Cardiovascular Risk factors for CKD

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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 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*
Mortality increase exponentially as GFR declines

Go et al NEJM 2004 351: 1296-1305
Construct

Cardiovascular disease | Kidney disease

Cardiomyopathy & Vascular Disease

Cardiomyopathy 2* to Vascular Disease

Endothelial dysfunction and Inflammation

Progression of CVD and CKD

Traditional Risk factors

Non-Traditional Risk factors
Simple observations...

- Anemia
- Hypertension
- Phosphate
  - PTH
  - H+
- Proteinuria

Low GFR

Cardiac and Vascular disease
Multiple interacting processes and complex biology.....

- Anemia
- Hypertension
- Erythropoietin
- Vitamin D
- Low GFR
- Endothelial cell dysfunction
- IL-1,2,4,6
- TNF alpha
- CRP
- Renin
- Ang II
- Aldosterone
- Proteinuria
- Phosphate
- PTH
- H+
CKD as a risk factor for CVD
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- Immunosuppressants

CVD as a risk factor for CKD
- Hypertension
- Obesity
- Dyslipidemia
- Diabetes
- Acute cardiac events
- CHF/ CAD
  - Underperfusion
  - Toxicity from Dye
  - Cholesterol emboli

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)

- Progression (established disease)

Risk factors for CVD

- Acute events?
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

Susceptibility

Overlap
Causal vs Markers/Surrogates?

Initiation

Progression

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

2 yr mortality (n~ 200,000 5% Medicare sample)

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

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Abnormal Mineral Metabolism as Risk factor

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What are the reasons that specific factors lead to CVD or CKD preferentially in different individuals?
CKD + CVD increases risk of adverse outcomes

Menon, Sarnak et al AJKD 2006
CKD as a risk factor for CVD
- Hypertension
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CVD as a risk factor for CKD
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  - Cholesterol emboli

Cardiovascular disease
## CKD Risk Factors to be tested

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.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Definition</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Susceptibility factors</strong></td>
<td>Increase susceptibility to kidney damage</td>
<td>Older age, family history of CKD, U.S. racial or ethnic minority status, reduced kidney mass, hyperfiltration states</td>
</tr>
<tr>
<td><strong>Initiation factors</strong></td>
<td>Directly initiate kidney damage</td>
<td>Diabetes, high blood pressure, obesity, dyslipidemia, autoimmune diseases, infections, stones, obstruction</td>
</tr>
<tr>
<td><strong>Progression factors</strong></td>
<td>Cause worsening kidney damage and faster GFR decline</td>
<td>Higher level of proteinuria</td>
</tr>
<tr>
<td><strong>End-stage (outcome) factors</strong></td>
<td>Increase morbidity and mortality in kidney failure</td>
<td>Lower dialysis dose (Kt/V), temporary vascular access, anemia, low serum albumin level, late referral</td>
</tr>
</tbody>
</table>
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/1.73m² at year 9?  

10,096 pts from ARIC  
Normal baseline kidney function  
9 years of follow up
Metabolic syndrome predicts CKD

OR =1.43 (1.18-1.73)

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

<table>
<thead>
<tr>
<th>CKD (n [%])</th>
<th>Metabolic Syndrome Absent</th>
<th>Metabolic Syndrome Present</th>
<th>Unadjusted</th>
<th>Age, Gender, and Race Adjusted</th>
<th>Multivariable Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR &lt;60 ml/min per 1.73 m²</td>
<td>484 (6%)</td>
<td>207 (10%)</td>
<td>1.69 (1.42 to 2.00)</td>
<td>1.53 (1.29 to 1.82)</td>
<td>1.43 (1.18 to 1.73)</td>
</tr>
<tr>
<td>Elevated serum creatinine</td>
<td>104 (1%)</td>
<td>52 (3%)</td>
<td>1.92 (1.37 to 2.68)</td>
<td>1.83 (1.30 to 2.57)</td>
<td>1.60 (1.11 to 2.30)</td>
</tr>
</tbody>
</table>

*Elevated serum creatinine for men >1.5 mg/dl and for women >1.3 mg/dl. Multivariable models adjusted for age, gender.

### Table 5. OR of developing CKD (eGFR <60 ml/min per 1.73 m²) over 9 years of follow-up by individual metabolic syndrome traits

<table>
<thead>
<tr>
<th>Metabolic Syndrome Trait</th>
<th>CKD (n [%])</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trait Absent</td>
<td>Trait Present</td>
<td>Unadjusted</td>
</tr>
<tr>
<td>Abdominal obesity</td>
<td>336 (6%)</td>
<td>355 (8%)</td>
</tr>
<tr>
<td>Elevated triglycerides</td>
<td>471 (6%)</td>
<td>220 (9%)</td>
</tr>
<tr>
<td>Low HDL</td>
<td>421 (6%)</td>
<td>270 (8%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>370 (5%)</td>
<td>319 (11%)</td>
</tr>
<tr>
<td>Impaired fasting glucose</td>
<td>603 (7%)</td>
<td>88 (8%)</td>
</tr>
</tbody>
</table>

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
Progression

**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

<table>
<thead>
<tr>
<th>Hematocit</th>
<th>Type 1 diab. ((n=127/934))</th>
<th>type 2 diab. ((n=150/1292))</th>
</tr>
</thead>
<tbody>
<tr>
<td>male</td>
<td>female</td>
<td></td>
</tr>
<tr>
<td>&gt; 50</td>
<td>&gt; 44</td>
<td>1.16 (0.53-2.53)</td>
</tr>
<tr>
<td>45-50</td>
<td>40-44</td>
<td>1.62 (0.75-3.46)</td>
</tr>
<tr>
<td>&lt; 40</td>
<td>&lt; 34</td>
<td>2.65 (1.40-5.02)</td>
</tr>
</tbody>
</table>

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/1.73m²

<table>
<thead>
<tr>
<th>MDRD eGFR (ml/min/1.73m²)</th>
<th>Slowing of GFR decline (ml/min/1.73m²/year)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 60</td>
<td>0.1</td>
<td>0.49</td>
</tr>
<tr>
<td>&lt; 50</td>
<td>0.6</td>
<td>0.07</td>
</tr>
<tr>
<td>&lt; 40</td>
<td>2.5</td>
<td>0.001</td>
</tr>
</tbody>
</table>

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?

CVD → At Risk → CKD

CVD → Death

CKD → Death
Initiation?

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

Independent Predictors of "rapid" Progression

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

Khan, N et al, JASN 2005
Medicare Patients with Cardiovascular Disease Have a High Prevalence of Chronic Kidney Disease and a High Rate of Progression to End-Stage Renal Disease

<table>
<thead>
<tr>
<th></th>
<th>CHF</th>
<th>AMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence CKD</td>
<td>60%</td>
<td>52%</td>
</tr>
<tr>
<td>Mean GFR</td>
<td>55.7</td>
<td>60.6</td>
</tr>
<tr>
<td>Median GFR</td>
<td>39.7</td>
<td>42.3</td>
</tr>
<tr>
<td>Incidence ESRD*</td>
<td>2.1%</td>
<td>1.1%</td>
</tr>
<tr>
<td></td>
<td>24/640</td>
<td>9/517</td>
</tr>
</tbody>
</table>

* 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

Cohort 1:
N=115,798

Cohort 2:
N=127,256

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

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>New dx of CKD</td>
<td>0.24</td>
<td>0.25</td>
<td>.644</td>
</tr>
<tr>
<td></td>
<td>N=275</td>
<td>345</td>
<td></td>
</tr>
<tr>
<td>New Dialysis/ TX</td>
<td>0.03 %</td>
<td>0.03 %</td>
<td>.632</td>
</tr>
<tr>
<td></td>
<td>N=33</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>4.5%</td>
<td>3.4%</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>N=5189</td>
<td>4325</td>
<td></td>
</tr>
</tbody>
</table>

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?

Chronic Kidney Disease ← Cardiovascular Disease

Circulatory Disease

Vascular Disease ← Cardiac Disease

Traditional & Non Traditional Risk factors

DM, HTN, Lipid abnormalities, RAS activation

PTH, Pi, Calcium, Vit D, Anemia, EPO deficiency

(....ADMA, C-RP, IL 6, Adiponectin, Fetuin....)

Endothelial Progenitor Cells

Endothelial Cell Dysfunction
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,* WILLEM JN. A.K.M. WINDT,* DIRK J. VAN VELDUISEN,‡ 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

Clinical observations  Clinical Trials

Physiology
Cell biology
Molecular mechanisms

New hypotheses/ validation
Interpretations / understanding

Patient Outcomes
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?

Factor X

CVD

CKD
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

CVD PROCESSES
Endothelial Cell Dysfunction / Reduced Endothelial Cell reactivity

- GFR
- EPO
- Hgb
- Vit D
- PTH
- Pi
- Inflammation

- Cardiovascular disease
- Proteinuria
- PWV/PP

- GFR
- Hgb
- Vit D
- PTH
- Pi
- Inflammation

- Endothelial Cell Dysfunction / Reduced Endothelial Cell reactivity
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

Cell Damage

Genetic, epigenetic
Environmental interactions

Inflammation

Cell repair

Fibrosis
Threshold Concept

Shared risk factors
amplification vs interaction
in whom and when
Towards an Integrated Understanding

Clinical observations → Clinical Trials

Physiology
Cell biology
Molecular mechanisms

New hypotheses/ validation
Interpretations /

understanding

Patient Outcomes
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-endothelialization 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 PTH
- 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
  - Prevents apoptosis via Neovascularization of ischemic myocardium
  - Mobilized pts with Acute MI
  - Increased with Statin therapy, and associated with acceleration of re-endothelialization
  - EPC, vascular function, CV risk
    - # Associated with Framingham risk score and forearm reactivity
    - Increased senescence associated with higher scores

Endothelial Progenitor Cells

C-RP  ↓  Reduce  ↓  IL-6, TNF  ↓  Increase  ↓  Smoking

↑  EPC  →  Vascular repair

↑  VEGF  →

↑  BM-CSF  →

↑  MMP-9  →

↑  Angiopoietin I  →

EPO  ↓

Statins  ↓

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

Normal \rightarrow Increased risk \rightarrow Damage \rightarrow ↓ GFR \rightarrow Kidney failure \rightarrow CKD death

Susceptibility factors \rightarrow Initiation factors \rightarrow Progression factors \rightarrow Progression factors \rightarrow End-Stage (outcome) factors

Complications
Endothelial Progenitor Cells

C-RP  ↓  IL-6, TNF  ↓  Smoking  ↓  EPC  →  Vascular repair

Reduce       Increase

VEGF  ↑  GM-CSF  ↑  MMP-9  ↑  Angiopoietin I

Vitamin D  EPO  Statins

Adapted from Szmitko et al Circulation 2003, 07:3093-3100
High prevalence of CKD in pts with AMI or CHF

*Figure 2. Distribution of GFR levels by disease.*

McLellan et al JASN 2004
Cardiovascular disease

Symptoms of ischemia

Disorders of perfusion

Disorders of muscle structure and function

Heart failure

Traditional Risk factors

CKD related Risk factors
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

Anemia

- Worsened EF and GFR
- Tissue hypoxia
- Cytokines
- Oxidative stress
- Malnutrition
- EPO Deficiency
- EPO resistance
- Impaired EPC

LVH, renal fibrosis, cell death

↑ LV diameter

↑ Plasma volume

Fluid retention

↑ Renin Angiotensin

Aldosterone ADH

↑ Heart rate/ SV

 Peripheral vasodilatation

↓ BP

↓ Renal blood flow

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?

From Menon et al in Brenner “The Kidney” in press