Lipid-Related Markers and Cardiovascular Disease Prediction

The Emerging Risk Factors Collaboration*

Routinely used risk prediction scores for cardiovascular disease (CVD) contain information on total cholesterol and high-density lipoprotein cholesterol (HDL-C) and several other conventional risk factors. There is considerable interest in whether CVD prediction can be improved by assessment of various additional lipid-related markers either to replace, or supplement, traditional cholesterol measurements in these scores.

Proposals to replace information on total cholesterol and HDL-C with single parameters, such as the total cholesterol:HDL-C ratio or non–HDL-C (ie, total cholesterol − HDL-C), have been motivated by a desire for greater simplicity and a belief that these parameters better reflect the underlying atherosclerotic process. For example, non–HDL-C reflects the cholesterol content of several proatherogenic lipoprotein subfractions (very low-density lipoprotein, intermediate-density lipoprotein, and chylomicron remnants) in addition to low-density lipoprotein cholesterol.

Similar considerations apply to proposals to replace information on total cholesterol and HDL-C with apolipoprotein B and apolipoprotein A-I. Because apolipoprotein B and A-I are the principal surface proteins found on proatherogenic lipoproteins and HDL, respectively, they might be more strongly related to CVD risk than is the cholesterol contained in these lipoproteins. However, perhaps partly due to inconclusive epidemiological evidence, there are conflicting guidelines about the relevance of apolipoprotein B and A-I to CVD prediction.

There is also debate about the value of supplementing conventional risk factors with targeted assessment of lipoprotein(a). In 2010, the European Atherosclerosis Society Consensus Panel recommended lipoprotein(a) measurement to augment risk assessment in people at intermediate (10%-<20%) or high (≥20%) predicted 10-year CVD risk. However, the 2010 American College of Cardiology Foundation/American Heart Association Task Force...

For editorial comment see p 2540.

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Context The value of assessing various emerging lipid-related markers for prediction of first cardiovascular events is debated.

Objective To determine whether adding information on apolipoprotein B and apolipoprotein A-I, lipoprotein(a), or lipoprotein-associated phospholipase A2 to total cholesterol and high-density lipoprotein cholesterol (HDL-C) improves cardiovascular disease (CVD) risk prediction.

Design, Setting, and Participants Individual records were available for 165 544 participants without baseline CVD in 37 prospective cohorts (calendar years of recruitment: 1968-2007) with up to 15 126 incident fatal or nonfatal CVD outcomes (10 132 CHD and 4994 stroke outcomes) during a median follow-up of 10.4 years (interquartile range, 7.6-14 years).

Main Outcome Measures Discrimination of CVD outcomes and reclassification of participants across predicted 10-year risk categories of low (<10%), intermediate (10%-<20%), and high (≥20%) risk.

Results The addition of information on various lipid-related markers to total cholesterol, HDL-C, and other conventional risk factors yielded improvement in the model’s discrimination: C-index change, 0.0006 (95% CI, 0.0002-0.0009) for the combination of apolipoprotein B and A-I; 0.0016 (95% CI, 0.0009-0.0023) for lipoprotein(a); and 0.0018 (95% CI, 0.0010-0.0026) for lipoprotein-associated phospholipase A2 mass. Net reclassification improvements were less than 1% with the addition of each of these markers to risk scores containing conventional risk factors. We estimated that for 100 000 adults aged 40 years or older, 15 436 would be initially classified at intermediate risk using conventional risk factors alone. Additional testing with a combination of apolipoprotein B and A-I would reclassify 1.1%; lipoprotein(a), 4.1%; and lipoprotein-associated phospholipase A2 mass, 2.7% of people to a 20% or higher predicted CVD risk category and, therefore, in need of statin treatment under Adult Treatment Panel III guidelines.

Conclusion In a study of individuals without known CVD, the addition of information on the combination of apolipoprotein B and A-I, lipoprotein(a), or lipoprotein-associated phospholipase A2 mass to risk scores containing total cholesterol and HDL-C led to slight improvement in CVD prediction.

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on Practice Guidelines did not support this recommendation.6,8 Similar uncertainties apply to the incremental predictive value of assessing circulating concentrations of lipoprotein–associated phospholipase A2.8

Complementing previous reports from this collaboration,13-15 the current analysis has 2 objectives. First, to determine whether replacing information on total cholesterol and HDL-C with various lipid parameters improves prediction of first-onset CVD outcomes. Second, to determine whether additional information on apolipoprotein B and A-I, lipoprotein(a), or lipoprotein-associated phospholipase A2 to prognostic models containing information on total cholesterol, HDL-C, and other conventional risk factors improves CVD risk prediction.

METHODS

Study Design

Details of this collaboration have been published.10 Eligible prospective studies had information for each participant on total cholesterol, HDL-C, age, sex, smoking status, diabetes, and blood pressure; assayed triglyceride, apolipoprotein B and A-I, lipoprotein(a), or lipoprotein-associated phospholipase A2 mass or activity; had not selected participants on the basis of having had previous CVD (defined in each study at the initial examination); recorded cause-specific mortality, vascular morbidity (nonfatal myocardial infarction or stroke), or both during follow-up using well-defined criteria; and recorded more than 1 year of follow-up. Because information on directly measured LDL-C, adiposity measures, family history of CVD, and socioeconomic factors was available only in subsets of the participants, these variables were not included in the main analysis. eTables 1-4 and eAppendix 1 provide study details, including assay methods, acronyms, and references (available at http://www.jama.com). Data from the Apolipoprotein Related Mortality Risk Study (AMORIS) could not be incorporated into these current analyses because it did not measure baseline levels of HDL-C, blood pressure, smoking status, body mass index, or diabetes (eTable 5).17 In registering fatal outcomes, all contributing studies in this analysis used International Classification of Disease coding to at least 3 digits and ascertainment was based on death certificates, with 29 studies also involving review of medical records, autopsy findings, and other supplementary sources. Studies used definitions of myocardial infarction based on World Health Organization or similar criteria and of stroke based on clinical and brain imaging features. The study was approved by the Cambridgeshire ethics review committee.

Statistical Analysis

Because recent risk scores have tended to combine coronary heart disease (CHD) and stroke outcomes due to the existence of shared risk factors and treatments,18 the primary outcome used herein was first-onset CVD, defined as fatal or nonfatal CHD event or any stroke. We compared prognostic models that replaced information on total cholesterol and HDL-C with various nontraditional lipid parameters that have been previously proposed, including the total cholesterol:HDL-C ratio (which is mathematically equivalent to the non–HDL-C:HDL-C ratio); the HDL-C:total cholesterol ratio; non–HDL-C; apolipoprotein B and A-I; apolipoprotein B:A-I ratio; apolipoprotein A-I:B ratio; total cholesterol and apolipoprotein A-I; apolipoprotein B and HDL-C, and log transformations of ratios.

We also evaluated supplementing risk scores containing total cholesterol and HDL-C with triglyceride, apolipoprotein B, apolipoprotein A-I, lipoprotein(a), and lipoprotein-associated phospholipase A2 mass or activity. Lipoprotein(a) was modeled nonlinearly by including linear and quadratic terms of log-transformed lipoprotein(a). Because of differences in the mean and standard deviation of concentrations of lipoprotein-associated phospholipase A2 recorded across studies using different assay methods (eTables 3 and 4), values were standardized within each study. Cox proportional hazards modeling allowed for separate baseline hazards by study (and, when appropriate, by trial group) and sex but estimated common coefficients (log hazard ratios) across studies. We censored deaths from non-CVD causes. Prognostic models were compared using measures of risk discrimination and reclassification.19-21 We extended our previous methods to a 2-stage approach allowing examination of between-study heterogeneity, calculating the C index and the D measure, and their changes, within each study separately before pooling results. Studies were weighted by numbers of CVD outcomes (eAppendix 2). Between-study heterogeneity in the risk discrimination measures and their changes was quantified by the I² statistic.22 The proportional hazards assumption was satisfied. For participants in studies with at least 10 years of follow-up, we constructed reclassification tables using data from studies that had recorded both fatal and nonfatal CVD outcomes to examine movement of participants between 3 predicted 10-year CHD risk categories (<10%, 10%-<20%, and ≥20%) upon addition of lipid-related markers to conventional risk factors and summarized these using the net reclassification improvement.20

Our clinical modeling involved 3 key assumptions. First, we assumed the use of sequential screening, ie, initial screening with conventional risk factors alone followed by additional measurement of further lipid-related markers in people at 10% to less than 20% predicted 10-year CVD risk. Second, we assumed statin allocation would reduce CVD risk by 20% in people without a history of CVD (including in people at <20% predicted 10-year risk). This estimate was derived from relative risk reductions observed with statins in a meta-analysis of randomized trials (eAppendix 2).8,23 Third, we assumed a policy of statin allocation per Adult Treatment Panel III guidelines,24 that is, people at 20% or more of predicted CVD risk plus others, such as people with diabetes irrespective of their predicted 10-year risk. Analyses were performed using Stata statistical software version 11.0 (StataCorp), 2-sided P values, and 95% CIs.
RESULTS

Individual records were available for 165,544 participants without baseline CVD in 37 prospective cohorts (calendar years of recruitment, 1968-2007) with up to 15,126 incident fatal and nonfatal CVD outcomes (10,132 CHD and 4,994 stroke events) recorded during median follow-up of 10.4 years (interquartile range [IQR], 7.6-14 years). The TABLE describes the baseline characteristics of participants and presents adjusted hazard ratios for CVD with baseline levels of risk factors (supplemented by eTables 1-3, available at http://www.jama.com).

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Table. Summary of Available Data and Hazard Ratios for Cardiovascular Disease With Measured Baseline Levels of Risk Factors

<table>
<thead>
<tr>
<th>Conventional risk factors</th>
<th>Mean (SD) or No. (No. of CVD Cases)</th>
<th>Hazard Ratioa (95% CI)</th>
<th>Mean (SD) or No. (No. of CVD Cases)</th>
<th>Hazard Ratioa (95% CI)</th>
<th>Mean (SD) or No. (No. of CVD Cases)</th>
<th>Hazard Ratioa (95% CI)</th>
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<tbody>
<tr>
<td>Age at survey, y</td>
<td>56.42 (8.41) 1.87 (1.73-2.02)</td>
<td>56.86 (8.38) 1.81 (1.69-1.93)</td>
<td>63.78 (7.52) 1.62 (1.43-1.83)</td>
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<tr>
<td>Sex</td>
<td>Men 68,520 (7,734) NAb 64,402 (7,910) NAb</td>
<td>15,814 (3,583) NAb</td>
<td>Women 71,061 (4,500) NAb 69,100 (4,729) NAb</td>
<td>16,261 (2,567) NAb</td>
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<tr>
<td>Current smoking</td>
<td>No 102,261 (7,137) 1.0 [Reference] 97,949 (7,483) 1.0 [Reference] 21,972 (3,677) 1.0 [Reference]</td>
<td></td>
<td>Yes 37,320 (5,097) 1.79 (1.66-1.94) 35,553 (5,156) 1.87 (1.73-2.02) 10,103 (2,473) 1.63 (1.38-1.91)</td>
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<tr>
<td>History of diabetes</td>
<td>No 131,610 (10,722) 1.0 [Reference] 126,328 (11,103) 1.0 [Reference] 29,904 (5,534) 1.0 [Reference]</td>
<td></td>
<td>Yes 79,711 (15,152) 2.04 (1.76-2.35) 71,74 (15,38) 2.05 (1.77-2.38) 21,717 (6,16) 1.76 (1.57-1.98)</td>
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<td>Systolic blood pressure, mm Hg</td>
<td>135.19 (18.38) 1.31 (1.26-1.37) 134.17 (18.15) 1.34 (1.29-1.38) 138.88 (21.04) 1.29 (1.24-1.35)</td>
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<tr>
<td>Traditional lipids, mg/dL</td>
<td>Total cholesterol 226 (42.5) 1.22 (1.17-1.27) 229 (42.1) 1.19 (1.15-1.24) 225 (41.7) 1.13 (1.10-1.22)</td>
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<tr>
<td>Lipoprotein(a), mg/dLc 115 (80-168)d 1.19 (1.15-1.23) 115 (80-168)d 1.18 (1.14-1.22) 97 (80-142)d 1.11 (1.05-1.16)</td>
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<td>Lipid-related markers</td>
<td>Non-HDL-C, mg/dL 175 (43.8) 1.27 (1.22-1.33) 178 (43.2) 1.25 (1.19-1.31) 173 (42.9) 1.18 (1.10-1.27)</td>
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<td>Apolipoprotein B, mg/dL</td>
<td>110 (29) 1.24 (1.19-1.29)</td>
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<td>Apolipoprotein A-I, mg/dL</td>
<td>146 (32) 0.87 (0.84-0.90)</td>
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<td>Apolipoprotein B:A-I ratio</td>
<td>0.7 (0.6-0.9)d 1.30 (1.24-1.36)</td>
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<td>Lipoprotein-associated phospholipase A2</td>
<td>Activity NAa 1.12 (1.04-1.20)</td>
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<td>Mass NAa 1.15 (1.09-1.21)</td>
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Abbreviations: CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; NA, not applicable.

SI conversion factors: To convert total cholesterol and HDL-C from mg/dL to mmol/L, multiply by 0.0259; triglycerides from mg/dL to mmol/L, multiply by 0.0113; lipoprotein(a) from mg/dL to mmol/L, multiply by 0.357; and apolipoprotein B and A-I from mg/dL to g/L, multiply by 0.01.

Hazard ratio (95% confidence interval) per 1 SD higher age, systolic blood pressure, measured biomarker level or compared to relevant reference category. Hazard ratios were adjusted for age, smoking status, systolic blood pressure, and history of diabetes, where appropriate.

Variables were log transformed.
Median and interquartile range.
Concentrations of lipoprotein-associated phospholipase A2 were standardized to a mean (SD) of 0 (1) within each study due to different assays yielding different absolute levels.

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ing total cholesterol and HDL-C and other conventional risk factors changed the C-index by the amounts shown in Figure 2 and eTable 7, available at http://www.jama.com. However, none of these lipid-related markers significantly improved CVD risk classification. Again, broadly similar results to those observed overall for the lipid-related markers were found in clinically relevant subgroups, including participants who reported using lipid-lowering medications at entry. Although there was tentative evidence of effect-modification in some groups (eFigures 3-6), cautious interpretation is required given the multiplicity of comparisons made. First, apolipoprotein A-I and B, as well as lipoprotein(a), could improve CVD prediction more in individuals with higher total cholesterol or in people initially classified at 10% to less than 20% predicted 10-year risk (P<.001 and P=.02, respectively; eFigures 3 and 4). Second, the addition of apolipoprotein B and A-I could preferentially improve CVD risk discrimination in men (P=.01), participants using blood pressure-lowering medications at entry (P=.005), and individuals with lower HDL-C (P=.02; eFigure 3). Third, the addition of apolipoprotein B and A-I significantly improved risk discrimination for CHD (C-index increase of 0.0010; P<.001) but not for stroke (C-index increase of −0.0002; P=.30). By contrast, addition of lipoprotein(a) or lipoprotein-associated phospholipase A2 mass provided improvements for CHD that were similar to those for stroke (eFigure 7).

Similar results to those described above were observed in analyses that used the D measure (eFigures 8 and 9), or that were restricted to studies with at least 10 years of follow-up (eFigure 10). Levels of lipid-related markers contributed relatively little to heterogeneity in the study-specific C-index, which was mostly due to differing age ranges across cohorts (eFigures 11-15). We could not reliably evaluate the effect of joint assessment of apolipoprotein B and A-I, lipoprotein(a), and lipoprotein-associated phospholipase A2 because only about 10% of the participants in this analysis had concomitant information on all these parameters.

Clinical Modeling
We modeled a population of 100 000 adults aged 40 years or older with similar age structure as the European standard population and an age- and sex-specific incidence of CVD as in the current study; 15 436 people would be initially classified at 10% to less than 20% 10-year predicted CVD risk using conventional risk factors alone, of whom 13 622 would remain after excluding those recommended for statin treatment by Adult Treatment Panel III guidelines (such as people with diabetes irrespective of their predicted 10-year risk24 (Figure 3 and eAppendix 2). For these 13 622 people, assessment of lipoprotein(a) would reclassify 555 people (4.1%) to 20% or greater predicted risk, 86 of whom would be expected to have a CVD event within 10 years; assessment of lipoprotein-associated phospholipase A2 mass would reclassify 365 people (2.7%), 72 of whom would be expected to have a CVD event within 10 years; and assessment of lipoprotein(a) or lipoprotein-associated phospholipase A2 mass would reclassify 154 people (1.1%), 16 of whom would be expected to have a CVD event within 10 years (eFigure 16). Assuming statin allocation per the Adult Treatment Panel III guidelines,24 such targeted assessment could help prevent about 17 (ie, 0.20×86) extra CVD outcomes over 10 years for those additionally tested for lipoprotein(a), 14 (0.20×72) extra CVD outcomes over 10 years for those tested for lipoprotein-associated phospholipase A2 mass, or 3 (0.20×16)
extra CVD outcomes over 10 years for those tested for a combination of apolipoprotein B or A-I. In other words, such targeted assessment of individuals at intermediate CVD risk could help prevent 1 extra CVD outcome over 10 years for every 801 assessed for lipoprotein(a) (ie, 13 622/17), 973 assessed for lipoprotein-associated phospholipase A2 mass (13 622/14), and 4541 assessed for the combination of apolipoprotein B and A-I (13 622/3). Under these circumstances, statins would be newly allocated to about 33 of 801 people (4.1%) assessed for lipoprotein(a), 26 of 973 people (2.7%) assessed for lipoprotein-associated phospholipase A2 mass, or 50 of 4541 (1.1%) assessed for the combination of apolipoprotein B and A-I. Alternatively, assuming use of the more selective statin allocation policies in Canada or the United Kingdom, then the numbers needed to screen listed above should each be multiplied by 0.6.

The model containing conventional risk factors include age, systolic blood pressure, smoking status, history of diabetes, total and high-density lipoprotein cholesterol (HDL-C), each included as individual linear terms. Models were stratified by sex.

*aNet reclassification improvement was calculated only for participants in studies with at least 10 years of follow-up. Change in C-index adding lipoprotein(a) greater than 30 mg/dL was 0.0001 (95% CI, −0.0001 to 0.0003).

*bTriglyceride values were log-transformed.

cP < .05 for comparison against model containing conventional risk factors.

dP < .001 for comparison against model containing conventional risk factors.

eLipoprotein(a) was modeled nonlinearly by including linear and quadratic terms of log-transformed lipoprotein(a).
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COMMENT
In contrast with some existing guidelines,1 6 7 9 the current analysis has shown that replacement of information on total cholesterol and HDL-C with various lipid parameters does not improve CVD prediction. For example, none of the following measures were superior to total cholesterol and HDL-C when they replaced traditional cholesterol measurements in risk prediction scores: the total cholesterol:HDLC ratio; non–HDL-C; the linear combination of apolipoprotein B and A-I; or the apolipoprotein B:A-I ratio. Furthermore, replacement of total cholesterol and HDL-C with apolipoprotein B and A-I actually significantly worsened risk discrimination. These findings applied to clinically relevant subpopulations, including people with diabetes and people with elevated triglyceride levels.

With regards to the value of adding information on various emerging lipid-related markers to risk scores already containing total cholesterol, HDL-C, and other conventional risk factors, we observed slight potential for improvement in CVD prediction. This conclusion was suggested by the following analyses. First, we showed that each of the lipid-related markers studied herein slightly increased CVD prediction when using measures (eg, the C index and D measure) that are independent of clinical risk categories. Second, we found that none of these markers significantly improved reclassification of participants across the clinical risk cutoff levels that are currently used to inform treatment decisions. Third, we modeled a scenario assuming targeted lipid-related marker assessment in people judged as being at intermediate risk (10%-<20% 10-year predicted CVD risk) after initial screening by conventional risk factors alone. If such targeted measurement were to be coupled with allocation of statins per US Adult Treatment Panel III guidelines,24 then our data suggest that it could help prevent 1 extra CVD outcome over 10 years for approximately every 4500 people additionally screened with a combination of apolipoprotein B and A-I, or about 800 people screened with lipoprotein(a), or about 1000 people screened with lipoprotein-associated phospholipase A2 mass.

The generalizability of our findings has been enhanced by inclusion of data from 165,000 participants in 15 countries and by the general lack of heterogeneity in the results. To enhance validity, we have restricted analysis to prospective studies with extended follow-up. For example, although some large retrospective case-control studies have reported stronger associations of apolipoprotein B and A-I with CHD than those observed herein, it remains uncertain to what extent this difference might be explained by factors such as changes in lipid levels observed in the hours after the onset of infarction in case-control studies of acute myocardial infarction.25-26 In contrast with literature-based reviews,27 our access to individual participant data has enabled time-to-event analysis, analysis of clinically relevant subgroups, and consistent comparison across studies. To estimate incremental improvement in CVD prediction, we have studied only people with complete information on conventional risk factors. Our findings are consistent with a separate and complementary analysis of the evidence from randomized trials of patients treated with statins.2,28

This study has potential limitations. Our analysis does not, of course, address etiological and therapeutic questions being explored in randomized trials. Reclassification analyses are intrinsically sensitive to choice of follow-up interval and clinical risk categories. Somewhat greater clinical impact than suggested by our analysis would be estimated if we had used less conservative modeling assumptions (eg, use of more effective statin regimens23 and longer time horizons) or alternative disease outcomes (such as an exclusive focus on CHD rather than on CHD plus stroke). Conversely, our clinical models could have overestimated potential benefits of assessing lipid-related markers because not all people eligible for statins will receive them or be willing, adherent, or able to take them.35 Although we did not find that our results varied importantly by assay methods used, further study of this issue is needed, perhaps particularly for lipid-related markers for which measurements have only recently been standardised.12,32 Furthermore, large studies are needed to assess whether concurrent assessment of lipoprotein(a) concentration and apolipoprotein(a) isoform size confers greater improvement in CVD prediction than lipoprotein(a) alone (such assessment was not possible in the current study because it lacked concomitant data on such isoforms). This study had a limited ability to study lipid-related markers in combination with one another and to investigate populations not of European descent.

In summary, in a study of individuals without known cardiovascular disease, replacing information on total cholesterol and HDL-C with apolipoprotein B and apolipoprotein A-I worsened CVD prediction. Furthermore, addition of the combination apolipoprotein B and A-I, lipoprotein(a), or lipoprotein-associated phospholipase A2 to risk scores containing total cholesterol and HDL-C, provided slight improvement in CVD prediction. The clinical benefits of using any of these biomarkers remains to be established.

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