WESTERN CANADA PD DAYS

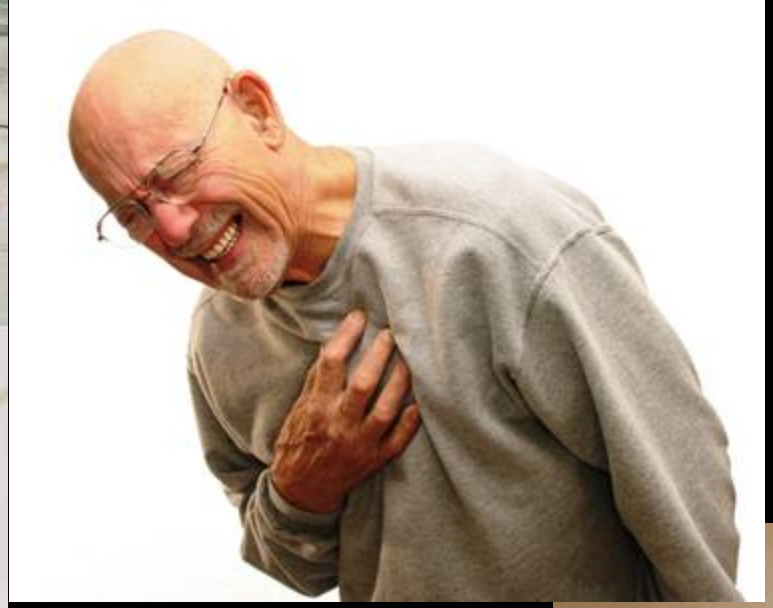
February 7th-9th, 2013

Cardiology and Nephrology – Specialties with Acronyms

The kidney is a 7 mile long artery.

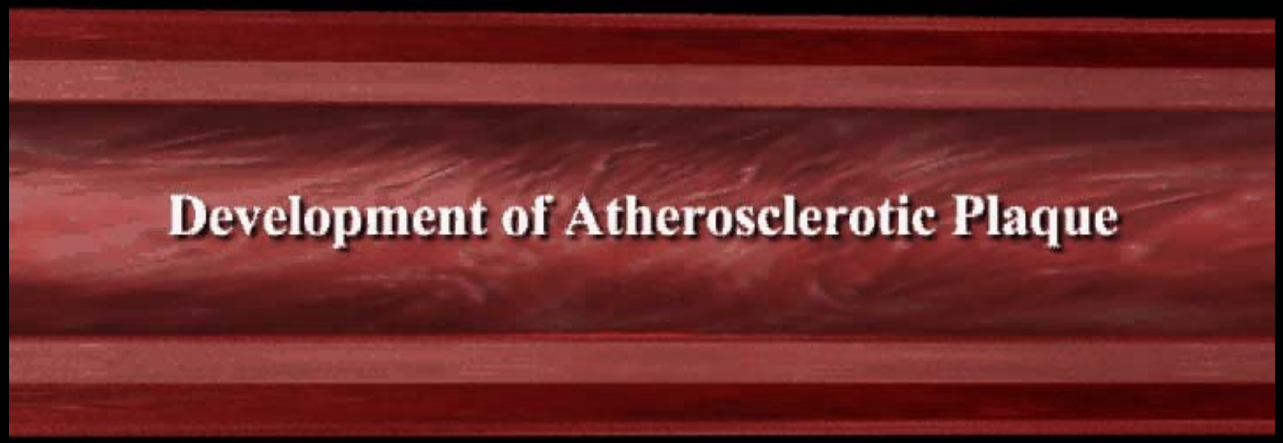
Duality of interest

- Actelion
- Amgen
- AstraZeneca
- Bayer
- Boehringer Ingelheim
- Bristol-Myers-Squibb
- CDN CV Society
- CHRC
- Merck / Schering
- Pfizer
- Sanofi Aventis
- Servier
- University of BC




DRAIN

Development of Atherosclerotic Plaque



Endothelium, platelets, macrophages, protein, cholesterol


Glagov's Model

Conventional vs Contemporary

What is CVD prevention?

"A coordinated set of actions, at public and individual level, aimed at eradicating, eliminating or minimizing the impact of cardiovascular diseases and their related disability.

The bases of prevention are rooted in cardiovascular epidemiology and evidence-based medicine"

A Dictionary of Epidemiology. 4th ed New York: Oxford University Press; 2001.

www.escardio.org/guidelines

European Heart Journal 2012:33;1635–1701
European Journal of Preventive Cardiology 2012;19: 4:585-667

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Why is CVD prevention needed?

Atherosclerotic CVD, especially CHD, remains the leading cause of premature death worldwide.

CVD affects both men and women; of all deaths that occur before the age of 75 years in Europe, 42% are due to CVD in women and 38% in men.

Prevention works: over 50% of the reductions seen in CHD mortality relate to changes in risk factors, and 40% to improved treatments.

www.escardio.org/guidelines

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European Journal of Preventive Cardiology 2012;19: 4:585-667

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For whom is CVD prevention needed

Recommendations regarding risk estimation	Class	Level	GRADE
Total risk estimation using multiple risk factors (such as SCORE) is recommended for asymptomatic adults without evidence of CVD.	I	C	Strong
High-risk individuals can be detected on the basis of established CVD, diabetes type 2 or type 1 with end-organ damage, moderate to severe renal disease, very high levels of individual risk factors or a high SCORE risk.	I	C	Strong

www.escardio.org/guidelines

European Heart Journal 2012:33;1635–1701
European Journal of Preventive Cardiology 2012;19: 4:585-667

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Hyperlipidemia

	Class	Level	GRADE
The recommended target levels are <5 mmol/L (<~ 190 mg/dL) for total plasma cholesterol and <3 mmol/L (<~ 115 mg/dL) for LDL cholesterol for subjects at low or moderate risk.	I	A	Strong
In patients at high CVD risk, a LDL-cholesterol goal <2.5 mmol/L (<~ 100 mg/dL) is recommended.	I	A	Strong
In patients at very high CVD risk, the recommended LDL cholesterol target is <1.8 mmol/L (<~ 70 mg/dL) or a ≥50% LDL-cholesterol reduction when the target level cannot be reached.	I	A	Strong
recognized as high-risk patients and be treated with lipid-lowering therapy.	I	A	Strong
In patients with an ACS, statin treatment in high doses has to be initiated while the patients are in the hospital.	I	A	Strong

www.escardio.org/guidelines

European Heart Journal 2012:33;1635–1701
European Journal of Preventive Cardiology 2012;19: 4:585-667

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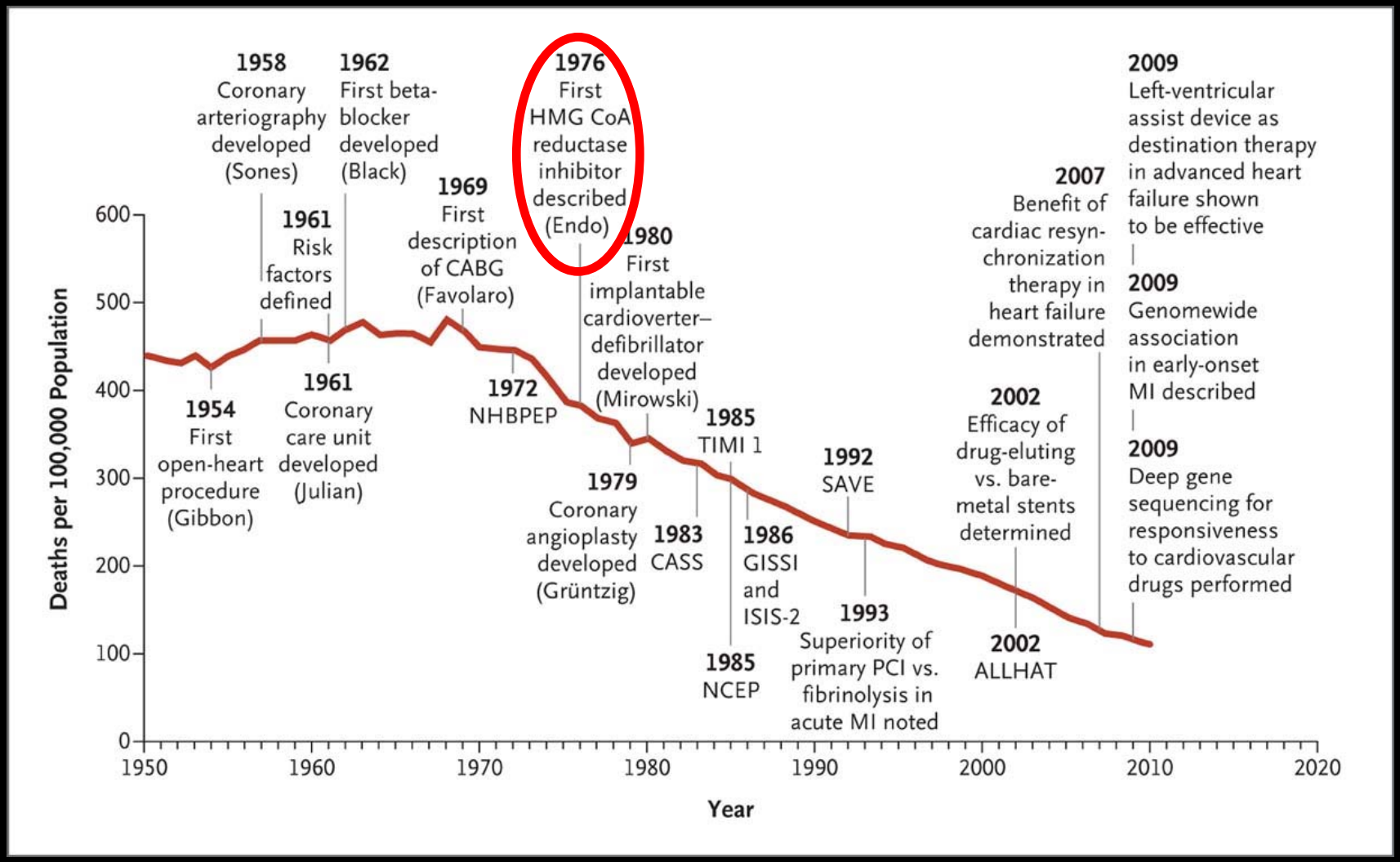
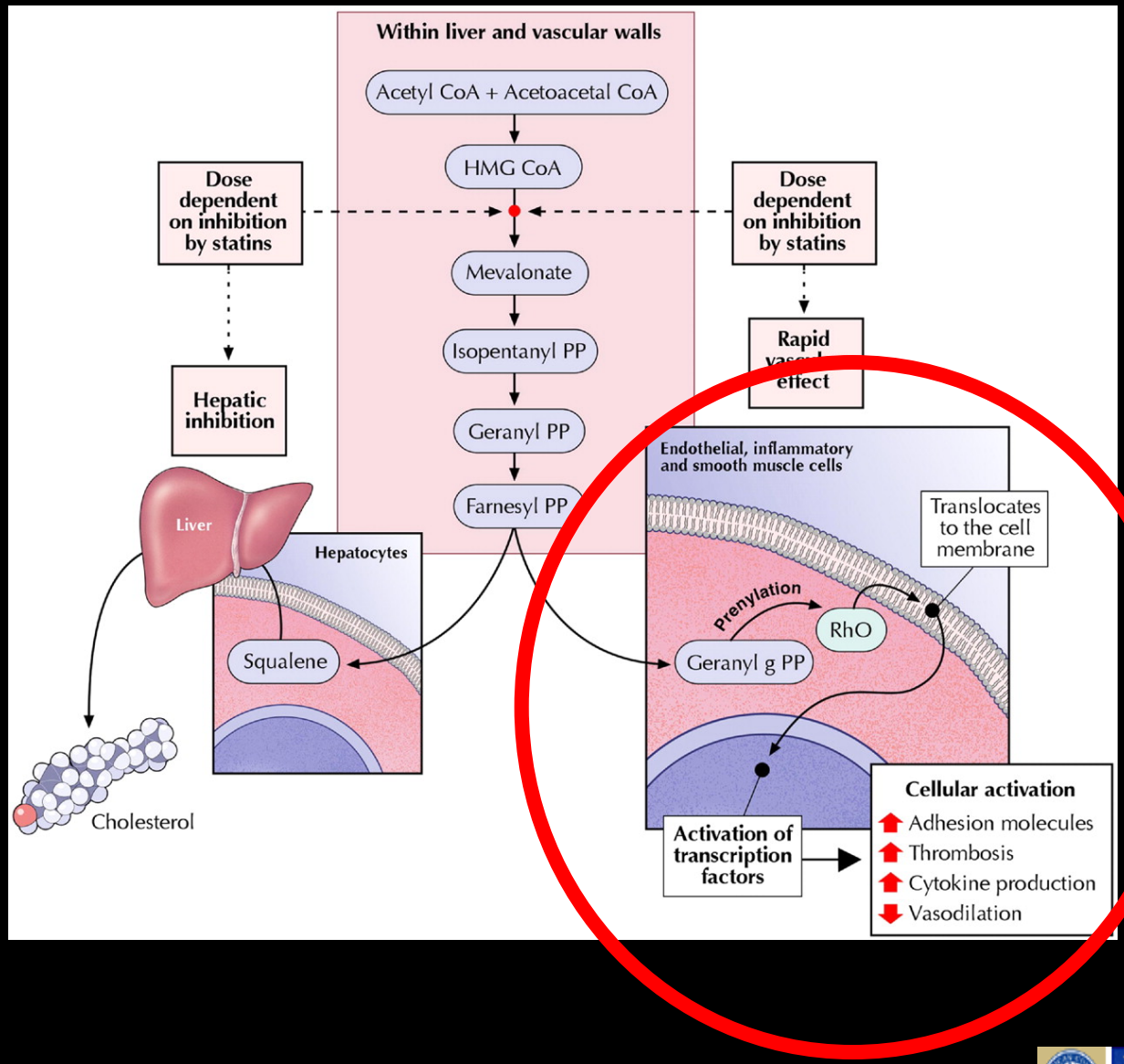
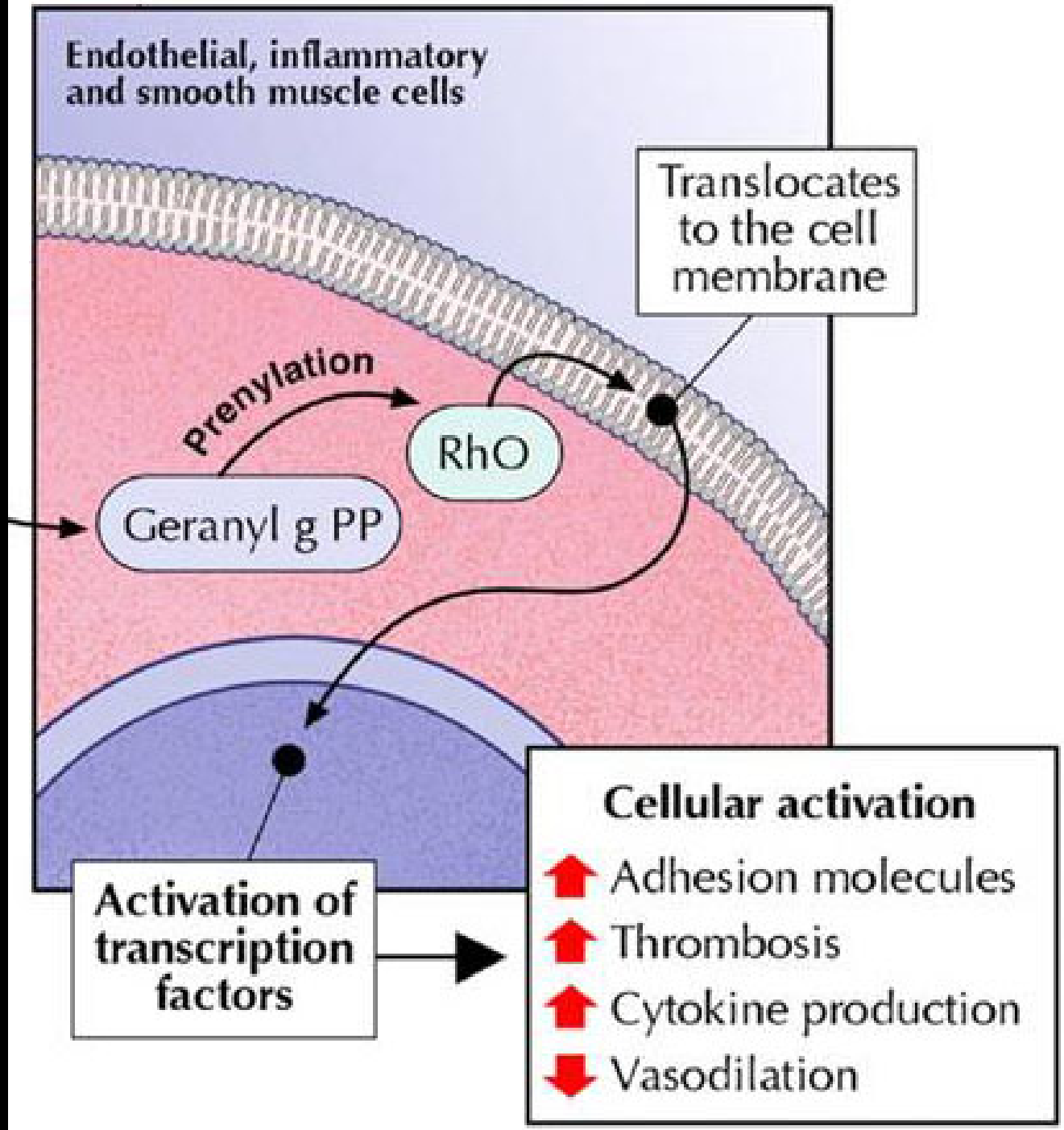
Decline in Deaths from Cardiovascular Disease in Relation to Scientific Advances.



Nabel EG, Braunwald E. N Engl J Med 2012;366:54-63

The NEW ENGLAND JOURNAL of MEDICINE




Endothelial, inflammatory and smooth muscle cells
Translocates to the cell membrane
Prenylation
RhO
Geranyl g PP
Activation of transcription factors
Cellular activation
Adhesion molecules
Thrombosis
Cytokine production
Vasodilation

Now on to the kidnies

From: The Scope of Coronary Heart Disease in Patients With Chronic Kidney Disease

J Am Coll Cardiol. 2009;53(23):2129-2140. doi:10.1016/j.jacc.2009.02.047

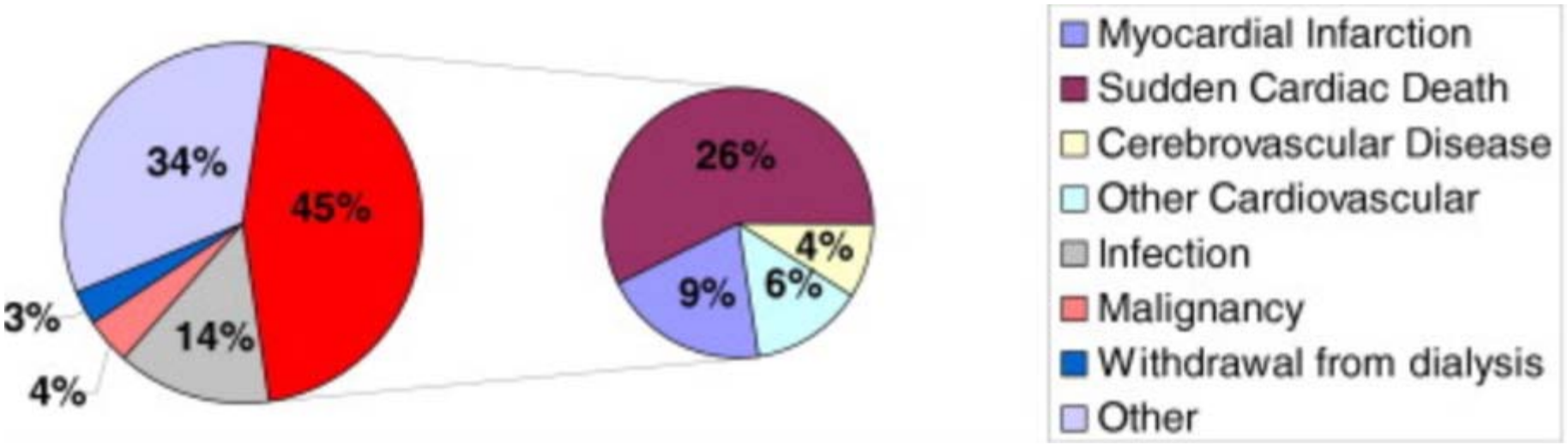


Figure Legend:

The Distribution of the Causes of Death in Patients With End-Stage Renal Disease in the U.S. Between 2003 and 2005 Cardiovascular disease accounts for 45% of all-cause mortality, including 26% from sudden cardiac death. Data are from the U.S. Renal Data System (10). In the figure, myocardial infarction refers to death that was labeled secondary to acute myocardial infarction or atherosclerotic heart disease, whereas sudden cardiac death refers to those labeled cardiac arrest or cardiac arrhythmias.

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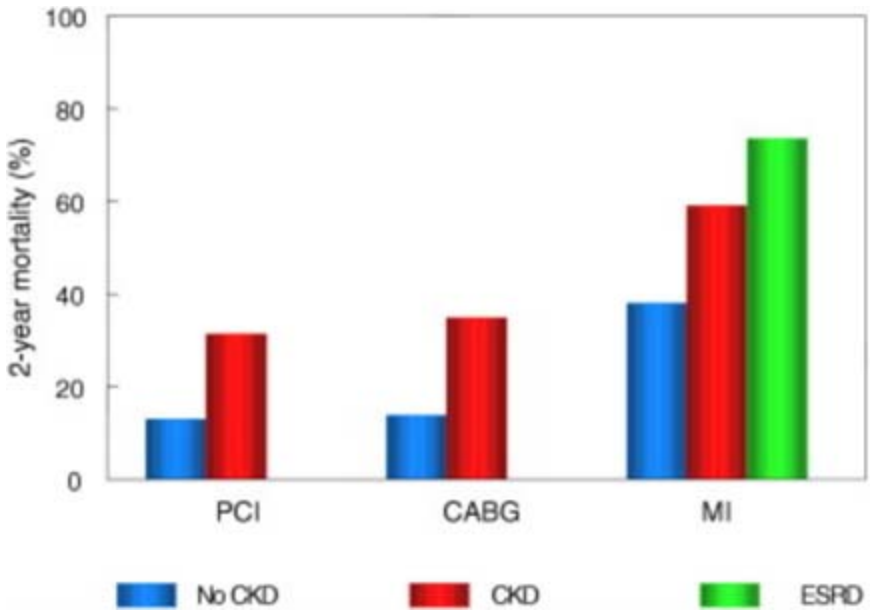


Figure Legend:

Mortality Is Increased in CKD Patients After MI, PCI, and CABG The 2-year mortality of Medicare patients (age 66 or older on the day of the event or treatment) after receiving first percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) or after incident myocardial infarction (MI) between the years 2000 and 2005 is higher in chronic kidney disease (CKD) patients than non-CKD patients. The mortality of end-stage renal disease (ESRD) patients hospitalized for MI reaches 73% to 74% at 2 years. This figure is based on data from the U.S. Renal Data System. USRDS 2008 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the U.S. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2008.

JASN®
Journal of the
American Society of Nephrology

The Clinical Epidemiology of Cardiac Disease in Chronic Renal Failure

Cardiac risk factors in chronic uremia

Traditional Cardiac Risk Factors	Risk Factors Altered by Uremia	Uremia-Related Risk Factors
Hypertension[a]	Dyslipidemia	Hemodynamic overload
Hyperlipidemia[a]	High lipoprotein(a)[a]	Anemia[a]
Diabetes mellitus[a]	Prothrombotic factors	Increased oxidant stress
Tobacco use[a]	Hyperhomocysteinemia	Hypoalbuminemia[a]
Physical inactivity		Inadequate dialysis
		Divalent ion abnormalities
		Metabolic acidosis
		Hypo/hyperkalemia

[a]Evidence available from longitudinal studies that demonstrated a significant risk for future cardiac events in chronic uremia.

Independent risk factors for the development of *de novo* ischemic heart disease in dialysis patients ([8])[a]

Parameter	Adjusted Relative Risk	*P* Value
Age (per year)	1.05	<0.001
Diabetes mellitus	3.97	<0.001
Echocardiographic diagnosis		
normal reference group		
concentric LVH	5.92	0.01
LV dilation	5.35	0.02
systolic dysfunction	12.2	0.002
Diastolic BP (per mmHg increase)	1.04	0.03
Serum albumin (per g/L increase)	0.93	0.03
Hemoglobin	NS	NS

[a]LVH, left ventricular hypertrophy; LV, left ventricular.

Risk Factors for Cardiac Disease in Patient with CKD

Sarnak. *Am J Kidney Dis*. 2000;35(suppl 1):S117
Block. *Am J Kidney Dis*. 1998;131:607
Kitiyakara. *Curr Opin Nephrol Hypertens*. 2000;9:477

Chronic kidney disease (CKD) should be considered a CHD equivalent

Randomized prospective studies report consistent and robust improvements in CVS outcomes with normal kidney function at increased risk of adverse CV events.

Meta-analyses and post-hoc analyses of studies of patients with mild to moderate renal dysfunction have also noted benefits with statin therapy

Secondary prevention of CVD in ESRD on dialysis

Trials of statin therapy in dialysis

- 4-D trial

4D trial: Primary end point

End point	Placebo	Atorvastatin	RR (95% CI)	p
CV death, nonfatal MI, or stroke (n)	243	226	0.92 (0.77-1.1)	0.37

Wanner C. American Society of Nephrology 37th Annual Meeting and Scientific Exposition; October 29-November 1, 2004; St Louis, MO.

4D trial: Component primary end point events

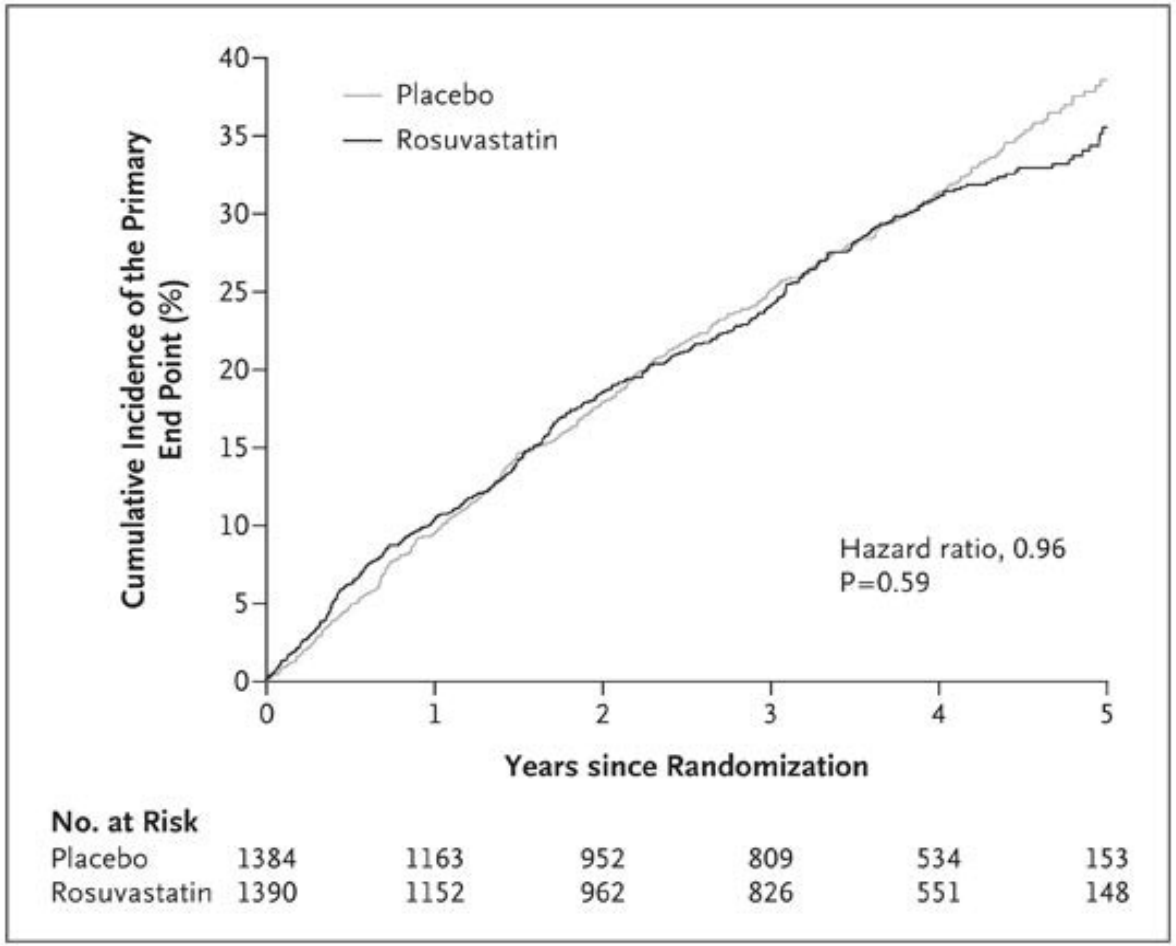
End point	Placebo	Atorvastatin
CV death (n)	129	104
Nonfatal MI (n)	76	69
Stroke (n)	38	53

Wanner C. American Society of Nephrology 37th Annual Meeting and Scientific Exposition; October 29-November 1, 2004; St Louis, MO.

Trials of statin therapy in dialysis

- 4-D trial
- AURORA trial

Kaplan–Meier Curves for the Primary End Point in the Two Study Groups.



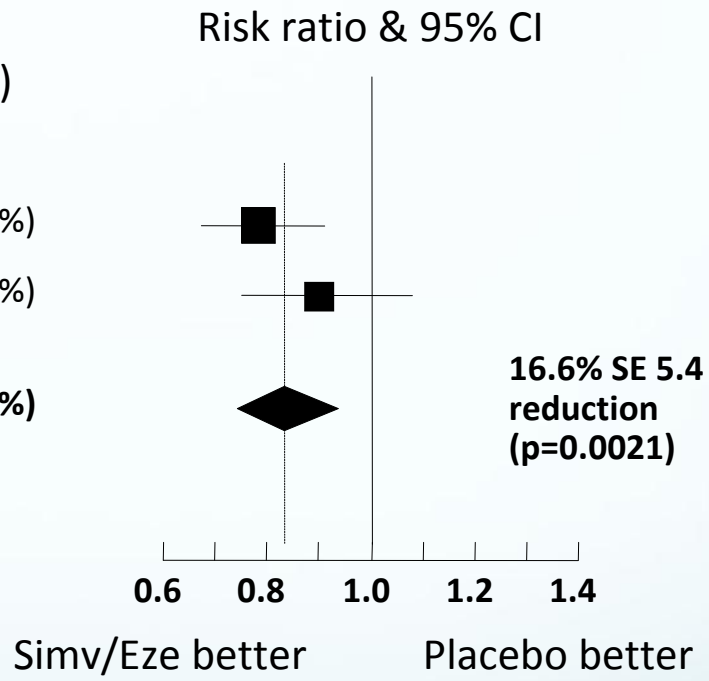
Fellström BC et al. N Engl J Med 2009;360:1395-1407.

Trials of statin therapy in dialysis

- 4-D trial
- AURORA trial
- SHARP trial

SHARP: Major Atherosclerotic Events by renal status

	Simv/Eze (n=4650)		Placebo (n=4620)	
Non-dialysis (n=6247)	296	(9.5%)	373	(11.9%)
Dialysis (n=3023)	230	(15.0%)	246	(16.5%)
Major Atherosclerotic Event	**526**	**(11.3%)**	**619**	**(13.4%)**



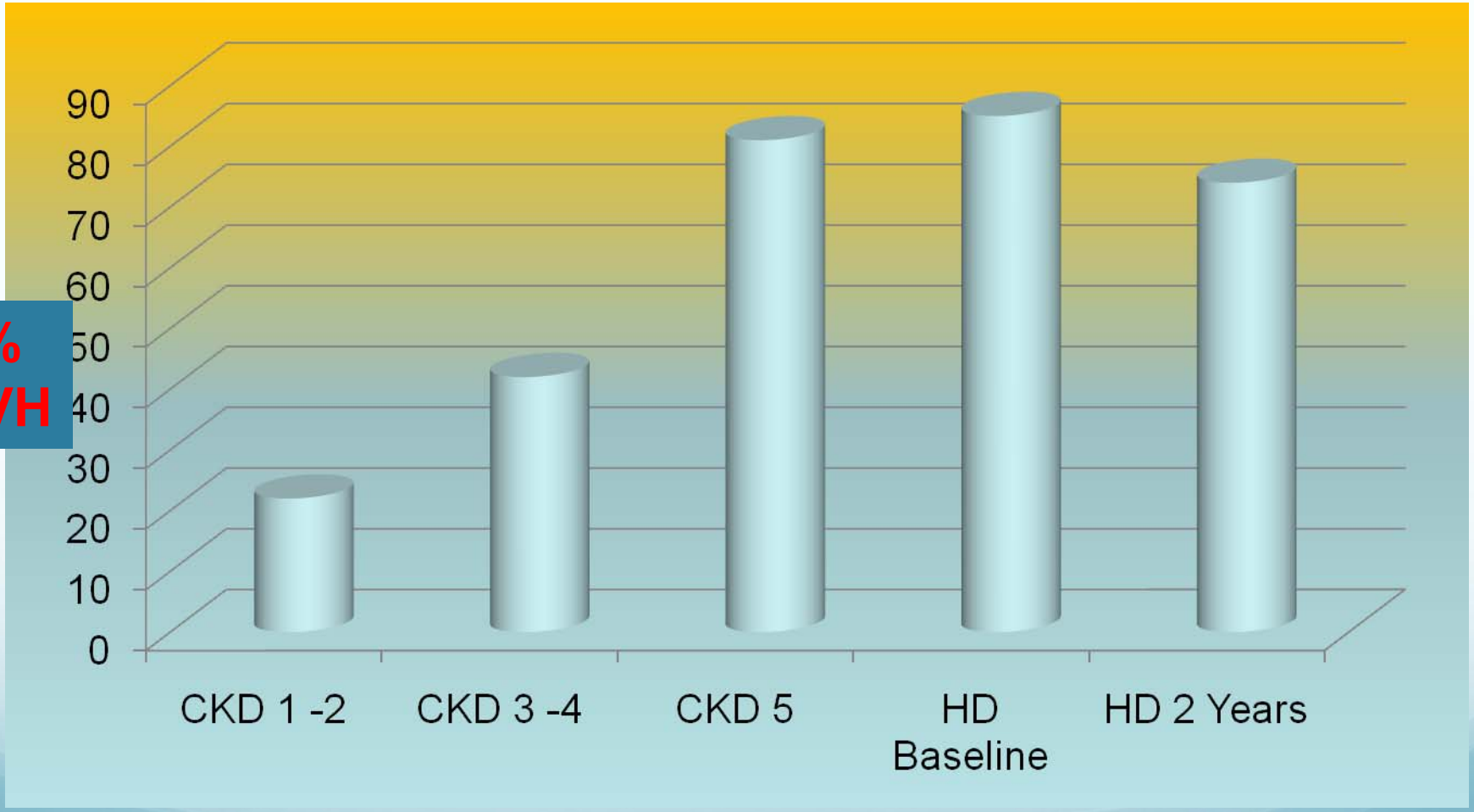
No significant heterogeneity between non-dialysis and dialysis patients (p=0.25)

How could these results possibly occur?

Is the patient on PD metabolically different than the non dialyzed patient?

Atherosclerotic CVD is apparently not the leading cause of CV death in patients on dialysis!!

It's LVH and Cardiomyopathy



glassock

JACC Journals

From: The Scope of Coronary Heart Disease in Patients With Chronic Kidney Disease

J Am Coll Cardiol. 2009;53(23):2129-2140. doi:10.1016/j.jacc.2009.02.047

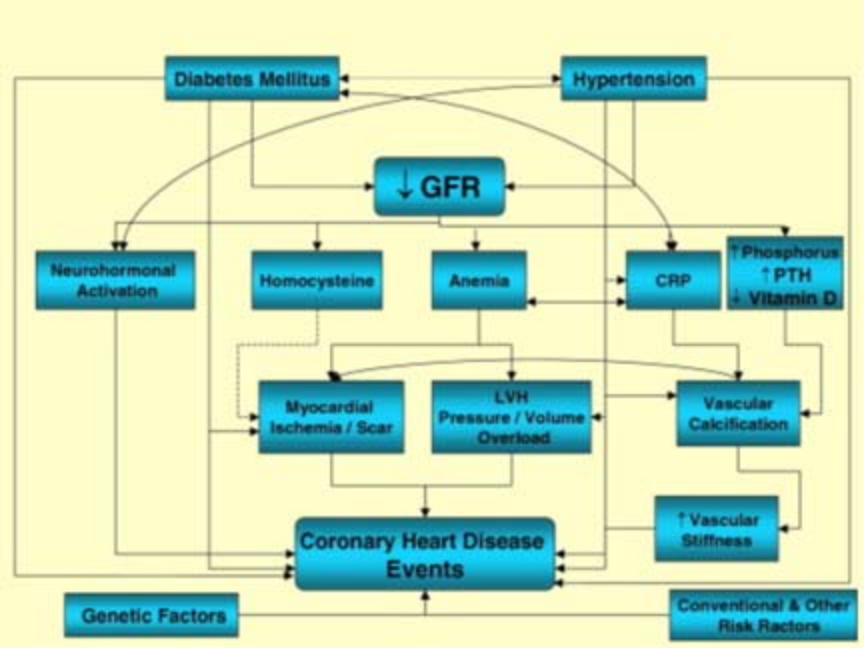
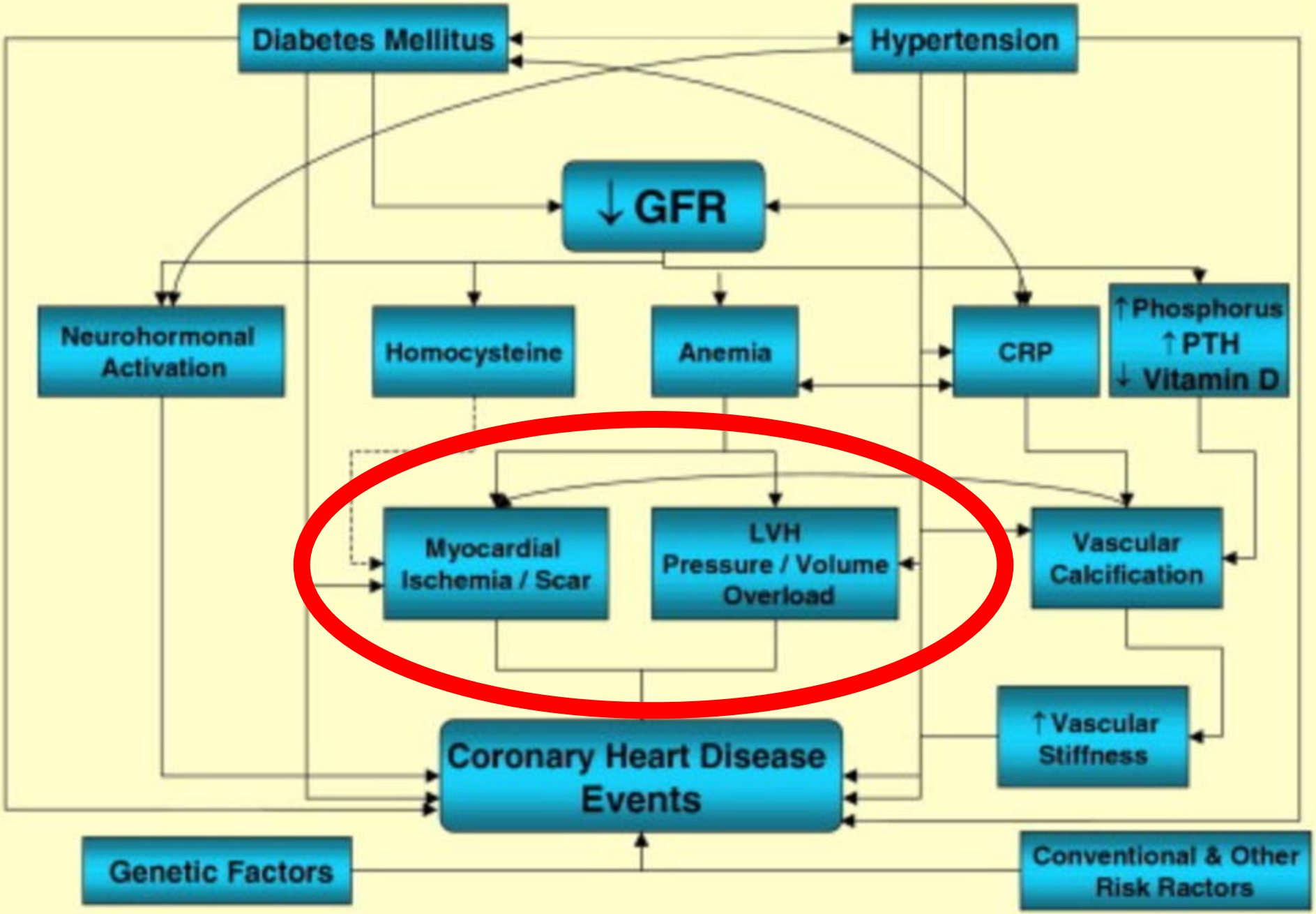


Figure Legend:

The Association Between Chronic Kidney Disease and Cardiovascular Events The relationship between chronic kidney disease and cardiovascular events is complex and is mediated via multiple pathways that are further explained in the CHD Risk Factors section. "Other risk factors" refers to several risk factors that are not directly related to decreased glomerular filtration rate (GFR) per se but are more common in patients with chronic kidney disease. CRP = C-reactive protein; LVH = left ventricular hypertrophy; PTH = parathyroid hormone.


Diabetes Mellitus
Hypertension
↓ GFR
Neurohormonal Activation
Homocysteine
Anemia
CRP
↑ Phosphorus
↑ PTH
↓ Vitamin D
Myocardial Ischemia / Scar
LVH Pressure / Volume Overload
Vascular Calcification
↑ Vascular Stiffness
Coronary Heart Disease Events
Genetic Factors
Conventional & Other Risk Factors

The Core Issues: LV Disease

- LV mass disease progresses as CKD progresses (not inevitably)
- Increased LV Mass is very prevalent in the incident ESRD patient (70%), with only minimal to modest improvement with conventional in-center HD (A bit better with PD)
- Non regressors have a very poor prognosis

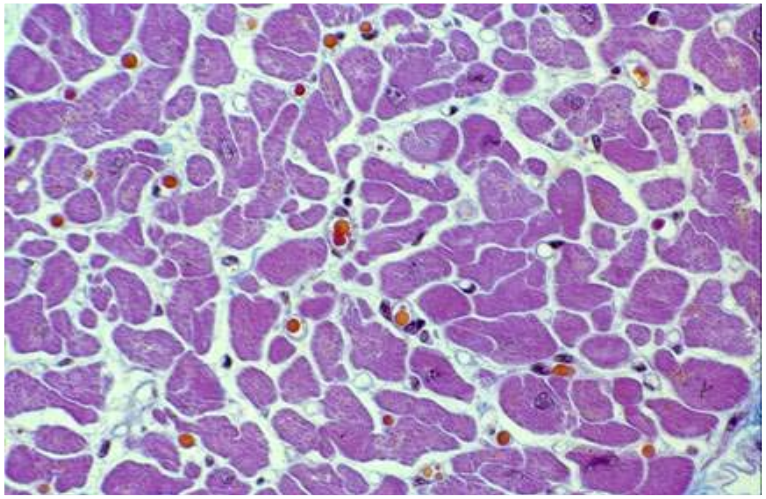
Glassock

Three of every four deaths and hospitalizations in dialysis patients can be linked to *sudden death or CHF*

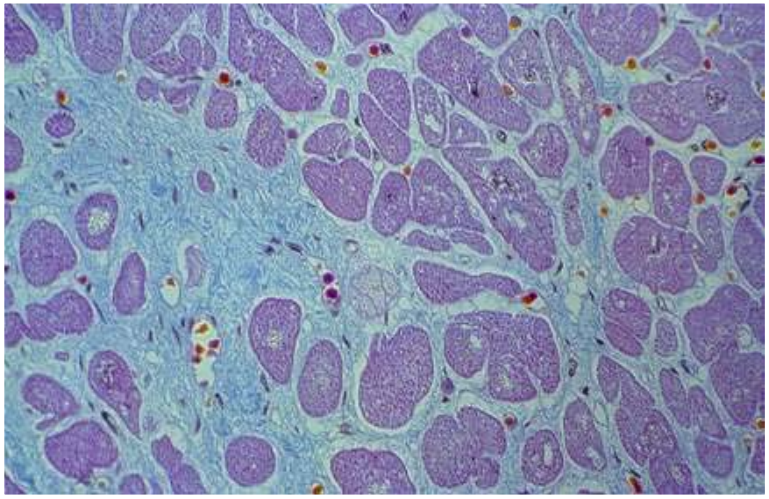
Left Ventricular in Origin

Glassock

Myocardial changes in patients with renal failure



normal morphology

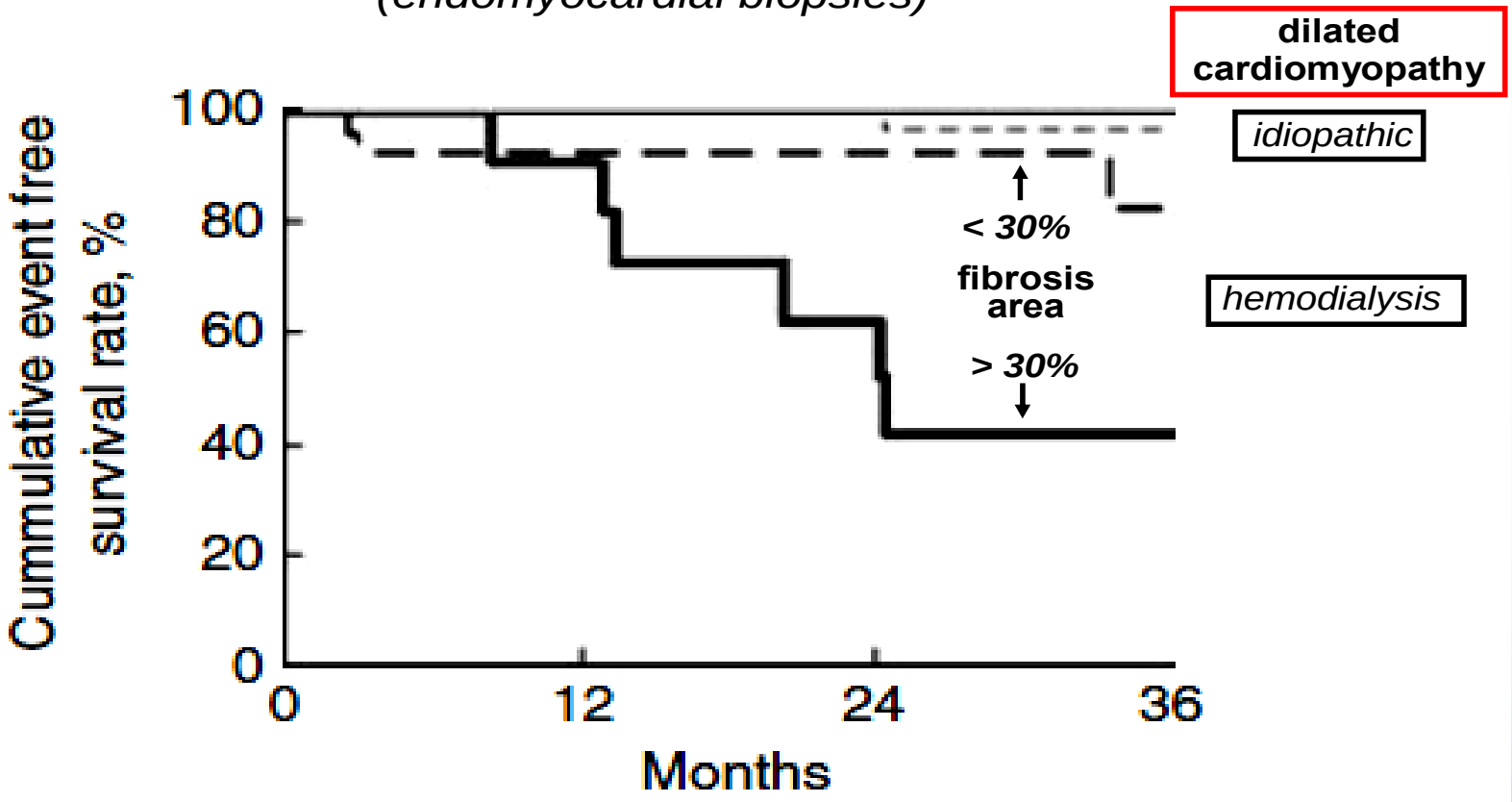


morphology of the myocardium of a patient with chronic renal failure

Cardiac fibrosis –

most powerful predictor of survival in HD patients

(endomyocardial biopsies)



Aoki, Kidn.Internat.(2005) 67:333

Ritz

Leading Causes of LV Muscle and Fibrotic Disease

- Hypervolemia
- Hypertension
- Inflammation (likely caused by hypervolemia)
- Cardiac stunning during overly aggressive ultrafiltration because of shortened dialysis

Volume Overload and LVH

- In experimental spontaneous hypertension, LV Mass increase is ***linked*** to volume expansion and salt intake, ***not to blood pressure***
- Salt-loading may increase LV mass through ***local effects*** (augmentation of A-II effects and TGFβ)

(Varagic J. et al Am J Physiol Heart Circ Physiol 290:Hi503, 2006; Wu HCM, et al Circulation 98:2621, 1998))

Consequences of LVH and cardiac fibrosis

- CHF
  - Difficulty attaining euvolemia with short Rx time
  - Because of ongoing hypervolemia, it is the leading cause of hospitalizations and death, especially in the first year, but ongoing.
  - High cause of re-hospitalization
- Arrhythmias
  - Fibrous tissue encircling myocytes with high electrical resistance; local delay of the spreading front of the action potential
    - Favors “re-entry” type of atrial and ventricular ARRYTHMIAS with high hospitalization and death

SUMMARY

- Do not initiate statin therapy in dialysis patients with mild or moderate increase in LDL-cholesterol
- Continue statin therapy in patients already receiving these agents (this is debated by some clinicians)
- These recommendations do not apply to patients with CKD who are not on dialysis

OBM


Thanks for listening.