CKD-CVD-Anemia: The Vicious Cycle

Dr Goh Heong Keong

Cinta Rasa Sayang, Sungai Petani

www.PassPACES.com/kidney.htm

Outline of Lecture

- Introduction
- Epidemiology of CKD in Malaysia/ World
- Complications of CKD
- Definition of Anemia
- Epidemiology of CVD in CKD patients
- CKD-CVD Relations
- CKD-CVD-Anemia- The Vicious cycle
- Conclusion

Introduction

Chronic kidney disease- increasing health burden in many countries.

The estimated prevalence of CKD in the US was 16.8% while in Asia the prevalence ranged from 12.1% to 17.5%.

Allon M, Robbin ML. Increasing arteriovenous fistulas in hemodialysis patients: problems and solutions. Kidney Int 2002; 62: 1109-24.

In Malaysia, the incidence and prevalence of patients with ESRD on dialysis had increased from 88 and 325 per million population (pmp) respectively in 2001 to 170 and 762 pmp respectively in 2009.

Definition of Chronic kidney disease

Table 11. Definition of Chronic Kidney Disease

Criteria
1. Kidney damage for ≥3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifest by *either*: • Pathological abnormalities; or • Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests
2. GFR <60 mL/min/1.73 m^2 for ≥3 months, with or without kidney damage

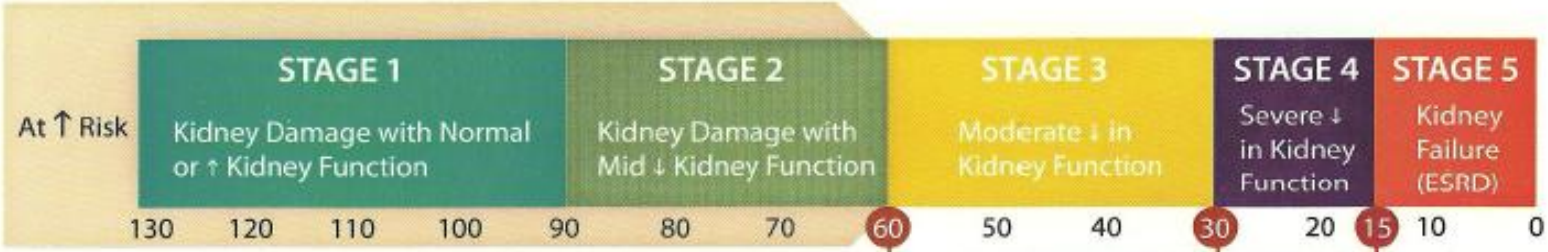
Methods to estimate GFR are discussed in Guideline 4. Markers of kidney damage are discussed in Guidelines 5–6.

Stages of Chronic kidney disease

Appendix 3 : CKD – Stages of CKD

Roche

Kidney Function: Glomerular Filtration Rate (GFR) (Guidelines 1 and 2)



If GFR <60, asess:
- Presence of anemia (Guideline 8): follow K/DOQI Anemia Guidelines
- Nutritional status (Guideline 9): follow K/DOQI Nutritional Guidelines
- Bone Metabolism (Guideline 10): follow K/DOQI Bone Metabolism Guidelines
- Indices of functioning and well-being (Guideline 12)

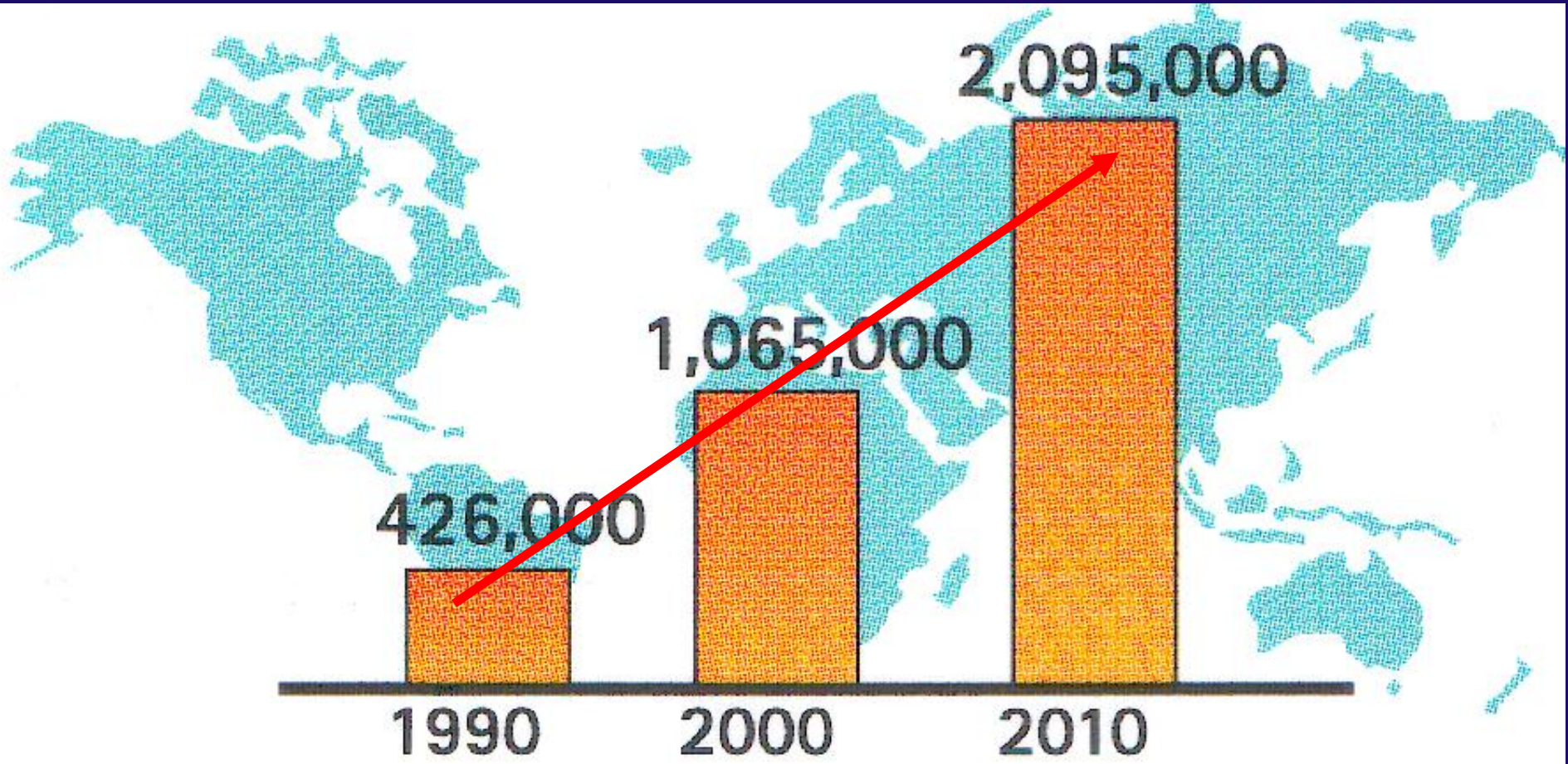
If GFR <30:
- Refer to nephrologist
- Prepare for Kidney Replacement Therapy (KRT)

If GFR <15, consider initiation of KRT.
Patients who may benefit from KRT at Higher levels of kidney function:
- Living donor transplant recipients
- Older patients
- Those with diabetes (this group is at highest risk for ASCVD)
- Those with ASCVD
- Those with other comorbid conditions

National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. Am J Kidney Dis 39, 2002(suppl 1). These Guidelines, as well as all other K/DOQI™ guidelines, can be accessed on the Internet at: www.kdoqi.org NKF Order No. 12-50-0157. Amgen Part No. P35184.

Epidemiology of CKD

Global maintenance dialysis population from 1990 to 2010



Lysaght, *J Am Soc Nephrol*, 2002

Prevalence of ESRD

(per million population),

2005

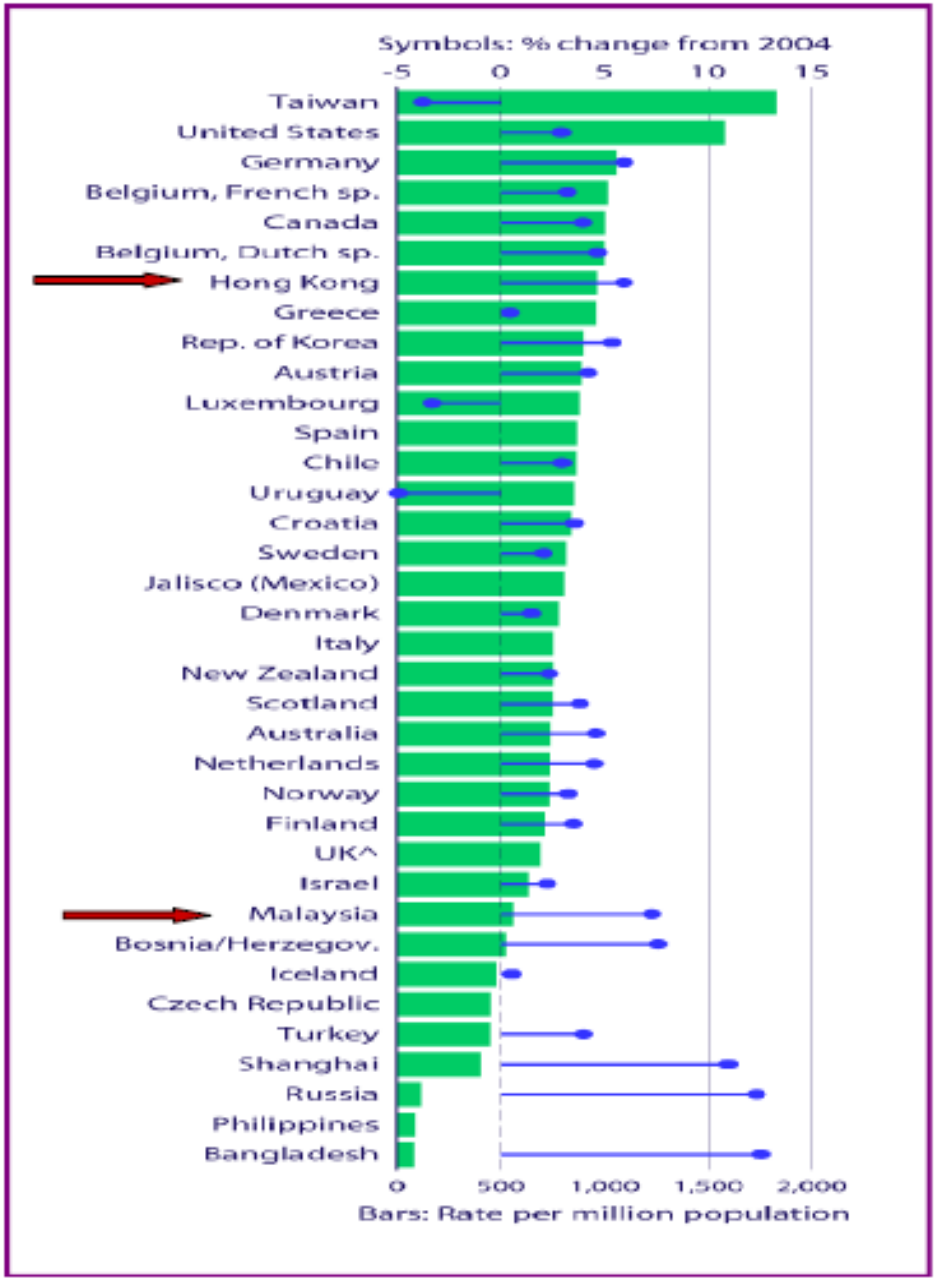
1. **Taiwan 1,830**
2. **USA 1,585**
3. **Germany 1,057**

7. HK 965

28. Malaysia 560

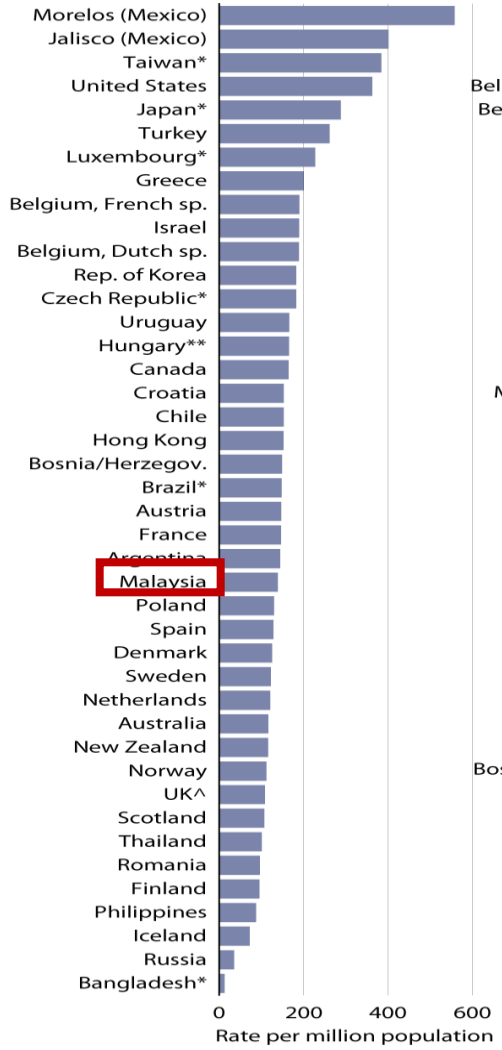
(Japan – no data - No. 1 in 2003)

USRDS 2007

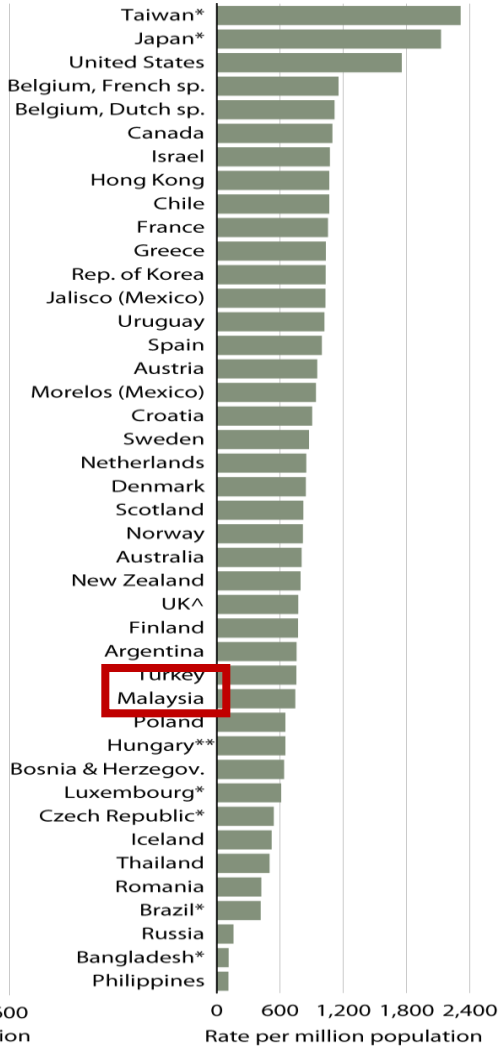


International comparisons on Incidence and prevalence, Transplantation of ESRD, 2008

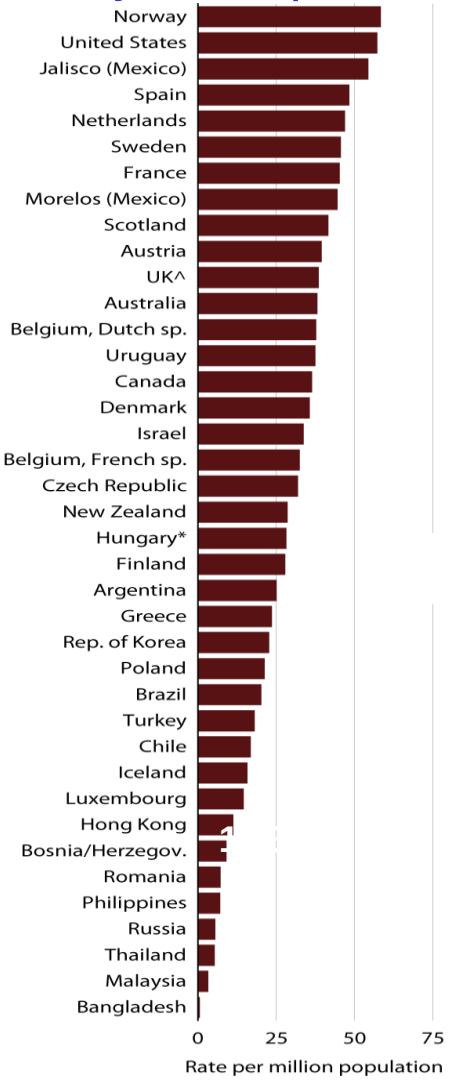
Incidence



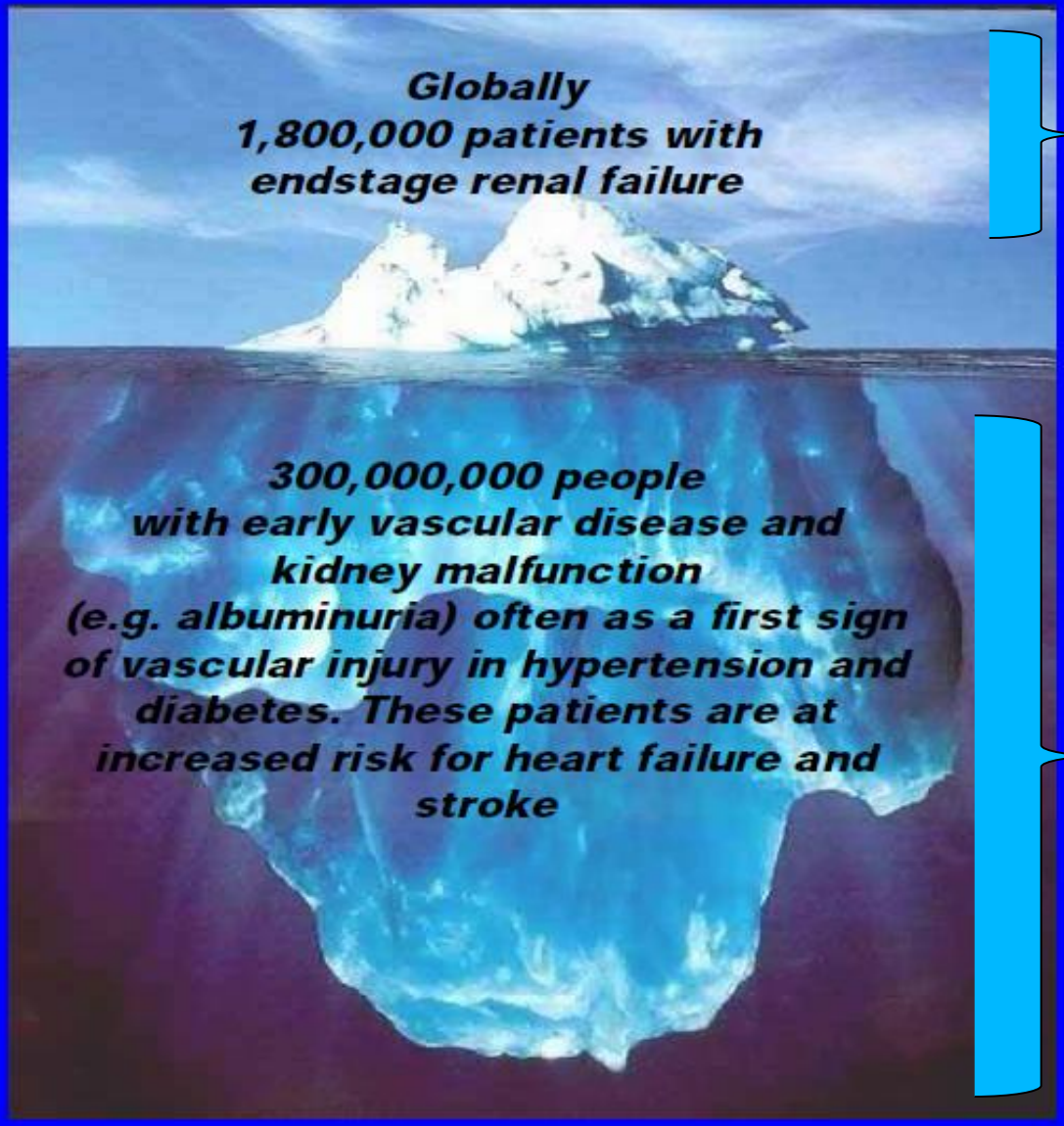
Prevalence



Kidney Transplantation



尿毒病患是冰山一角，慢性腎臟病者知多少？



25000

??

??

Stages of CKD in US – Estimated Prevalence

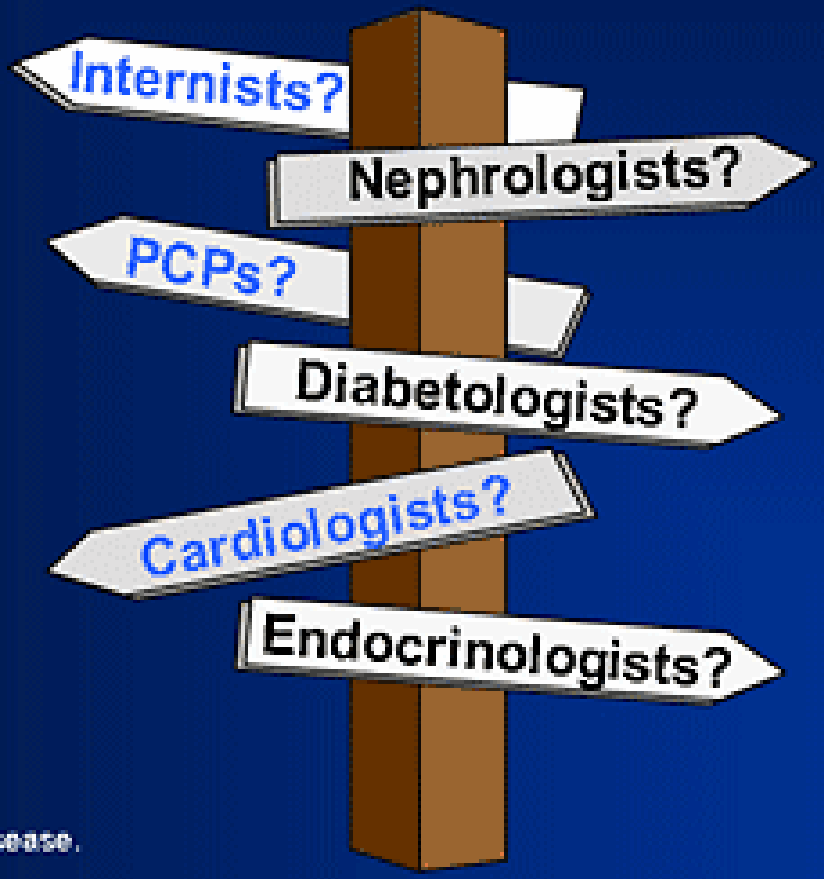
Stage of CKD	Description	GFR	Detection, Evaluation, and Management*	Prevalence†	
				%	No. of Cases (95% CI)
		ml/min/1.73 m²			*millions*
1	Kidney damage with normal or increased GFR	>90	Diagnosis and treatment Treatment of coexisting conditions Slowing progression Risk reduction for cardiovascular disease	2.8	5.6 (4.0–7.2)
2	Kidney damage with mild decrease in GFR	60–89	Estimation of progression	2.8	5.7 (4.2–7.2)
3	Moderate decrease in GFR	30–59	Evaluation and treatment of complications	3.7	7.4 (6.0–8.9)
4	Severe decrease in GFR	15–29	Referral to nephrologist and consideration for kidney replacement therapy	0.1	0.30 (0.02–0.5)
5	Kidney failure	<15	Replacement (if uremia present)	0.2	0.30‡

US Estimates from **Stevens: N Engl J Med** *, 2006*

Complications of CKD

Care Is Fragmented

Who is currently caring for patients with CKD?



CKD = chronic kidney disease.

http://www.medscape.org/viewarticle/533695_3

Complications Associated With CKD

- Anemia
- Cardiovascular disease
- Diabetes
- Dyslipidemia
- Hypertension
- Malnutrition
- Metabolic acidosis
- Osteodystrophy

Zabetakis PM, et al. *Am J Kidney Dis.* 2000;36(6 suppl 3):S31-S38.

Definition of Anemia

Anemia: hemoglobin (Hgb) concentration below 13.0 g/dL for adult males and post-menopausal women

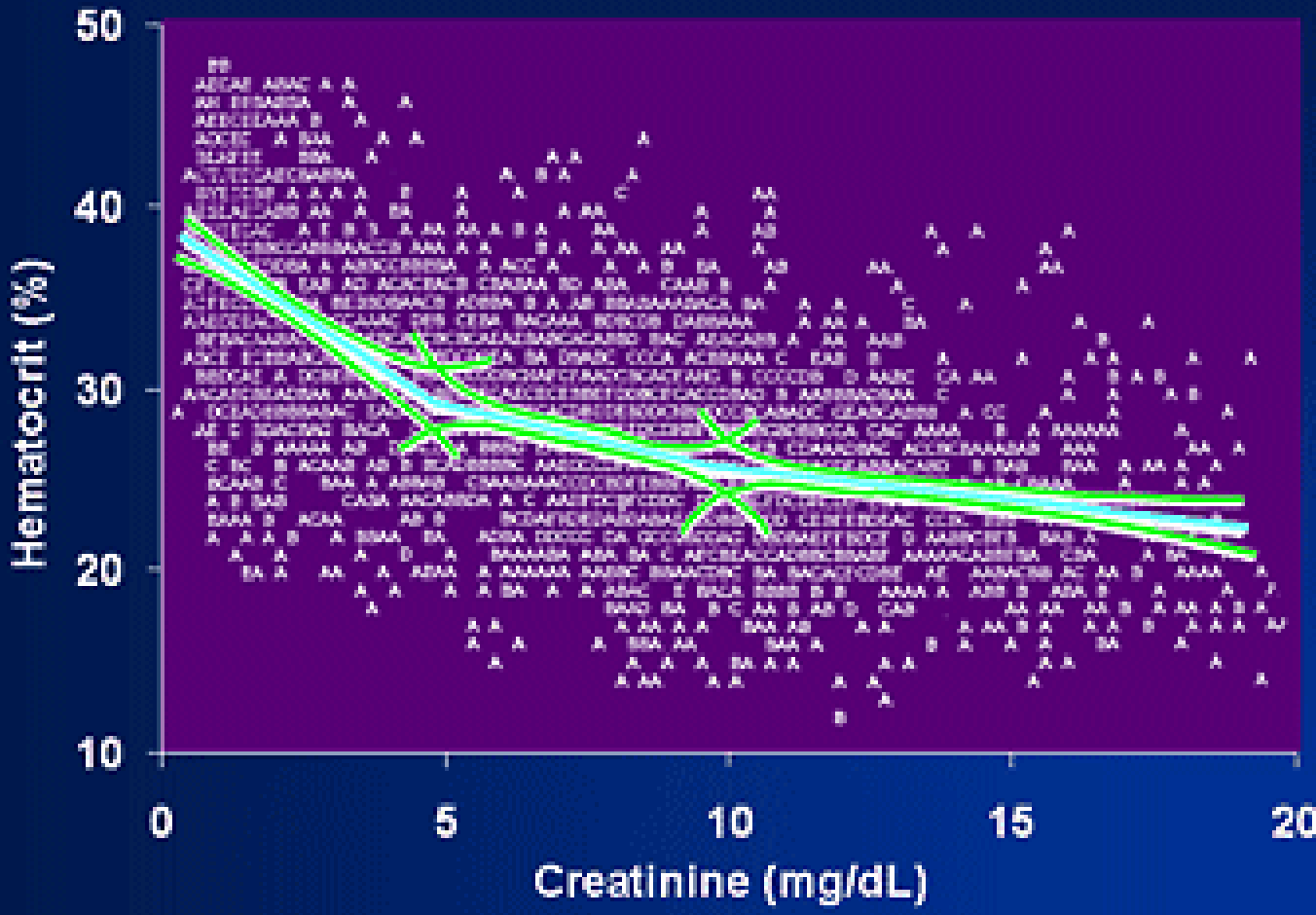
Hgb below 12.0 g/dL for premenopausal women

Based on this criteria, nearly 90% of patients with a glomerular filtration rate <25 to 30 mL/min have anemia, many with Hgb levels below 10 g/dL

Anemia of chronic kidney disease is due primarily to reduced production of erythropoietin by the kidney and to shortened red cell survival

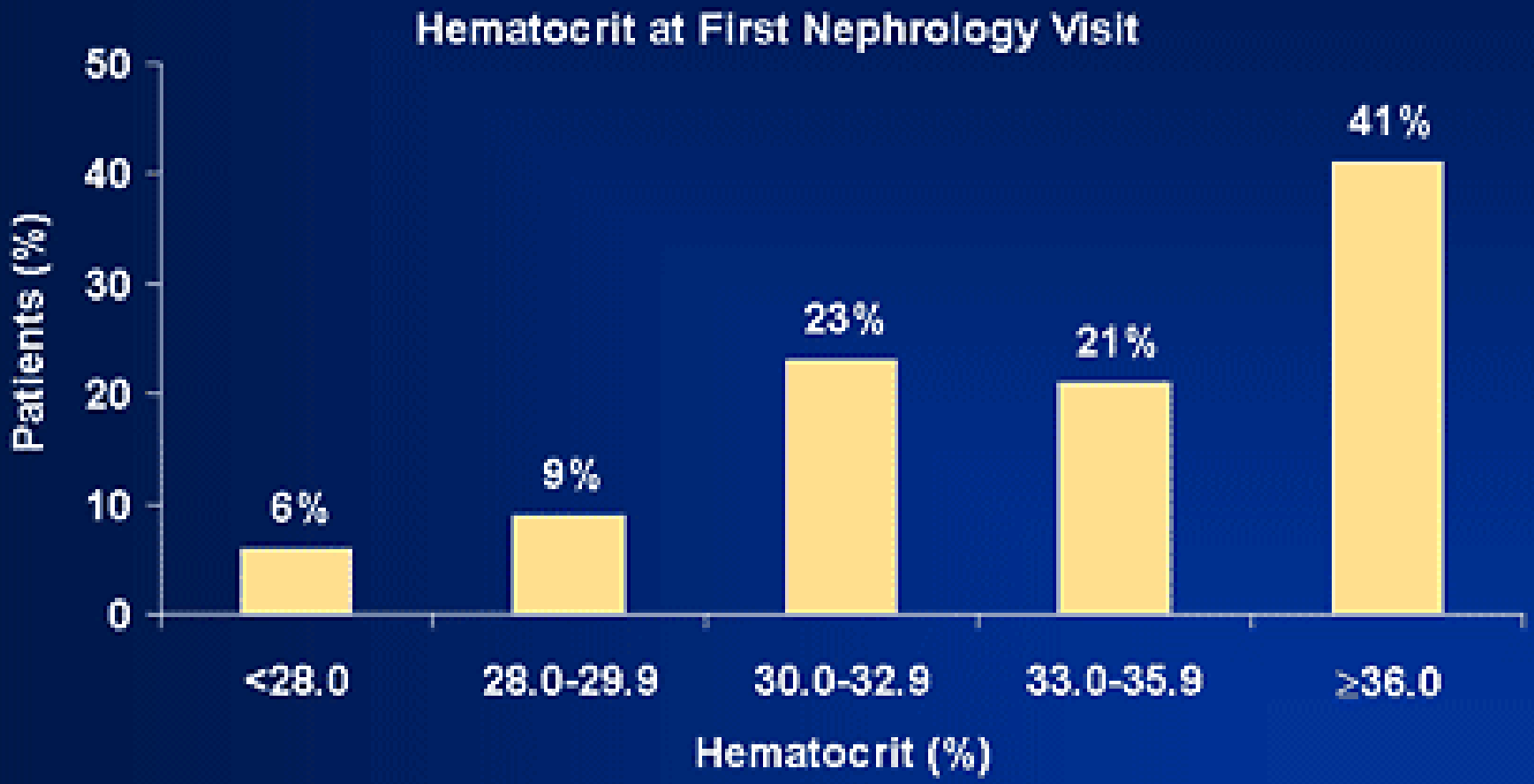
Kazmi, WH, et al. Anemia: An Early Complication of Chronic Renal Insufficiency. American Journal of Kidney Diseases 2001; 38:803

Hematocrit and Renal Function



Adapted from Hakim RM, et al. *Am J Kidney Dis*. 1988;11:238-247.

Majority of Patients With CKD Are Anemic at First Nephrology Visit



Kazmi WH, et al. *Am J Kidney Dis*. 2001;38:803-812.

Epidemiology of CVD in CKD

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 3112-3119

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

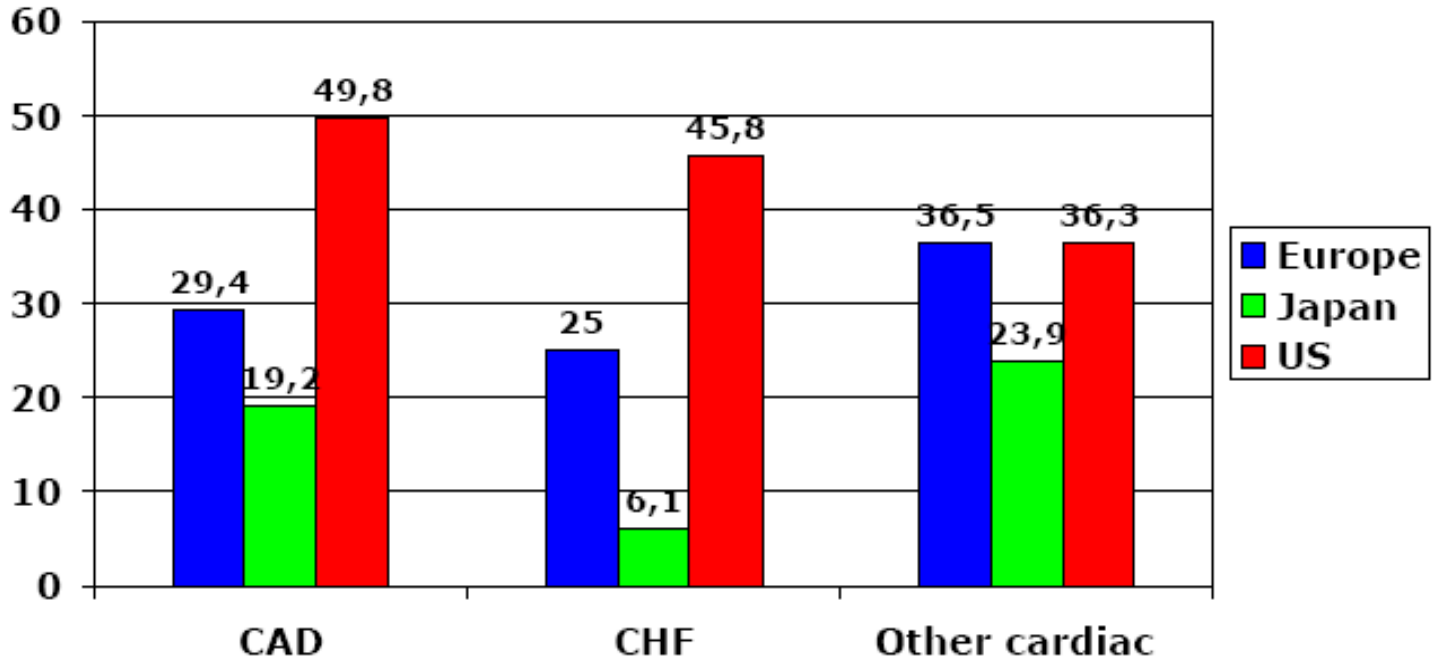
TABLE 2. Approximate Prevalence of CVD in the General Population and CKD

	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

DOPPS 1 data

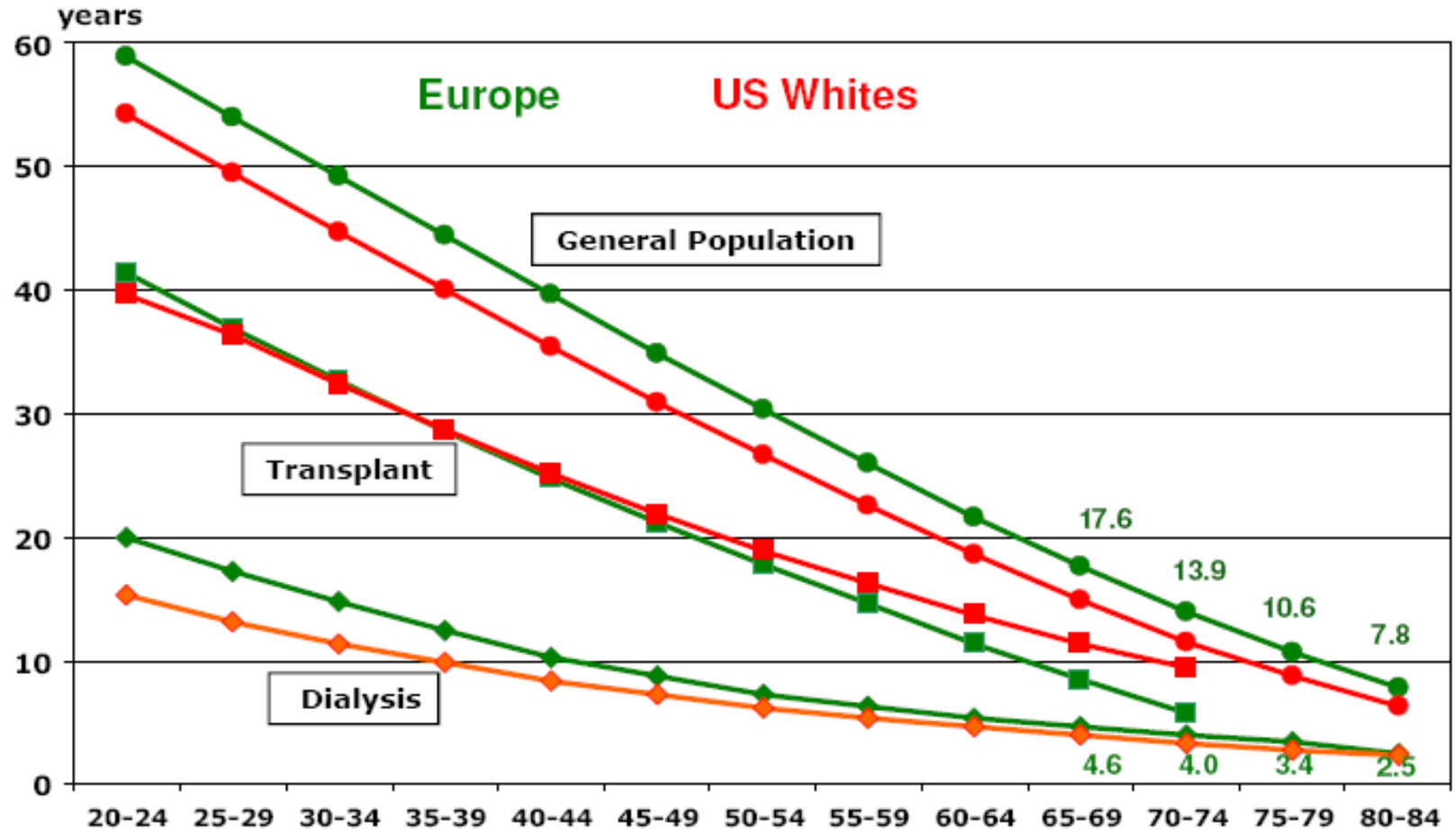
Prevalence of cardiovascular co-morbidity in HD patients at 'baseline'



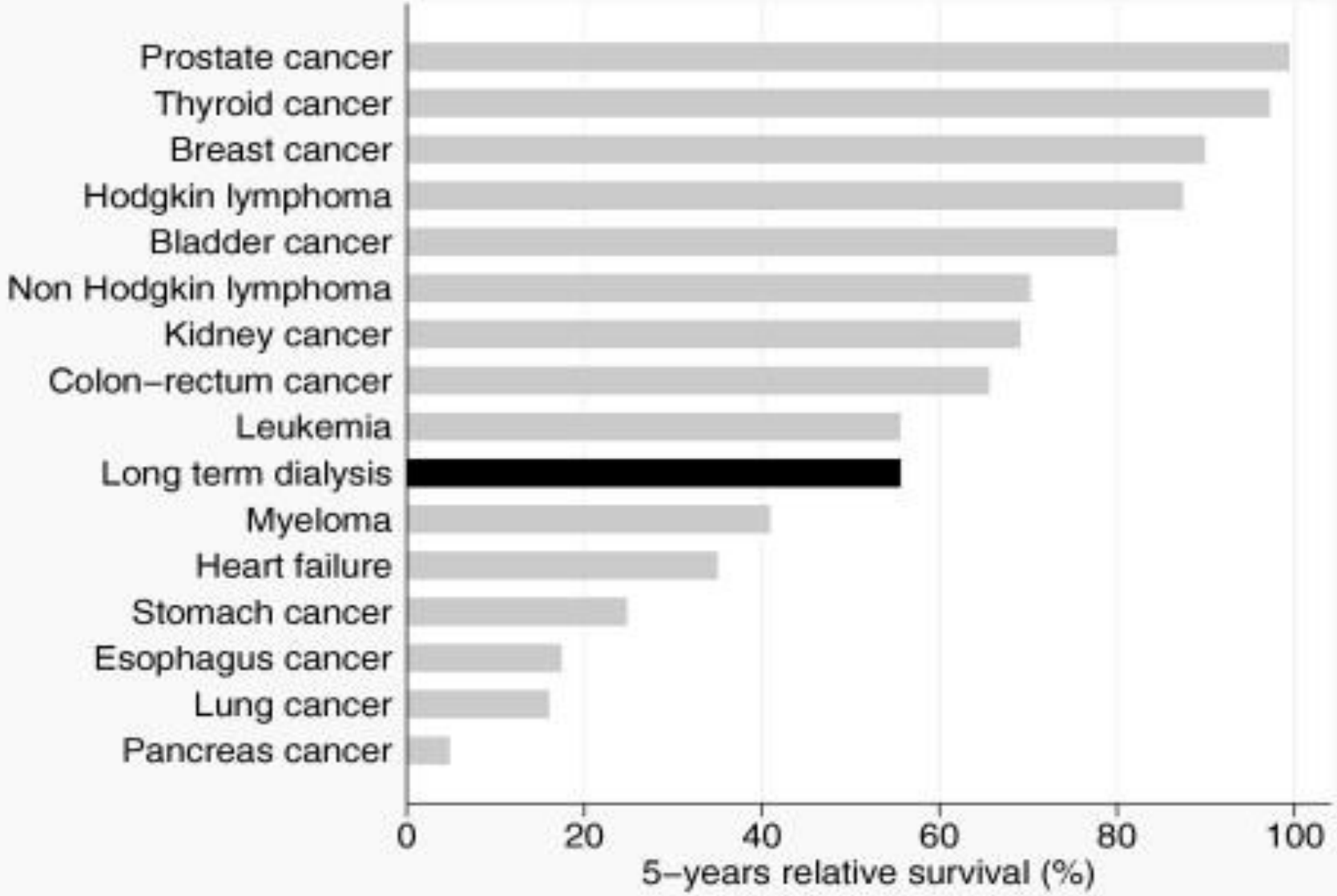
Goodkin DA et al. Association of Comorbid Conditions and Mortality in Hemodialysis Patients in Europe, Japan, and the United States: The Dialysis Outcomes and Practice Patterns Study (DOPPS). J Am Soc Nephrol 2003;14:3270–3277

CKD-CVD- The relations

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

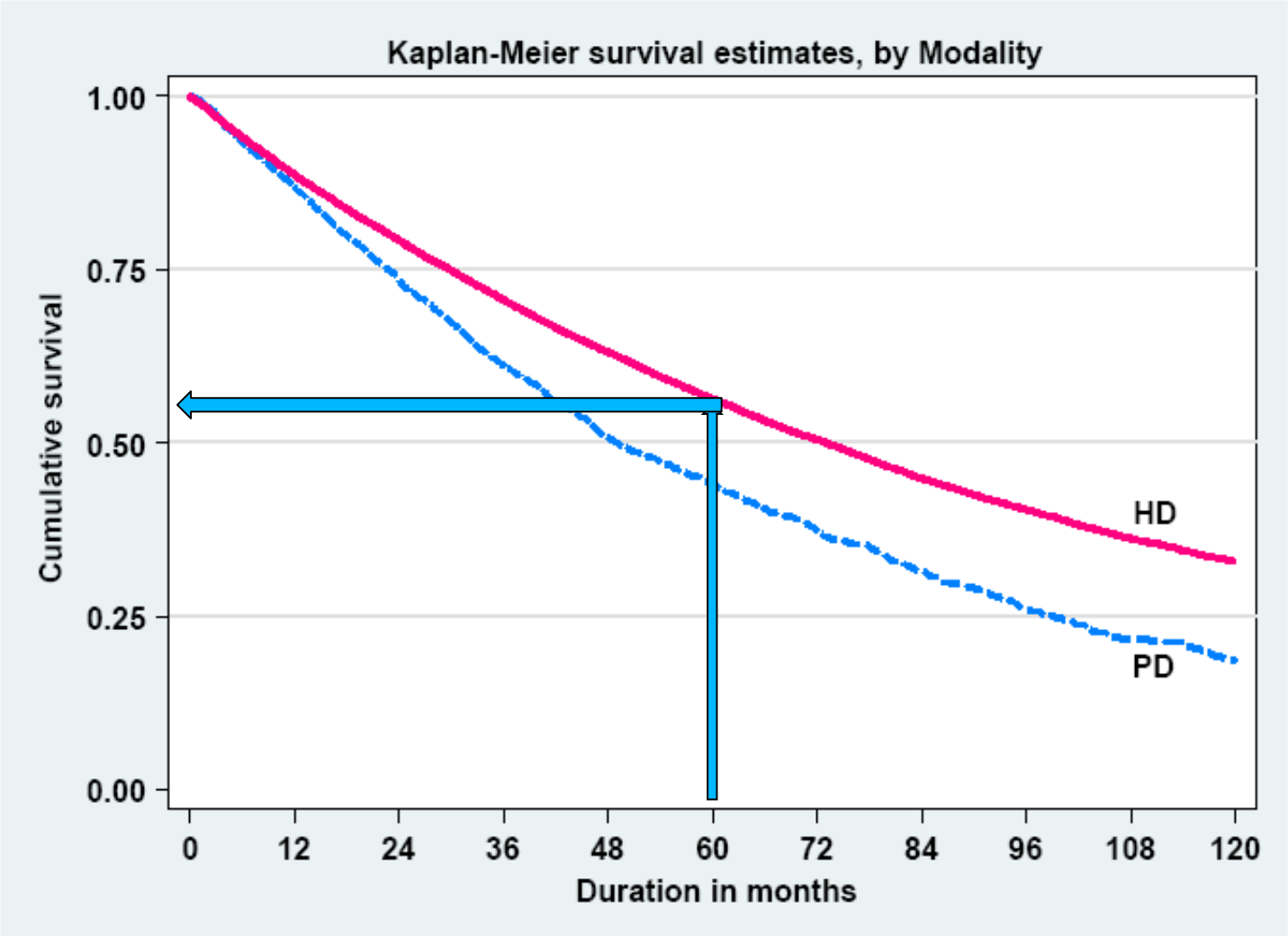


ERA-EDTA Registry data and USRDS data



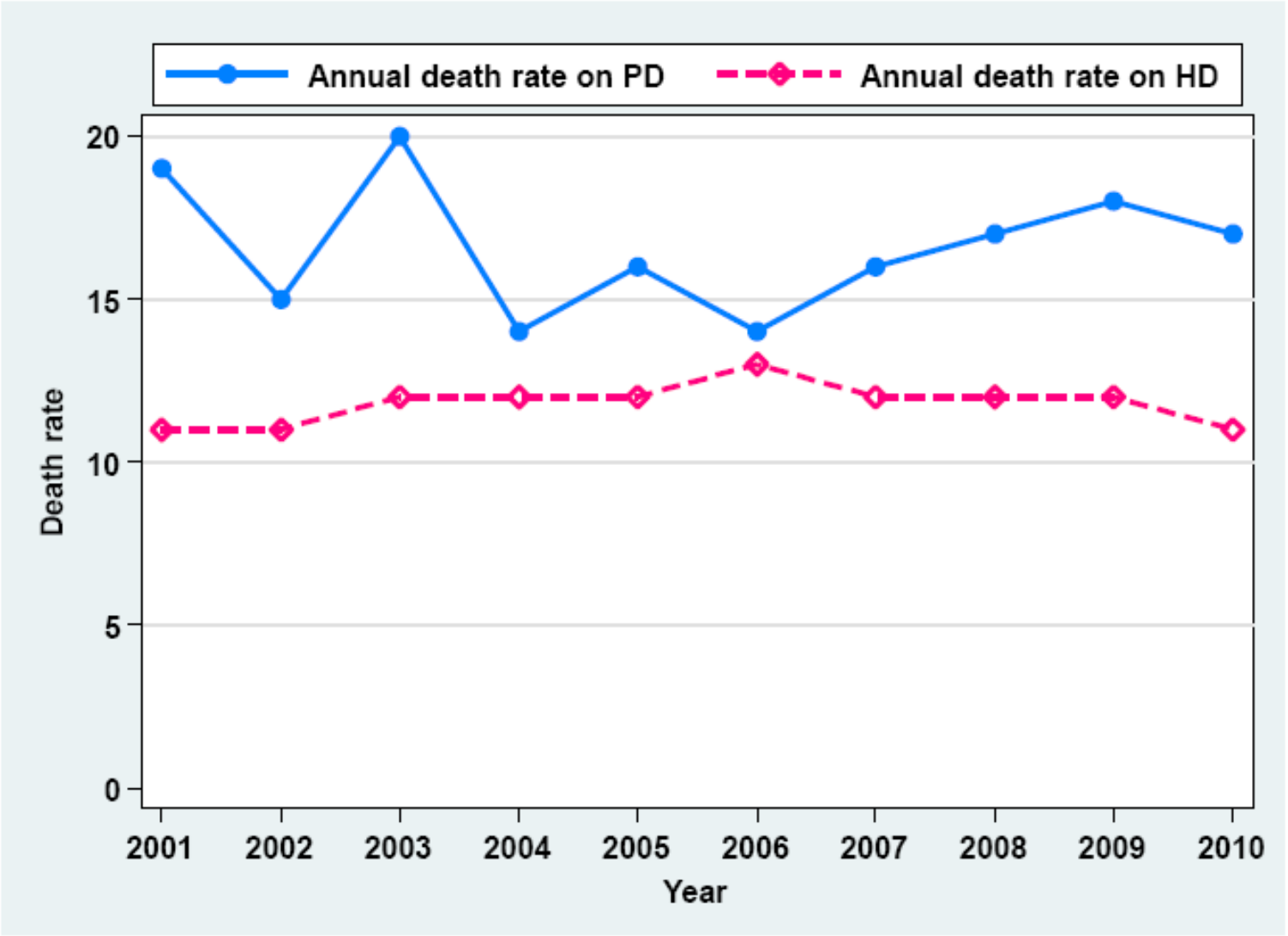
Maurizio Nordio et al 2012,AJKD

Figure 3.2.1(a): Patient survival by dialysis modality analysis (censored for change of modality)



18th MDTR report 2010, Malaysia

Figure 3.1.1: Death Rates on Dialysis 2001-2010



18th MDTR report 2010, Malaysia

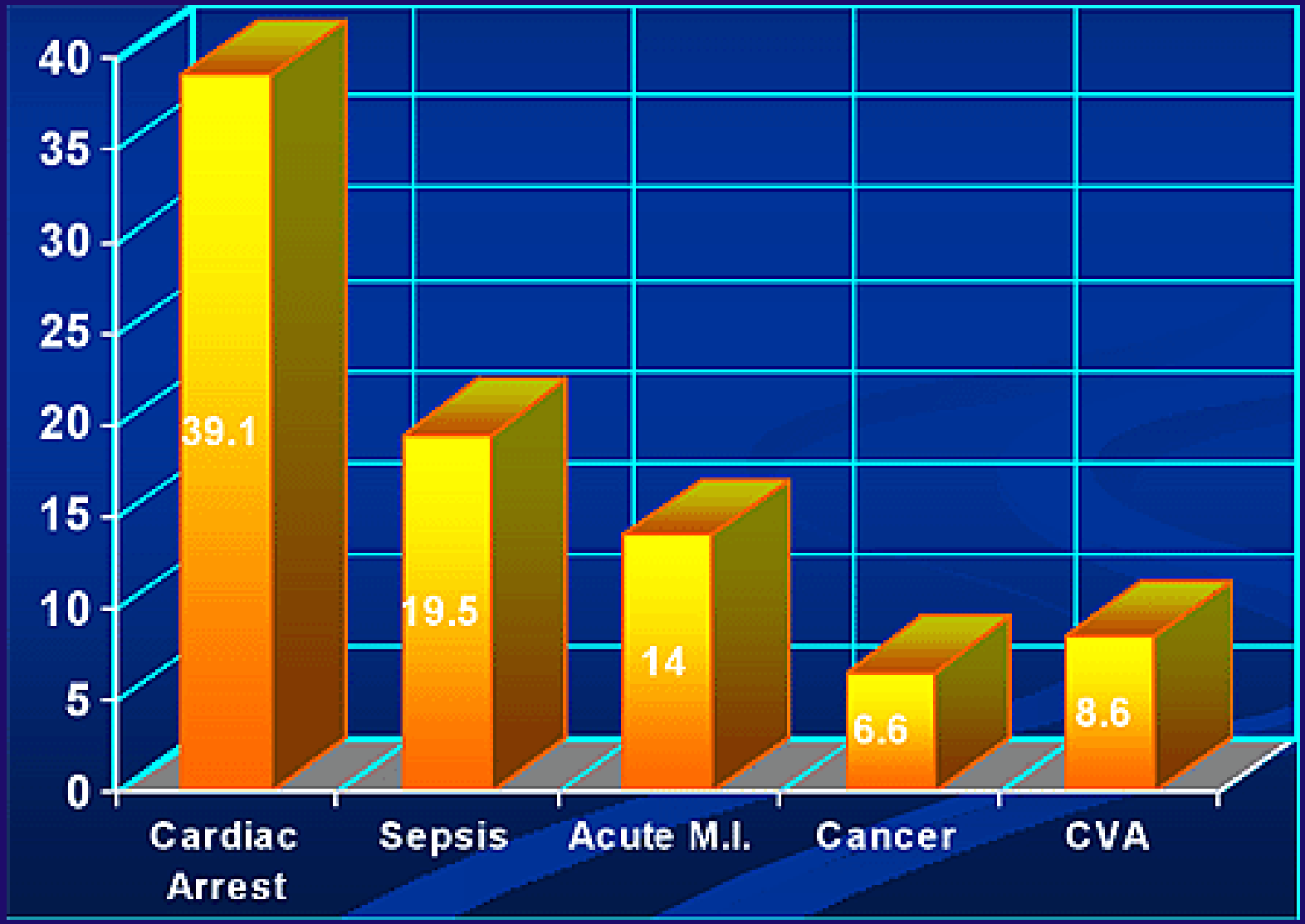
Table 3.1.2: Causes of Death on Dialysis 2001-2010

Year / Causes of Death	2001		2002		2003		2004		2005	
	n	%	n	%	n	%	n	%	n	%
Cardiovascular	221	26	313	33	341	28	341	26	376	25
Died at home	228	27	212	22	290	24	307	23	320	21
Sepsis	134	16	148	15	197	16	166	13	179	12
PD peritonitis	30	4	16	2	14	1	13	1	22	1
GIT bleed	18	2	24	3	29	2	24	2	29	2
Cancer	18	2	18	2	28	2	20	2	28	2
Liver disease	11	1	16	2	25	2	29	2	26	2
Withdrawal	20	2	18	2	26	2	9	1	11	1
Others	89	10	104	11	161	13	325	25	406	27
Unknown	81	10	90	9	100	8	84	6	116	8
TOTAL	850	100	959	100	1211	100	1318	100	1513	100

Year / Causes of Death	2006		2007		2008		2009		2010	
	n	%	n	%	n	%	n	%	n	%
Cardiovascular	517	28	516	26	682	31	871	34	871	34
Died at home	354	20	343	17	423	19	492	19	507	20
Sepsis	235	13	222	11	336	15	570	22	605	24
PD peritonitis	22	1	16	1	25	1	30	1	34	1
GIT bleed	26	1	31	2	43	2	44	2	51	2
Cancer	41	2	34	2	53	2	54	2	69	3
Liver disease	35	2	37	2	44	2	26	1	31	1
Withdrawal	23	1	27	1	24	1	34	1	29	1
Others	392	22	552	28	366	17	195	8	108	4
Unknown	170	9	206	10	194	9	262	10	269	10
TOTAL	1815	100	1984	100	2190	100	2578	100	2574	100

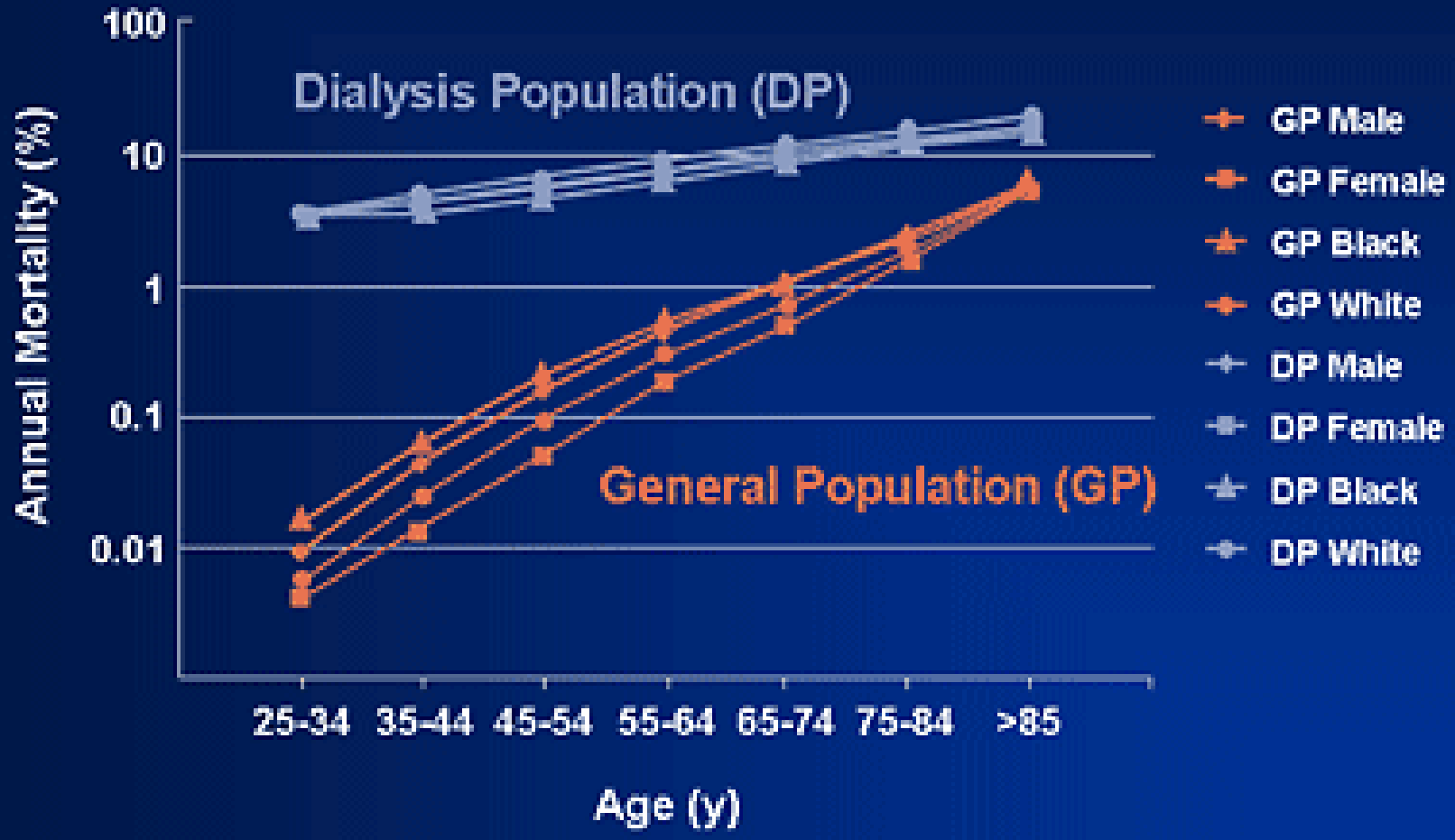
18th MDTR report 2010, Malaysia

Causes of Death in Dialysis



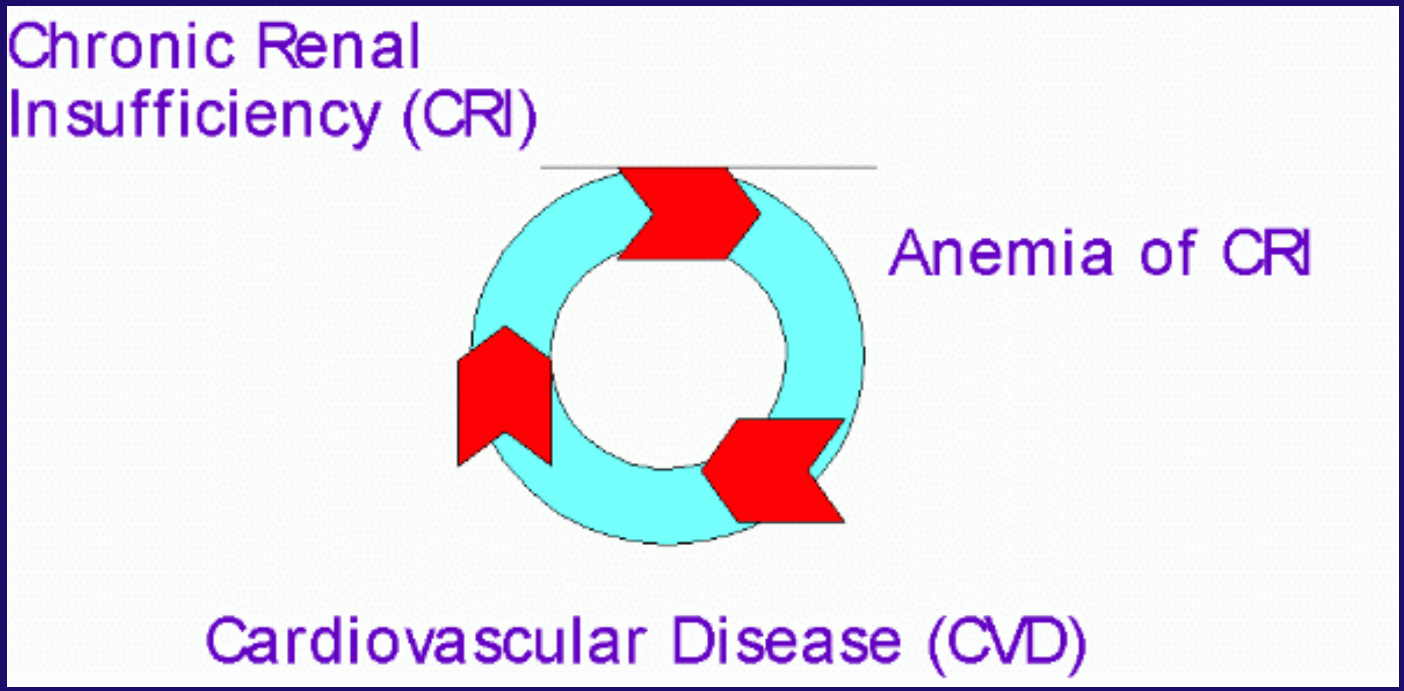
USRDS 2005.

Cardiovascular Mortality



Adapted from Sarnak MJ, et al. *Am J Kidney Dis.* 2000;35(4 suppl 1):S117-S131.

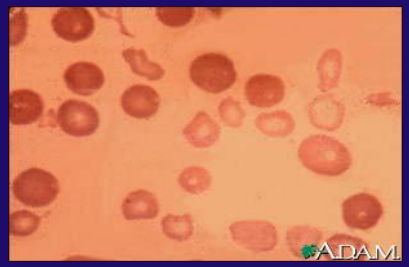
CKD-CVD-Anemia- The Cycle



Cardiovascular Disease (CVS)

Chronic kidney disease (CKD)

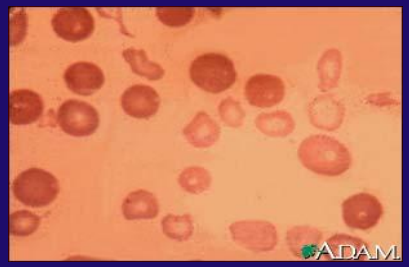
Anemia



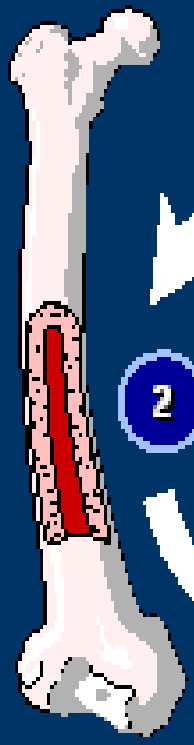
Cardiovascular Disease (CVS)

Chronic kidney disease (CKD)

Anemia

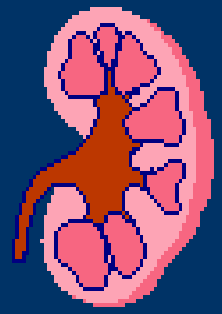


Erythropoiesis



Bone Marrow

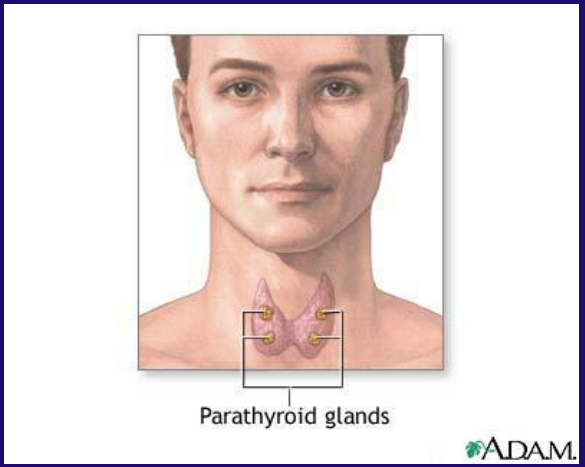
1. Kidney senses hypoxia (anemia) and increases endogenous erythropoietin production
2. Erythropoietin acts on the E-progenitor cells in the bone marrow to produce new red blood cells
3. Kidney senses increased tissue oxygenation
4. Kidney decreases erythropoietin production

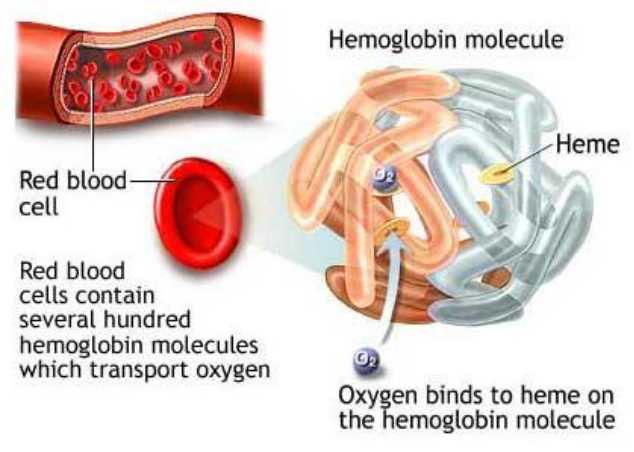


Kidney

Other causes of anemia in CKD

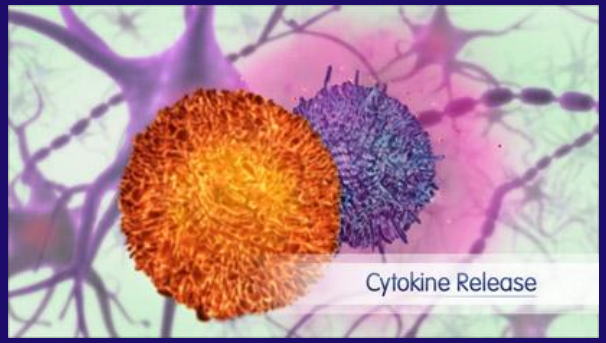
Increased PTH





Chronic Inflammation

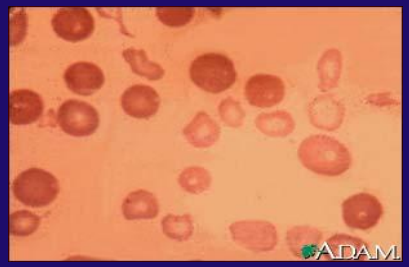
Iron Deficiency



Cardiovascular Disease (CVS)

Chronic kidney disease (CKD)

Anemia

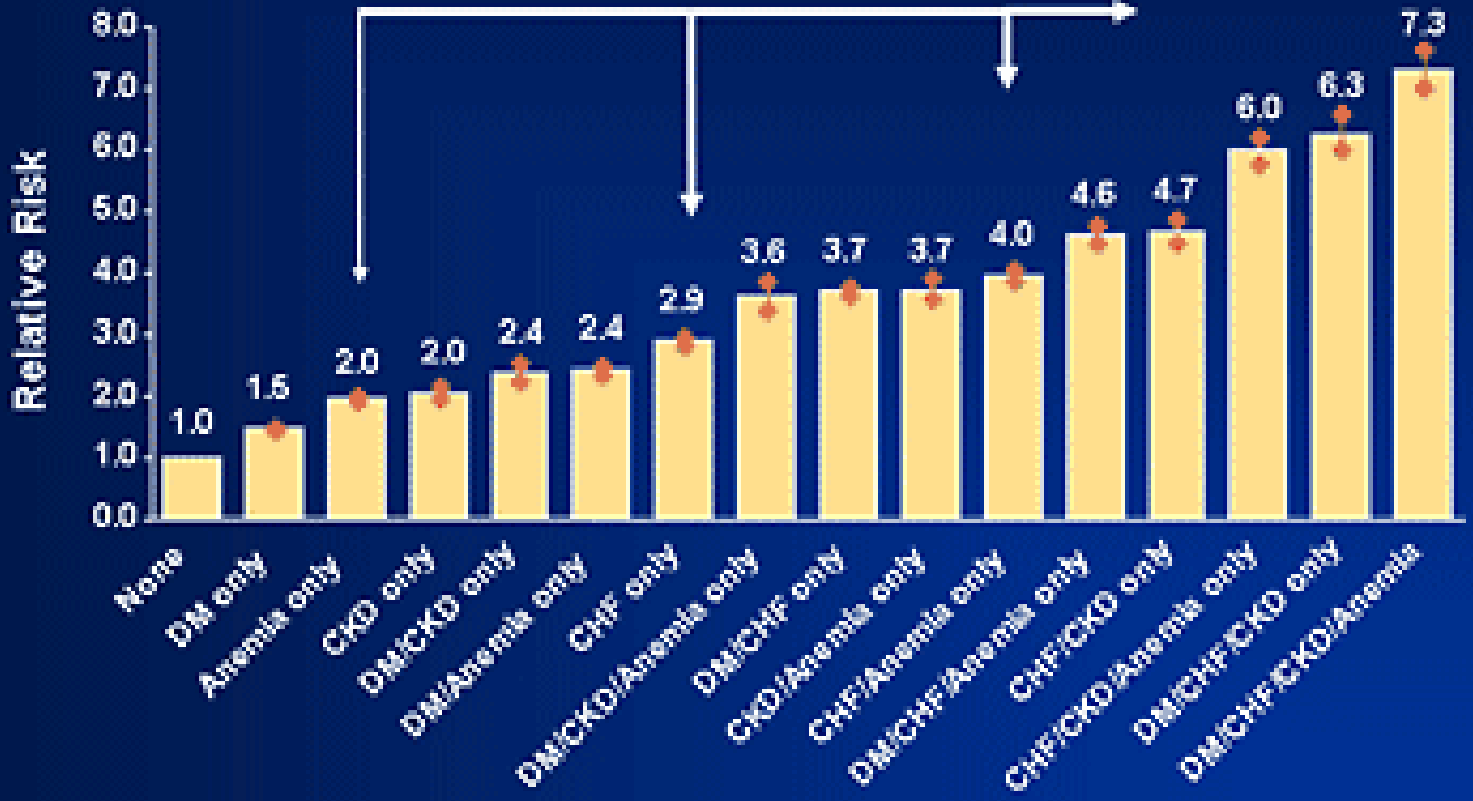


Consequences of Anemia in CKD

- Cardiovascular
  - Left ventricular hypertrophy (LVH)
  - Precipitating factor for congestive heart failure (CHF)
  - Exacerbation of angina
- Reductions in
  - Aerobic capacity
  - Overall well-being
  - Cognition

Ersley AJ. *N Engl J Med.* 1991;324:1339-1344.

Anemia Is a Mortality Multiplier



DM = diabetes mellitus.
Medicare sample (5%) follow-up from 1996 to 1997 of enrollees aged ≥65 years, adjusted for age, sex, and race.

Collins AJ. *Adv Stud Med.* 2003;3(3C):S194-S197.

Left Ventricular Hypertrophy in CKD

- LVH is an independent predictor of cardiac death
- Hypertension, anemia, and diabetes are modifiable predictors of LVH
  - BP increase of 5 mm Hg is associated with 3% increase in LVH risk
  - Hb decrease of 1.0 g/dL is associated with 6% increase in LVH risk

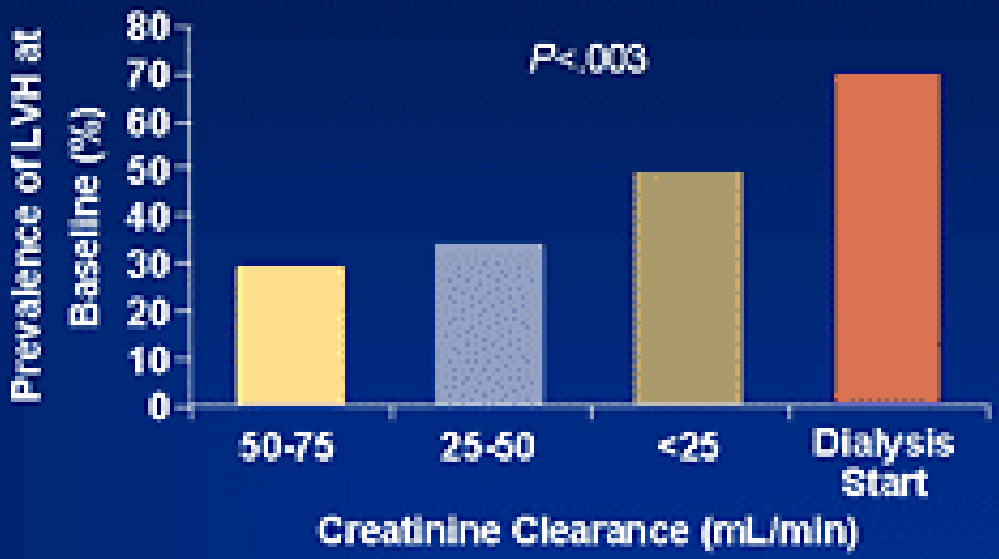
Foley RN, et al. *Kidney Int.* 1995;47:186-192.
Levin A, et al. *Am J Kidney Dis.* 1996;27:347-354.

Cardiovascular Care Is Suboptimal in Patients With CKD

Predictors of LVH

Risk Factors	↑ Risk of LVH
Decrease in Hb by 1.0 g/dL	6%
Increase in systolic BP by 5 mm Hg	3%

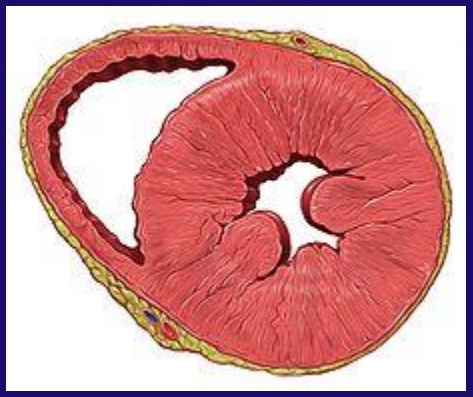
Prevalence of LVH in CKD



- LVH is an independent risk factor for death in patients with ESRD
- 11% of patients with CKD on BP medication have optimal levels

Coresh J, et al. *Arch Intern Med*. 2001;161:1207-1216; Levin A, et al. *Am J Kidney Dis*. 1996;27:347-354; Levin A, et al. *Am J Kidney Dis*. 1999;34:125-134.

Anemia



Left ventricular hypertrophy

Cardiovascular disease

If a cure is not achieved, the kidneys will pass on the disease to the heart

Huang Ti Nei Ching Su Wen
The Yellow Emperor's Classic of Internal Medicine
~2000 B.C.

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

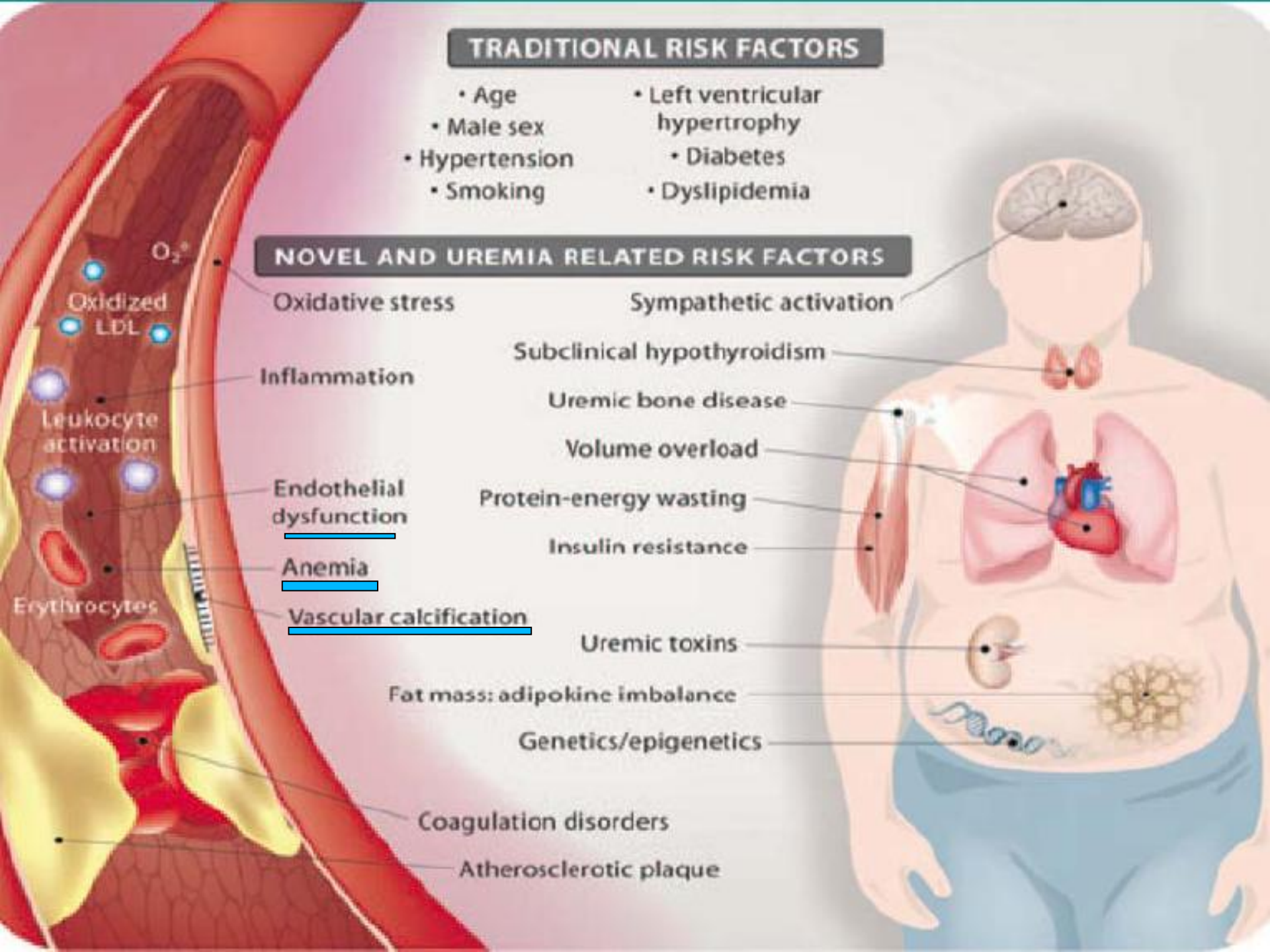
TABLE 6. Traditional and Nontraditional Cardiovascular Risk Factors in CKD

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**


TRADITIONAL RISK FACTORS
• Age
• Male sex
• Hypertension
• Smoking
• Left ventricular hypertrophy
• Diabetes
• Dyslipidemia
NOVEL AND UREMIA RELATED RISK FACTORS
O_2^-
Oxidized LDL
Oxidative stress
Sympathetic activation
Subclinical hypothyroidism
Inflammation
Uremic bone disease
Leukocyte activation
Volume overload
Endothelial dysfunction
Protein-energy wasting
Insulin resistance
Anemia
Erythrocytes
Vascular calcification
Uremic toxins
Fat mass: adipokine imbalance
Genetics/epigenetics
Coagulation disorders
Atherosclerotic plaque

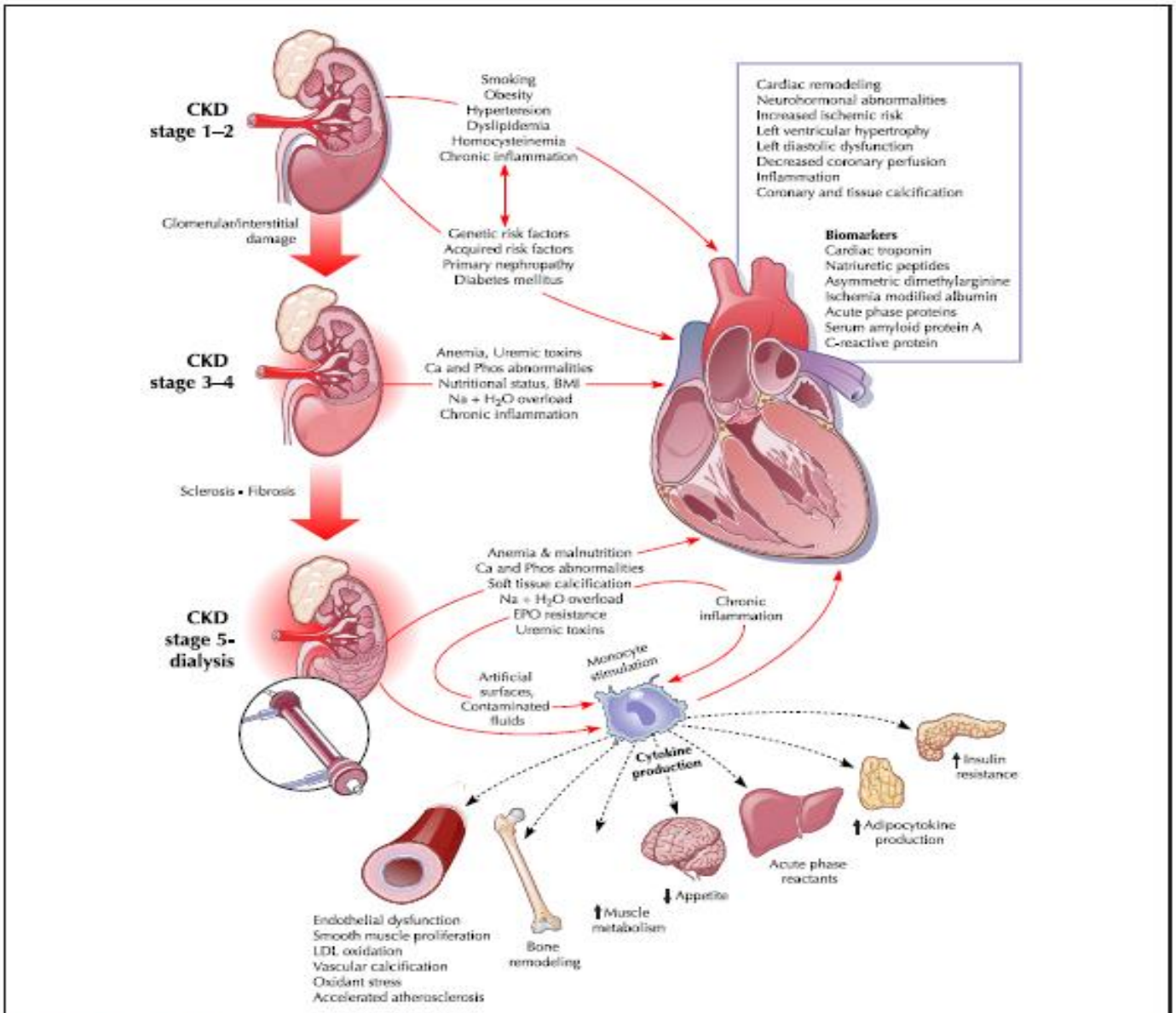


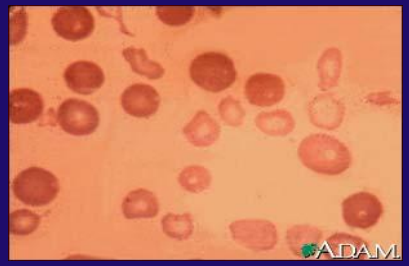
Figure 4 CRS Type 4

Pathophysiological interactions between heart and kidney in type 4 cardiorenal syndrome (CRS) or "chronic renocardiac syndrome" (chronic kidney disease [CKD], e.g., chronic glomerular disease, contributing to decreased cardiac function, cardiac hypertrophy, or increased risk of adverse cardiovascular events). BMI = body mass index; EPO = erythropoietin; LDL = low-density lipoprotein. Figure illustration by Rob Flewell.

Cardiovascular Disease (CVS)

Chronic kidney disease (CKD)

Anemia



Journal of the American College of Cardiology
© 2008 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 52, No. 19, 2008
ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2008.07.051

STATE-OF-THE-ART PAPER

Cardiorenal Syndrome

Claudio Ronco, MD,* Mikko Haapio, MD,† Andrew A. House, MSc, MD,‡ Nagesh Anavekar, MD,§ Rinaldo Bellomo, MD¶

Vicenza, Italy; Helsinki, Finland; London, Ontario, Canada; and Melbourne, Australia

JACC
JOURNAL of the AMERICAN COLLEGE of CARDIOLOGY

The prevalence of renal dysfunction in chronic HF has been reported to be approximately 25%

Chronic HF is likely to be characterized by a long-term situation of reduced renal perfusion, often predisposed by microvascular and macrovascular disease.

Renal insufficiency is highly prevalent among patients with HF and is an independent negative prognostic factor in both diastolic and systolic ventricular dysfunction and severe
HF

Hillege HL, Nitsch D, Pfeffer MA, et al. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. Circulation 2006;113:671– 8.

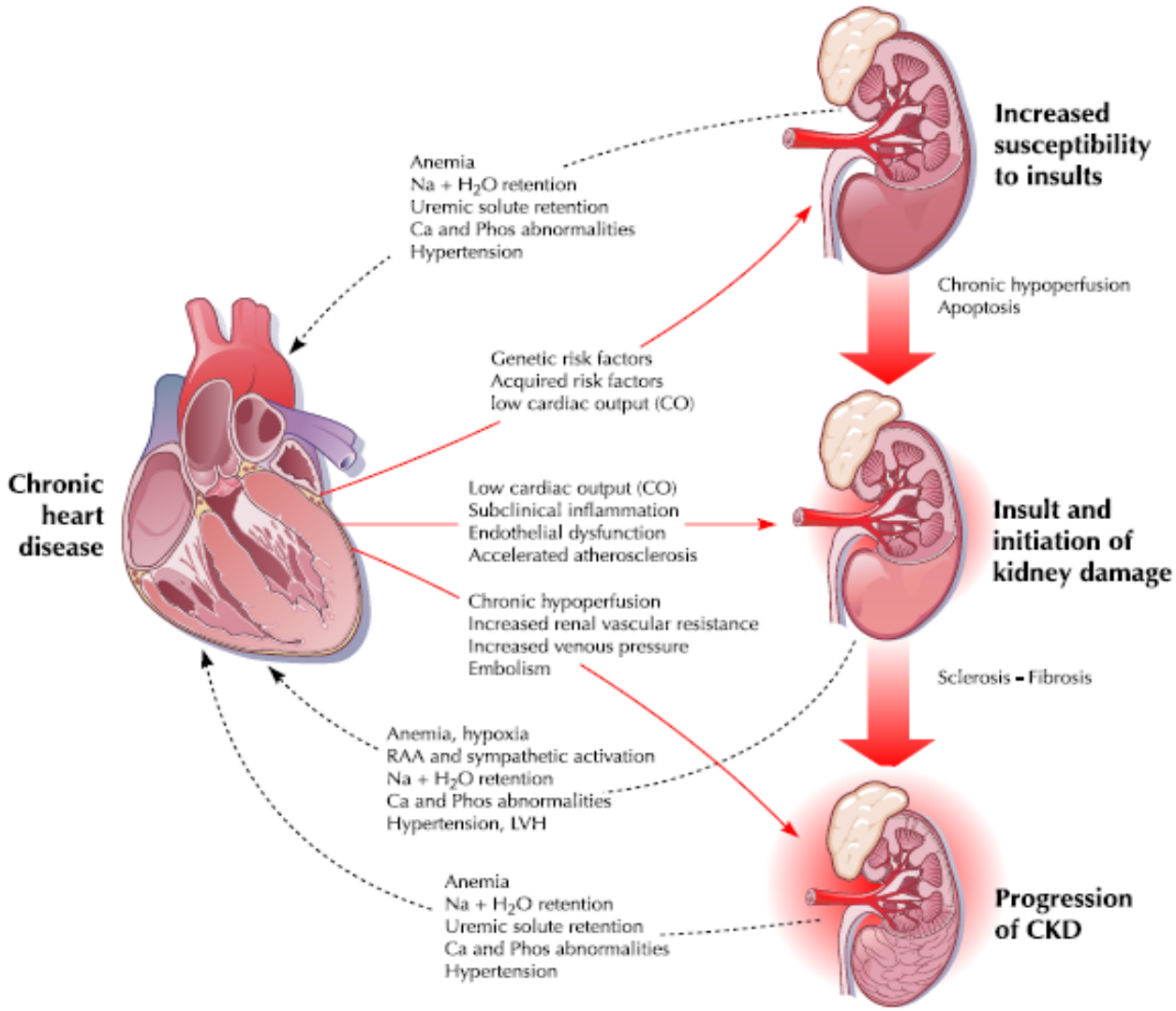


Figure 2 **CRS Type 2**

Pathophysiological interactions between heart and kidney in type 2 cardiorenal syndrome (CRS) or "chronic CRS" (chronic abnormalities in cardiac function, e.g., chronic heart failure) causing progressive chronic kidney disease (CKD). Figure illustration by Rob Flewell. LVH = left ventricular hypertrophy; RAA = renin angiotensin aldosterone.

Conclusion

CVD remains prevalent among CKD patients and contribute to the majority death among chronic dialysis patients.

Interaction between heart and kidney during dysfunction of each or both organs has practical clinical implications and should be addressed in the management.


Protect your kidneys, Save your heart.
World Kidney Day
10 March 2016

THANK YOU