Large Scale Analysis of Lifetime Risk of Cardiovascular Disease in Europe and Population Attributable Risk of Cardiovascular Risk Factors in the Biomarkers for Cardiovascular Risk Assessment in Europe (BiomarCaRE) project

Stefan Blankenberg for BiomarCaRE investigators
Background/Rationale

- Calculation of Life Time Risk (LTR) estimates cumulative risk of developing a disease during remaining lifespan.
- Despite treatment success, Cardiovascular Disease (CVD) remains the single leading cause of morbidity and mortality in adults worldwide.
- Whereas LTR of cancer and other diseases is well described, reports on LTR of CVD in the European population are limited.
Background/Rationale

- The classical cardiovascular risk factors explain a proportion of CVD events.
- To estimate the effect of known risk factors by Population Attributable Risk (PAR) a harmonized large sample set including a substantial amount of events is needed.
- The magnitude of effect of classical RF on development of CVD remains unclear and might leave room for novel biomarkers.
Objectives

- We aim to:
  - better understand the risk for CVD in Europe (LTR)
  - quantify the importance of risk factors for CVD development (PAR)
  - understand whether there is room left to improve risk prediction by inclusion of novel biomarkers (biomarkers)
Participating Countries and Cohorts
Methods – About the risk factors

- Smoker status (dichotomized)
- Diabetes (dichotomized)
- Systolic blood pressure (categorized: 120-140 mmHg, 140-160 mmHg, ≥160 mmHg)
- Hypertension (dichotomized)
- Weight: based on BMI categories of the WHO definition (categorized: underweight, pre-obese, obese)
- Obesity (dichotomized: <30 BMI, ≥30 BMI)
- LDL (categorized: <100 mg/dL, 100-130 mg/dL, 130-160 mg/dL, 160-190 mg/dL, ≥190 mg/dL)
- Hypolipoproteinemia (dichotomized: LDL <190 mg/dL, LDL ≥190 mg/dL)

Novel biomarkers:
- High-sensitive cardiac troponin I (hsTnI) (dichotomized at 6 ng/L)
- N-terminal pro brain natriuretic peptide (NT-proBNP) (dichotomized at 100 ng/mL)
Statistical analysis

a. The lifetime risk (LTR) for CVD was computed
   - for men and women at age decades: <35, 35-44, 45-54, 55-64, 65-74, and ≥75;

b. For the calculation of CVD lifetime risk (cumulative incidence) survival analysis was compared to competing risk of non CVD death.

c. The population attributable risk (PAR) of each primary risk exposure (smokers, diabetes mellitus, systolic blood pressure, BMI, LDL) was estimated for the 10-year incidence of CVD.
## Results – Baseline characteristics of the study population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of individuals</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>205,002</td>
</tr>
<tr>
<td>Years of baseline examinations</td>
<td>range in years</td>
</tr>
<tr>
<td></td>
<td>1982 - 2013</td>
</tr>
<tr>
<td>Men</td>
<td>N (%)</td>
</tr>
<tr>
<td></td>
<td>121,353 (59.2)</td>
</tr>
<tr>
<td>Women</td>
<td>N (%)</td>
</tr>
<tr>
<td></td>
<td>83,649 (40.8)</td>
</tr>
<tr>
<td>Age at baseline examination</td>
<td>years</td>
</tr>
<tr>
<td></td>
<td>52.1</td>
</tr>
</tbody>
</table>

### Cardiovascular risk factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>N (%)</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily smoker</td>
<td>N (%)</td>
<td>78,100 (39.6)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>N (%)</td>
<td>9,567 (4.7)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>N (%)</td>
<td>90,331 (44.3)</td>
</tr>
<tr>
<td>Body-mass-index (kg/m²)</td>
<td></td>
<td>25.8</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td></td>
<td>134.0</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td></td>
<td>224.0</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td></td>
<td>52.2</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td></td>
<td>136.3</td>
</tr>
</tbody>
</table>

### Medication

<table>
<thead>
<tr>
<th>Medication</th>
<th>N (%)</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensive</td>
<td>N (%)</td>
<td>26,116 (15.7)</td>
</tr>
</tbody>
</table>

### Outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N (%)</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalent CVD</td>
<td>N (%)</td>
<td>9,583 (4.7)</td>
</tr>
<tr>
<td>Incident CVD</td>
<td>N (%)</td>
<td>23,297 (11.4)*</td>
</tr>
</tbody>
</table>

* after exclusion of the corresponding prevalent cases
Prevalence of risk factors by survey time
Time line of survey years’ ranges
Results – Endpoints after exclusion of the corresponding prevalent cases

- Cardiovascular disease event: N=23,297
- Major coronary disease event: N=18,791
- Myocardial infarction: N=16,457
- Stroke: N=7,714
- Cardiovascular mortality: N=6,588
- Total mortality: N=39,377
Results — lifetime risk (individuals aged 55 with no CVD death as competing risk and by sex

![Cumulative incidence function](image)

- CVD in women
- Death before CVD in women
- CVD in men
- Death before CVD in men

Age, years

Cumulative incidence function
Results — lifetime risk for CVD events for individuals aged 50 years by risk factors presence
### Results — lifetime risk (%) for CVD events for individuals aged 50, 60, 70, and 80 years by risk factors (RF) presence

<table>
<thead>
<tr>
<th></th>
<th>No RFs</th>
<th>1 RF</th>
<th>2 RFs</th>
<th>At least 3 RFs</th>
</tr>
</thead>
<tbody>
<tr>
<td>50, years</td>
<td>0.1 (0.0, 0.4)</td>
<td>0.5 (0.3, 0.9)</td>
<td>0.8 (0.5, 1.4)</td>
<td>3.2 (2.0, 5.2)</td>
</tr>
<tr>
<td>60, years</td>
<td>1.4 (1.1, 1.9)</td>
<td>3.7 (3.3, 4.3)</td>
<td>7.3 (6.5, 8.1)</td>
<td>13.0 (11.3, 15.0)</td>
</tr>
<tr>
<td>70, years</td>
<td>5.3 (4.4, 6.5)</td>
<td>10.5 (9.5, 11.5)</td>
<td>17.3 (15.9, 18.8)</td>
<td>25.6 (23.2, 28.3)</td>
</tr>
<tr>
<td>80, years</td>
<td>13.2 (10.2, 17.1)</td>
<td>19.0 (16.5, 21.8)</td>
<td>28.9 (25.6, 32.6)</td>
<td>42.2 (36.0, 49.0)</td>
</tr>
</tbody>
</table>
Results — lifetime risk by risk factor smoking status

Individuals index age 50 years
Results — lifetime risk by risk factor diabetes

Individuals index age 50 years

Cumulative incidence function

Age, years

Non-diabetic
Diabetic
Results — lifetime risk by risk factor obesity

![Graph showing cumulative incidence function by BMI categories (Normal, Underweight, Pre-obese, Obese) over age (50 years to 80 years).]
Results — lifetime risk by risk factor systolic blood pressure
Results — lifetime risk by risk factor low density lipoprotein
### Results — population attributable risk

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Male HR (95% CI)</th>
<th>Male Adjusted PAR (%)</th>
<th>Female HR (95% CI)</th>
<th>Female Adjusted PAR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily smoker</td>
<td>1.82 (1.68, 1.97)</td>
<td>4.5</td>
<td>2.23 (1.94, 2.55)</td>
<td>2.4</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.19 (1.90, 2.52)</td>
<td>11.6</td>
<td>2.51 (2.06, 3.07)</td>
<td>11.1</td>
</tr>
<tr>
<td>SBP 120-140 mmHg</td>
<td>1.17 (1.01, 1.34)</td>
<td>0.8</td>
<td>1.56 (1.18, 2.05)</td>
<td>0.9</td>
</tr>
<tr>
<td>SBP 140-160 mmHg</td>
<td>1.62 (1.41, 1.87)</td>
<td>4.1</td>
<td>1.85 (1.40, 2.46)</td>
<td>2.9</td>
</tr>
<tr>
<td>SBP ≥ 160 mmHg</td>
<td>2.07 (1.78, 2.42)</td>
<td>10.7</td>
<td>3.00 (2.25, 4.01)</td>
<td>12.0</td>
</tr>
<tr>
<td>Underweight</td>
<td>1.28 (0.78, 2.08)</td>
<td>2.0</td>
<td>1.33 (0.84, 2.10)</td>
<td>0.9</td>
</tr>
<tr>
<td>Pre-obese</td>
<td>1.31 (1.20, 1.43)</td>
<td>2.2</td>
<td>1.26 (1.09, 1.46)</td>
<td>1.1</td>
</tr>
<tr>
<td>Obese</td>
<td>1.48 (1.31, 1.67)</td>
<td>3.9</td>
<td>1.55 (1.31, 1.83)</td>
<td>3.0</td>
</tr>
<tr>
<td>LDL 100-130 mg/dL</td>
<td>1.17 (0.96, 1.43)</td>
<td>0.7</td>
<td>0.99 (0.71, 1.38)</td>
<td>0.0</td>
</tr>
<tr>
<td>LDL 130-160 mg/dL</td>
<td>1.53 (1.26, 1.85)</td>
<td>2.7</td>
<td>1.05 (0.77, 1.45)</td>
<td>0.2</td>
</tr>
<tr>
<td>LDL 160-190 mg/dL</td>
<td>1.83 (1.51, 2.21)</td>
<td>4.6</td>
<td>1.29 (0.94, 1.77)</td>
<td>1.5</td>
</tr>
<tr>
<td>LDL ≥190 mg/dL</td>
<td>2.59 (2.13, 3.15)</td>
<td>9.6</td>
<td>1.40 (1.02, 1.93)</td>
<td>3.1</td>
</tr>
<tr>
<td>Total with all risk factors</td>
<td>43.9</td>
<td></td>
<td>29.9</td>
<td></td>
</tr>
<tr>
<td>Total with all risk factors+hsTnI+NT-proBNP</td>
<td>50.6</td>
<td></td>
<td>32.2</td>
<td></td>
</tr>
</tbody>
</table>

Tab. Hazard ratios and adjusted PARs analyzing CVD event due to risk factors by sex.
Limitations

- These calculations rely on a European mainly white population of caucasian origin.
- The PAR is currently based on classical cardiovascular risk factors and neglects behavioral health factors.
- PAR is calculated based on a 10 years incidence of CVD.
- Some cohorts started sampling in the 80s and early 90s when preventive cardiovascular strategies and medication differed substantially from today.
- So far, we do not report similar magnitude of results across northern, southern, western and eastern Europe.
The BiomarCaRE project offers a combined analyses of European data from more than 200,000 individuals derived from 12 cohorts over a period of 40 years.

The presence of elevated levels of risk factors at all ages translated into markedly higher lifetime risk of CVD.

The PAR of differs across classical risk factors substantially but only explains roughly the half of incident events.

Room is left to identify novel potentially causal risk factors of CVD.

BiomarCaRE is an ongoing project and further cohorts are continuously included to improve our understanding of LTER and PAR in Europe.
Thank you

BiomarCaRE Laboratory, UKE
Tanja Zeller
Satya Bhowmik
Sarah Dünger
Sabine Gerth
Tim Hartmann
Katharina Peetz
Caroline Röthemeier

BiomarCaRE Data Center
Kari Kuulasmaa, THL
Ari Haukijärvi, THL
Jukka Konto, THL
Tarja Tuovinen, THL
Andreas Ziegler, IMBS Lübeck
Arne Schillert, IMBS Lübeck

BiomarCaRE SME
Cavadis B.V.: Heiko Breek
Fleet Bioprocessing Ltd: Alastair Dent
Biocrates Life Science AG: Manuel Kratzke
Biocartis S.A.: Patrick van den Bogaard

BiomarCare Steering Committee
Heiko Breek, Cavadis
Gerard Pasterkamp, UMC Utrecht
Kari Kuulasmaa, THL
Veikko Salomaa, THL
Stefan Blankenberg, UKE
Tanja Zeller, UKE
Wolfgang Koenig, UULM

BiomarCaRE Project Management
Erik Werner, Research Network Services Ltd.
Simone Schnella, UKE

BiomarCaRE Coordinators
Tanja Zeller, UKE
Stefan Blankenberg, UKE

BiomarCaRE Statistician Team:
Francisco Ojeda, UKE
Nataliya Makarova, UKE

Cohorts
Estonia: Andres Metspalu
FinRisk, ATBC: Veikko Salomaa
Northern Sweden: Per-Gunnar Wiklund, Stefan Söderström
Tromsø: Inger Njelstad, Ellisiv B Mathiesen
Glostrup: Torben Jørgensen
HAPIEE: Martin Bobak
Scottish Monica: Hugh Tunstall-Pedoe, Jill Belch
PRIME Belfast: Frank Kee,
Caerphilly: Frank Kee
SHIP: Henry Völzke, Marcus Dörr, Stephan Felix
PRIME France: Jean Dallongeville
GHS: Philipp Wild, Thomas Münzel
KORA Monica: Barbara Thorand, Annettes Peters
MONICA Italy Brianza: Marco Ferrario, Giovanni Veronesi
MONICA Italy Rome, Friuli: Luigi Marzio Biasucci, Filippo Crea
Moli-Sani: Licia Iacoviello
MONICA Catalonia: Teresa Padró, Susana Sans
Atherogene, StenoCardia: Renate Schnabel,
Stefan Blankenberg
APACE: Christian Müller
KAROLA: Wolfgang König, Dietrich Rothenbacher
IBIS-2:Wolfgang König, Dietrich Rothenbacher
JUPITER: Paul Ridker, Brendan Everett
TRANSCEND: Sonia Anand
WHS: Paul Ridker, Brendan Everett