Cardiovascular Risk factors for CKD

A Levin

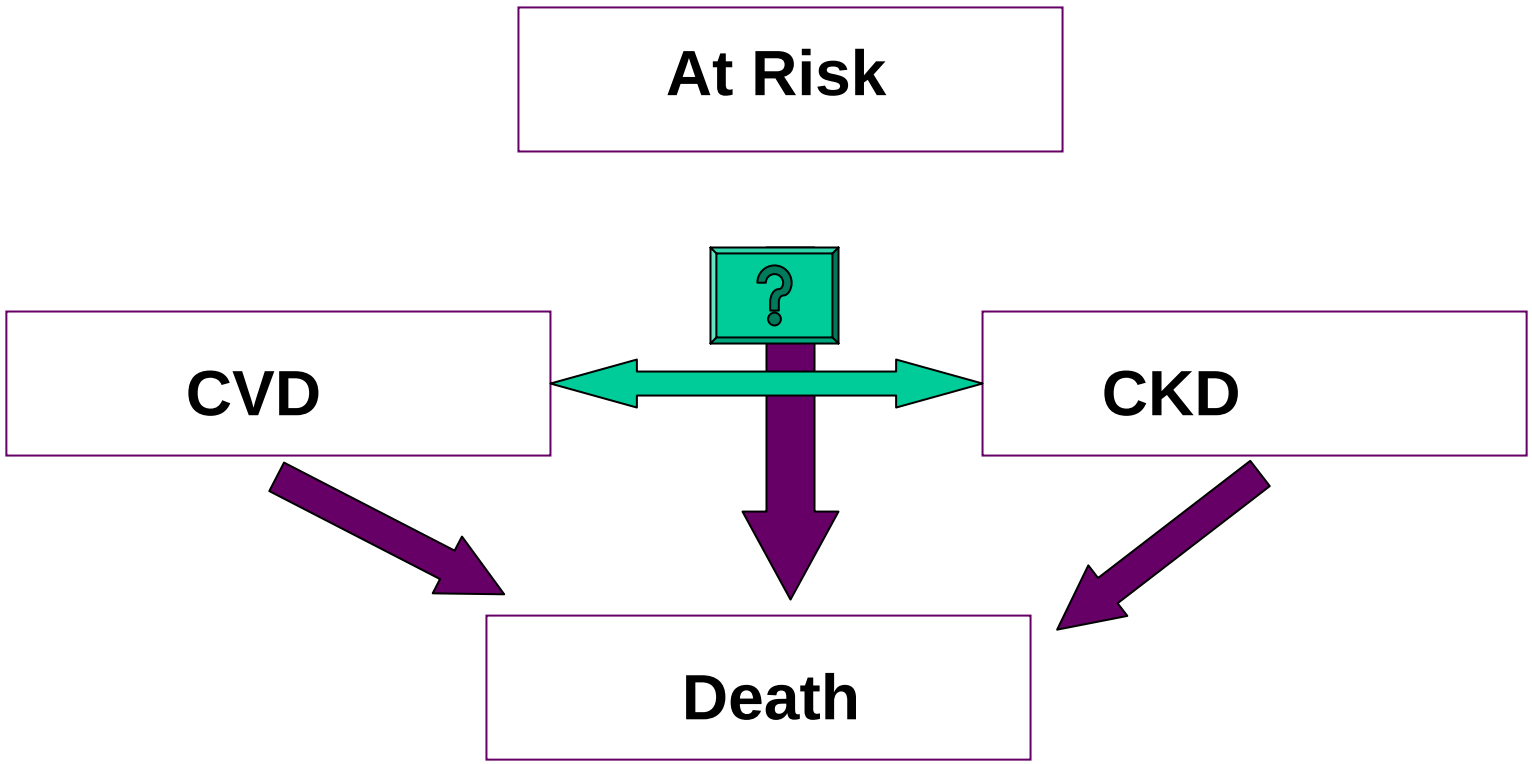
MD FRCPC

University of British Columbia

Objectives

- **CVD and CKD:**
  - **incidence, prevalence and outcomes**
  - **Complexity of interactions**
- **Framework for study of**
  - **Susceptibility, initiation and progression factors**
  - **Biological basis for considering CVD as CKD risk factor and implications**
- **Unanswered questions**

Can we conceive of CVD or its risk factors as important in the initiation or progression of CKD?



Of kidneys and hearts

CKD

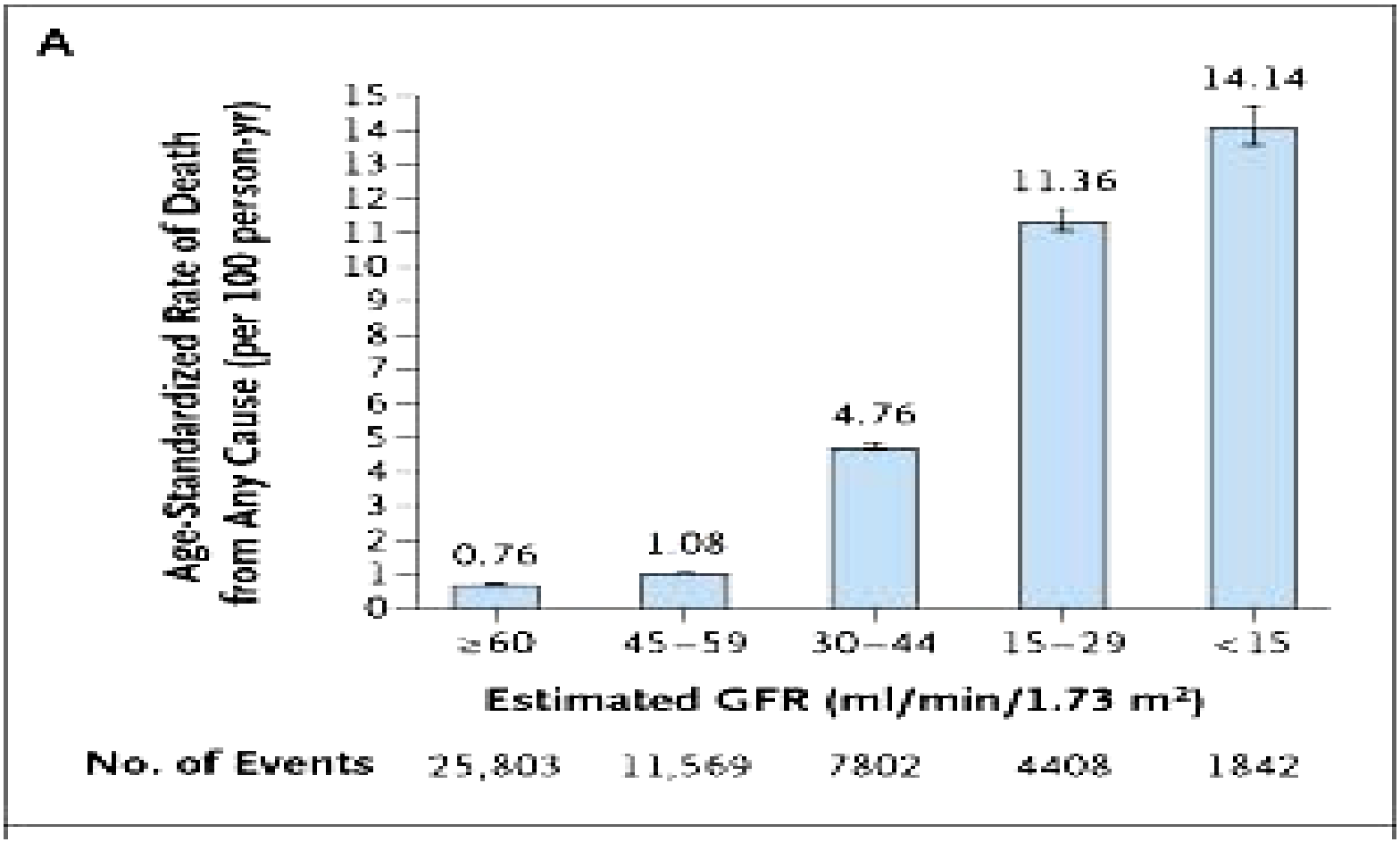
CKD as a risk factor for CVD

- Hypertension
- Bone and mineral disorder
- Dyslipidemia
- Sympathetic overactivity
- Salt- and volume overload
- Anemia
- Uremic toxins
- “Undertreatment”
- Immunosuppressants

Extensive evidence in this field will serve as a model

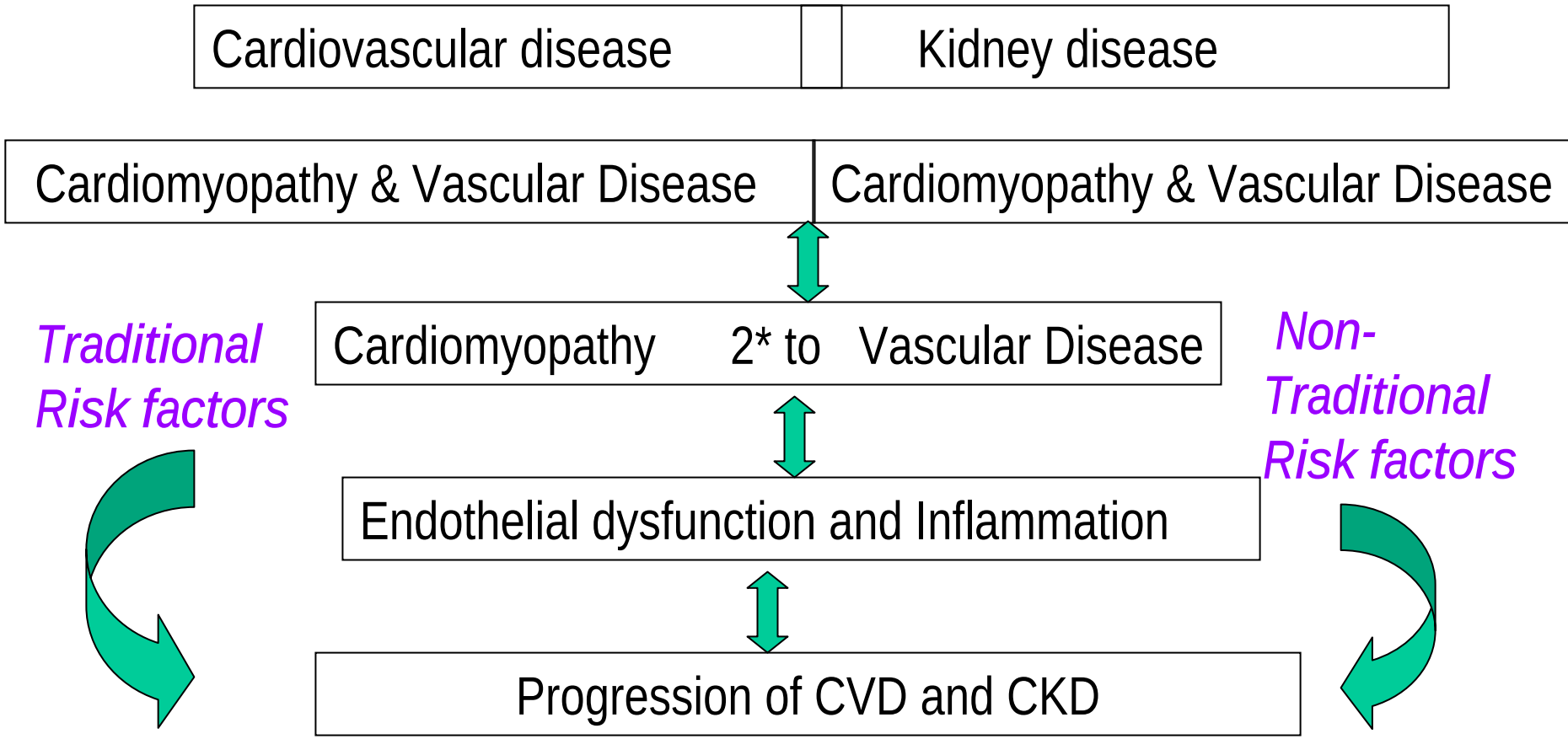
Cardiovascular disease

Mortality increase exponentially as GFR declines

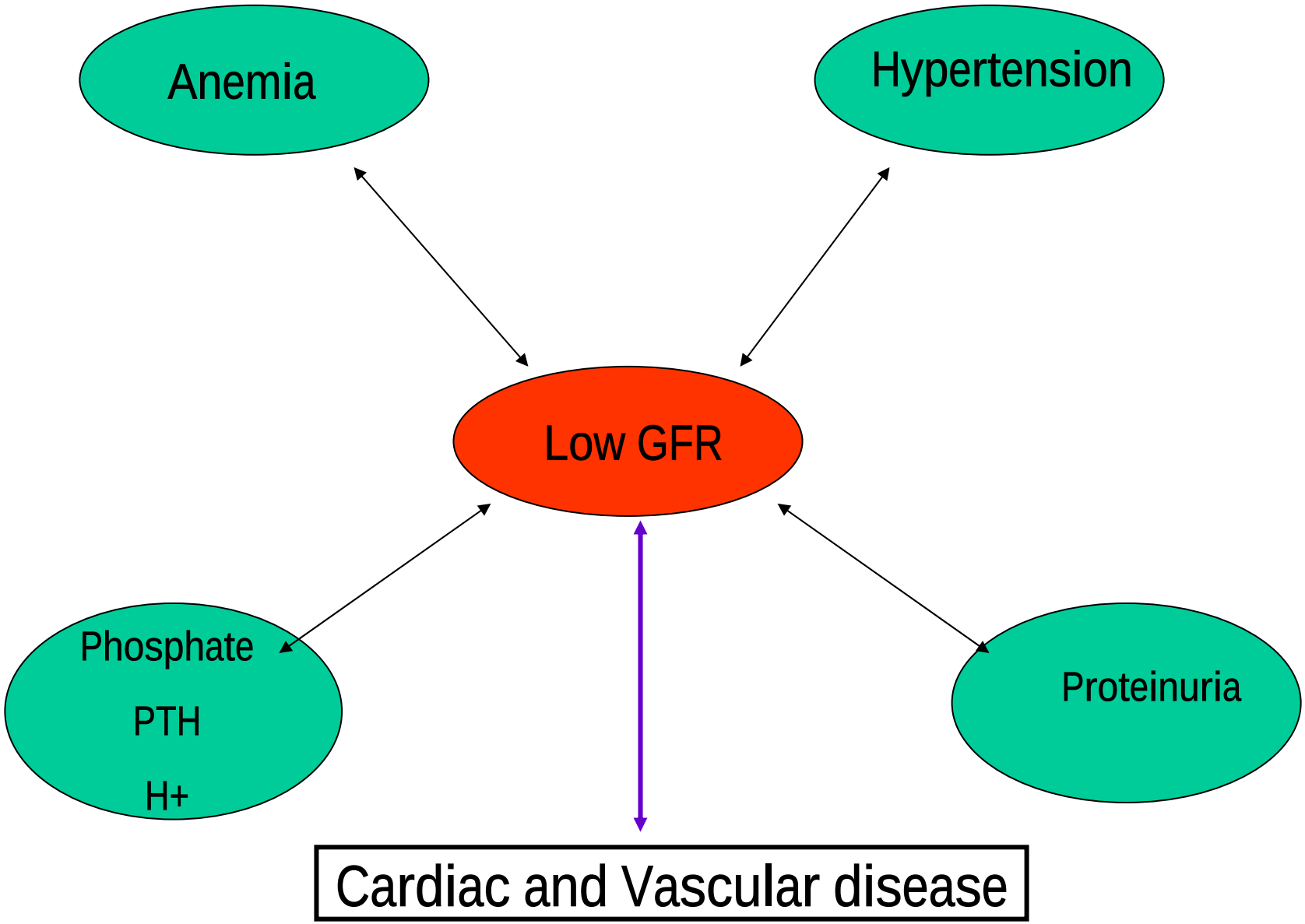


Go et al NEJM 2004 351: 1296-1305

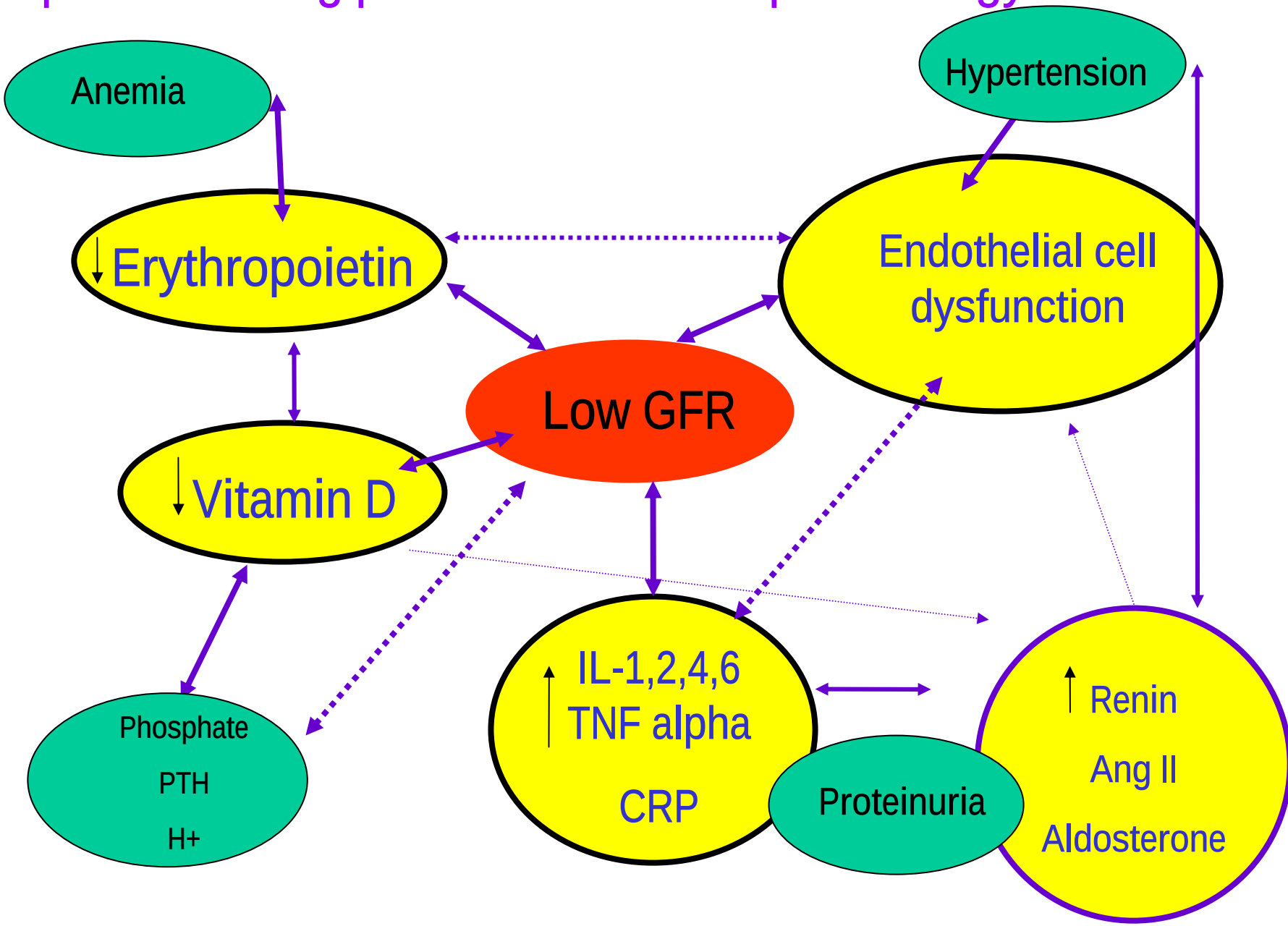
Construct

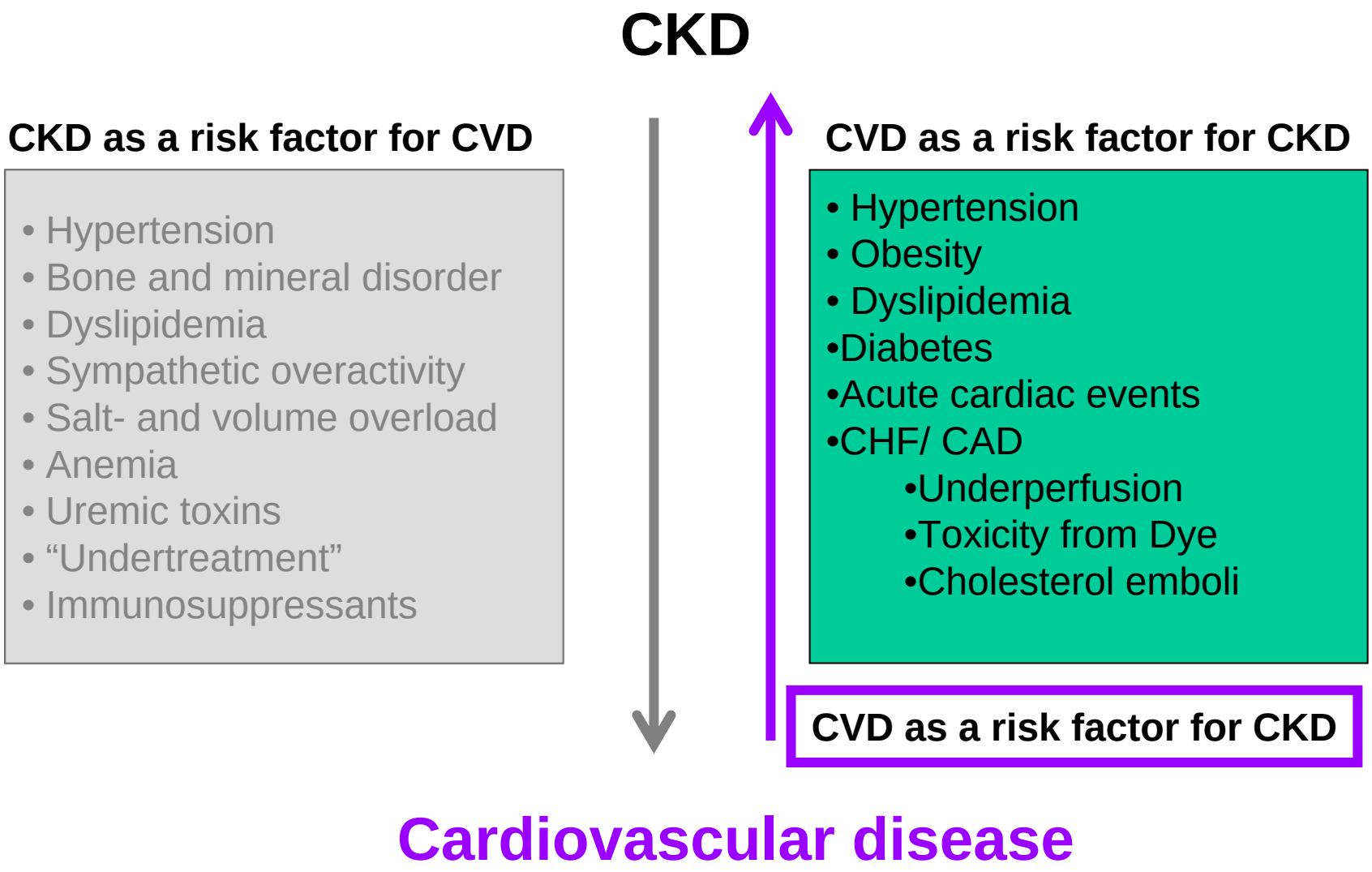

Cardiovascular disease
Kidney disease
Cardiomyopathy & Vascular Disease
Cardiomyopathy & Vascular Disease
Traditional Risk factors
Cardiomyopathy 2* to Vascular Disease
Non-Traditional Risk factors
Endothelial dysfunction and Inflammation
Progression of CVD and CKD

Simple observations…



Multiple interacting processes and complex biology…..

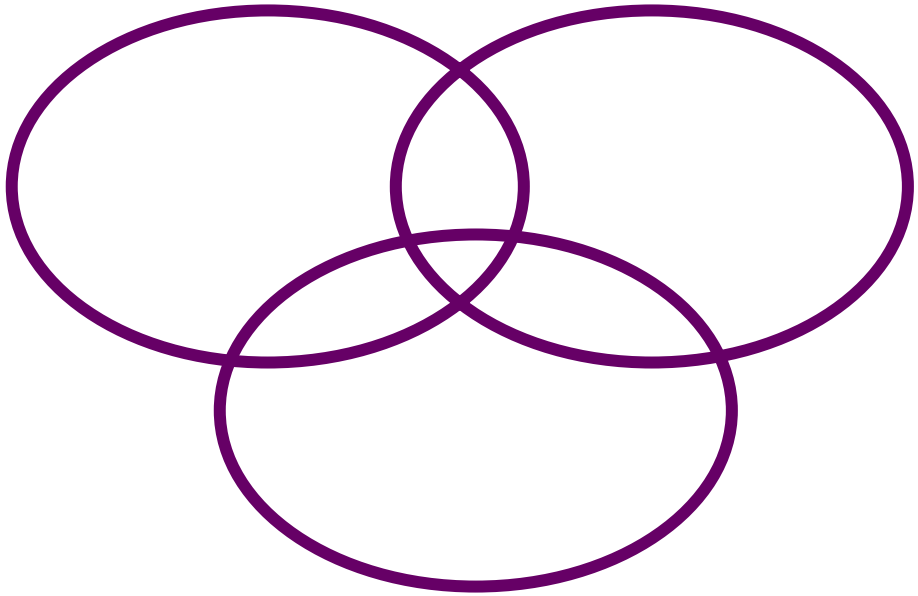



CKD
CKD as a risk factor for CVD
• Hypertension
• Bone and mineral disorder
• Dyslipidemia
• Sympathetic overactivity
• Salt- and volume overload
• Anemia
• Uremic toxins
• "Undertreatment"
• Immunosuppressants
CVD as a risk factor for CKD
• Hypertension
• Obesity
• Dyslipidemia
•Diabetes
•Acute cardiac events
•CHF/ CAD
•Underperfusion
•Toxicity from Dye
•Cholesterol emboli
CVD as a risk factor for CKD
Cardiovascular disease

Defining a framework for systematic study

- **Risk factors for CKD**
  - **Susceptibility and Initiation (no disease)**
  - **Progression (established disease)**
- **Risk factors for CKD are risk factor conditions commonly associated with CVD:**
  - **DM**
  - **HTN**
  - **Dyslipidemia**
  - **Smoking**

Risk factors for CKD



Susceptibility

(no disease)

Genetics

Ethnicity

???

Initiation

(no disease)

Acute events?

Progression

(established disease)

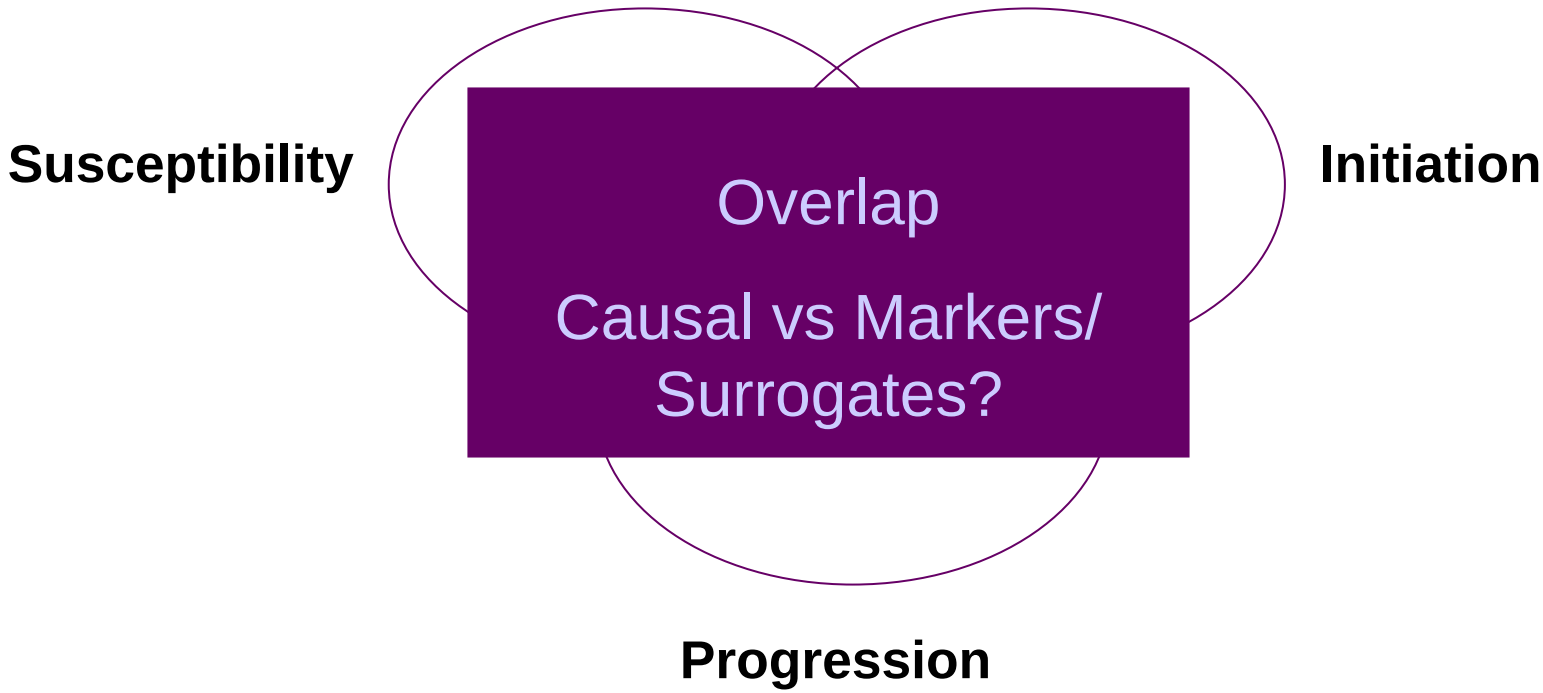
Risk factors for CVD

Defining a (Causal) Risk factor:

- **Evidence of cause and effect relationship between variable and disease of interest**
- **Bradford Hill Criteria:**
  - **Strength of association**
  - **Consistency**
  - **Specificity**
  - **Temporality**
  - **Biological Gradient**
  - **Plausibility**
  - **Coherence**
  - **Experimental evidence**
  - **Analogy**

- **Non causal risk factors~ markers/ surrogates**

Risk factors for CKD



Risk factors for CVD

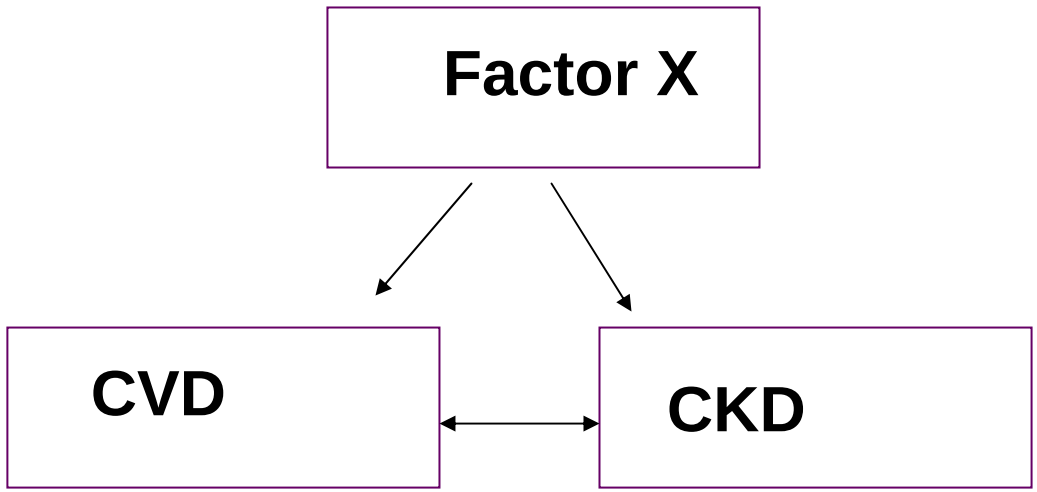
Common factors associated with adverse outcomes in CVD and CKD

- **Traditional**
  - **Hypertension**
  - **Diabetes**
  - **Dyslipidemia**
  - **Family history**
  - **Smoking**
  - **Obesity**

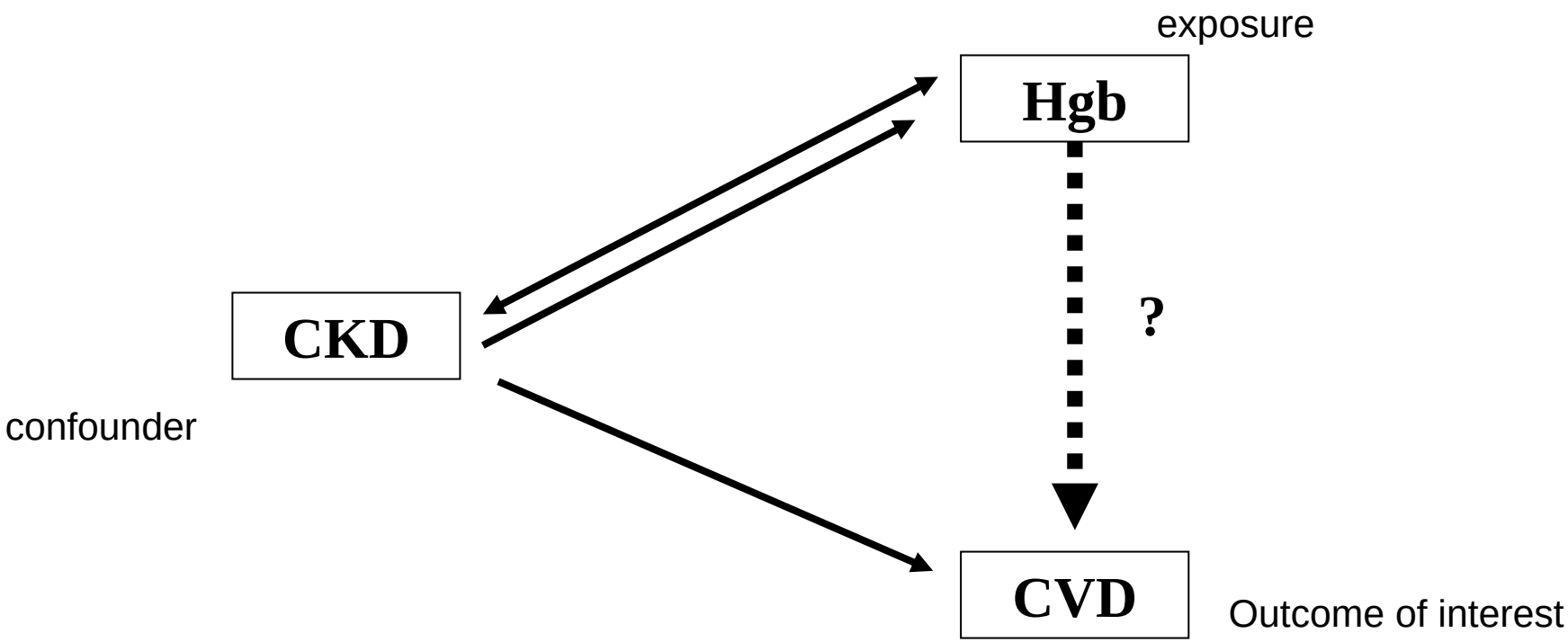
'Non traditional'

- **Anemia**
- **iPTH excess**
- **Calcium phosphate abnormalities**
- **Vitamin D deficiency**
- **Kidney function**
- **Albuminuria/ Proteinuria**

What are the reasons that specific factors lead to CVD or CKD preferentially in different individuals?

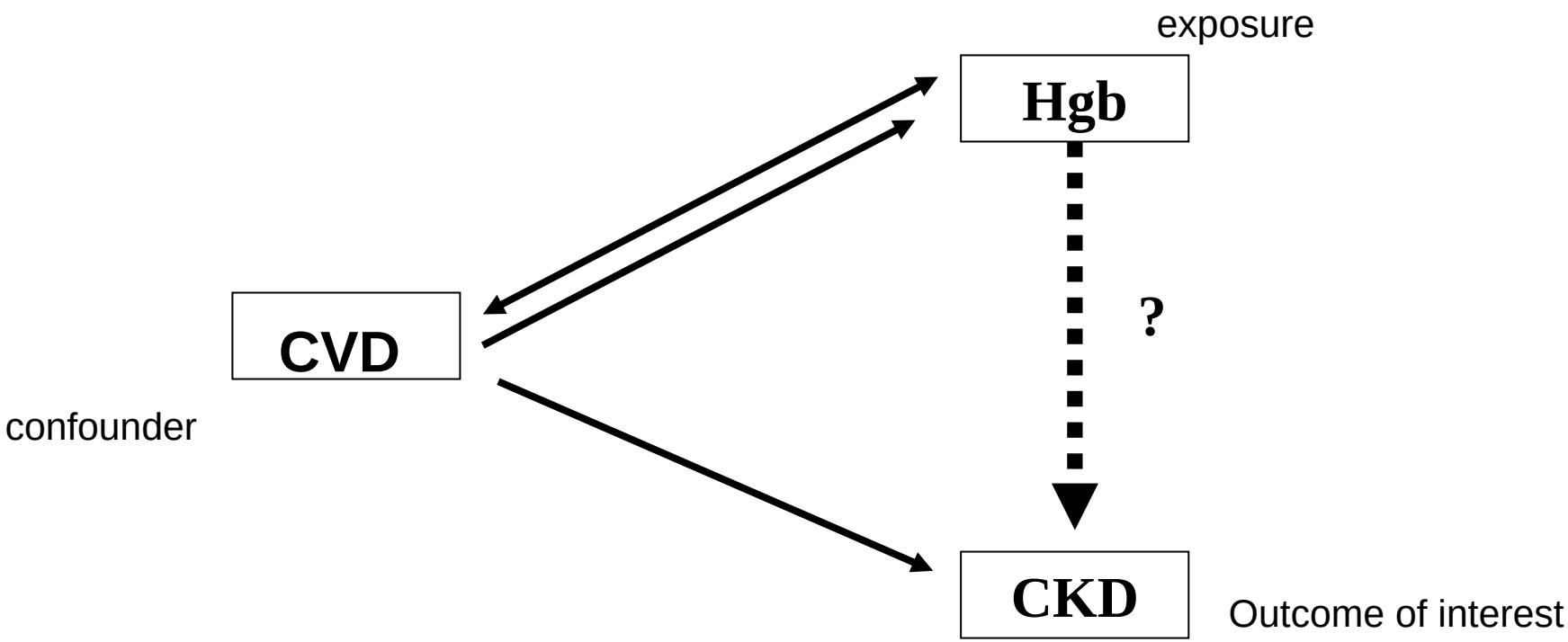


Anemia as Risk factor for CVD



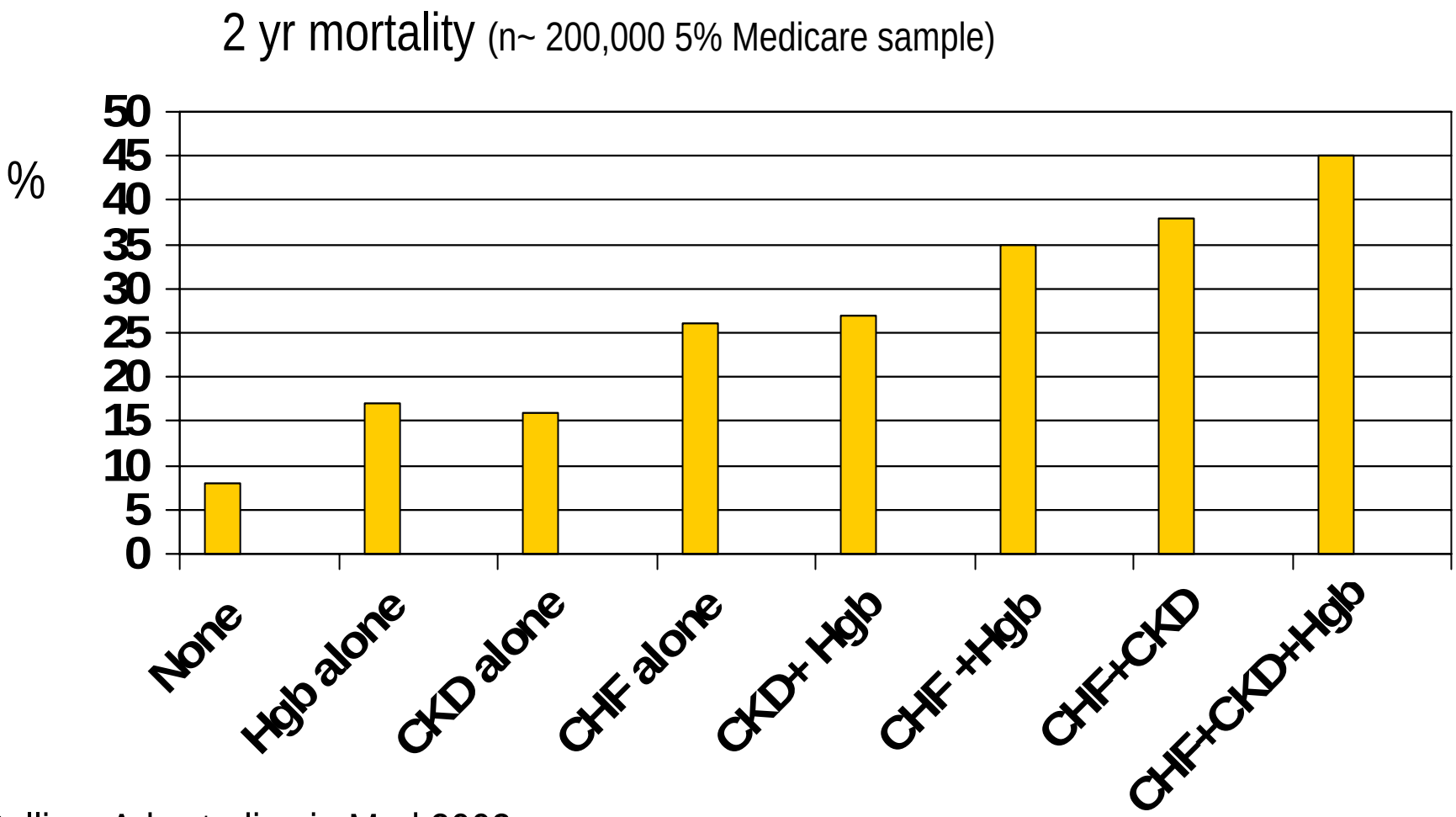
The confounder (C) is causally associated with the outcome of interest (Y) and either causally or noncausally associated with exposure (E); these associations may distort the association of interest: whether E causes Y

Anemia as Risk factor for CKD



The confounder (C) is causally associated with the outcome of interest (Y) and either causally or noncausally associated with exposure (E); these associations may distort the association of interest: whether E causes Y

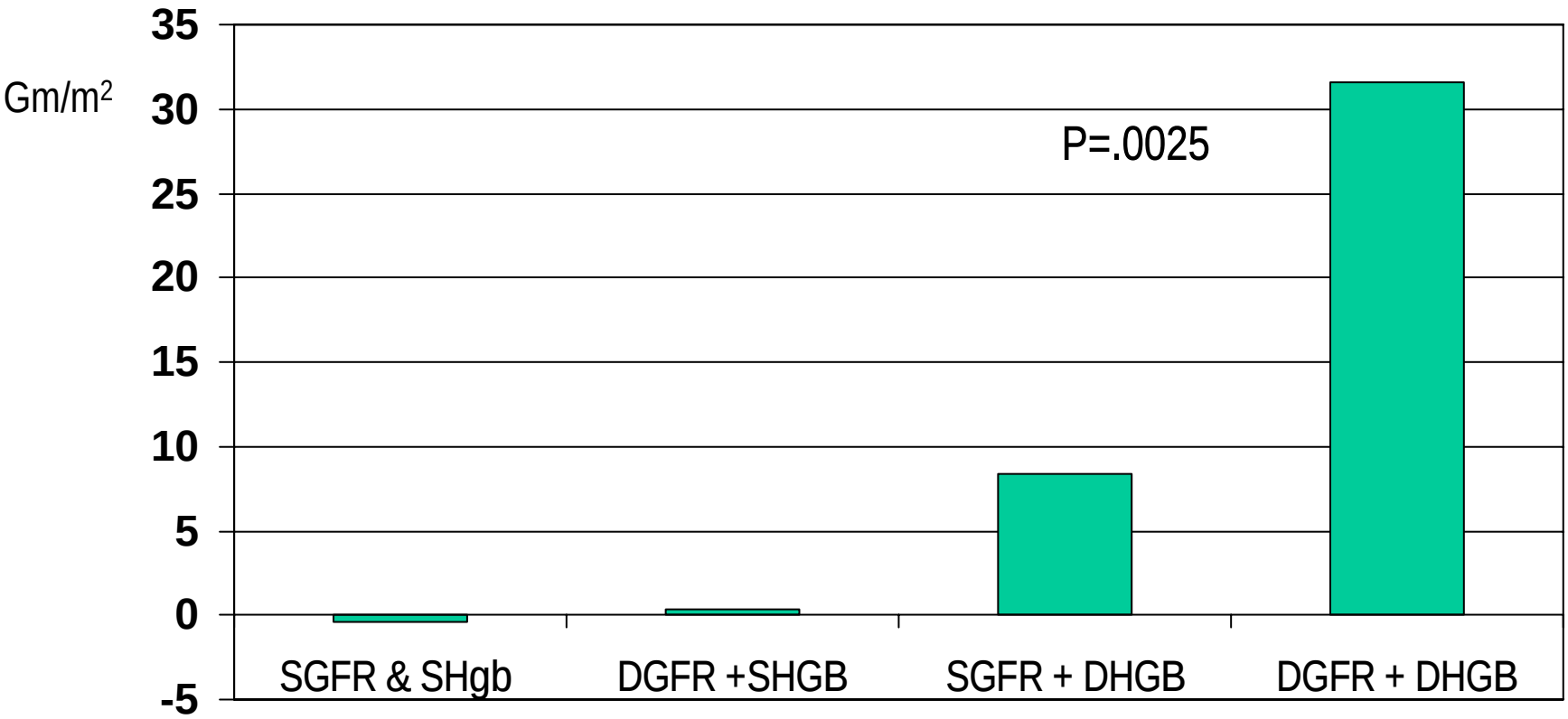
Synergistic effect of CKD,CHF and Anemia as risk factors for Death



Collins, Adv studies in Med 2003

LVMI growth
is greater if both GFR and Hgb decline

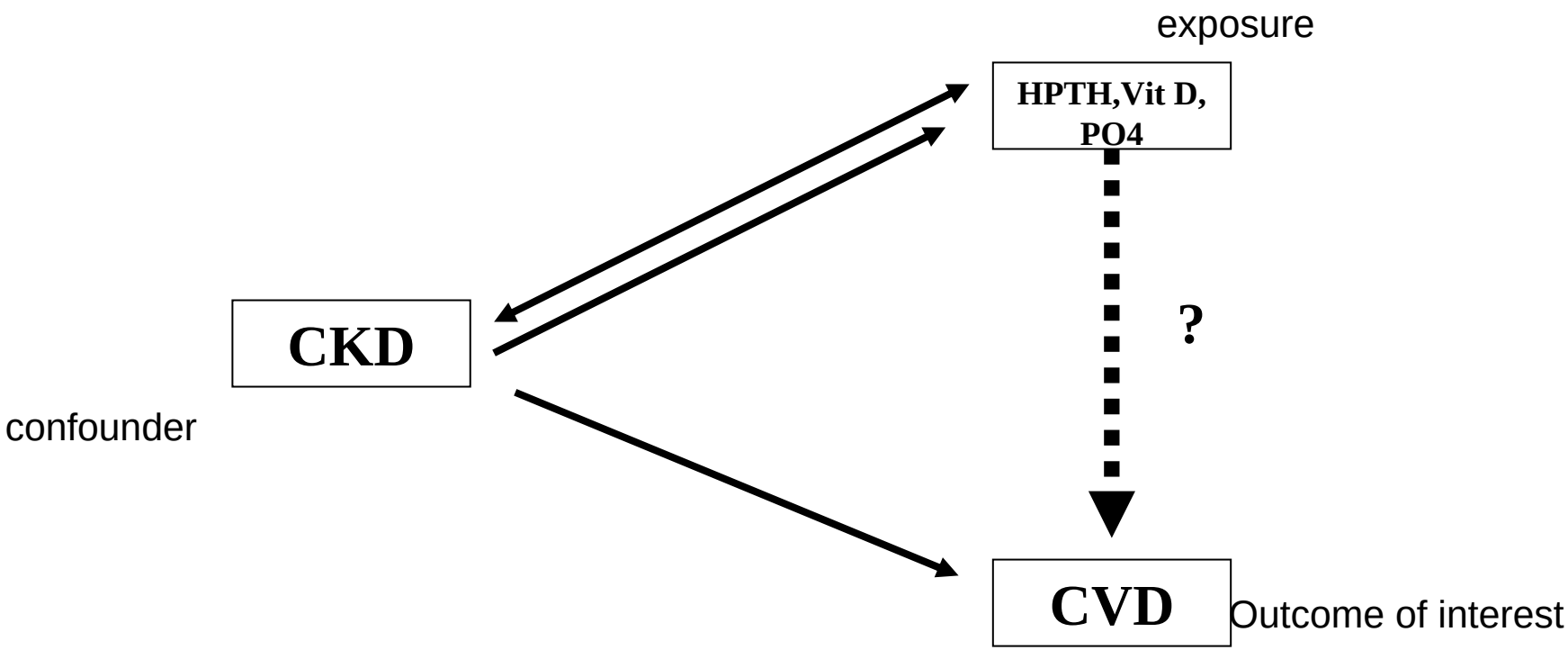
S = Stable,no change Hgb or GFR , D= Decline Hgb >10g/L or GFR >10 ml/min



24 mo RCT in CKD pts comparing EPO therapy to maintain vs treat low Hgb
N= 152

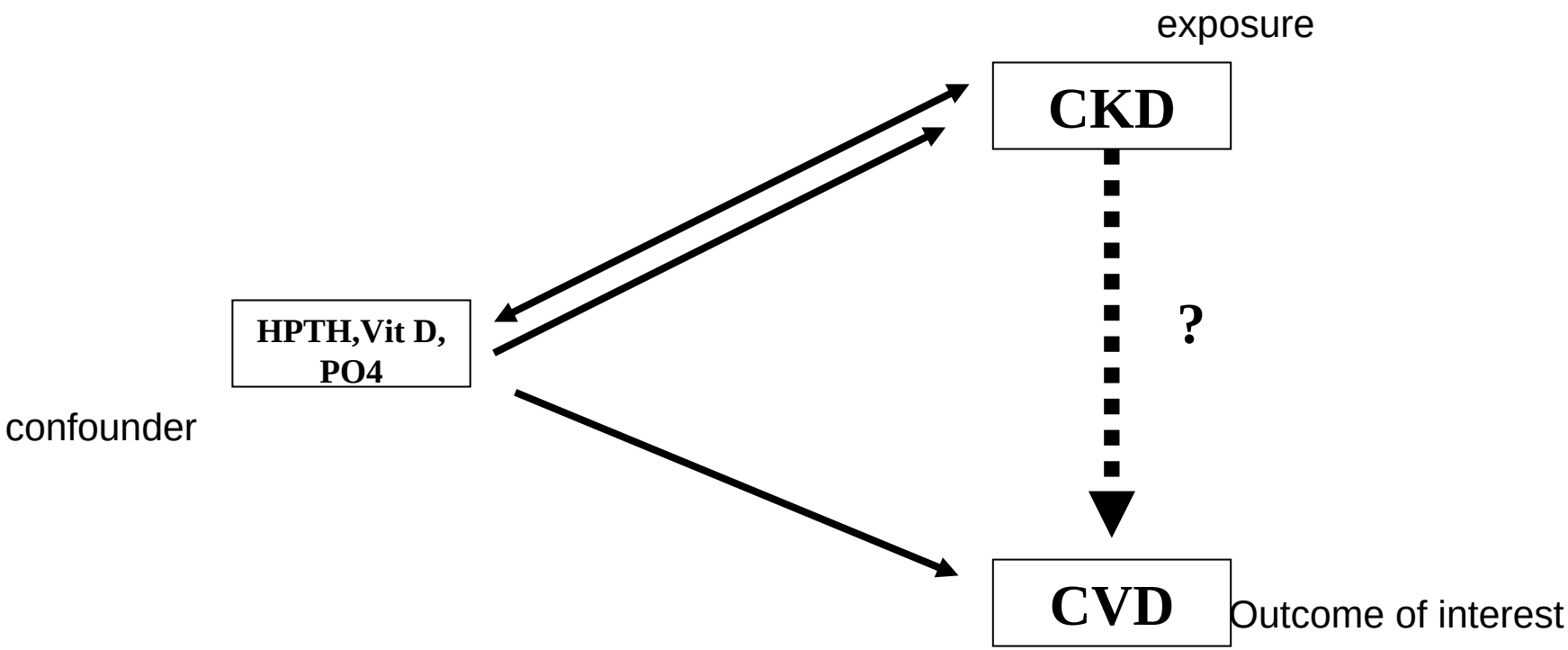
Levin et al , AJKD 2005

Abnormal Mineral Metabolism as Risk factor



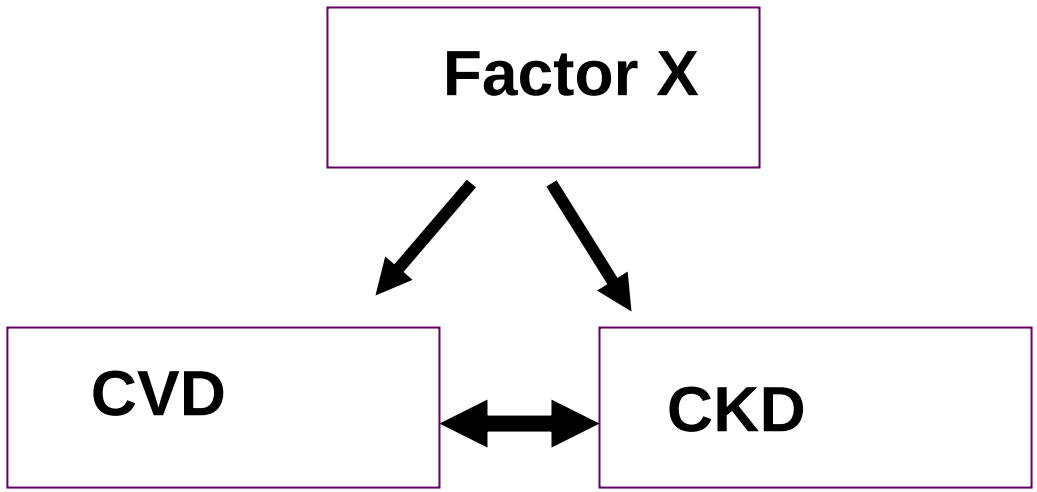
The confounder (C) is causally associated with the outcome of interest (Y) and either causally or noncausally associated with exposure (E); these associations may distort the association of interest: whether E causes Y

Abnormal Mineral Metabolism as Risk factor



The confounder (C) is causally associated with the outcome of interest (Y) and either causally or noncausally associated with exposure (E); these associations may distort the association of interest: whether E causes Y

What are the reasons that specific factors lead to CVD or CKD preferentially in different individuals?



CKD + CVD increases risk of adverse outcomes

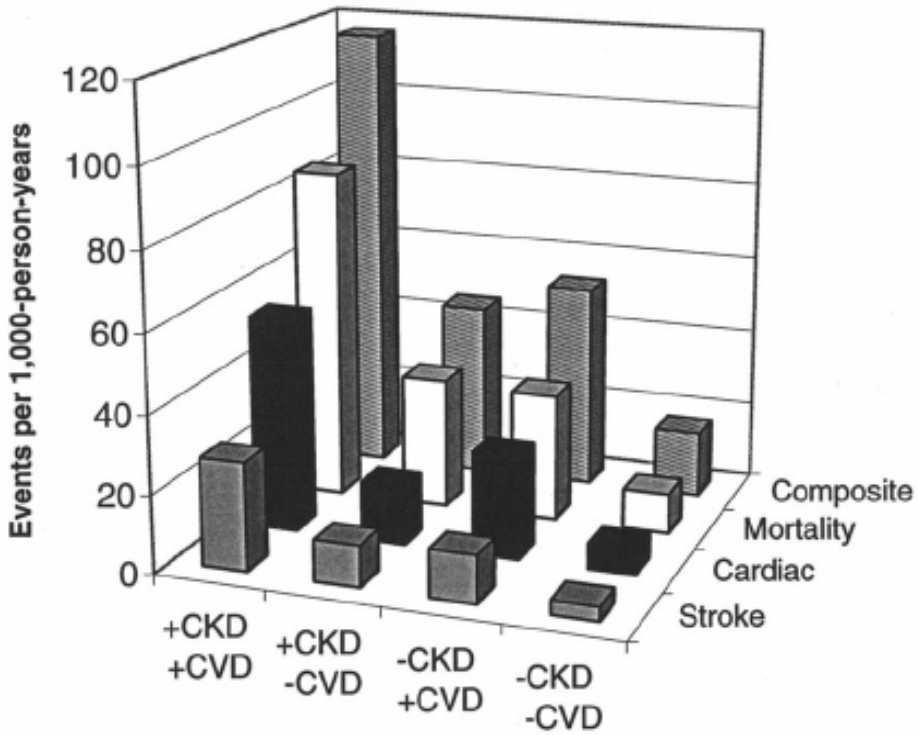
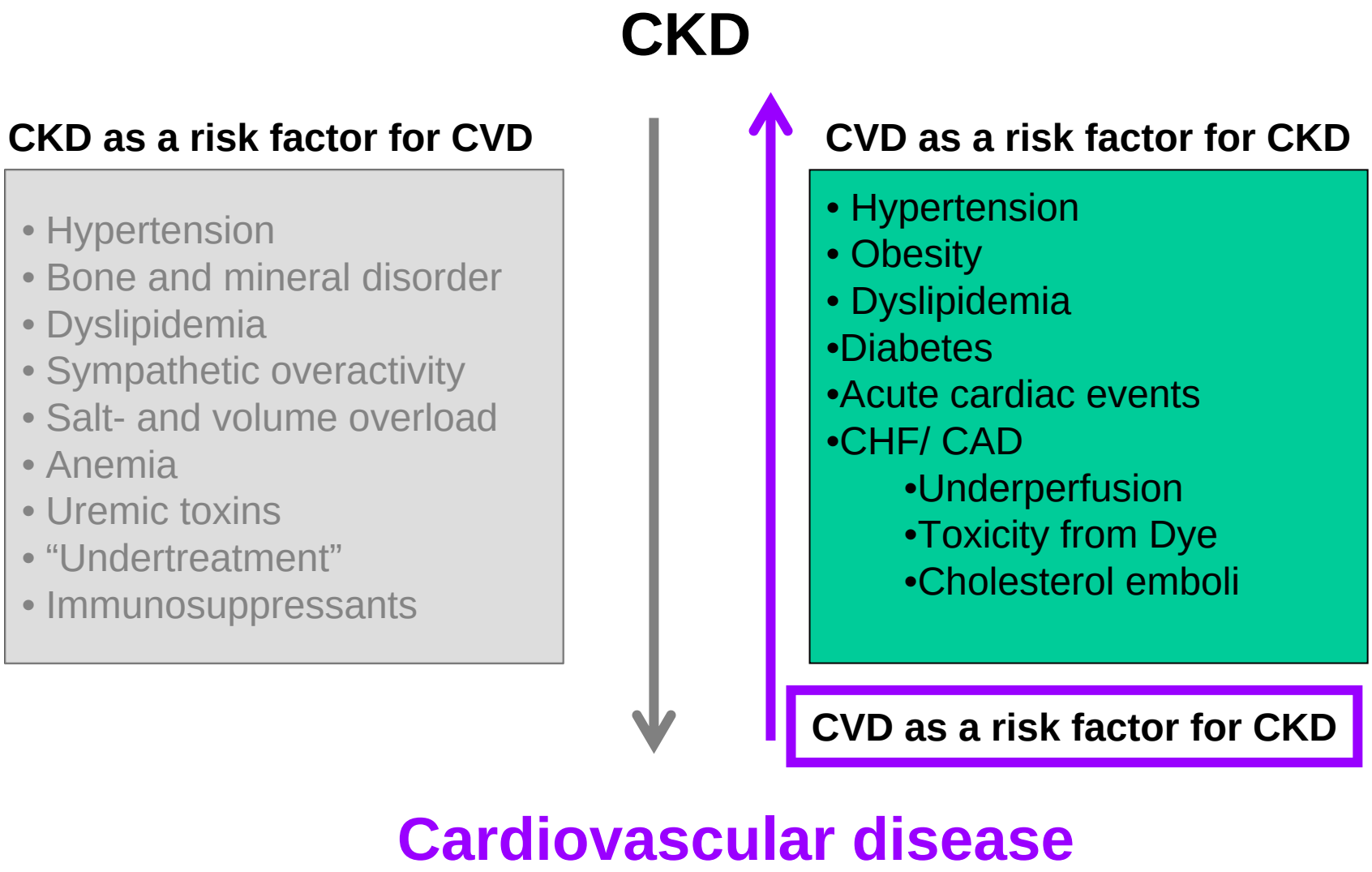


Fig 2. Unadjusted event rates for individuals with and without CKD and CVD. Cardiac events include MI and fatal CHD. Stroke includes both fatal and nonfatal stroke events. Mortality includes all causes of death, and the composite outcome includes any cardiac, stroke, or mortality event.

Menon, Sarnak et al AJKD 2006

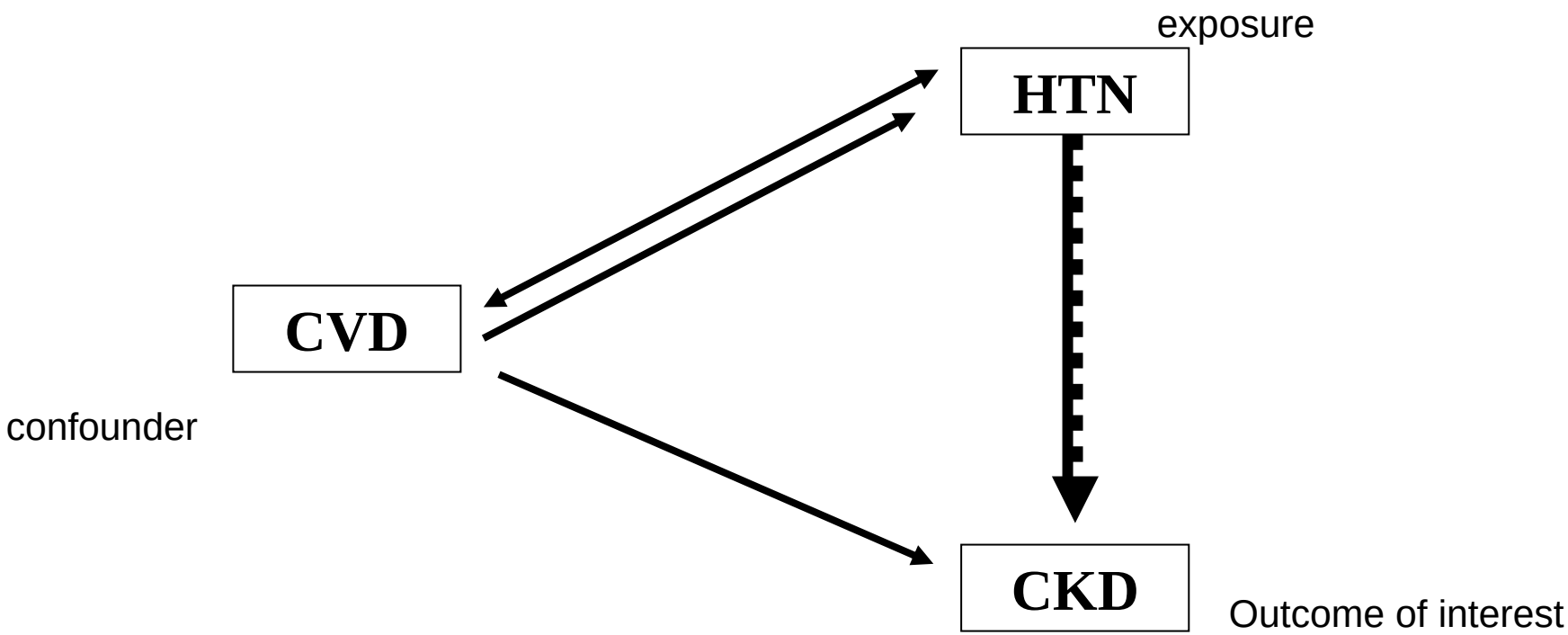

CKD
CKD as a risk factor for CVD
• Hypertension
• Bone and mineral disorder
• Dyslipidemia
• Sympathetic overactivity
• Salt- and volume overload
• Anemia
• Uremic toxins
• "Undertreatment"
• Immunosuppressants
CVD as a risk factor for CKD
• Hypertension
• Obesity
• Dyslipidemia
•Diabetes
•Acute cardiac events
•CHF/ CAD
•Underperfusion
•Toxicity from Dye
•Cholesterol emboli
CVD as a risk factor for CKD
Cardiovascular disease

CKD Risk Factors to be tested

Risk Factor	Definition	Examples
Susceptibility factors	**Increase susceptibility to kidney damage**	**Older age, family history of CKD, U.S. racial or ethnic minority status, reduced kidney mass, hyperfiltration states**
Initiation factors	**Directly initiate kidney damage**	**Diabetes, high blood pressure, obesity, dyslipidemia, autoimmune diseases, infections, stones, obstruction**
Progression factors	**Cause worsening kidney damage and faster GFR decline**	**Higher level of proteinuria**
End-stage (outcome) factors	**Increase morbidity and mortality in kidney failure**	**Lower dialysis dose (Kt/V), temporary vascular access, anemia, low serum albumin level, late referral**

Factors that are implicated at different stages in the development and progression of CKD are listed in the initial category in which they could potentially appear.

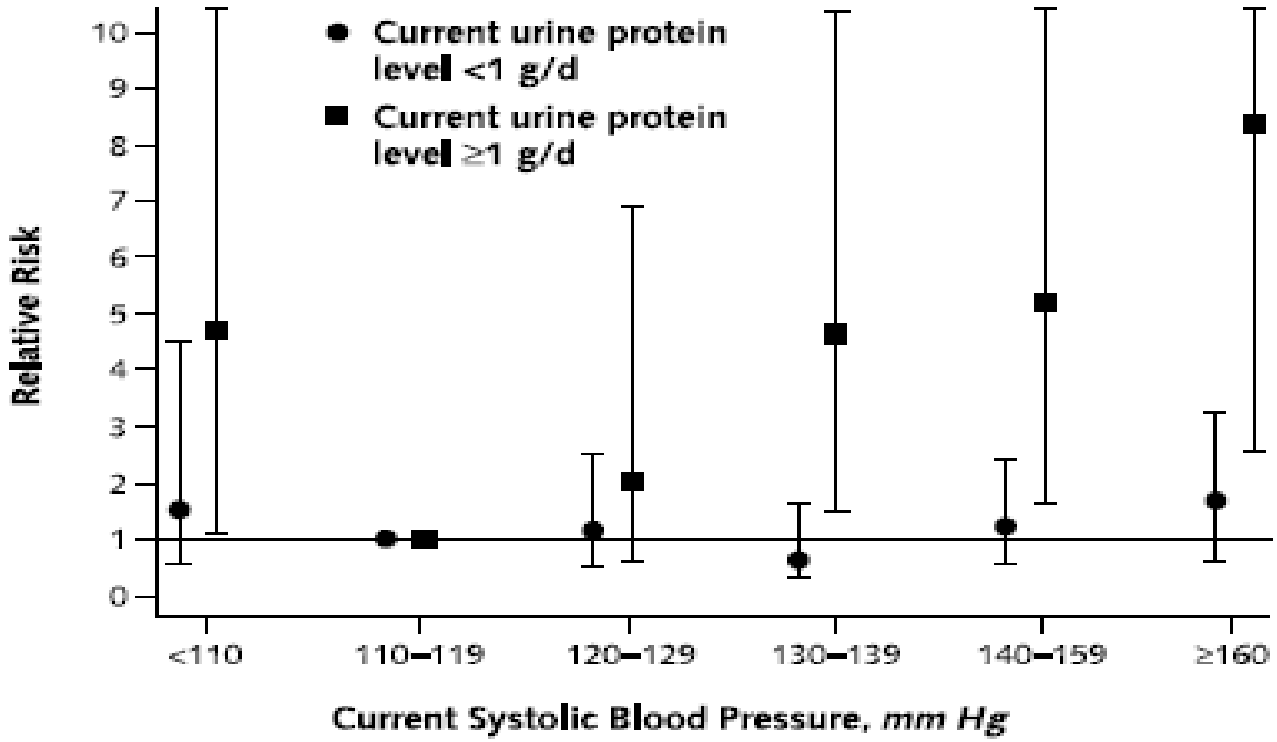
HTN as Risk factor for CKD



The confounder (C) is causally associated with the outcome of interest (Y) and either causally or noncausally associated with exposure (E); these associations may distort the association of interest: whether E causes Y

Progression

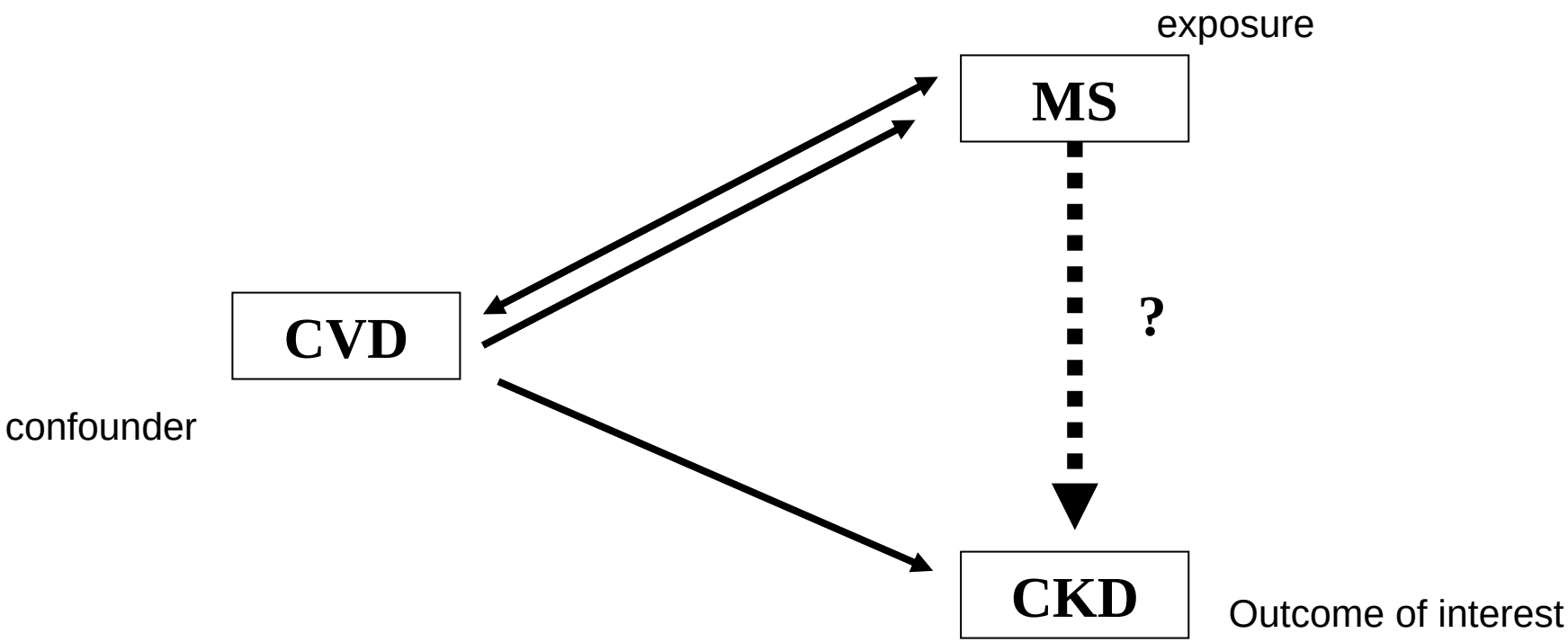
Relative risk for kidney disease progression based on current level of systolic blood pressure and current urine protein excretion



Jafar et al Ann Int Med 2003

Pt level meta-analysis ACEi

Metabolic syndrome as Risk factor for CKD



The confounder (C) is causally associated with the outcome of interest (Y) and either causally or noncausally associated with exposure (E); these associations may distort the association of interest: whether E causes Y

What is the incidence of CKD (defined as GFR < 60 ml/min/ 1.73m^2 at year 9?

10,096 pts from ARIC

Normal baseline kidney function

9 years of follow up

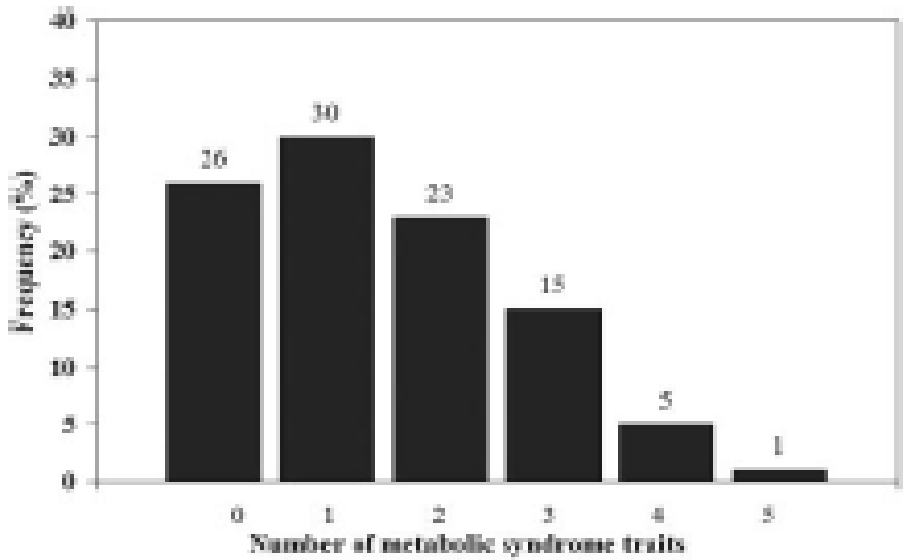


Figure 2. Distribution of metabolic syndrome traits in study participants.

Kurella, Lo and Chertow JASN 2005

Metabolic syndrome predicts CKD

OR =1.43 (1.18-1.73)

J Am Soc Nephrol 16: 2134–2140, 2005

Table 2. OR of developing CKD over 9 years of follow-up by presence or absence of the metabolic syndrome[a]

	CKD (*n* [%])		OR (95% CI)		
	Metabolic Syndrome Absent	Metabolic Syndrome Present	Unadjusted	Age, Gender, and Race Adjusted	Multivariable Adjusted
eGFR <60 ml/min per 1.73 m^2	484 (6%)	207 (10%)	1.69 (1.42 to 2.00)	1.53 (1.29 to 1.82)	1.43 (1.18 to 1.73)
Elevated serum creatinine	104 (1%)	52 (3%)	1.92 (1.37 to 2.68)	1.83 (1.30 to 2.57)	1.60 (1.11 to 2.30)

[a]Elevated serum creatinine for men >1.5 mg/dl and for women >1.2 mg/dl. Multivariable models adjusted for age, gender

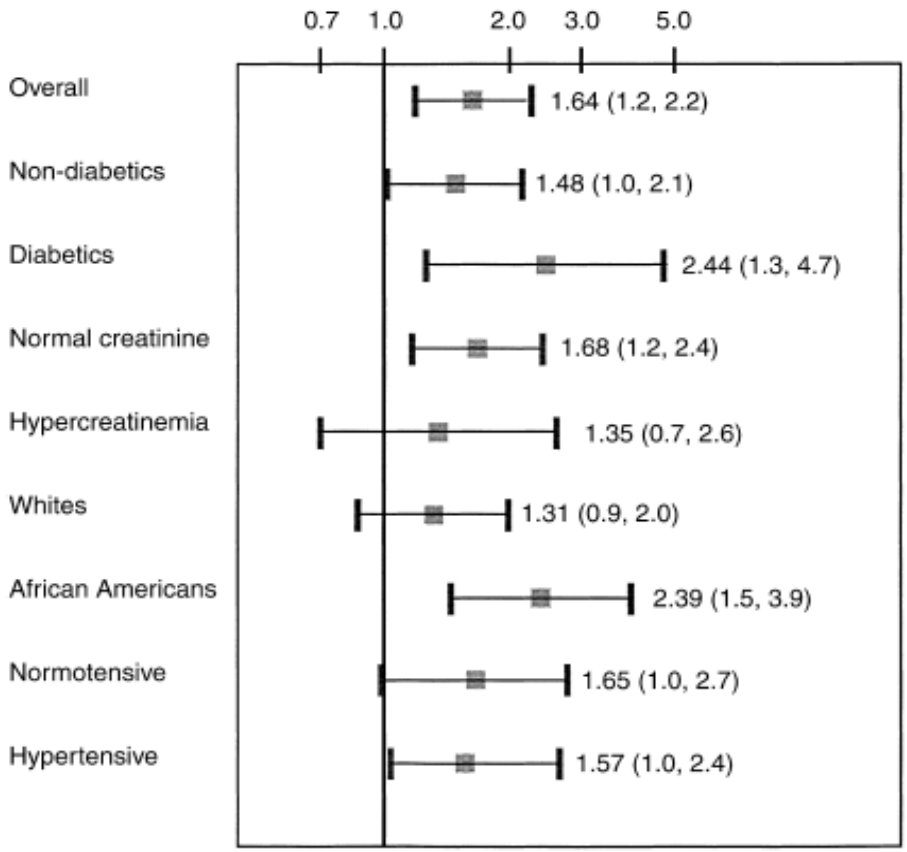
Table 5. OR of developing CKD (eGFR <60 ml/min per 1.73 m^2) over 9 years of follow-up by individual metabolic syndrome traits

Metabolic Syndrome Trait	CKD (*n* [%])		OR (95% CI)	
	Trait Absent	Trait Present	Unadjusted	Age, Gender, and Race Adjusted
Abdominal obesity	336 (6%)	355 (8%)	1.27 (1.09 to 1.48)	1.18 (1.00 to 1.40)
Elevated triglycerides	471 (6%)	220 (9%)	1.48 (1.25 to 1.74)	1.34 (1.12 to 1.59)
Low HDL	421 (6%)	270 (8%)	1.19 (1.02 to 1.40)	1.27 (1.08 to 1.49)
Hypertension	370 (5%)	319 (11%)	2.19 (1.87 to 1.56)	1.99 (1.69 to 2.35)
Impaired fasting glucose	603 (7%)	88 (8%)	1.17 (0.93 to 1.48)	1.11 (0.87 to 1.40)

OR =1.11(IGT)- 1.99 (HTN)

Kurella, Lo and Chertow JASN 2005

Hypertriglyceridemia predicts change in creatinine >0.4 mg/dl over 9 years



ARIC study between Visit 1 and 2

Adjusted for age, gender, race, baseline creatinine, systolic BP, medications, diabetes

Muntner et al , KI (58) 2000

Risk for CKD progression in ETDRS (Early Treatment of Diabetic Retinopathy)

2226 pat., 5 yrs. follow-up

risk factors for ESRD;
common to type 1 and type 2

- **total cholesterol**
- **serum creatinine**
- **low serum albumin**
- **anemia**

Hematocit		Type 1 diab. *(n= 127/934)*	type 2 diab. *(n=150/1292)*
male	female	1.00	1.00
> 50	> 44	1.16 (0.53-2.53)	1.36 (0.61-3-.04)
45-50	40-44	1.62 (0.75-3.46)	1.86 (0.85-4.08)
40-45	34-40	**4.62 (1.63-13.09)**	**4.12 (1.62-10.39)**
< 40	< 34	**2.65 (1.40-5.02)**	

Cusick et al., *Kidney Int 2004*

Lipid lowering studies as opportunities for evaluation of CKD progression ?

Lipid lowering and progression of CKD in the CARE study

- 4159 survivors of AMI with total cholesterol <6 mmol/l (<240 mg/dl)
- 3384 Calculated MDRD GFR's
- 690 MDRD eGFR <60 ml/min/1.73m^2

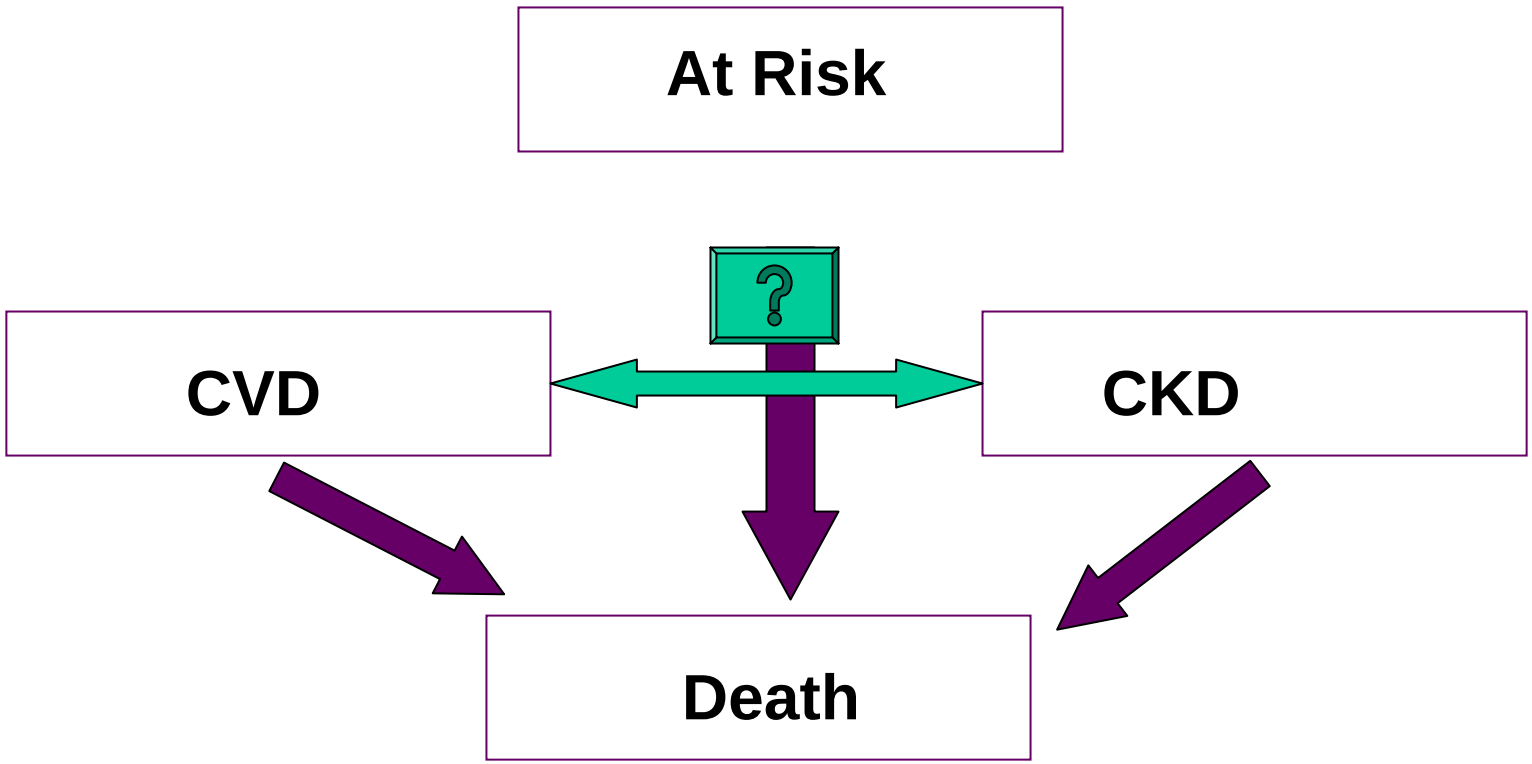
MDRD eGFR (ml/min/1.73m^2)	Slowing of GFR decline (ml/min/1.73m^2/year)	p value
< 60	0.1	0.49
< 50	0.6	0.07
< 40	2.5	0.001

Tonelli et al, JASN 2003;14:1605-1613

Limited data and limitations of data

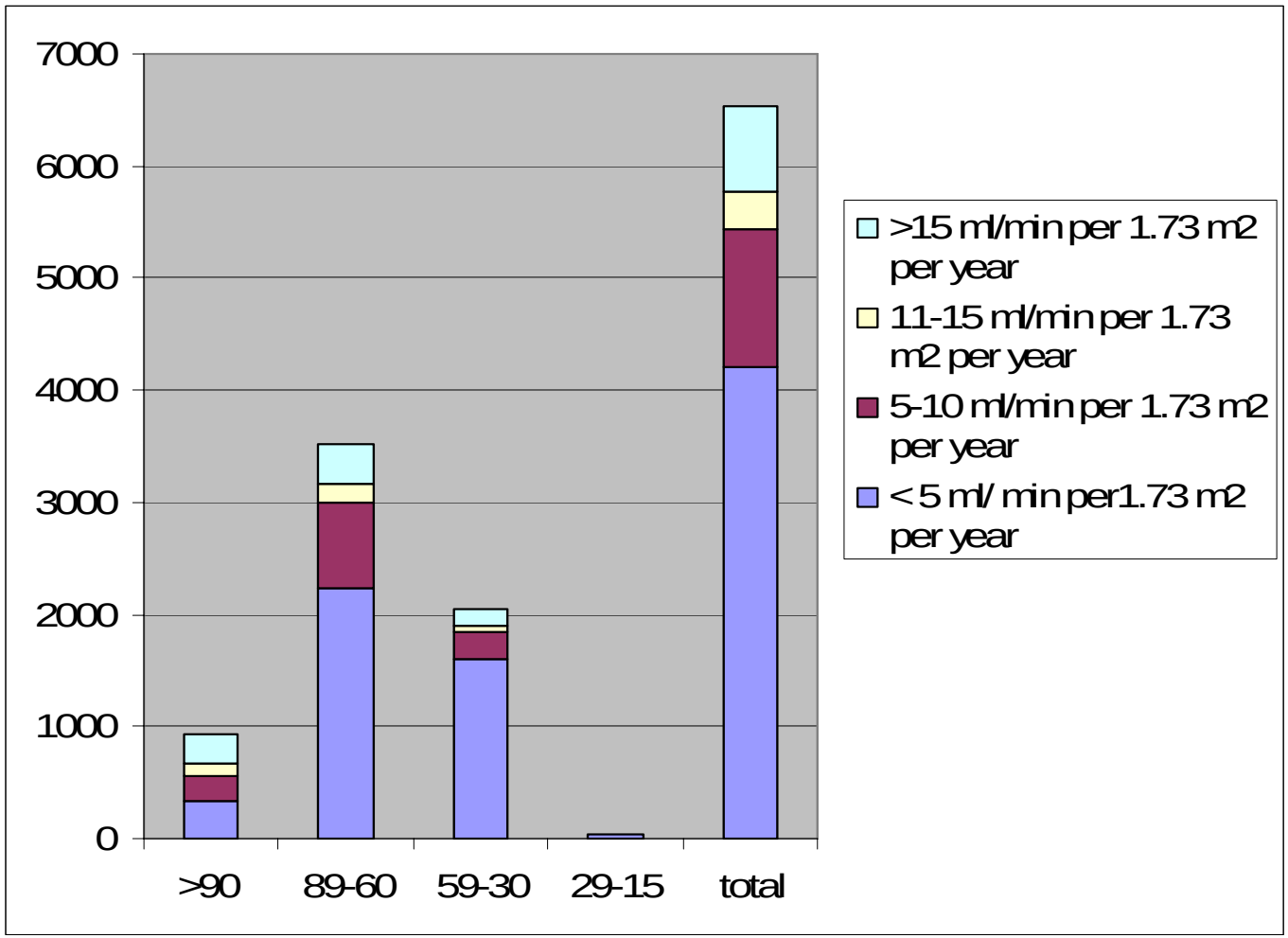
- **Bidirectional causality**
  - **difficult to tease out in published studies**
- **Issues related to**
  - **Completeness of measurements/ diagnosis of kidney function**
    - **Creatinine, albuminuria**
  - **CVD assessment**
    - **Symptoms vs documentation**
  - **Timing and intervals of testing**
  - **Primary outcomes of study**

Is there data in CVD populations which supports the concept of CVD as a risk factor for CKD initiation or progression?



Initiation?

SOLVD : A substantial number of pts had 'rapid progression' CKD



GFR (ml/min per 1.73 m2)

Independent Predictors of "rapid' Progression

Older Age,
Female
Non -White
EF worsening
NYHA Class
Hgb (Hct)

Khan, N et al, JASN 2005

J Am Soc Nephrol 15: 1912–1919, 2004

Medicare Patients with Cardiovascular Disease Have a High Prevalence of Chronic Kidney Disease and a High Rate of Progression to End-Stage Renal Disease

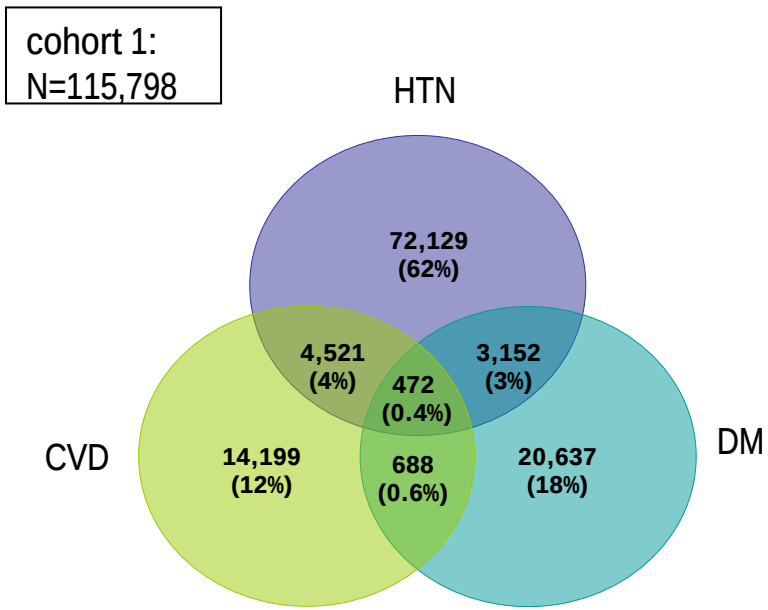
WILLIAM M. MCCLELLAN,*†‡ ROBERT D. LANGSTON,* and RODNEY PRESLEY*
*Georgia Medical Care Foundation, Atlanta, Georgia; †Rollins School of Public Health, Emory University, Atlanta, Georgia; and ‡Division of Kidney Disease, Emory University, Atlanta, Georgia

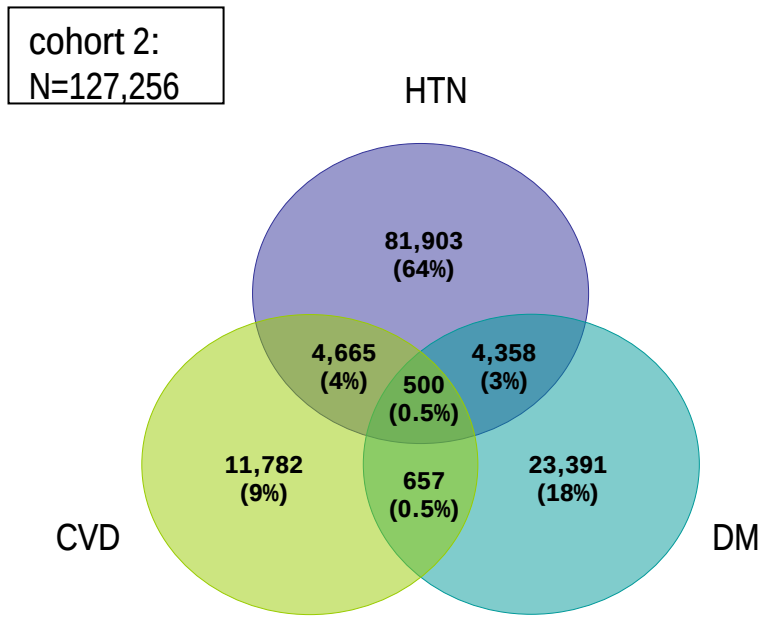
	CHF	AMI
Prevalence CKD	**60%**	**52%**
Mean GFR	**55.7**	**60.6**
Median GFR	**39.7**	**42.3**
Incidence ESRD*	**2.1%** **24/640**	**1.1%** **9/517**

* Within 12 mo after discharge for hospitalization for CHF or AMI

Newly diagnosed Cohorts at risk for CKD in BC Canada

DM, HTN or CVD





Age	59.8 y	58.8 y
Gender F	50.8%	51.0%

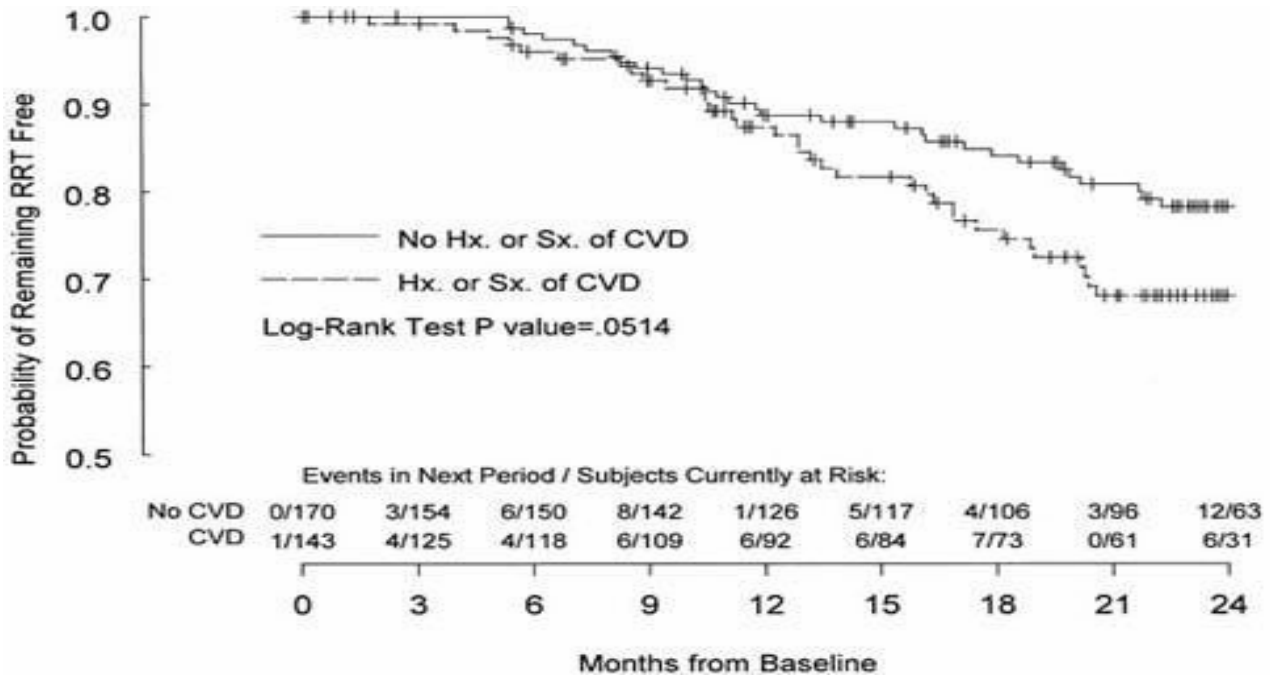
Levin et al CSN 2005

Of those newly identified in a high risk cohort, a small proportion were assigned a new diagnosis of CKD or progressed to significant end points within 2 years

	Cohort 1	Cohort 2	
• New dx of CKD	0.24	0.25	.644
	N=275	345	
• New Dialysis/ TX	0.03 %	0.03 %	.632
	N=33	38	
• Death	4.5%	3.4%	.001
	N=5189	4325	

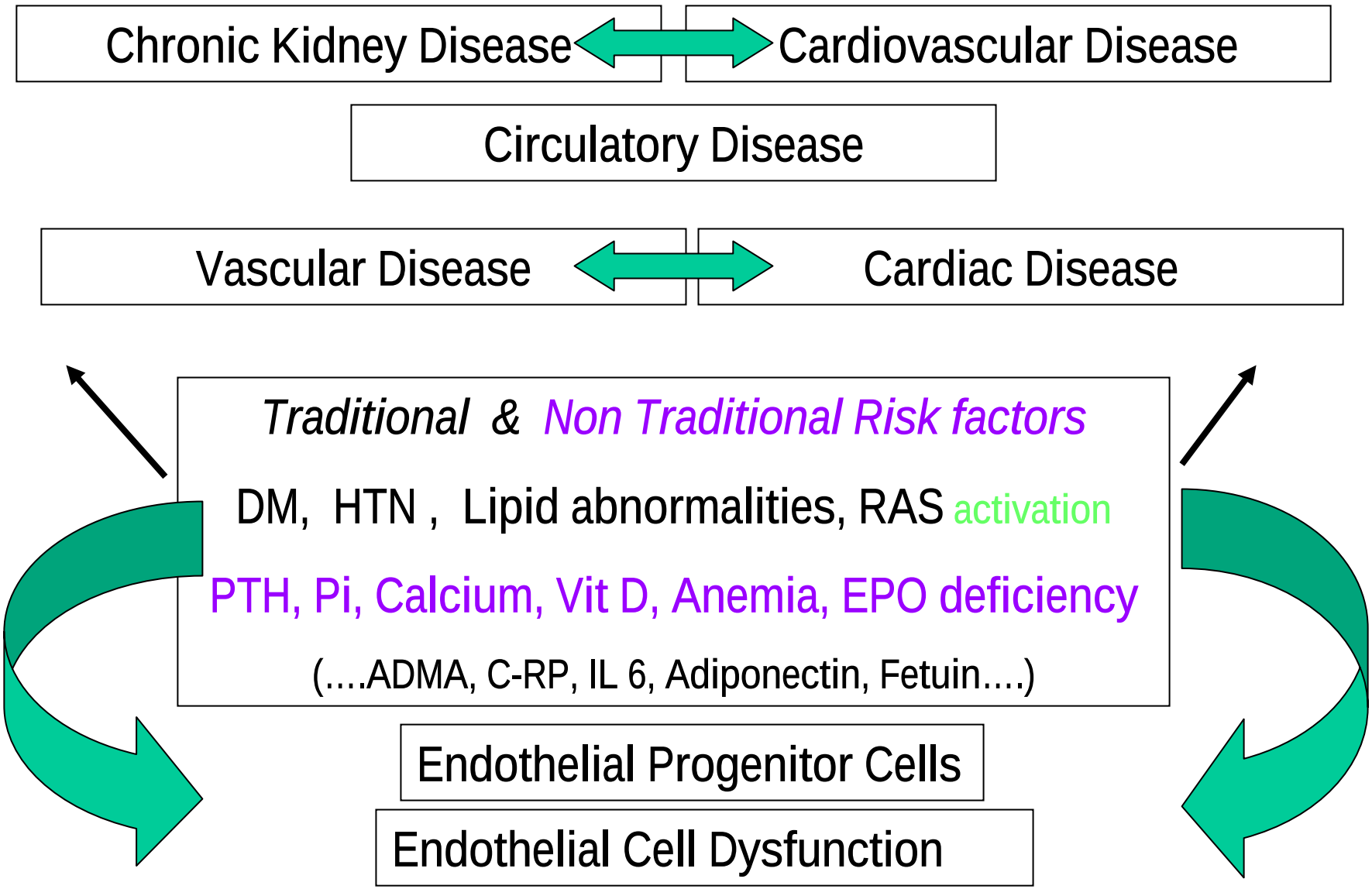
Levin et al CSN 2005

In pts with CKD those with CVD are more likely to commence RRT



Levin et al AJKD 2001

Biological Plausibility?



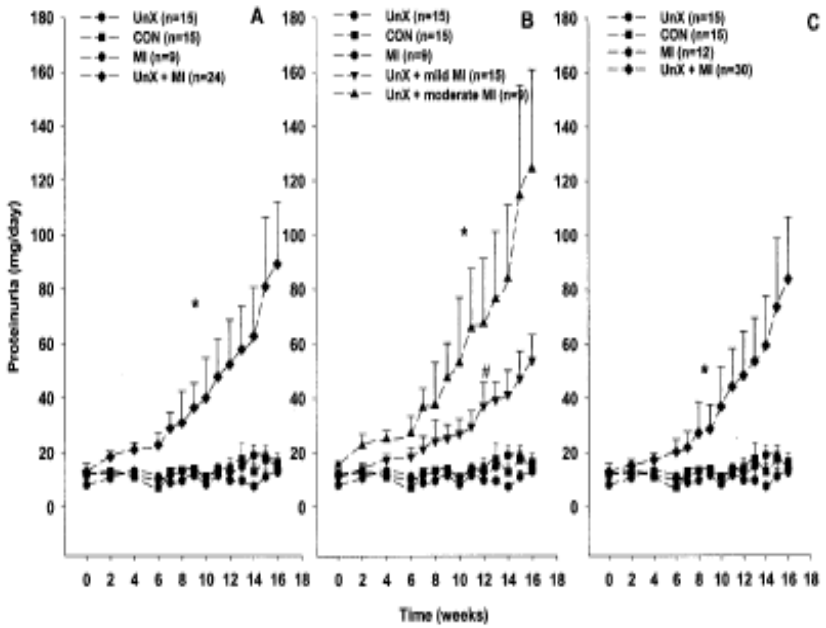
Cardiac events and subsequent kidney events

Myocardial Infarction Enhances Progressive Renal Damage in an Experimental Model for Cardio-Renal Interaction

RICHARD P.E. VAN DOKKUM,* WOUTER B.A. EIJKELKAMP,* ALEX C.A. KLUPPEL,* ROB H. HENNING,* HARRY VAN GOOR,† MARIN CITGEZ,* WILLEMIJN A.K.M. WINDT,* DIRK J. VAN VELDHUISEN,‡ PIETER A. DE GRAEFF,* and DICK DE ZEEUW*

*Departments of *Clinical Pharmacology, †Pathology, and ‡Cardiology, Groningen University Medical Center, The Netherlands.*

JASN 2004 15:3103-110



Animal model of AMI demonstrates changes in proteinuria and biopsy proven FSGS

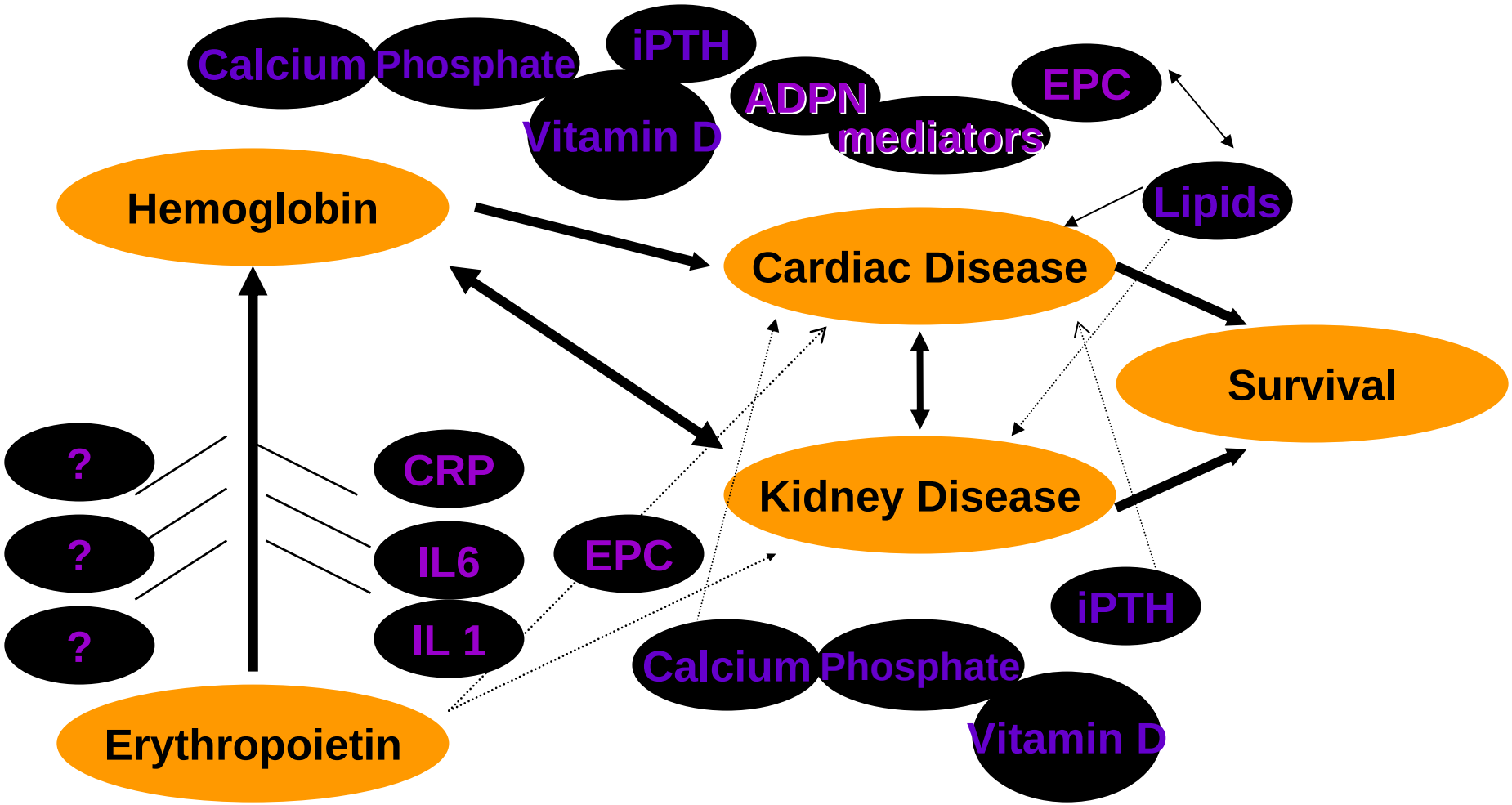
Unilateral Nephrectomy + AMI

Differential AMI size

Sham controls

Worse proteinuria and FSGS with larger AMI size

Complexity of relationships make current research findings difficult to interpret



Unanswered questions

Unanswered questions

- **In whom is CVD a risk factor for CKD?**
- **Is there an independent or similar mechanism by which pts susceptible to CVD are more likely to develop CKD?**
- **Are acute cardiac events potential initiators of CKD in susceptible individuals ?**
- **Research framework requires careful consideration of**
  - **Study design**
  - **Confounders**
  - **Opportunities**

Interactions between Risk Factors?

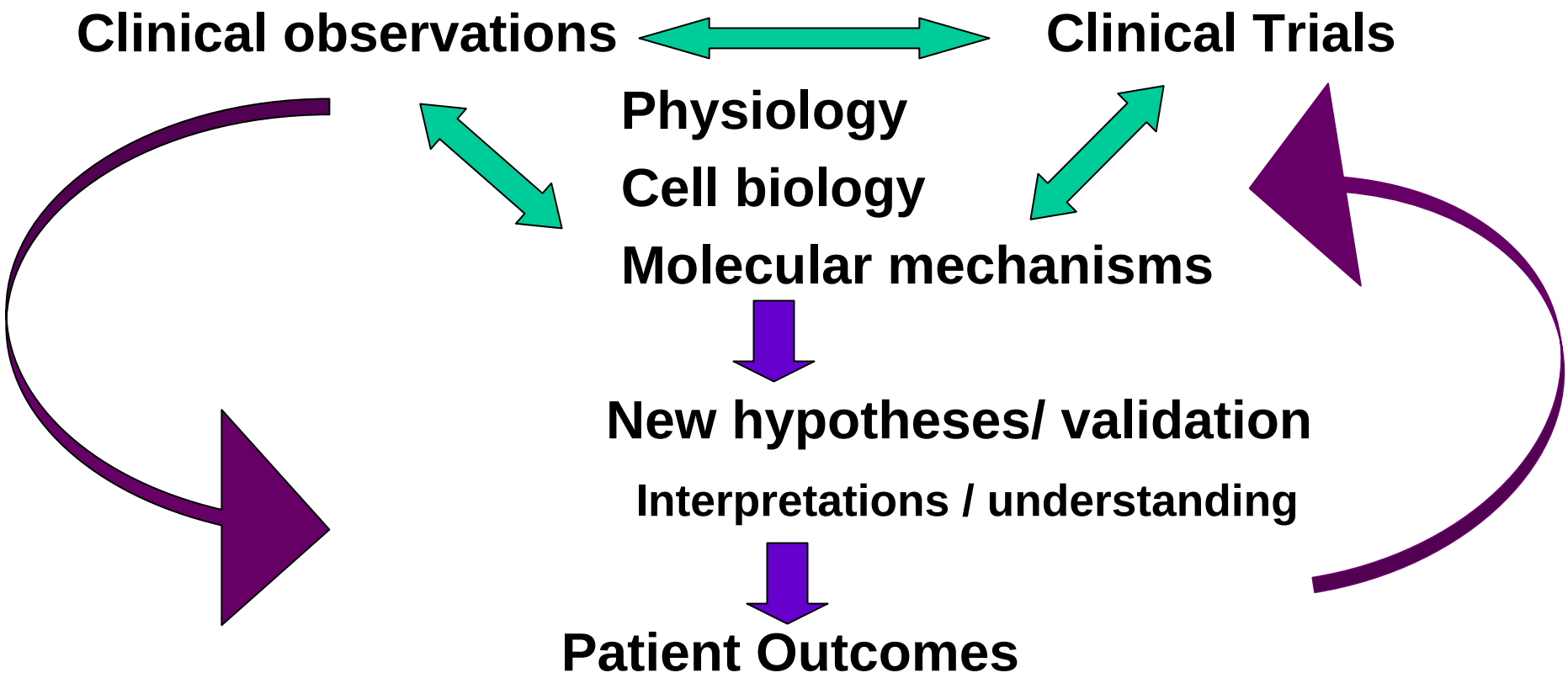
Potential study design/ opportunities for research

- **Secondary analyses of CVD trials**
  - **Interventions targeted at CVD risk factor may in fact reduce incidence of CKD**
- **Design interventional trials to track both CVD and CKD outcomes equally (power)**
- **Natural experiments**
  - **Cardiac transplant pts +/- existing CKD: outcomes post tx**
  - **Acute cardiac events and incident CKD:**
    - **Defining high risk / susceptible individuals**

Why?

- **Understanding complexity of incident CKD and progression in relation to CVD risks may change focus of interventions?**

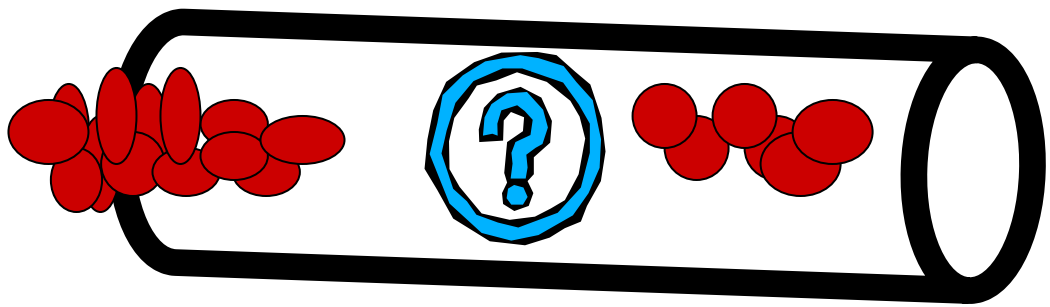
Towards an Integrated Understanding



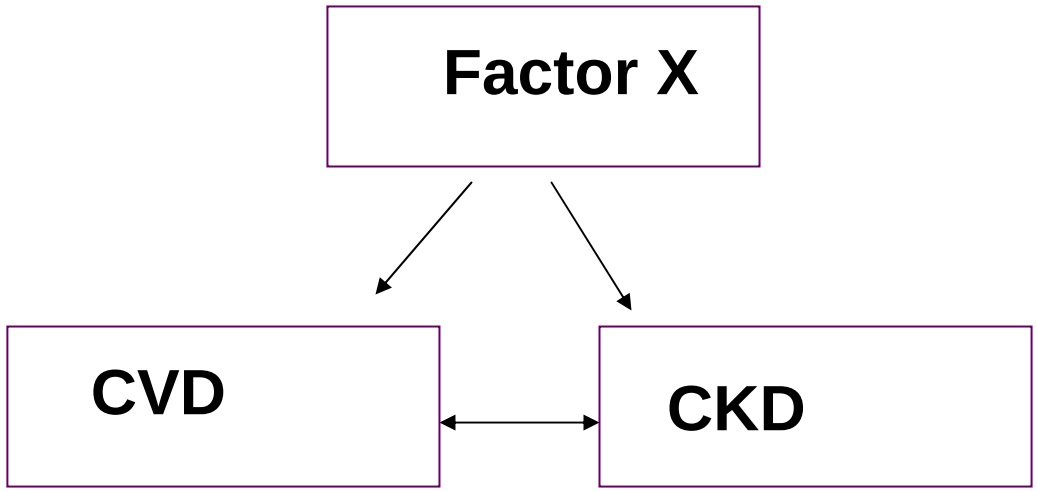
Summary

- **CVD in CKD is due to both traditional and non traditional risk factors, which are complexly linked**

- **Understanding vascular disease in CKD patients, and defining the optimal targets for various abnormalities will depend on an understanding of the complexity of the relationships between easily measured factors and underlying biology**

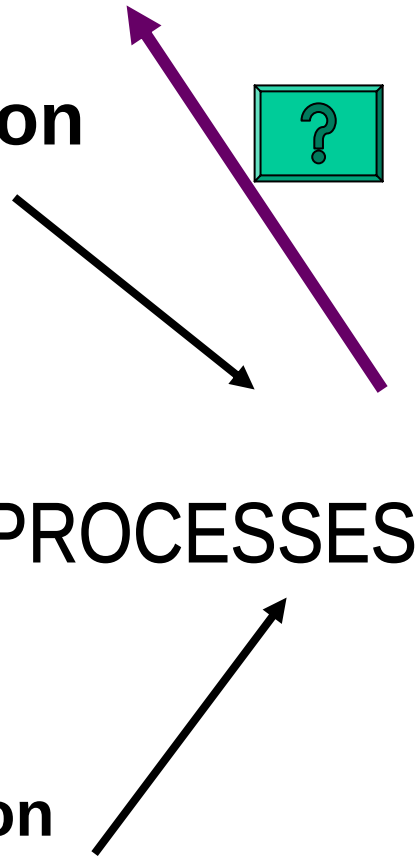


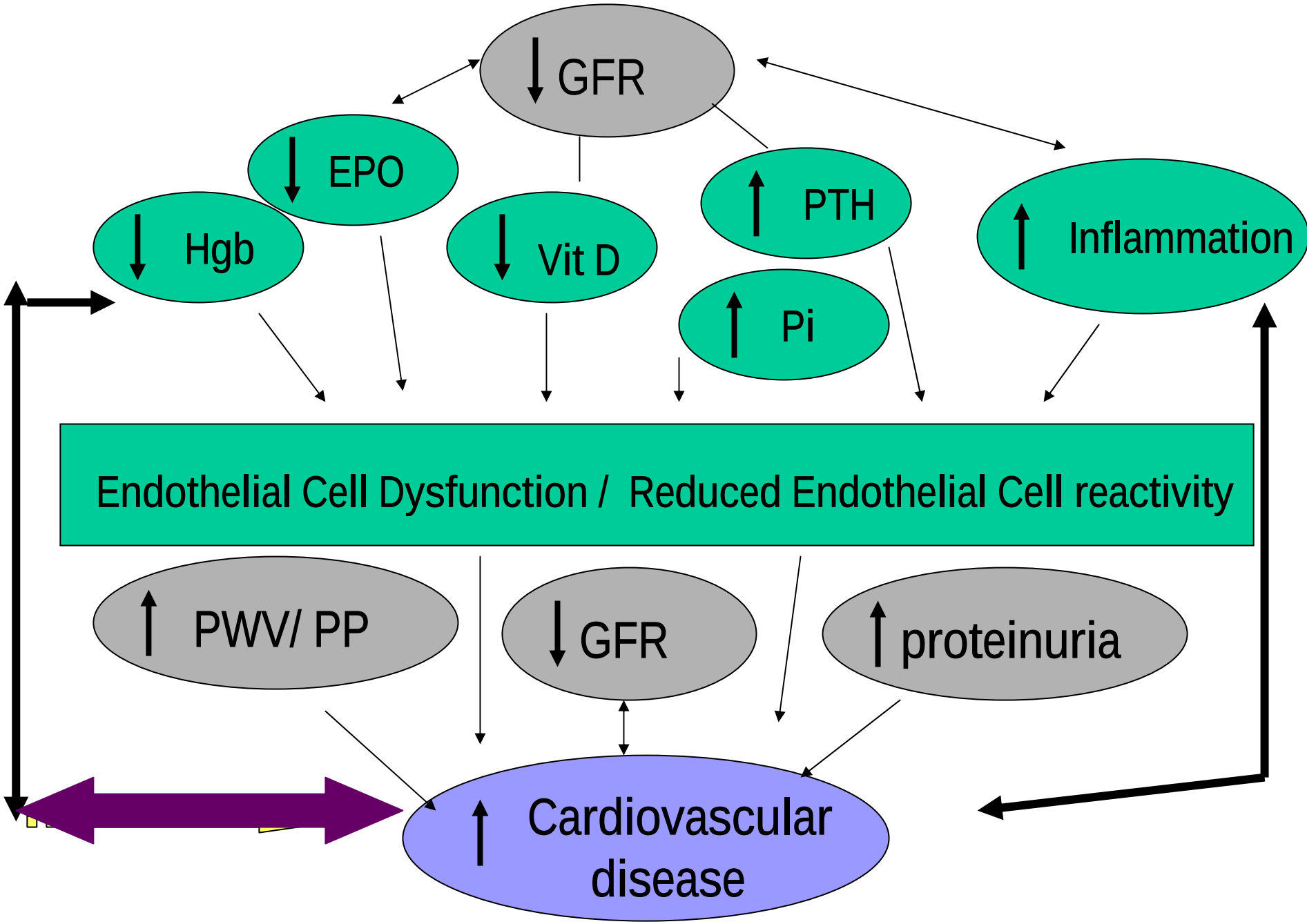
What are the reasons that specific factors lead to CVD or CKD preferentially in different individuals?



Chronic Kidney Disease

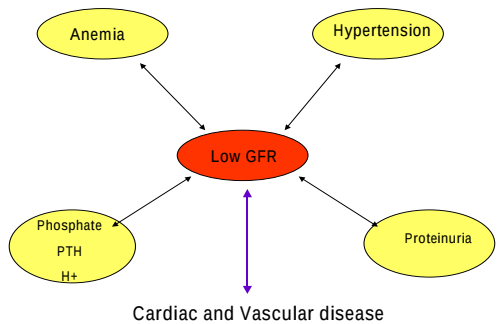
- **Disturbances of endocrine function**
  - **Erythropoietin hormone synthesis**
  - **Impaired Vit D hormone synthesis**
  - **Elevated PTH**
  - **Activation of RAS**
- **End organ dysfunction**
  - **Bone marrow fibrosis**
  - **Myocardial fibrosis**
  - **Vascular smooth muscle proliferation**
- **Inflammation**
  - **CRP, IL 6 and other cytokines, TNF**




GFR
EPO
Hgb
Vit D
PTH
Pi
Inflammation
Endothelial Cell Dysfunction / Reduced Endothelial Cell reactivity
PWV/ PP
GFR
proteinuria
Cardiovascular disease

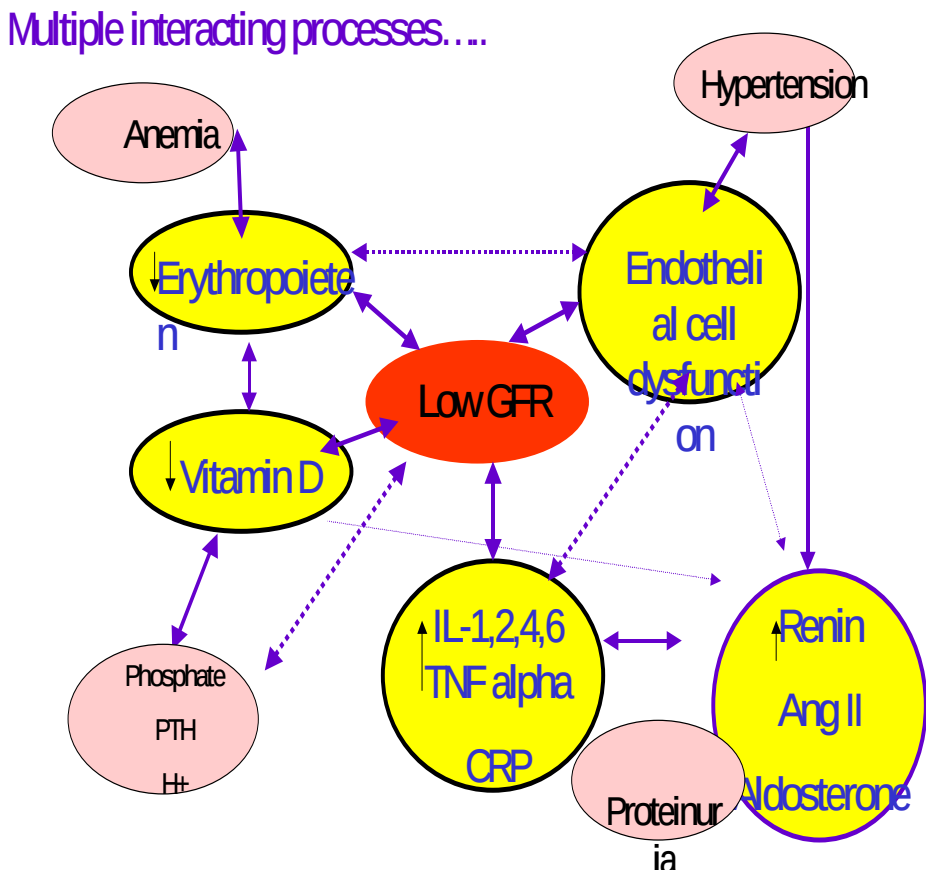
Clinical Observations

- **Clinical studies in CKD describe abnormalities associated with outcomes of biological processes**
- **Simplistic approach to targeting levels of 'abnormalities' and outcomes:**
- **Conflicting results in clinical trials**



But, more integrated perspective….

- Within the clinical context ,
  - hormone deficiency/ excess
  - Activation of inflammation
- Rational Treatment strategies
  - RAAS blockade
    - ACEi, ARB, (aldo antagonism)
  - Erythropoietic stimulating agents
  - Vitamin D supplementation
  - Diet restrictions
    - Reduce protein , phosphat and acid load
    - Anti-oxidant supplementation



Biological Processes

Mechanical,Infectious,Toxic,Oxidative,Allergic

Injury

Genetic , epigenetic

Environmental interactions

Cell Damage

Inflammation

Cell repair

Fibrosis

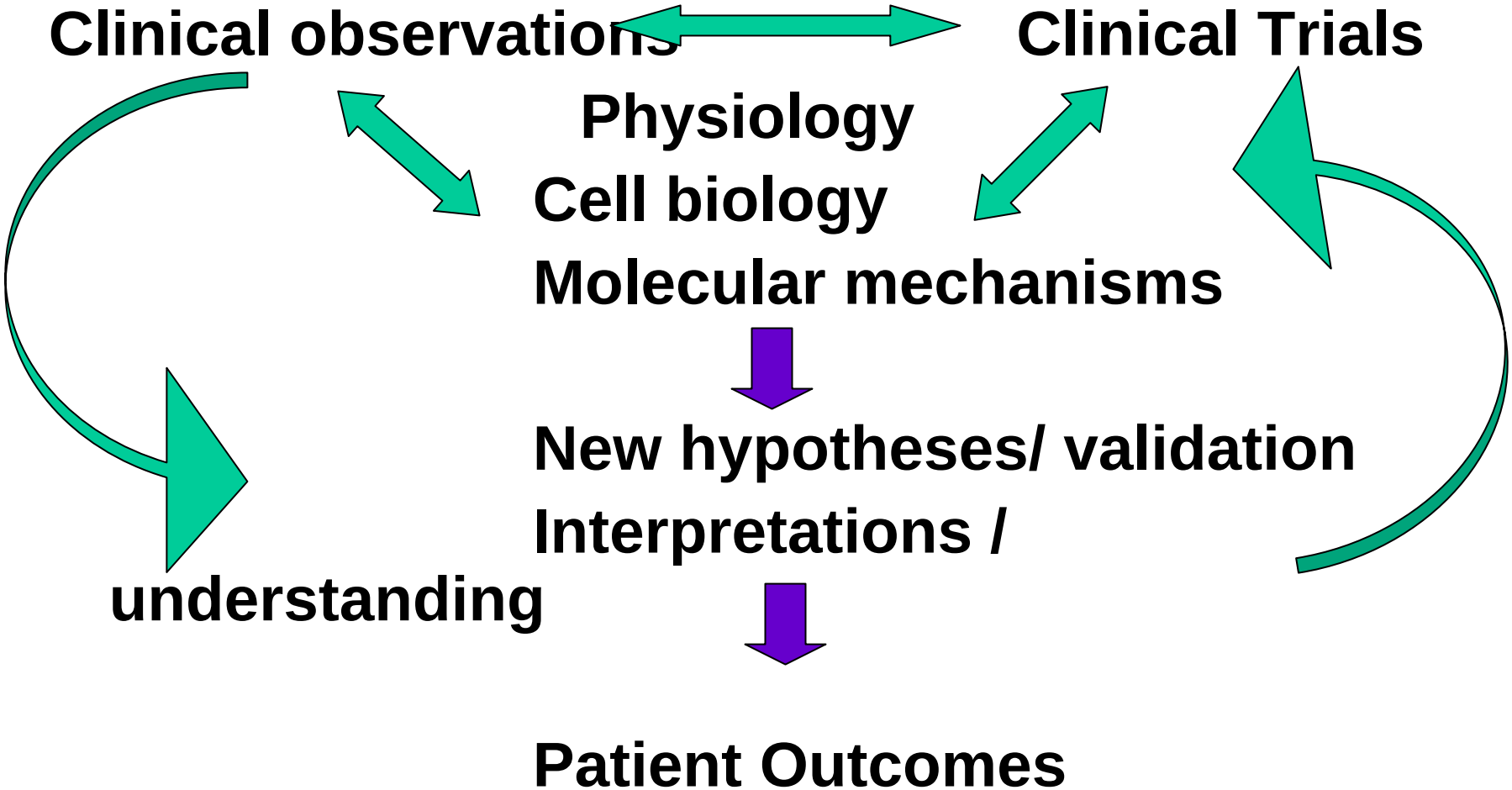
Threshold Concept

Shared risk factors

amplification vs interaction

in whom and when

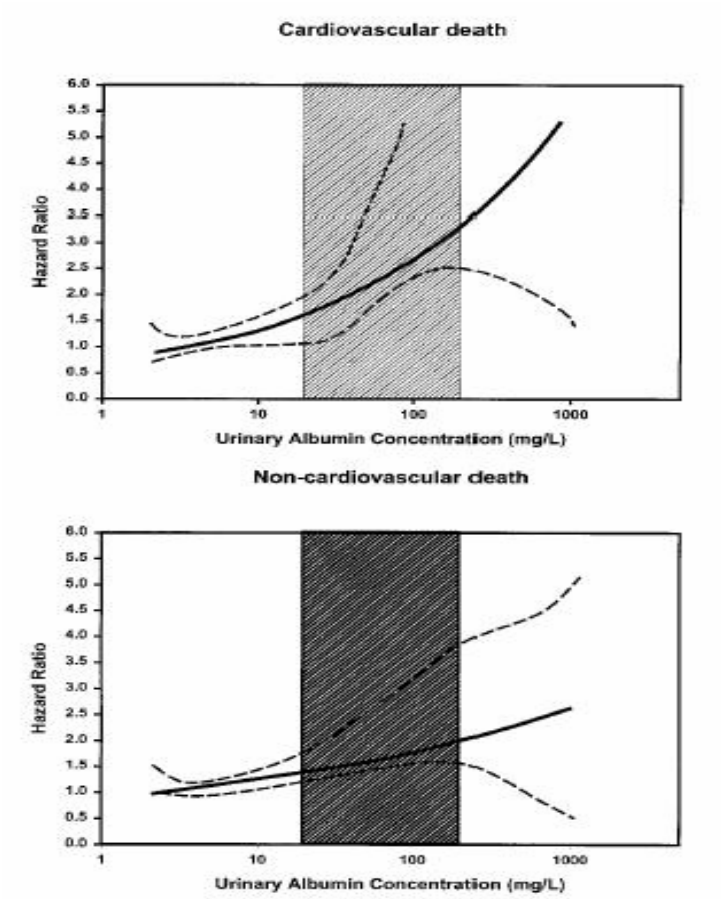
Towards an Integrated Understanding



Overview

- **Biological Processes**
- **Cardiovascular disease in CKD**
  - **Clinical observations**
  - **Biological mechanisms**
  - **Clinical trials**
- **Implications for clinical care and research**

Urinary albumin predicts CVD and non CVD death



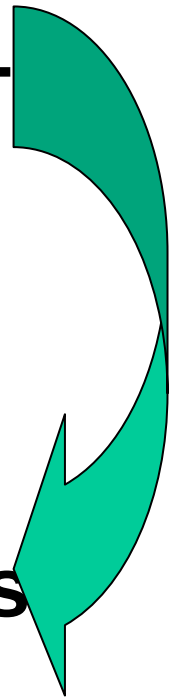
Endothelial Progenitor Cells

- **Endothelial maintenance**
  - **Facilitate angiogenesis**
  - **Re-endothelialiazation and neovascularization**

- **Located in Bone marrow**
  - **Adjacent to hematopoietic stem cells**
  - **Express CD34+, VEGFR**
    - **antigens shared by embryonic and hematopoietic stem cells**
  - **Can be measured in circulation**

Integrating the Facts:

- Hgb and Erythropoietin
- Calcium, Phosphate and PT
- Vitamin D
- Inflammatory cytokines



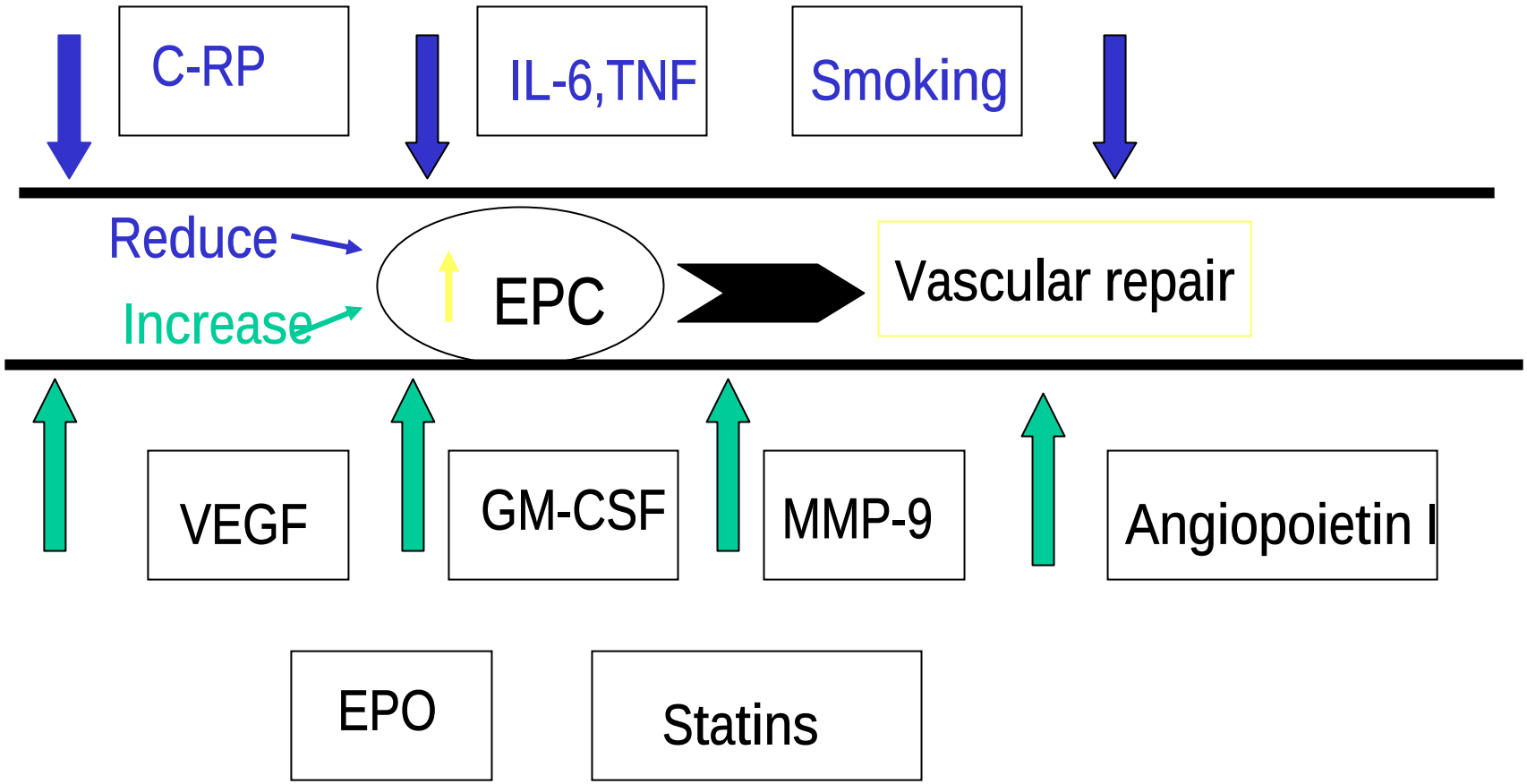
- Endothelial Progenitor Cells

Endothelial Progenitor Cells (EPC) Accumulating Evidence for clinical importance

- **Endothelial Progenitor Cells**
  - **# and migratory activity inversely correlates with risk factors for CAD[1]**
  - **Prevents apoptosis[2] via Neovascularization of ischemic myocardium**
  - **Mobilized pts with Acute MI[3]**
  - **Increased with Statin therapy, and associated with acceleration of re-endothelialization[4,5]**
  - **EPC, vascular function, CV risk[6]**
    - **# Associated with Framingham risk score and forearm reactivity**
    - **Increased senescence associated with higher scores**

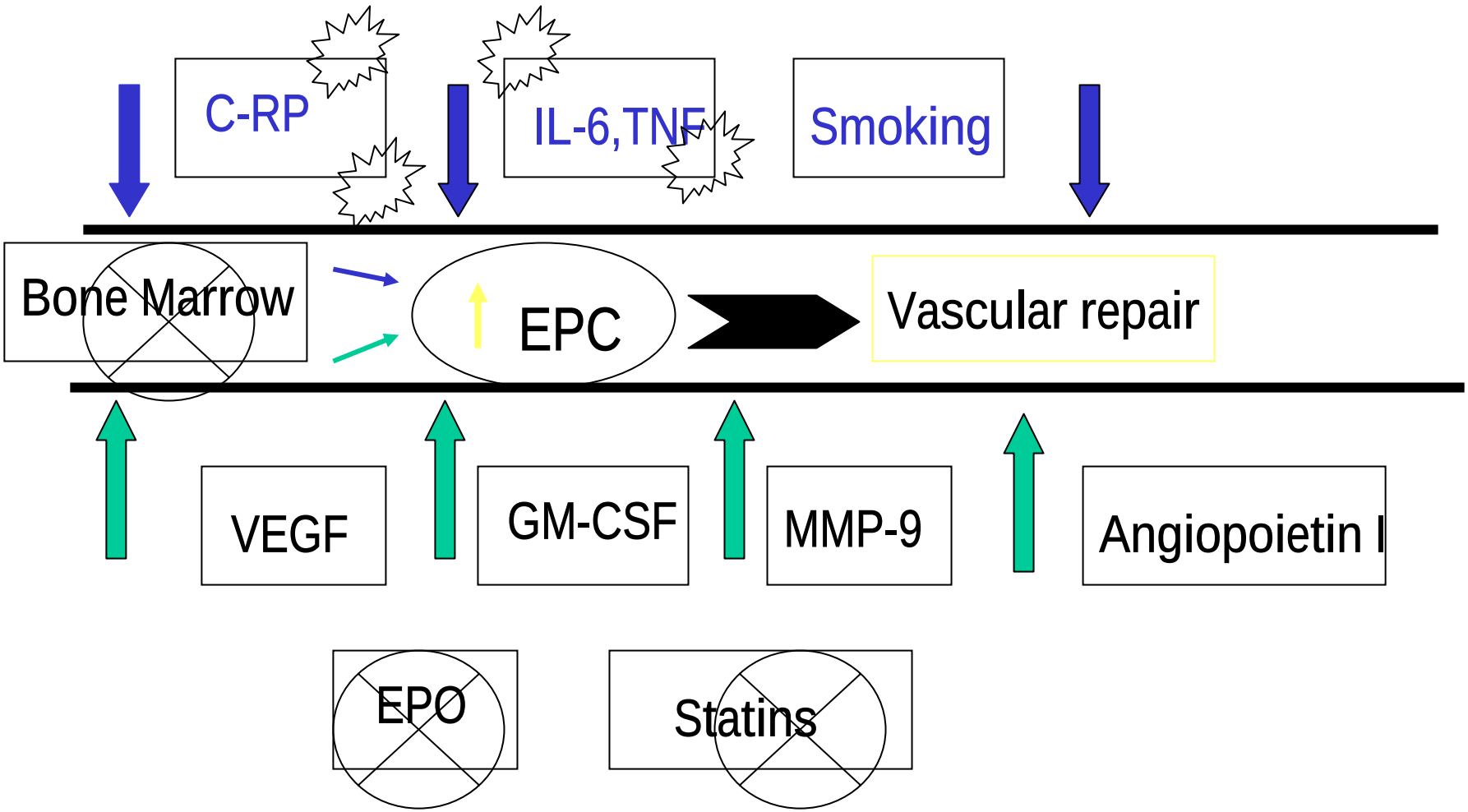
1.Vasa et al Circ Res 2001,89;2. Kocher et al, Nature Med 7(4) 2001; 3.Shintani et al, Circ 2001 :103; 4.Walter et al, Circ 2002:105; 5. Llevador et al JCI 2001 :108; 6. Hill et al, NEJM 2003,348

Endothelial Progenitor Cells



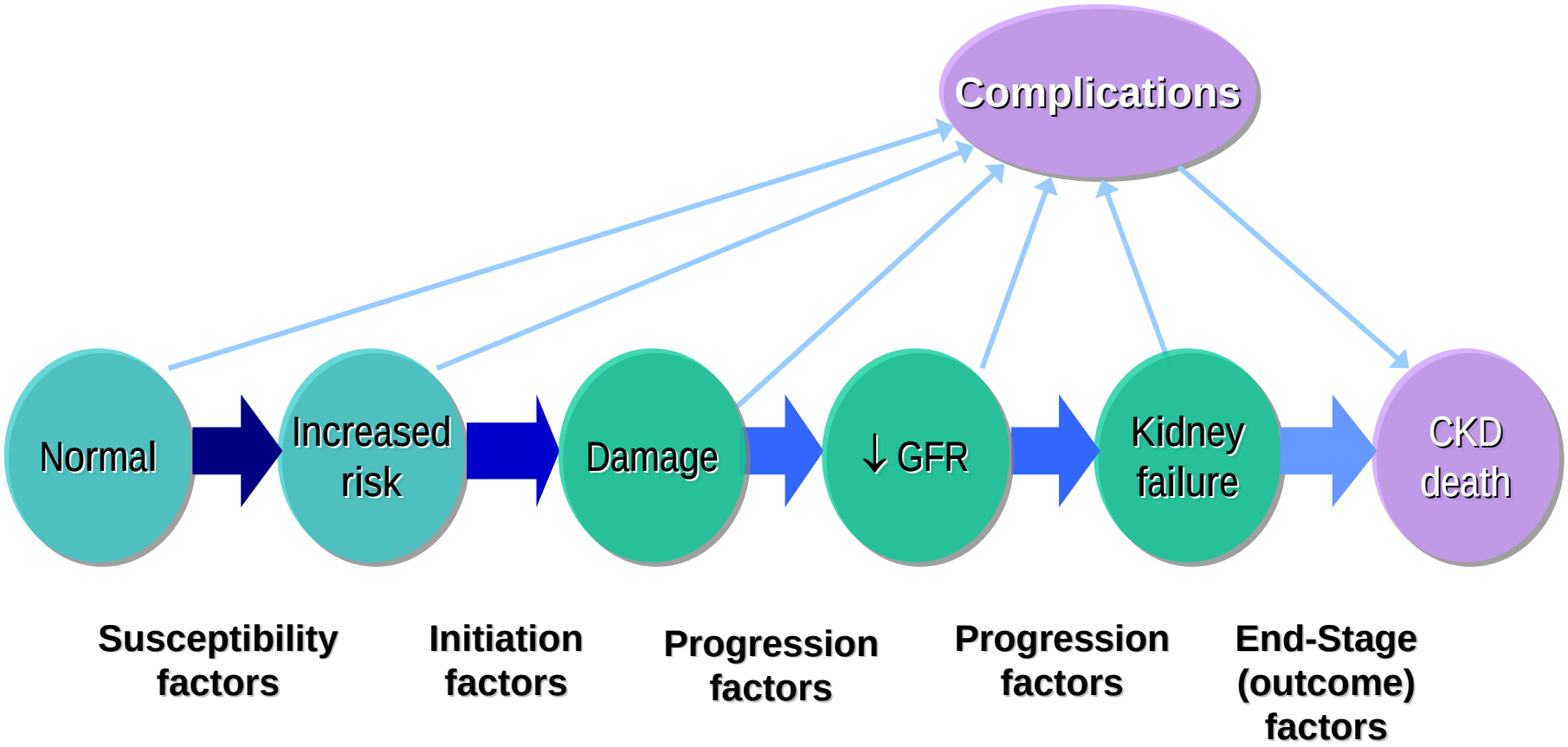
Adapted from Szmitko et al Circulation 2003, 07:3093-3100

EPC and CKD

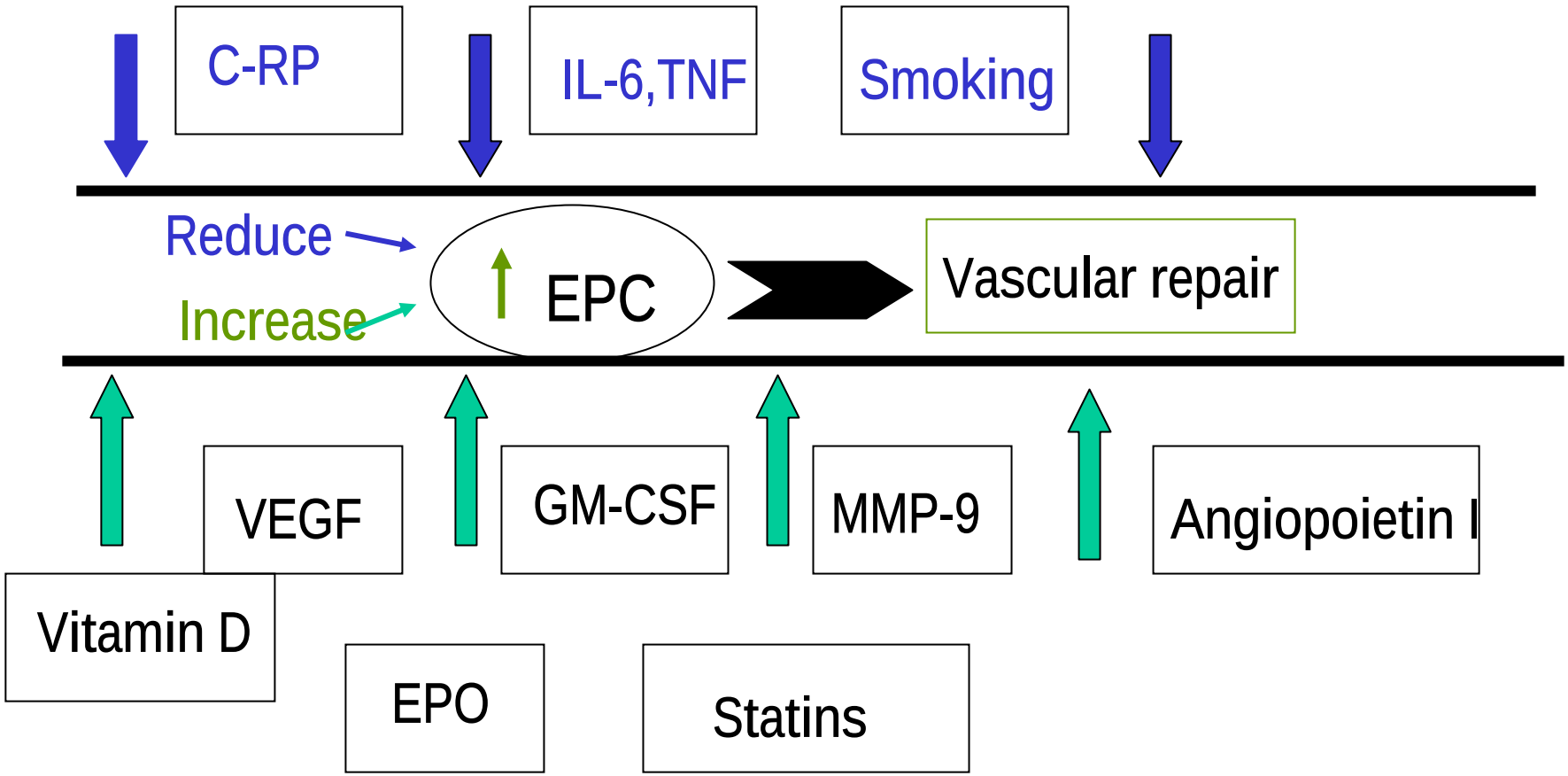


Adapted from Szmitko et al Circulation 2003, 07:3093-3100

Conceptual Model for CKD



Endothelial Progenitor Cells



Adapted from Szmitko et al Circulation 2003, 07:3093-3100

High prevalence of CKD in pts with AMI or CHF

J Am Soc Nephrol 15: 1912–1919, 2004

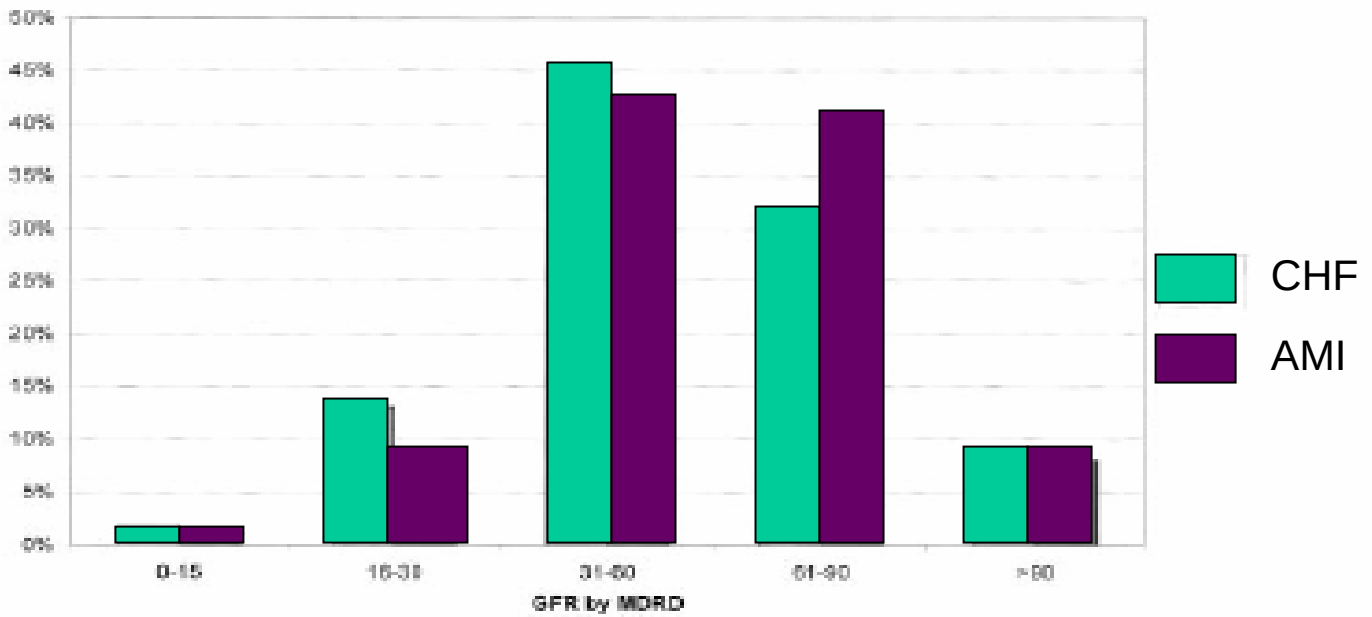
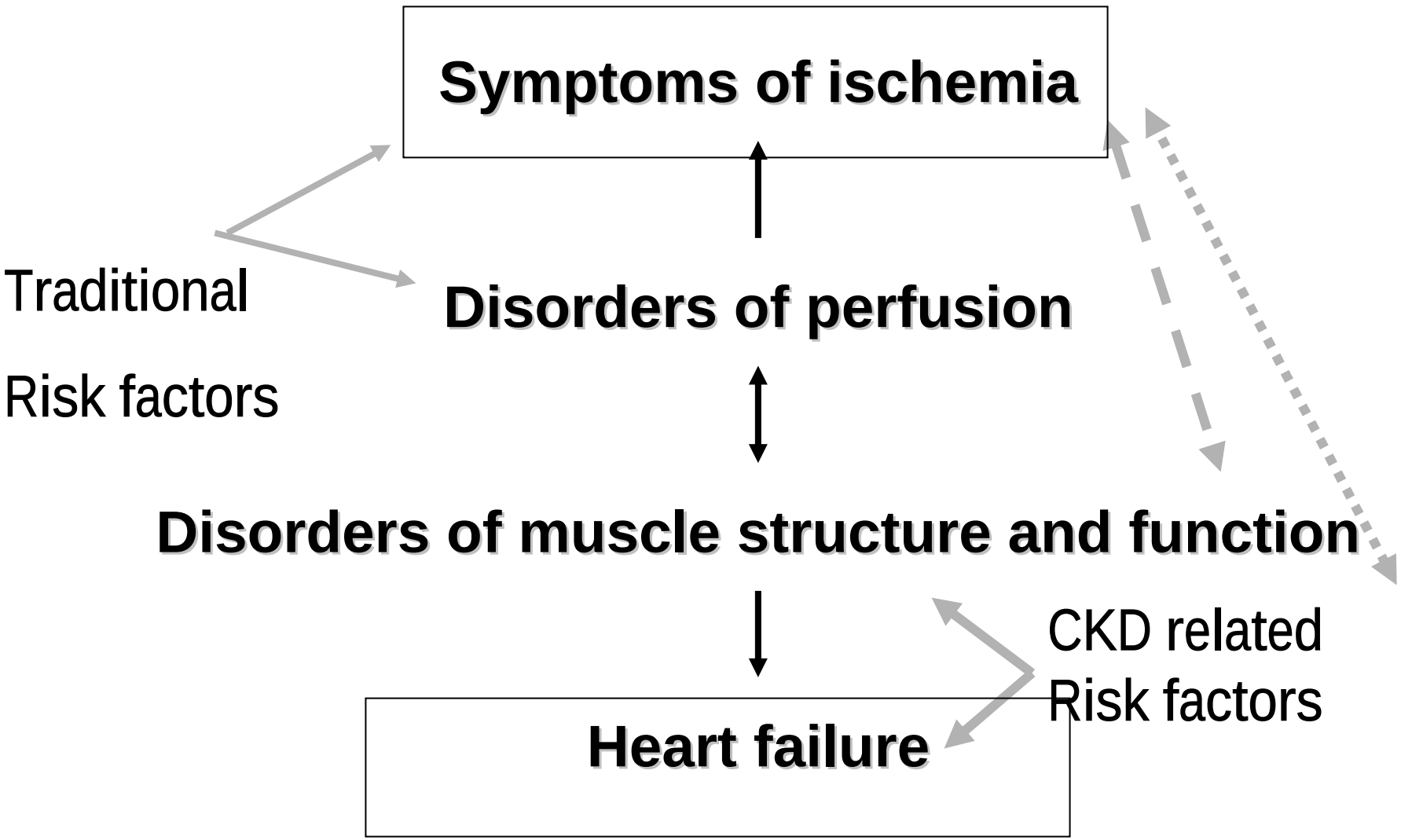


Figure 2. Distribution of GFR levels by disease.

McLellan et al JASN 2004

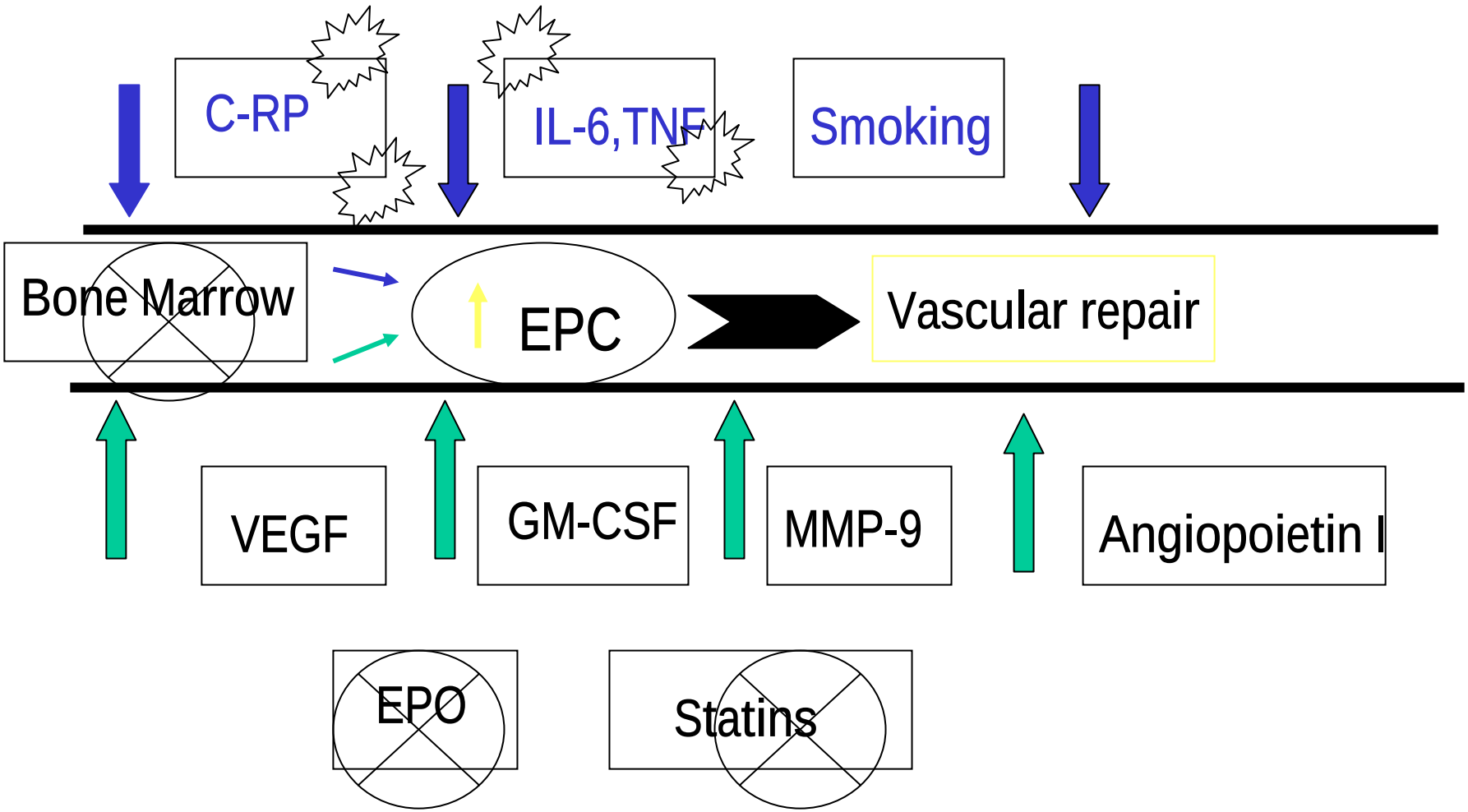
Cardiovascular disease



Factors associated with progression in CKD

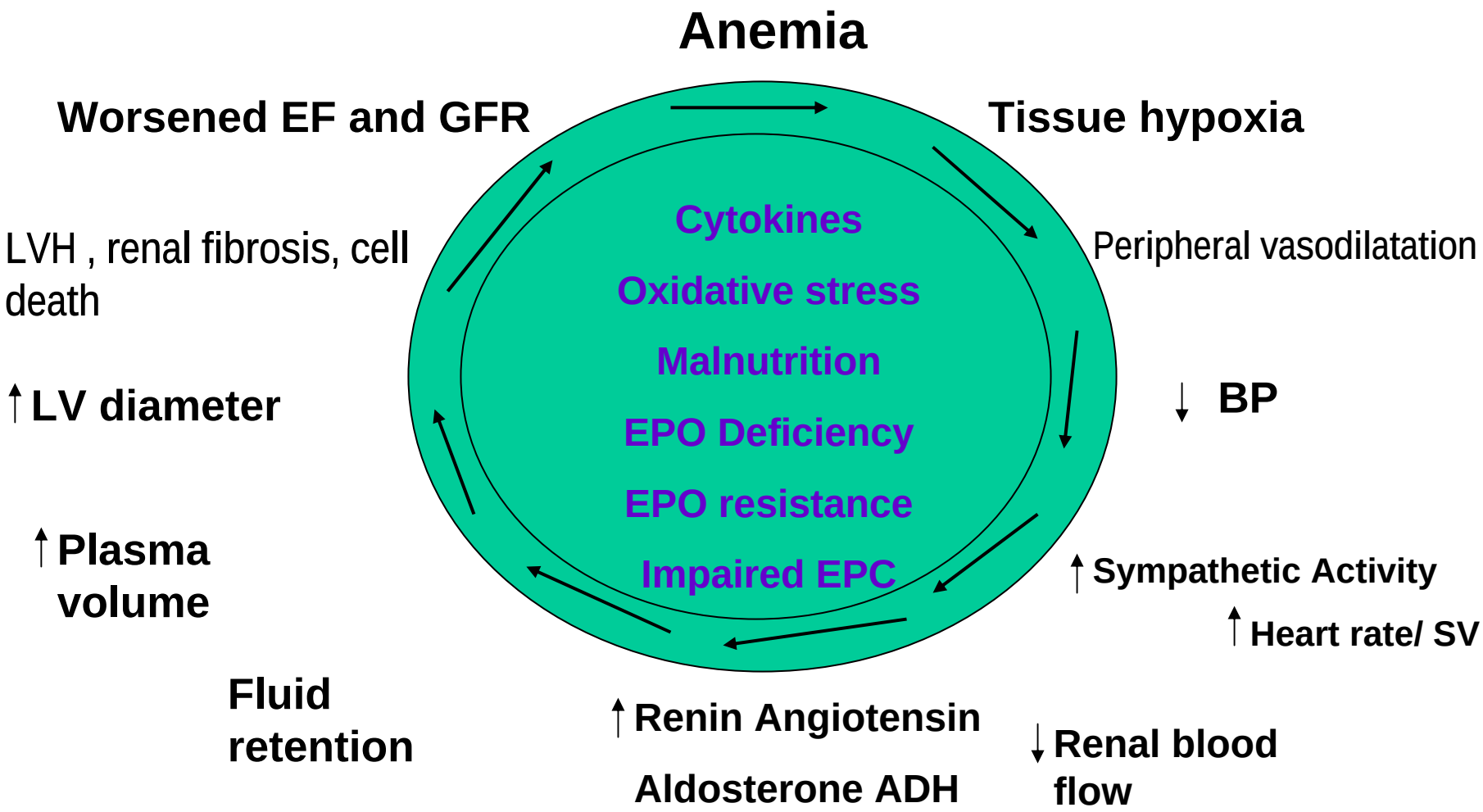
- **Traditional CVD**
  - Hypertension
  - Diabetes
  - Dyslipidemia
  - Family history
  - Smoking
  - Oxidative stress
- **Kidney specific**
  - Anemia
  - iPTH excess
  - Calcium phosphate abnormalities
  - Vitamin D deficiency
  - Kidney function per se
  - Albuminuria / Proteinuria

EPC and CKD



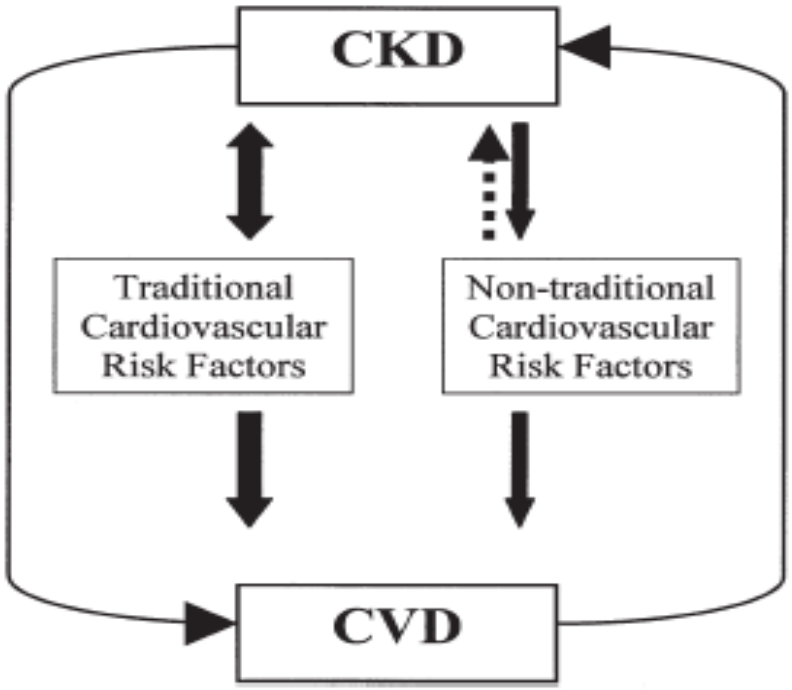
Adapted from Szmitko et al Circulation 2003, 07:3093-3100

Cycle of worsening HF, CKD and Anemia



Adapted from McCullough et al Reviews in CVM 2005

Can we conceive of CVD or its risk factors as important in the initiation or progression of CKD?



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

From Menon et al in Brenner " The Kidney"in press