Microalbuminuria; a cardiovascular or a renal risk factor or both?

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University Medical Center
Groningen
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Common and Novel Risk factors for Cardiovascular and Renal Disease progression

- Age
- Gender
- Body Weight
- Smoking
- Blood pressure
- Cholesterol
- Diabetes
- CRP, pro-BNP etc
- Hemoglobin
- GFR
- Albuminuria!

Novel Risk markers or FACTORS?


de Zeeuw; Oct 2004
**Albuminuria; a target for renal and cardiovascular protection?**

- Albuminuria is related to renal and CV risk:
  - The higher albuminuria, the more risk (for early patients as well as healthy individuals)
  - Independent of other risk markers
  - Preceding other risk markers

- Lowering albuminuria is related to renal and CV risk reduction:
  - The more albuminuria reduction, the more risk reduction
  - Independent of other risk marker reduction

- Common origin for albuminuria and CV and renal disease?
Addenbrooke’s Nephropathy Cohort: Albuminuria predicts CV outcome in diabetes with albuminuria >30mg/d

Yuyun et al; Diabet Med 2003
LIFE; Baseline albuminuria associated with cardiac events \textit{in hypertension with LVH}; $(n=8206)$

Wachtell et al; Ann Intern Med 2003

3.5 mg/mmol = 30 mg/day
PREVEND; Albuminuria predicts CV mortality in the *general population* (4 yr follow-up)

*Hillege et al; Circulation 2002*
Framingham; Albuminuria determines survival free CVD in the non-diabetic, non-hypertensive subjects (n=1568)

Arnlov et al, Circulation 2005
PREVEND; Albuminuria predicts moderate CKD in the general population (4 yr)

Verhave et al. Kidney Int 2004
Albuminuria; a target for renal and cardiovascular protection?

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- Common origin for albuminuria and CV and renal disease?
LIFE; Baseline albuminuria as determinant of cardiac events in hypertension with LVH

n=8,206

Primary composite endpoint rate
Adjusted composite endpoint rate*

* Adjusted for ECG LV mass, Framingham Risk Score, and study treatment allocation

CV endpoint rate / 1000 patient-years of follow-up

Microalbuminuria

Wachtell et al; Ann Intern Med 2003

3.5 mg/mmol = 30 mg/day
Framingham; Albuminuria determines survival free CVD

*the non-diabetic, non-hypertensive subjects* (n=1568)

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### Dr. Arnlov et al., Circulation 2005

![Graph showing CVD free survival over years with Albuminuria status](Image)

<table>
<thead>
<tr>
<th>Metric</th>
<th>UACR &lt; median</th>
<th>UACR &gt; median</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>783</td>
<td>785</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>54</td>
<td>56</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>27.3</td>
<td>26.4</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>118</td>
<td>119</td>
</tr>
<tr>
<td>Total/HDL chol ratio</td>
<td>4.3</td>
<td>4.1</td>
</tr>
<tr>
<td>Scr (mg/dL)</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>IFG (%)</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>17</td>
<td>17</td>
</tr>
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Albuminuria; a target for renal and cardiovascular protection?

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- Common origin for albuminuria and CV and renal disease?
PREVEND; Albuminuria predicts new onset diabetes (n= 5654; follow-up 4,2 jr)

Brantsma et al; Diabetes Care 2005
PREVEND; Albuminuria predicts new onset hypertension (n=4635; follow-up 4.2 jr)

Brantsma et al; JASN 2006
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Drugs Reducing Albuminuria

- RAAS-intervention, ACEi and All-A (end point trials)
  - Low Protein Diet (end point trials)
  - Non-Steroidal-Antiinflammatory Drugs (no prospective endpoint trials)
  - Glucosamino Glycans eg Sulodexide (trial stopped)
  - Endothelin Antagonists (trial stopped)
  - Statins (trials ongoing)
  - Vitamine D analogues (trial ongoing)
  - Renin-inhibitors (trial ongoing)
LIFE; Treatment (ARB, losartan) associated with lowering albuminuria is cardioprotective in hypertension with LVH

Ibsen et al; Hypertension 2005
PREVEND-IT; Treatment associated with lowering of albuminuria reduces CV morbidity/mortality in “healthy” microalbuminurics (n=800).

![Graph showing effect of ACEi on albuminuria and CV morbidity/mortality.](image)

Asselbergs et al; Circulation 2004
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- Common origin for albuminuria and CV and renal disease?
IRMA-2; Treatment associated with lowering of albuminuria reduces RENAL morbidity in hypertensive microalbuminuric type 2 diabetes. Prevention of transition to overt proteinuria.

**Effect on albuminuria**

![Graph showing the effect of Irbesartan on albuminuria](image)

**Effect on Renal Morbidity**

![Graph showing the effect of Irbesartan on renal morbidity](image)

*Anderson S et al. Diabetes Care 2003*
PREVEND-IT; Initial ACE-I (fosinopril) induced albuminuria reduction related to CV risk protection (n=800)

Event free survival

Follow-up (Months)

Albuminuria reduction > 25%

Albuminuria reduction < 25%

Data adapted from Asselbergs et al; Circulation 2004
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• Lowering albuminuria is related to renal and CV risk reduction:
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• Common origin for albuminuria and CV and renal disease?
Initial All-A (losartan) induced reduction in albuminuria predicts long term CV/renal risk in normotensive type diabetes (n=67)

Zandbergen et al; Diabetes Care 2007

Albuminuria reduction >30% (70 to 40 mg/d)
Albuminuria increase >30% (80 to 220 mg/d)
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• Common origin for albuminuria and CV and renal disease?
Possible interaction between Renal dysfunction and Cardiac dysfunction in the general population.

Healthy population
- decreased GFR

Microalbuminuria

CKD
- Proteinuria
- Anaemia

Cardiovascular dysfunction

ESRD

CHF

Death

de Zeeuw
CATS; Renal Function (eGFR) determines CV outcome

in first myocardial infarction patients

Hillege et al; Eur Heart J 2003
PREVEND; Effect of myocardial infarction on renal function in general population

** Matched control cohort of subjects without ischaemic cardiac event, based on age, gender, serum creatinine, urinary albumin excretion, body mass index, mean arterial pressure, serum cholesterol, triglycerides, serum glucose, and smoking.

_Eijkelkamp et al; Am J Cardiol 2007_
# KDOQI based Renal dysfunction classes

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<th>Stage</th>
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<td>1</td>
<td>&gt; 90</td>
<td>+</td>
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<tr>
<td>2</td>
<td>60 - 89</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
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</tr>
<tr>
<td>5</td>
<td>&lt; 15 or RRT</td>
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*K/DOQI Clinical Practical Guidelines*
*Am J Kidney Dis 2003*
PREVEND; Incidence of cardiovascular events for stage of chronic kidney disease

![Graph showing the incidence rate per 1000 person years for different stages of chronic kidney disease (CKD). The graph is on a logarithmic scale and shows an increasing trend from stage 1/2 to stage 5.]

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*K/DOQI Clinical Practical Guidelines*
*Am J Kidney Dis 2003*
PREVEND; eGFR or microalbuminuria and CV risk
Microalbuminuria more important (Age/sex adjusted)

Survival curves are adjusted for age and sex.

Brantsma et al, NDT in press

Follow-up in years

Proportion free of cardiovascular event
PREVEND; eGFR or microalbuminuria and CV risk
Microalbuminuria more important (Age/sex adjusted)

Survival curves are adjusted for age and sex.
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PREVEND; eGFR or microalbuminuria and CV risk
Microalbuminuria more important (Age/sex adjusted)
Possible interaction between Renal dysfunction and Cardiac dysfunction in the general population

Healthy population
  Microalbuminuria
  Vascular Dysfunction
  CKD
  Proteinuria
  Anaemia
  ESRD
  Cardiovascular dysfunction
  CHF
  Death

de Zeeuw
Urinary albumin excretion and age (cross sectional) in general population children and adults

De Zeeuw et al, JASN, 2006
adapted from Verhave et al, JASN 2003
Lehrnbecher et al. Pediatr Nephrol 1998 (children);
Urinary albumin excretion and age (cross sectional) in general population children and adults

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The albumin molecule

diovascular protection?
The albumin molecule, which ever way you look at it, related to cardiovascular protection?
Summary

- Cardiac and renal dysfunction show interactions. Renal dysfunction predicts cardiac dysfunction, and cardiac dysfunction predicts renal dysfunction.

- The mechanism is still unknown, but a common inborn vulnerability of the vasculature could make the kidney and the heart seemingly interact.
Summary

- Hypothesis: Increased albumin levels are an early indicator of general vascular dysfunction. This may also affect the kidney resulting in a decreased GFR. Both the vascular dysfunction and the hormonal consequences of renal dysfunction can result in cardiac damage. Cardiac damage may result in further vascular dysfunction with renal implications.

TREATMENT IMPLICATION?

Treat the kidney to cure the heart.

Treat the heart to cure the kidney?