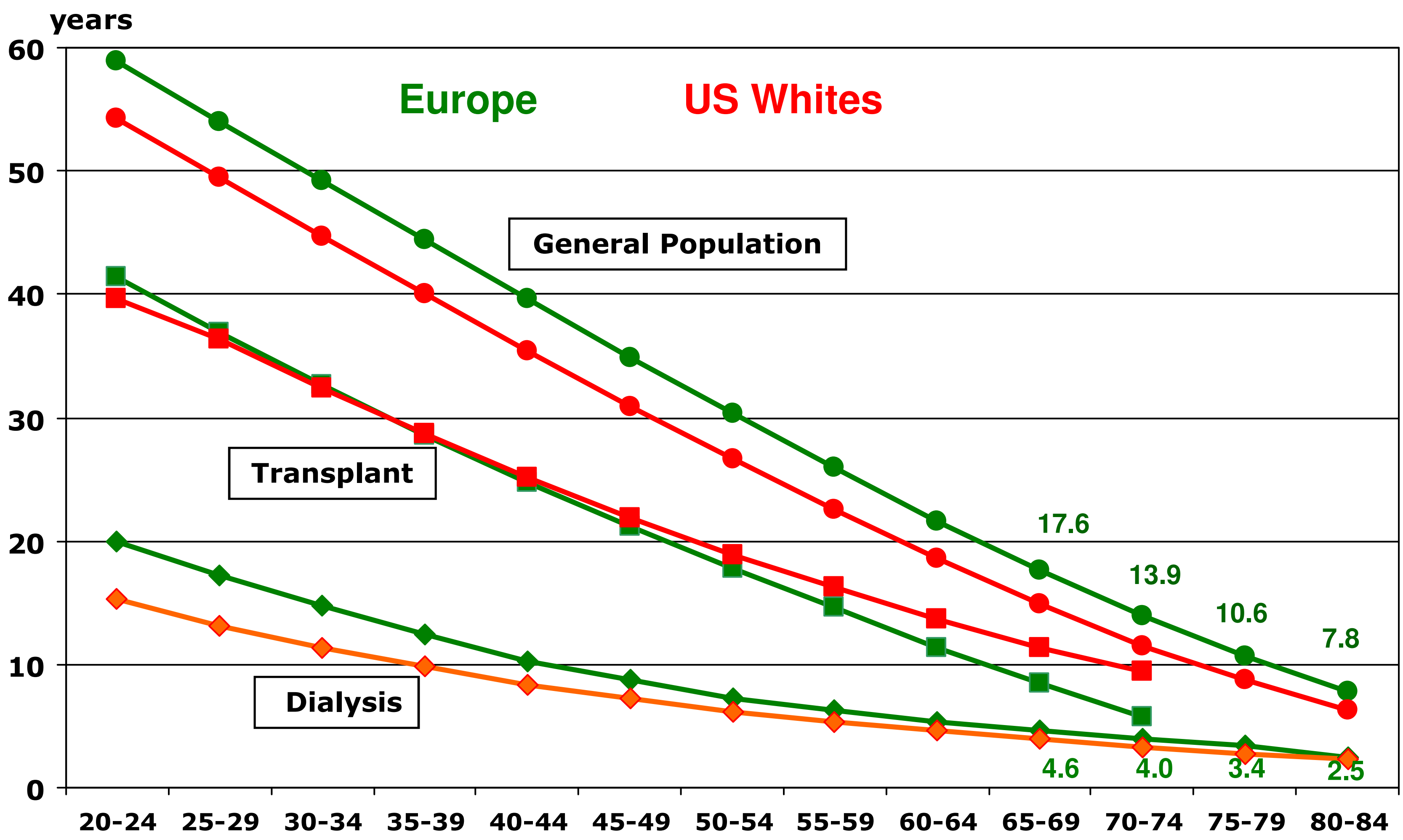
Cardiovascular Disease in CKD Stage 5

Kitty Jager

ERA-EDTA Registry

KDIGO Controversies Conference
Cardiovascular Disease in CKD: what is it and what can we do about it?
29-31 October 2010, London

Expected remaining lifetimes in adult CKD Stage 5 as compared to the General Population



ERA-EDTA Registry data and USRDS data

Increased prevalence of CVD

CARDIOVASCULAR DISEASE IN CHRONIC RENAL DISEASE

Clinical Epidemiology of Cardiovascular Disease in Chronic Renal Disease

Robert N. Foley, MB, Patrick S. Parfrey, MD, and Mark J. Sarnak, MD

American Journal of Kidney Diseases, Vol 32, No 5, Suppl 3 (November), 1998: pp S112-S119

Kidney Disease as a Risk Factor for Development of Cardiovascular Disease

A Statement From the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention

Mark J. Sarnak, MD, Cochair; Andrew S. Levey, MD, Cochair;
Anton C. Schoolwerth, MD, Cochair; Josef Coresh, MD, PhD; Bruce Culleton, MD;
L. Lee Hamm, MD; Peter A. McCullough, MD, MPH; Bertram L. Kasiske, MD; Ellie Kelepouris, MD;
Michael J. Klag, MD, MPH; Patrick Parfrey, MD; Marc Pfeffer, MD, PhD; Leopoldo Raij, MD;
David J. Spinosa, MD; Peter W. Wilson, MD

Circulation 2003;108;2154-2169 *Hypertension* 2003;42;1050-1065

US data

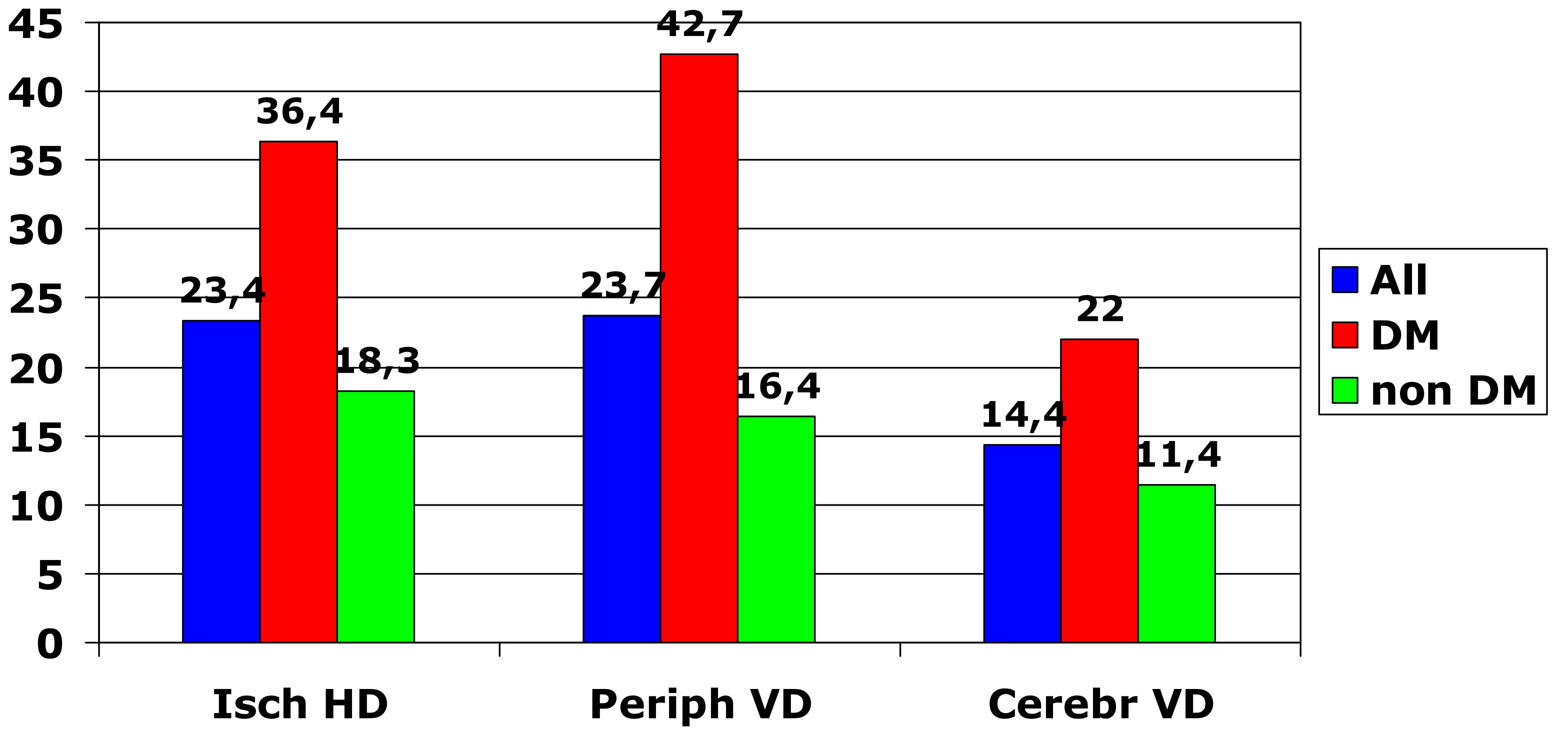
TABLE 2. Approximate Prevalence of CVD in the General Population and CKD

	Ischemic Heart Disease (Clinical)	LVH (Echo)	Heart Failure (Clinical)
General population	8–13*	20†	3–6‡
CKD stages 3–4 (diabetic and nondiabetic kidney disease)	NA	25–50 (varies with level of kidney function)§	NA
CKD stages 1–4 (kidney transplant recipients)	15‖	50–70¶	NA
CKD stage 5 (hemodialysis)	40#	75**	40#
CKD stage 5 (peritoneal dialysis)	40#	75**	40#

Increased prevalence of CVD

ERA-EDTA Registry data (5 countries – 1994 to 2001)

Prevalence of cardiovascular co-morbidity at the start of dialysis

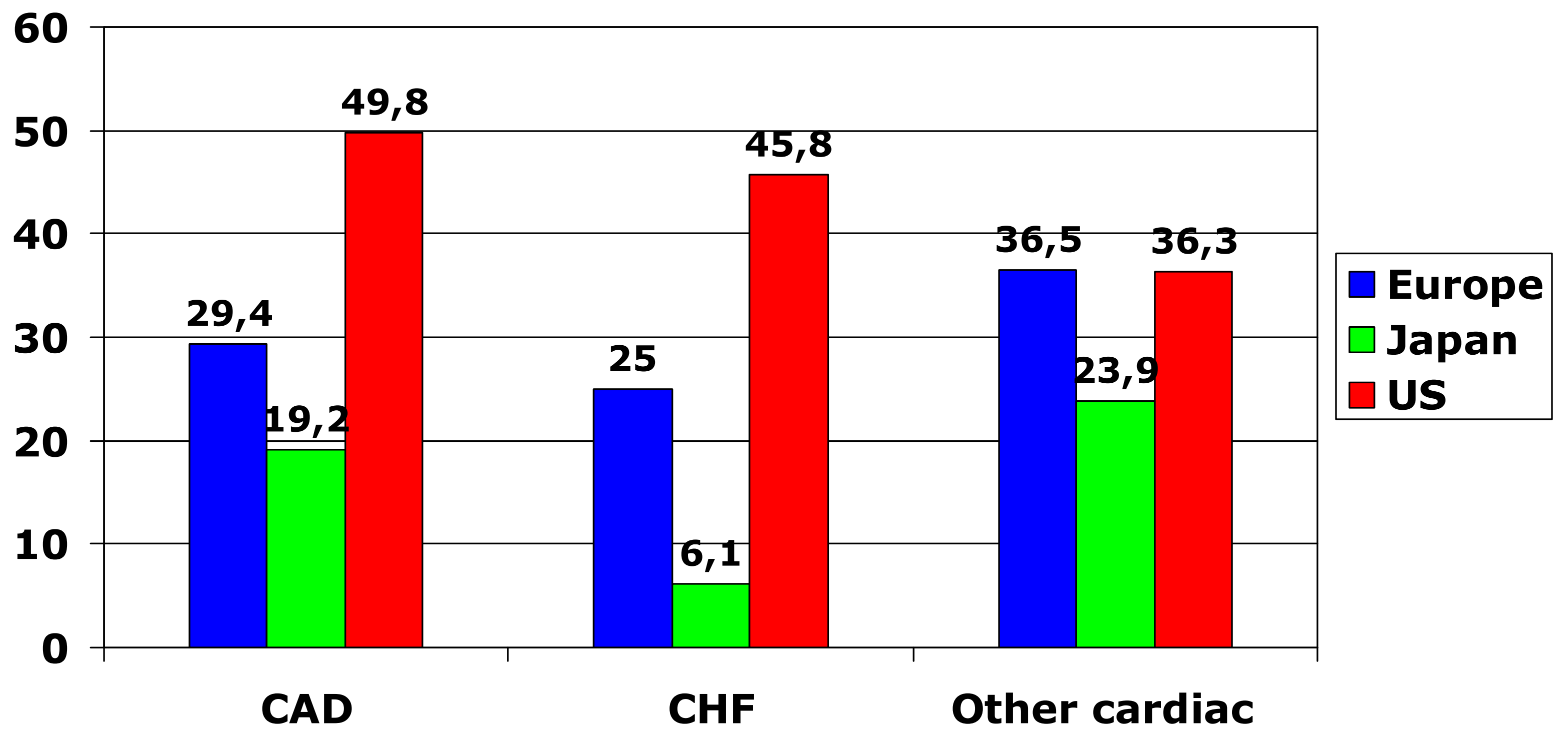


Stel VS et al. Prevalence of co-morbidity in different European RRT populations and its effect on access to renal transplantation. NDT 2005: 2803–2811

Increased prevalence of CVD

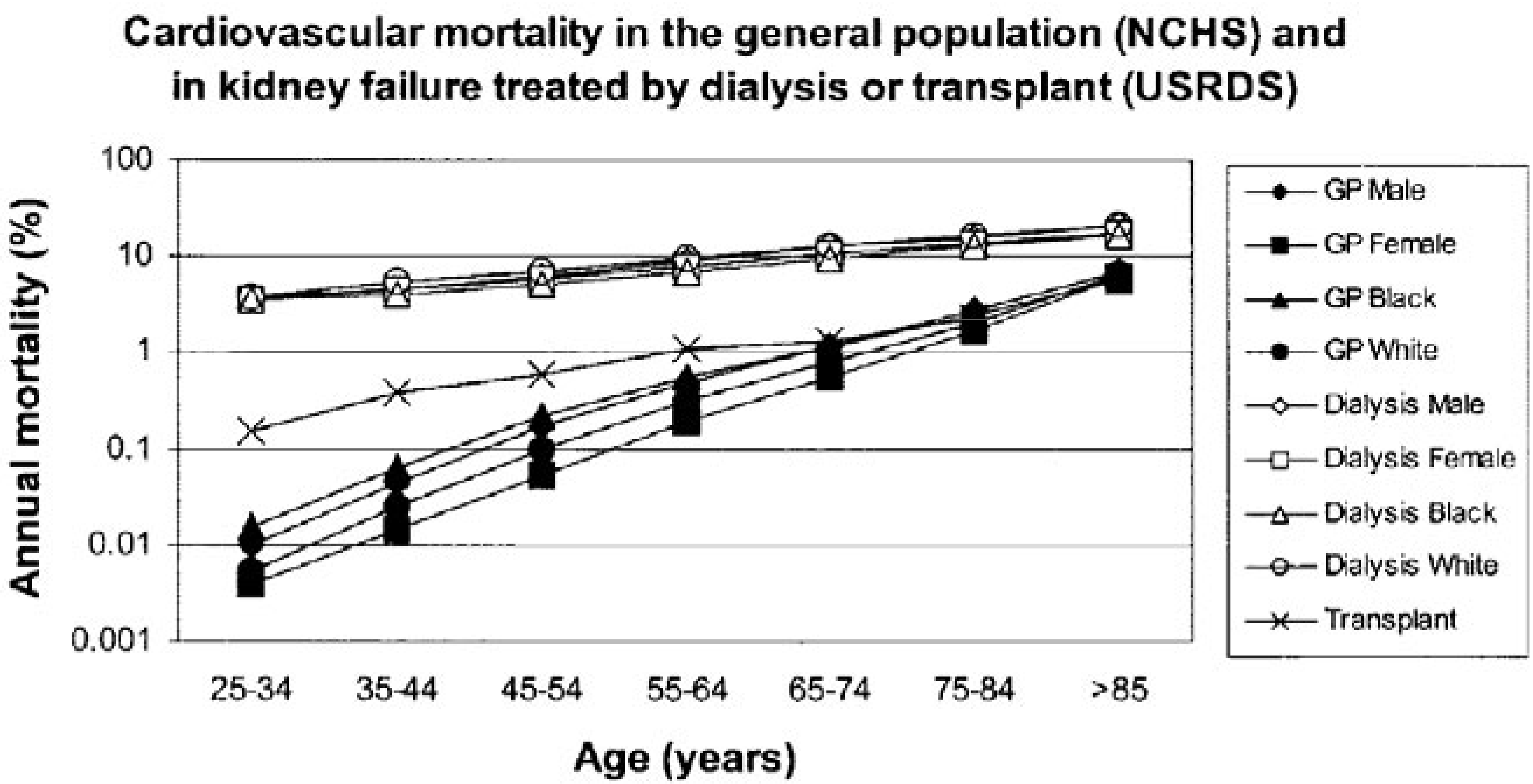
DOPPS 1 data

Prevalence of cardiovascular co-morbidity in HD patients at 'baseline'



Goodkin DA et al. Association of Comorbid Conditions and Mortality in Hemodialysis Patients in Europe, Japan, and the United States: The Dialysis Outcomes and Practice Patterns Study (DOPPS). J Am Soc Nephrol 2003;14:3270–3277

Increased cardiovascular mortality



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Circulation 2003;108;2154-2169

Hypertension 2003;42;1050-1065

Increased cardiovascular mortality

Table 3. Cardiovascular and Noncardiovascular Mortality Rates (per 1000 Person-Years), Their Difference, and the Excess Risk of Cardiovascular Mortality Over Noncardiovascular Mortality in the Dialysis Population as Compared With the General Population

Age, y	Cardiovascular[a] Patients	Cardiovascular[a] General Population	Noncardiovascular[a] Patients	Noncardiovascular[a] General Population	Absolute Excess ΔCV[b]	Absolute Excess Δnon-CV[b]	Absolute Excess Excess[c]
				All			
Age category, y							
20-24	3.9	0.0	16.0	0.5	3.8 (2.2 to 5.5)	15.5 (10.0 to 20.9)	−11.6 (−17.3 to −5.9)
25-34	11.0	0.1	18.7	0.7	10.9 (8.8 to 13.1)	18.0 (15.2 to 20.8)	−7.1 (−10.6 to −3.5)
35-44	21.2	0.2	25.8	1.1	20.9 (18.7 to 23.2)	24.7 (22.2 to 27.2)	−3.8 (−7.1 to −0.5)
45-54	34.6	0.7	41.7	2.4	33.9 (31.8 to 36.1)	39.4 (37.0 to 41.7)	−5.4 (−8.6 to −2.3)
55-64	55.1	2.0	68.8	5.5	53.1 (50.9 to 55.2)	63.3 (60.9 to 65.7)	−10.2 (−13.5 to −7.0)
65-74	90.0	6.8	111.7	12.9	83.3 (81.0 to 85.6)	98.8 (96.3 to 101.4)	−15.6 (−19.0 to −12.1)
75-84	119.8	23.8	162.1	30.6	96.0 (92.9 to 99.1)	131.5 (127.9 to 135.1)	−35.5 (−40.2 to −30.8)
≥85	158.1	84.3	245.1	78.0	73.8 (63.6 to 84.0)	167.0 (154.4 to 179.7)	−93.2 (−109.5 to −77.0)
Unstandardized[d]	74.9 (73.7 to 76.0)	4.872 (4.87 to 4.88)	97.3 (96.0 to 98.6)	7.045 (7.04 to 7.05)	70.0 (68.8 to 71.1)	90.3 (89.0 to 91.6)	−20.3 (−22.0 to −18.6)
Standardized[e]	42.9 (42.0 to 43.8)	4.9[f]	57.1 (56.0 to 58.2)	7.0[f]	38.1 (37.2 to 39.0)	50.1 (48.9 to 51.2)	−12.0 (−13.4 to −10.5)

"The directly standardized cardiovascular mortality rate was 8.8 (95% CI, 8.6-9.0) times higher in patients starting dialysis than in the general population."

de Jager DJ, Grootendorst DC, Jager KJ, van Dijk PC, Tomas LMJ, Ansell D, Collart F, Finne P, Heaf JG, De Meester J, Wetzels JFM, Rosendaal FR, Dekker FW. Cardiovascular and Noncardiovascular Mortality Among Patients Starting Dialysis. *JAMA. 2009;302(16):1782-1789*

Why is cardiovascular mortality so much increased?

- CKD is common in people with CVD and with CVD risk factors
- CKD is associated with an increased risk of adverse outcomes in these conditions

TABLE 6. Traditional and Nontraditional Cardiovascular Risk Factors in CKD

Traditional Risk Factors	Nontraditional Factors
Older age	Albuminuria
Male sex	Homocysteine
Hypertension	Lipoprotein(a) and apolipoprotein(a) isoforms
Higher LDL cholesterol	Lipoprotein remnants
Lower HDL cholesterol	Anemia
Diabetes	Abnormal calcium/phosphate metabolism
Smoking	Extracellular fluid volume overload
Physical inactivity	Electrolyte imbalance
Menopause	Oxidative stress
Family history of CVD	Inflammation (C-reactive protein)
LVH	Malnutrition
	Thrombogenic factors
	Sleep disturbances
	Altered nitric oxide/endothelin balance

Circulation 2003;108;2154-2169

And more ....

- **High prevalence of traditional risk factors in CKD**
- **As renal function deteriorates non-traditional risk factors play an increasing role in GFR loss and cardiovascular damage**

Causality of risk factors

In order to be regarded as a **causal** risk factor there ideally needs to be

- biological plausibility as to why the factor may promote CVD risk
- demonstration that the risk factor level increases with severity of kidney disease
- demonstration of an association between the risk factor and CVD in observational studies in CKD and
- demonstration in placebo-controlled clinical trials that treatment of the risk factor decreases CVD outcomes

Circulation 2003;108:2154-2169

Negative "cardiovascular RCTs" in CKD

- **CREATE**
  failed to show a reduction of cardiovascular events by early complete correction of anemia

- **4D**
  failed to show a statistically significant effect of atorvastatin on a composite primary end point of cardiovascular death, nonfatal myocardial infarction, and stroke in patients with diabetes receiving hemodialysis

- **CHOIR**
  showed that the use of a target hemoglobin level of 13.5 g/dl (as compared with 11.3 g/dl) was associated with increased risk of a composite mainly cardiovascular endpoint and no incremental improvement in the quality of life

- **AURORA**
  failed to show a significant effect of initiation of treatment with rosuvastatin on the composite primary end point of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke

- **AASK**
  failed to show an effect of intensive blood-pressure control on kidney disease progression in black patients with hypertensive chronic kidney disease

Why trials in dialysis patients may be negative

Possibility 1 *There is a benefit (a true effect) of the intervention, but it was not detected in this specific trial*

Possibility 2 *There is indeed no effect in the dialysis population*

Novak JE, Inrig JK, Patel UD, Califf RM, Szczech LA. Negative trials in nephrology: what can we learn? Kidney Int 2008;74:1121–1127

Jager KJ, Stel VS, Zoccali C, Wanner C, Dekker FW. The issue of studying the effect of interventions in renal replacement therapy - to what extent may we be deceived by selection and competing risk? NDT 2010 – ahead of print 10 September

Why trials in dialysis patients may be negative

Possibility 1 *There is a benefit (a true effect) of the intervention, but it was not detected in this specific trial*

<u>1st potential cause - 'Flawed' RCT design</u>

– selected patient populations in RCTs
  - strict in- and exclusion criteria → enrollment of relatively healthy subjects
  - refusal rate usually higher in worse patients → healthy volunteer bias

  ~~ increases the risk of a study being underpowered

– unequal distribution of unmeasured confounders ~~ if so, unable to adjust

– some endpoints or other patient characteristics may be difficult to determine

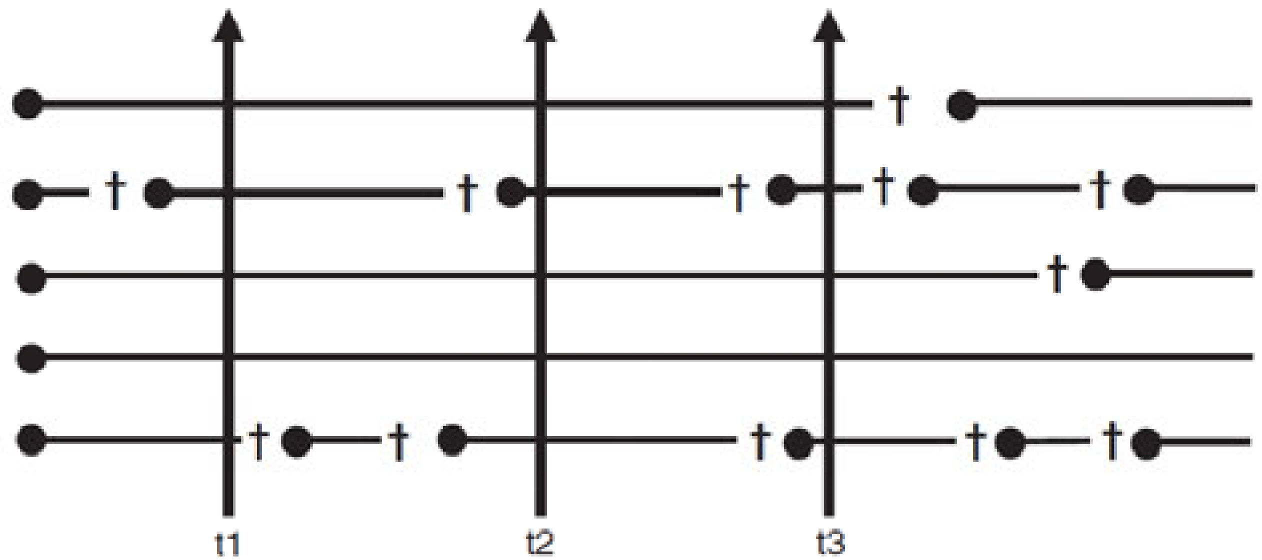
  ~~ adjucation helps, but may not entirely solve the problem

– studies in prevalent dialysis patients may suffer from survivor bias

  ~~ incident patients to be preferred

Why trials in dialysis patients may be negative

Survivor bias in studies using prevalent dialysis patients



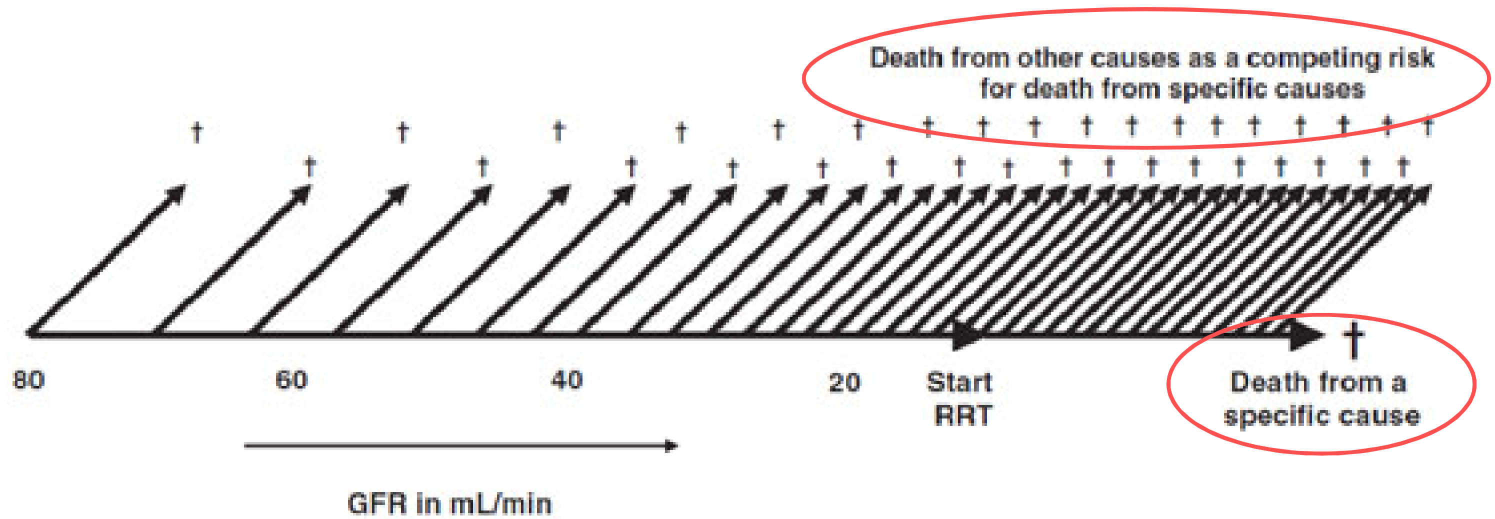
● = start of dialysis † = death t = time of sampling patients

- When prevalent patients are sampled at any of the time points (t1, t2 or t3), those who live longest - the survivors - (3/5 patients) will be over-represented
- Survivor bias may distort the relative risk in either direction

Why trials in dialysis patients may be negative

Possibility 1 *There is a benefit (a true effect) of the intervention, but it was not detected in this specific trial*

2nd potential cause - Mortality in this patient population is extremely high



Beneficial effects may be masked by

- increased mortality from other causes inducing a 'dilution' of the effect
  ~~ 'low signal to noise ratio'
- dilution increased by the heterogeneity of cardiac death (ischaemic /sudden death / heart failure)

Why trials in dialysis patients may be negative

Modifiable risk factors associated with sudden cardiac arrest within hemodialysis clinics

Patrick H. Pun[1,2], Ruediger W. Lehrich[1], Emily F. Honeycutt[2], Charles A. Herzog[3] and John P. Middleton[1]

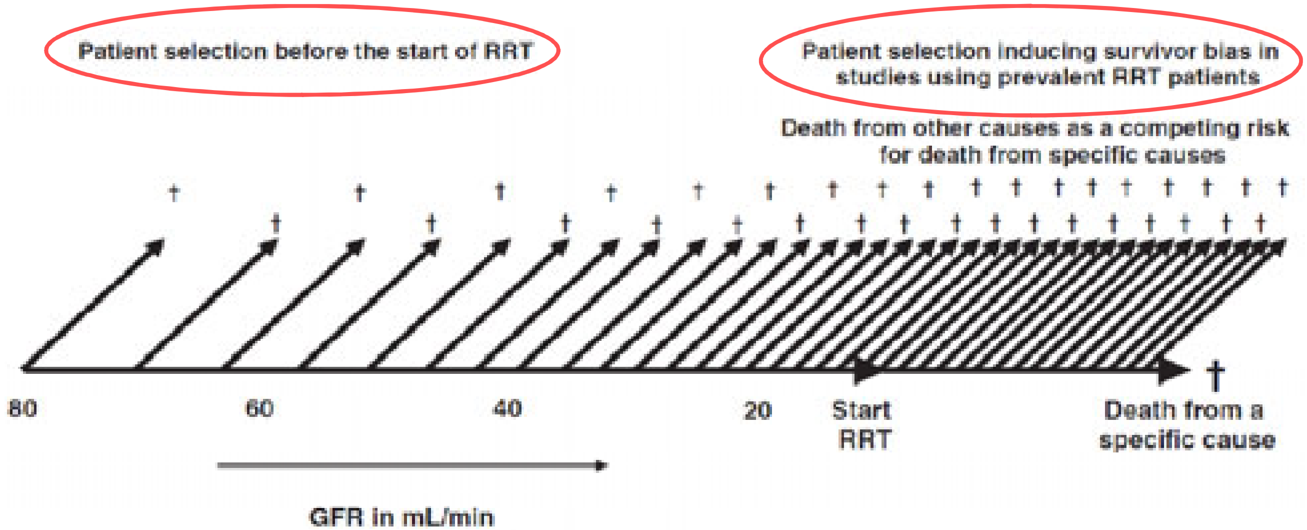
Kidney Int advance online, 1 September 2010

- Case control study to identify dialysis-related factors associated with increased risk of sudden cardiac arrest
- 502 cases who experienced a sudden cardiac arrest and 1632 age- and dialysis-vintage-matched controls
- Sudden cardiac arrest was associated with:
  - low potassium dialysate (<2 meq/l)
  - increased ultrafiltration volumes
  - low calcium dialysate
  - predialysis serum creatinine levels
- Traditional risk factors like history of CHD and CHF were NOT significantly influential

Why trials in dialysis patients may be negative

Possibility 2 *There is indeed no effect in the dialysis population*

<u>Dialysis patients are a 'selected' group compared to the general population</u>



'Survival of the fittest' ?

- Genetic make-up allowing better adaptation to an increasingly disadvantageous uraemic milieu over the course of decreasing renal function?
- Less vulnerable to traditional risk factors?

Problem further increased when using prevalent dialysis patients inducing survivor bias

CKD as risk factor for other chronic diseases

CKD is also associated with an increased risk of adverse outcomes in other chronic diseases like infection and cancer

Cardiovascular Health Study - a community-based cohort of older individuals

Table 4. Adjusted association of cystatin C with cause-specific mortality rates

	Fourth Quartile Cystatin C (>1.22) *versus* First Quartile (<0.93)		Fourth Quartile eGFR <60.17) *versus* First Quartile (>81.4)	
	HR (95% CI)[a]	*P* Value	HR (95% CI)[a]	*P* Value
Dementia	1.01 (0.58 to 1.75)	0.978	1.09 (0.63 to 1.91)	0.754
Pulmonary disease	2.67 (1.21 to 5.89)	0.015	0.73 (0.38 to 1.38)	0.327
Infection	4.65 (2.03 to 10.63)	<0.001	2.07 (1.04 to 4.12)	0.039
Cancer	1.79 (1.33 to 2.42)	<0.001	1.30 (0.97 to 1.74)	0.081
Other	2.71 (1.69 to 4.35)	<0.001	2.25 (1.39 to 3.65)	0.001

[a]Adjusted for age, race, and gender.

Fried LF. Kidney Function as a Predictor of Noncardiovascular Mortality. J Am Soc Nephrol 2005;16:3728–3735

CKD as risk factor for non-cardiovascular mortality

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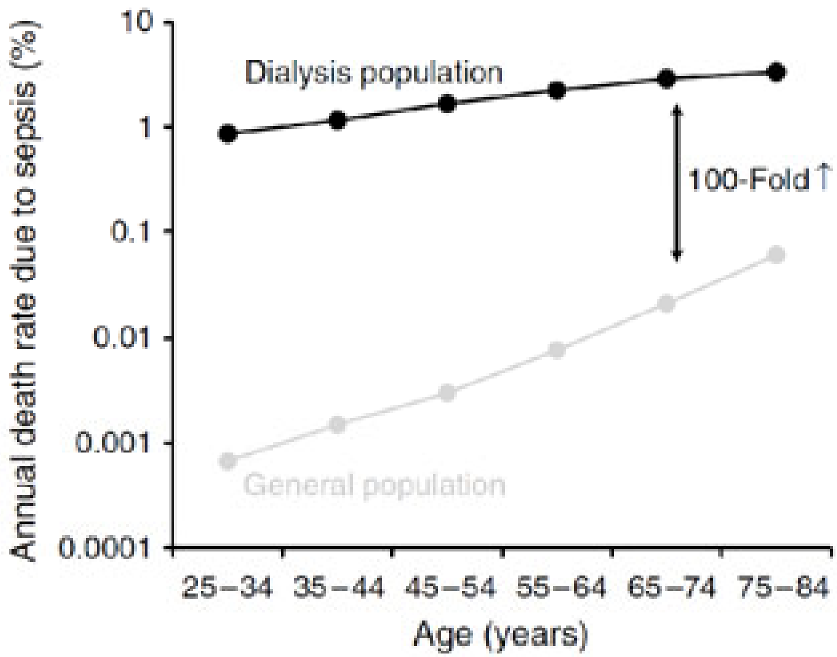
8.8 times higher **8.1 times higher**

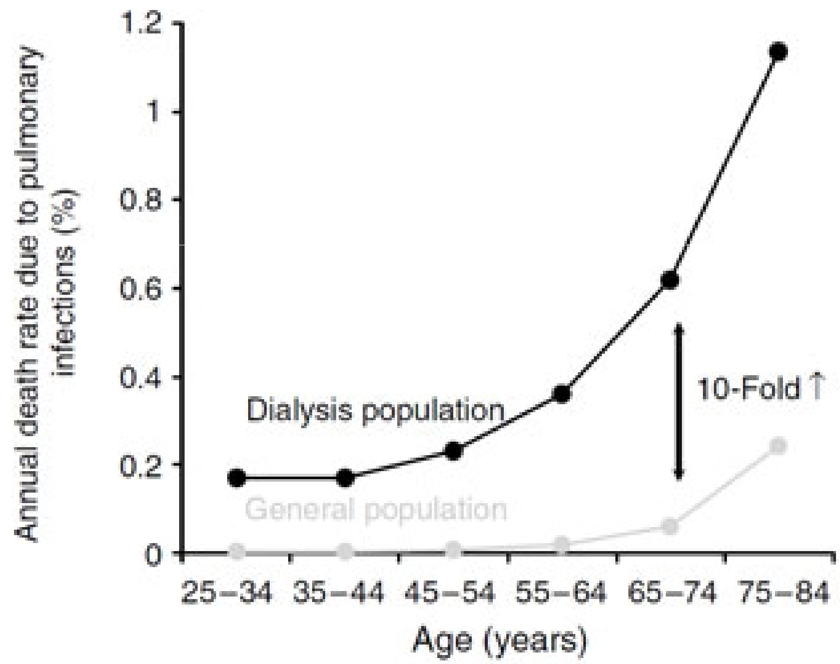
"The directly standardized NON cardiovascular mortality rate was 8.1 (95% CI, 7.9-8.3) times higher in patients starting dialysis than in the general population."

de Jager DJ, Grootendorst DC, Jager KJ, van Dijk PC, Tomas LMJ, Ansell D, Collart F, Finne P, Heaf JG, De Meester J, Wetzels JFM, Rosendaal FR, Dekker FW. Cardiovascular and Noncardiovascular Mortality Among Patients Starting Dialysis. *JAMA. 2009;302(16):1782-1789*

CKD as risk factor for non-cardiovascular mortality



SEPSIS



PULMONARY INFECTIONS

Jaber BL. Bacterial infections in hemodialysis patients: pathogenesis and prevention. Kidney Int 2005; 67: 2508–2519

Conclusions

- Compared to the general population life expectancy in adult CKD stage 5 patients is on average reduced to
  - ~ 30% in dialysis patients
  - ~ 60% in transplant patients
- Both the prevalence of CVD and cardiovascular mortality are importantly increased
- RCTs on treatment of traditional cardiovascular risk factors have frequently provided negative results

Conclusions

- A true effect of such interventions may not be detected due to
  - ‘flawed’ RCT design
  - ‘low signal to noise ratio’ due to high mortality inducing a ‘dilution’ of the effect increased by heterogeneity of cardiac death

- Lack of effect in this ‘selected’ population
  - ‘survival of the fittest’
  - survivor bias in studies using prevalent patients

    $\rightarrow$ both may hamper the generalizability of results in the general population to the dialysis population and vice versa

    $\rightarrow$ results from high quality studies in incident RRT patients with very limited in- and exclusion criteria are likely the ones best qualified to be extrapolated to other RRT populations

Conclusions

- CKD is not only associated with unfavourable cardiovascular outcomes, but also with (unfavourable outcomes of) other chronic diseases
- This underlines the importance of understanding the relationship between CKD, CVD and other chronic diseases
- Research into this area is much needed
  - Common cause?
  - Role of the immune system?
  - Causal pathway of cardiac disease in patients undergoing dialysis?

Thank you