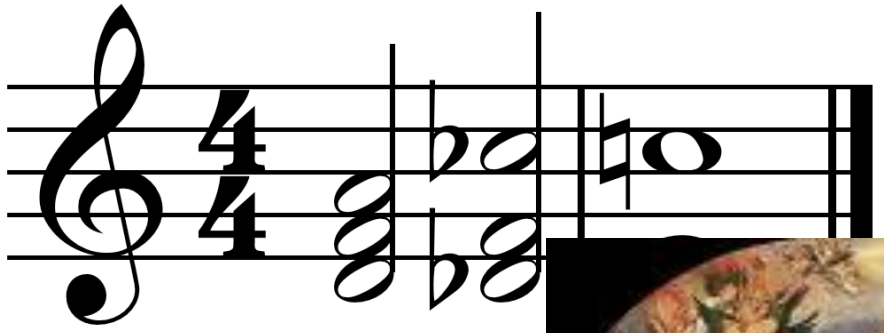
Cardio-renal disease and *diabetes*: Is one a subset of the other?

David Goldsmith
London, UK

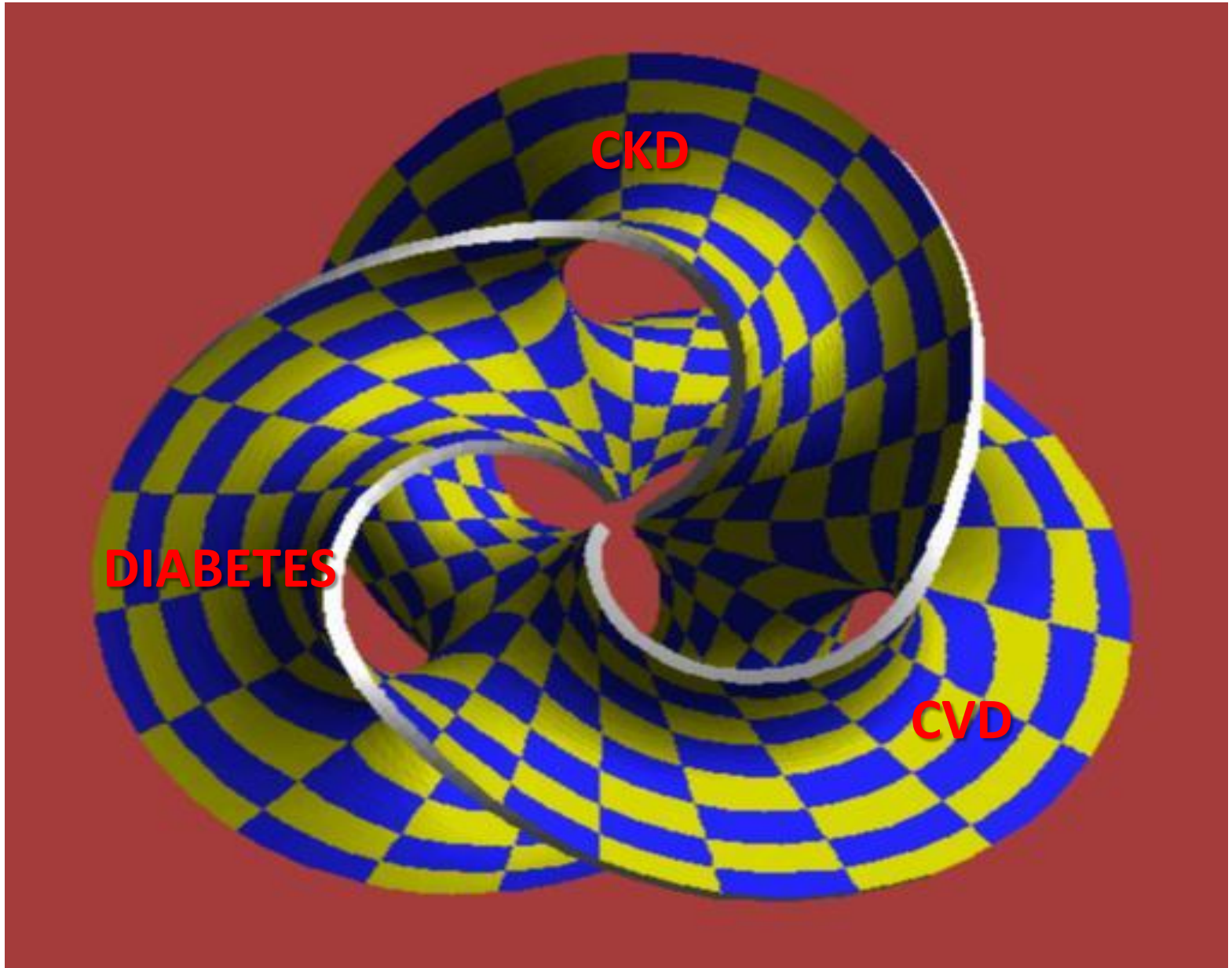
ABCD meeting, RCP London, Autumn 2014

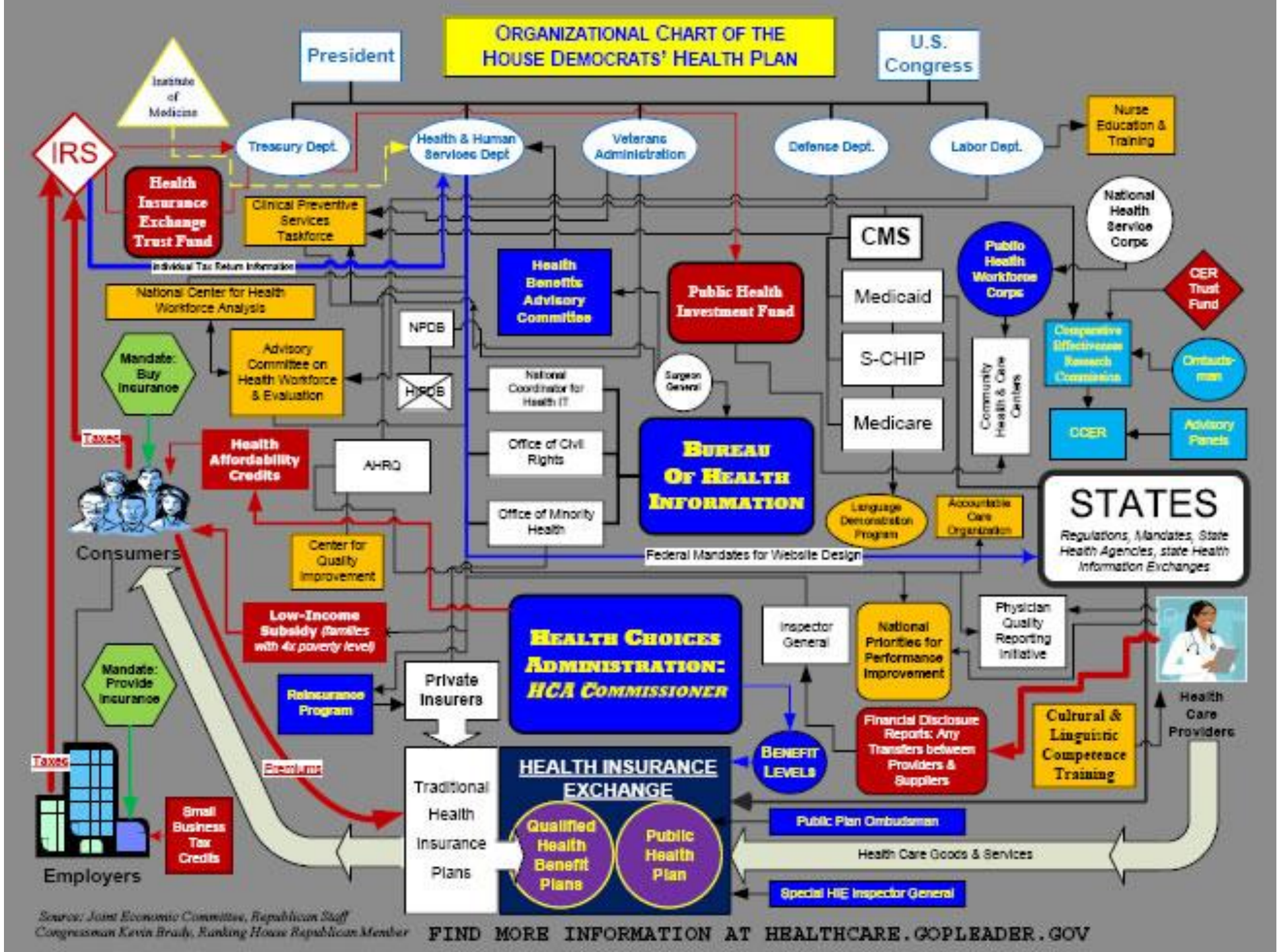
The rule of 3 !

Famous Threesomes…



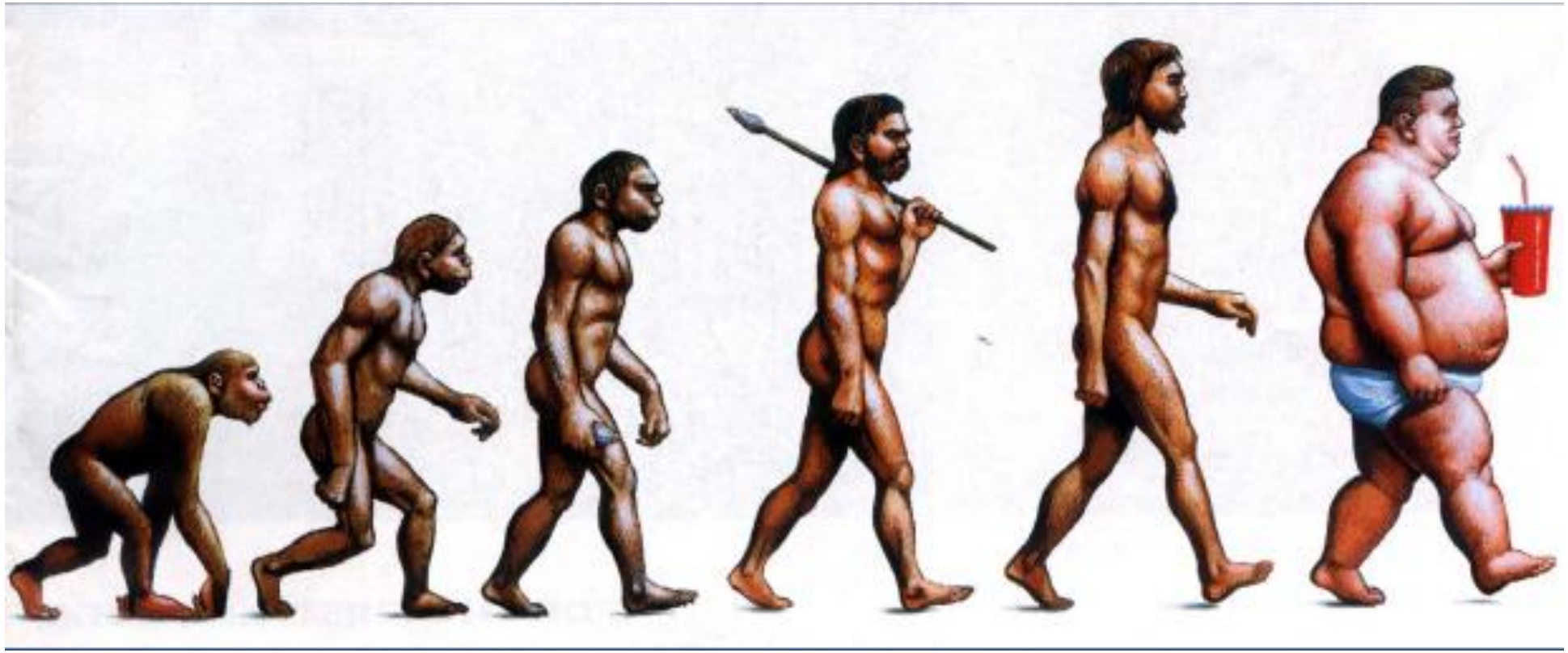
CKD, Diabetes and CVD




ORGANIZATIONAL CHART OF THE HOUSE DEMOCRATS' HEALTH PLAN
President
U.S. Congress
Institute of Medicine
IRS
Treasury Dept.
Health & Human Services Dept.
Veterans Administration
Defense Dept.
Labor Dept.
Nurse Education & Training
Health Insurance Exchange Trust Fund
Clinical Preventive Services Taskforce
Individual Tax Return Information
National Center for Health Workforce Analysis
Health Benefits Advisory Committee
Public Health Investment Fund
CMS
Medicaid
S-CHIP
Medicare
Public Health Workforce Corps
National Health Service Corps
CER Trust Fund
Comparative Effectiveness Research Commission
Ombudsman
NPDB
HIPDB
Advisory Committee on Health Workforce & Evaluation
Mandate: Buy Insurance
Taxes
Health Affordability Credits
AHRQ
National Coordinator for Health IT
Office of Civil Rights
Office of Minority Health
Surgeon General
BUREAU OF HEALTH INFORMATION
Community Health & Care Centers
DCER
Advisory Panels
Consumers
Center for Quality Improvement
Language Demonstration Program
Accountable Care Organization
STATES
Regulations, Mandates, State Health Agencies, state Health Information Exchanges
Federal Mandates for Website Design
Low-Income Subsidy (families with 4x poverty level)
HEALTH CHOICES ADMINISTRATION: HCA COMMISSIONER
Inspector General
National Priorities for Performance Improvement
Physician Quality Reporting Initiative
Mandate: Provide Insurance
Reinsurance Program
Private Insurers
Health Care Providers
Financial Disclosure Reports: Any Transfers between Providers & Suppliers
Cultural & Linguistic Competence Training
BENEFIT LEVELS
Taxes
Employers
Small Business Tax Credits
Premiums
Traditional Health Insurance Plans
HEALTH INSURANCE EXCHANGE
Qualified Health Benefit Plans
Public Health Plan
Public Plan Ombudsman
Health Care Goods & Services
Special HIE Inspector General
Source: Joint Economic Committee, Republican Staff
Congressman Kevin Brady, Ranking House Republican Member
FIND MORE INFORMATION AT HEALTHCARE.GOPLEADER.GOV

"Mr. Osborne, may I be excused? My brain is full."

Evolution … ?

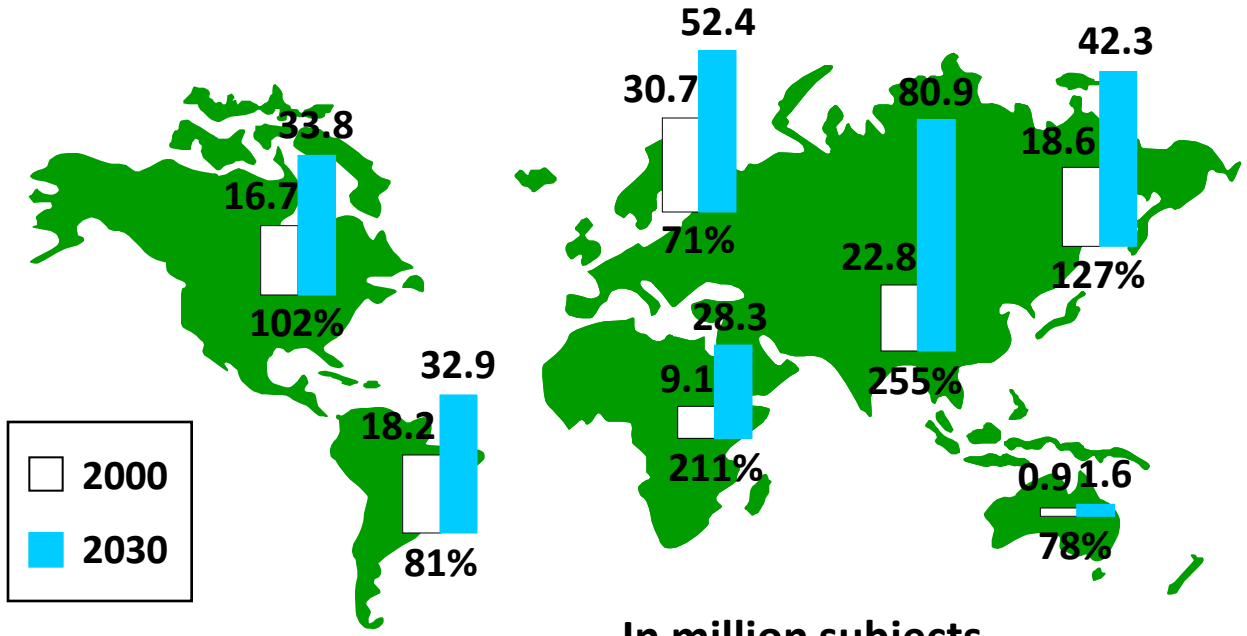


Diabetes: a Worldwide Epidemic

The Globesity Festival

OCTOBER 22-28, 2007 / NEW YORK CITY

The global burden of diabetes (2000–2030)

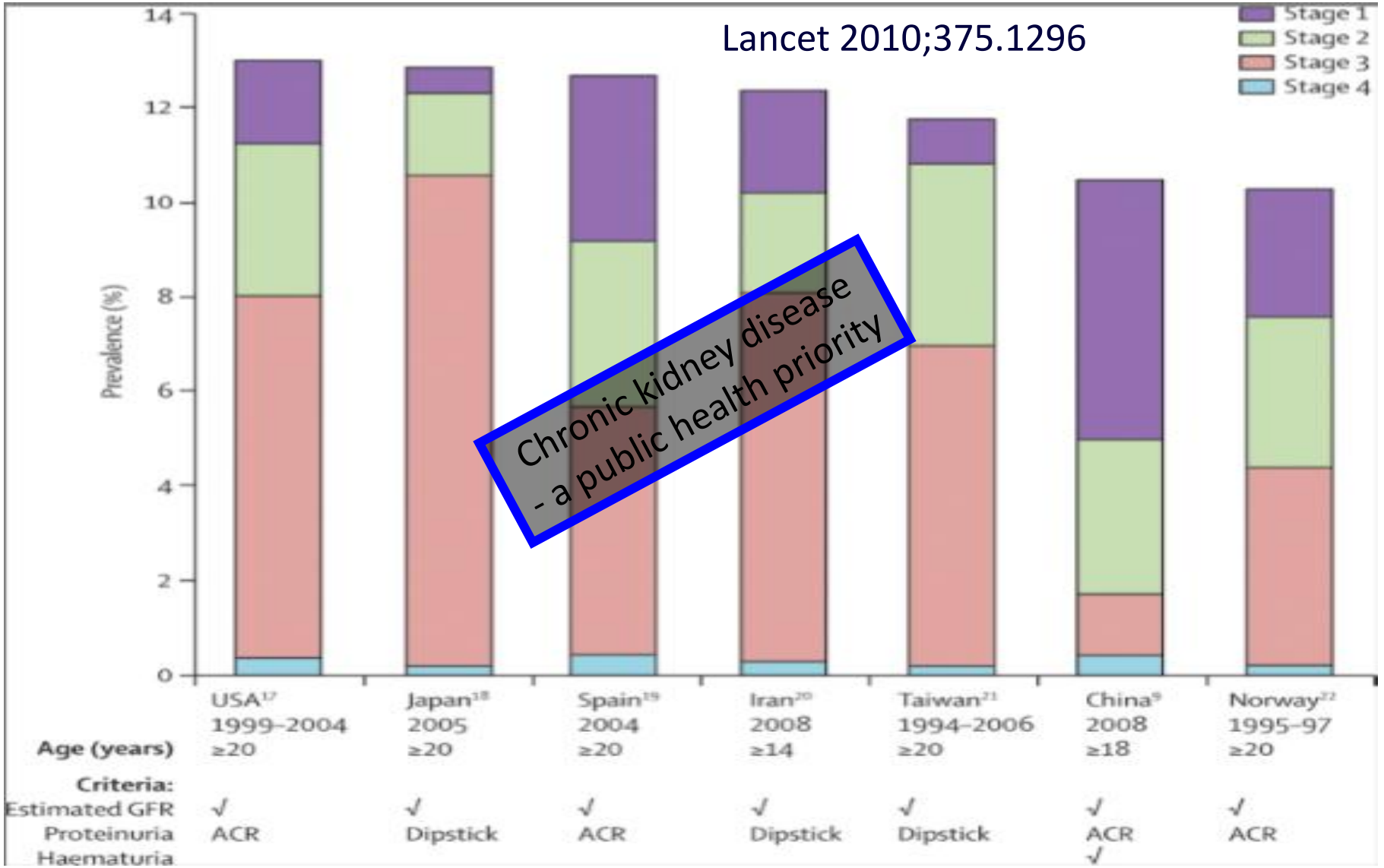


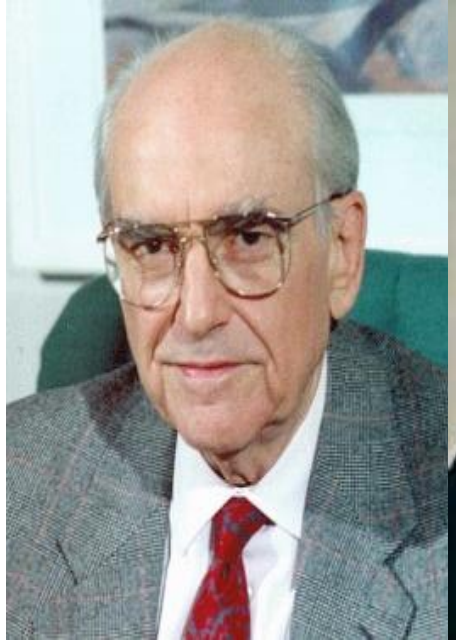
In million subjects

	World	Developed	Developing
2000	154 m	55 m	99 m
2030	370 m	84 m	286 m

WHO, March 2003

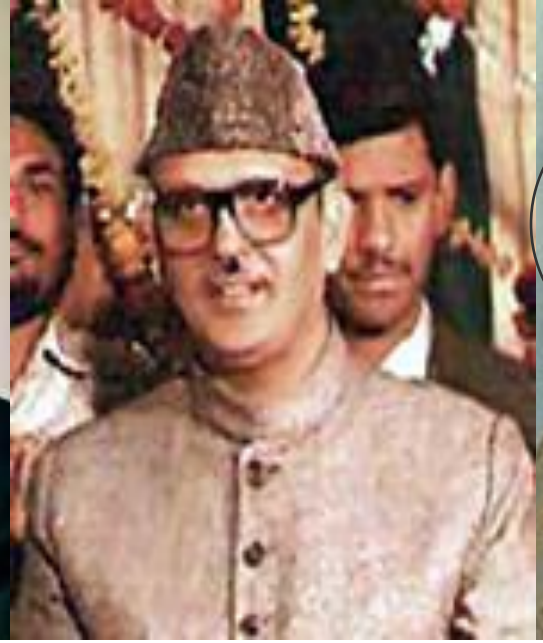
Chronic Kidney Disease
- Its More Common Than You Think





G Papandreo, Greece, RIP

Y Andropov, Soviet Union, RIP



VP Singh, India, RIP

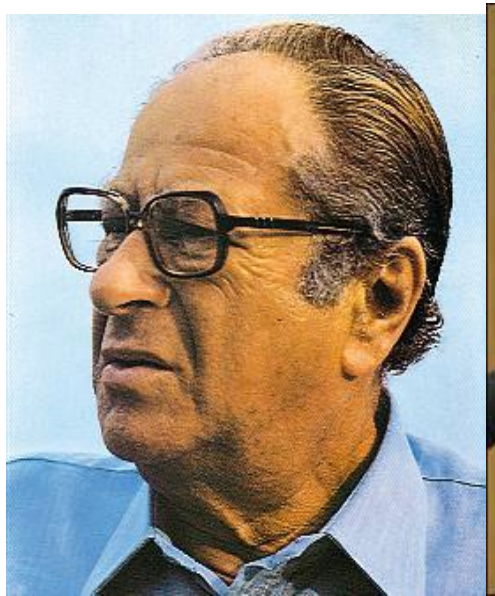
Kim Jong Il, RIP

B Kreisky, Austria, RIP

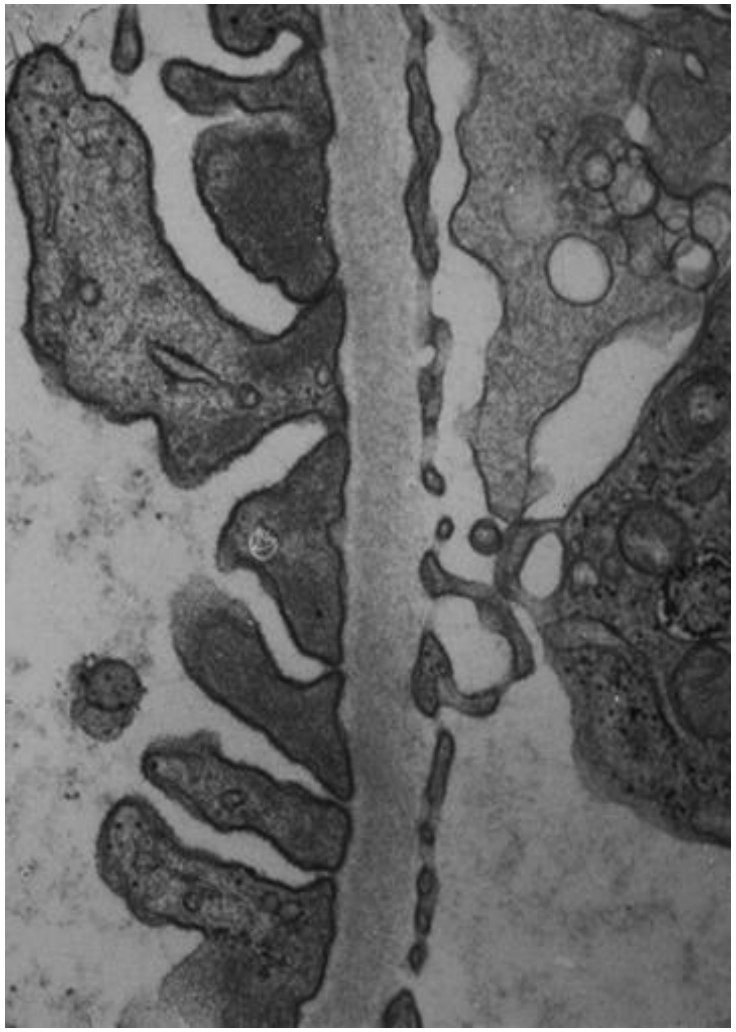
K Dae-jung, South Korea, RIP

F Marcos, Phillipines, RIP

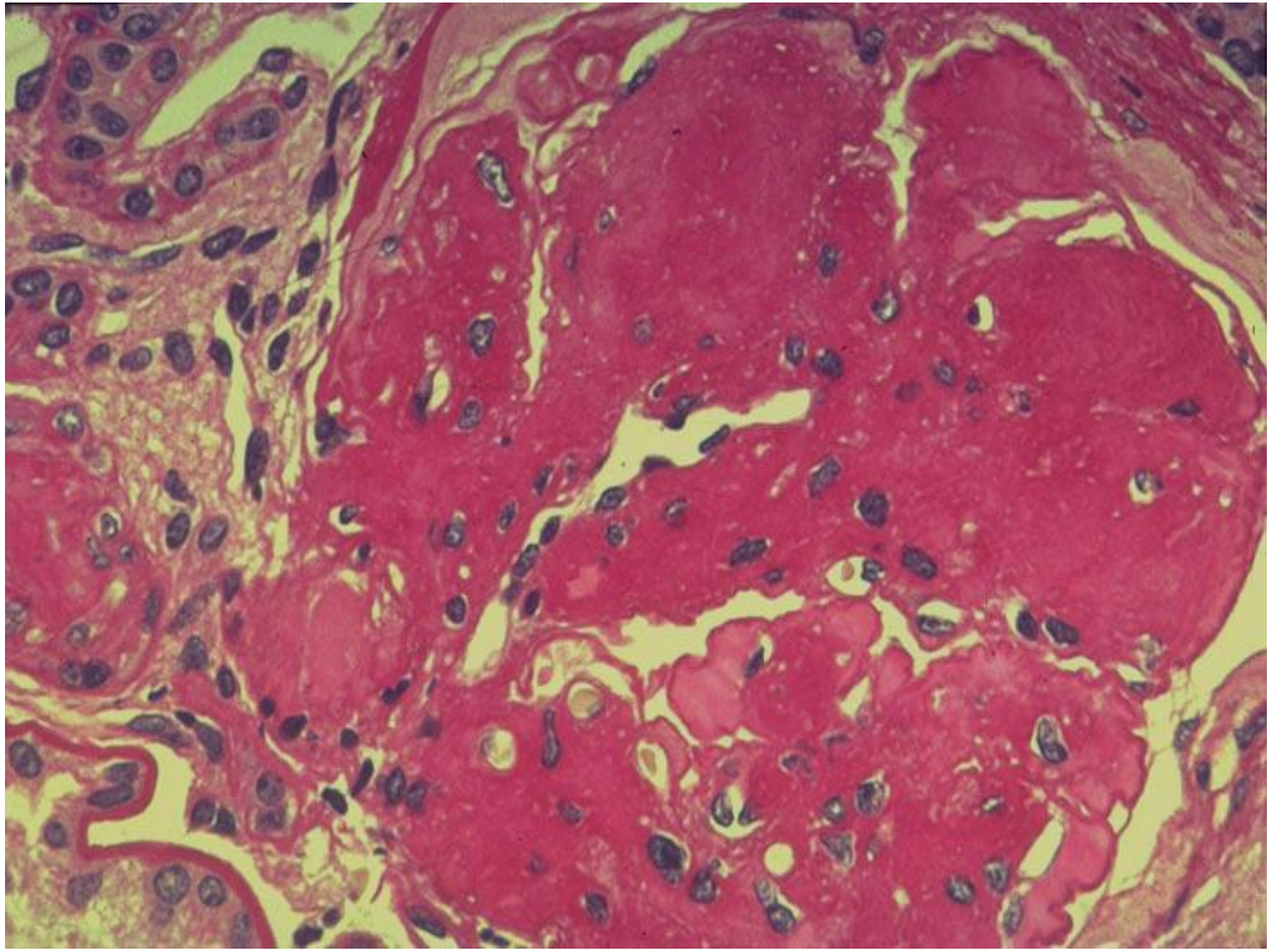
O Bin Laden, RIP



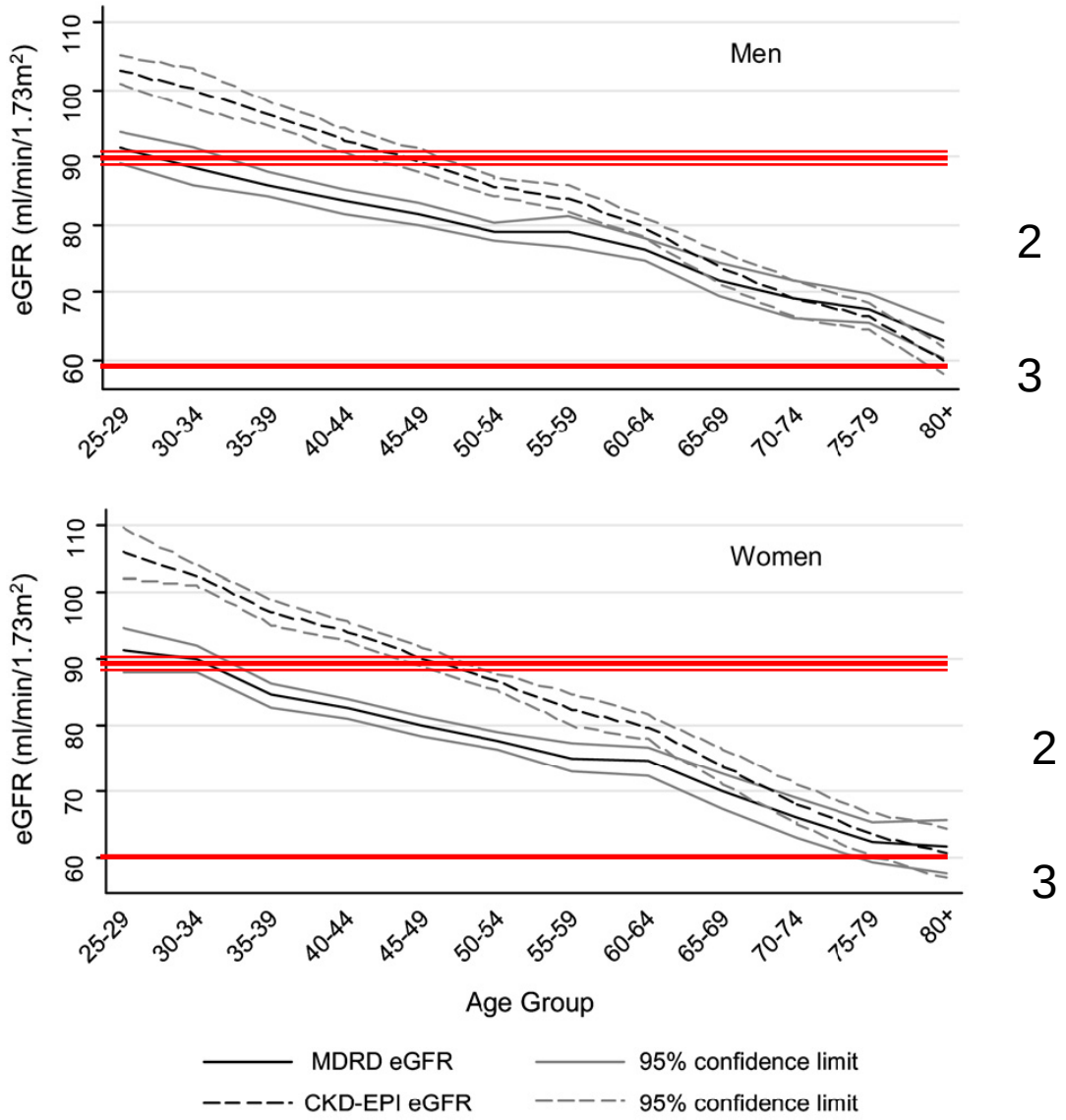
GLOMERULAR BASEMENT MEMBRANE



GLOBAL GLOMERULOSCLEROSIS



Age related prevalence of CKD



2

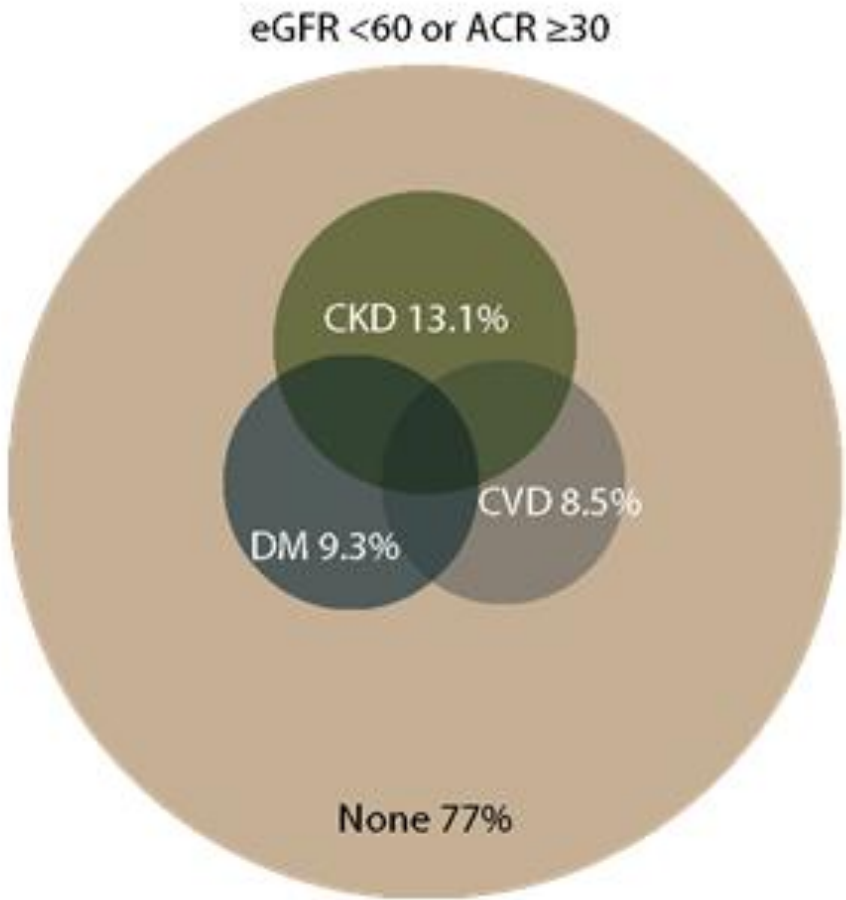
3

2

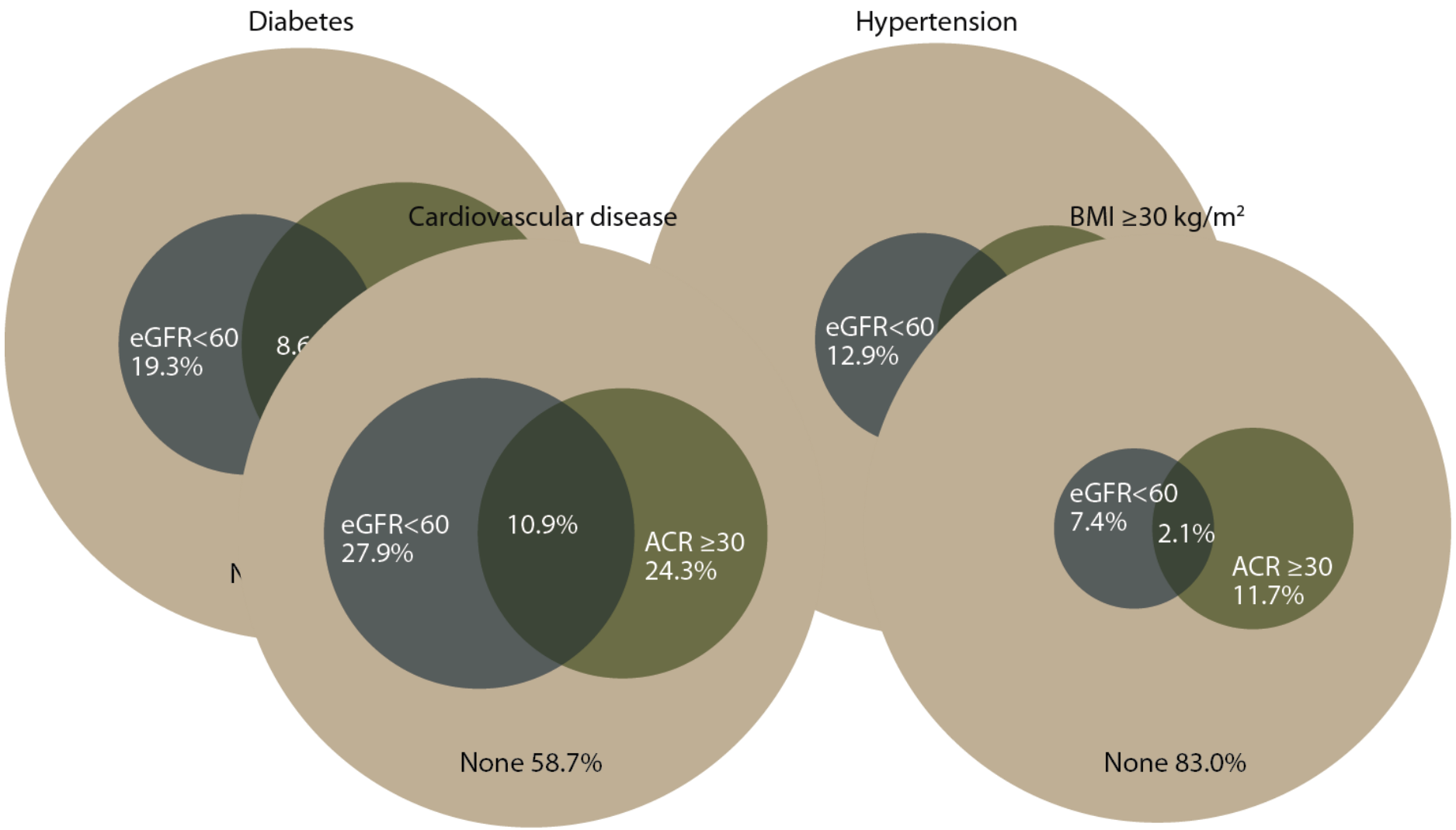
3

CKD – still prevalent?
Data from USRDS registry

Distribution of NHANES 2005–2010 participants with diabetes, cardiovascular disease, & single-sample markers of CKD



The prevalence is increased in several risk cohorts

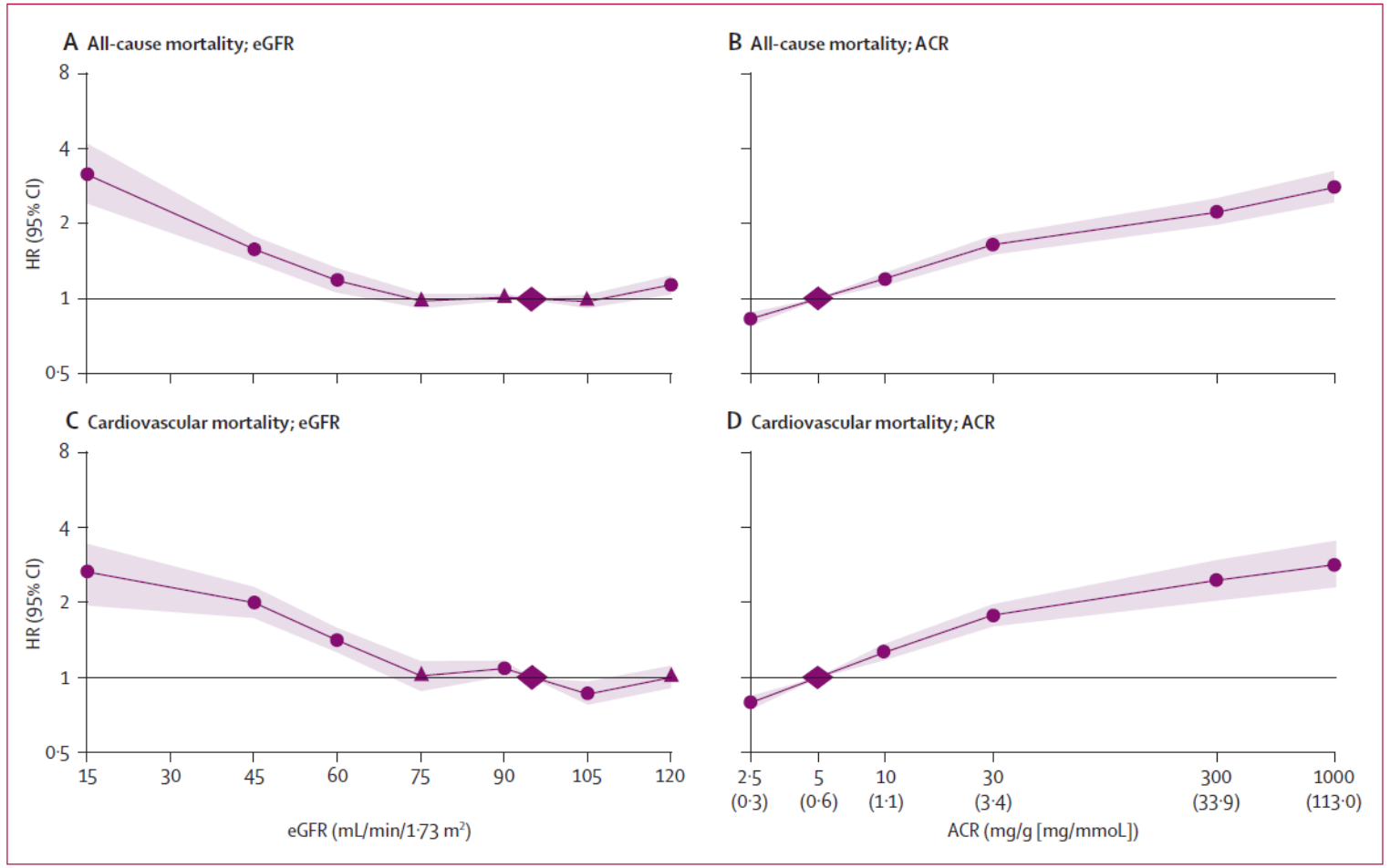


NHANES 1988–1994 & 2005–2010 participants age 20 & older; single sample estimates of eGFR & ACR. eGFR calculated using the CKD-EPI equation.

Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis

*Chronic Kidney Disease Prognosis Consortium**

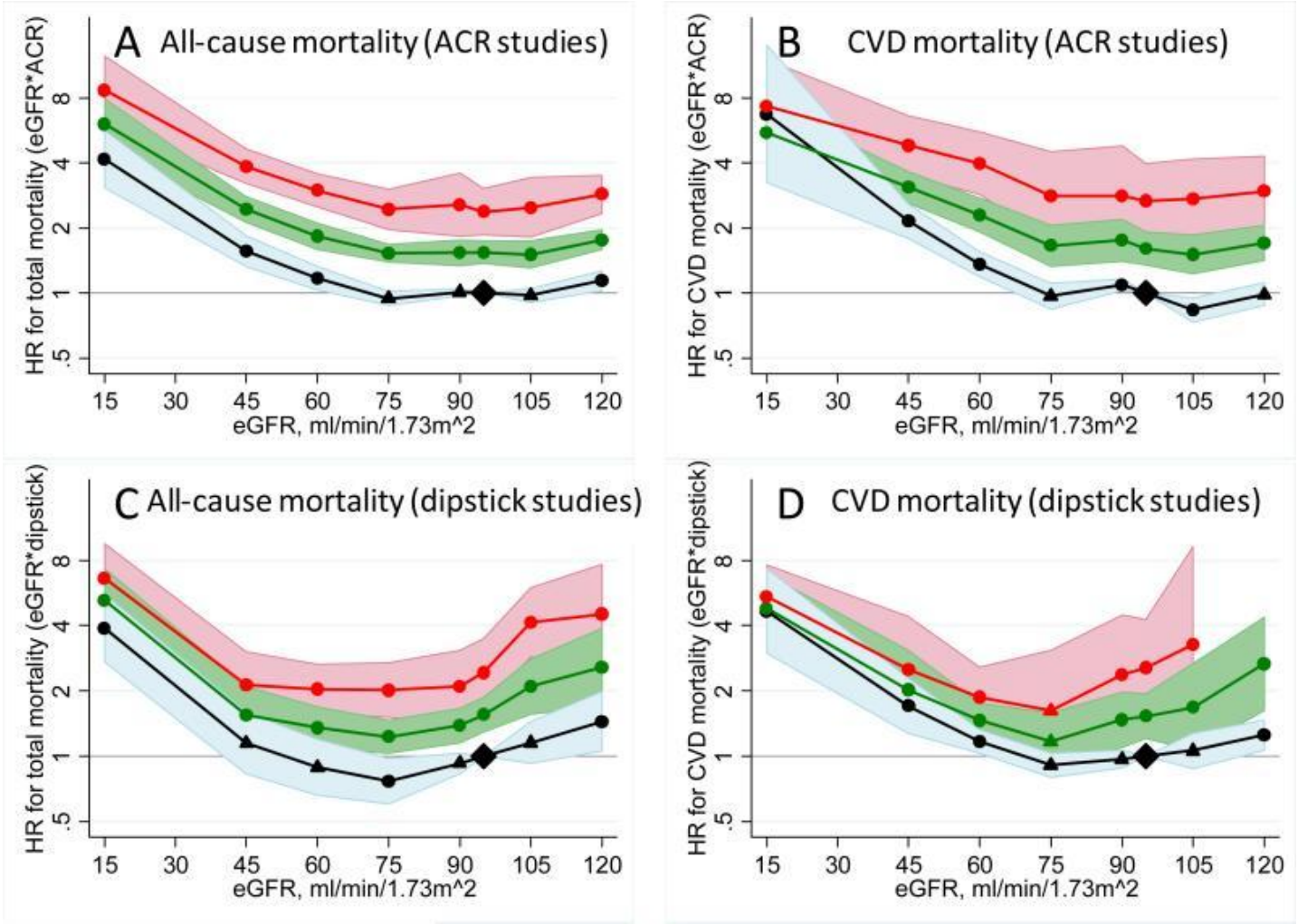
Lancet May 21 2010



105 872 participants (730 577 person-years)

Multiplicative impact of eGFR and Proteinuria on mortality in general population

Matsushita et al. Chronic Kidney Disease Prognosis Consortium Lancet 2010

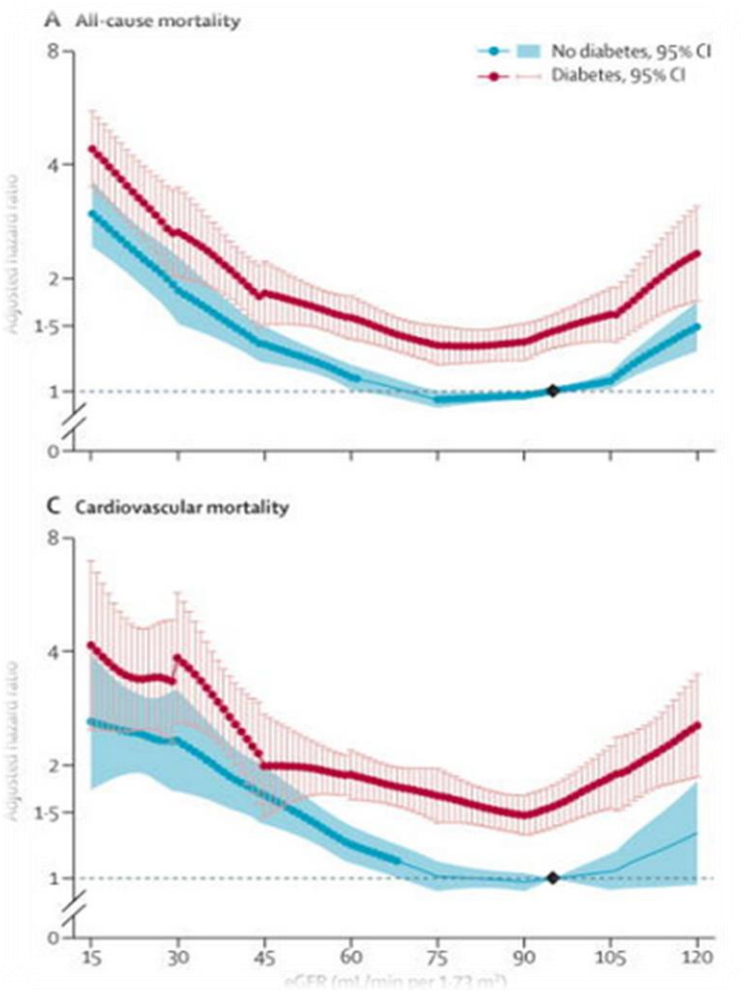


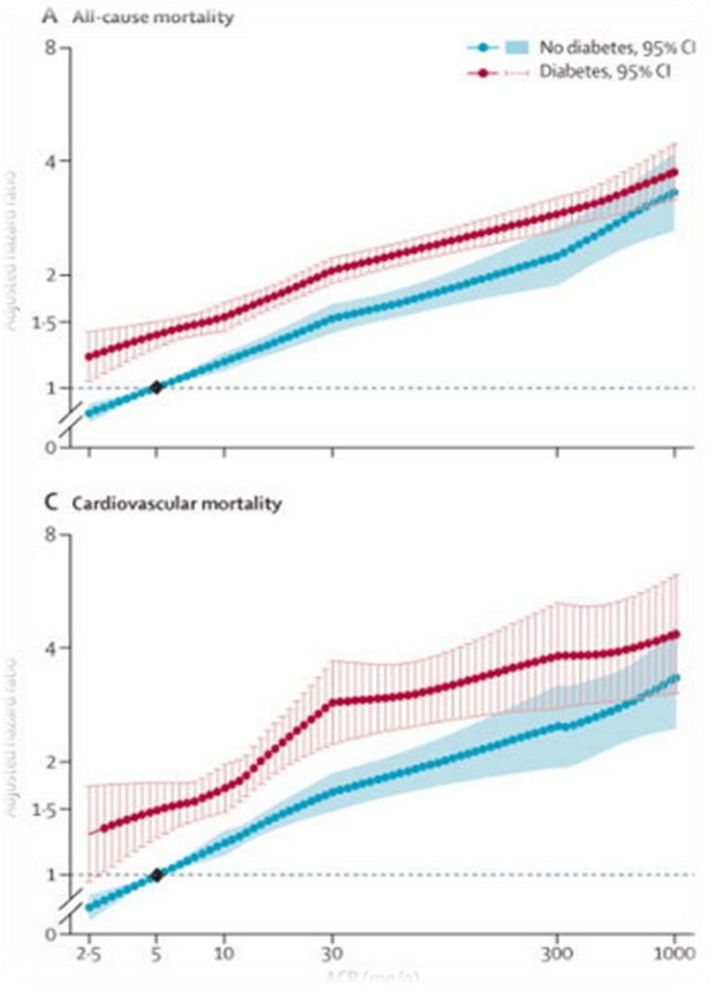
ACR: <30 [black], 30-299 [green], and ≥300 [red]

eGFR and proteinuria associated with mortality *in diabetes*

Mahmoodi , Chronic Kidney Disease Prognosis Consortium. Lancet 2012

N - 1 024 977 participants (128 505 with diabetes) from 30 general population and high-risk CV cohorts and 13 CKD cohorts.





CKD - classification and prognosis (KDIGO)

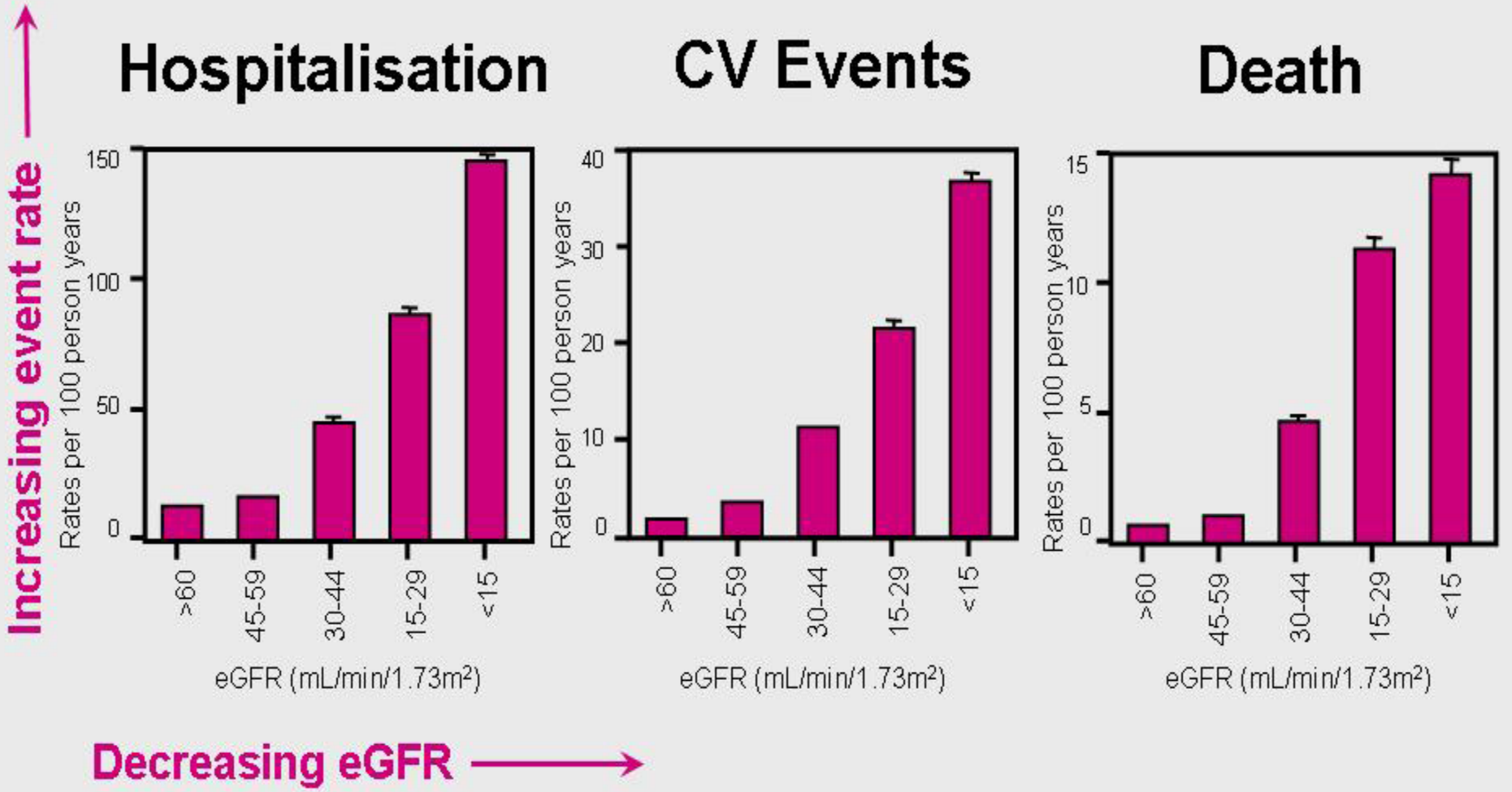
Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/ 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

Kidney International Supplements (2013) 3, 5–14; doi:10.1038/kisup.2012.77

CKD and complications

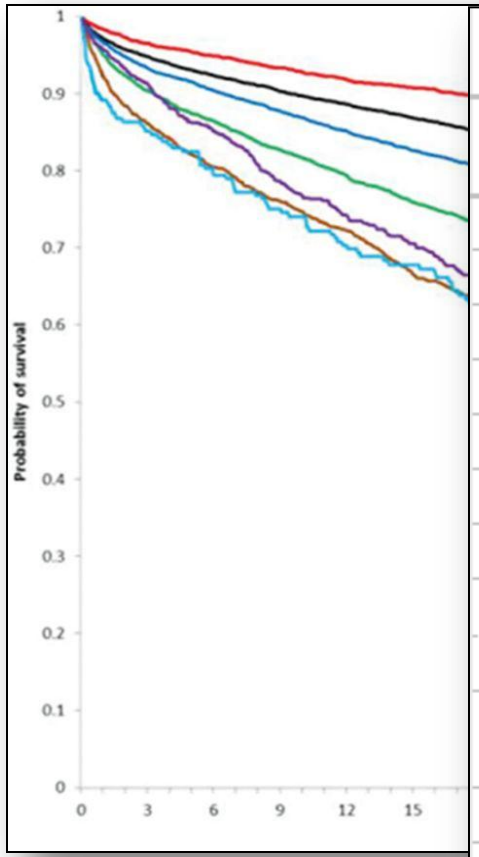


Adapted from Go *et al. NEJM* 2004; 351:1296-1305

eGFR and Outcomes in *Heart Failure*

The Cardiovascular Research Network PRESERVE Study

24 331 adults with heart failure and preserved or reduced left ventricular ejection fraction stratified by levels of renal function.

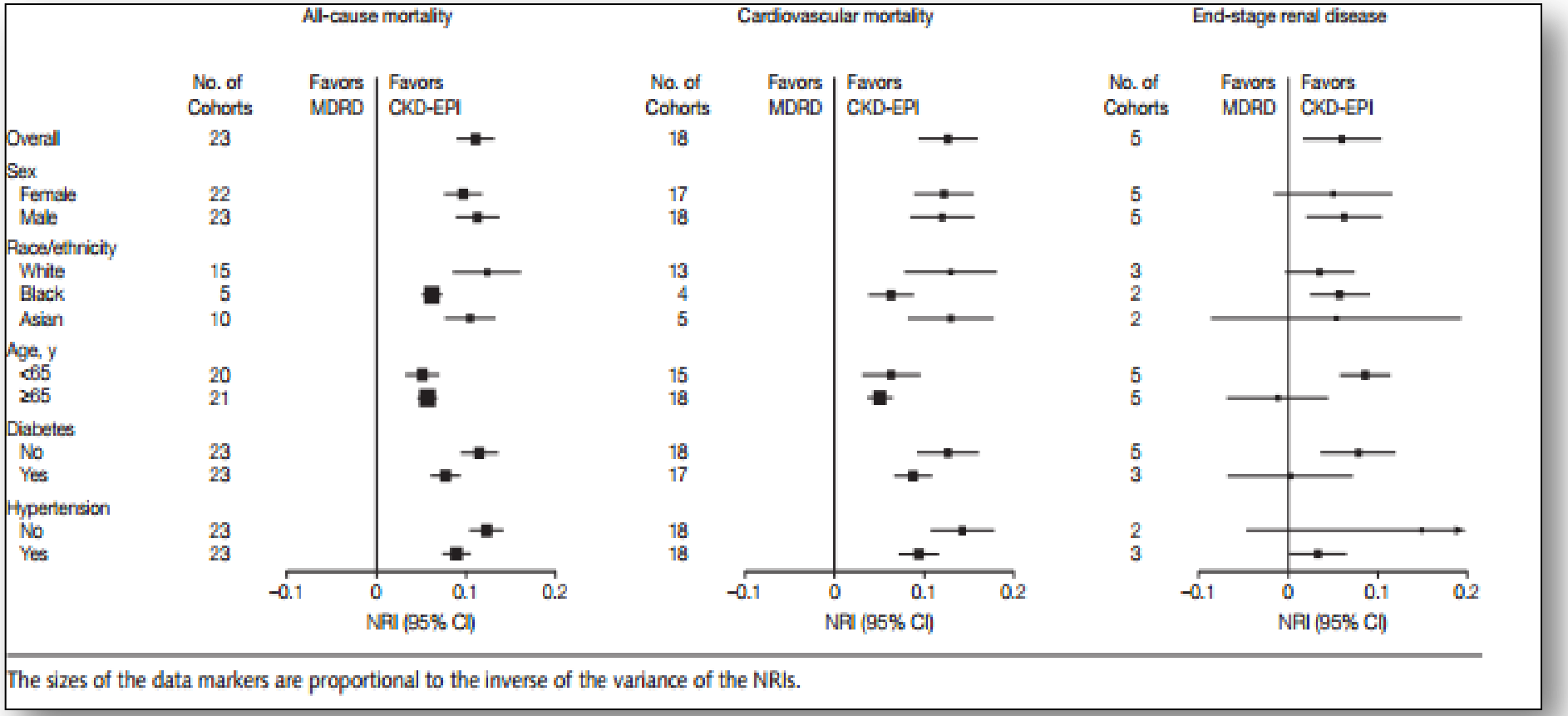


	Death From Any Cause Adjusted Hazard Ratio (95% Confidence Interval)	
	Preserved Systolic Function* (n=14 579)	Reduced Systolic Function† (n=9752)
eGFR (mL/min per 1.73 m^2) category, n (%)		
60–89	Reference	Reference
45–59	0.99 (0.90–1.09)	1.08 (0.96–1.22)
30–44	1.16 (1.05–1.27)	1.29 (1.14–1.46)
15–29	1.57 (1.41–1.76)	2.15 (1.87–2.48)
<15	3.22 (2.60–3.98)	3.69 (2.81–4.84)
Dialysis	1.90 (1.61–2.23)	2.51 (2.05–3.07)
Urine dipstick protein excretion		
Negative/trace or undocumented	Reference	Reference
1+	1.53 (1.41–1.67)	1.41 (1.27–1.57)
2+	1.54 (1.39–1.71)	1.44 (1.27–1.63)
3+	1.61 (1.39–1.87)	1.23 (1.01–1.49)

Smith D H et al. Circ Cardiovasc Qual Outcomes. 2013;6:333-342

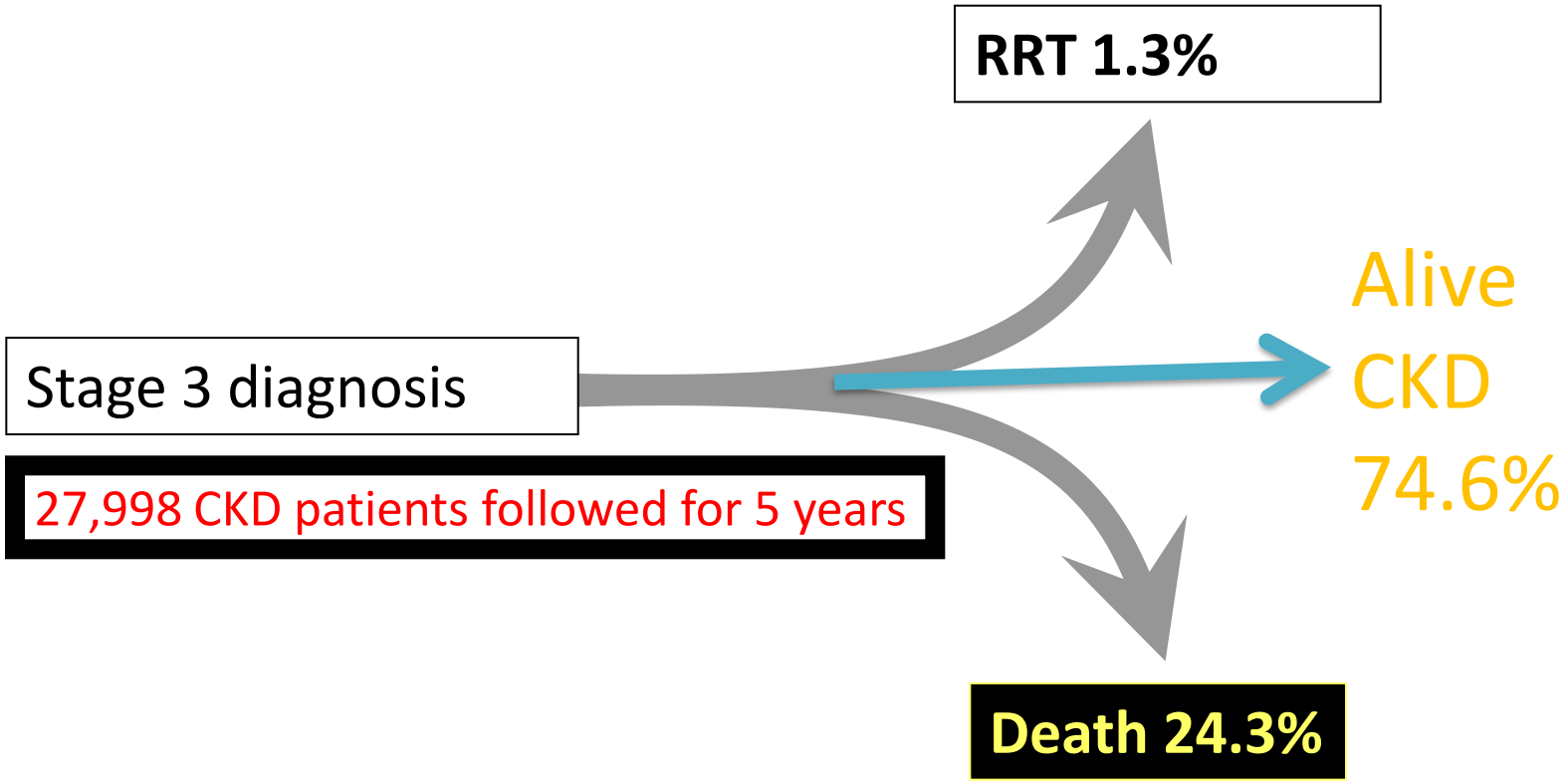
Comparison of risk prediction using the CKD-EPI equation and the MDRD Study equation for eGFR

Mahmoodi , Chronic Kidney Disease Prognosis Consortium. JAMA 2012



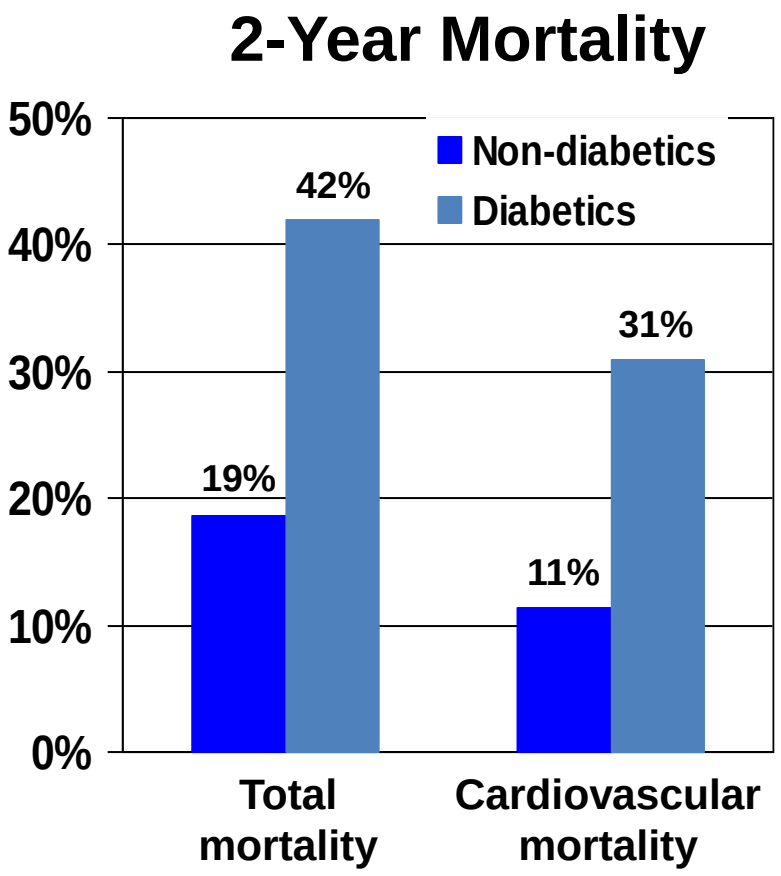
CKD-EPI equation - more accurately categorized the risk for mortality and ESRD than did the MDRD Study equation across a broad range of populations.

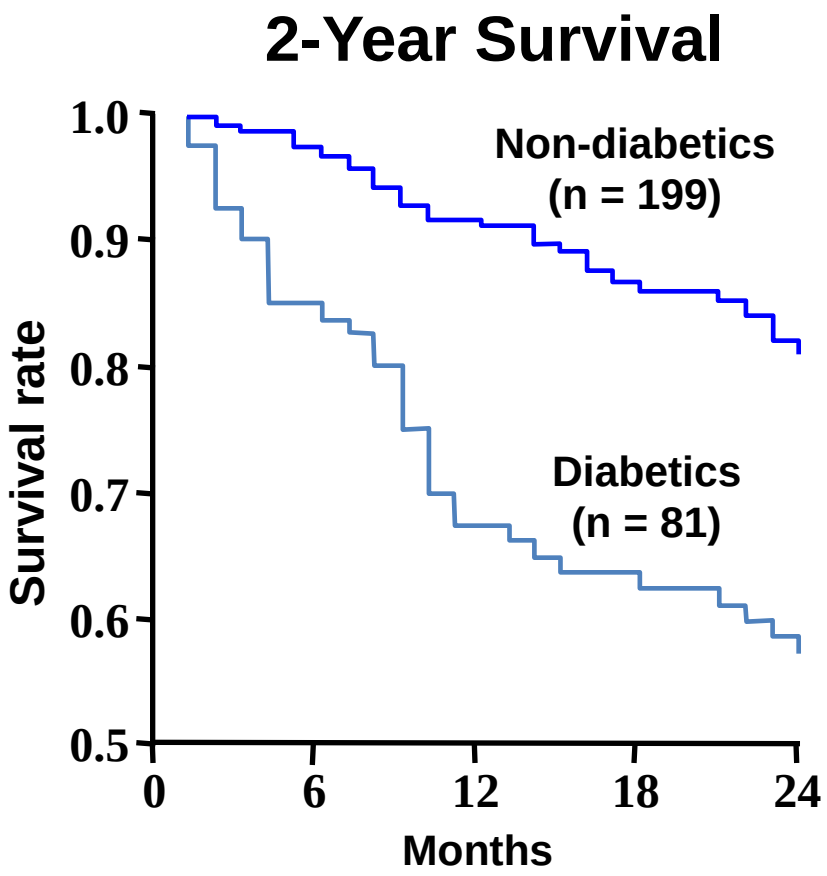
CKD Stage 3 outcomes
CARDIO-NEPHROPROTECTION



Adapted from Keith et al *Arch Intern Med* 2004

Mortality among Haemodialysis Patients with End-Stage Renal Failure





Cardio-Renal Syndrome

Background

Pathophysiology

Management

Conclusions

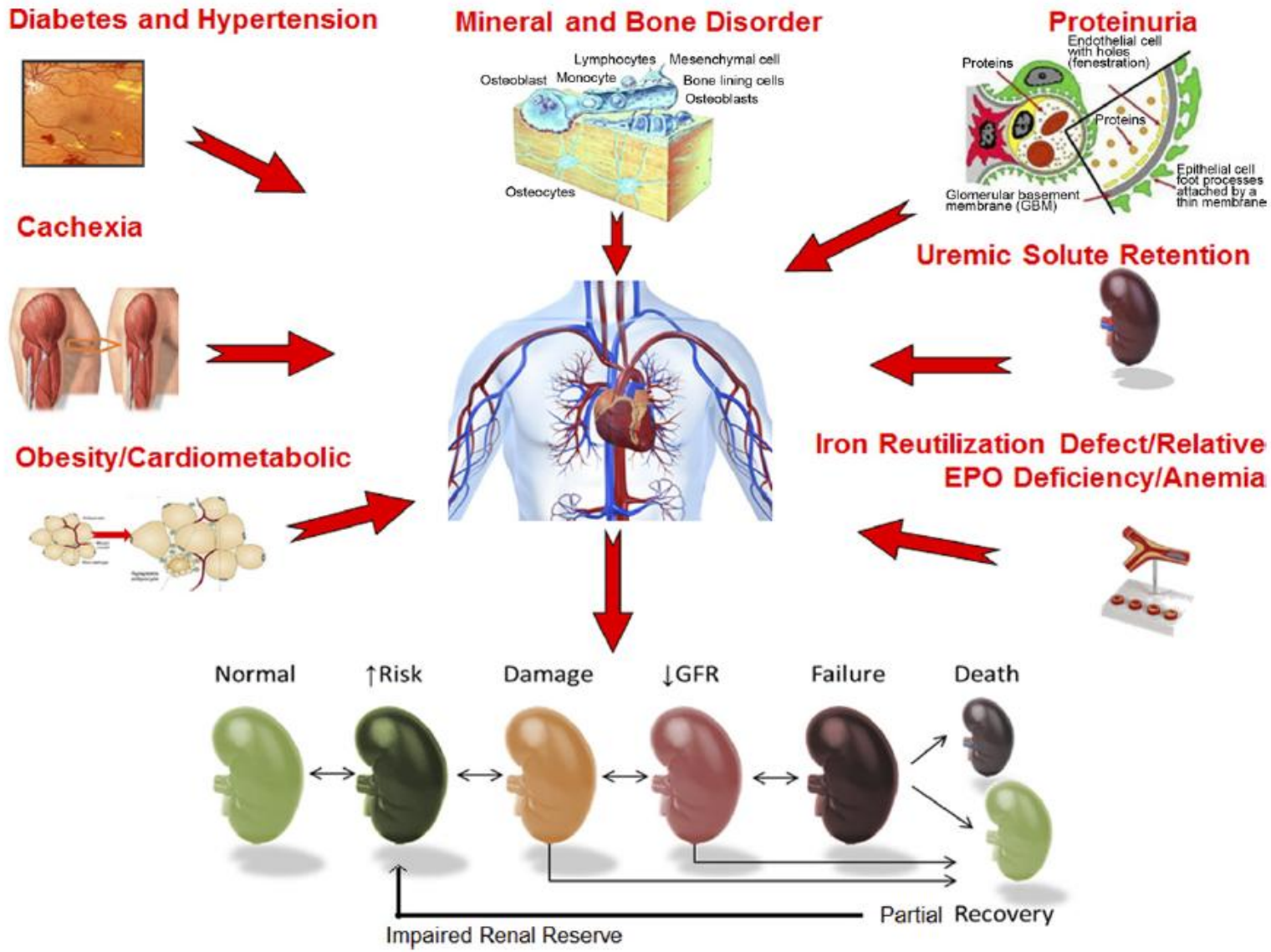


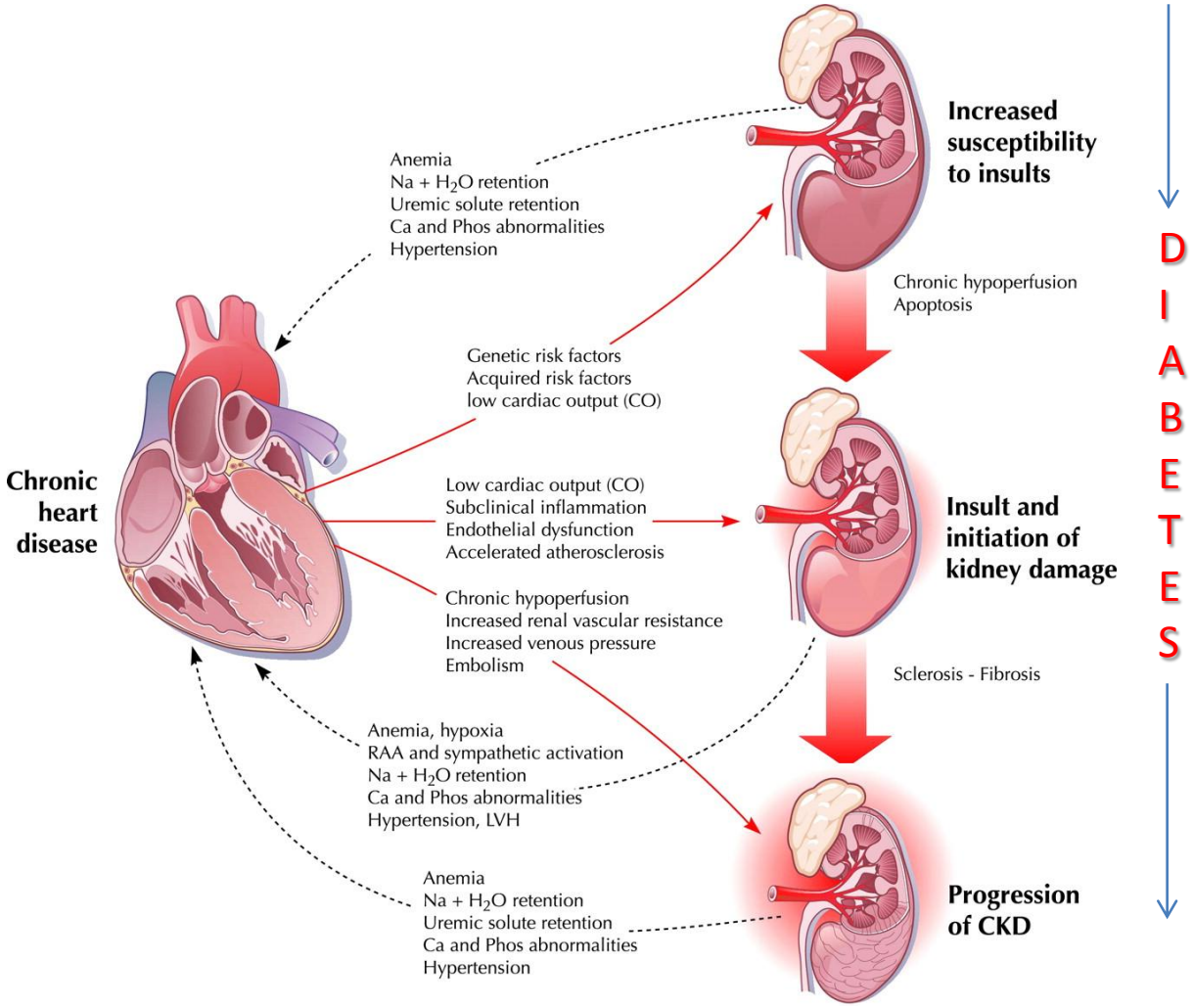
Figure 2 **Predisposing Factors for CRS**

Obesity and cardiometabolic changes in the cardiovascular system, including diabetes and hypertension, and later in the course of disease, cachexia, biochemical, and hormonal changes due to bone and mineral disorder, proteinuria, uremic solute retention, and anemia, all contribute to the risk for developing cardiorenal syndrome (CRS) type 1. The course of this syndrome can lead to permanent renal failure and need for dialysis or partial renal recovery. EPO = erythropoietin; GFR = glomerular filtration rate.

Cardio-renal Syndrome : Subtypes

- Type I, acute CRS
- Type II, chronic CRS
- Type III, acute reno-cardiac syndrome
- Type IV, chronic reno-cardiac syndrome
- Type V, secondary CRS -- sepsis, amyloidosis

“Cardio-Renal Nexus”

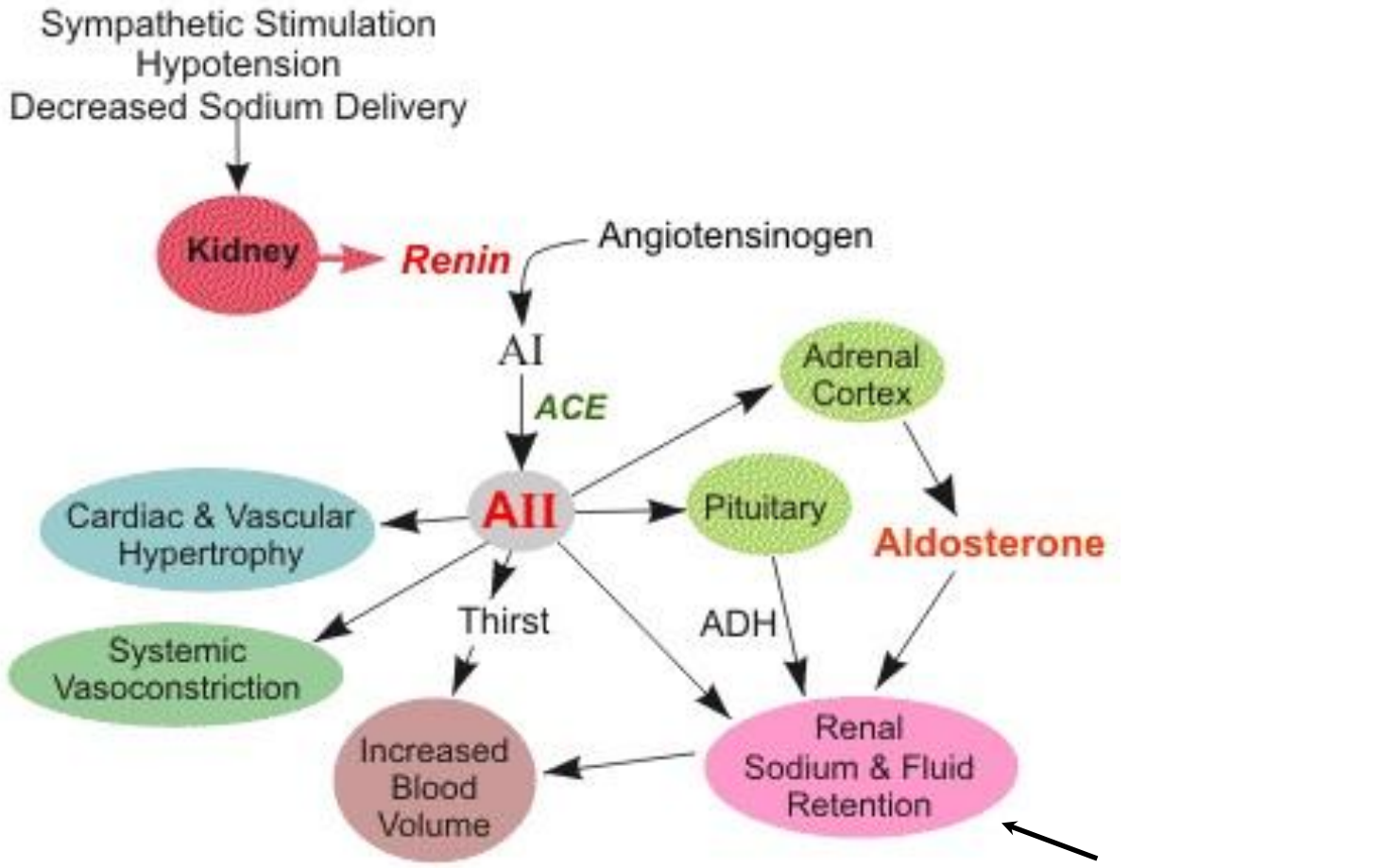


Ronco, C. et al. J Am Coll Cardiol 2008;52:1527-1539

Pathophysiology

- Neurohormonal Factors:
    - SNS, RAAS, AVP System
- Hemodynamics:
    - Loss of Cardiac Output
    - Transrenal perfusion pressure
    - Intrarenal hemodynamics

Neurohormonal Axis



Cardio-Renal Syndromes

CHF patients at increased risk for CRS:

- Hypertension
- Diabetes
- Severe Vascular Disease
- Elderly

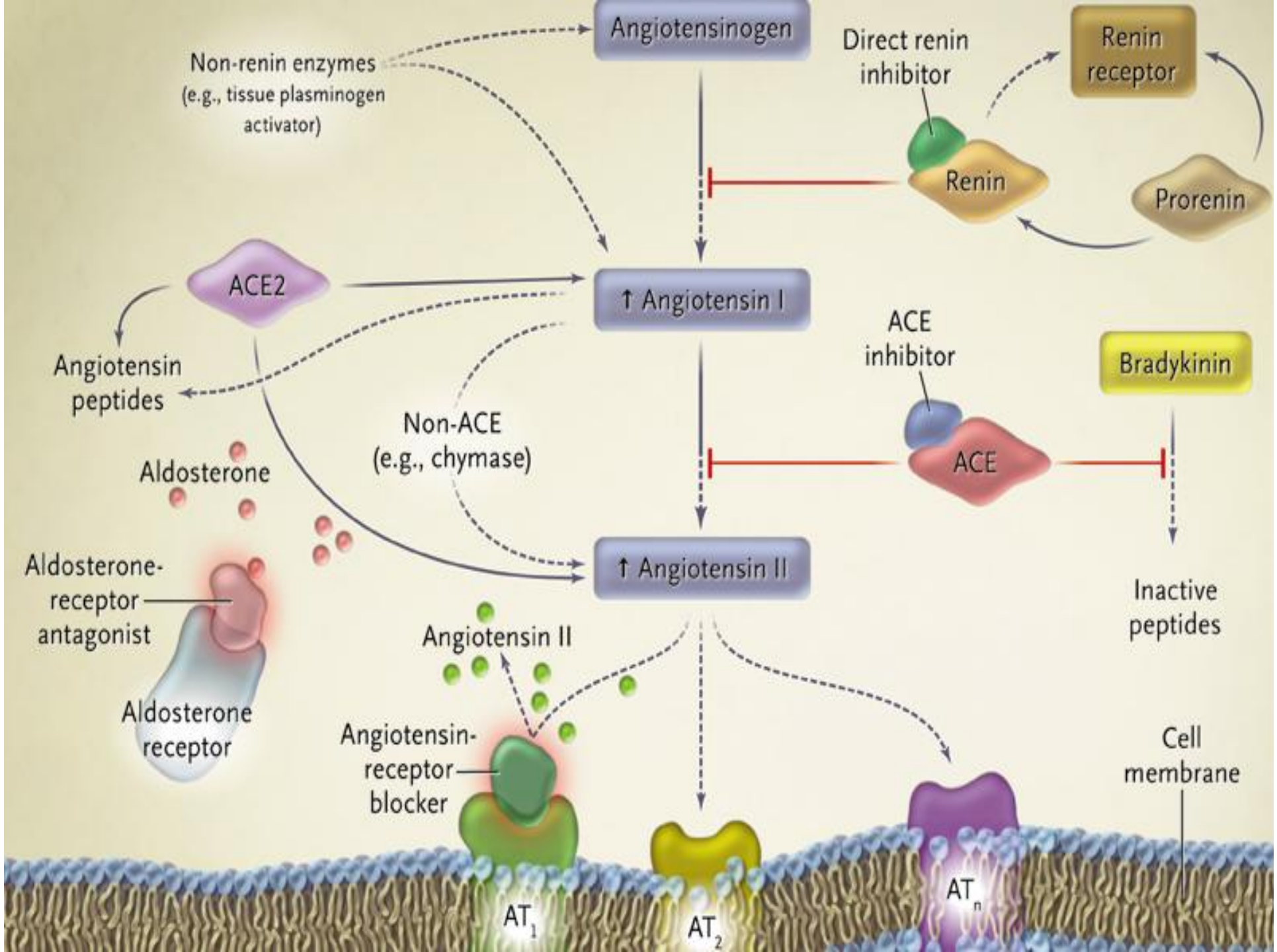
CVD, CKD, Diabetes

(1) What is the nature of the relationship between CKD, CVD, diabetes ?

(2) What are the drivers for the relationship ?

(3) What interventions or measures can be taken to break the relationship ?

A Marriage made in Hell !


Angiotensinogen
Non-renin enzymes
(e.g., tissue plasminogen
activator)
Direct renin
inhibitor
Renin
receptor
Renin
Prorenin
ACE2
↑ Angiotensin I
Angiotensin
peptides
ACE
inhibitor
Bradykinin
Non-ACE
(e.g., chymase)
Aldosterone
ACE
Aldosterone-
receptor
antagonist
↑ Angiotensin II
Inactive
peptides
Angiotensin II
Aldosterone
receptor
Angiotensin-
receptor
blocker
Cell
membrane
AT1
AT2
ATn

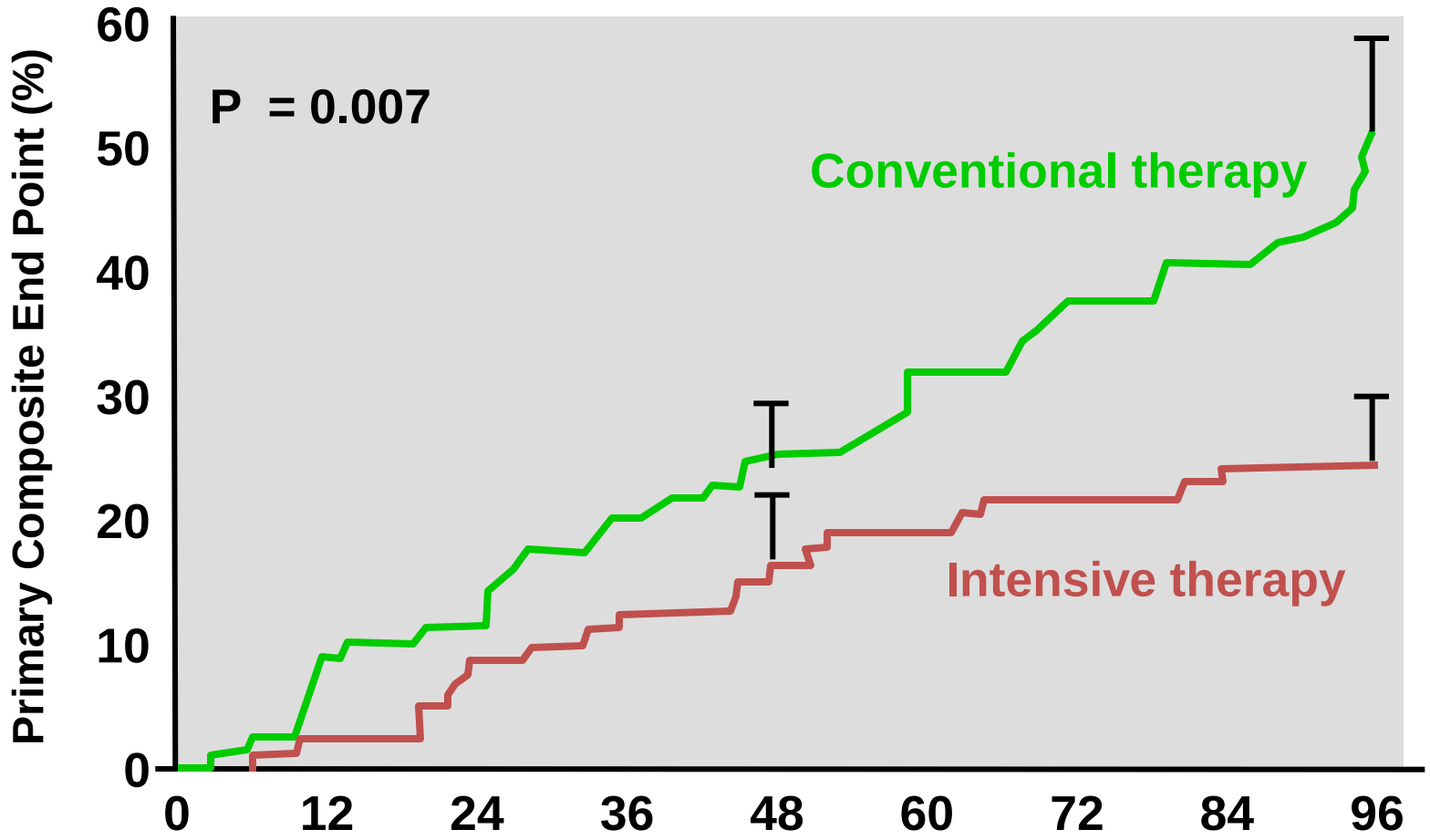

POGMA

One approach ….

Treatment – Multifactorial Intervention - Steno 2 Study

- 160 T2DM patients with microalbuminuria
- Randomised to intensive v conventional
- Intensive treatment for 7.8 yrs
    - Glycaemia
    - Blood pressure
    - Lipids
    - ACEI
    - Aspirin
    - Antioxidants
    - Lifestyle – smoking & exercise

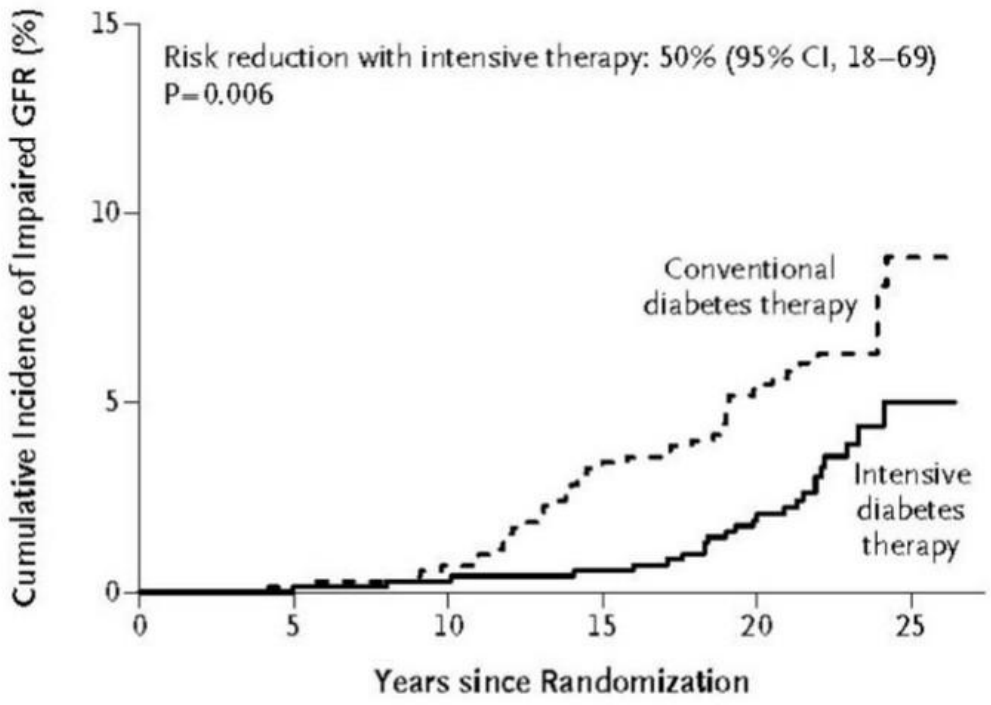
Gaede et al NEJM 2003 and 2009



No. at Risk									
Usual	80	72	70	63	59	50	44	41	13
Intensive	80	78	74	71	66	63	61	59	19

DCCT / EDIC

N Engl J Med 2011; 365:2366-237



No. at Risk						
Intensive therapy	711	704	684	672	619	108
Conventional therapy	730	719	697	657	594	90

Figure 1. Cumulative Incidence of an Impaired Glomerular Filtration Rate, According to Treatment Group.

DCCT / EDIC

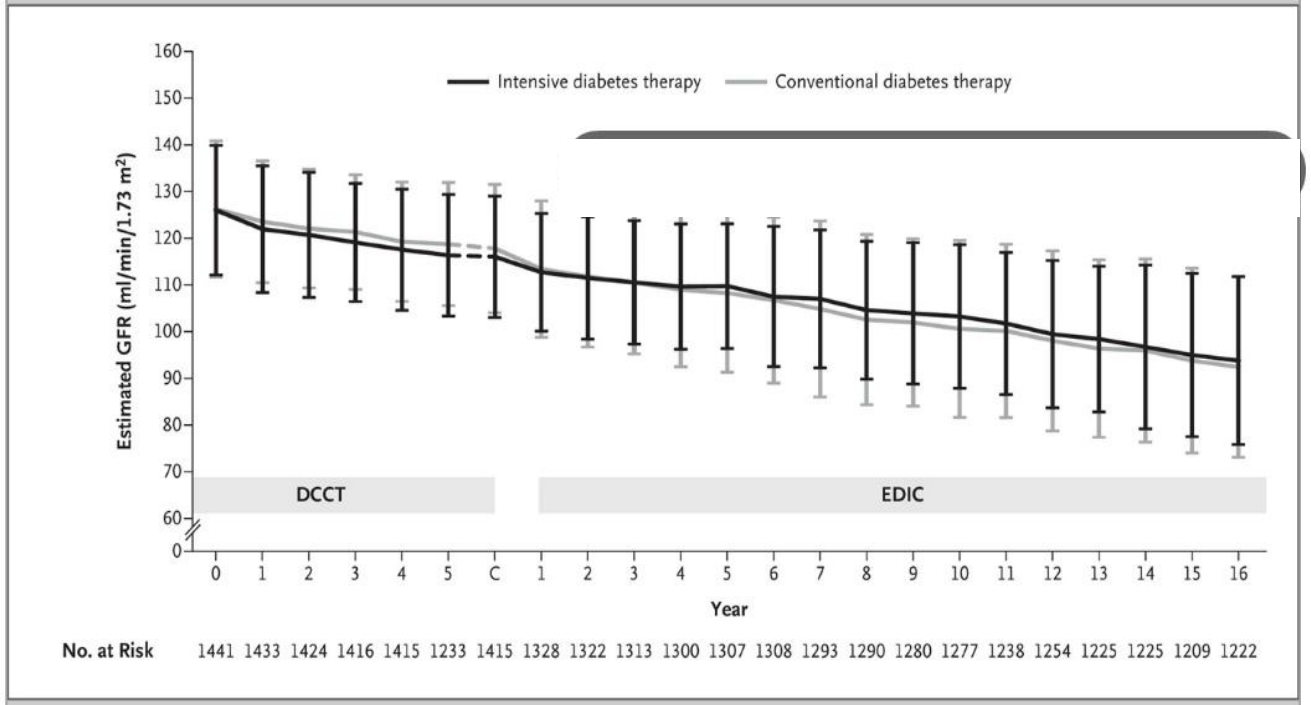
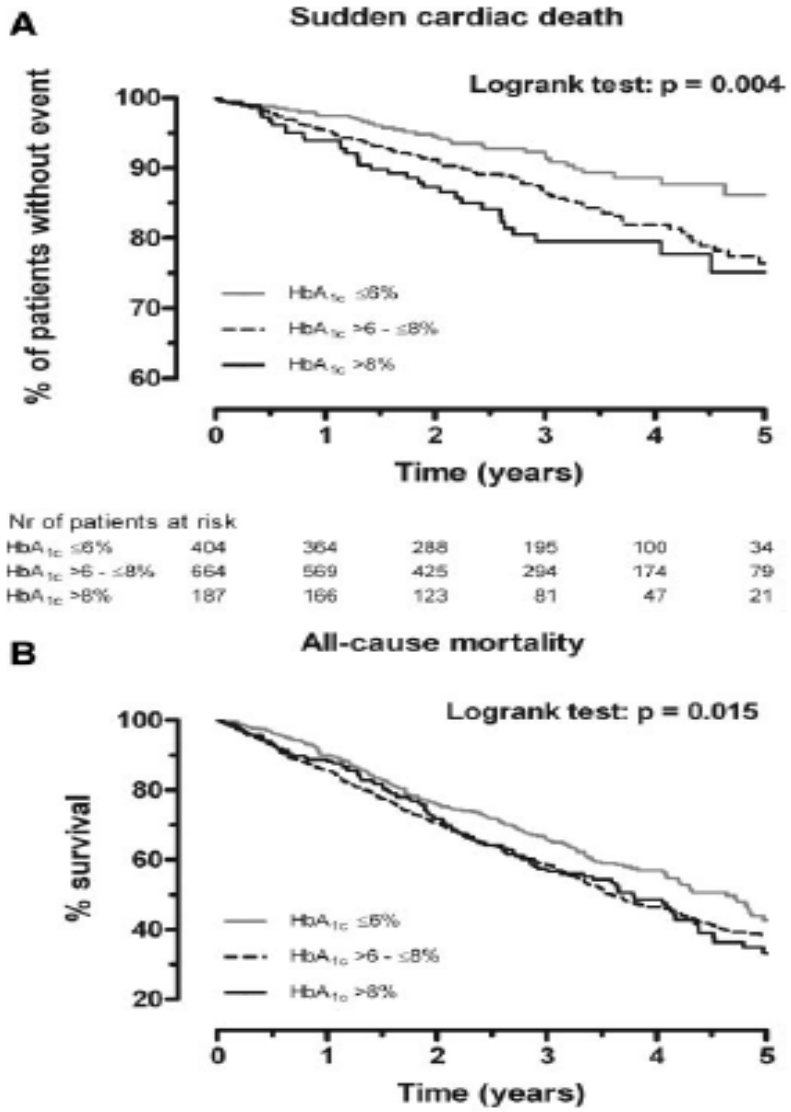
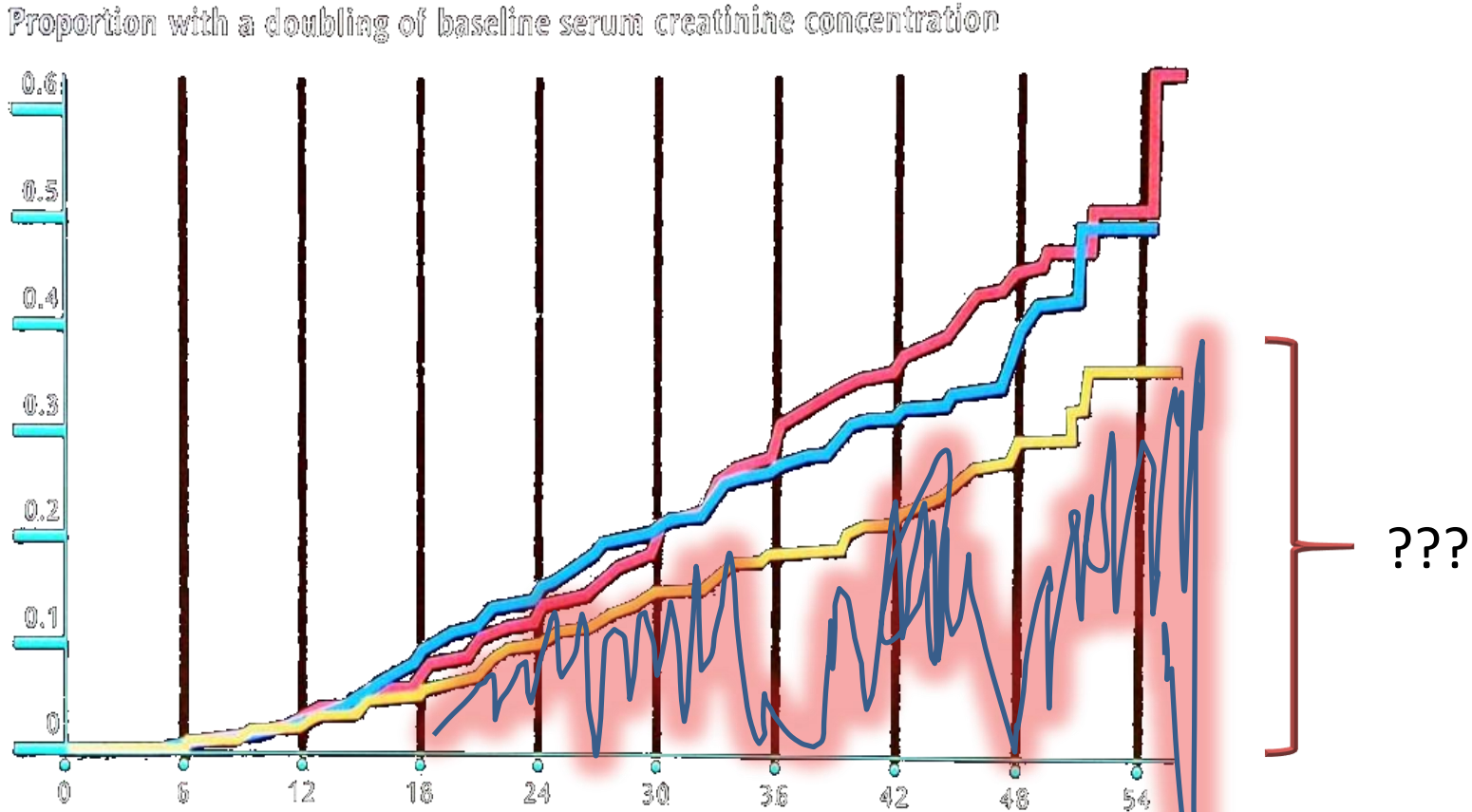


Figure 2. Estimated GFR over Time.

The simple means of the estimated GFR are shown over time in the Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) study, according to the group to which the participants had been randomly assigned (intensive diabetes therapy or conventional diabetes therapy) in the DCCT. I bars indicate interquartile ranges. C denotes the DCCT closeout visit.

Diabetes control and outcomes – dialysis CKD stage 5





No. at risk										
Irbesartan	579	534	495	457	363	273	191	131	57	5
Amlodipine	567	516	476	439	347	254	166	108	40	5
Placebo	569	527	482	436	360	252	173	107	47	2

Novel Approaches urgently needed

Novel targets to tackle the problem

- ***Oxidative stress and inflammation***

  Studies determining the effects of new therapeutic agents and where they are in development - Nrf-2 inhibitors, Pyridoximine, Pentoxifylline, MCP-1 antagonists

- ***Antifibrotics***

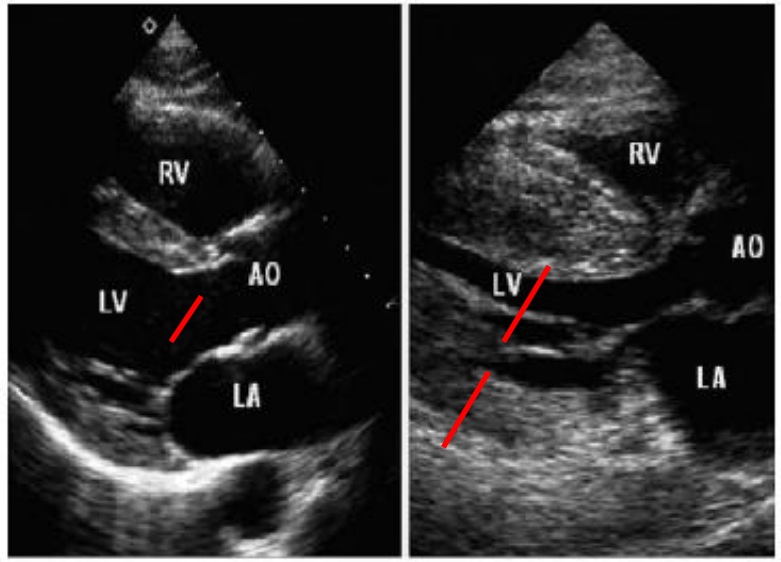
  Studies determining new therapeutic agents targeting fibrosis – Endothelin 1 antagonists, Pirfenodine, Vitamin D and VEGF antagonists

New therapies for DN [(http://www.clinicaltrials.gov/show/NCT01858532 Agent	Target	Studies	Effect
Nrf-2 activator (triterpenoid RTA dh404)	Nrf-2	Animal	Restores Nrf-2 activity decreases oxidative stress
Pyridoxamine dihydrochloride (Vitamin B6)	Advanced glycation end product (AGE) inhibitor	Human	Decreases AGE levels, ACR and improves Creatinine
Endothelin 1A antagonist (Atrasentan)	Endothelin 1A receptor	Animal and human	Reduction in ACR in DN and non-diabetic CKD
Pentoxifylline	TNF-α blockade	PREDIAN – human phase 3 trial	Reduction of proteinuria in addition to ACEi/ARB
Pirfenodine	TGF-β	Small RCT Animal studies	Improved GFR at 1 year – gastrointestinal side effects
Anti-CTGF monoclonal Antibody (FG-3019)	CTGF	Animal and human	Reduction in ACR in microalbuminurics
Paracalcitriol (Vitamin D)	Vitamin D	Small RCT –VITAL study	Reduction in ACR in DN. No effect on overall mortality
RS102895	Chemokine receptor CCR2 antagonist	Animal Human – phase 2 (CCX140-B)	Animal – reduction in ACR, improved histological features, decrease oxidative stress with improved glucose tolerance
VEGF antibody antagonist	Vascular Endothelial Growth Factor (VEGF)	Animal	Decrease glomerular hypertrophy, hyperfiltration and albuminuria

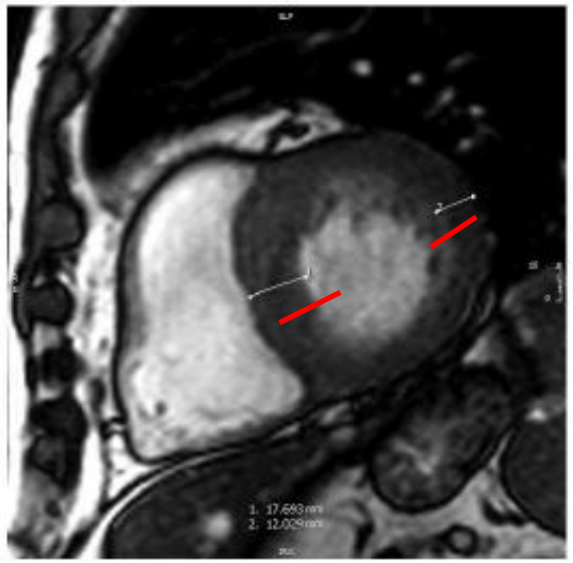
LVH / LVF

- Diabetes
- CKD
- Obesity
- Hypertension

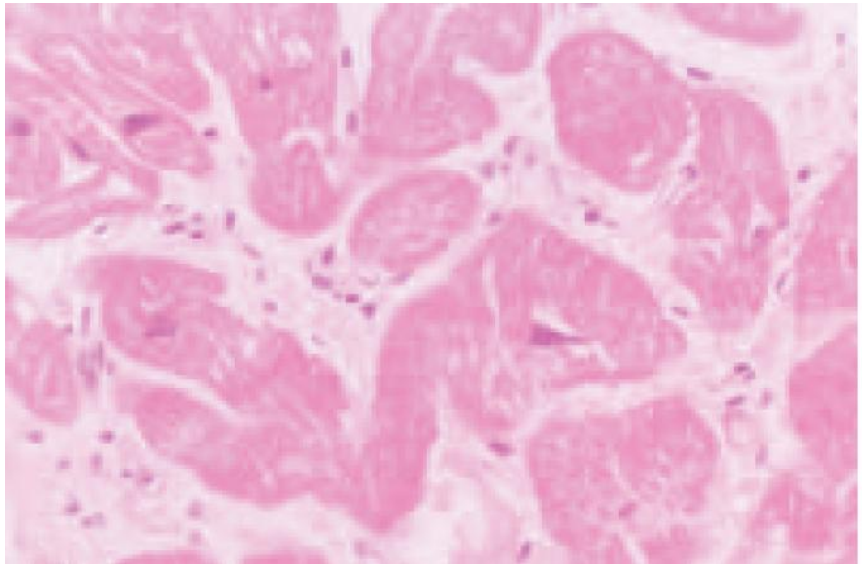
LVH - Imaging

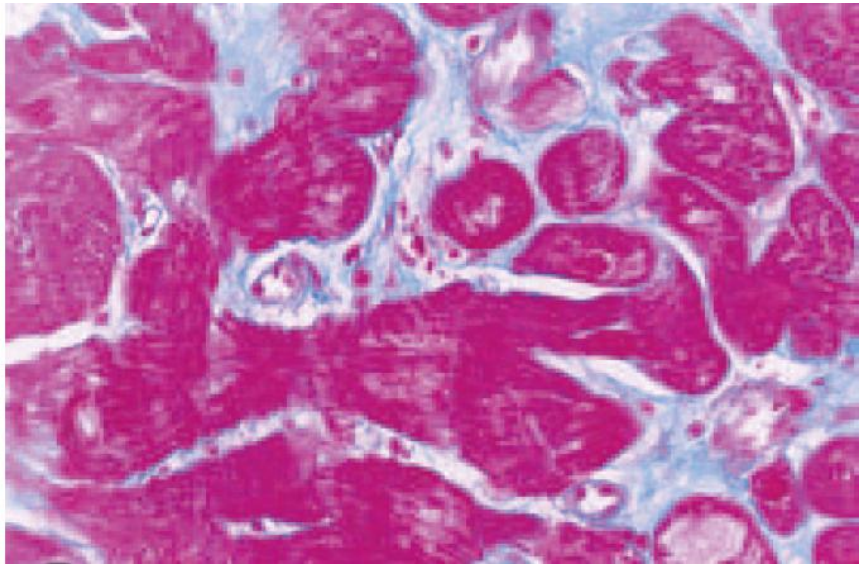


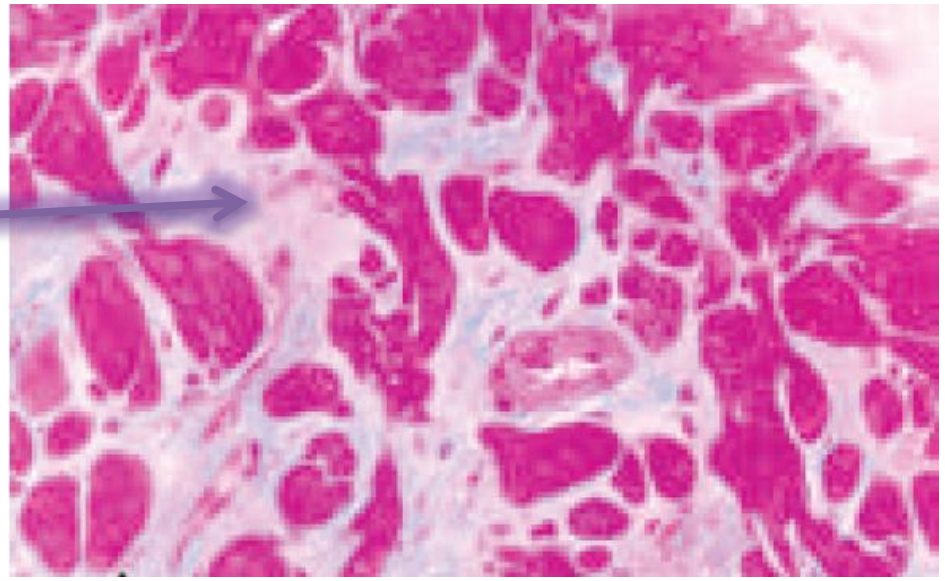
C



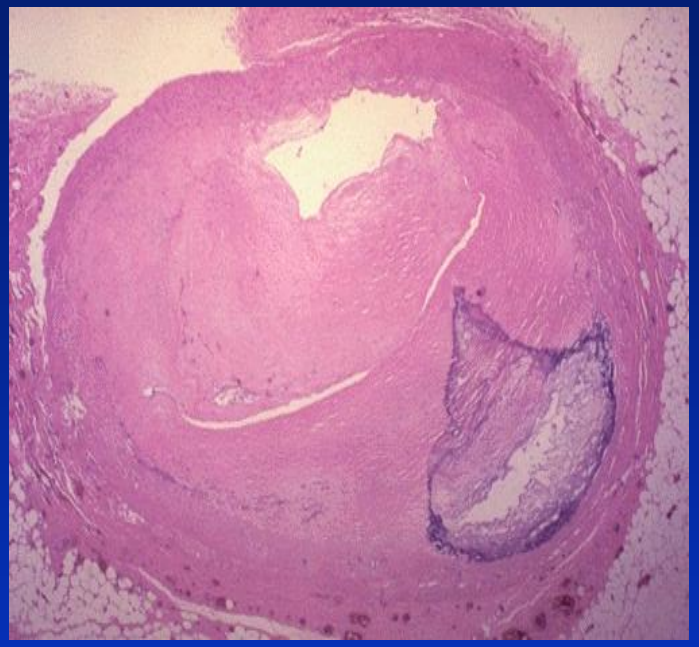
LVH





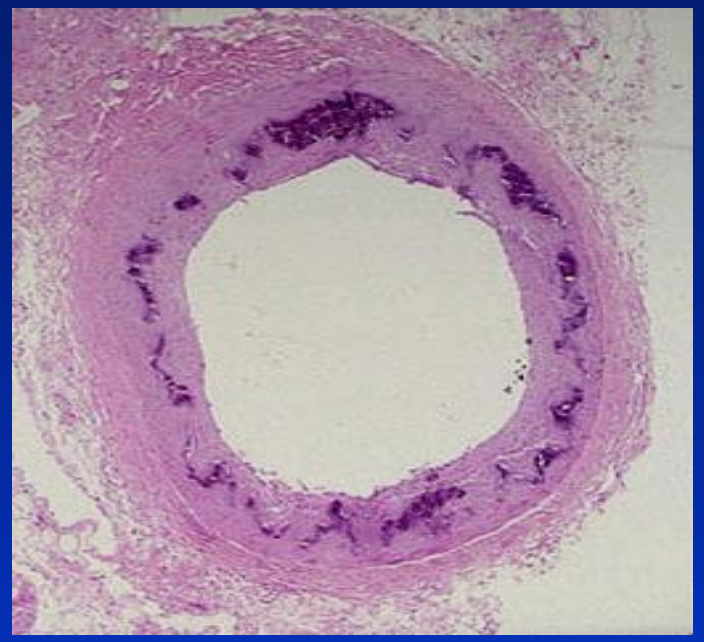


Atherosclerosis vs. uraemic arteriopathy



Atherosclerosis

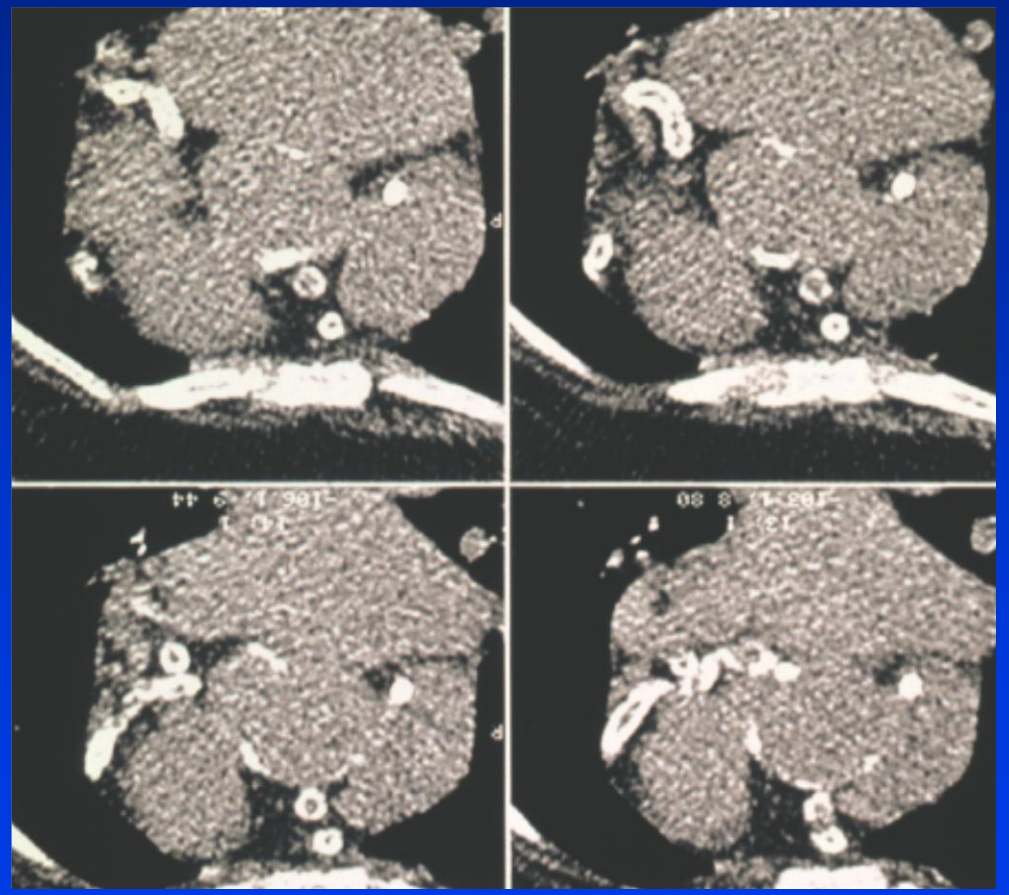
- Inflammation
- Lipid
- Intimal calcification



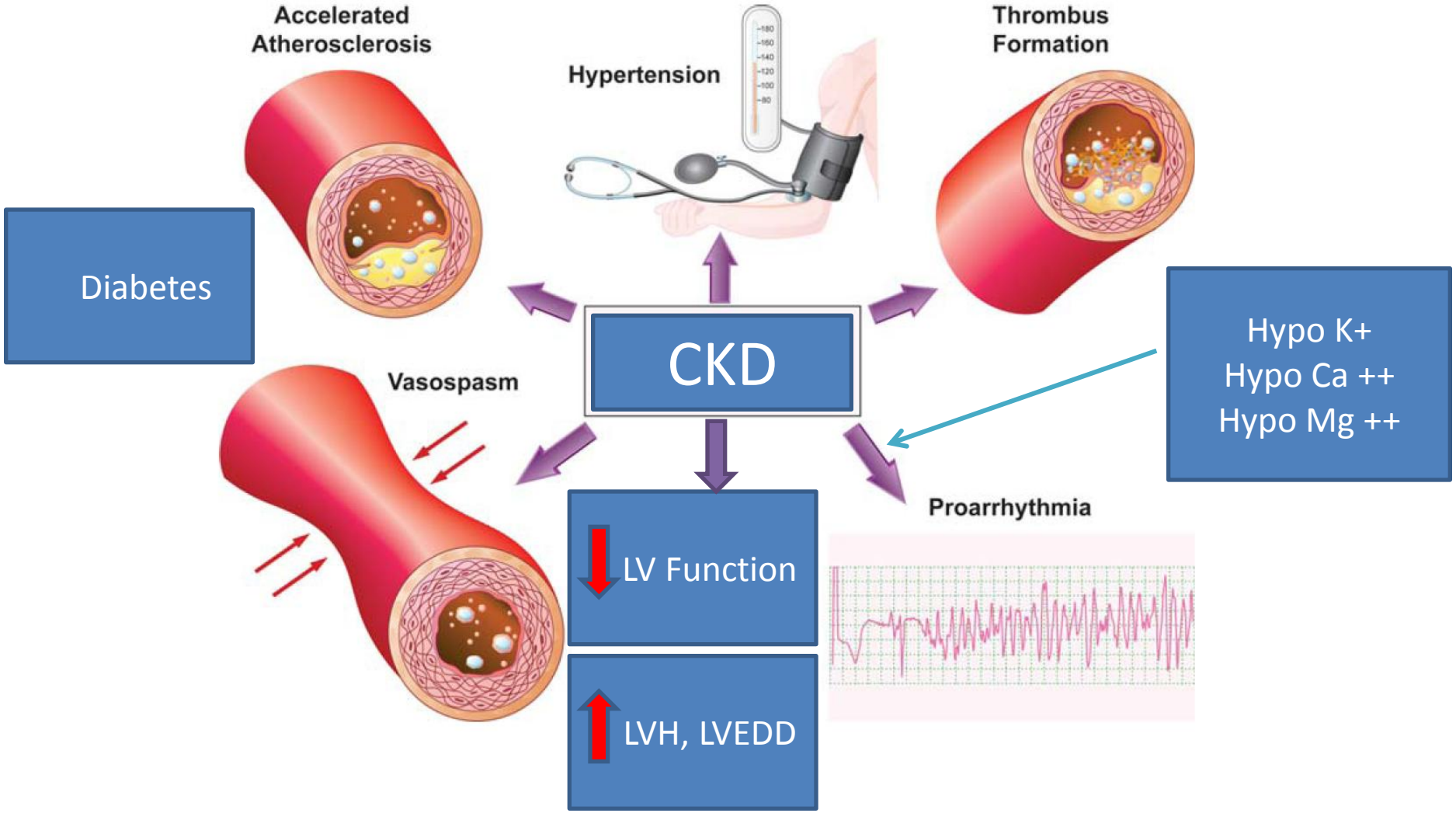
Uraemic arteriopathy

- No inflammation
- No lipid
- Medial calcification

Coronary artery calcification on EBCT



Sudden death culprits



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"The editors and the various authors should be congratulated for delivering an integrated body of work which is highly relevant to a broad medical audience and which aims to improve patient care."

Professor John Deanfield, UCL, London

This book provides a comprehensive overview of the clinical challenges faced during the treatment of patients with cardiorenal syndrome (CRS). The bidirectional link that associates renal and cardiovascular diseases means that patients with CRS have an increased risk of hospital admission and mortality as a result of their coexistence yet, there are no agreed guidelines for their management.

Cardio-Renal Clinical Challenges takes clinical presentations and clinical problems as its base, and then discusses the evidence for best management of common clinical problems and the reasons for the complex interplay between the cardiac and renal systems. In addition, the link between heart failure and chronic kidney disease (CKD) can impose a considerable epidemiological burden thus this text also aims to address the issue of organizing healthcare to maximize both the opportunities for prevention and best healthcare economic returns.

This book will be of immediate value and practical interest to all consulting and trainee cardiologists and renal physicians. And it is hoped that it will encourage greater investigation and collaboration between the fields of nephrology and cardiovascular medicine.

Goldsmith
Covic
Spaak
Editors
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Internal Medicine

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David Goldsmith
Adrian Covic
Jonas Spaak
Editors

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