UKE Paper of the Month Januar 2020

Application of non-HDL cholesterol for population-based cardiovascular risk stratification: results from the Multinational Cardiovascular Risk Consortium.

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ABSTRACT:

BACKGROUND: The relevance of blood lipid concentrations to long-term incidence of cardiovascular disease and the relevance of lipid-lowering therapy for cardiovascular disease outcomes is unclear. We investigated the cardiovascular disease risk associated with the full spectrum of bloodstream non-HDL cholesterol concentrations. We also created an easy-to-use tool to estimate the long-term probabilities for a cardiovascular disease event associated with non-HDL cholesterol and modelled its risk reduction by lipid-lowering treatment.

METHODS: In this risk-evaluation and risk-modelling study, we used Multinational Cardiovascular Risk Consortium data from 19 countries across Europe, Australia, and North America. Individuals without prevalent cardiovascular disease at baseline and with robust available data on cardiovascular disease outcomes were included. The primary composite endpoint of atherosclerotic cardiovascular disease was defined as the occurrence of the coronary heart disease event or ischaemic stroke. Sex-specific multivariable analyses were computed using non-HDL cholesterol categories according to the European guideline thresholds, adjusted for age, sex, cohort, and classical modifiable cardiovascular risk factors. In a derivation and validation design, we created a tool to estimate the probabilities of a cardiovascular disease event by the age of 75 years, dependent on age, sex, and risk factors, and the associated modelled risk reduction, assuming a 50% reduction of non-HDL cholesterol.

FINDINGS: Of the 524 444 individuals in the 44 cohorts in the Consortium database, we identified 398 846 individuals belonging to 38 cohorts (184 055 [48·7%] women; median age 51·0 years [IQR 40·7-59·7]). 199 415 individuals were included in the derivation cohort (91 786 [48·4%] women) and 199 431 (92 269 [49·1%] women) in the validation cohort. During a maximum follow-up of 43·6 years (median 13·5 years, IQR 7·0-20·1), 54 542 cardiovascular endpoints occurred. Incidence curve analyses showed progressively higher 30-year cardiovascular disease event-rates for increasing non-HDL cholesterol categories (from 7·7% for non-HDL cholesterol <2·6 mmol/L to 33·7% for ≥5·7 mmol/L in women and from 12·8% to 43·6% in men; p<0·0001). Multivariable adjusted Cox models with non-HDL cholesterol lower than 2·6 mmol/L as reference showed an increase in the association between non-HDL cholesterol concentration and cardiovascular disease for both sexes (from hazard ratio 1·1, 95% CI 1·0-1·3 for non-HDL cholesterol 2·6 to <3·7 mmol/L to 1·9, 1·6-2·2 for ≥5·7 mmol/L in women and from 1·1, 1·0-1·3 to 2·3, 2·0-2·5 in men). The derived tool allowed the estimation of cardiovascular disease event probabilities specific for non-HDL cholesterol with high comparability between the derivation and validation cohorts as reflected by smooth calibration curves analyses and a root mean square error lower than 1% for the

estimated probabilities of cardiovascular disease. A 50% reduction of non-HDL cholesterol concentrations was associated with reduced risk of a cardiovascular disease event by the age of 75 years, and this risk reduction was greater the earlier cholesterol concentrations were reduced.

INTERPRETATION: Non-HDL cholesterol concentrations in blood are strongly associated with long-term risk of atherosclerotic cardiovascular disease. We provide a simple tool for individual long-term risk assessment and the potential benefit of early lipid-lowering intervention. These data could be useful for physician-patient communication about primary prevention strategies.

FUNDING: EU Framework Programme, UK Medical Research Council, and German Centre for Cardiovascular Research.

STATEMENT:

By using individual level data of a multinational population-based cohort dataset, our study provides the most comprehensive analysis of long-term risk for cardiovascular disease related to non-HDL cholesterol. The tool developed from this analysis could facilitate shared decision making in primary prevention by estimating lifetime risk of atherosclerotic cardiovascular disease up to 75 years of age, as well as the potential for individualized benefit from lowering non-HDL cholesterol concentrations over a lifetime.

BACKGROUND:

This work was performed at the Department of Cardiology in the group of Professor Stefan Blankenberg who is also the coordinator of an EU-funded project to improve risk estimation of cardiovascular disease in Europe (BiomarCaRE). For the current study and future projects, the authors established the *Multinational Cardiovascular Risk Consortium* including currently 23 cohorts of the MORGAM/BiomarCaRE project as well as further 21 population-based individual levels cohorts from Australia, Europe and USA. Fabian Brunner and Christoph Waldeyer have strong research interests in the field of primary prevention with a special focus on biomarkers and coronary artery disease. The current study was funded by EU Framework Programme, UK Medical Research Council, and German Centre for Cardiovascular Research.