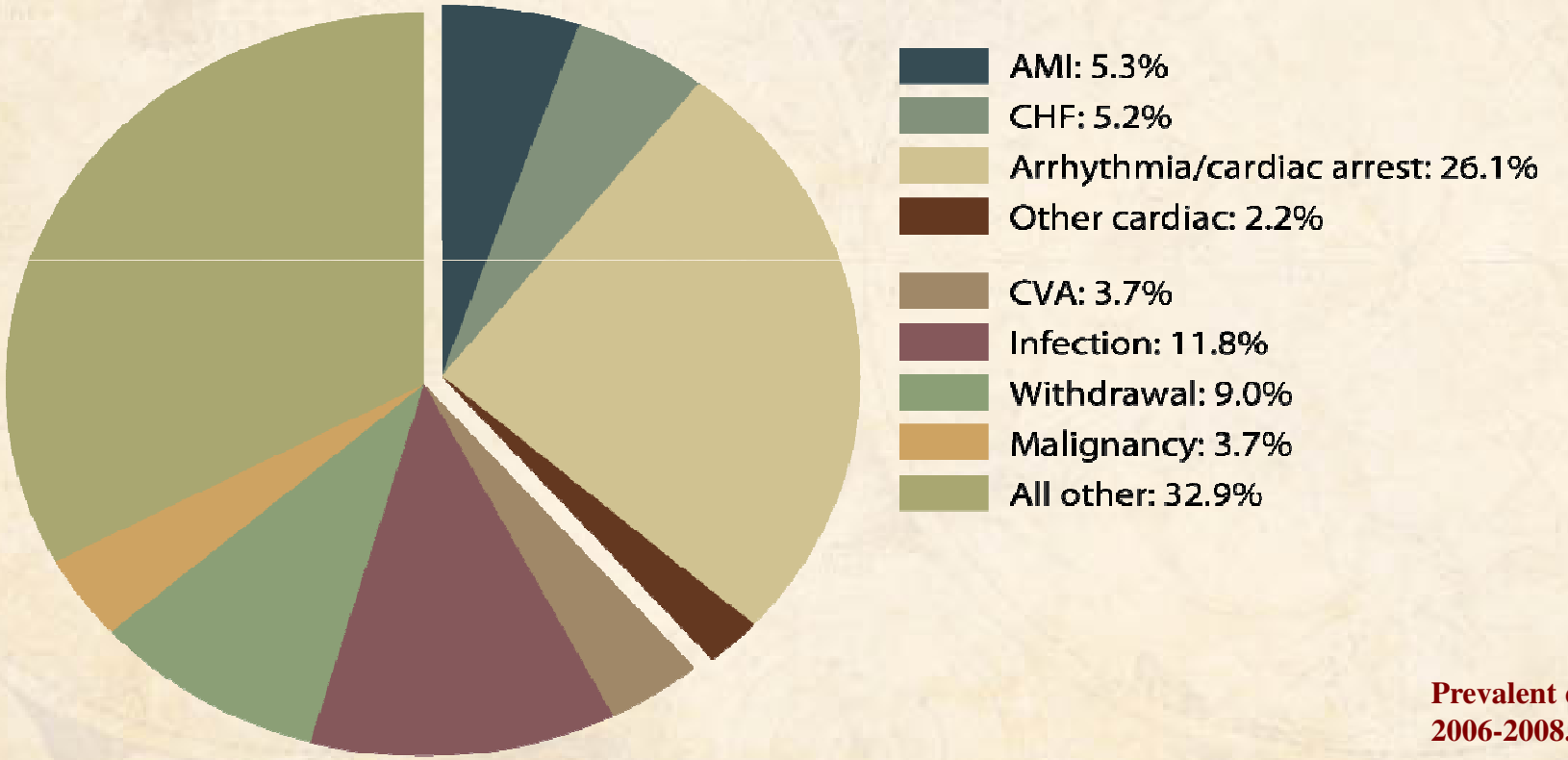
Introduction

- 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
- 382,343 US dialysis and 165,639 renal transplant pts in 2008.

Causes of death in prevalent dialysis patients, 2006–2008

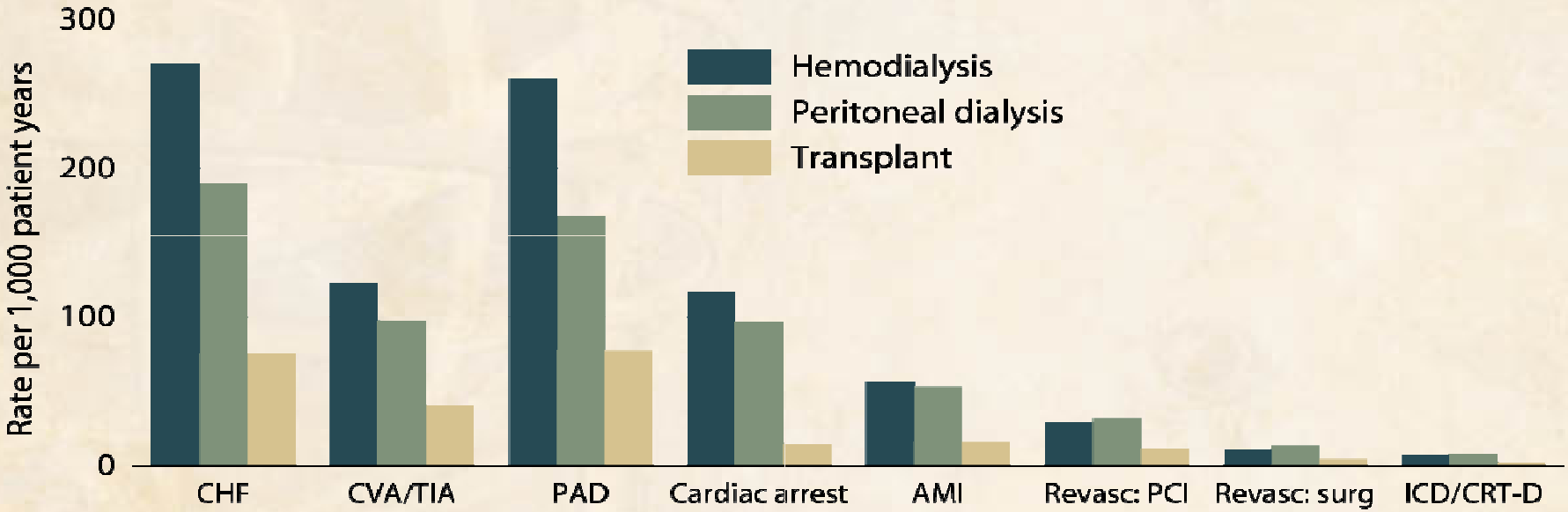
Figure 9.1 (Volume 2, 2010 ADR)



Prevalent dialysis patients, 2006-2008.

USRDS

Event rates of cardiovascular diagnoses & procedures, by modality



Point prevalent ESRD patients on January 1, 2005

USRDS

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  - Includes deaths not truly sudden cardiac (e.g. patients withdrawn from dialysis)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

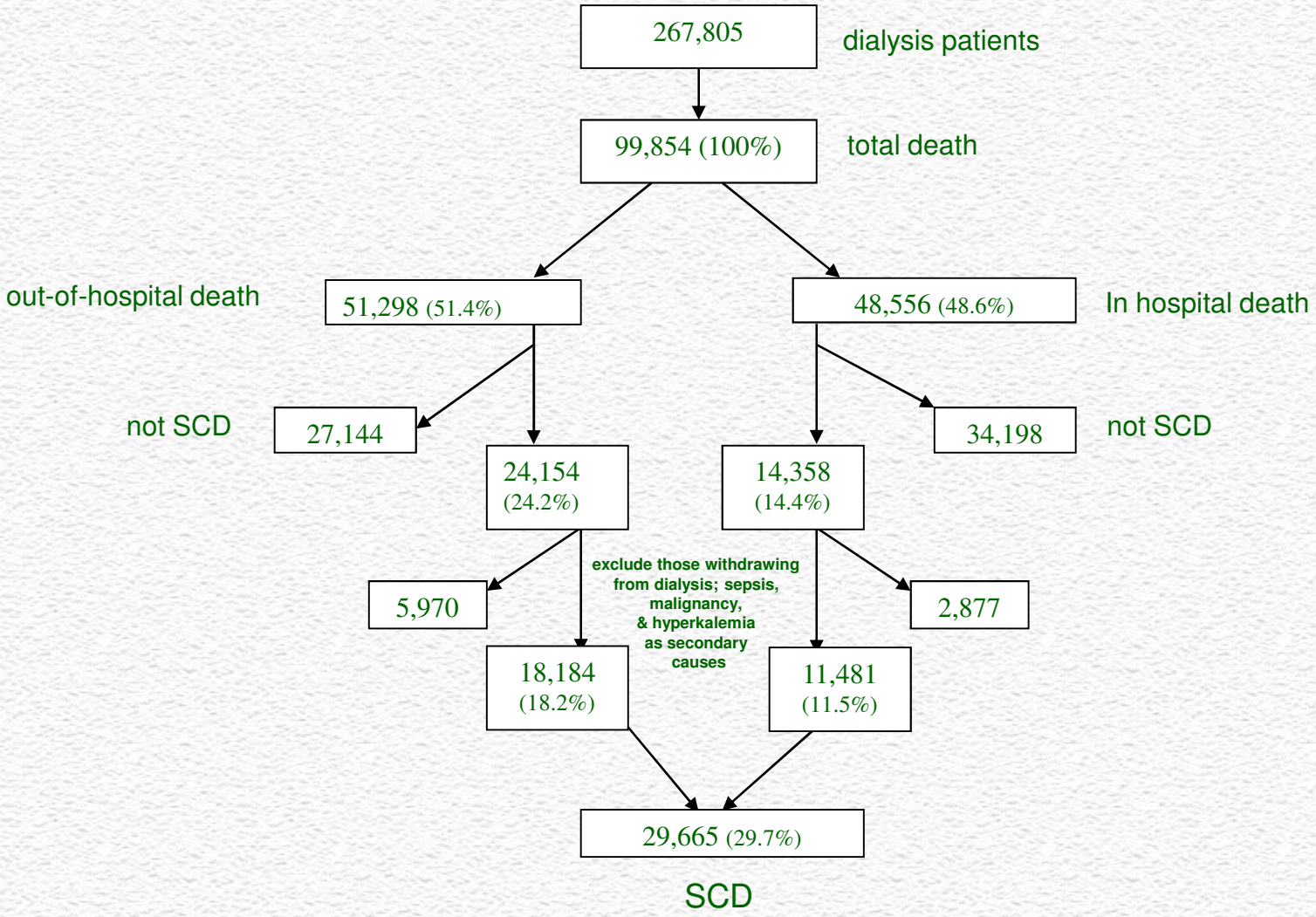
"CVSSC ADR Method" for SCD

- **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**

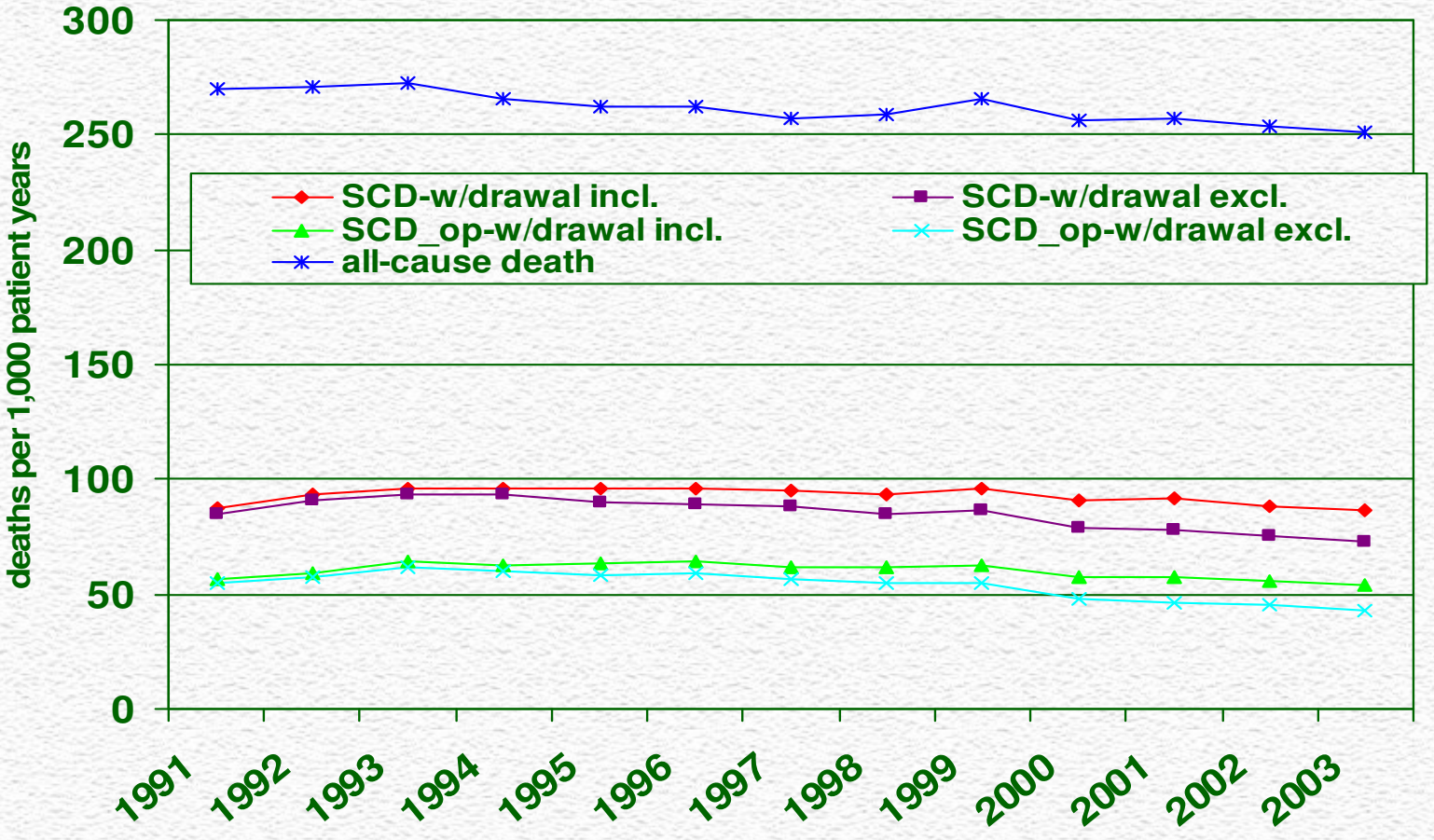
  OR
  - **If no claim data, primary cause of death is cardiac on Form 2746**
- **SCD in-hospital:**
  - **Inpatient claim for v.fib/cardiac arrest and primary cause of death due to cardiac disease on Form 2746.**

  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)



Prevalent dialysis patients
adjusted SCD rates



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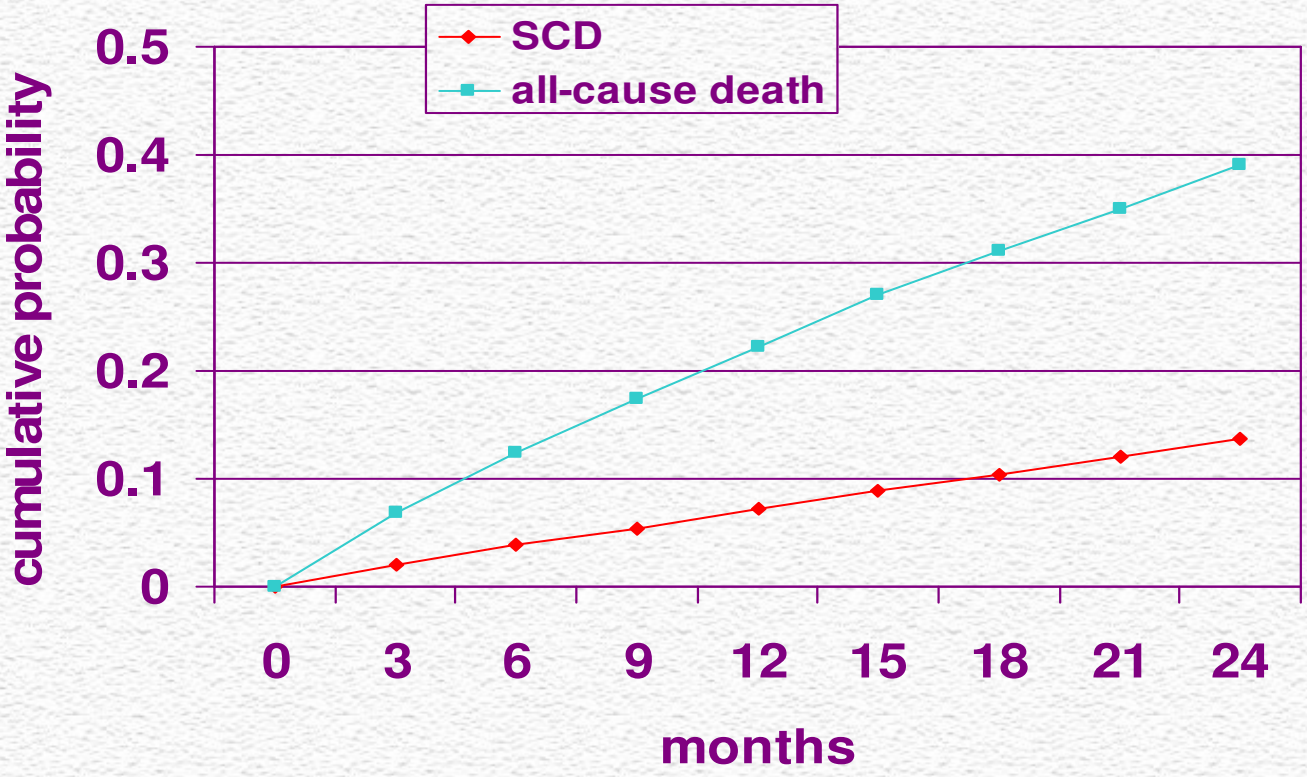
Cumulative probability of SCD & all-cause death

2002 prevalent dialysis patients



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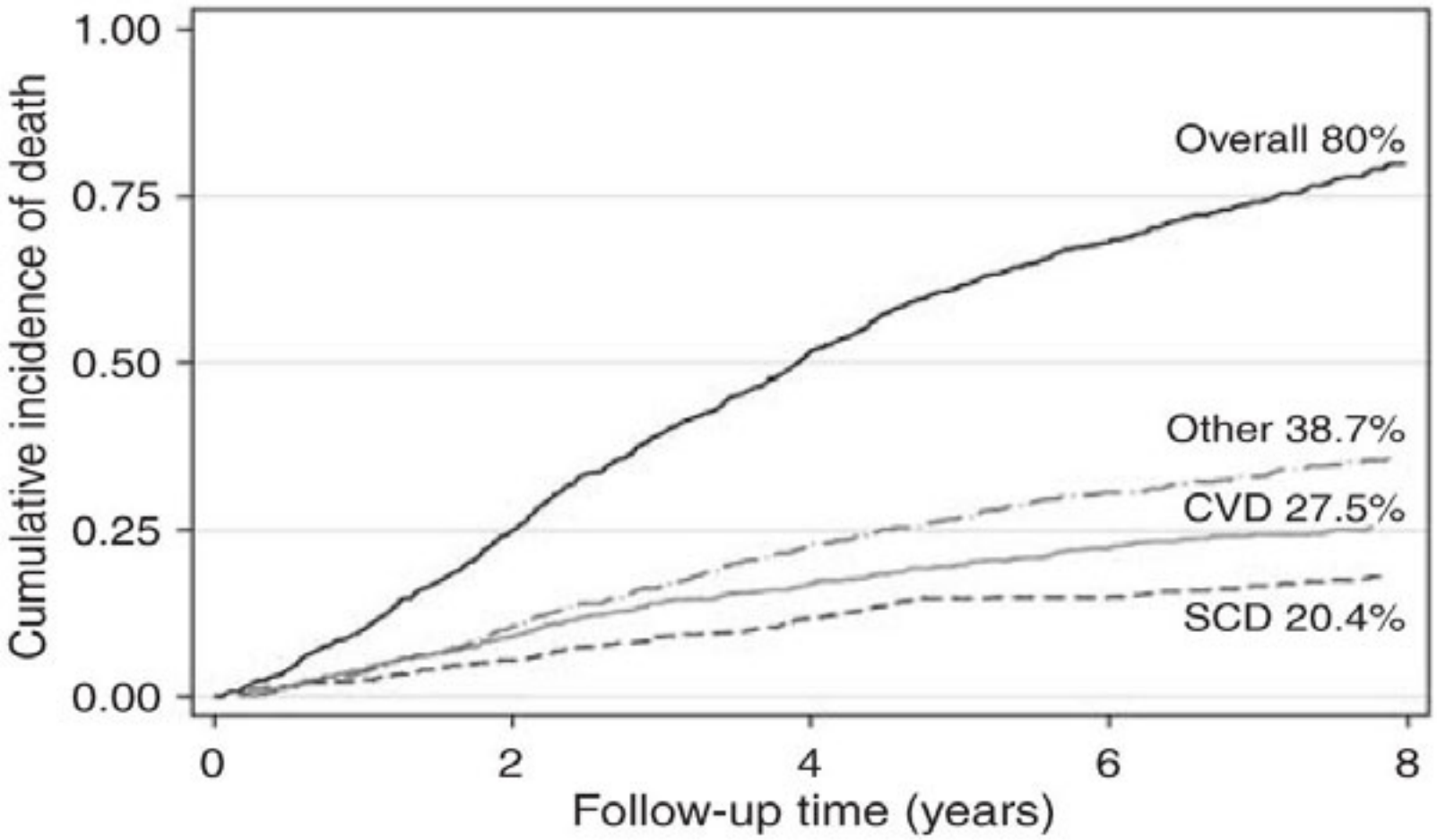
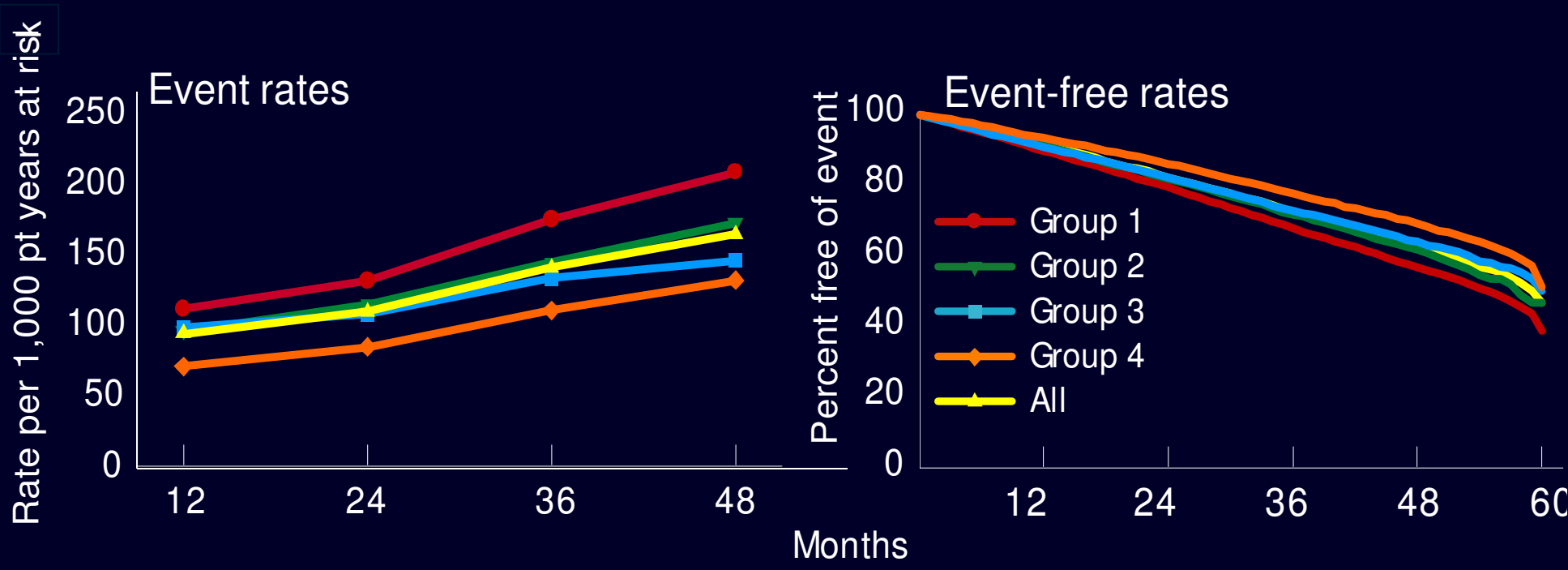


Figure 1 | Cumulative incidence of overall mortality and specific causes of death (including sudden cardiac death, other cardiovascular causes and other causes of death) in the CHOICE cohort.

Parekh et al. *Kidney International* 2008;74;1335

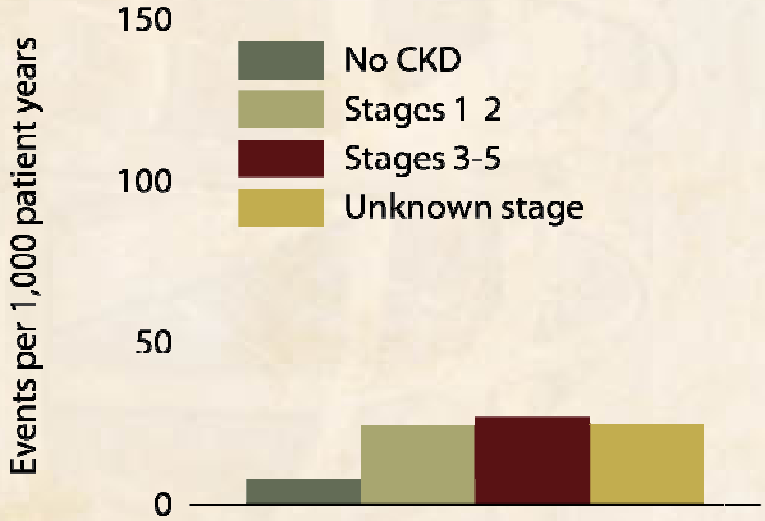
Event rates & adjusted event-free survival: cardiac arrest

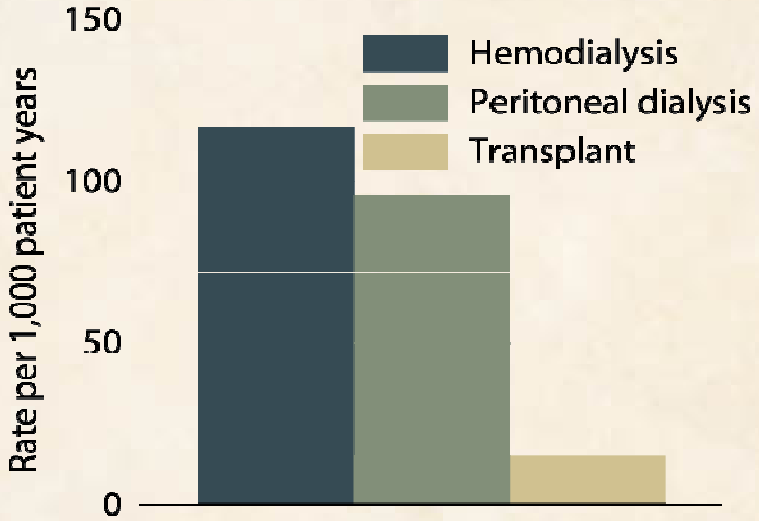


Cardiac Arrest in CKD

USRDS

Unadjusted cardiac arrest event rates



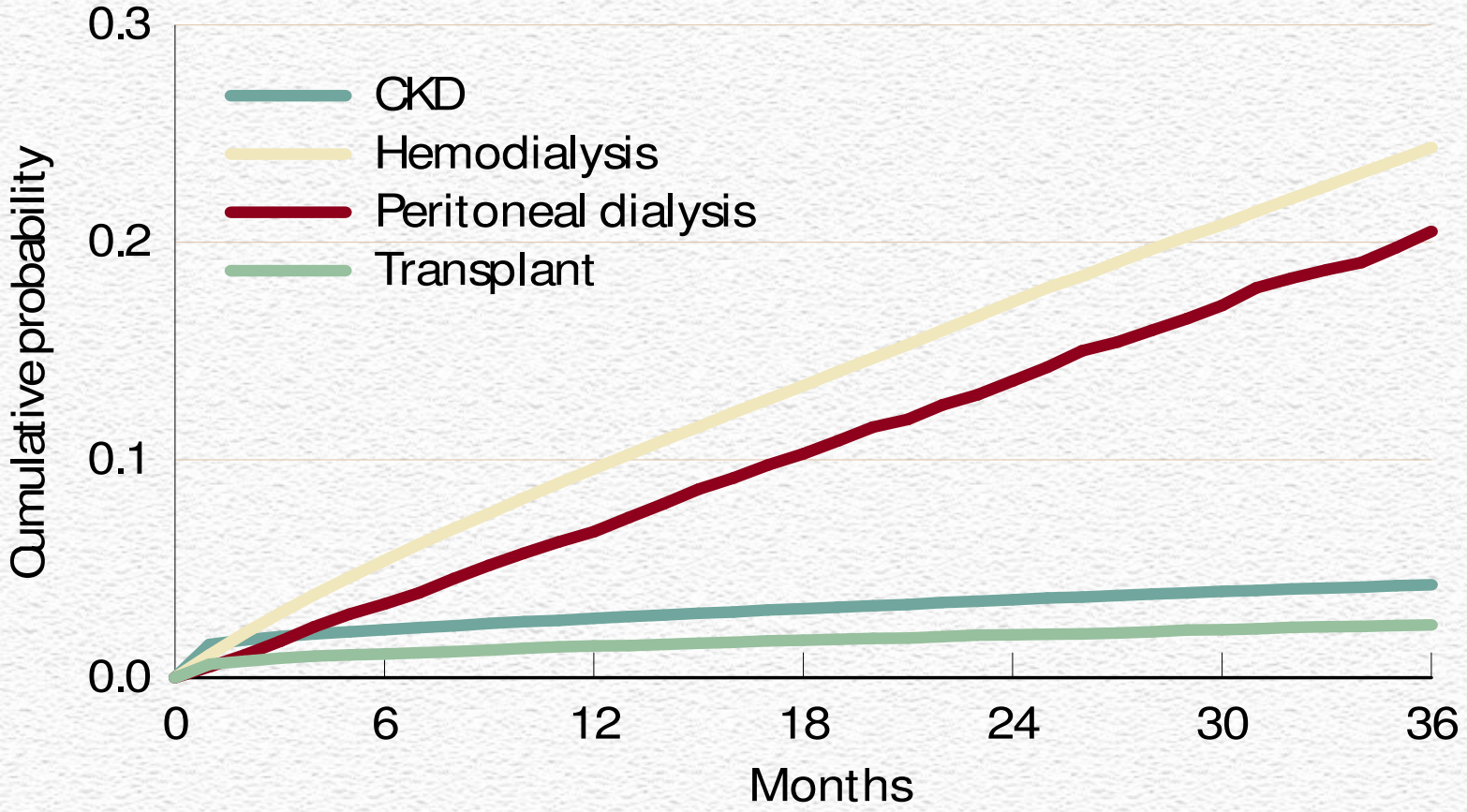


CKD *Stages*

1 eGFR ≥90, albumin/creatinine ratio (ACR) ≥30 mg/g
2 eGFR 60–89, ACR ≥30 mg/g
3 eGFR 30–59
4 eGFR 15–29
5 eGFR <15 (dialysis pts excluded from analyses)

USRDS

Probability of cardiac arrest in incident patients, overall



2006 ADR

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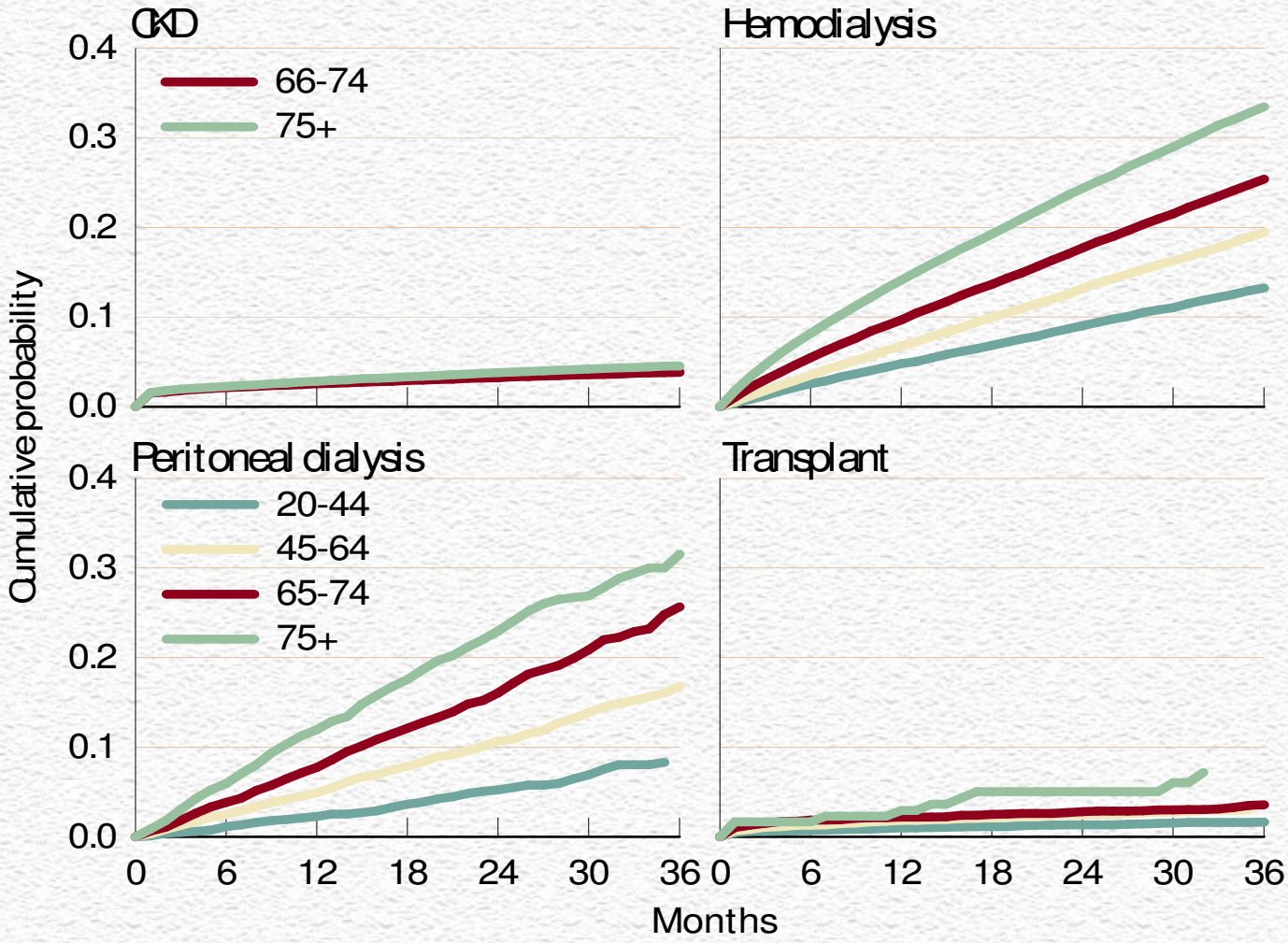
Probability of cardiac arrest in incident patients, by age



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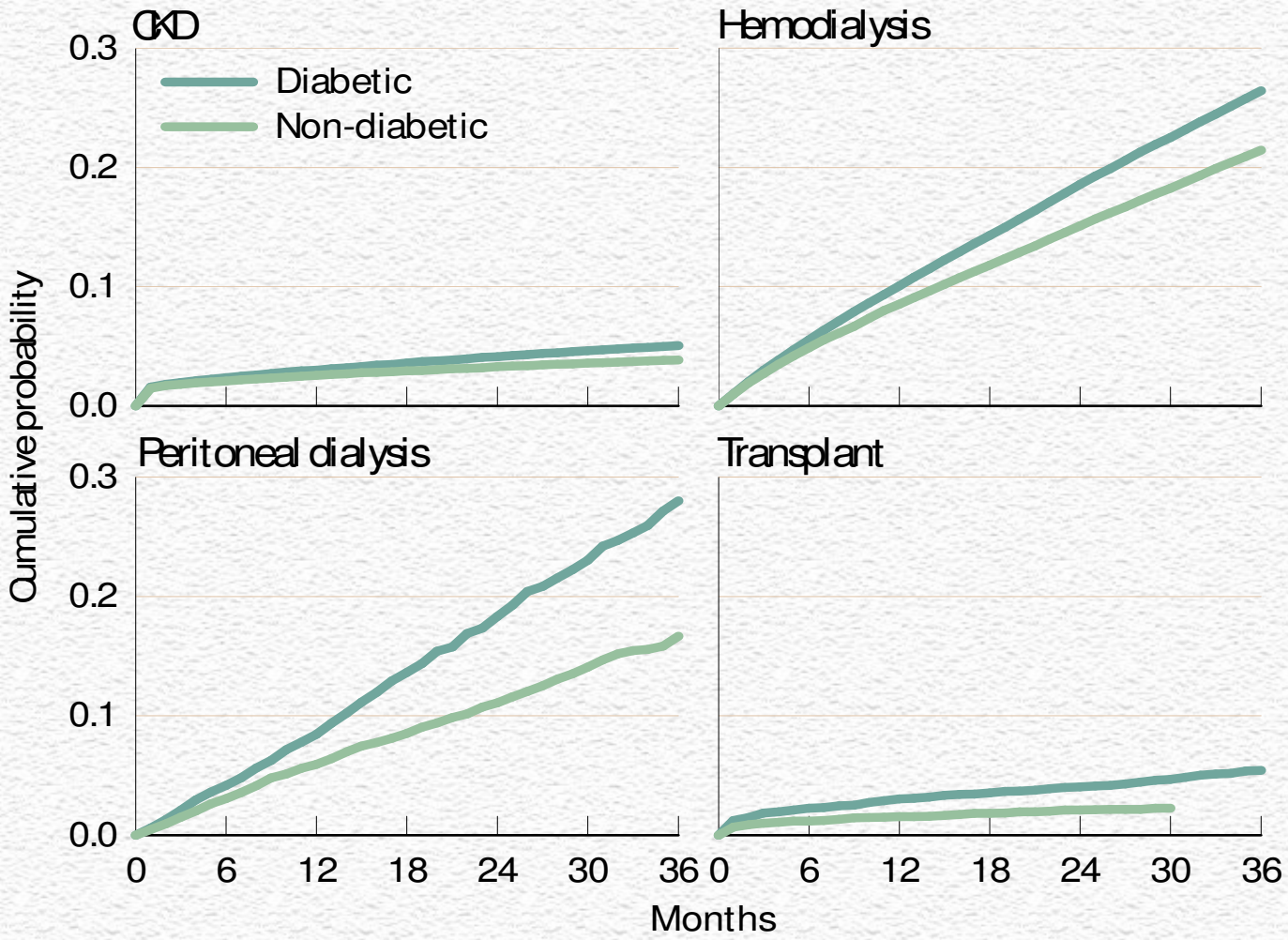
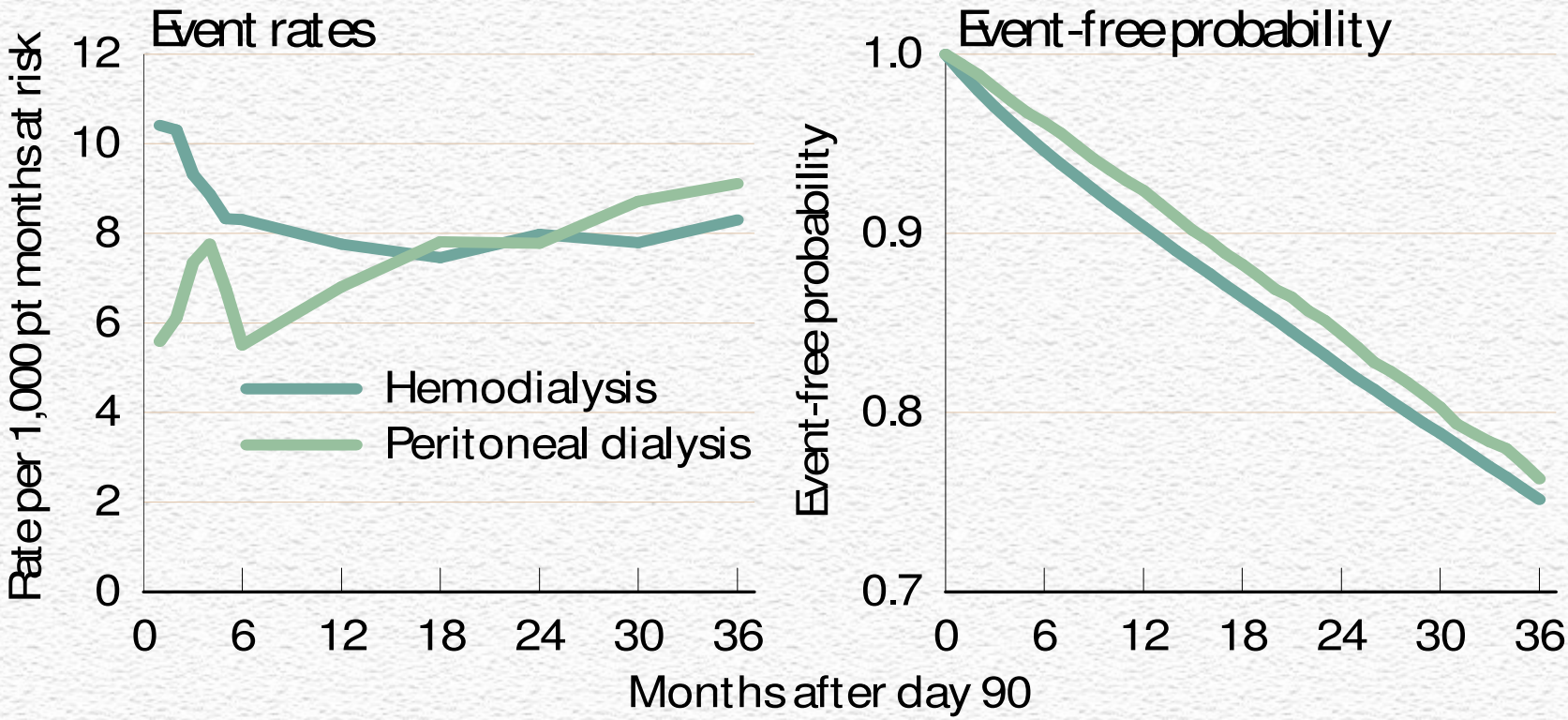
Probability of cardiac arrest in incident patients, by diabetic status



2006 ADR

USRDS

Event rates & event-free probabilities, incident patients: cardiac arrest



2006 ADR

USRDS

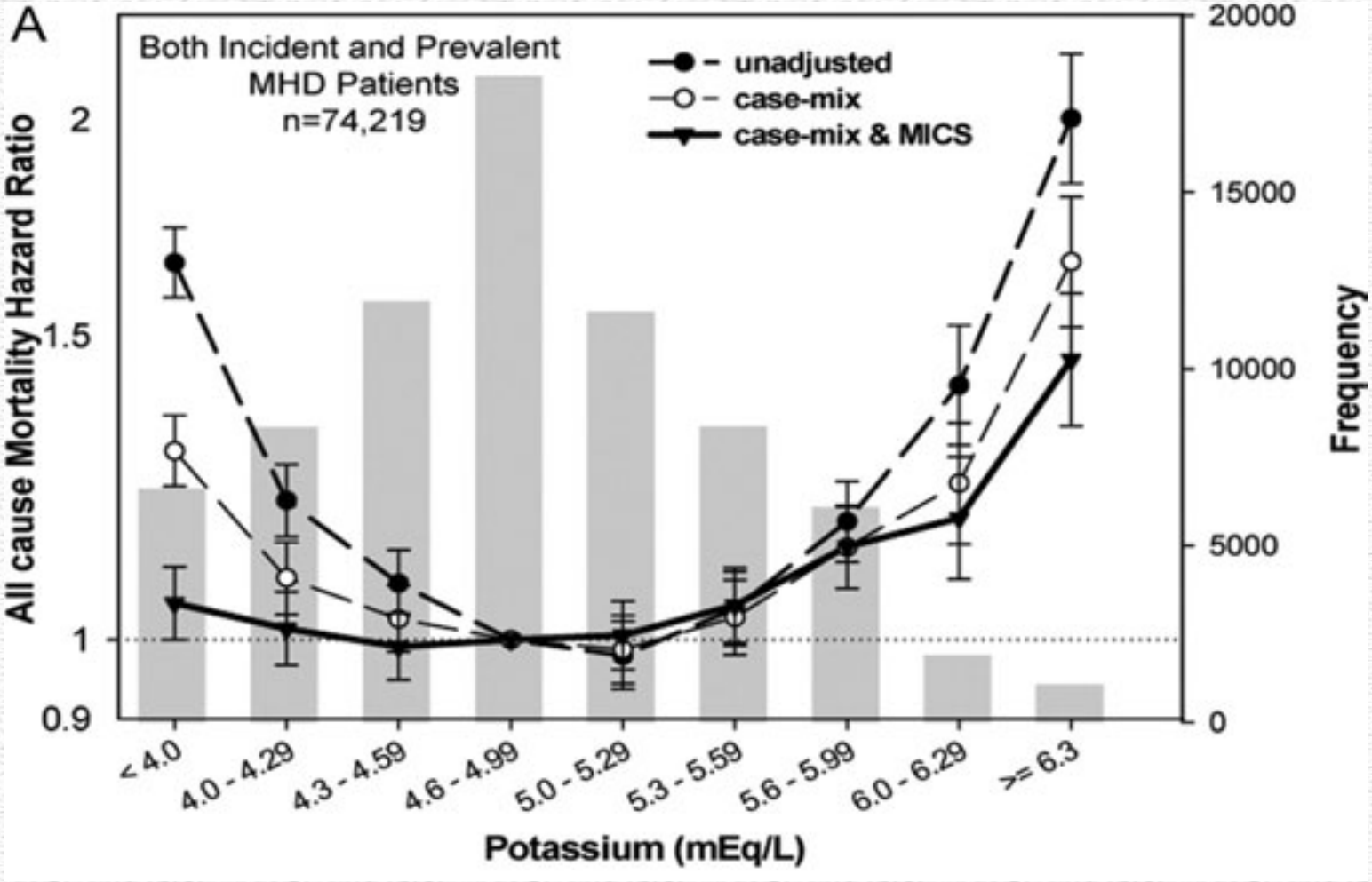
Serum Potassium in SCD

- Karnik et al (Kidney International, 60: 350-357, 2001): 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

Serum Potassium in SCD

- Bleyer et al (Kidney International, 69, 2268-2273, 2006): 88 HD pts (North Carolina) with sudden death, prior monthly lab studies in 77pts.
- 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%)

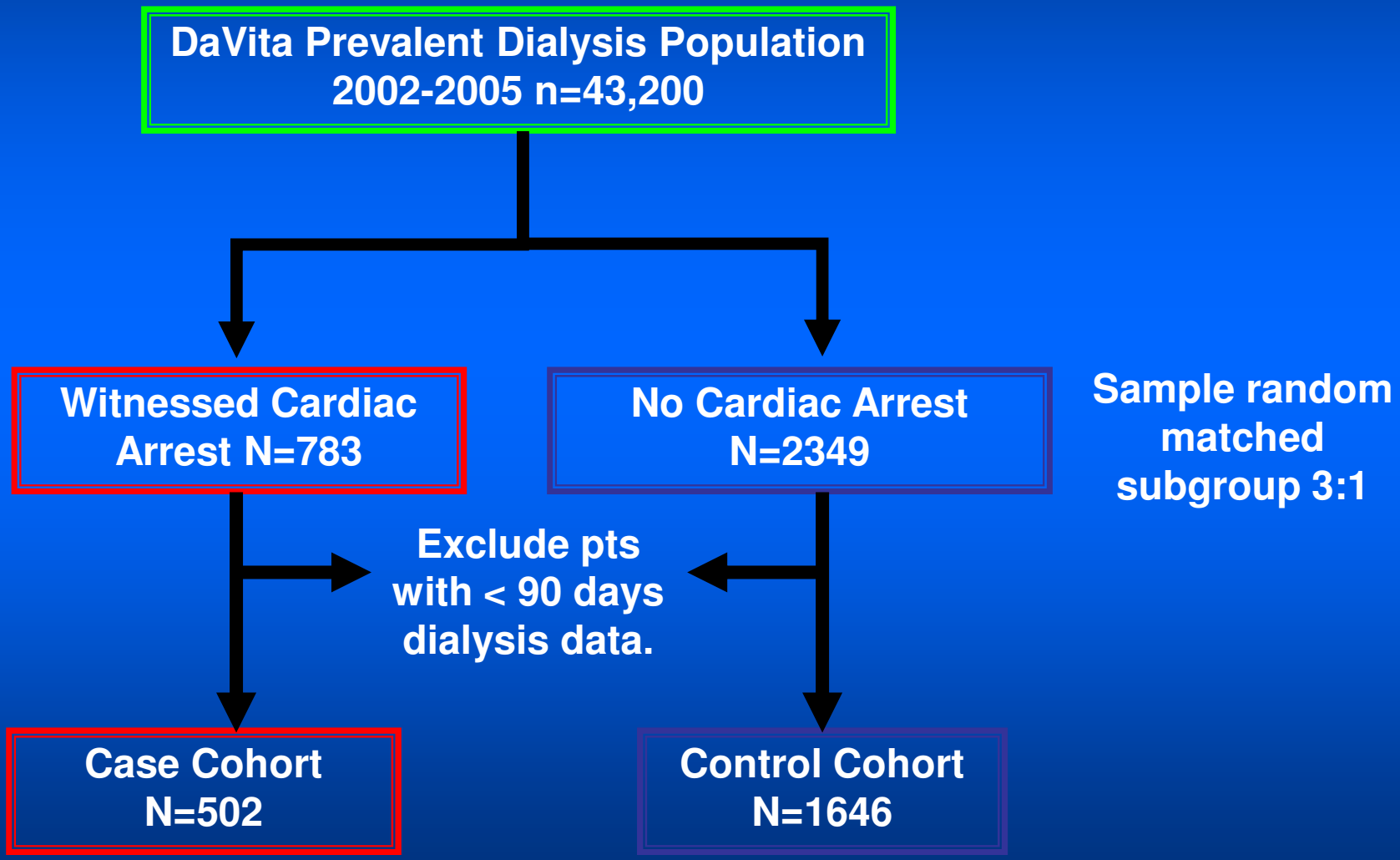
Hazard ratios of all-cause mortality for predialysis serum K



Kovesdy, C. P. et al. Clin J Am Soc Nephrol 2007;2:999-1007

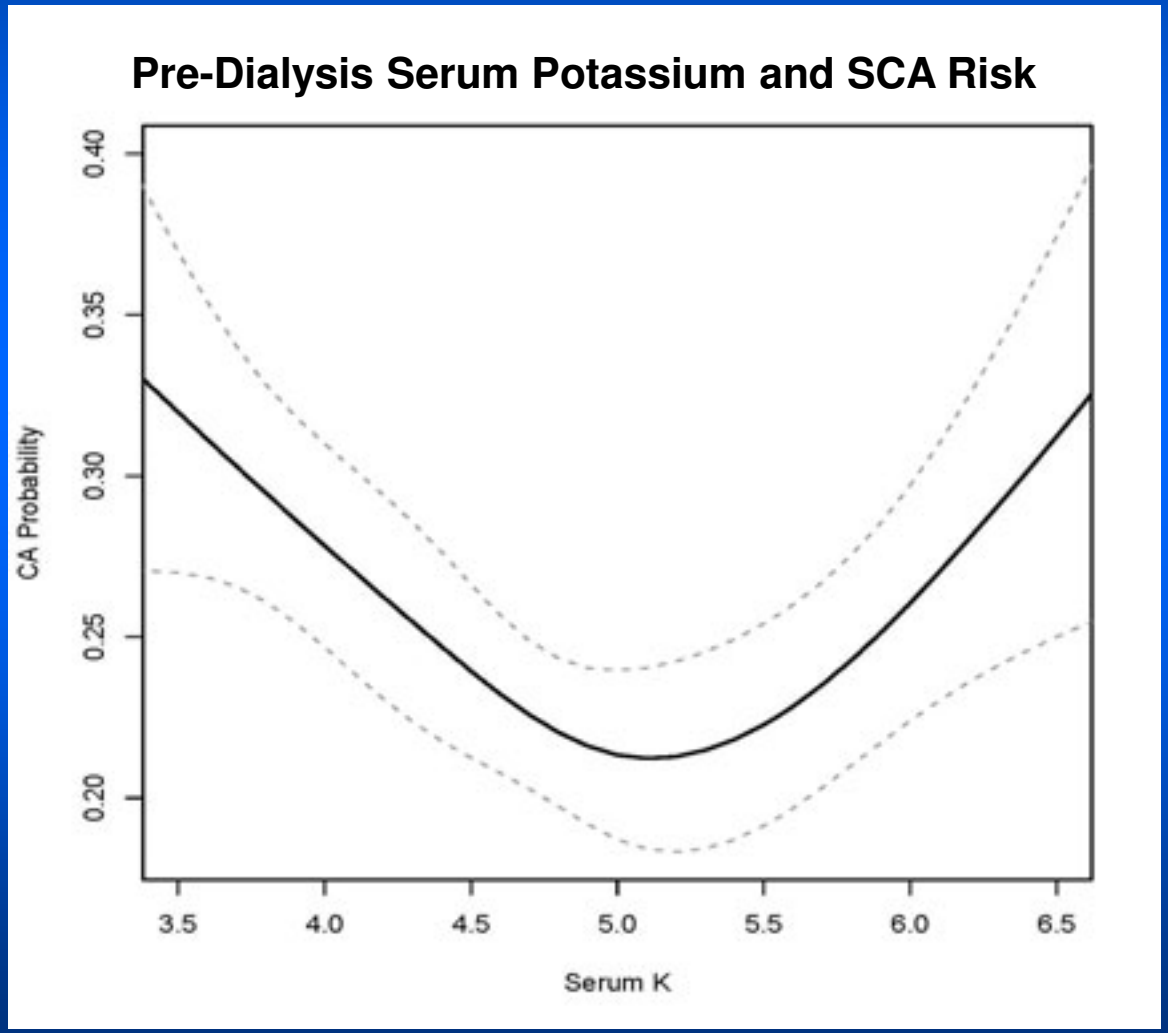
Modifiable Risk Factors Associated with Sudden Cardiac Arrest in Hemodialysis Clinics

(Pun et al, Kidney International, 2010).

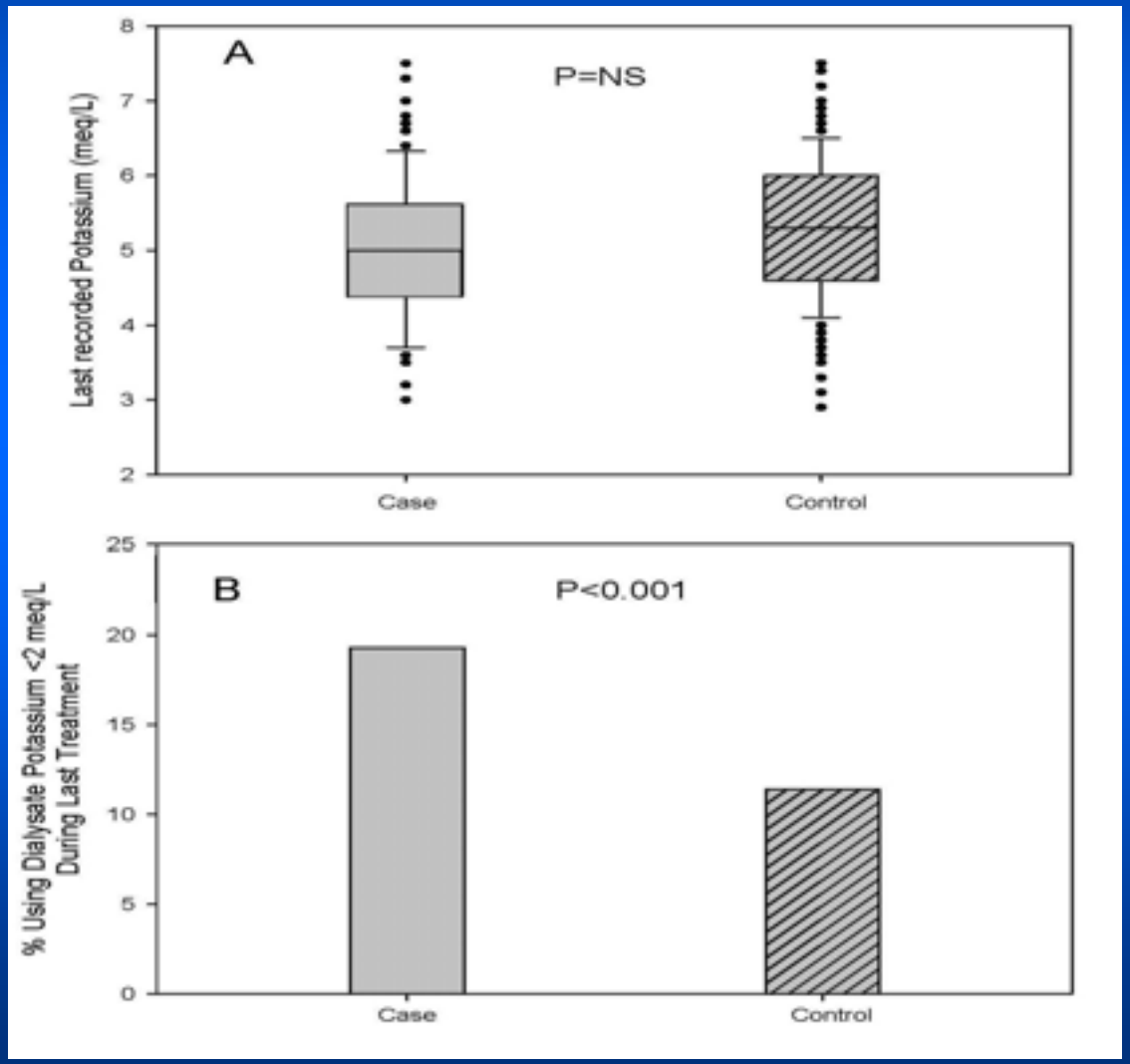


Potassium Homeostasis and Risk of SCA: Predialysis Potassium

- 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

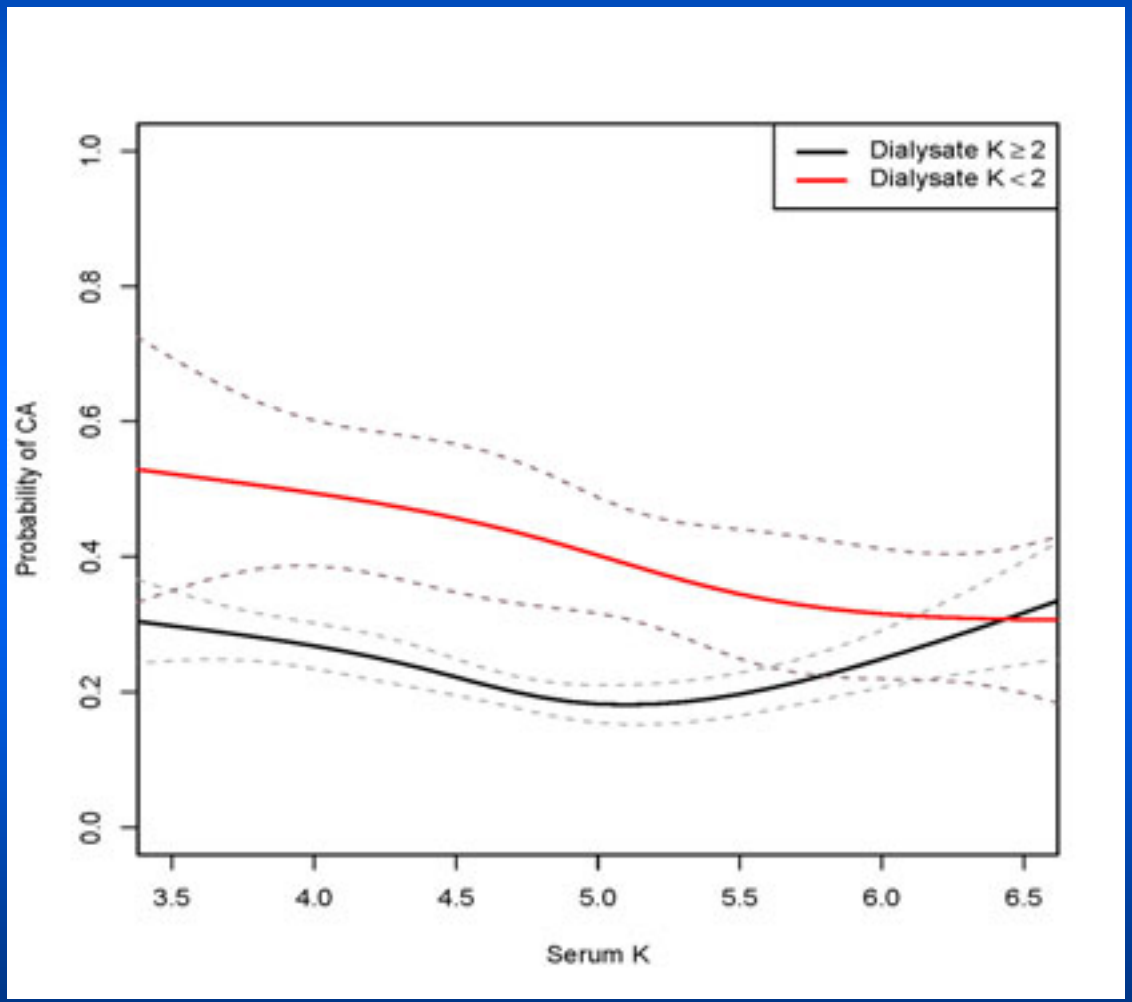
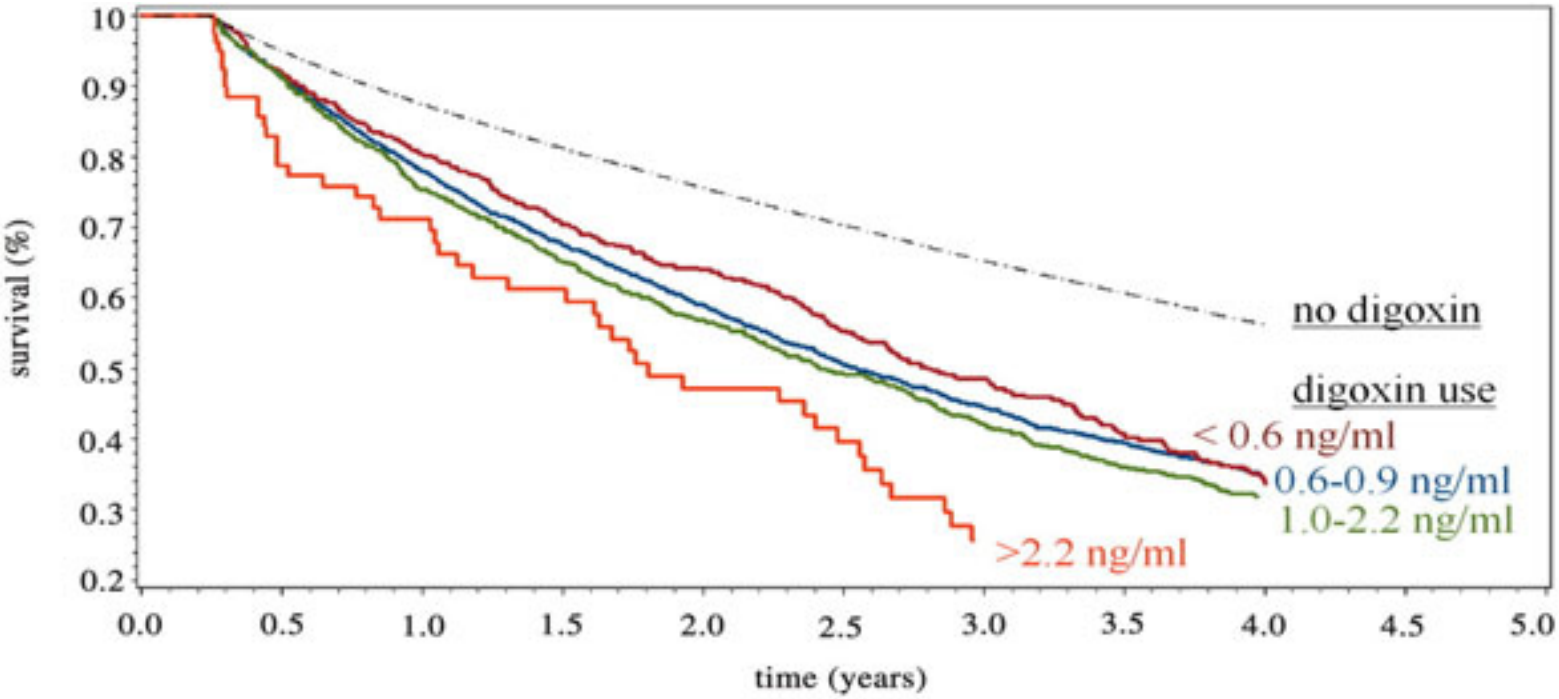
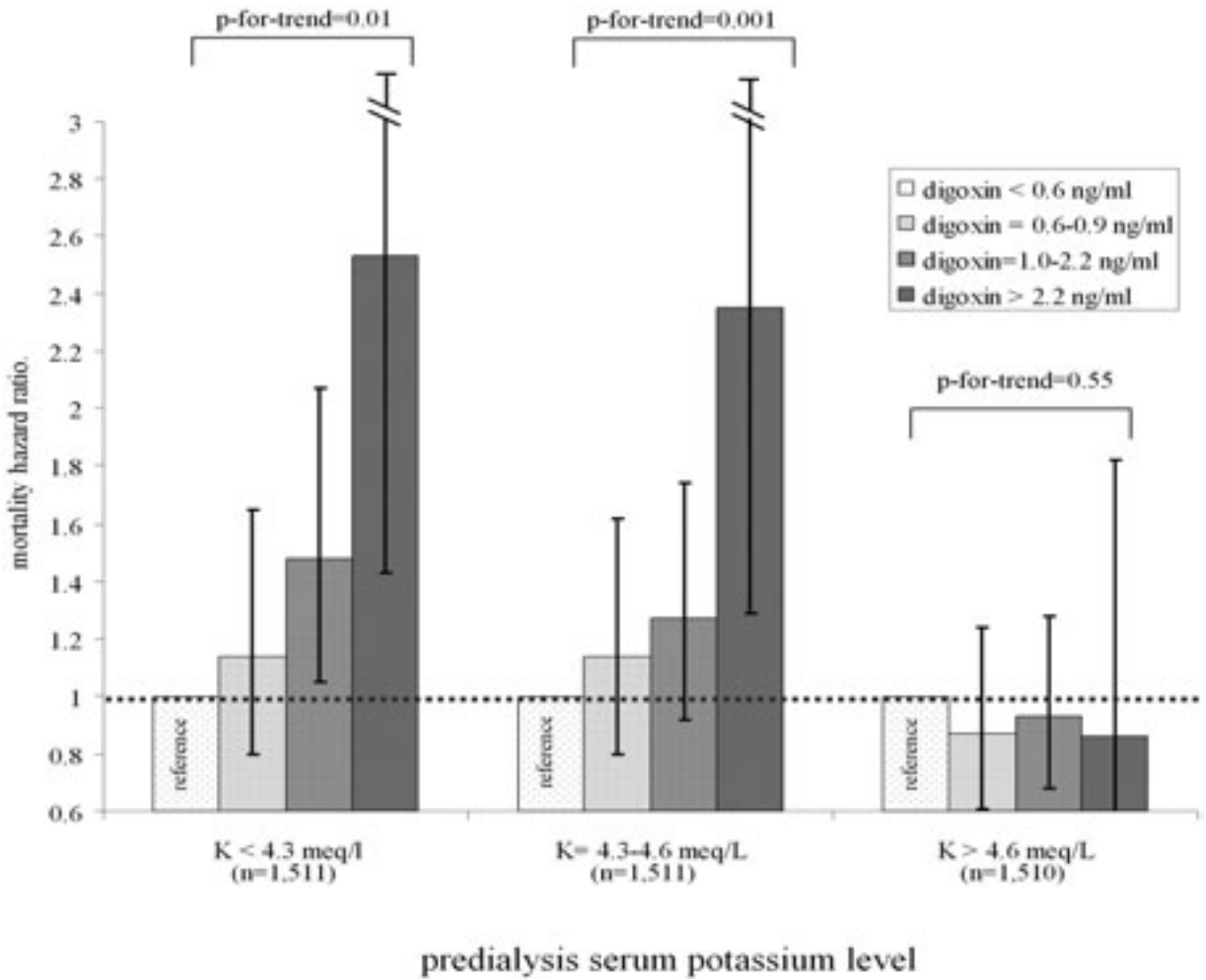


Figure 1. Crude survival curves show decreased survival with digoxin use



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

Figure 3. 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;21:1550-1559

JASN

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

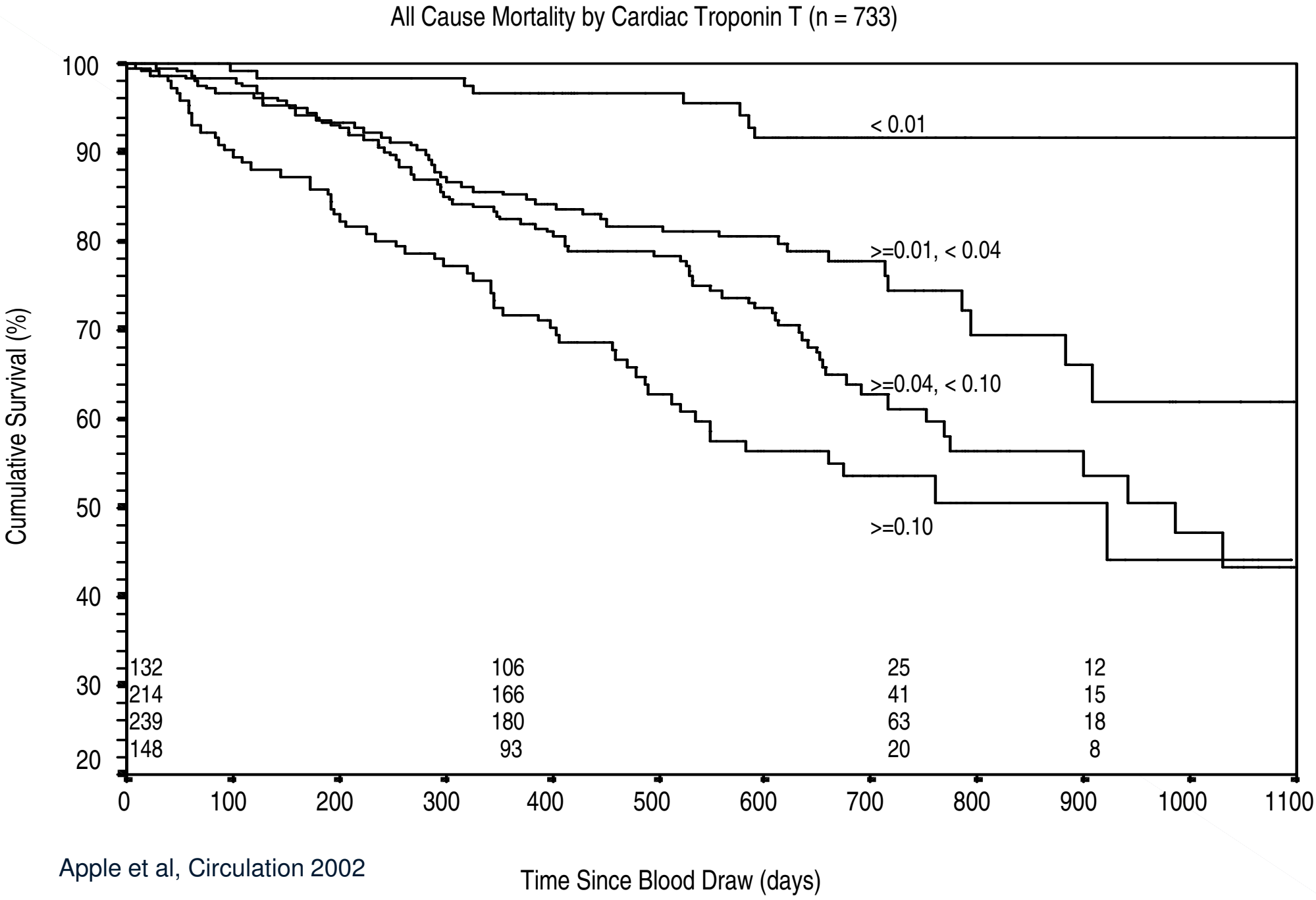
- Reducing the risk of sudden cardiac death
- Improving the likelihood of surviving cardiac arrest

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



Apple et al, Circulation 2002

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

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?
  - 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)

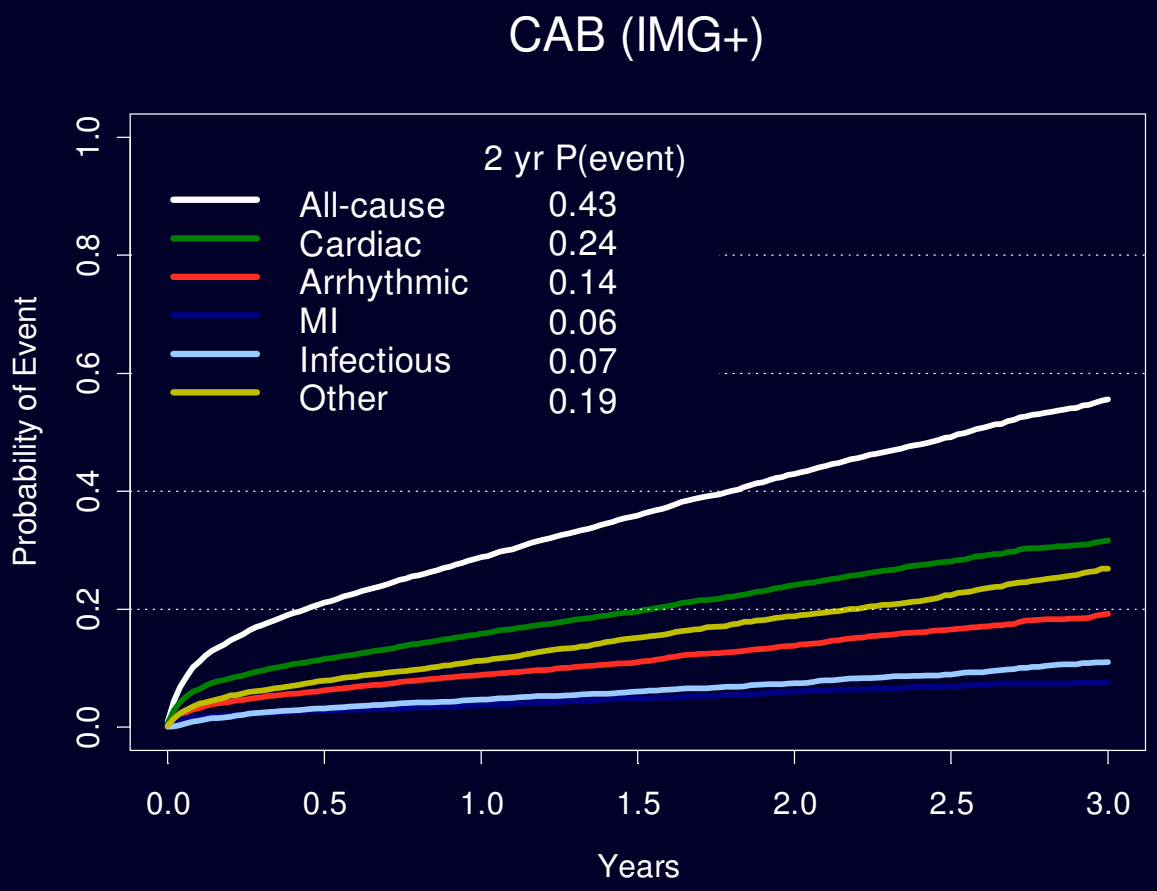
"Physiologic Dialysis"

- 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

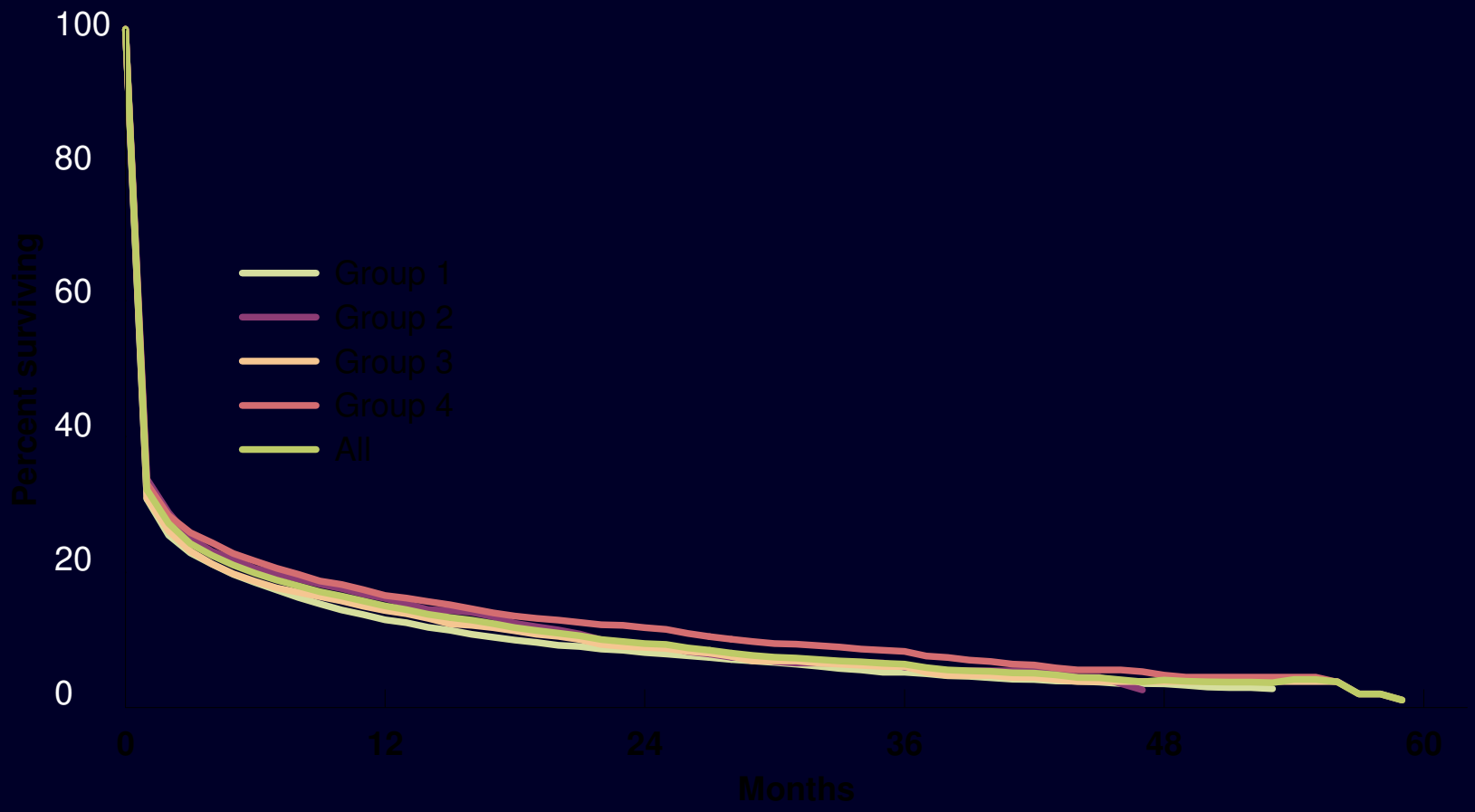


Surviving cardiac arrest: strategies for reducing lethality

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



2002 USRDS Annual Data Report

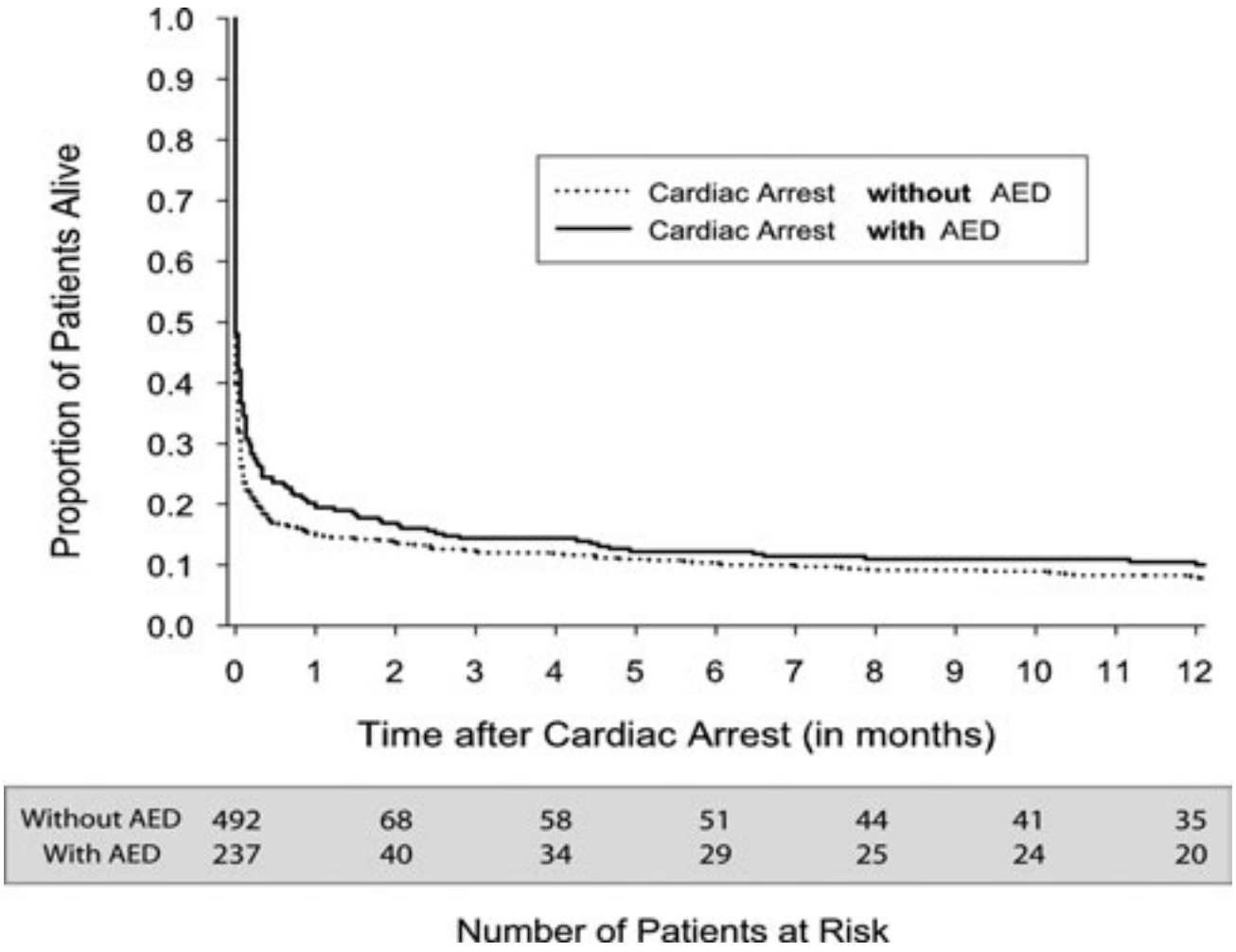
Cardiac arrest in the dialysis unit

- 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 41patients
- 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)



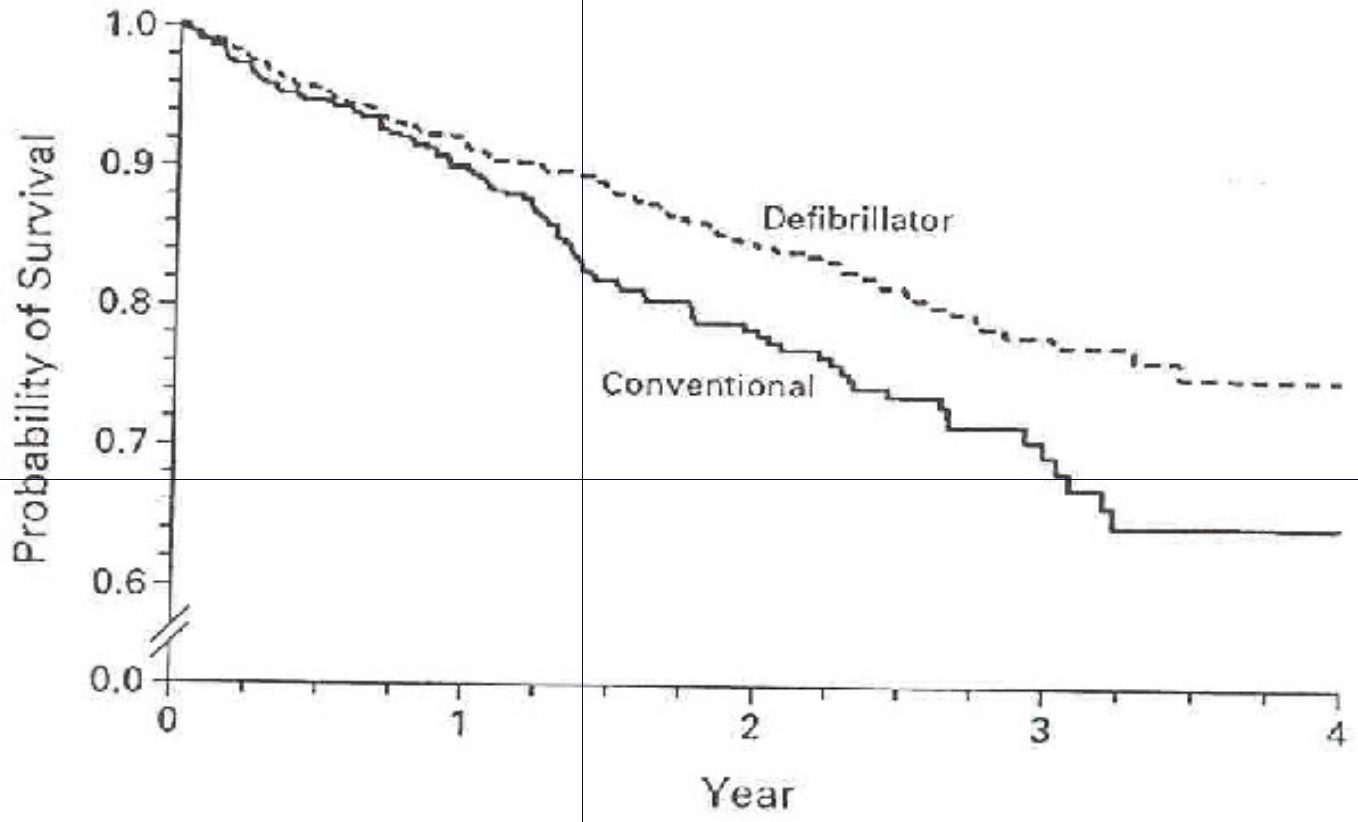
Lehrich, R. W. et al. J Am Soc Nephrol 2007;18:312-320

JASN

ICD's in ESRD Patients

USRDS

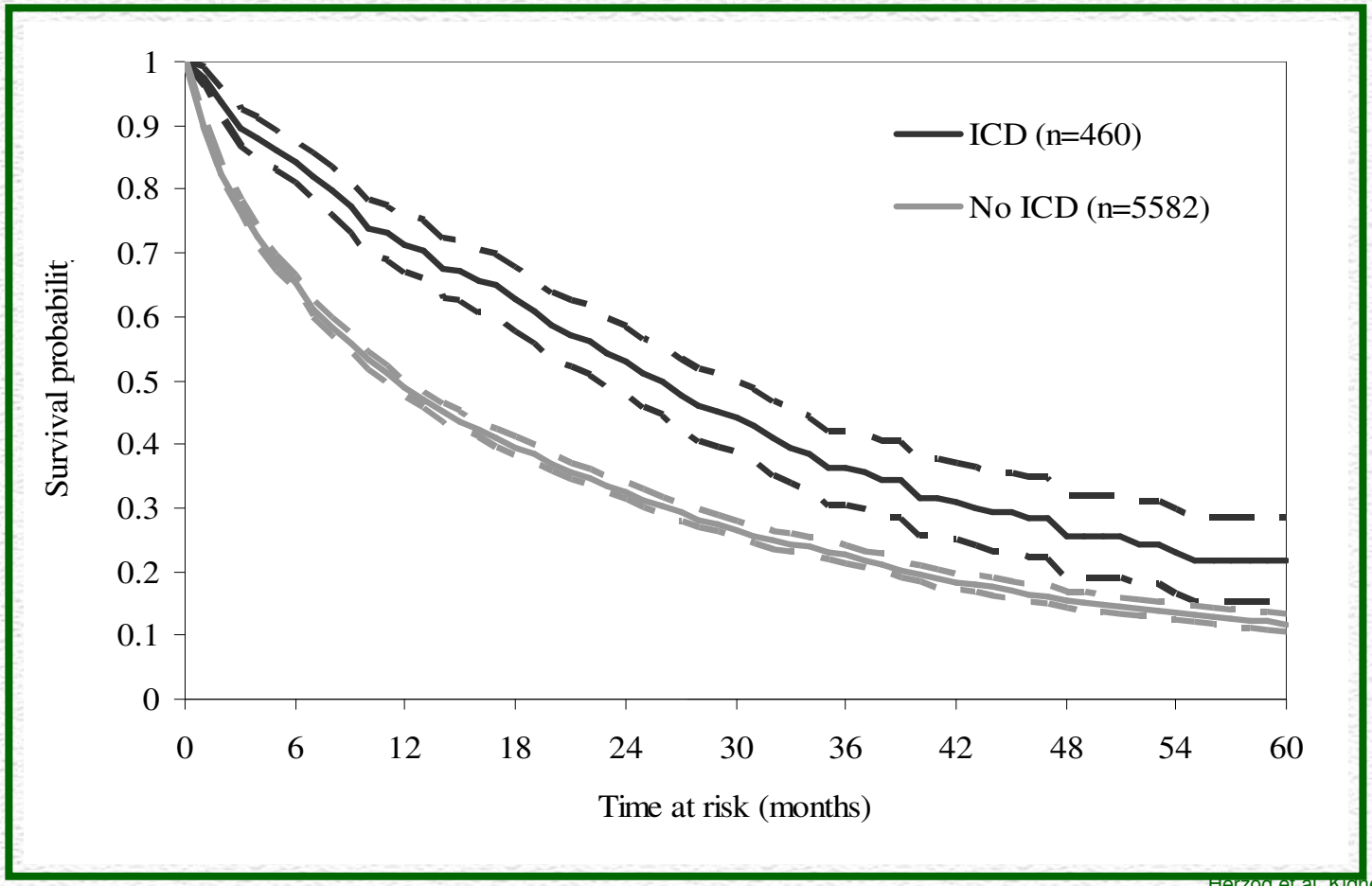
MADIT-2



No. at Risk					
Defibrillator	742	503 (0.91)	274 (0.84)	110 (0.78)	9
Conventional	490	329 (0.90)	170 (0.78)	65 (0.69)	3

Moss et al *New England Journal of Medicine* 2002

Survival of dialysis patients after cardiac arrest



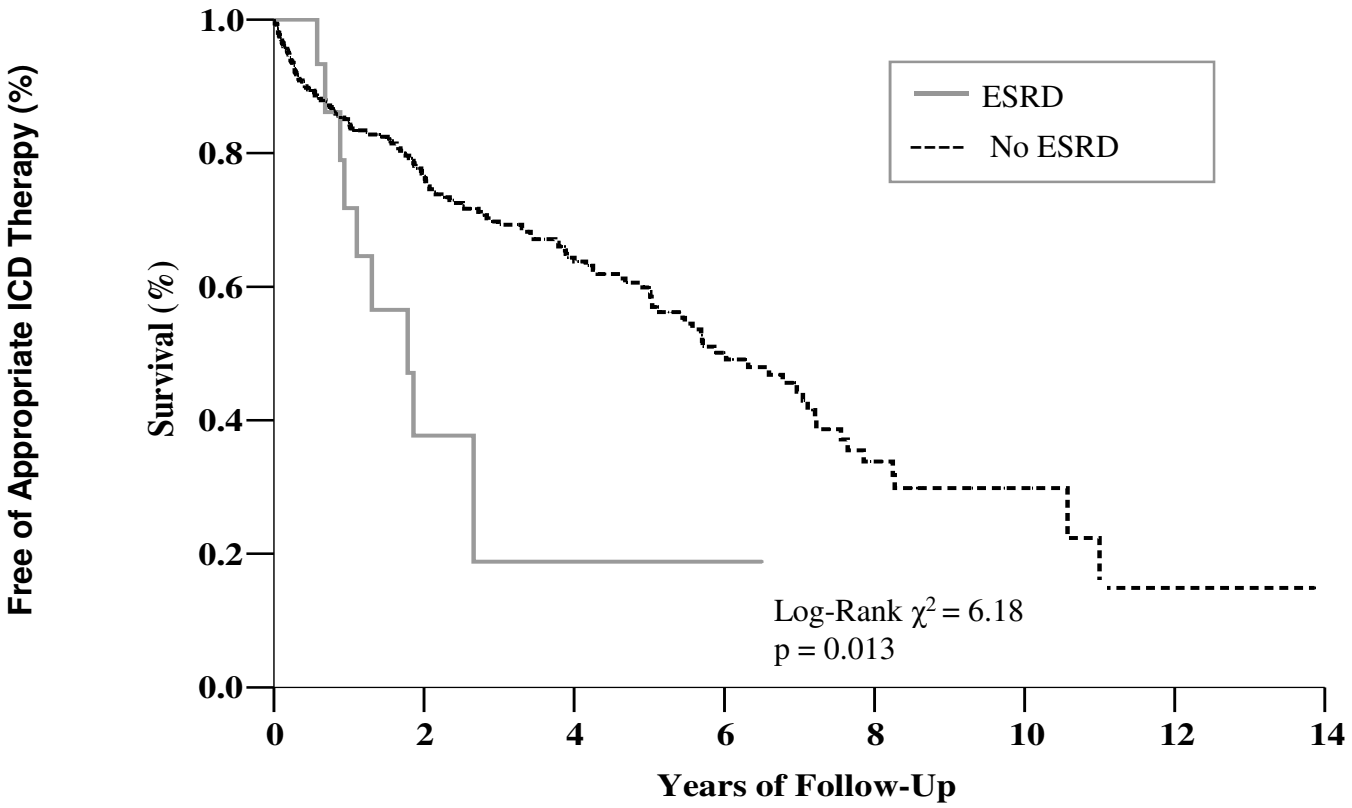
Number at risk:					
No ICD	2,239	1,149	562	246	100
ICD	243	136	61	25	12

Herzog et al, Kidney International, 2005

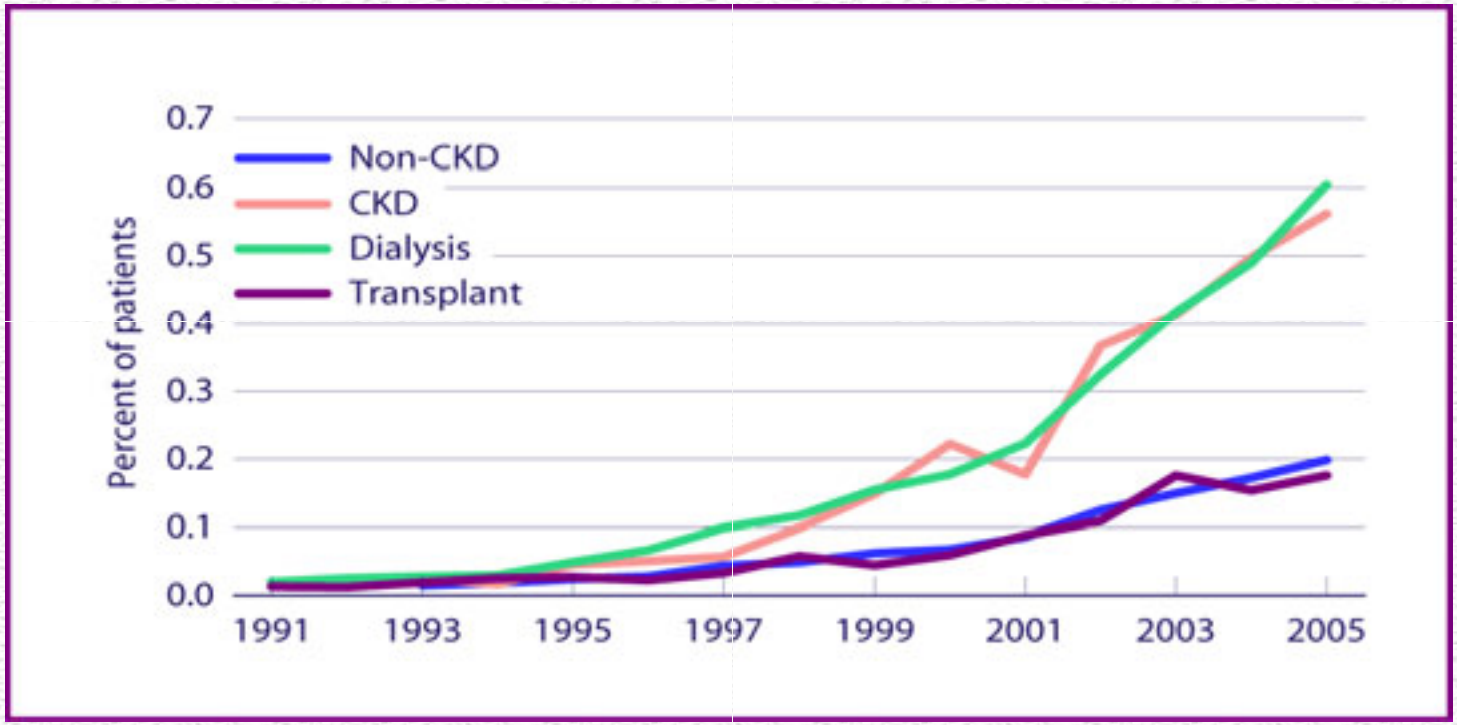
USRDS

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

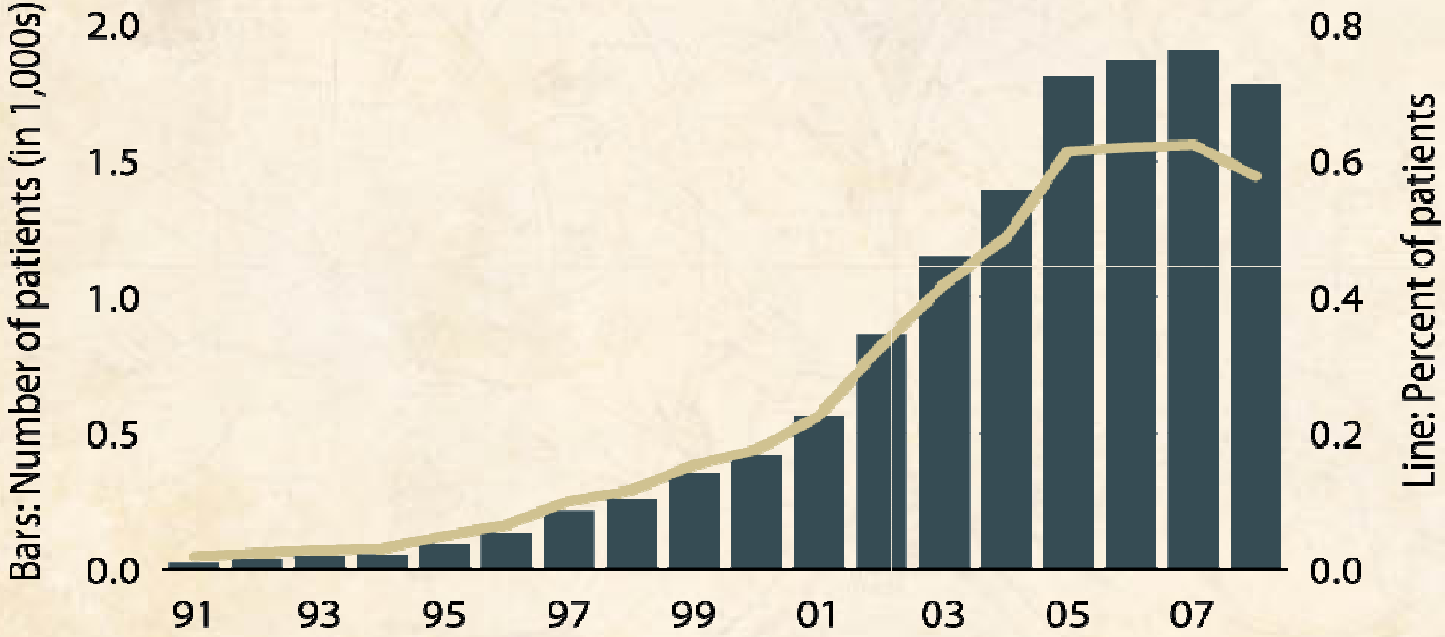


CKD/non-CKD: prevalent general Medicare patients, age 66 & older, 1993–2005. ESRD: period prevalent patients, age 20 & older.

USRDS

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

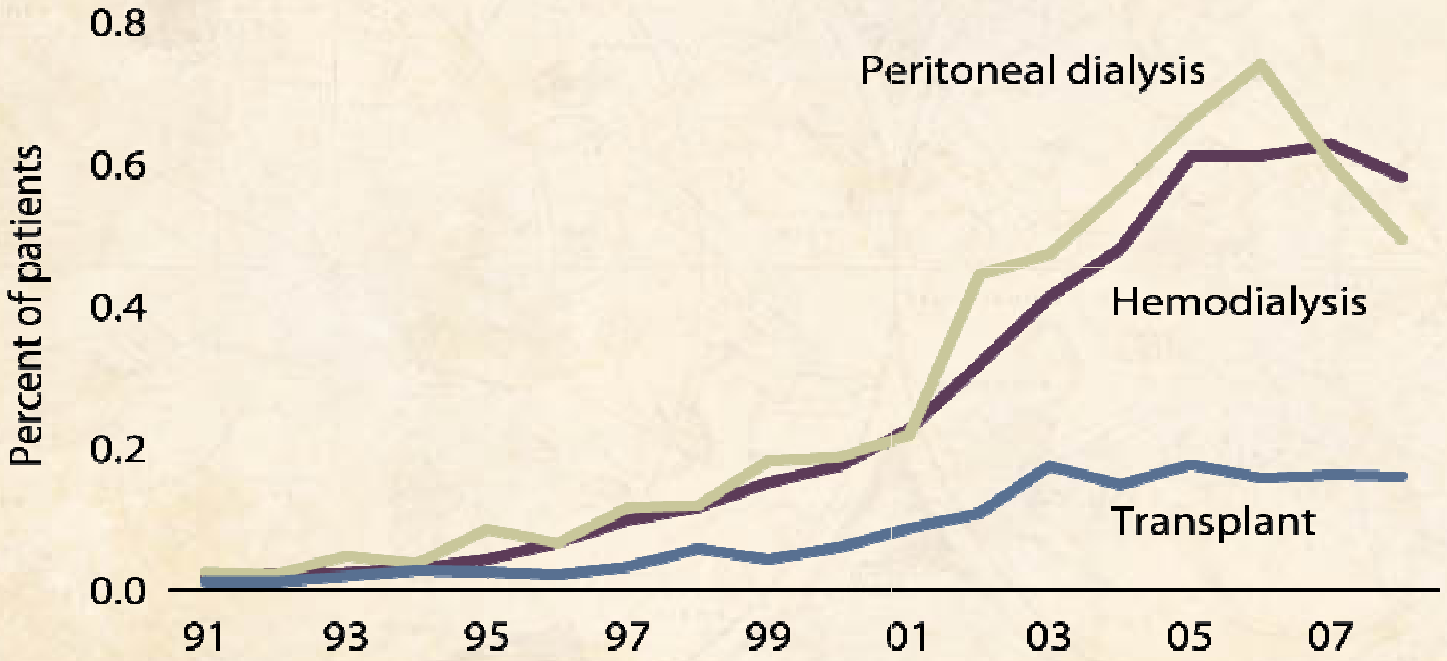
Figure 9.2 (Volume 2)



Period prevalent dialysis patients.

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

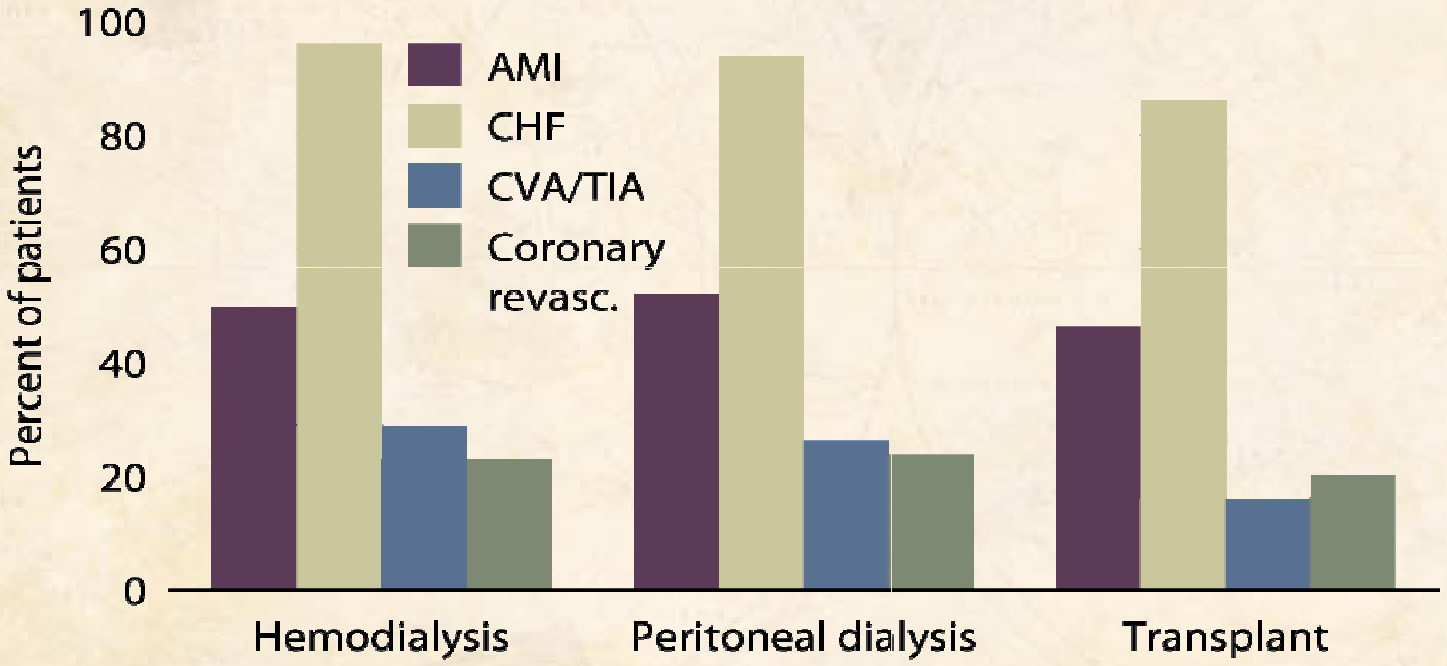
Figure 9.3 (Volume 2)



Period prevalent ESRD patients.

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

Figure 9.4 (Volume 2)

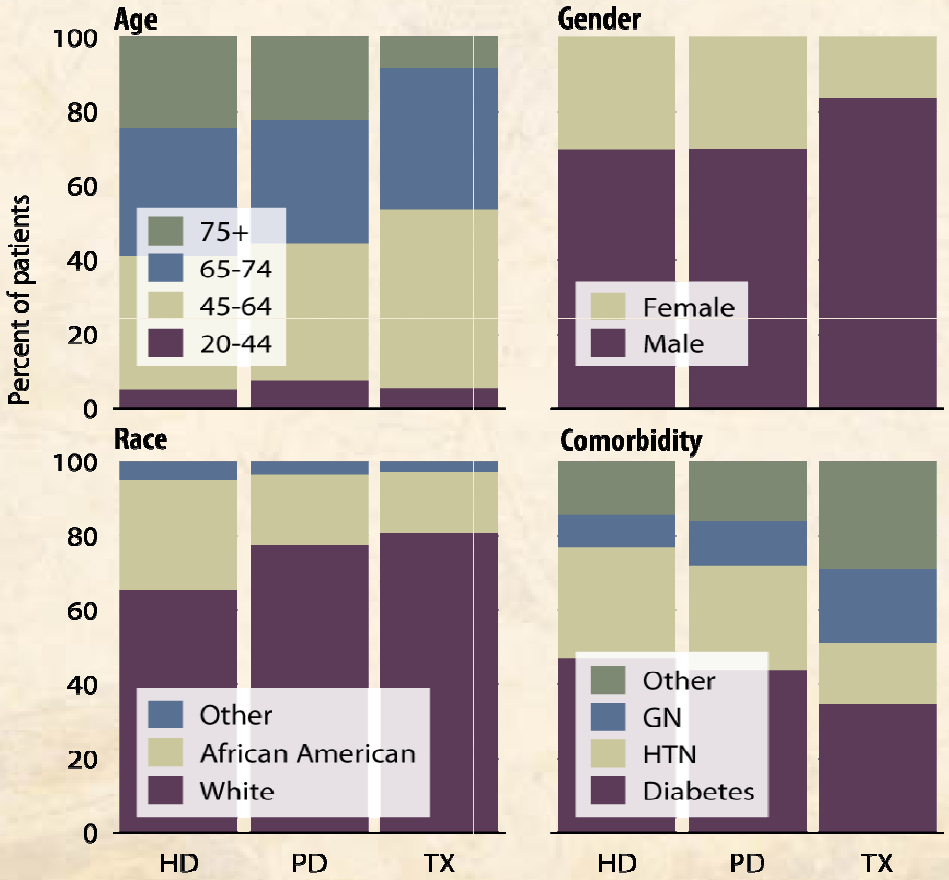


Period prevalent ESRD patients, 1999-2008.

USRDS

Demographics of ESRD patients receiving ICDs/CRT-Ds, 1999–2008

Figure 9.5 (Volume 2)

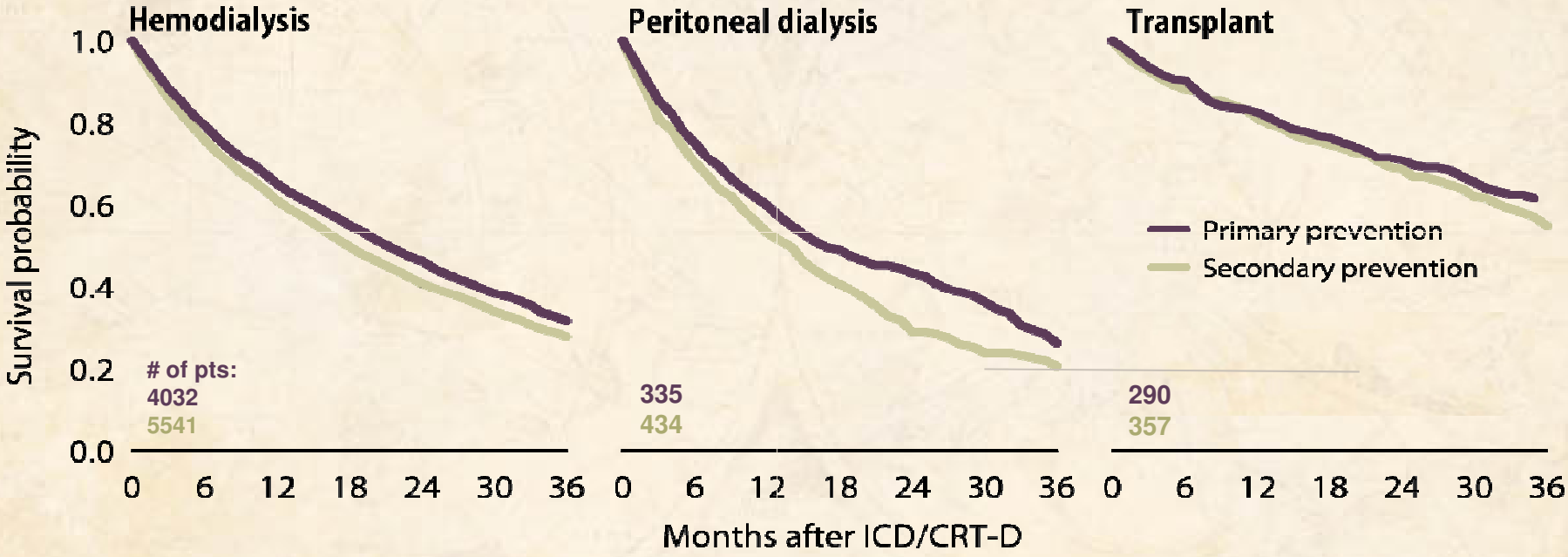


Period prevalent ESRD patients, 1999-2008.

USRDS

All-cause survival following implantation of ICDs/CRT-Ds, by modality, 1999–2008

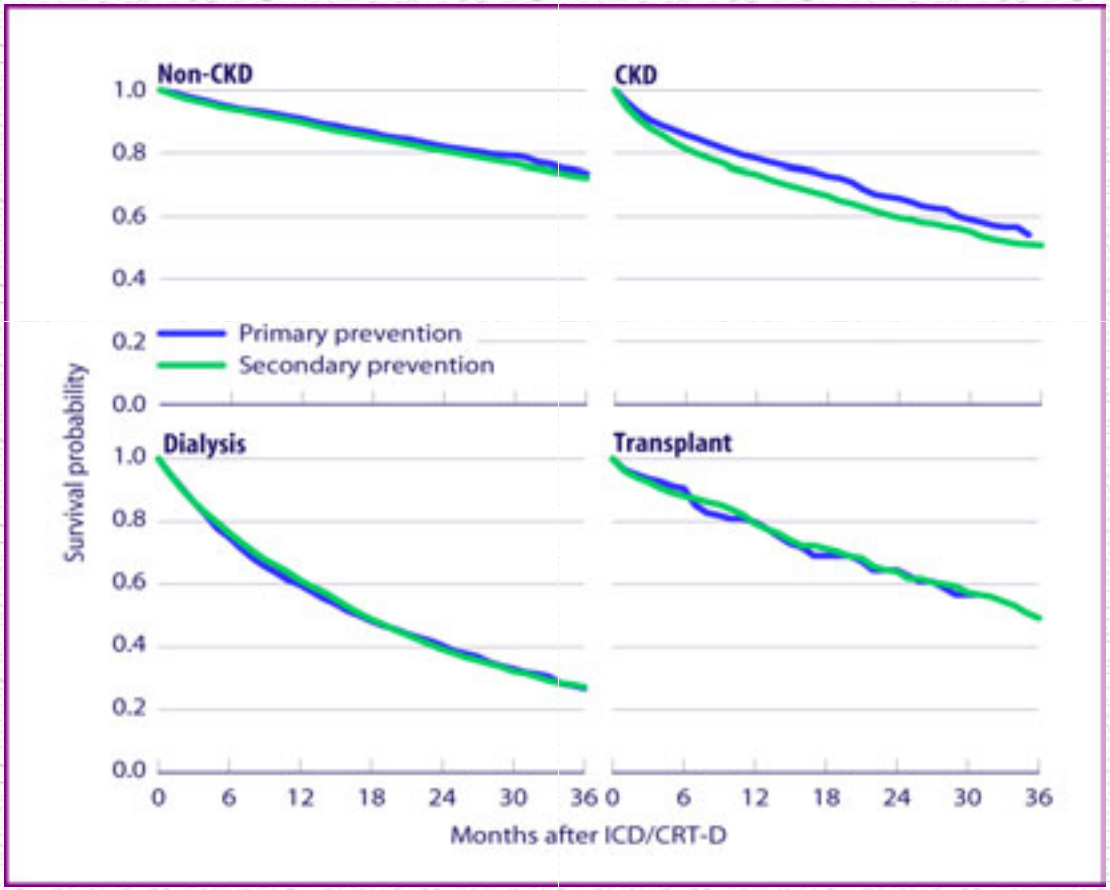
Figure 9.6 (Volume 2)



Period prevalent ESRD patients, 1999-2008.

USRDS

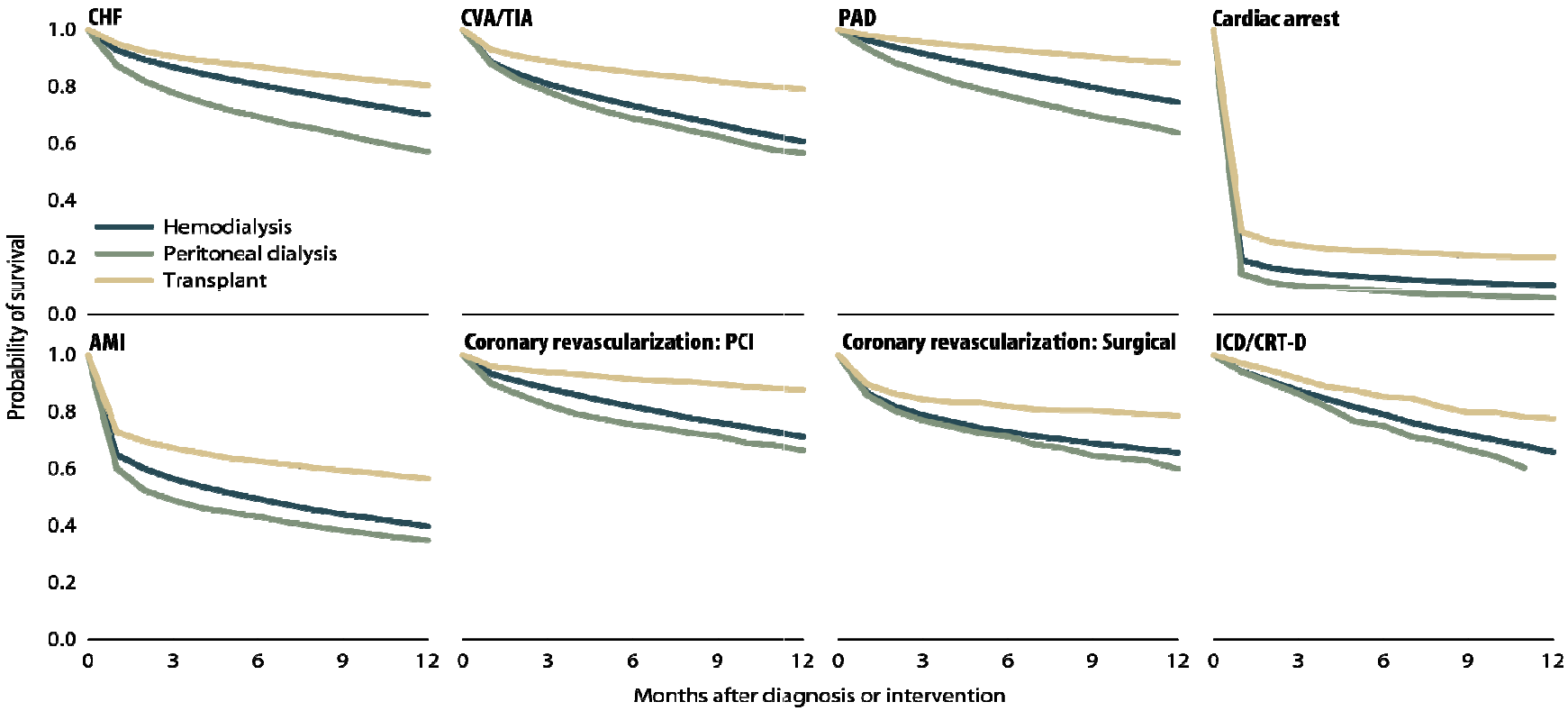
All-cause survival after implantation of ICD/CRT-D



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.

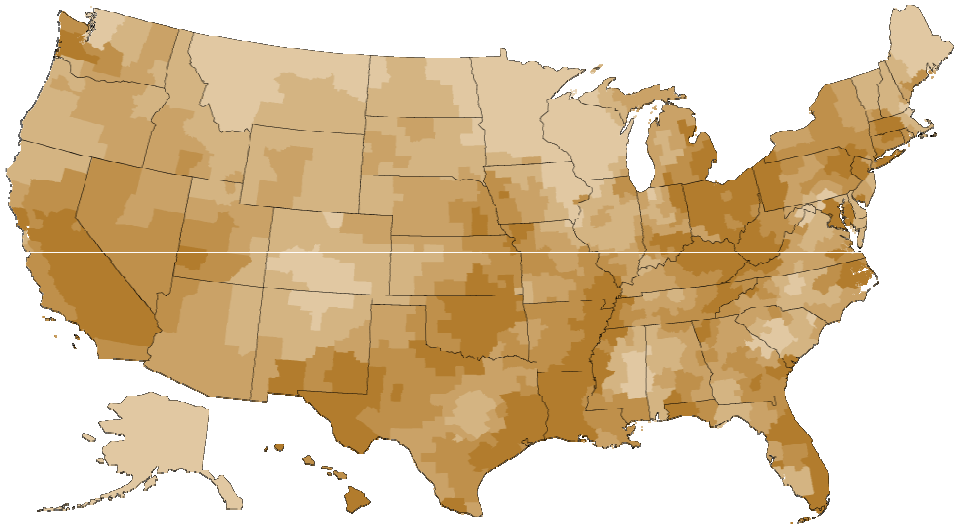
USRDS

Survival of patients with cardiovascular diagnoses & procedures, by modality

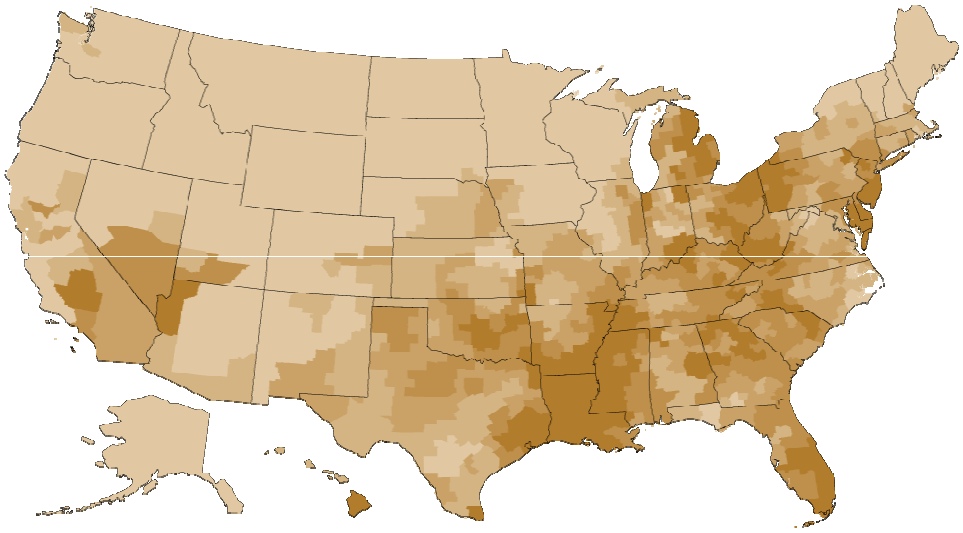


January 1, 2005 point prevalent ESRD patients, age 20 & older, with a first cardiovascular diagnosis or procedure in 2005–2007.
USRDS 2009 ADR

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**

Study Design, continued

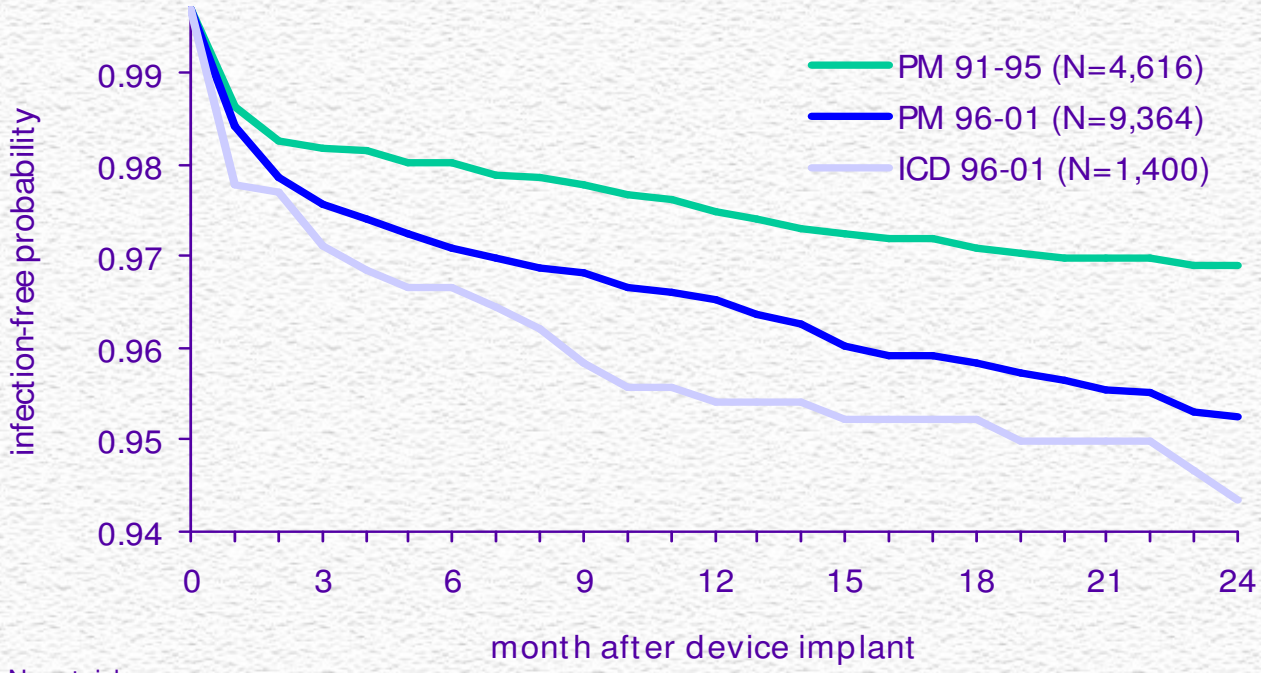
Exclusion Criteria

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 4,616	2,978	2,202	1,687	1,288
PM 96-01 9,364	5,603	3,751	2,532	1,702
ICD 96-01 1,400	919	599	414	275

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)
- HCMC stress echo database: 771 unique prevalent dialysis pts (1992-2005): 692 pts (90%) with LVEF ≥50% (Herzog, unpublished data).

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

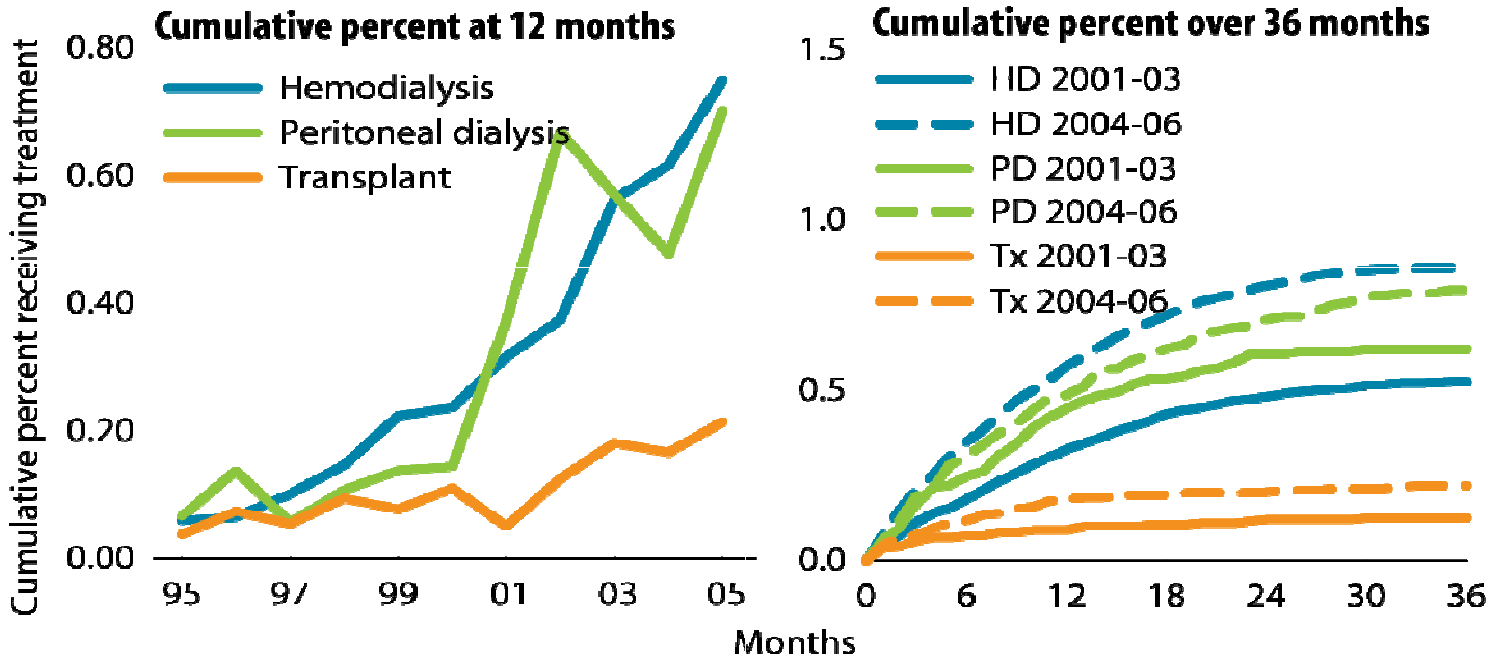
ICD Trial in Dialysis Patients: Coda (Why should we do this?)

- 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.

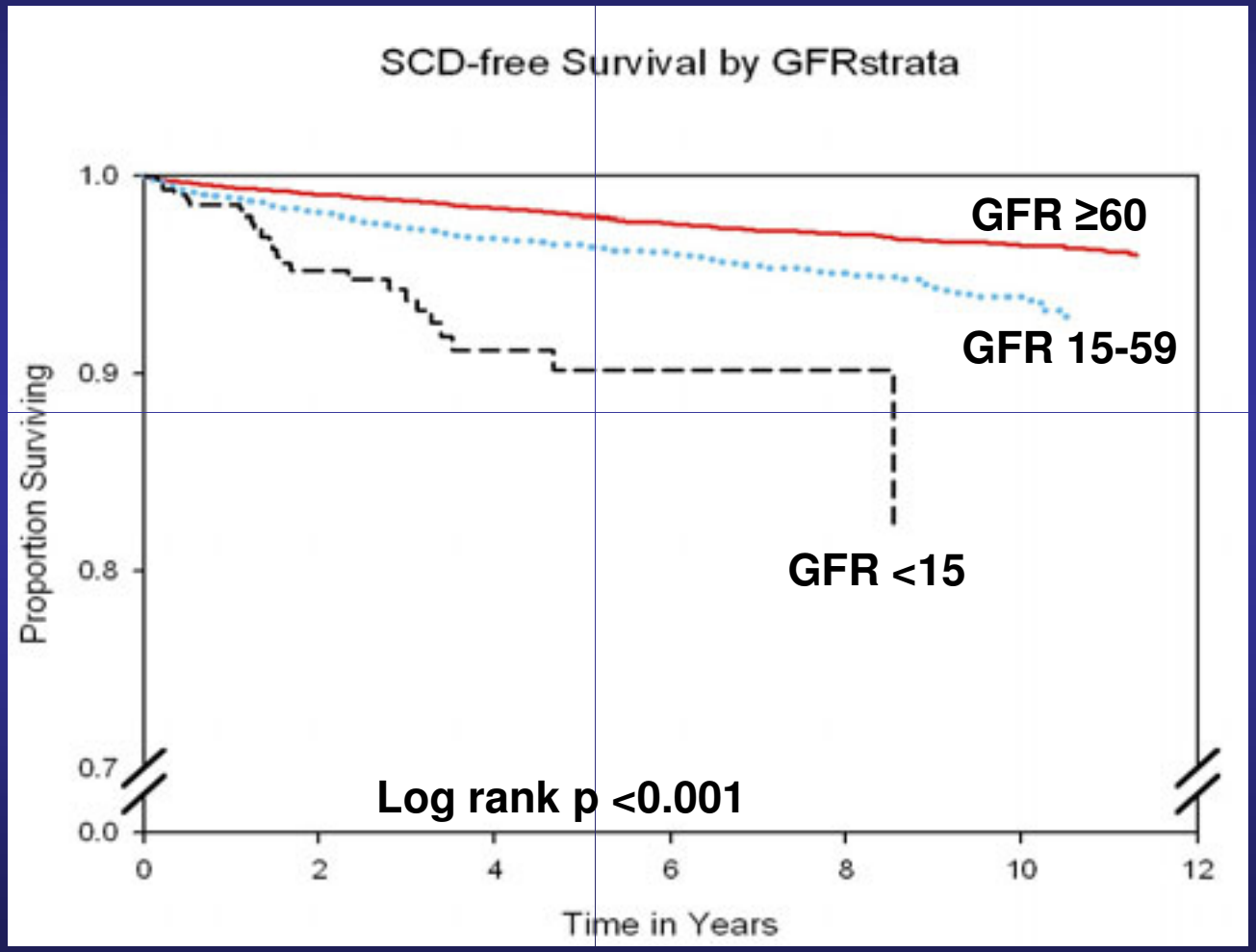
USRDS 2008 ADR

Multivariable Analysis

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

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



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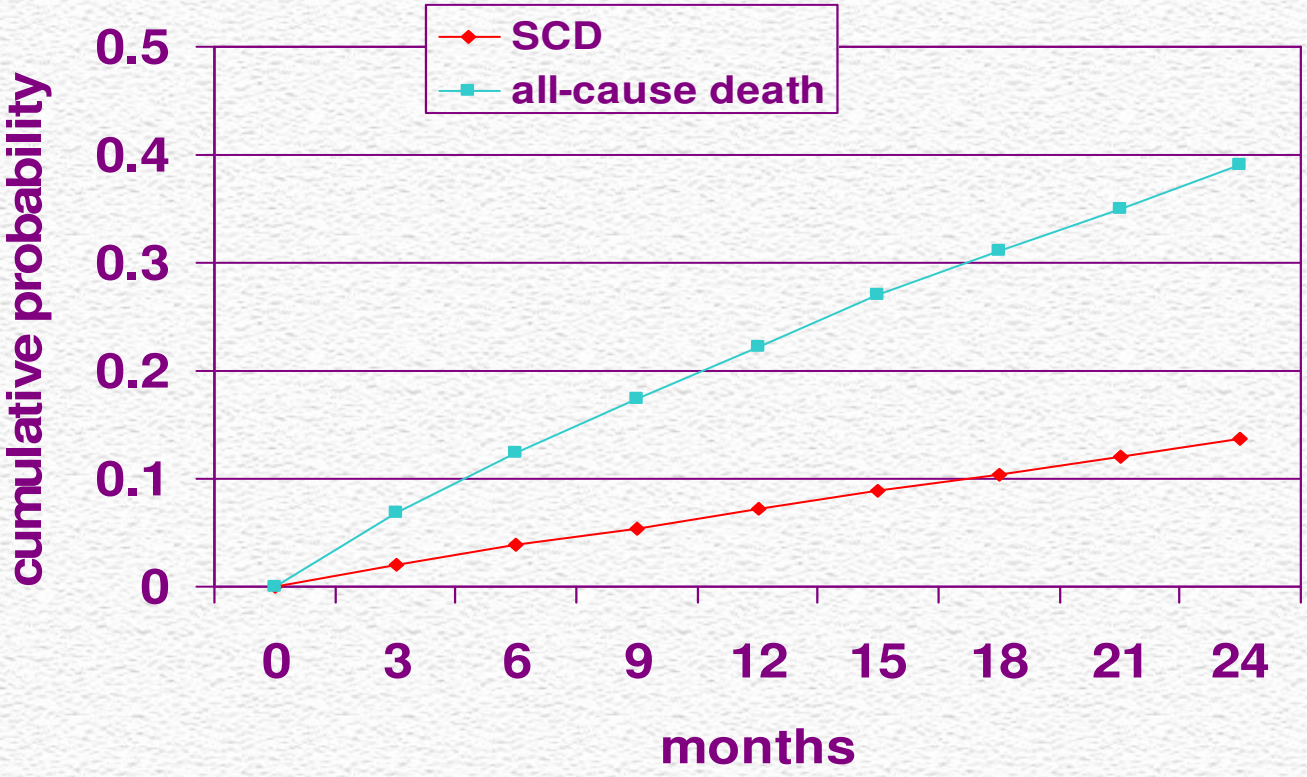
Cumulative probability of SCD & all-cause death

2002 prevalent dialysis patients



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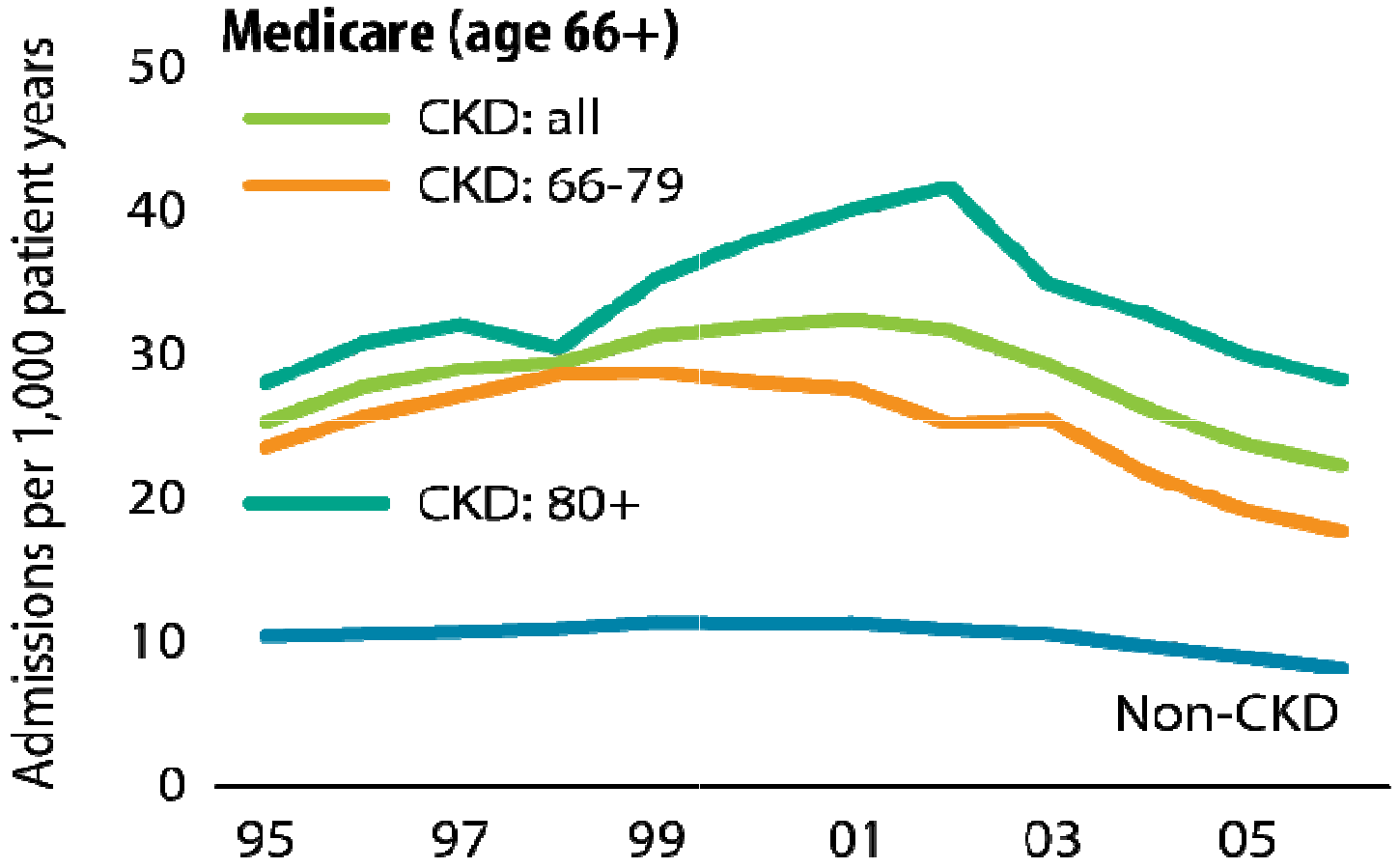
Adjusted AMI admission rates in elderly patients



2005 reference year

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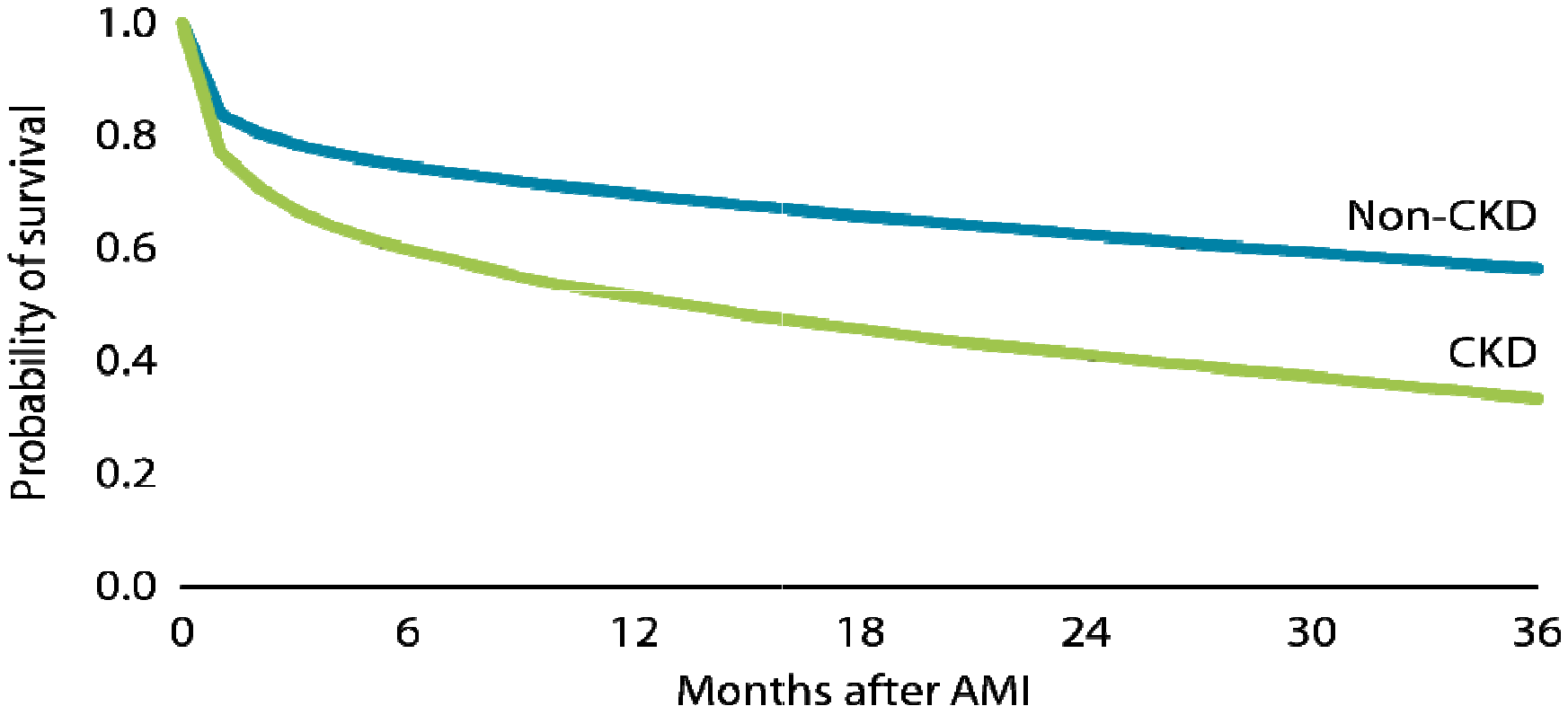
All-cause survival after acute myocardial infarction, by CKD status



Prevalent Medicare patients age 66+, 2000-2005

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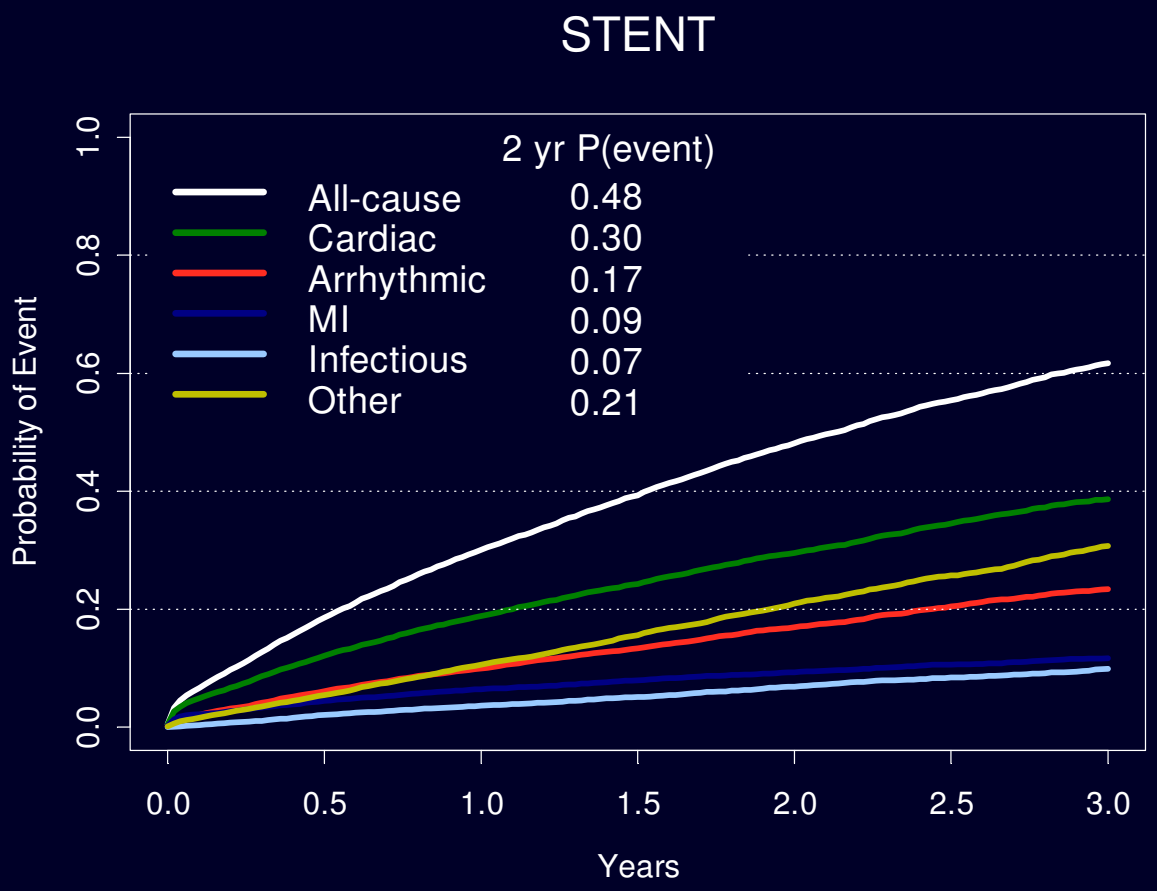
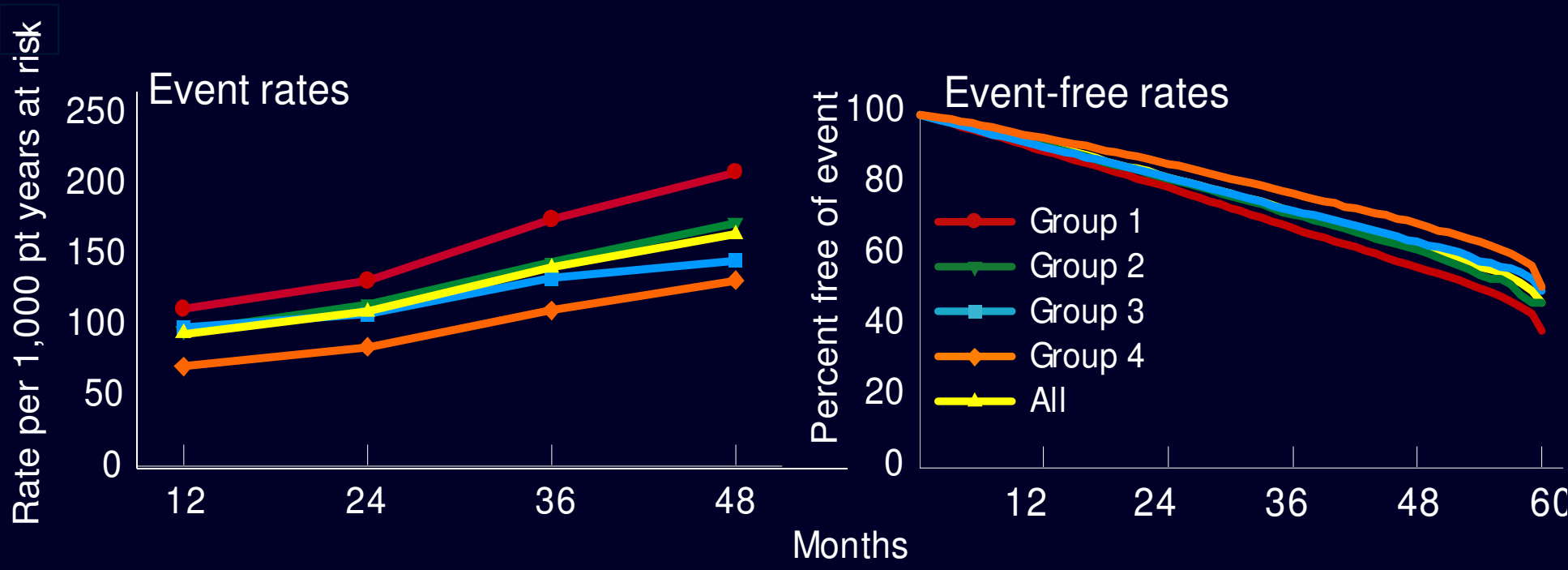
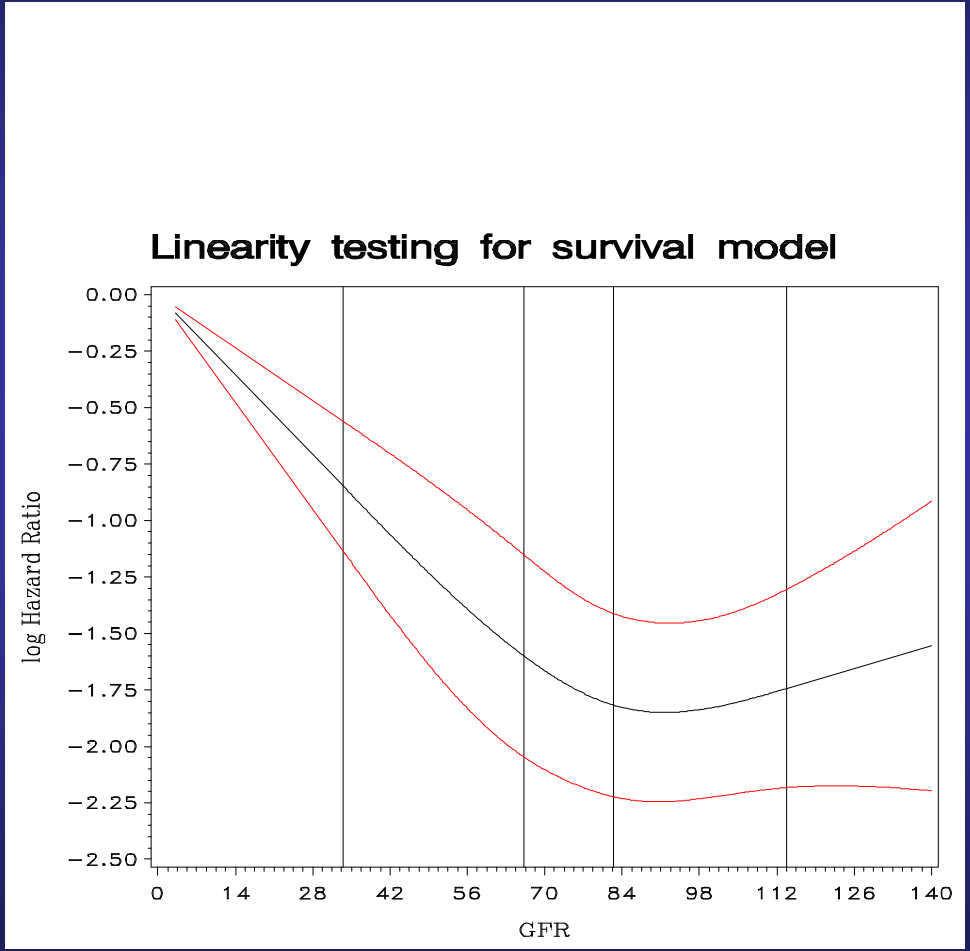
Probability of all-cause and cause-specific death



Event rates & adjusted event-free survival: cardiac arrest



Linear Relationship Between SCD Risk and Declining GFR



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Multivariable Model

	Variable	Chi-Square	P Value	Hazard Ratio	95% CI
49%	NY Heart Association Class (HR per increase in 1 class)	37.5	<0.0001	1.226	1.149, 1.309
	History of Diabetes	27.3	<0.0001	1.631	1.358, 1.960
36.5%	GFR (HR per 10 unit decrease)	25.5	<0.0001	1.125	1.075, 1.178
	Number of Diseased Vessels	15.1	0.0001	1.251	1.117, 1.401
	History of MI	15.0	0.0001	1.419	1.189, 1.693
	Any Valvular Disease	12.1	0.0005	1.437	1.172, 1.762
	History of COPD	10.2	0.0014	1.570	1.191, 2.069
	History of Peripheral Vascular Disease	7.2	0.0073	1.376	1.090, 1.737

Overall Chi-Square= 341.7

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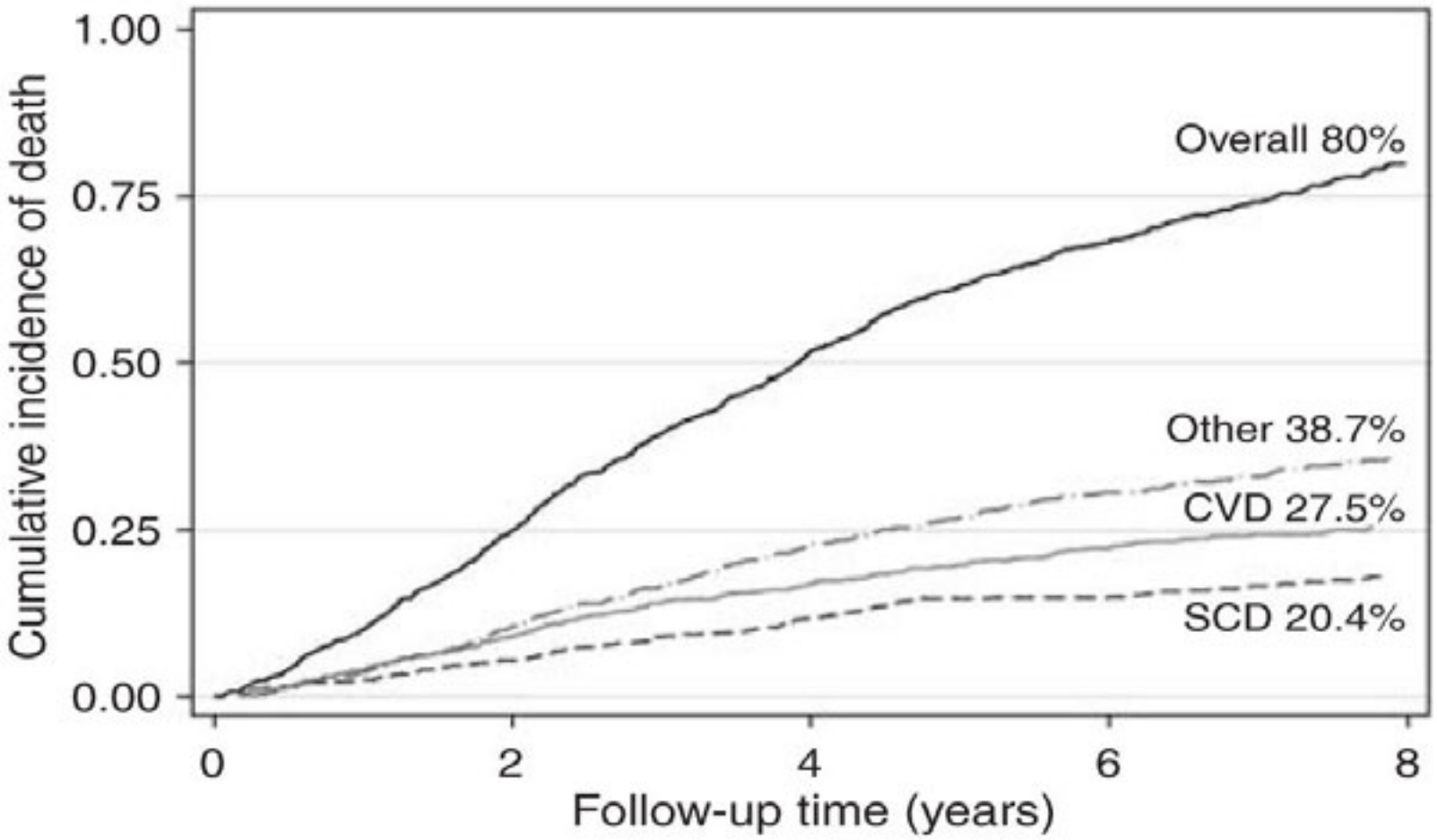

Figure 1 | Cumulative incidence of overall mortality and specific causes of death (including sudden cardiac death, other cardiovascular causes and other causes of death) in the CHOICE cohort.

Parekh et al. *Kidney International* 2008;74;1335