Application of Non-HDL-Cholesterol for
Population-based Cardiovascular Risk Stratification

Stefan Blankenberg on behalf of the
Multinational Cardiovascular Risk Consortium
Declaration of interest

- Others (ASPIRE Cardiovascular grant award, Pfizer)
- Consulting/Royalties/Owner/Stockholder of a healthcare company (Abbott Diagnostics, Amgen, Bayer, Siemens Healthcare, Novartis)
Background

- Causal relationship between blood cholesterol concentration and cardiovascular disease (CVD) is well proven.

- Association between baseline lipid concentrations and very long-term cardiovascular outcomes in the population remains rather sparse.

- Current guideline recommendations for primary prevention are based on the 10-year CVD risk potentially underestimating the cumulative lifetime risk particularly in younger adults.

- In high risk individuals lipid lowering therapy to prevent CVD events is well established. Evidence is less clear for primary prevention in particular in younger individuals.
Objectives

We aim to

- describe the impact of non-HDL-C concentration on long-term risk for CVD
- establish a tool to easily assess the long-term risk probabilities for CVD according to categories of non-HDL-C, age, sex and number of risk factors
- evaluate the potential benefit of an early lipid lowering strategy according to the tools categories
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MORGAM/BiomarCaRE
- ATBC
- DanMONICA Study, RCPH
- EGCUT
- ESTHER Study
- FINRISK
- GHS
- Kaunas Study
- KORA MONICA
- Krakow Study
- MATISS Rome Study
- Moli-Sani Study
- MONICA Brianza Study
- MONICA Catalonia
- MONICA Friuli
- MONICA Newcastle
- MONICA PAMELA
- Northern Sweden MONICA Study
- Novosibirsk Study
- PRIME
- SHHEC
- SHIP
- Tromsø Study
- Warsaw Study

Further population-based cohorts worldwide
- AusDiab
- Atherosclerosis Risk in Communities Study (ARIC)
- ATTICA
- British Regional Heart Study (BRHS)
- Cardiovascular Health Study (CHS)
- Dallas Heart Study (DHS)
- DETECT
- Dubbo Study of the elderly
- Framingham Heart Study (FHS)
- HAPIEE
- Health 2000/2011
- Heinz Nixdorf RECALL Study
- HUNT
- Jackson Heart Study (JHS)
- Malmö Diet and Cancer Study
- Malmö Prevention Project
- Melbourne Collaborative Cohort Study (MCCS)
- Multi-Ethnic Study of Atherosclerosis (MESA)
- PREVEND Study
- ULSAM Study
### Multinational Cardiovascular Risk Consortium

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<td>Warsaw Study</td>
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36 cohorts  
19 countries  
3 continents
Methods

Study population
Out of 511,988 individuals of the Multinational Cardiovascular Risk Consortium we excluded individuals with prevalent CVD (N=33,234). Information about harmonized incident CVD was available in 380,087 individuals.

Derivation analyses were performed in the MORGAM/BiomarCaRE dataset and results were validated in the non-MORGAM/non-BiomarCaRE cohorts.

Primary clinical outcome
non-fatal or fatal CVD defined as the first occurrence of myocardial infarction, unstable angina, coronary death, coronary revascularization, or ischemic stroke.

During max. f/u of 43 years, 47,972 endpoints occurred.
Methods

Multivariable analyses
Analyses were adjusted for potential confounders: age, sex, cohort, and modifiable classical cardiovascular risk factors (smoking status, diabetes, obesity, and arterial hypertension).

Non-HDL-cholesterol
Based on the 2016 ESC/EAS dyslipidaemia guidelines non-HDL-C concentrations were calculated to be 0.8 mmol/L (30 mg/dL) higher compared to LDL-C levels. Threshold concentrations were displayed in mmol/l assuming 1 mmol/l = 38.67 mg/dL.
### Baseline characteristics

<table>
<thead>
<tr>
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<th>All (N= 380,087)</th>
<th>Derivation (N= 226,661)</th>
<th>Validation (N= 153,426)</th>
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<tr>
<td>Examination age (years)</td>
<td>50·7 (40·6, 59·2)</td>
<td>50·4 (38·5, 58·3)</td>
<td>51·0 (45·0, 61·0)</td>
</tr>
<tr>
<td>Follow-up time years, range</td>
<td>0·43·6</td>
<td>0·30·8</td>
<td>0·43·6</td>
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<tr>
<td>Follow-up years</td>
<td>13·2 (6·8, 20·1)</td>
<td>10·3 (5·6, 16·9)</td>
<td>20·0 (12·3, 26·5)</td>
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<tr>
<td>Female %</td>
<td>48·4</td>
<td>47·8</td>
<td>49·4</td>
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<tr>
<td>Risk SCORE</td>
<td>1·0 (0·2, 3·4)</td>
<td>1·2 (0·2, 3·8)</td>
<td>0·8 (0·2, 2·7)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25·7 (23·1, 28·8)</td>
<td>25·8 (23·1, 28·9)</td>
<td>25·6 (23·1, 28·7)</td>
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<tr>
<td>Arterial hypertension %</td>
<td>39·8</td>
<td>40·2</td>
<td>38·9</td>
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<tr>
<td>Diabetes mellitus %</td>
<td>4·7</td>
<td>4·1</td>
<td>5·7</td>
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<tr>
<td>Daily smoker %</td>
<td>33·7</td>
<td>36·5</td>
<td>28·6</td>
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<tr>
<td>Cholesterol lowering medication %</td>
<td>4·6</td>
<td>3·7</td>
<td>5·9</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td>3·6 (2·9, 4·3)</td>
<td>3·6 (2·9, 4·3)</td>
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<tr>
<td>Non-HDL-cholesterol (mmol/L)</td>
<td>4·3 (3·5, 5·2)</td>
<td>4·4 (3·6, 5·2)</td>
<td>4·2 (3·4, 5·0)</td>
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Long-term incidence of CVD according to non-HDL-C

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<th>Non-HDL-C (mmol/L)</th>
<th>CVD Incidence</th>
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<tr>
<td>&lt;2·6</td>
<td>p&lt;0·001</td>
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<tr>
<td>2·6 to &lt;3·7</td>
<td></td>
</tr>
<tr>
<td>3·7 to &lt;4·8</td>
<td></td>
</tr>
<tr>
<td>4·8 to &lt;5·7</td>
<td></td>
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<tr>
<td>≥5·7</td>
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<2·6 mmol/L [< 100 mg/dL]
2·6 to <3·7 mmol/L [100 to <145 mg/dL]
3·7 to <4·8 mmol/L [145 to <185 mg/dL]
4·8 to <5·7 mmol/L [185 to <220 mg/dL]
≥5·7 mmol/L [≥220 mg/dL]
Sex-Specific Linear Association between Long-term incidence of CVD and non-HDL-C
Age- and sex-specific association of non-HDL-C and CVD
Age- and sex-specific association of non-HDL-C and CVD
Model of long-term CVD risk prediction and the simulated benefit of lipid reduction
Long-term risk model

Five non-HDL-C categories
Long-term risk model

Five non-HDL-C categories

Three age-categories within each non-HDL-C category
Long-term risk model

Five non-HDL-C categories

Three age-categories within each non-HDL-C category

Number of further CV risk factors (aHT, diabetes, smoking, obesity)
Long-term risk model

- Five non-HDL-C categories
- Three age-categories within each non-HDL-C category
- Number of further CV risk factors (aHT, diabetes, smoking, obesity)

Probability (%) for non-fatal or fatal CVD by the age of 75 years
Long-term risk model and simulated lifetime lipid reduction

- Five non-HDL-C categories
- Three age-categories within each non-HDL-C category
- Number of further CV risk factors (aHT, diabetes, smoking, obesity)

Probability (%) for non-fatal or fatal CVD by the age of 75 years

Modelled risk for non-fatal or fatal CVD by the age of 75 years after hypothetical lifetime reduction of non-HDL-C by 50%
Example: A healthy young man with slightly elevated non-HDL-C of 4.0 mmol/L (155 mg/dL), <45 years of age, and no further CV risk factors. For this individual the non-HDL-based long-term risk for non-fatal or fatal CVD by the age of 75 years is 19.0% and could be reduced to 12.7% by 50% lifetime reduction of non-HDL-C blood level (RRR 33%, NNT 15.9).
Limitations

Endpoint information is mainly based on medical reports or local registers. However, endpoint information in all cohorts were harmonized on individual data level according to MORGAM specifications.

The therapeutic benefit of lipid lowering therapy is a hypothetical model assuming lifetime lipid lowering therapy. Therefore, the present study only simulates insights on the benefits of a potential early intervention in primary prevention.

Cohorts were largely based on high income countries (Western Europe, Australia, North America). The generalizability of the findings to other regions, or individuals from other racial/ethnic groups needs to be investigated.
Conclusion

- We observed a strong graded association of non-HDL-C blood levels and incident CVD during very long-term follow-up with increasing effects over time.

- The risk circles allow the non-HDL-C associated prediction of long-term CVD risk and demonstrate the potential benefit of hypothetical lifetime lipid lowering strategies.

- This simple tool may be practically useful for the physician-patient communication about primary prevention strategies.
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