Biomarkers in risk prediction of heart and kidney disease

Winfried März
Medizinische Universität Graz,
Medizinische Klinik V
Medizinische Fakultät Mannheim,
Universität Heidelberg,
Synlab Akademie,
Mannheim
Privatärzte Mannheim

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Conflicts of Interest

Research Grants and Honoraria:
Abbott Diagnostics, Aegerion Pharmaceuticals, Astrazeneca, AMGEN, BASF, Danone Research, Sanofi, Siemens Diagnostics, Numares

Employment: Synlab Holding Deutschland GmbH
The good news …
Age-adjusted mortality rates Germany 1998 to 2013

<table>
<thead>
<tr>
<th>women</th>
<th>men</th>
</tr>
</thead>
<tbody>
<tr>
<td>death per 100,000 inhabitants</td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>CAD</td>
</tr>
<tr>
<td>CVD</td>
<td>CVD</td>
</tr>
<tr>
<td>MammaCa</td>
<td>lungCa</td>
</tr>
<tr>
<td>COPD</td>
<td>COPD</td>
</tr>
<tr>
<td>Gesundheitsberichterstattung des Bundes – RKI – destatis 2015</td>
<td></td>
</tr>
</tbody>
</table>
... and the yet bad news
Causes of death Germany 2013

<table>
<thead>
<tr>
<th>Rank</th>
<th>Women</th>
<th>%</th>
<th>Men</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CAD (I20-I25)</td>
<td>13,3</td>
<td>CAD (I20-I25)</td>
<td>15,6</td>
</tr>
<tr>
<td>2</td>
<td>CVD (I60-I69)</td>
<td>7,6</td>
<td>Lung Cancer (C33-C34)</td>
<td>6,9</td>
</tr>
<tr>
<td>3</td>
<td>Heart failure (I50)</td>
<td>6,5</td>
<td>CVD (I69-I69)</td>
<td>5,4</td>
</tr>
<tr>
<td>4</td>
<td>Dementia (F01, F03, G30)</td>
<td>5,2</td>
<td>COPD (J40-J47)</td>
<td>4,2</td>
</tr>
<tr>
<td>5</td>
<td>Hypertension (I11,I13)</td>
<td>4,6</td>
<td>Heart failure (I50)</td>
<td>3,7</td>
</tr>
<tr>
<td>6</td>
<td>Breast Cancer (C50)</td>
<td>3,8</td>
<td>Colon Cancer (C18-C21)</td>
<td>3,2</td>
</tr>
<tr>
<td>7</td>
<td>Lung Cancer (C33-C34)</td>
<td>3,3</td>
<td>Prostate Cancer (C61)</td>
<td>3,1</td>
</tr>
<tr>
<td>8</td>
<td>COPD (J40-J47)</td>
<td>3,2</td>
<td>Accidents (V01-X59)</td>
<td>2,6</td>
</tr>
<tr>
<td>9</td>
<td>Diabetes mellitus (E0-E14)</td>
<td>3,0</td>
<td>Dementia (F01, F03, G30)</td>
<td>2,5</td>
</tr>
<tr>
<td>10</td>
<td>Colon Cancer (C18-C21)</td>
<td>2,6</td>
<td>Diabetes mellitus (E0-E14)</td>
<td>2,4</td>
</tr>
<tr>
<td></td>
<td>Total CVD</td>
<td>32,0</td>
<td>Total CVD</td>
<td>24,7</td>
</tr>
</tbody>
</table>

Gesundheitsberichterstattung des Bundes, RKI und destatis, 2015

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**Agenda**

Cardiovascular risk assessment
- Traditional risk factors and their limitations
- Emerging Biomarkers to improve risk assessment

Renal markers impacting on cardiovascular risk
- Chronic kidney disease and risk of heart disease
- Lipoprotein metabolism
Why risk prediction?

Inconsistency of Risk Scores
DETECT Study 2003

Median-Werte der Scores in Perzentil 1 bis 10

Limitations of current CVD risk
Scientific

- Already used to guide therapy but...
  - Poor discrimination
  - Inconsistency of prediction models
  - Different endpoints (MACE vs. CVD mortality)
  - Poor representation of genetic factors (e.g. family history)
  - Intermediate risk groups ill defined
  - Diabetes mellitus mostly treated as coronary risk equivalent
  - Only one risk stratification algorithm available for patients with stable coronary disease (Marshner)
  - Novel biomarkers not included
Limitations of CVD risk prediction

Practical

- Lack of knowledge
- Confusion due to different recommendations and guidelines
- Confusion due to different endpoints
- Require linking clinical and laboratory findings
- No straight forward tools available in primary care
- In Germany
  - Ten out of 100 physicians know about risk algorithms
  - One out of 100 uses them in daily practice

traditional

Oxidative Stress

NO Endothelial Dysfunction

Calcification Factors

Sympathetic activity

BNP
Development requirements

- Utilize the potential of novel biomarkers for improved risk prediction
- Non-redundancy of selected predictor variables
- Biomedical plausibility (representation of organ systems and pathophysiology)
- Actionable markers
- Ease and convenience of implementation on automated analyzers
- Transportability and ease of re-calibration
- Complete independence from anamnestic and clinical information

The evidence base

LUdwigshafen RIsk and Cardiovascular Health (LURIC) Study

- One of the first German biobanks to investigate heart disease
- Heart Center Ludwigshafen, Universities of Freiburg, Ulm, and Graz
- Inclusion criteria
  - Coronary angiogram
  - Clinically stable with the exception of acute coronary disease
- Recruitment 1997 to 2001 (n = 3500)
- Comprehensive clinical, biochemical and genetic characterization
- Follow-up 9.9 years
Coropredict 1.0

<table>
<thead>
<tr>
<th>Variable</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>LDL-C</td>
<td>Not part of the risk function</td>
</tr>
<tr>
<td>HDL-C</td>
<td>Not part of the risk function</td>
</tr>
<tr>
<td>HbA1c</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Cotinin</td>
<td>Smoking</td>
</tr>
<tr>
<td>Cystatin C</td>
<td>Kidney function</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Lifestyle</td>
</tr>
<tr>
<td>NT-pro-BNP</td>
<td>Cardiac function, volume regulation</td>
</tr>
<tr>
<td>TnT</td>
<td>Myocardial necrosis</td>
</tr>
<tr>
<td>Galektin 3</td>
<td>Fibrosis</td>
</tr>
<tr>
<td>CRP (ST2)</td>
<td>Chronic Inflammation</td>
</tr>
</tbody>
</table>

Example for Discrimination
patients with stable CAD – CVD mortality

Cardiovascular mortality in quartiles of Coropredict (stable CAD, n=640)

Integrated Coropredict Scores ranked and stratified into quartiles, mean of 10 years of follow up

AUC=0.801
Implementation

Replicated in an independent cohort
VIVIT cohort - stable CAD – CVD mortality

<table>
<thead>
<tr>
<th>Deciles of predicted risk</th>
<th>Mortality (%)</th>
<th>7 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>45</td>
<td></td>
</tr>
</tbody>
</table>

"risk predicted" "risk observed"
Extrapolation to subjects without history of CVD?

Recalibrated for primary prevention
DETECT Study 2003
Prevalence of CKD in primary care
Germany  n = 4339

Gergei I et al. submitted CKD-EPI 2004
overall prevalence 29.7%

Gergei I et al. submitted CKD-EPI 2007
overall prevalence 36.1%

Cystatin C is more sensitiv in „creatinine-blind" sector

Cystatin C is a better indicator for long-term prognosis than creatinine

The main threat in patients with chronic kidney disease is cardiovascular death rather than progression to dialysis

AHA Scientific Statement

Kidney Disease as a Risk Factor for Development of Cardiovascular Disease

A Statement From the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention

*Circulation*. 2003;108:2154–2169
Major Causes of Atherosclerosis

- Age
- Sex
- Smoking
- Hypertension
- Diabetes mellitus
- LDL Cholesterol
- Low HDL-Cholesterol

Will they act differently in CKD?

- Hypertension
- Diabetes mellitus
- LDL Cholesterol
- Low HDL-Cholesterol
HDL-Cholesterol and CHD-risk


Biological functions of HDL

Eur Heart J 2013;34:3531-3534
HDL „dysfunction“

- Coronary heart disease
- Chronic kidney disease
- Diabetes mellitus
- Anti-phospholipid syndrome
- Rheumatoid arthritis
- Morbus Crohn


HDL, CKD and CVD mortality
Ludwigshafen Risk and Cardiovascular Health Study

SAA displaces Apo AI from HDL


SAA „inactivates“ HDL

Calculation of „effective“ HDL-C from SAA

<table>
<thead>
<tr>
<th>measured HDL-C (mg/dl)</th>
<th>Biologically active HDL-C' (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SAA 2-6 mg/l</td>
</tr>
<tr>
<td>20</td>
<td>23·5</td>
</tr>
<tr>
<td>30</td>
<td>34·8</td>
</tr>
<tr>
<td>40</td>
<td>46·1</td>
</tr>
<tr>
<td>50</td>
<td>57·4</td>
</tr>
<tr>
<td>60</td>
<td>68·6</td>
</tr>
</tbody>
</table>

Many CVD biomarkers (e.g. troponins, natriuretic peptides) are altered in CKD.

Would this mean that the need the be interpreted differently in CKD?
NT-proBNP and renal function
Ludwigshafen Risk and Cardiovascular Health Study

NT-proBNP and cardiovascular mortality
Ludwigshafen Risk and Cardiovascular Health Study
Die Deutsche Diabetes Dialyse Studie
Conclusions

• Biomarkers need to be evaluated according to clinical outcomes.
• There is no single biomarker reflecting all CVD risk conditions.
• The novel biomarker combination Coropredict allows to identify patients at high risk of CVD death independent of clinical information.
• Further research has indicated that other, even newer biomarkers hardly would beat the Coropredict combination.
• Chronic kidney disease strongly impacts on cardiovascular risk.
• Cardiac biomarkers in part capture the risk conferred by chronic kidney disease, indicating a cardio-renal continuum.